From
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Autism in Iceland

Prevalence, diagnostic instruments, development, and association of autism with seizures in infancy

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ÁGRIP

Einhverfa á Íslandi – Algengi, greiningartæki, framvinda og tengsl einhverfu við flog hjá ungbörnum

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Markmið: Að meta algengi einhverfu og einhverfurófsraskana (ER); að skoða samsvörun greiningartækja sem notuð voru til að greina ER; að lýsa stöðugleika og breytingum hjá börnum á leikskólaaldri með ER; að lýsa tengslum milli kippaflogaveiki ungbarna (KFU) og annarra floga á fyrsta æviári við ER; að skoða hvort KFU spái meiri áhættu fyrir ER borið saman við önnur óvakin flog.
Efniviður og aðferðir: Þátttakendur voru börn sem voru greind með ER og skráð á Greiningar- og ráðgjafarstöð ríkisins og Barna- og unglingageðdeild Landspítalans ásamt börnum sem höfðu komið á barnadeildir spítalana og greinst með óvakin flog á fyrsta æviári. Skilgreining á einhverfu var byggð á ICD-10, en til að athuga hvort einkenni uppfylltu greiningarskilmerki var stuðst við greiningartækin Autism Diagnostic Interview-Revised (ADI-R), Childhood Autism Rating Scale (CARS) og Autism Diagnostic Observation Schedule (ADOS). Viðeigandi þroskaprófum var beitt í öllum tilvikum í samræmi við aldur og þroska.
Niðurstöður: Lægra algengi einhverfu fannst í hópi fæddum 1974-1983 heldur en í hópi fæddum 1984-1993, eða 4.2/10,000 (95% vikmörk, 2.3-6.2) og 13.2/10,000 (95% vikmörk, 9.8-16.6) en báðum hópum var fylgt eftir til 1. desember 1998. Í nokkuð yngri hópi, fæddum 1992-1995, sem fylgt var eftir til 1. janúar 2004, var algengi allra ER 48/10,000 (95% vikmörk, 37.9-58.0).

Samsvörun milli ADI-R og CARS var 66.7% (κ = .40) þegar skilgreiningu ADI-R á einhverfu var beitt (að greiningarmörkum væri náð á öllum þremur einkennasviðum). Samsvörun milli greiningartækjana jókst í 83.3% (κ = .66), þegar lækkaður var þröskuldur á ADI-R skilgreiningu. Hópurinn sem náði greiningarmörkum bæði á ADI-R og CARS var vitsmunalega skertari og í honum voru fleiri stúlkur en hópnum sem náði aðeins greiningarmörkum á CARS.

Í eftirfylgdarrannsókn á börnum á leikskólaaldri minnkuðu einkenni einhverfu, eins og þau voru skilgreind á CARS, frá tíma 1. til tíma 2. fyrir hópinn í heild (p = .001). Yfir 90% barnanna sem voru greind með dæmigerða einhverfu á tíma 1. voru með sömu greiningu á tíma 2. Meðalframmistaða á þroskaprófum var stöðug fyrir allan hópin (p = .209) en mikil munur kom fram á framvindu milli einstaklinga. Börn með einhverfugreiningu voru vitsmunalega skertari en hin sem greindust með aðrar ER.

Tengslum milli óvakinna floga á fyrsta æviári og ER var lýst í tveimur hópum. Í öðrum hópnum með KFU var algengi ER 35.3% (95% vikmörk, 14.2-61.7). Í hinum hópnum með önnur flog á fyrst æviári (ekki KFU) var algengi ER 7.1% (95% vikmörk, 2.7-14.9). Ef miðað var við tímabilið sem skaraðist í þessum hópum (1982-1998), þá var nýgengi óvakinna floga á fyrsta ári 163.4 per 100,000 mannár (95% vikmörk, 135.6-195.3). Í þessum þátttakendahópi í heild (N=95) voru 13 börn með ER eða 13.7% (95% vikmörk, 7.5-22.3), átta stúlkur og fimm drengir. Öll börnin með ER nema eitt voru einnig með þroskahömlun. Líkindahlutfall (LH) fyrir ER með tengsl við KFU var 1.55 (95% vikmörk, 0.33-7.37), leiðrétt fyrir sjúkdómsvakin flog, og LH fyrir ER með tengls við sjúkdómsvakin flog var 8.73 (95% vikmörk, 1.88-40.54), leiðrétt fyrir KFU.

Umræða og ályktanir: Aukning hefur orðið á algengi einhverfu og ER á Íslandi og er hún mest áberandi í yngstu aldurshópunum. Greiningarmörk við 30 stig á CARS byggja á víðari skilgreiningu á einhverfu en þriggja einkennasviða skilgreining ADI-R. Það er mikilvægt að taka tillit til mikils breytileika í einkennafræði og þroskun hjá börnum með ER á leikskólaaldri. Algengi ER hjá börnum með óvakin flog á fyrsta æviári er mun hærra en hjá börnum almennt. Sjúkdómsvakin flog á fyrsta æviári auka áhættu á ER, ekki tegund flogaveikinnar sem slík. Ekki er hægt að útiloka möguleg viðbótaráhrif floga, sérstaklega þegar KFU á í hlut.

Lykilorð: Einhverfa, einhverfurófsraskanir, greiningarviðtal fyrir einhverfu (ADI-R), algengi, nýgengi, flog á ungbarnastigi.

ABSTRACT

Autism in Iceland – Prevalence, diagnostic instruments, development and association of autism with seizures in infancy

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Aims: To estimate the prevalence of autism and autism spectrum disorders (ASDs); to study the agreement of the diagnostic instruments used for ascertainment of ASD cases; to describe stability and change in preschool-aged children diagnosed with ASDs; to describe the association between infantile spasms (IS) and other types of seizures in the first year of life and ASD; to determine whether IS predict higher risk of ASD as compared to other unprovoked seizures.

Material and Methods: Participants were children diagnosed with ASD and registered at two tertiary institutions and children diagnosed with unprovoked seizures in the first year of life and registered at the in-patient pediatric facilities in the country. The definition of autism was based on the ICD-10 and the Autism Diagnostic Interview-Revised (ADI-R) was used for case ascertainment, accompanied by the Childhood Autism Rating Scale (CARS) and/or the Autism Diagnostic Observation Schedule. Appropriate cognitive tests were used for all participants according to their age and developmental level.

Results: A lower prevalence was found for autism in a cohort born 1974-1983 than for a cohort born 1984-1993, or 4.2/10,000 (95% CI, 2.3-6.2) and 13.2/10,000 (95% CI, 9.8-16.6) respectively, both groups with a follow-up date of December 1st 1998. In a younger cohort (1992-1995) with a follow-up date January 1st 2004, the prevalence estimate for all ASDs was 48/10,000 (95% CI, 37.9-58.0).

The observed agreement between ADI-R and CARS was 66.7% (κ = .40) when ADI-R definition for autism was applied (i.e., scores reaching cutoff in three symptom domains on the ADI-R). The agreement increased to 83.3% (κ = .66) with less stringent ADI-R criteria. The group reaching cutoffs on both instruments was more cognitively impaired and contained more girls than the group reaching cutoffs on CARS only.

In a follow-up of preschool children, autistic symptoms as measured by CARS decreased from time 1 to time 2 for the total group (p = .001). Over 90% of the children who received childhood autism diagnosis at time 1 stayed in the same diagnostic category at time 2. Mean intellectual/developmental quotients (IQ/DQ) for the whole group were stable (p = .209), but there were considerable individual differences. Children with autism were more cognitively impaired than children with other ASD diagnoses.

The association of unprovoked seizures in the first year of life and ASD was described in two groups. In the study group with IS, the prevalence of ASD was 35.3% (95% CI, 14.2-61.7), but in the other study group with unprovoked seizures (other than IS) the prevalence of ASD was 7.1% (95% CI, 2.7-14.9). In the overlapping period (1982-1998) of the two studies, the incidence of all unprovoked seizures in the first year of life was 163.4 per 100,000 person years (95% CI, 135.6-195.3). Of the total group (N=95), 13 children or 13.7% (95% CI, 7.5-22.3) had ASD, eight girls and five boys. All but one of the children with ASD had intellectual disability. The odds ratio (OR) for ASD associated with IS was 1.55 (95% CI, 0.33-7.37), adjusted for symptomatic seizures, and OR for ASD associated with symptomatic origin of seizure was 8.73 (95% CI, 1.88-40.54), adjusted for IS. **Discussion and conclusions:** There has been an increase in the prevalence of autism and ASDs in Iceland, which is most apparent in the younger age groups. The 30-point cutoff on CARS is based on a wider concept of autism than the three-domain definition on ADI-R. It is important to respect individual differences in developmental trajectories in preschool children with autism, both in relation to autistic behaviors and developmental measures. The prevalence of ASD in children with unprovoked seizures in the first year of life exceeds that of the general population. The symptomatic origin of seizures in the first year of life increases the risk of ASD, not the seizure type as such, although the additive effects of the seizures themselves, particularly IS, can not be excluded.

Key words: Autism, autism spectrum disorder, Autism Diagnostic Interview-Revised, prevalence, incidence, seizures in infancy.

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CONTENTS

ABBREVIATIONS

AA = atypical autism

ADI-R = Autism Diagnostic Interview-Revised

ANOVA = analysis of variance

APA = American Psychiatric Association

ASD = autism spectrum disorder

CARS = Childhood Autism Rating Scale

CA = childhood autism

CO = communication impairment domain on the ADI-R

CI = confidence interval

DCAP = Department of Child and Adolescent Psychiatry

DSM-III = Diagnostic and Statistical Manual of Mental Disorders, third edition

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, fourth edition

DQ = developmental quotient

EEG = electroencephalogram

FXS = fragile-X syndrome

ICD-9 = International Classification of Diseases, 9^{th} revision

ICD-10 = International Classification of Diseases, 10^{th} revision

ID = intellectual disability (previously termed mental retardation)

IS = infantile spasms

IQ = intelligence quotient

κ = Cohen's kappa

MRI = Magnetic resonance imaging

NRC = National Research Council

OR = odds ratio

PDD = pervasive developmental disorder

RB = repetitive behavior domain on the ADI-R

SDCC = State Diagnostic and Counseling Center

SI = social impairment domain on the ADI-R

TSC = tuberous sclerosis complex

WHO = World Health Organization

LIST OF TABLES

LIST OF ORIGINAL PAPERS

This thesis is based on the following original papers, which will be referred to by the Roman numerals:

I. Magnusson, P., & Saemundsen, E. (2001). Prevalence of autism in Iceland. *Journal of Autism and Developmental Disorders, 31*,153-163.

II. Saemundsen, E., Magnusson, P., Smari, J., & Sigurdardottir, S. (2003). The Autism Diagnostic Interview-Revised and the Childhood Autism Rating Scale: convergence and discrepancy in diagnosing autism. *Journal of Autism and Developmental Disorders, 33*, 319-328.

III. Jonsdottir, S.L., Saemundsen, E., Asmundsdottir, G., Hjartardottir, S., Asgeirsdottir, B.B., Smaradottir, H.H., Sigurdardottir, S., & Smari, J. (2007). Follow-up of children diagnosed with pervasive developmental disorders: stability and change during the preschool years. *Journal of Autism and Developmental Disorders, 31*, 1361-1374.

IV. Saemundsen, E., Ludvigsson, P., & Rafnsson, V. (2007). Autism spectrum disorders in children with a history of infantile spasms – A population based study. *Journal of Child Neurology, 22*, 1102-1107.

V. Saemundsen, E., Ludvigsson, P., Hilmarsdottir, I., & Rafnsson, V. (2007). Autism spectrum disorders in children with seizures in the first year of life – A population based study. *Epilepsia, 48*, 1724-1730.

VI. Saemundsen, E., Ludvigsson, P., & Rafnsson, V. (2007). *Risk of autism after infantile spasms – A population based study nested in a cohort with seizures in the first year of life*. Manuscript submitted for publication.

DECLARATION OF CONTRIBUTION

Paper I

Pall Magnusson (PM) and Evald Saemundsen (ES) were equally responsible for the design of the study, and the collection of data, PM at the Dept. of Child and Adolescent Psychiatry, Landspitali University Hospital, and ES at the State Diagnostic and Counseling Center (SDCC). Both authors analyzed the data, worked on the first draft of the manuscript, edited it together, and approved the final version of the manuscript. PM and ES are guarantors.

Paper II

ES and PM designed the study together but ES was responsible for procedures. ES and PM were both responsible for collection of data on diagnostic instruments at the SDCC. ES was responsible for other data sources, except for medical data collected by Solveig Sigurdardottir (SS). ES was responsible for analyzing the data in close cooperation with Jakob Smari (JS) and PM. ES wrote the first draft of the manuscript. All authors were responsible for its editing and all approved the final version of the manuscript. ES and PM are guarantors.

Paper III

Sigridur Loa Jonsdottir (SLJ) and ES were responsible for the design of the study and for the collection of data at the SDCC in cooperation with Gudlaug Asmundsdottir (GA), Sigrun Hjartardottir, Bryndis B. Asgeirsdottir, Hrafnhildur H. Smaradottir, and SS. SLJ, ES, and GA analyzed the data in close cooperation with JS. SLJ and ES wrote the first draft of the paper and were responsible for its editing, and all authors approved the final version of the manuscript. SLJ and ES are guarantors.

Paper IV

ES, Petur Ludvigsson (PL) and Vilhjalmur Rafnsson (VR) were responsible for the design of the study. ES collected the data which was analyzed by all three authors. ES wrote the first draft, but ES and VR were responsible for writing the manuscript. All authors were responsible for its editing and all approved the final version of the manuscript. ES is guarantor.

Paper V

ES, PL, and VR designed the study. PL and Ingibjorg Hilmarsdottir collected data on unprovoked seizure diagnoses in the first year of life and ES gathered all developmental data, and the diagnoses of neurodevelopmental disorders. ES, PL, and VR were responsible for analyzing the data. ES wrote the first draft, but ES and VR were responsible for writing the manuscript. All authors were responsible for its editing and all approved the final version of the manuscript. ES is guarantor.

Paper VI

ES, PL, and VR designed the study. ES and PL were responsible for the collection of data. VR and ES were responsible for analyzing the data with the help of Helgi Sigvaldason. ES wrote the first draft, but ES and VR were responsible for writing the manuscript. ES, PL, and VR were responsible for the editing of the manuscript and all approved its final version. ES is guarantor.

INTRODUCTION

Definition of concepts and a historical note

Autism is a neurodevelopmental disorder with onset in most cases during infancy or early childhood. In 1943, Kanner published his careful observations in a paper termed *Autistic disturbances of affective contact*, where he described the behavioral features of 11 children, eight boys and three girls, all with serious impairments in interpersonal social and communication skills, who also displayed a restricted range of interests, insistence on sameness, and stereotyped repetitive movements. The concept of autism was originally used by Bleuler in his description of certain features of the thinking of schizophrenic patients (Rutter, 1978). Unfortunately, this association between autism and psychosis lingered on, and was a source of some confusion as to the nature of autism (Volkmar & Klin, 2005). In the ninth revision of the International Classification of Diseases (ICD-9) (WHO, 1977) autism was still classified as a childhood psychotic condition.

Almost four decades after Kanner's original description of autism, the concept of *pervasive developmental disorder* (PDD) was introduced in the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) of the American Psychiatric Association (APA, 1980) as an umbrella term for autism and autistic-like conditions (Gillberg, 1991a). The concept of PDD bore witness to changing views in this field, highlighting the idea that autism was a developmental disorder (Wing, 2005). Also, the term PDD was meant to steer away from theoretical presuppositions about etiology (Volkmar & Klin, 2005). PDD was chronologically linked to the idea that autism represented a part of a *continuum* (Wing, 1981; Wing & Gould, 1979), for which Lotter (1966) was probably the first to provide empirical support. The term PDD has been criticized for its lack of specificity, and for the fact that severe cognitive impairment without autism may certainly be considered a PDD (Gillberg, 1991a), and the designation "pervasive" may seem inappropriate when describing high-functioning individuals with autism (Baird et al., 1991).

Somewhat later, the word *spectrum* was introduced and was favored over the concept of continuum as the former was considered more precise, implying range of clinical pictures in lieu of a uniform dimension (Wing, 2005). Thus, *autism spectrum disorder* (ASD) also became an umbrella term for life-long developmental

disorders of brain function, with autism representing the more severe end of the spectrum (Tuchman & Rapin, 2002). The concept of spectrum has received support from epidemiological studies (e.g. Lotter, 1966; Nordin & Gillberg, 1996; Wing & Gould, 1979), twin and family studies (e.g. Bailey, Palferman, Heavey, & Le Couteur, 1998), as well as from prospective studies of siblings of autistic probands (e.g. Yirmiya & Ozonoff, 2007).

The two terms, PDD and ASD, are frequently used as synonyms (Volkmar & Klin, 2005) in spite of the above-mentioned criticism of PDD, and the fact that PDD includes two rare disorders: Rett's syndrome, which is a progressive X-linked genetic disorder almost exclusively found in females (Van Acker, Loncola, & Van Acker, 2005), and childhood disintegrative disorder, which presents with a distinctive onset in the form of severe regression after the age of 2 years following on a period of seemingly normal development, with autism being the end state (Volkmar, Koenig, & State, 2005). Another narrower definition of ASD excludes the above two disorders (Rice et al., 2007). Since PDD and ASD are used interchangeably in the literature, this usage necessarily applies to the research presented in this thesis. However, for the sake of clarity and easier lecture, ASD was preferred whenever possible.

Diagnostic issues

Diagnostic criteria and classification

The behavioral features described by Kanner were later refined and became recognized as the *triad of impairments* (Rutter, 1978; Wing & Gould, 1979), which became the basis of current definitions of autism by international classification systems, i.e. ICD-10 (WHO, 1993) and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition or DSM-IV (APA, 1994) (see Table 1). International consensus as to the classification of autism is reflected in the ICD-10 and DSM-IV definitions, which are practically identical (Buitelaar, Van der Gaag, Klin, & Volkmar, 1999; Lord & Risi, 1998; Sponheim, 1996).

Diagnosis of autism is based on the frequency and intensity of qualitative abnormalities in (1) reciprocal social interaction and (2) communication, and the presence of (3) restricted, repetitive, and stereotyped patterns of behavior. The minimum requirement for the diagnosis of autism is a total of at least six symptoms

from the above domains, with at least two from (1) and at least one from each of (2) and (3) (WHO, 1993). This means that impairment in social interaction weighs more heavily in the definition of autism than the other two symptom domains.

Table 1 ICD-10 F84 diagnostic classification of pervasive developmental disorders (PDDs)

F84.0	Childhood autism
F84.1	Atypical autism
F84.2	Rett´s syndrome
F84.3	Other childhood disintegrative disorder
F84.4	Overactive disorder associated with mental retardation and stereotyped movements
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified

Note. The ICD-10 PDD categories F84.0, F84.2, F84.3, and F84.5 may roughly be considered parallel to the corresponding DSM-IV PDD categories (autistic disorder, Rett's disorder, childhood disintegrative disorder, and Asperger's disorder). Three of the ICD-10 categories, atypical autism, other PDDs, and PDD unspecified (F84.1, F84.8, F84.9), may be considered to be included in the DSM-IV PDD-NOS category. The ICD-10 F84.4 category does not have any correspondence with the DSM-IV.

(Adapted from Jonsdottir et al. 2007b)

At present, biological markers for autism are not known. Thus, diagnostic decisions are based on medical and behavioral data, including diagnostic instruments for autism that systematically gather information on past and present behaviors (Gillberg, Nordin, & Ehlers, 1996; Lord, 1997; Volkmar & Klin, 2005). Clinicians and researchers alike are faced with complicated decisions regarding the classification within the autism spectrum, and regarding the boundaries between the autism spectrum and other neurodevelopmental disorders (Buitelaar et al. 1999; Leekam, Libby, Wing, Gould, & Gillberg, 2000; Lord, 1995; Mahoney et al. 1998;

Mayes, Calhoun, & Crites, 2001). Expert clinicians are reliable and accurate in differentiating between children with ASDs and those without ASDs on the basis of diagnostic criteria proposed by the international frameworks. However, differentiating between autism and atypical autism (or PDD-NOS) remains problematic (Buitelaar et al. 1999; Mahoney et al., 1998), in particular if the possibility of Asperger's syndrome needs to be addressed as well (Gilchrist et al., 2001; Howlin & Asgharian, 1999; Macintosh & Dissanayake, 2004; Mattila et al., 2007; Walker et al., 2004). Besides the current international diagnostic frameworks, practice parameters for screening and diagnosis have been formulated across disciplines (Filipek et al., 1999) and within disciplines (Filipek et al., 2000; Johnson et al., 2007; Volkmar, Cook, Pomeroy, Realmuto, & Tanguay, 1999).

Diagnostic instruments

A wide range of screening and diagnostic instruments of autism spectrum disorders have been devised during the recent decades (see Coonrod & Stone, 2005 and Lord & Corsello, 2005 for reviews). Three main groups have been described: questionnaires, observation schedules and interviews. Of these, observation schedules and interviews seem to be best suited for diagnosis (Le Couteur et al. 1989). At present, neither method is sufficient in the diagnosis of autism, so clinicians are advised to use both interviews with caregivers and systematic direct observation of behavior, and preferably to use instruments that translate into current diagnostic frameworks (Risi et al., 2006).

Etiological considerations

Genetics

Autism is a disorder of brain development with a genetic component, although the genetic mechanisms are not known (Minshew, Sweeney, Bauman, & Webb, 2005; Szatmari, 2003). Early case series reported that 2% to 3% of families with autistic proband contained more than one child with autism (Santangelo & Folstein, 1999). It is complicated to estimate the recurrence risk for autism, as the diagnosis of autism in a child may affect the reproductive behavior of the parents. This "stoppage", or not having another child after the one diagnosed with autism, may underestimate the relative risk in siblings. Researchers have tried to circumvent this

problem by counting only siblings born after the autistic proband, which increases the risk estimate for siblings to 8.6% (Ritvo et al. 1989).

The first twin study showed a significant difference in the concordance of monozygotic (MZ) pairs versus dizygotic (DZ) for autism (Folstein & Rutter, 1977). Further studies confirmed the genetic influence on the underlying liability for autism, the concordance rates for autism in MZ and DZ pairs being 60% and 5% respectively (Rutter, 2000). If the concordance was extended to a mixture of more subtle social and cognitive deficits that were qualitatively related to autism, it was raised to 90% in MZ pairs with only a slight increase for DZ pairs (Bailey et al., 1995). Other twin studies have described a "broader phenotype" or a "lesser variant" of autism in siblings of autistic probands that is estimated at 10% to 20% (Le Couteur et al., 1996). Family studies have also provided evidence for the existence of a broader phenotype of autism in first degree relatives as well as in extended pedigrees (Bailey et al., 1998; Bolton et al., 1994; Pickles et al., 2000; Piven et al., 1994; Szatmari et al., 2000).

Associated medical conditions

In addition to genetic causes, numerous medical conditions have a possible etiological relationship with the autistic syndrome, including seizures (Barton & Volkmar, 1998; Gillberg & Coleman, 1996; Kielinen, Rantala, Timonen, Linna, & Moilanen, 2004; Rutter, Bailey, Bolton, & Le Couteur, 1994). However, instances with associated medical conditions with a known or suspected etiological relationship with autism constitute only a fraction of autism cases, or 10%-15% (Barton & Volkmar, 1998; Kielinen et al. 2004; Szatmari, 2003).

The largest portion of these conditions stems from fragile-X syndrome (FXS) and tuberous sclerosis complex (TSC). Prevalence of FXS in autism has been estimated at 2.5% to 6% in males, and somewhat lower in females because of the modifying effect of a second X chromosome (Clifford et al., 2007). A recent study on the autism spectrum phenotype in males and females with FXS and a full mutation of the FMR1 gene showed 27% of males and 13% of females with a relatively strict definition of autism spectrum disorder, but 67% of males and 23% of females with less stringent definition (Clifford et al. 2007). Prevalence of TSC in children with autism has been estimated at 1.1%, and the prevalence of autism or ASD in TSC has been estimated at 44% and 66% respectively in epidemiological

samples (Bolton, 2004). A host of other chromosomal or genetic disorders have been associated with autism, e.g. velo-cardio facial syndrome, Prader-Willi syndrome, Angelman syndrome, Smith-Magenis syndrome, and PKU (Baieli, Pavone, Meli, Fiumara, & Coleman, 2003; Bonati et al. 2007; Cohen et al. 2005; Dimitropulos & Schultz, 2007; Gillberg & Coleman, 1996; Vorstman et al. 2006).

Environmental factors

Autism is a neurologically determined behavioral syndrome with multiple etiologies, so it is hardly surprising that environmental factors may also be influential in the development of the disorder, especially if "environmental" can include any event after fertilization (Szatmari, 2003). Such associations have been reported for congenital rubella and congenital cytomegalovirus infections, as well as postnatal viral encephalitis (Ghaziuddin, Al-Khouri, & Ghaziuddin, 1986; Ghaziuddin, Tsai, Eilers, & Ghaziuddin, 1992; Gillberg, 1986; Gillberg, 1991b; Gillberg & Coleman, 1996). Alcohol, thalidomide, and valproic acid, have all been associated with various dysmorphic features and neurodevelopmental disabilities, including autism (Arndt, Stodgell, & Rodier, 2005; Miyazaki, Narita, & Narita, 2005; Rasalam et al., 2005). Maternal administration of thalidomide or valproic acid during pregnancy is implicated in abnormal development of serotonergic neurons in the offspring (Miyazaki et al., 2005). Other environmental risk factors associated with autism have been suggested (Lawler, Croen, Grether, & Van de Water, 2004; Newschaffer, Fallin, & Lee, 2002).

Lately the measles, mumps and rubella (MMR) vaccination has been implicated in the increase of diagnosed cases of autism. This possibility has been studied extensively and has largely been ruled out as a causal factor in increased incidence of autism and ASD (Rutter, 2005). Especially important in this respect was a natural experiment that took place in Yokohama, Japan, where the MMR vaccination was discontinued while the cumulative incidence of ASD continued to rise (Honda, Shimizu, & Rutter, 2005).

Severe global privation in early childhood is known to have serious short and long-term effects on the health and development of the affected children. The English and Romanian Adoptees (ERA) Study Team has reported a high prevalence of autism and "quasi-autistic patterns" in children from Romania adopted into U.K families where most of them were reared in institutions of poor to appalling

conditions (Rutter et al., 1999). The question then arises whether severe global privation in infancy and early childhood can cause autism. Although there is no absolute answer to this question, the cited research has certainly underscored the importance of not ignoring autistic features in these children, as they need to be targeted for intervention along with the frequent incidence of malnutrition and attachment disorder.

Neurological aspects

Neuropathology

There is virtually no part of the human brain that has not been implicated in autism. Postmortem studies of the brains of individuals with well documented autism have not shown any anomalies of gross brain structure (Minshew et al., 2005). However, one of the most consistent morphologic findings in autism is increased brain volume and macrocephaly (Courchesne et al., 2001; Fombonne, Roge, Claverie, Courty, & Fremolle, 1999; Lainhart et al., 1997; Miles, Hadden, Takahashi, & Hillman, 2000).

In a MRI study of boys with autism, 90% had brain volumes larger than a control group of normal children aged 2 to 4 years, and 37% met criteria for macrocephaly (Courchesne et al., 2001). For the autistic group, head circumference at birth was normal according to neonatal clinical records. Since excessive brain size was not present at birth, but recognizable by 2 to 3 years of age, it was suggested that this overgrowth would have begun between these points in time. In another study based on head circumference data from 48 children with ASD, the researchers timed a sudden and excessive increase in head size between 1 to 2 months and 6 to 14 months, and concluded that "accelerated rate of growth might serve as an early warning signal of risk for autism" (Courchesne, Carper, & Akshoomoff, 2003, p. 337). Changes in brain growth may possibly be linked to observable early development of autistic symptomatology (Cox et al., 1999; Mraz, Green, Dumont-Mathieu, Makin, & Fein, 2007).

In a post-mortem study of the brains of nine individuals with autism, Bauman and Kemper demonstrated abnormalities in the limbic system as well as in the cerebellum and related structures in all the brains studied (Minshew et al., 2005). These abnormalities consisted mainly of patterns of small neuronal cell size and increased cell packing density in the structures that make up the limbic system. In the cerebellum, a considerable reduction was observed in the number of Purkinje

cells (Minshew et al. 2005). Although the latter finding seems to be robust, structural imaging studies provide mixed evidence regarding specific cerebellar abnormalities, possibly because of lack of matching on age, gender and intelligence quotient (IQ) (Minshew et al., 2005; Penn, 2006).

The temporal lobes and the limbic system have been implicated in the neuropathology of autism for a long time (Bolton & Griffiths, 1997; Hauser, DeLong, & Rosman, 1975; Riikonen & Amnell, 1981; Schain & Yannet, 1960). Both the hippocampus and amygdala are functionally associated with memory, social behavior, cognition, and emotion, and the left temporal lobe subserves language processing in the majority of the population. Since all of these functions are more or less impaired in autism, the study of the above anatomical loci has certain face-validity.

In a study on autism and macrocephaly, there were no temporal lobe abnormalities of volume observed (Bigler et al. 2003). The researchers concluded that "temporal lobe abnormalities that may be associated with autism are likely to be more related to functional organization within the temporal lobe than to any gross volumetric difference" (p. 2066). Even if the anatomical evidence is mixed, there is support for reversal of the normal asymmetry between the hemispheres, with atrophy of the left planum temporale as well as the left inferior prefrontal gyrus, which may fit the overall picture of increased left-handedness and ambidexterity in autism (Minshew et al. 2005). These findings may, however, be linked to the presence or absence of specific language impairment (De Fosse et al. 2004).

Other interesting leads in studying the abnormal brain organization in autism involve inverse correlation between the degree of cerebellar abnormality and the degree of frontal lobe abnormality (Carper & Courchesne, 2000), minicolumnar pathology in frontal and temporal lobes (Casanova, Buxhoeveden, Switala, & Roy, 2002), white matter asymmetries (Waiter et al., 2005), and dysfunction of the mirror neuron system (Hadjikhani, Joseph, Snyder, & Tager-Flusberg, 2006).

Association of autism and epilepsy

Epilepsy, defined as recurrent episodes of unprovoked, paroxysmal seizure activity (Cowan, 2002), was one of the first biological factors to be associated with autism (Creak, 1963; Rutter & Lockyer, 1967; Schain & Yannet, 1960). This discovery was especially important in light of an influential causal hypothesis of autism,

which grew out of Kanner's original paper, where autistic symptomatology was seen as a severe emotional reaction on the part of the infant vis-à-vis certain personality traits (or lack there of) in the parents.

Since these early reports, a number of studies have found increased rates of epilepsy in individuals with autism and autism spectrum disorders (e.g. Danielsson, Gillberg, Billstedt, Gillberg, & Olsson, 2005; Deykin & MacMahon, 1979; Elia, Musumeci, Ferri, & Bergonzi, 1995; Gillberg & Steffenburg, 1987; Giovanardi-Rossi, Posar, & Parmeggiani, 2000; Mouridsen, Rich, & Isager, 1999; Olsson, Steffenburg, & Gillberg, 1988; Pavone et al., 2004; Steffenburg & Gillberg, 1986; Tuchman, Rapin, & Shinnar, 1991; Volkmar & Nelson, 1990; Wong, 1993). Seizures in autism can appear at any age but two peak periods of seizure onset have been reported, i.e. in early childhood (Danielsson et al., 2005; Elia et al., 1995; Olsson et al., 1988; Steffenburg & Gillberg, 1986; Volkmar & Nelson, 1990; Wong, 1993) and in early adolescence (Deykin & MacMahon, 1979; Gillberg & Steffenburg, 1987; Giovanardi-Rossi et al., 2000; Hara, 2007; Kawasaki, Yokota, Shinomiya, Shimizu, & Niwa, 1997; Volkmar & Nelson, 1990). There are indications that the first peak may consist primarily of symptomatic seizures and the second peak of idiopathic seizures (see below) (Elia et al., 1995; Hara, 2007).

Large differences are found in the rates of epilepsy in autism (5%-44.5%) which reflect different referral groups, age groups, diagnostic groups, and differences in ascertainment (Elia et al., 1995; Tuchman & Rapin, 2002; Wong, 1993). Two large follow-up studies of individuals with autism in Japan (Hara, 2007) and Sweden (Danielsson et al., 2005) estimated the cumulative risk for epilepsy by young adulthood at 25% and 38% respectively. This difference in figures may partly be explained by the fact that in the Japanese study, all potential participants with neurological diseases were excluded. Since lower IQ level predicts higher incidence of epilepsy (Airaksinen et al., 2000), it is interesting to note that the proportion of individuals with severe intellectual disability (ID) (IQ<50) was similar in the Japanese study (75%) and the Swedish study (71%). Such a high proportion of participants with severe ID limits the generalizability of the results of these studies (Ballaban-Gil & Tuchman, 2000).

The major risk factor for epilepsy in autism is severe ID (IQ<50) (Danielsson et al., 2005; Elia et al., 1995; Steffenburg, Steffenburg, & Gillberg, 2003; Tuchman et al., 1991). The cumulative risk of epilepsy in autism rises with

the severity of cognitive impairment, and the presence of cerebral palsy or other motor disabilities (Tuchman & Rapin, 2002). A previous abnormal electroencephalogram (EEG) in young children with ASD is associated with increased risk of developing epilepsy (Akshoomoff, Farid, Courchesne, & Haas, 2007) and this applies also to epileptiform EEG abnormalities in older age groups (Hara, 2007).

Partial seizures with or without generalization is the most frequent seizure type in autism (Danielsson et al., 2005; Giovanardi-Rossi, Parmeggiani, Bach, Santucci, & Visconti, 1995; Hara, 2007; Olsson et al., 1988). EEG foci in both the frontal and temporal lobes have been reported to predominate in autism (Hara, 2007; Kawasaki et al., 1997). Both of the latter studies relied on cohorts with many individuals with severe ID. Severe deficits in receptive language are associated with epilepsy in children with autism. All three, autism, severe receptive language disorder and epilepsy, implicate temporal lobe dysfunction (Tuchman & Rapin, 2002).

Infantile spasms and autism

Age-specific incidence of epilepsy in childhood is highest during a child's first year (Camfield, Camfield, Gordon, Wirrell, & Dooley, 1996; Hauser, Annegers, & Kurland, 1993; Olafsson et al., 2005; Sidenvall, Forsgren, Blomquist, & Heijbel, 1993; Tsuboi, 1988). Infantile spasms (IS) make up a considerable proportion of epileptic seizures between 1 and 12 months and present only in infants and young toddlers (Bednarek, Motte, Soufflet, Plouin, & Dulac, 1998; Hrachovy & Frost, 2003; Riikonen, 1982), with a peak incidence between four to seven months of age (Hrachovy & Frost, 2003; Ludvigsson, Olafsson, Sigurdardottir, & Hauser, 1994). Clinical manifestations are characterized as flexor or extensor spasms. The most common EEG pattern associated with infantile spasm is hypsarrhythmia (Hrachovy & Frost, 2003).

IS have many known precipitating factors of pre-, peri-, and postnatal origins. These include tuberous sclerosis, malformation of cortical development, prematurity, hypoxic-ischemic injury, congenital infections, inborn errors of metabolism, genetic syndromes, and chromosomal abnormalities (Ludvigsson et al., 1994; Riikonen & Donner, 1979; Zupanc, 2001). When such factors are present, the IS (or the patients) are classified as symptomatic. If there is no evidence of prior

developmental deviance or precipitating factors, the spasms are classified as cryptogenic (Ludvigsson et al., 1994) or idiopathic (Sidenvall & Eeg-Olofsson, 1995). A distinction between symptomatic and cryptogenic etiology is of importance for outcome studies, since the cryptogenic group has a better prognosis (Hrachovy & Frost, 2003; Riikonen, 1982). The average incidence of IS is approximately 0.31 per 1,000 live births with higher rates associated with higher geographical latitudes (Hrachovy & Frost, 2003). In a review of 67 studies with average follow-up period of 31 months, the mortality of children with previous IS was 12% and only 16% of children with a history of IS had normal development (Hracovy & Frost, 2003).

The possible association between IS and autism was noted (Creak 1963; Schain & Yannet, 1960) prior to the comprehensive study of Riikonen and Amnell (1981). The latter study was based on a sample of 192 surviving children, born between 1960 and 1976, who had been examined or treated for IS in three main pediatric hospitals in Helsinki, Finland. The 13-point Rendle-Short scale was used in screening for autistic symptoms and Rutter's criteria were used for the definition of autism. Twenty-four children (12.5%) were diagnosed with autism. All of these had presented with autistic symptoms before the age of three years. Other authors have studied autism in relation to IS, but usually focusing on a subgroup of children with TSC which is one of many possible antecedents to IS (e.g. Asano et al., 2001; Askalan et al., 2003; Bolton & Griffiths, 1997; Hunt & Dennis, 1987; Hunt & Shepherd, 1993).

A causal relationship between epileptiform abnormalities and autism has not been clearly established (Ballaban-Gil & Tuchman, 2000). However, it is well documented that in some cases, seizures are present prior to the diagnosis of ASDs (Danielsson et al., 2005; Olsson et al., 1988; Steffenburg et al., 2003; Wong, 1993). This sequence is particularly evident in IS, since their onset occurs in 94% of cases during the first year of life (Hrachovy & Frost, 2003), but autism is rarely diagnosed until after 2 years of age. On the other hand, since children having IS of cryptogenic origin have a better outcome in general and are far less likely to have neurodevelopmental disorders than their peers having spasms of symptomatic origin (Hrachovy & Frost, 2003), this inevitably generates the hypothesis that it is the etiology of early seizures that is associated with ASD, not the seizure type as such (Askalan et al. 2003; Olsson 1988).

In their study on IS with multiple etiologies and autism, Riikonen and Amnell (1981) noted that in some autism cases, EEG abnormalities with a temporal focus were recorded before the onset of IS. Also, EEG abnormalities with a temporal focus occurred in 17 out of 24 individuals in their autistic group either before or after IS, with similar distribution between the temporal lobes (left 7/17, right 10/17). Bolton and colleagues (Bolton et al., 2002) studied neuro-epileptic determinants of ASD in TSC. They found that the presence of cortical tubers in the temporal lobes were associated with ASD without preference for either the left or the right hemisphere. Temporal lobe epileptiform discharges on the EEG were also associated with ASD in the participants with temporal lobe tubers. Both the age of seizure onset and evidence of temporal lobe EEG focus were independently associated with developmental outcome, even when IQ was controlled for in multivariate analyses (Bolton et al., 2002).

Autistic regression

In about one-third of autism cases there is a history of developmental regression (Ballaban-Gil & Tuchman, 2000). The onset is most frequently reported between the ages of 18 to 24 months, and is often gradual as opposed to sudden or acute. Sometimes the onset follows some preceding event, e.g. a birth of a sibling, a change in domicile or other environmental changes, vaccination of the child, accident or sudden sickness without any indications of infectious diseases affecting the brain. The regression involves loss of words, usually in children already presenting delayed speech and limited vocabulary, but may also involve changes in sleeping or eating habits, mood, or preoccupations, or the transition to less constructive play or diminished motivation to engage in social interaction (Lord, Shulman, & DiLavore, 2004; Tuchman & Rapin, 1997). However, typical autistic regression rarely affects motor skills. Even when parents seek immediate help, the children are seldom referred to specialized services, and thus expert clinicians rarely get the opportunity to follow the children through this phase of autistic development (Tuchman & Rapin, 1997). The norm is that autistic regression is described retrospectively by parents. Autistic regression is usually temporary and most of the children will reach some plateau and then start gradually to regain their lost skills in due course. Consequently, the concept of “regression” is debated (Kobayashi & Murata, 1998). The association of autistic regression and epilepsy remains obscure,

especially regarding the possibility that subclinical epilepsy may be a causal factor in autistic regression (e.g., Baird, Robinson, Boyd, & Charman, 2006; Kobayashi & Murata, 1998; Tuchman & Rapin, 1997).

Epidemiology of autism and ASD

Incidence

On a behavioral level, the onset of ASD is in most cases during infancy or early childhood, although it is difficult to ascertain the precise time for each individual. Thus, age of onset of ASD may simply amount to the age of recognition of the disorder (Volkmar, Stier, & Cohen, 1985). The ICD-10 criterion for onset in autism states that "abnormal or impaired development is evident before the age of 3 years in at least one of the following areas: (1) receptive or expressive language as used in social communication; (2) the development of selective social attachment or of reciprocal social interaction; (3) functional or symbolic play" (WHO 1993 pp. 147-148). Since a minority of cases is diagnosed prior to 36 months of age (although the numbers are steadily increasing), the age of onset is frequently determined retrospectively, and the developmental deviation is inferred to be within this age range.

Instead of trying to infer the time of the first discernible behavioral symptoms of autism, the date of ASD diagnosis can be used to define the age of onset when estimating the incidence rate (Powell et al., 2000). Another method is to calculate cumulative incidence by following a specified birth cohort to a certain age when autistic features should be clearly observable (e.g. by 5 years of age) and then counting the number of cases (Honda, Shimizu, Misumi, Niimi, & Ohashi, 1996; Honda et al., 2005). However, since autism is a life-long disorder, most researchers who have studied the frequency of autism have chosen to present their results in the form of prevalence estimates (mostly point prevalence), with notable exceptions (Honda et al., 1996; Honda et al., 2005; Jick, Beach, & Kaye, 2006; Kaye, del Mar Melero-Montes, & Jick, 2001; Powell et al., 2000; Smeeth et al., 2004).

Prevalence

The first prevalence studies of autism (1966-1986) using various diagnostic criteria reported the prevalence of 0.7 to 5.6 per 10,000 (Fombonne, 2003) and at that time, autism was considered a rare disorder. From the late 80s to the early 90s, results

with higher figures started to accumulate, indicating a shift in the frequency of diagnosed cases with autism. In his review of 32 surveys published from 1966 to 2001, Fombonne (2003) combined surveys in two groups according to the median year of publication. Thus, 16 studies were published in the period 1966-1991 with the median prevalence of 4.4 per 10,000, and another 16 studies were published in the period 1992-2001 with the median prevalence of 12.7 per 10,000.

The latest prevalence figures for autism only (not including all ASDs) in children from various parts of the world (Stafford, UK; the northern part of Yokohama City, Japan; Gothenburg, Sweden; Montreal Island, Canada; South Thames, UK) range from 18.9 to 38.9 per 10,000 (Baird et al. 2006b; Chakrabarti & Fombonne, 2005; Fombonne, Zakarian, Bennett, Meng, & McLean-Heywood, 2006; Gillberg, Cederlund, Lamberg, & Zeijlon, 2006; Honda et al., 2005). Considering the frequency of all ASD or all PDD categories (excluding Rett's syndrome and disintegrative disorder) in the above studies, prevalence figures double or triple from those for autism only, and range from 51.0 to 116.1 per 10,000. All of these studies used either the ICD-10 or the DSM-IV diagnostic criteria, but relied on different detection and ascertainment methodologies in different cohort sizes and different age groups. The European Union's definition of a rare disorder is a condition that affects five or fewer people in every 10,000. If ASD affects 0.5% to 1.0% of the population, it cannot be considered a rare disorder any more (Gillberg & Wing, 1999).

Trends over time

As incidence rates are based on the count of new cases, they are in theory more sensitive to changes in possible risk factors affecting the disorder in question compared with prevalence estimates (Powell et al., 2000). However, whatever method is used to calculate the frequency of autism, both incidence and prevalence studies of autism have had difficulties in disclosing secular trends, or "true" changes in the frequency of autism, especially in light of evolving behavioral definitions of the disorder, immense variability in case-finding methods between studies and the variability in awareness of the disorder over time (Fombonne, 2003).

One way to overcome some of these obstacles would be to enter the same age groups at different points (albeit relatively close) in time, in the same confined geographical area using the same case detection methods and case definitions. No

change in the estimated prevalence of the disorder at the two time points would render increased incidence unlikely, although secular trends would continue to be unknown. This was the methodology adopted in consecutive studies by Chakrabarti and Fombonne (2001, 2005) in preschool populations in Stafford, UK. Their results were almost identical, estimating the prevalence of all PDDs at about 60 per 10,000. Since the rate in the later study was almost the same as in the previous study in the same area, surveyed with the same methods, the authors concluded that this suggested stable incidence.

Gender differences

All prevalence studies on autism or ASD describe male preponderance and in the review by Fombonne (2003) the range of male-female ratio varied from 1.3:1 to 16:1 with a mean of 4.3. The male-female ratio seems to be less pronounced when autism is associated with severe ID (IQ<50) where this ratio approaches 2:1 or less, compared with higher functioning individuals (Bryson & Smith, 1998; de Bildt et al., 2005; Fombonne, 2003; Nordin & Gillberg, 1996). This difference of male-female ratio between groups may indicate different etiological factors for individuals with IQ<50 compared with those with IQ>50 (Bryson & Smith, 1998), or a different combination of etiological factors in these groups.

Association of intellectual disability with autism

About 70% of cases with autism have IQs below 70 (Fombonne, 2003), but the opposite is true for other ASDs where the majority has an IQ above 70 (Chakrabarti & Fombonne, 2005). This underscores the changing field of autism. As more cases accumulate with less severe autistic symptomatology, the proportion of individuals with ASD who are without ID and are of male gender becomes larger (Bailey, Philips, & Rutter, 1996; Bryson & Smith, 1998; Fombonne, 2003).

In a recent study on the prevalence of ASDs in children and adolescents with ID, the figure of 16.7% was suggested as the most reliable and well-founded estimate of ASDs in a large population-based sample (de Bildt et al., 2005). In accordance with previous research on individuals with ID (e.g. Nordin & Gillberg, 1996; Steffenburg et al., 2003), de Bildt et al. found a higher prevalence (26.1%) of ASDs in individuals with IQ≤50 than the prevalence (9.3%) for individuals with IQ51-70 (based on DSM-IV-TR IQ classification). The authors noted that there

were relatively few participants from the mild ID level (IQ51-70), so it is possible that their results overestimated the prevalence of autism in ID (de Bildt et al., 2005). When children and adolescents with ID also have active epilepsy, the prevalence of ASDs may be still higher (Steffenburg, Gillberg, & Steffenburg, 1996; Steffenburg et al., 2003).

Other common co-morbidities

The most prevalent early concerns of parents regarding their child's development relate to speech and language (Glascoe, 1997; Saemundsen, Hannesdottir, Hermannsdottir, & Arnkelsson, 1998) and the first concern of most parents of children with autism is language delay or regression in speech development (De Giacomo & Fombonne, 1998; Short & Schopler, 1988; Siegel, Pliner, Eschler, & Elliott, 1988). In fact, most of the children later diagnosed with autism have delayed language development and a subgroup never acquires functional speech. Other ASDs than autism present with a more mixed picture ranging from the development of fluent speech at a very early age (with a subgroup reading by 3 to 4 years) to a complete and lifelong mutism. When ID is present, delayed speech may simply reflect overall developmental delay, but specific language impairment is also a feature of autism, with or without ID (see Tager-Flusberg, Paul, & Lord, 2005 for a review). Another curious aspect of language development in a subgroup of children with autism is a language-test profile showing more impairment in receptive language than in speech production (Tager-Flusberg & Caronna, 2007).

Children and adolescents with autism have an elevated risk for psychiatric disorders compared to children in general (Leyfer et al., 2006), compared to children with ID (Brereton, Tonge, & Einfeld, 2006), and within a group of children with ID matched for age, gender, and nonverbal IQ (Bryson & Smith, 1998). Leyfer and colleagues (2006) modified the Kiddie Schedule for Affective Disorders and Schizophrenia for use with children with autism and reported on the prevalence of DSM-IV defined psychiatric disorders. The lifetime prevalence of the most common disorders was 44% for specific phobias, 37 % for obsessive compulsive disorder, and 31% for attention-deficit hyperactivity disorder (ADHD). In addition, 10% of the children had experienced at least one episode of major depression, and when subsyndromal cases were included, the rate increased to 24%. None of the children with autism met criteria for schizophrenia or related disorders (Leyfer et

al., 2006). However, their study group (N = 109) was based on two samples from different regions in the US, participating in different types of studies, and with an over-representation of the male gender (94%).

In a recent case-control study of adults diagnosed as children with atypical autism with an average observation time of 36.9 years, 68.5% of the autistic group had been in contact with psychiatric hospitals during the follow-up period, compared with 10.9% of the comparison group. Schizophrenia spectrum disorders were most common, or 34.8% (Mouridsen, Rich, & Isager, 2007). These results are in sharp contrast to previously published research on psychiatric problems in ASD, where depression has been reported as the most common psychiatric condition in clinical samples of adults, with no strong evidence for increased risk for schizophrenia (Shea & Mesibov, 2005).

Outcome

Cognitive measures have played an important role in predicting outcome in autism, and IQ is still the most robust predictor of later functioning (Billstedt, Gillberg, & Gillberg, 2005; DeMyer, Hingtgen, & Jackson, 1981; Freeman, Ritvo, Needleman, & Yokota, 1985; Gillberg & Steffenburg, 1987; Lotter, 1978; Venter, Lord, & Schopler, 1992). Reviews of earlier follow-up studies show that cognitive measures are stable over time for children with autism as a group, with the majority scoring below 70 on standardized cognitive tests (DeMyer et al., 1981; Lotter, 1978). Later follow-up studies of children with autism have confirmed this stability, but have also demonstrated important individual changes over time, both in direction and amount (Eaves & Ho, 1996, 2004; Freeman et al., 1991; Lord & Schopler, 1989; Sigman & Ruskin, 1999; Venter et al., 1992; Yang, Jong, Hsu, & Chen, 2003).

In a large scale (N = 120) outcome study of individuals with autism or atypical autism born in 1962-1974 with a follow-up period of 13 to 22 years, the prognosis was rather bleak, with 71% of the participants having poor to very poor outcome (Billstedt et al., 2005). Only one participant did not meet diagnostic criteria for ASD upon follow-up. This study probably represents the most severe end of the autism spectrum, with over 90% of the participants with ID upon follow-up into late adolescence and adulthood. Conversely, children diagnosed with ASD other than autism are more likely to demonstrate higher cognitive functioning and to have milder symptoms than children diagnosed with autism (Baird et al., 2000;

Chakrabarti & Fombonne, 2005). There are indications that different diagnostic categories predict different outcomes, and children who, as a group, have milder forms of autism may fare better than those diagnosed with "core" autism (Smith, Groen, & Wynn, 2000; Szatmari et al., 2000).

More children are now diagnosed with autism and at an earlier age than one to two decades ago (Chakrabarti & Fombonne, 2005; Howlin & Moore, 1997). Earlier detection makes earlier intervention possible, which may improve the overall functioning of children with autism and thus affect their outcome (Dawson & Osterling, 1997; National Research Council (NRC), 2001; Rogers, 1998; Smith, 1999). Hence, recently diagnosed young cohorts may be less impaired and show better outcome than cohorts diagnosed previously (Seltzer et al., 2003).

Intervention

Autism is a lifelong disorder that has no known cure. As the presentation of the disorder is heterogeneous depending on a multitude of genetic, environmental, and developmental factors, many different needs of the individual and his or her family must be addressed throughout the life-span. Following diagnosis, parents may be in need of general information on autism, genetic counseling (McMahon, Baty, & Botkin, 2006), emotional support, or other types of support (Thorsteinsdottir & Gudlaugsdottir, 2007). Parents may be troubled by non-specific problems associated with autism, like irregular sleep or feeding habits of the child, gastrointestinal problems (Filipek, 2005), or they may want to tackle autistic behaviors head-on and learn everything about possible treatments and educational options. Children with autism are sometimes referred for speech and language therapy, physical therapy, or occupational therapy. Pharmacotherapy may be indicated for various problems (see above), but may also play a role in controlling challenging behaviors, like hyperactivity, aggression or self-injury (Francis, 2005). Comorbid conditions, such as anxiety, tics, depression, and epilepsy can influence the well-being and participation of the child, or hinder effective management of autistic behaviors. Thus, such symptoms may need to be targeted in order to enhance the benefits of comprehensive behavioral or educational programs (Francis, 2005).

Early intervention encompasses family-centered services as well as education, teaching and treatment of children with autism during infancy, the toddler

period, and the preschool years. Research on autism has identified a set of common elements that have proven effective, and are used in many empirically supported treatment methods (Dawson & Osterling, 1997; Rogers, 1998; Stahmer, 2007). Nevertheless, no comprehensive program has proven effective for all children with autism and no program has presented unequivocal empirical evidence for its effectiveness based on randomized controlled trials. Of the teaching programs offered to parents of children with autism, only applied behavioral analysis has made a continuous effort to research the efficacy of intervention, and results from such studies have repeatedly reported significant gains (Howard, Sparkman, Cohen, Green, & Stanislaw, 2005; Lovaas, 1987; McEachin, Smith, & Lovaas, 1993; Sallows & Graupner, 2005).

Tertiary diagnostic and counseling services for autism in Iceland

In 1960, the Municipal Child Guidance Clinic (MCGC) was established under the auspices of the Reykjavik Department of Public Health, which was the first time mental health services were publicly offered to Icelandic children and adolescents up to 15 years of age (Hannesdottir, 2002). The first prevalence study on psychiatric disorders in Iceland used one-stage methodology and included a sample of 1100 children in Reykjavik between the ages of 5 and 15 years. Data was gathered at the MCGC over 1965 and 1966. No mention of autism appeared in the results of this study (Bjornsson, 1974). It is possible that cases of autism in the above-age groups had already been found, as all children who had attended the clinic from its establishment in 1960 for assessment and therapy were excluded from the study, as were their siblings (Bjornsson, 1974). However, according to interviews with several clinicians working at the time, a more likely interpretation is that there were few diagnosed cases of autism before 1970. The first person diagnosed with autism in Iceland is thought to have been a 10 year-old girl who received her diagnosis at the Department of Child and Adolescent Psychiatry (DCAP) shortly after its establishment (Pall Asgeirsson, personal communication, 2007).

Diagnostic and counseling services for children with autism started when the DCAP at the University Hospital began accepting referrals in the year 1971. With the DCAP, interdisciplinary diagnostic procedures were instigated in the context of day-care observation and treatment facilities, where children received services for several weeks, several months or even years. At the end of this service period, the

children were followed by various professions, sometimes through elementary school or longer. The first prevalence study specifically on autism in Iceland was based on children born 1964-1973 and diagnosed with "psychosis" prior to 1 July 1976 (Magnusson, 1977). In this study, the author used Creak's nine points (Creak, 1961) as diagnostic criteria, and diagnostic categories proposed by Rutter (Rutter, Shaffer, & Sturge, 1975). The author screened clinical registries of various services for the diagnosis of psychosis and/or ID. These included all pediatric in-patient facilities in the country, plus a large institution for individuals with ID (Kopavogshaeli), the MCGC, and the DCAP where most of the 19 cases were found in the above age groups (1964-1973). Including four cases of "disintegrative psychosis", the prevalence of "childhood psychosis" was estimated at 4.4/10,000 with a ratio of males to females 1.4:1. Excluding disintegrative psychosis, the prevalence estimate for infantile autism changed to 3.5/10,000 and the male-female ratio changed to 1.1:1.

The State Diagnostic and Counseling Center (SDCC) was founded in 1986 by the Ministry of Social Services. Its predecessor "Greiningardeild Oeskjuhlidarskola Kjarvalshusi", established in 1975, had developed as a small interdisciplinary diagnostic and counseling unit attached to a special school for children with ID. The main task of the SDCC is diagnosis and evaluation of children with major developmental disabilities and handicaps and subsequent counseling to parents and other services. After 1990, the SDCC began to take a more active role in the diagnosis and evaluation of children with autism, and diagnoses were frequently made in collaboration between the SDCC and the DCAP. Until 1996, the SDCC referred all children with autism or other ASDs to the DCAP to finalize the diagnostic process and/or for follow-up services. In 1997, it was decided on a ministry level to transfer the responsibility for services for children with autism from the DCAP to the SDCC. Continuity of services in the transition period was ensured by close cooperation of experts from the two centers (Magnusson & Saemundsen, 2001).

At the SDCC, assessment and diagnosis is carried out by transdisciplinary teams consisting of specialized pediatricians, clinical child psychologists, social workers, and various other professions, e.g., speech and language pathologists, occupational therapists, developmental therapists, and special education teachers. During the data collection of the present thesis the composition of the team varied

in each individual case, but always included at least the first three professions mentioned. All the children had a physical examination, neurological evaluation, and a hearing test. In addition, based on clinical findings, a thorough diagnostic work-up was carried out which included auditory evoked potentials, ophthalmologic evaluation, EEG, neuro-imaging, chromosomal analysis, and blood and urine metabolic studies. The Autism Diagnostic Interview-Revised (ADI-R) and the Childhood Autism Rating Scale (CARS) were administered as well as developmental tests. The diagnosis was based on the results of diagnostic instruments and developmental tests combined with medical data, clinical observations from team members, and other relevant data, with the aim of presenting a coherent picture of the child's strengths and weaknesses. Following the diagnostic procedure, the parents were informed of the results, as were the professionals involved, including preschool or elementary school staff. Reading material was suggested to the parents and professionals and courses on autism were provided as well as courses and workshops on the education and treatment of children with autism. All children diagnosed with ASD received counseling from the SDCC during their preschool years, and the majority was reevaluated before entry to elementary school (Jonsdottir et al. 2007b).

From the late 1980s to early 1990s, there was a steady increase of referrals to the DCAP and especially to the SDCC for possible autism. These changes coincided with reports from different parts of the world of increased prevalence of autism (Bryson, Clark, & Smith, 1988; Gillberg, Steffenburg, & Schaumann, 1991; Matsuishi et al., 1987). This created a renewed interest in studying the prevalence of autism in Iceland, which previously was thought to be stable. In the year 1992, a formal decision was taken at the SDCC and the DCAP to use the ADI-R for all children with suspected autism, thus setting the standard of case definition for future studies on autism in Iceland. The fact that first the DCAP and then the SDCC were the only facilities that received referrals for possible autism in children from 1971 onwards created a unique possibility for research on autism in Iceland. The records of both institutions became the main sources of information on diagnosed cases with autism.

AIMS

The objectives of the present thesis were to estimate the prevalence of autism and autism spectrum disorder (ASD) in different age groups **(I, III)**; to study the agreement of the diagnostic instruments for autism used for case ascertainment **(II)**; to describe stability and change in preschool-aged children diagnosed with ASD **(III)**; to describe the association between infantile spasms (IS) and other types of seizures in the first year of life and ASD **(IV, V)**; and to determine whether IS predict higher risk of ASD as compared to other unprovoked seizures **(VI)**.

MATERIAL AND METHODS

Participants

Different populations were studied according to different research questions. Study on the prevalence of autism and ASD **(I)** was based on individuals born 1974-1993, and autism cases diagnosed at the DCAP or the SDCC prior to 1 December 1998, and individuals born 1992-1995 and diagnosed with ASD at the SDCC before 1 January 2004 **(III)**. The participants in the study on the agreement between diagnostic instruments **(II)** were children aged 22 months to 9 years referred to the SDCC because of suspected autism, and diagnosed during the period October 1993 through March 1997. Similarly, the preschool children (born 1992-1995) participating in the follow-up study **(III)** were diagnosed with ASD at the SDCC and then reevaluated before entry into elementary school. The study on the association of seizures in the first year of life and ASD **(IV, V, VI)** was based on two overlapping periods, children diagnosed with IS 1981-1998, and children diagnosed with other unprovoked seizures 1982-2000.

Detection of autism

Studies I, II, III

In Iceland, the primary health care centers that are distributed all over the country administer at no cost health and developmental surveillance of children from birth to 6 years of age. Their coverage is at least 99% according to the Directorate of Health. The system is designed to provide comprehensive capture of health problems and

developmental disorders at different ages. The procedures are diverse and have different emphasis according to age groups, screening for problems in various developmental areas. These include hearing and vision, motor skills, language- and cognitive development, and behavioral and emotional difficulties. However, during the time the data was collected for the present thesis, the developmental surveillance procedures did not contain any items directed specifically at autistic behaviors at any age.

If there is a suspicion of a developmental disorder at the primary health care level and a need for referral, there are many different referral routes according to geographical location and traditions. These routes have not been studied in Iceland, but by definition they should lead to an increased level of specialization or secondary pediatric services, that in the case of suspected ASD would end at the tertiary level of services, the DCAP or the SDCC, depending on the time and reason for referral (see Introduction). In the educational system (preschools included) and the service system for people with disabilities there are also relatively straightforward referral patterns from psychological services to the tertiary level. Since the DCAP and the SDCC were the only specialized institutions serving children with ASD and their families, their registers became the natural source of information for the estimation of the frequency of ASD. Hence, the number of cases registered at the DCAP and the SDCC may be regarded as a measure of the efficacy of the Icelandic service system in detecting ASDs.

Studies IV, V, VI

The parents of all living children with a history of IS in the first year of life were contacted by letter, followed by a telephone call, to inform them of the study objectives. For other unprovoked seizures in the first year of life, the procedure was slightly different: in a separate study, parents were asked several questions regarding the child's seizures, development and behavior. The parents of children with a known neurodevelopmental disorder or parental concern regarding developmental skills or behavior were contacted again by mail, followed by a telephone call, and asked to participate in a further study on autistic behaviors. The parents of both groups who agreed to participate gave their written informed consent, and were subsequently asked to complete a questionnaire (see below), which was used as an initial test of autistic behaviors. If the child had a severe motor handicap in

combination with profound ID (IQ<20), then the parents were not asked to complete the questionnaire, but instead the child was observed in his/her school setting. When the behavioral score on the questionnaire reached or exceeded a certain cutoff, diagnostic instruments for autism were applied (see below).

Case definition of autism (I, II, III, IV, V, VI)

Diagnostic criteria and diagnostic classification were based on the ICD-10 (WHO, 1992, 1993), except for several older individuals whose diagnoses were based on the ICD-9. The transition from the ICD-9 to the ICD-10 classification system in Iceland (1989, draft version) took place in 1992 when the ADI-R came into use, i.e. the ICD-10 period and the ADI-R usage coincided. The English versions of the ICD-10 were formally published in 1992 (*Clinical description and diagnostic guidelines*) and 1993 (*Diagnostic criteria for research*). (See Table 1 for a list of diagnostic categories).

Definition of seizures (IV, V, VI)

The identification of IS cases has been described previously (Ludvigsson et al., 1994). Ascertainment bias is considered minimal, since IS is the most common catastrophic epilepsy in childhood (Shields, 2000); thus cases of IS are unlikely to go unnoticed or not to be referred for specialized services (see Introduction). For other seizures in the first year of life, the primary source of data was hospital records in electronic and hard copy from the Landspitali University Hospital and the Landakotsspitali, both in Reykjavik, and the Regional Hospital in Akureyri, which were the only pediatric in-patient facilities in the country during the study period. For this latter group, the inclusion criteria were at least one unprovoked seizure during the age range between 28 days and 12 months (based on gestational age). Included in the study group were all cases with a convincing description of an epileptic seizure by an eye-witness, or a description of a seizure in the presence of other supportive evidence, i.e., epileptiform changes on EEG, CNS infection, stroke, or other cerebral pathologies known to be related to seizures, or a family history of seizures in the first year of life in a first-degree relative. Febrile seizures were excluded.

Epilepsy was defined as recurrent episodes of unprovoked, paroxysmal seizure activity (Cowan, 2002). The children were classified cryptogenic if they had normal neurological and developmental history, normal neurological examination, no

known associated etiological factor, and negative diagnostic evaluation. All others were classified as symptomatic (Ludvigsson et al., 1994). Electroencephalography was not performed systematically, but EEGs were available for 94% of the participants. The EEG tracings sampled during the first year of life were classified as non-focal, ever epileptiform right temporal focus, and ever epileptiform left temporal focus.

Measures

Diagnostic instruments

The Autism Diagnostic Interview-Revised (ADI-R) (Rutter, Le Couteur, & Lord, 2003) **(I, II, III, IV, V, VI)** is a standardized, semi-structured, investigator-based interview for caregivers of individuals with autism, which provides a diagnostic algorithm for the ICD-10 and the DSM-IV definitions of autism. Reliability and validity have been shown to be adequate (Le Couteur et al. 1989; Lord, Rutter, & Le Couteur, 1994; Lord, Storoschuck, Rutter, & Pickles 1993; Lord et al. 1997; Rutter et al., 2003b). An ADI-R diagnosis of CA requires reaching or exceeding cutoffs in all three ICD-10 symptom domains, i.e., impairment in reciprocal social interaction (SI), communication (CO), and repetitive behaviors and stereotyped patterns (RB), given that abnormality of development is evident at or before 36 months. The ADI-R has been translated into Icelandic by two psychologists and a child psychiatrist. The back-translation was reviewed by one of the authors of the ADI-R and, subsequently, appropriate alterations were made to the Icelandic translation to ensure comparability of the two versions. Official use of the ADI-R in Iceland started 1992. The ADI-R was used for case ascertainment for 75% of the participants diagnosed with ASD in study I, but all participants diagnosed with ASD in studies II, III, IV, V, VI.

The Childhood Autism Rating Scale (CARS) (Schopler, Reichler, & Renner, 1988) **(I, II, III, IV, V, VI)** was originally developed as an observational instrument (Prizant, 1992). It consists of 15 items, which are scored on a seven point Likert scale, and all the items contribute equally to the total score. According to the CARS manual, autism is defined by a score of ≥ 30 points. This instrument has been shown to have a high degree of internal consistency, inter-rater and test-retest reliability, as well as high criterion-related validity and good discriminant validity (DiLalla & Rogers, 1994; Eaves & Milner, 1993; Garfin, McCallon, & Cox,1988; Lord, 1995; Nordin, Gillberg, & Nydén, 1998; Schopler, et al., 1988; Sevin, Matson, Coe, Fee,

& Sevin, (1991). CARS has been used in Iceland since 1989. A pilot study has been carried out on the validity and reliability of an Icelandic translation (Einarsdottir & Haraldsdottir, 1992).

The conceptual difference between the CARS definition of autism and the ICD-10/DSM-IV definition is reflected in that the CARS total score employs no weighting of different items, whereas the three-threshold approach of the current diagnostic frameworks accords extra weight to the area of social deficits (Lord & Risi, 1998; Prizant, 1992). Furthermore, CARS assesses some areas of nonspecific difficulties, e.g. ID, language delay and activity level, that are not included in the ICD-10 or the DSM-IV definition of autism (Lord & Risi, 1998; Prizant, 1992).

The Autism Diagnostic Observational Schedule (ADOS) (Lord, Rutter, DiLavore, & Risi, 2001) **(IV, V, VI)** is a semi-structured, standardized assessment of social interaction, communication and repetitive behaviors, developed to accompany the ADI-R when autism or ASDs are suspected. ADOS provides algorithms and cutoffs for both autism and ASD. It consists of four modules, the selection of which depends on the verbal status and age of the individual to be assessed. Reliability and validity have been shown to be adequate (Berument et al., 2005; de Bildt et al., 2004; Gotham, Risi, Pickles, & Lord, 2007; Lord et al., 2000; Lord et al., 2001; Risi et al., 2006). The ADOS instructions have been translated into Icelandic by a certified translator and two psychologists. A back-translation into English was approved by the publisher.

The Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003) **(IV, V, VI)**, previously named Autism Screening Questionnaire (ASQ), is a screening measure for autistic behaviors developed from the ADI-R (Berument, Rutter, Lord, Pickles, & Bailey, 1999; Rutter et al., 2003a). It contains 40 items that require yes or no responses from parents. There are two versions, a lifetime version and a current version. A score of 15 points on the SCQ is the recommended cutoff to distinguish between ASDs and other diagnoses. The SCQ has been translated into Icelandic by two psychologists. A back-translation into English was approved by the publisher.

Developmental tests

Various developmental measures were used according to the age of the participants and their developmental level. These include the Bayley Scales of Infant

Development (Bayley, 1969; Bayley, 1993) **(I, II, III, IV, V, VI)**, the Leiter International Performance Scale (Arthur, 1952; Levine, 1982) **(I, II)**, the Peabody Picture Vocabulary Test-Revised (Dunn & Dunn, 1981) **(I)**, the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1967, 1989) **(I, II, III, IV, V, VI)**, the Wechsler Intelligence Scale for Children (Wechsler, 1949; Hannibalsson, 1971) **(I, II)**, the Wechsler Intelligence Scale for Children-Third Edition (Wechsler, 1992) **(IV, V, VI)** the Wechsler Adult Intelligence Scale-Third Edition (Wechsler, 1997) **(V, VI)** and the Vineland Adaptive Behavior Scales, Survey Form (Sparrow, Balla, & Cicchetti, 1984) **(III, IV, V, VI)**.

Statistical analysis

Confidence intervals (CI) at the 95% level were calculated for prevalence estimates according to "the traditional method" (Newcombe & Altman, 2003) **(I, III)**. When prevalence was calculated as the percentage of cases, the exact 95% CI were found assuming binomial distribution **(IV, V, VI)** (Armitage & Berry, 1991). Incidence of seizures and 95% CI were calculated assuming Poisson distribution **(VI)** (Armitage & Berry, 1991). Pearson Chi-square was used to compare categorical data **(I, II, III, V)**, and Fisher's Exact Test when a cell had an expected count of less than five. Cohen's kappa was used to calculate chance-corrected agreement of diagnostic tests, and coefficient alpha to calculate their internal consistency **(II)**. One-way analysis of variance (ANOVA) was used to compare diagnostic groups **(II, III)** followed by the Scheffé post hoc test when appropriate **(II)**. T-test was used to compare group means **(I, V)**. Non-parametric tests were used when the data were not normally distributed: Mann-Whitney U for between-groups measures **(III)**, Wilcoxon matched-pairs signed-ranks test for comparing paired measures **(III, V)**, and Spearman´s rho for assessing correlation between variables **(II, III)**. For the calculation of sensitivity and specificity **(V)**, Wilson's method was used (Altman, 2003). Case-control data was stratified according to the method of Mantel-Haenszel (Mantel & Haenszel, 1959) and a multivariate case-control analysis was performed using a logistic regression analysis (Breslow & Day, 1980) **(VI)**.

RESULTS

Prevalence of autism (I)

Crude measures, prevalence estimates per 10,000 for ICD-9 infantile autism (IA), ICD-10 childhood autism (CA), and ICD-10 atypical autism (AA), as well as male-female ratios are shown in Table 2 for the follow-up date 1 December 1998. A lower prevalence was found for autism and AA in a cohort born 1974-1983 than for a cohort born 1984-1993, or 4.2/10,000 and 13.2/10,000 respectively, with a trend for more males than females in the younger cohort. There were more cases of autism with ID (95%) in the younger cohort than in the older one (67%).

The distribution of ADI-R and CARS mean scores showed higher scores for CA than AA, as expected. In the case of AA, the mean scores on the ADI-R exceed their respective cutoff points except for the Repetitive Behavior and Stereotyped Patterns (RB) domain. Not reaching cutoff in this domain was by far the most common atypicality in symptomatology, since 16 out of 20 children with AA scored below the cutoff on the RB scale. If tested against the null hypothesis of equal distribution between the three domains, the observed distribution turns out to be highly unlikely (p = .001).

Table 2 Prevalence of infantile autism/childhood autism (IA/CA) and atypical autism (AA) and male-female ratios for two cohorts

Birth cohorts	Population	Diagnostic categories	N	M:F ratio	Prevalence per 10,000	95% CI [a]
1974-1983 [b]	42,403	IA/CA	16	3	3.8	1.9-5.6
		IA/CA+AA	18	2	4.2	2.3-6.2
1984-1993 [c]	43,153	IA/CA	37	3.6	8.6	5.8-11.3
		IA/CA+AA	57	4.2	13.2	9.8-16.6

[a] Confidence Interval

[b] In this cohort, 13 subjects were classified according to ICD-9 and 5 subjects according to ICD-10.

[c] In this cohort, 6 subjects were classified according to ICD-9 and 51 subjects according to ICD-10.

Agreement between diagnostic instruments (II)

The sample comprised 54 children, aged 22 to 114 months (mean age 45.4 months) referred for possible ASD. ADI-R and CARS were applied separately, and the raters of each instrument were blind to each other's scoring. Significant correlations ($p <$ .001) were found between the CARS total score and the ADI-R domain and total scores: CARS, SI = 0.81; CARS, CO = .60; CARS, RB = .69; CARS, ADI-R total = .81. Further results of the agreement between the two instruments are presented according to the classification of autism or non-autism under three conditions defined by different domain thresholds on ADI-R with the 30+ points definition of CARS held constant (Table 3). There was no instance of a child reaching cutoffs on ADI-R but not on CARS. The observed agreement between the two instruments increased steadily from the most stringent conditions (scores reaching cutoffs in three domains on ADI-R) to the least stringent (scores reaching cutoff on one domain on ADI-R). The chance-corrected agreement varied accordingly. The change from the first to the second condition resulted in increased agreement in the diagnosis of autism between the instruments, while the diagnosis of non-autism remained practically constant.

Comparison of diagnostic groups

For the one-way ANOVA, independent variables were defined by group status: (1) those scoring at or above all three symptom domains on ADI-R and at or above the 30-point cutoff on CARS; (2) those reaching cutoffs on ADI-R but not CARS; (3) those reaching cutoff on CARS, but not ADI-R; and (4) those not reaching cutoffs on either instrument (see condition one in Table 3). Dependent variables were age at diagnosis, IQ/DQ, CARS total score, ADI-R total score, and ADI-R domain scores.

For ADI-R symptom domains (SI, CO, RB) and total scores, the ANOVA showed significant differences ($p <$ .001) between groups for SI, CO, RB, and total scores. Post hoc comparisons revealed progressively less severe autistic symptomatology from the group scoring above cutoffs on both instruments to the non-autistic group (not reaching cutoffs on either instrument) for SI, CO verbal subjects, and total scores. Also, the ANOVA showed a significant difference between groups for CARS ($p <$ .001) and all post hoc comparisons between pairs of groups were significant as well.

Table 3 Agreement between Autism Diagnostic Interview-Revised (ADI-R) and Childhood Autism Rating Scale (CARS) in the diagnosis of autism according to different conditions defined by the ADI-R (cutoffs reached or exceeded in three, two or one symptom domains)

ADI-R conditions	CARS ≥ 30	CARS < 30
Condition one[a)]		
3 domains	18	0
2, 1, 0 domains	18	18
Condition two[b)]		
3, 2 domains	28	1
1, 0 domains	8	17
Condition three[c)]		
3, 2, 1 domains	35	2
0 domains	1	16

[a)] Observed agreement = 66.7%; Cohen's kappa = .40

[b)] Observed agreement = 83.3%; Cohen's kappa = .66

[c)] Observed agreement = 94.4%; Cohen's kappa = .87

Further comparison of the characteristics of the two autistic groups, the ADI-R/CARS group and the CARS-only group, revealed both similarities and differences. The male-female composition of the ADI-R/CARS group showed the ratio of 3.5:1, while the CARS-only group showed a preponderance of boys (17:1). The ADI-R/CARS group contained more nonverbal subjects (61%) than the CARS-only group (33%), although this difference did not reach statistical significance. The difference between the mean IQ/DQ of the two groups is also apparent in their respective IQ/DQ distributions. For the ADI-R/CARS group, this distribution was 50% (IQ< 50), 39% (IQ50-69), and 11% (IQ≥70). For the CARS-only group, this distribution was quite different or 17% (IQ< 50), 39% (IQ50-69), and 44% (IQ≥70). In the CARS-only group, 10 subjects (56%) reached cutoff scores in two ADI-R domains, with the most common combination being SI + CO. Only one subject had another combination (CO + RB).

Follow-up of preschool children (III)

Altogether, 62 children in the 1992-1995 birth cohort were diagnosed with ASD during the preschool years. In addition, 25 children born between 1992 and1995 received an ASD diagnosis later. Hence, 87 of 18.133 children in this birth cohort were diagnosed with ASD, bringing the prevalence estimate January 1, 2004 to 48 per 10,000 (95% CI, 37.9-58.0) and the male-female ratio to 5.2:1.

Forty-one children met intake criteria of being diagnosed early during the preschool years (time 1) and reevaluated before entry into elementary school (time 2). Diagnostic groups at time 2 were used as independent variables: the childhood autism (CA) group and the other ASDs group. The dependent variables at both times were IQ/DQ, verbal status, and CARS total scores, and in addition the ADI-R domain scores at time 1 and adaptive behavior total scores at time 2 (see Table 4).

All but two of the children diagnosed with ASD at time 1 still had an ASD diagnosis at time 2. These two children (excluded from the study) had cognitive scores in the moderate ID range (IQ35-49) that remained stable over time. Of the total group, 13 children (32%) changed diagnostic category at time 2. Over 90% of the children who received a CA diagnosis at time 1 stayed in the same diagnostic category at time 2.

According to the CARS scores, autistic symptoms decreased from time 1 to time 2 for the total group (p = .001). The mean paired change between times amounted to 2.41 points. There was also a significant change in mean scores for the CA group (p = .013). Change in mean CARS scores for the other ASDs group was not significant (p = .101), although the difference in mean scores exceeded that of the CA group (Table 4). In spite of great individual differences over time (+/- 12.5 points), there was a strong correlation between the CARS measures at time 1 and time 2 (p < .001). Not surprisingly, the children in the CA group had more severe autistic symptoms on CARS than children in the other ASDs group, whether on time 1 (p = .002) or time 2 (p = .003). This difference remained significant when age at time 1 (p = .016) and period between assessments (p = .01) were used as covariates.

Mean cognitive performance for the whole group (N = 41) was stable (p = .209) with a strong correlation between measures over time (p < .001). Most stability was seen in the IQ/DQ groups scoring 70 or higher, and lower than 35. Most change proportionally over time was apparent in the 35-49 IQ/DQ group, where almost half of the children moved to a lower IQ/DQ range and the other half moved to a higher

IQ/DQ range. Considerable change was also seen in the 50-69 IQ/DQ group over time, where two children scored above 100, six children scored above 70 and two below 50 at time 2.

Table 4 Comparison of means of children's standardized test scores by diagnostic group and time of first ASD diagnosis (time 1) and time of reevaluation (time 2)

	CA (n = 30)		Other ASDs (n = 11)		Total (N = 41)	
	M	SD	M	SD	M	SD
ADI-R[a]						
Social Interaction	14.90	4.88	9.45**	3.21	13.37	5.06
Communication	11.20	3.61	9.82	3.22	10.83	3.53
Repetitive Behavior	2.70	1.53	1.64	1.36	2.41	1.55
CARS[b]						
Time 1	38.83[c]	6.12	33.20[d]*	1.99	37.39[e]	5.89
Time 2	36.88	7.03	29.64**	4.23	34.94	7.13
IQ/DQ[f]						
Time 1	53.97	18.06	64.27	13.56	56.73	17.43
Time 2	55.53	25.38	75.73*	13.66	60.95	24.41
VABS[g]						
ABC	51.24[c]	11.09	61.73*	10.53	54.13[h]	11.80

[a]ADI-R = Autism Diagnostic Interview – Revised (only available at time 1). [b]CARS = Childhood Autism Rating Scale. [c]n = 29. [d]n = 10. [e]n = 39. [f]IQ/DQ = Intelligence Quotient/Developmental Quotient. [g]VABS/ABC = Vineland Adaptive Behavior Scales/Adaptive Behavior Composite Score (only available at time 2). [h]n = 40.

*$p < .05$

**$p < .01$

According to the ADI-R definition of verbal status, about half (46.3%) of the total group had phrased speech at time 1 while 70.7% had phrased speech at time 2. In the CA group, 11 children had phrased speech at time 1 and 18 at time 2. The corresponding figures for the other ASDs group were 8 and 11. Comparison between groups at time 2 revealed differences, with 60% of the CA group having phrased

speech, while in the other ASDs group, all the children had phrased speech (p = .018).

There was no relationship between the number of hours in special education per week and change in scores from time 1 to time 2, whether in IQ/DQ scores (p = .586) or CARS scores (p = .726). When looking specifically at children in the CA group, no relationship was found between the amount of time spent in special education and change in scores from time 1 to time 2, in IQ/DQ scores (p = .789) or CARS scores (p = .482).

Seizures in the first year of life and autism (IV, V, VI)

Studies IV and V described the association between seizures in the first year of life and ASD. In the study group with IS occurring during the 1981-1998 period, the prevalence of ASD was 35.3% (95% CI, 14.2-61.7) **(IV)**. In the other group with unprovoked seizures (other than IS) occurring during the 1982-2000 period, the prevalence of ASD was 7.1% (95% CI, 2.7-14.9) **(V)**. The remainder of the analyses are based on the overlapping period (1982-1998) of the two studies, with 121 children who had unprovoked seizures, regardless of type, during the first year of life. The incidence of all unprovoked seizures in the first year of life was 163.4 per 100,000 person years (95% CI, 135.6-195.3) **(VI)**.

Of the 121 children with unprovoked seizures during the 17-year inclusion period (1982-1998), five had died and one lived abroad. The parents of the remaining 115 children were invited into a study of possible ASD of whom 95 participated (82.6%). Of these, 17.9% had IS and 81.1% had other types of seizures. The majority of the children or 87.4% had epilepsy (more than one unprovoked seizure). Most of the seizures were classified as cryptogenic (75.8%). Females outnumbered males by 1.8 to one. One-fourth (24/95) of the sample had ID. Thirteen children or 13.7% (95% CI, 7.5-22.3) had ASD, eight females and five males. Six of the children with ASD had IS, and seven had other types of epilepsy (Table 5). All but one of the autistic children had ID, and six had profound ID (IQ<20).

Of the children with autism, congenital abnormalities were noted in five: one had a porencephalic cyst in the left hemisphere, malformation of the cerebellum, and spastic hemiplegia; one had congenital toxoplasmosis and blindness; one had tuberous sclerosis complex, and two had trisomy 21 (Down's syndrome). Two additional children had cerebrovascular accident: one had a prenatal ischemic lesion

in the lentiform nucleus stretching to the left temporal lobe, and one had tentorial rupture perinatally with massive subdural hemorrhage. Thus, there were seven children (53.8%) diagnosed with ASD who had known brain abnormalities, of whom six were girls **(IV, V, VI)**.

Table 5 Characteristics of cases and controls in a cohort of children with seizures in the first year of life

	Cases n = 13 (%)	Controls n = 82 (%)
Infantile spasms	6 (46.2)	11 (13.4)
Symptomatic seizures	9 (69.2)	14 (17.1)
Epilepsy (> 1 seizure)	13 (100)	70 (85.4)
Males	5 (38.5)	29 (35.4)
Born 1990 or earlier	6 (46.2)	36 (43.9)
Mental age < 24 months	4 (30.8)	8 (9.8)
EEG performed	12 (92.3)	77 (93.9)
Abnormal EEG	11 (91.7) [a]	17 (22.1) [a]
Epileptiform, right TL[b]	1 (8.3) [a]	3 (3.9) [a]
Epileptiform, left TL[b]	4 (33.3) [a]	4 (5.2) [a]

[a)] Percentages of those with EEG

[b)] TL = temporal lobe

The crude odds ratio (OR) for autism associated with IS was 5.53 (95% CI, 1.25-23.06) and the Mantel-Haenszel stratification on year of birth and gender yielded similar OR, or 5.52 (95% CI, 1.24-22.30) and 5.88 (95% CI, 1.26-27.02) respectively. When year of birth and gender were adjusted for in a multivariate analysis, the results were similar with an OR of 5.81 (95% CI, 1.52-22.25). Since the difference between crude, stratified, and adjusted estimates were minor, age and gender were not adjusted for in the remainder of the regression analysis.

Table 6 shows the adjusted OR, taking into account whether the seizures were of symptomatic origin. The OR was 1.55 (95% CI 0.33-7.37) for children with IS compared to those without IS, adjusted for symptomatic origin of seizures. The OR was 8.73 (95% CI 1.88-40.54) for children with symptomatic origin of seizures compared to those with non-symptomatic seizures, adjusted for IS. Applying a

restriction to mental age ≥ 24 months and running the regression analysis again resulted in higher ORs. The OR was 2.59 (95% CI, 0.34-19.96) for children with IS compared to those without IS, adjusted for symptomatic origin of seizures. The OR was18.00 (95% CI, 3.33-97.29) for symptomatic origin of seizures compared to those without symptomatic seizures, adjusted for IS.

Table 6 Adjusted odds ratios and 95% confidence intervals (CI) from logistic regression of autism risk among cases and controls according to infantile spasms and symptomatic origin of seizures

	Cases n = 13	Controls n = 82	Odds ratio[a]	95% CI
Not infantile spasms	7	71	1	Reference
Infantile spasms	6	11	1.55	0.33 to 7.37
Non-symptomatic seizures	4	68	1	Reference
Symptomatic seizures	9	14	8.73	1.88 to 40.54

[a] Data have been calculated in unique multivariate analysis, taking into account simultaneously all the variables.

DISCUSSION

The prevalence estimate found for a cohort born 1974-1983 was close to the range of 4-5 per 10,000 typically reported in studies relying on Kanner's description of autism and published before 1985 (Bryson & Smith, 1998; Gillberg, 1995; Magnusson, 1977; Wing, 1993), while the estimate for a cohort born 1984-1993 was considerably higher or 13.2/10,000 **(I)**. Even the latter figure was considered to be conservative, as this study (I) concentrated on CA and a narrow definition of AA. This interpretation of previous results was substantiated when another study at a later date estimated the prevalence for all ASDs to be 48/10,000 in children born 1992 to 1995 **(III)**. These results have been confirmed in overlapping age groups (1994-1998) followed to December 1st 2005, where the corresponding figure for all ASDs was 58.5/10,000 (95% CI, 48.3-68.6) (Saemundsen, Magnusson, Sigurdardottir & Rafnsson, 2006). Taken together, these results demonstrate increased prevalence of autism and ASDs in Iceland, which is most apparent in the younger age groups.

One of the issues brought up in the earliest study **(I)** was the high rate of ID as defined by IQ/DQ measures in the younger cohort, or 95% for the CA group and 84% for CA and AA combined. These figures were higher than usually reported in prevalence studies on autism, or around 70%. One of the hypotheses ventured to explain this difference was the rule of selecting IQ/DQ measures closest to the date of diagnosis, which would possibly skew the distribution toward the ID range (IQ/DQ<70), especially in children tested at a very young age. This hypothesis was based on research that indicated that many children with autism who were tested with the Bayley scales below 3 years of age showed large increases in IQ/DQ when they were tested at an older age with other instruments, having received early intervention in the interim (Lord & Schopler, 1989).

In a study following a selected sample of Icelandic preschool children **(III)** from the time of first ASD diagnosis to entry into elementary school many of the children (78%) were tested with the Bayley scales early on, and then reevaluated at a later date, either with the same or a different test. A considerable proportion of children (8/41) moved from the ID IQ/DQ range (IQ<70) to the "normal" range (IQ≥70), but only one child moved from the "normal" range to the ID range.

These results lend support to the notion that the IQ/DQ distribution in the younger cohort of the prevalence study **(I)** was skewed in the direction of more

severe cognitive impairment by using the developmental tests closest to the first diagnosis of ASD, instead of the most recent measure. We conclude, therefore, that this distribution with a high rate of ID is, to a certain extent, a function of the number of children diagnosed early during the preschool years, and that this distribution is not atypical to the degree of undermining the representativity of our autistic sample. Further support for this interpretation may be found in the fact that the high proportion of ID in the younger age groups should have predicted a low male-female ratio (see Introduction), but on the contrary this ratio remained typical, or 3.6 for CA and 4.2 for AA.

The asymmetry in the mean symptom profile of the ADI-R in the group of children diagnosed with AA is of interest i.e. these children were more likely not to reach cutoff in the domain of repetitive and stereotyped behavior patterns than in the social and communication impairment domains. On a neurological level, there are indications for a certain dissociation between autistic symptomatology in the social-communication domain versus the repetitive behavior domain (Asano et al., 2001). Also, researchers studying the classification of ASD have questioned the requirement that all persons with ASD have a symptom from the restrictive, repetitive and stereotypic list (Tanguay, Robertson, & Derrick, 1998; Walker et al., 2004).

Significant correlations were found between the ADI-R domains scores and the ADI-R total score and the CARS total score, which supports the concurrent validity of the two instruments **(II)**. As predicted, CARS classified more cases with autism than ADI-R when they were compared on the basis of the 30-point cutoff score on CARS and the requirement of reaching or exceeding cutoffs in the three symptom domains of ADI-R. The agreement between the instruments increased considerably when the number of thresholds required for diagnosis on ADI-R was changed from three to two. Thus, autism as defined by the three thresholds on ADI-R seems to be more restrictive than the category of autism as defined by the 30-point cutoff on CARS. This is in line with Lord´s (1995, 1997) results comparing the accuracy of ADI-R and CARS in a group of children followed from age 2 to age 3. However, results from the study of Pilowsky and colleagues (1998) of a clinical group with a wider age-range (2 - 34 years) did not show a clear trend in this respect.

In a study of the stability of a diagnosis of autism between the ages of 20 to 42 months (Cox et al., 1999) it was reported that symptoms of RB were less frequent at age 20 months than at 42 months, at which age they were reported in most children

with autism. These researchers studied the effects of adjusting the cutoff scores in the RB domain of the ADI-R from three to two points. In their study, this increased the number of children correctly classified with autism and ASD at 20 months, but had no effect at 42 months. In the sample of the present study, this adjustment increased the observed agreement between the ADI-R and the CARS from 66.7% to 81.2% and the chance-corrected agreement from .40 to .63 (see also Ventola et al., 2006).

Post hoc comparisons between the groups revealed significantly lower cognitive abilities and more severe symptomatology in the group reaching or exceeding cutoffs on both diagnostic instruments compared with the group diagnosed only by CARS and the non-autistic group. This more impaired group contained more girls and more nonverbal subjects than the group diagnosed by CARS only. Although these latter differences were not significant, the total picture is in line with what might be expected in the light of recent research findings, that in moving from the more severe end of the autistic spectrum towards less severe symptomatology, one would expect to find higher levels of intelligence and higher male-female ratios (Bailey et al., 1996; Fombonne, 2003; Wing, 1993).

The results of this study **(II)** indicate that the 30-point cutoff on CARS represents a broader diagnostic concept of autism than the three-threshold definition of ADI-R. This suggests that CARS may be used effectively as an initial diagnostic test of ASD in secondary health care and educational settings to facilitate decisions about referral to the tertiary level of services.

All the participants in the follow-up study **(III)** attended preschool and received eclectic intervention on average for about 30 hours per week. The mean cognitive performance of the whole group was stable but autistic symptoms decreased from time 1 to time 2, as measured by CARS. When the study group was split according to diagnostic groups at time 2, outcome measures at time 2 showed more impairment for the CA group than for the other ASDs group: autistic symptoms were more severe, adaptive scores were lower, and the trend was toward lower IQ/DQs. At time 2, 30% of the CA group had IQ/DQ scores of ≥ 70 and 60% had phrased speech according to the ADI-R definition, while the respective figures for the other ASDs group were 73% and 100%. The great majority of the children diagnosed with CA at time 1 received the same diagnosis at time 2, which reflects the stability of the diagnosis of autism (Cox et al., 1999; Lord, 1995; Moore & Goodson, 2003; Stone, Ousley, Hepburn, Hogan, & Brown, 1999). On an individual

basis, huge differences were documented in autistic symptomatology and developmental measures from time 1 to time 2 in both directions. Some children showed developmental stagnation and increased autistic behaviors over time, while others made significant gains both in cognitive measures and diminished autistic features. The number of hours in special education per week did not affect IQ/DQ scores or CARS scores.

Children diagnosed with ASDs according to the ICD-10 in this study seemed to fare better as a group regarding IQ/DQ and overall level of language than had been reported in the earliest follow-up studies on children with autism (e.g. DeMyer et al., 1981; Lotter, 1978).

Studies IV and V described the association between unprovoked seizures in the first year of life and ASD in two overlapping cohorts and this material was the foundation for study VI which tested the hypothesis that IS predict higher risk of ASD as compared to other seizures with onset in the first year of life. At the descriptive level, there seemed to be more cases of autism in the IS group (35%) **(IV)** compared to children with seizures other than IS (7%) **(V)**. Previous to the present study, only two population-based studies had reported on the rate (9%-12.5%) of autism in children with a history of IS (Riikonen & Amnell, 1981; Sidenvall & Eeg-Olofsson, 1995). However, to our knowledge, this is the first population-based study **(V)** on ASD in children who had unprovoked seizures with onset in the first year of life, other than IS. Both of the figures, 7% and 35%, exceed distinctly the prevalence of ASD around 0.6% in the general population (Chakrabarti & Fombonne, 2005; Ellefsen, Kampmann, Billstedt, Gillberg, & Gillberg, 2007; Gillberg et al., 2006; Saemundsen et al., 2006). Furthermore, both studies **(IV, V)** had in common a high rate of ID, and an unusual male-female ratio in the groups diagnosed with ASD.

The incidence of all unprovoked seizures **(VI)** of 163.4 per 100,000 person years in the first year of life during the period 1982 to 1998 was similar to the incidence reported in the same population in a prospective study, or 130.2 per 100,000 person years (95% CI, 77.1-205.7) (Olafsson et al., 2005). The similarity of these incidence estimates, or even higher incidence in the present study **(VI)**, found with different methods supports the view that our cohort reflects the status in the population.

When classification of seizures was controlled for in a logistic regression analysis, IS was not an independent risk factor for ASD. This is in accordance with the results of a recent study on children with active epilepsy and ID, where no difference in the distribution of IS was found between ASD group and non-ASD groups (Steffenburg et al., 2003). The results of the present study showed significant association between seizures of symptomatic origin and ASD, suggesting a causal association of ASD with neuropathological phenomena rather than with the seizure type as such. This does not, however, preclude the possibility that the seizures themselves, particularly IS, have an additive effect on pathological processes already present (Bolton et al., 2002).

A restriction to those participants with a mental age of 24 months or higher was applied in order to increase the diagnostic accuracy of autism (Rutter et al., 2003b). This resulted in higher odds ratios, further strengthening the association between autism and symptomatic seizures.

All the cases had epilepsy, so in this study it was not possible to evaluate the role of epilepsy in association with ASD. As EEG is clinically indicated in epilepsy, and the EEG is often found abnormal in epilepsy, introducing the pattern of EEG tracings into the multivariate analysis would automatically invite circular reasoning, and hence such analysis was not performed.

Our results indicate that children who have epilepsy in the first year of life and who later develop ASD may constitute a subgroup with a higher frequency of known brain abnormalities and who are more often female than is reported for other children with ASD. Over-representation of females in autistic groups is usually associated with severe cognitive impairment (IQ<50) (Bryson & Smith, 1998; de Bildt et al., 2005), which fits the description of our autistic group **(VI)**.

The clinical material in the studies presented in this thesis was based on diagnosed and recorded cases. For children with autism, the sources were the records of the DCAP and SDCC **(I, II, III)**. For children with a history of seizures in the first year of life, the sources were the records of all the in-patient pediatric facilities in the country **(IV, V, VI)**. Such clinical material is usually found to underestimate frequencies compared to two-stage or multi-stage surveys that are more likely to give accurate estimates of the frequency of particular diseases or disorders (Baird et al. 2006b; Bristol et al. 1996; Bryson, Clark, & Smith, 1988). The efficacy of the

Icelandic health care, social, and educational services in detecting cases of ASD can be measured indirectly by examining rates over time and by comparison with recent findings of multi-stage or epidemiological studies from abroad. On the other hand, the efficacy of the pediatric departments in detecting cases with unprovoked seizures and epilepsy in the first year of life can be measured by comparing the incidence found in our retrospective study to a recent prospective study on the incidence of seizures in Iceland. Our data compares favorably both for ASD (Chakrabarti & Fombonne, 2005; Ellefsen et al., 2007; Gillberg et al., 2006) and seizures (Olafsson et al. 2005).

However, the inherent weakness of case-registers to estimate prevalence is exemplified in our studies on the association of autism in the two groups with seizures in the first year of life **(IV, V)**. Systematic search in these vulnerable groups revealed several unidentified cases of autism, all of whom had ID including two who had Down´s syndrome. In comparison, an earlier prevalence study reported no individual with Down´s syndrome among 75 cases with autism in a cohort born 1974-1993 **(I)**. Underestimating the possibility of autism does not only concern children with ID, but also higher functioning children, especially when they do not have serious language delay or serious cognitive impairment (Jonsdottir, Saemundsen, Antonsdottir, Sigurdardottir, & Olafsson, 2007). These higher functioning children are more likely to be diagnosed after 6 years of age, and more likely to have received another developmental diagnosis compared to children who are more impaired (Jonsdottir et al., 2007a). Then again, some of the higher functioning children are probably never referred for ASD (Baird et al., 2006b).

We report increased prevalence of autism and other ASDs in Iceland, which coincides with similar reports from different parts of the Western world (Fombonne, 2003). This increase first became noticeable around 1990, but the figures get higher as we move closer to the present time. The latest reports suggest approximately 0.6% as an estimate (Chakrabarti & Fombonne, 2005; Ellefsen et al., 2007; Fombonne et al., 2006; Gillberg et al., 2006), compared to the figure of 0.04% used for the organization of services prior to 1990 (Fombonne, 2003). At the same time, research has not substantiated increased incidence of ASDs or a “true” increase in the number of affected individuals (Fombonne, 2005; Rutter, 2005). So far, no new genetic or environmental risk factors have been identified that could explain the relative sudden increase in prevalence estimates of ASDs. Several plausible explanations of

increased prevalence of autism and ASDs have been advanced. First, a new and a broader definition of autism (Kielinen, Linna, & Moilanen, 2000), published almost simultaneously in the ICD-10 and the DSM-IV frameworks, formed the basis for common language between clinicians and researchers, and new diagnostic instruments based on this definition further facilitated diagnostic reliability and validity (Lord et al., 2001; Rutter et al., 2003b, 2005). Second, Asperger´s syndrome (or disorder) appeared for the first time in the ICD-10 and DSM-IV, so there was an actual increase in the number of diagnostic categories contained in these systems (APA, 1994; Rutter, 2005; WHO, 1993). Third, various medical disorders or syndromes were previously thought to exclude the possibility of autism diagnosis, but this view no longer prevails (Gillberg & Coleman, 1996; Rutter, 2005). Fourth, the concept of autism spectrum has facilitated the identification of variable phenotypic expression of ASD (Rutter, 2005; Wing, 2005). Fifth, brain science has advanced during recent decades and has affected knowledge on neurodevelopmental disorders in general and of ASDs in particular, not only on a professional level, but also by lay people (Rapin, 2005; Tager-Flusberg, 1999). Sixth, knowledge has increased on how the brain dysfunction causing social and communication difficulties (with or without repetitive behaviors) may impair those affected in interpersonal relationships and hinder their participation in society (Carter, Davis, Klin, & Volkmar, 2005; Tager-Flusberg et al., 2005). Finally, a growing body of evidence supports the notion that early intervention can change the course of neurodevelopmental disorders, including ASD (NRC, 2001) and this further promotes early diagnosis (Yirmiya & Ozonoff, 2007).

In all events, an increase in prevalence estimates is a fact, and more children are being referred to specialized services for ASD. The Icelandic health, social, and education systems have had difficulties accommodating this increase in referrals, and meeting the needs of children subsequent to ASD diagnosis, e.g. quality controlled education and treatment (Jonsdottir et al. 2007b), education to parents, and family support in general (Thorsteinsdottir & Gudlaugsdottir, 2007). Also, with increased knowledge of ASD, earlier detection of the disorder should be possible, especially considering the results of a recent study in Iceland where 76% of parents of children diagnosed with ASD had mentioned to professionals their concerns regarding the development of the child before the age of 3 years (Jonsdottir et al., 2007a). In this particular study, the mean age of first ASD diagnosis was just below 6 years. Other

studies on very young populations indicate that it is possible, at least in some cases, to diagnose ASD during the second year (Bryson et al., 2007; Yirmiya & Ozonoff, 2007). Earlier detection allows for earlier intervention, and hopefully better prognosis.

CONCLUSIONS

There has been an increase in the prevalence of autism and autism spectrum disorders in Iceland, which is most apparent in the younger age groups.

The 30-point cutoff on CARS is based on a wider concept of autism than the three domains definition on ADI-R. Convergence between the instruments increased considerably when the ADI-R cutoff on the repetitive behavior domain was relaxed. CARS should be useful at the secondary level of services for children with suspected autism spectrum disorder.

There are considerable individual differences in developmental trajectories in preschool children with autism spectrum disorders, both in relation to autistic behaviors and developmental measures. Thus, it is important to monitor closely the development of preschool children diagnosed with autism spectrum disorders.

High prevalence of autism spectrum disorder was found in children with infantile spasms and other types of unprovoked seizures in the first year of life exceeding that of the general population. An overrepresentation of intellectual disability and the female gender was found in these groups of children with autism spectrum disorder.

The symptomatic origin of seizures in the first year of life increased the risk of autism, not the seizure type as such, although the additive effects of the seizures themselves, particularly infantile spasms, cannot be excluded.

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Prevalence of Autism in Iceland

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This clinic-based study estimated the prevalence of autism in Iceland in two consecutive birth cohorts, subjects born in 1974–1983 and in 1984–1993. In the older cohort classification was based on the ICD-9 in 72% of cases while in the younger cohort 89% of cases were classified according to the ICD-10. Estimated prevalence rates for Infantile autism/Childhood autism were 3.8 per 10,000 in the older cohort and 8.6 per 10,000 in the younger cohort. The characteristics of the autistic groups are presented in terms of level of intelligence, male:female ratio, and age at diagnosis. For the younger cohort scores on the Autism Diagnostic Interview-Revised and the Childhood Autism Rating Scale are reported as well. Results are compared with a previous Icelandic study and recent population-based studies in other countries based on the ICD-10 classification system. Methodological issues are discussed as well as implications for future research and service delivery.

KEY WORDS: Autism; prevalence; epidemiology; Autism Diagnostic Interview-Revised; Childhood Autism Rating Scale.

INTRODUCTION

Previous knowledge of the prevalence of autism in Iceland stems from a case register study conducted in the seventies (Magnússon, 1977). In the light of recent discussions of a possible increase in the prevalence of autism and of the importance of recent epidemiological data for the development of services, it was felt to be of interest to gather data from case registers on two consecutive birth cohorts in Iceland.

Population-based studies are considered to yield more reliable estimates of prevalence than studies employing the case register method which is likely to underestimate prevalence, even when entire birth cohorts are followed up (Bryson, Clark, & Smith, 1988). In estimating prevalence, treatment-based or case register studies are seen as having several limitations including (a) uncertainty of having found all relevant settings, (b) unwillingness of some settings to participate, and (c) possible underestimation of high-functioning individuals who may not be served in special settings (Bristol *et al.*, 1996).

In an extensive review Wing (1993) examined 16 population-based studies of the prevalence of autism published in the period 1966–1991. Age-specific rates of autism varied from 3.3 to 16.0 per 10,000. Such wide variation in rates most likely reflects differences in case detection and case definition (Fombonne, du Mazaubrun, Cans, & Grandjean, 1997).

In a case register study, the problem of case detection depends on the extent of coverage of the service systems involved and their efficacy in capturing developmental disorders. The level of awareness of autism and knowledge of autistic conditions in the population and among professionals is likely to affect estimates of prevalence (Arvidsson *et al.*, 1997; Wing, 1993). Increased knowledge is likely to result in a higher number of cases being referred because of suspected autism which may increase the number of cases detected. Reluctance to make diagnoses of serious developmental disorders in infants and young children

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may also affect the detection of autism (Sponheim & Skjeldal, 1998).

Case definition presents an obstacle for the interpretation of prevalence studies since researchers may employ different diagnostic criteria. In the studies reviewed by Wing (1993), case definition was based on five different sets of criteria ranging from Kanner's criteria to DSM-III-R (American Psychiatric Association [APA], 1987). Research has established that different diagnostic systems provide varying broadness in their concept of autism which may lead to differences in prevalence rates. Recent studies have shown that the ICD-10 system (World Health Organization [WHO], 1992, 1993) seems to be most in line with clinicians' diagnoses (Volkmar, Cicchetti, Bregman, & Cohen, 1992; Volkmar *et al*., 1994).

Several recent studies of prevalence have used ICD-10 or equivalent criteria. As can be seen in Table I, rates of autism vary considerably across studies even when the possibly confounding factor of different diagnostic systems is held constant. Besides differences in case detection methodology, several factors may account for these divergences. Honda, Shimizu, Misumi, Niimi, and Ohashi (1996) argue that the size of the population may be an important factor affecting estimates of prevalence. Different age groups studied may influence results (Fombonne & du Mazaubrun, 1992). Migration may also be a confounding factor (Gillberg, Steffenburg, & Schaumann, 1991; Honda *et al*., 1996).

In the studies employing ICD-10 criteria (Table I) the male:female ratios ranged from 1.8 to 4.5. Various methods were used to estimate intellectual level including clinical judgment. The proportion of autistic subjects of normal or near normal intelligence ranged from 0–50% (Arvidsson *et al*., 1997; Fombonne & du Mazaubrun, 1992; Fombonne *et al*., 1997; Honda *et al*., 1996). The proportion of subjects with moderate to profound retardation (IQ < 50) was 50–83% (Arvidsson *et al*., 1997; Fombonne *et al*., 1997; Honda *et al*., 1996; Sponheim & Skjeldal, 1998).

The possibility of an increased prevalence of autism has been a subject of some discussion (Fombonne, 1996, 1998; Gillberg, 1995; Gillberg *et al*., 1991; Wing, 1993, 1996). An increased frequency of diagnoses of autism in specialized centers could have several different explanations, among them, a secular increase in incidence. However, it could also reflect changes in referral patterns and diagnostic practices. Fombonne (1998) has concluded that there is no evidence for an increased incidence of autism over time.

In Iceland, Magnússon (1977) published a case register study on the prevalence of autism in the birth cohort 1964–1973. Magnússon used Creak's nine points (Creak, 1961) as diagnostic criteria and diagnostic categories proposed by Rutter, Shaffer, and Sturge (1975). In this cohort Magnússon found a prevalence of 3.5 per 10,000 (95% confidence interval 1.7–5.2) for Infantile autism and the male:female ratio was 1.1.

The focus of the present study was on the most severe end of the autistic spectrum. The objectives were (a) to estimate the prevalence of autism in Iceland in children born in two periods, 1974–1983 and 1984–1993, (b) to compare this estimate with the result of the previous Icelandic study of children born in 1964–1973, and recent epidemiological studies of autism employing the ICD-10 classification system.

MATERIAL AND METHOD

Area and Population Studied

Iceland is an island of 103,000 km^2 thought to have been settled from Norway around 900 AD. According to the first census in 1703 the population was 50,358. Due to natural disasters and epidemics the population was approximately the same at the beginning of the 19th century. However, since then the population has been increasing (Thorarinsson, 1968). The population speaks one language and is considered genetically homogeneous (Bjarnason *et al*., 1973; Jorde, Eriksson, Morgan, & Workman, 1982). According to Statistics Iceland, public registers cover 100% of the population.

Table I. Prevalence Figures per 10,000 from Five Recent Studies in Four Countries Employing the ICD-10 Classification System

Country	Author	Year	Population screened	Age group	Autism	*CI*	M:F ratio
France	Fombonne & du Mazaubrun	1992	274,816	5.5/6.9	4.9	4.1–5.7	2.1:1
Japan	Honda *et al.*	1996	8,537	5	21.1	11.4–30.8	2.4:1
Sweden	Arvidsson *et al.*	1997	1,941	3–6	31	7–55	4.5:1
France	Fombonne *et al.*	1997	325,347	6–16	5.35	4.6–6.1	1.8:1
Norway	Sponheim & Skjeldal	1998	65,688	3–14	3.8	2.3–5.3	2:1

During the period 1974–1998, the number of inhabitants increased steadily from 216,628 in 1974 to 240,443 in 1984 and to 275,277 on 1 December 1998. Of the population 61% lived in the capital and surrounding area. Of the 1997 population, 1.8% were immigrants with foreign citizenship. Immigrants of non-European citizenship accounted for 0.5% of the total population. In the period 1971–1997, 3,127 individuals obtained Icelandic citizenship by law. Of these 49% were of non-European origin. Information was not available on the number of immigrants with Icelandic citizenship actually living in Iceland in the period of the study. Therefore the total number of immigrants with or without Icelandic citizenship could not be determined. Small changes in the net immigration over time indicate a relatively stable population. External migration per 1,000 inhabitants during 5-year periods in 1971–1995 ranges from –3.4 to 0.5 (Statistics Iceland, 1998). Internal migration is not relevant to the estimation of prevalence of autism in this study since the whole country and the area studied are the same.

The Service System

Fifty-five primary health care centers cover the whole country. They have the legal responsibility of health and developmental surveillance of all children from birth to 6 years of age. In this age period, every child is seen at least eight times by a physician and additionally four to six times by a public health nurse. The percentage of children covered by this system is at least 99% according to the Directorate of Health in Iceland. After entry into elementary school, every child is evaluated by a physician at ages 6, 9, and 12. The system is designed to provide comprehensive capture of health problems and developmental disorders. The screening procedures contain items looking for auditory and visual deficits as well as delays in the areas of motor, language and social development, and symptoms of behavioral and emotional disorders. The procedures contain no items screening specifically for autistic symptoms. If developmental disorders are suspected, referrals are made to the secondary level of services which, in this context, consists of pediatricians in private practice and pediatric hospital units.

The great majority of Icelandic children, 89.3% of 4-year-olds in 1997 (Statistics Iceland, 1999), attend kindergarten and all children attend elementary school. The teachers are responsible for monitoring their pupils' development and for referring any cases suspected of developmental disorders to the school psychological and pedagogical services. In smaller communities where such services are nonexistant, referrals are made to the primary or secondary level of health services.

In case of suspicion or preliminary diagnosis of pervasive developmental disorder (PDD) at the primary or secondary levels of services (health or educational), the children are in all cases referred to the tertiary level of services. This consists of two specialized centers, the Department of Child and Adolescent Psychiatry of the National University Hospital (DCAP) and the State Diagnostic and Counseling Center (SDCC). Both institutions cover the whole country.

Until 1996, all children with autism or other types of PDDs were referred to the DCAP which provided diagnostic expertise as well as treatment and counseling since its founding in 1971. After 1990, another center, the SDCC, began to take a more active role in the diagnosis and evaluation of children with autism. Diagnoses were frequently made in collaboration between the two centers. In 1997, it was decided to transfer the responsibility for services for individuals with autism entirely to the SDCC. Continuity of services in the transition period was ensured by close cooperation of experts from the two centers. One or both of the authors and their co-workers were involved in the follow-up of all the children diagnosed with autism in the cohorts studied.

The SDCC was founded in 1986 by the Ministry of Social Services. The main task of the SDCC is diagnosis and evaluation of children with major developmental disabilities and handicaps and subsequent counseling to parents and other services. Referrals come mainly from the secondary level services of the health system and from the psychological and pedagogical services of the educational system. The SDCC is headed by a developmental pediatrician and various professions are represented (pediatricians, psychologists, physiotherapists, occupational therapists, social workers, special education teachers, speech and language pathologists). It has the legal responsibility of keeping records of all developmental disorders leading to handicap. In addition, all professionals who detect a case of serious developmental disorder are required by law to indicate this to the SDCC.

Sources of Information and Organization of Data

The accumulation of data was based on the ongoing registration of children, born in the period 1974–1993, diagnosed with autism before 1 December 1998. The case register of the DCAP was the main source of information for the first half of the period. In

the latter half, information from the records of the SDCC plays an increasing role in accordance with the transfer of responsibilities between the two centers. Since a previous estimate of the prevalence of autism in Iceland (Magnússon, 1977) comprised children diagnosed with autism born in the 10-year period of 1964–1973, it was decided to use a similar approach in the present study, dividing cases into two groups according to year of birth, 1974–1983 and 1984–1993. All the children were diagnosed at either the DCAP or the SDCC. In each case, the earliest autism spectrum diagnosis was selected as the case diagnosis. The younger cohort (1984–1993) was considered a sample reflecting more recent diagnostic practices in Iceland.

Classification Systems and Diagnostic Procedures

Diagnostic classification was made either according to the ICD-9 (WHO, 1978) or the ICD-10 (WHO, 1993). The transition to the ICD-10 classification system (1989, draft version) took place in 1991 when the Autism Diagnostic Interview–Revised (Le Couteur *et al*., 1989; Lord, Rutter, & Le Couteur, 1994; Lord, Storoschuk, Rutter, & Pickles, 1993) came into use. One or both of the authors were involved in the diagnosis of all the children diagnosed with autism in both cohorts.

The ICD-9 classifications were based on developmental measures, observation of the children, interviews with caregivers, and relevant neurobiological investigations. The data were then evaluated by an interdisciplinary team which made a decision on diagnosis. The team always included child psychiatrists, clinical child psychologists, psychiatric social workers, psychiatric nurses, and sometimes a speech therapist and a special education teacher.

The ICD-10 classifications were in all cases based on the Autism Diagnostic Interview–Revised (ADI-R). The diagnostic algorithm used was the proposed ADI-R algorithm for ICD-10 (Revised September 1993). During the period 1991–1993, the algorithm (March 1991) based on the ICD-10 1989 draft version was used. All diagnoses made with this version were subsequently recoded according to the 1993 revised version. All the ADI-R interviews with parents were conducted by the authors, who received appropriate training at the Institute of Psychiatry, University of London. A further diagnostic assessment was made with the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988) by experienced clinicians. A reliability and validity pilot study of the CARS has been performed in an Icelandic population with satisfactory results (Einarsdóttir & Haraldsdóttir, 1992). The concomitant use of the ADI-R and the CARS in the diagnosis of autism is the subject of separate study (Sæmundsen, Magnússon, & Smári, 1999). The ADI-R and CARS data were then reviewed together with developmental measures and other relevant information by an interdisciplinary team consisting of a child psychiatrist and/or a neurodevelopmental pediatrician, a clinical child psychologist, and additionally various other professionals. The composition of the interdisciplinary teams changed somewhat during the long period under study.

Diagnostic Categories

The ICD-9 period diagnoses of Infantile autism were made in accordance with the guidelines of the ICD-9 manual and based on a consensus of the diagnostic team. No children diagnosed with "Psychosis with origin specific to childhood, other" according to ICD-9 were included in the autistic group in this study. The reason was that no such cases were found and the category seems not to have been used in Iceland.

Case definition in the ICD-10 period was based on three conditions:

1. The children included in our autistic group all fulfilled diagnostic criteria in two or three domains in the ADI-R (i.e., impairment of social interaction, communication, or restricted, repetitive or stereotyped patterns of behavior and interests). Subjects exceeding cutoff points in three areas of abnormality were classified as having Childhood autism. It was decided to restrict the use of the category Atypical autism to those subjects who exceeded cutoff points in two out of three areas of abnormality on the ADI-R. In accordance with ICD-10, atypicality of age of onset was defined by onset after 36 months of age. Children who met criteria for Asperger syndrome were not included. The methodology of this study was considered likely to underestimate the prevalence of high-functioning subjects such as those with Asperger syndrome. A case in point is a pilot study of the prevalence of Asperger syndrome in a circumscribed area in Iceland (Magnússon & Gunnarsdóttir, 1994) which indicated that Asperger syndrome was underdiagnosed.
2. Children assessed with the CARS were included in the Childhood autism group only if they received scores equal to or higher than 30 points. This was not an inclusion criterion for the Atypical autism group.
3. Subjects were included in the autistic group only if the diagnostic decision of the team was in accordance with the results of the ADI-R and the CARS.

Developmental Measures

In both the younger and the older cohorts, various developmental measures were used according to the age of the subjects and their developmental level. The measures reported here were made with the Bayley Scales of Infant Development (Bayley, 1969, 1993), the Leiter International Performance Scale (Arthur, 1952; Levine, 1982), the Peabody Picture Vocabulary Test-Revised (Dunn & Dunn, 1981), the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1967, 1989) and the Wechsler Intelligence Scale for Children (Hannibalsson, 1971; Wechsler, 1949). In the case of the Bayley scales and the Wechsler tests, global IQ/DQ figures were used. Nine children did not have IQ/DQ figures from the Bayley or Wechsler scales since they had been tested with the Leiter scale and the Peabody test. In these cases, global DQ figures were calculated by averaging the age–ratio quotients from these two tests. In cases where several measures existed for an individual child, the measure closest to the time of diagnosis was selected.

The Two Cohorts and Calculation of Prevalence

The population studied consisted of two birth cohorts, individuals born 1 January 1974 to 31 December 1983, and those born 1 January 1984 to 31 December 1993. Census day was 1 December 1998. The first cohort was 15–24 years of age and the second cohort was 5–14 years old in 1998. All subjects in the study were living in Iceland at the time of the study. One autistic subject born in the period covered was deceased on census day and another one had moved abroad; these two are not included in the study.

Statistical Analysis

P value < .05 was considered statistically significant. Confidence intervals were calculated at the 95% level. Chi-square was used to compare categorical data and the t test was used to compare group means.

RESULTS

Diagnostic Categories and Prevalence

Table II shows crude measures and prevalence per 10,000 for ICD-9 Infantile autism (IA), ICD-10 Childhood autism (CA), and ICD-10 Atypical autism (AA) in the two cohorts.

The two subjects with Atypical autism in the older cohort were diagnosed using ICD-10 criteria. No children with atypical age of onset (> 3 years) were found in either cohort. None of the subjects diagnosed with Atypical autism fulfilled ICD-10 criteria for Asperger syndrome, since all had significant delays in either language or cognitive development or both.

In the older cohort, two boys received the diagnosis of ICD-9 Disintegrative psychosis while no comparable cases were found in the younger cohort. If the two cohorts are taken together (population: 85,556) this amounts to a prevalence of 0.23 per 10,000. No cases of ICD-10 Rett syndrome were found in the present study. However, the younger cohort includes three girls who fulfill criteria for Childhood autism, while their course and symptomatology resembles what has been described as atypical forms of Rett syndrome or Rett variants (Gillberg, 1989; Hagberg & Skjeldal, 1994; Zappella, Gillberg, & Ehlers, 1998). No cases of ICD-10 Overactive disorder associated with mental retardation and stereotyped movements were found in the registers of the two institutions.

Characteristics of the Autistic Group

Male:Female Ratio

The male:female ratios found in the two cohorts are shown in Table II. The ratio for the Atypical autism group in the younger cohort was 5.7. A comparison of the male:female ratio of the Infantile autism/Childhood autism groups of the two cohorts did not show a significant difference, $\chi^2(1, N = 53) = 0.07$, $p = .79$. The

Table II. Prevalence of Infantile Autism/Childhood Autism (IA/CA) and Atypical Autism (AA) and Male:Female Ratios for Two Cohorts

Birth cohorts	Population	Diagnostic categories	*n*	M:F ratio	Prevalence per 10,000	*CI*[a]
1974–1983[b]	42,403	IA/CA	16	3	3.8	1.9–5.6
		IA/CA+AA	18	2	4.2	2.3–6.2
1984–1993[c]	43,153	IA/CA	37	3.6	8.6	5.8–11.3
		IA/CA+AA	57	4.2	13.2	9.8–16.6

[a] Confidence interval (95%).
[b] In this cohort 13 subjects were classified according to ICD-9 and 5 subjects according to ICD-10.
[c] In this cohort 6 subjects were classified according to ICD-9 and 51 subjects according to ICD-10.

Table III. Level of Intelligence of Children with Infantile Autism/Childhood Autism (IA/CA) and Atypical Autism (AA) in Two Cohorts (Percentages)[a]

	Birth cohorts		
		1984–1993	
IQ/DQ	1974–1983 IA/CA $n = 15$[b]	IA/CA $n = 37$	AA $n = 20$
< 50	40	46	30
50–69	27	49	35
≥ 70	33	5	35

[a] The AA group of the 1974–1983 cohort consisted of only 2 subjects.
[b] Test results for one subject missing.

Table IV. Distribution of Age at Diagnosis of Subjects with Infantile Autism/Childhood Autism (IA/CA) and Atypical Autism (AA) in Two Cohorts[a]

		1984–1993	
Age in years	1974–1983 IA/CA $n = 16$	IA/CA $n = 37$	AA $n = 20$
<2	1	0	0
2	3	7	2
3	6	11	5
4	1	7	6
5	0	5	1
6	1	1	1
≥7	4	6	5

[a] The AA group of the 1974–1983 cohort consisted of only 2 subjects.

difference between the male:female ratios of the IA/CA and AA groups in the younger cohort was found to be nonsignificant as well, $\chi^2(1, N = 57) = 0.36$, $p = .54$.

Level of Intelligence

Table III shows the distribution of intellectual and developmental quotients. In the 1974–1983 cohort, 67% fell into the retarded range. The corresponding figures for the 1984–1993 cohort were 95% for IA/CA, and 65% for AA. For IA/CA and AA taken together in the 1984–1993 cohort, this proportion was 84%. The difference between the proportion of IA/CA subjects with IQ/DQ < 70 in the two cohorts turned out to be statistically significant, $\chi^2(2, N = 52) = 7.49$, $p = .02$. When the categories IA/CA and AA are combined in the younger cohort the difference becomes nonsignificant, $\chi^2(2, N = 72) = 2.75$, $p = .25$.

Age at Diagnosis

The median age at diagnosis was 43 months (range 20–204) for the IA/CA group of the 1974–1983 cohort. For the 1984–1993 cohort, the median was 48 months (range 26–165) for the IA/CA group (Table IV). A *t* test did not show a significant difference between the means of the two cohorts, $t(51) = 0.46$, $p = .65$.

In the group diagnosed by ICD-10 criteria in the younger cohort, the median age at diagnosis was 49 months (range 26–165) for the group with Childhood autism, and 52 months (range 33–170) for the group with Atypical autism. A *t* test did not show a significant difference between the means of the two groups, $t(49) = -0.55$, $p = .58$.

Immigration

All the children in the older cohort had nonimmigrant parents. In the younger cohort seven children, all of whom were born in Iceland, had immigrant parents. Three had immigrant fathers and four had immigrant mothers. One father and two mothers were of European origin. Non-Europeans were 3.5% of the total parent group. One mother was North American, while two fathers and one mother were of Asian origin.

Distribution of ADI-R and CARS Scores in the 1984–1993 Cohort

Table V shows the distribution of ADI-R and CARS mean scores for 51 subjects diagnosed with ICD-10.

A *t* test showed a significant difference between the CARS scores of the Childhood autism group and the Atypical autism group, $t(48) = 3.58$, $p = .001$. It should be noted that in the case of Atypical autism the mean scores on the ADI-R exceed their respective cutoff points except for the Repetitive Behavior and Stereotyped Patterns (RB) domain. Not reaching cutoff in this domain was by far the most common atypicality in symptomatology since 16 out of 20 AA subjects scored below the cutoff on the RB scale. Two subjects scored below cutoff in the Social Interaction domain and 2 subjects in the Communication domain. If tested against the null hypothesis of equal distribution between the three domains the observed distribution turns out to be highly unlikly and statistically significant, $\chi^2(2, N = 20) = 19.6$, $p = .001$.

DISCUSSION

The study of the rate of autism in two consecutive birth cohorts in Iceland yielded an estimated prevalence of Infantile autism/Childhood autism of 3.8 per 10,000 in the older cohort (1974–1983), and a prevalence of 8.6 per 10,000 in the younger cohort (1984–1993). Con-

Table V. Means and Standard Deviations of ADI-R Content Domain Scores and CARS Scores of Verbal and Nonverbal Subjects Born 1984–1993 and Diagnosed with Childhood Autism and Atypical Autism according to the ICD-10 Classification System[a]

ICD-10 diagnosis	CARS[e] *M* (*SD*)	ADI-R/SI[b] *M* (*SD*)	ADI-R/CO[c] *M* (*SD*)	ADI-R/RB[d] *M* (*SD*)
Childhood autism				
Verbal (*n* = 17)	37.4 (3.8)	16.1 (3.6)	16.2 (2.2)	4.8 (2.1)
Nonverbal (*n* = 14)	44.1 (6.5)	18.6 (5.6)	12.0 (2.7)	4.0 (1.2)
Atypical autism				
Verbal (*n* = 14)	35.5 (2.6)	13.0 (3.7)	11.9 (4.1)	2.4 (0.8)
Nonverbal (*n* = 6)	36.8 (2.9)	18.5 (4.9)	10.5 (3.1)	1.7 (0.5)

[a] A complete list of ADI-R and CARS scores is available from the authors upon request.
[b] SI = Social Interaction (cutoff score = 10).
[c] CO = Communication (cutoff scores: verbal = 8, nonverbal = 7).
[d] RB = Repetitive Behavior (cutoff = 3).
[e] CARS score missing for 1 subject.

fidence intervals did not overlap. The rate found in the older cohort of this study was close to the range of 4–5 per 10,000 typically found in studies relying on Kanner's description of autism and published before 1985 (Bryson & Smith, 1998; Gillberg, 1995; Wing, 1993).

The rate found in the older cohort was close to the rate of 3.5 per 10,000 previously described in Iceland in children born 1964–1973 (Magnússon, 1977). The male:female ratio of Magnússon's Infantile autism group was 1.1:1. The male:female ratios of the older and younger cohorts of the present study were 3:1 and 3.6:1, respectively. The older cohort contains a smaller proportion of subjects falling into the retarded range than the younger one, 67% versus 95%. Comparison with Magnússon's (1977) study in terms of intellectual level is hampered by the fact that his figure of 84% of mental retardation includes subjects with Disintegrative psychosis.

In view of the considerable difference between the rates of autism in the two cohorts, the problem of case definition has to be addressed since two different classification systems were employed. In the older cohort, 72% of the subjects were classified according to the ICD-9. However, in the younger group, 89% were classified according to the ICD-10 (see Table II). If the ICD-10 provides a broader conception of autism than the ICD-9, this may account for some of the increase found. Steinhausen and Erdin's (1991) study found no remarkable change in the frequencies of "Psychosis with origin specific to childhood" according to which diagnostic system was employed. However, the ICD-9 and the ICD-10 Diagnostic Criteria for Research, on which the ADI-R is based, represent somewhat different approaches to diagnosis. The ICD-9 provided diagnostic guidelines, close to Kanner's description of autism and without specific cutoff points. The ICD-10 and ADI-R represent a more dimensional or spectrum-oriented approach with empirically based cutoff points. In the second approach, borderline cases (where the behavioral manifestations of autism diverge from classical descriptions) may have a higher probability of being classified as autism.

Since a large majority of the subjects of the younger cohort were diagnosed with the ICD-10 this group was used for comparison with recent epidemiological studies using this classification system (see Table I). The confidence interval for the prevalence of Infantile Autism/Childhood autism found in this cohort overlapped with the confidence intervals of two of the reported studies, Fombonne *et al*. (1997) and Arvidsson *et al*. (1997). The prevalence rate found in the younger cohort thus seemed to be on an intermediary level between the studies finding the lower rates of 3.8–5.35 per 10,000 and those finding the higher rates of 21 and 31 per 10,000 (see Table I). The male:female ratio of the IA/CA group of the younger cohort fell within the range of 1.8–4.5:1 found in the ICD-10 studies. The proportion of subjects in the younger cohort with normal or near normal intelligence (5%) was relatively low, although it fell within the range of 0–50% found in those of the ICD-10 studies that provide data on the subject (Arvidsson *et al*., 1997; Fombonne *et al*., 1997; Honda *et al*., 1996).

Differences in case detection methods may also account for some of the divergence in published prevalence rates (Fombonne, 1998; Wing, 1993). In the present study, the problem of case detection depends on the sensitivity of those instances of the service system designed to capture developmental disorders. While this system is constantly developing, it is not possible to pinpoint any structural changes likely to result in an increased number of referrals for autism in Iceland. However, an increased awareness of the heterogeneity in the

expression of autistic conditions is a possible explanation (Bryson & Smith, 1998; Wing, 1993). This may increase the number of subjects referred for evaluation to specialized centers, which in turn may result in an increased number of diagnosed cases. An indication of this may be found in the fact that after 1996, the number of referrals to the SDCC for suspicion of autism from special schools for the mentally handicapped increased noticeably. All the individuals referred were older than 7 years of age and on 1 December 1998, the census day of the present study, three of the referred subjects had received a diagnosis of Childhood autism and three had been diagnosed with Atypical autism. All the subjects were mentally retarded and belonged to the younger cohort of this study. Increased sensitivity to autistic symptoms in specialized services for the mentally handicapped may thus have a selective effect, at least in the short term, on the composition of the autistic group. These subjects also account for the higher median age at diagnosis in the younger cohort.

When Atypical autism is included, the prevalence in the younger cohort of our study rises to 13.2 per 10.000. The ratio Atypical autism:Childhood autism is roughly 1:3. This ratio was 1:2 and 1:4, respectively, in the Swedish and Norwegian studies based on the ICD-10 (Arvidsson *et al*., 1997; Sponheim & Skjeldal, 1998). Although the diagnostic classifications in all three studies were based on the ICD-10, none used exactly the same criteria to define Atypical autism. No cases of Atypical autism (atypicality of age of onset) were found in this study. Neither were any such cases found in two recent studies (Arvidsson *et al*., 1997; Sponheim, 1996).

It follows from the definition of Atypical autism in the present study (reaching or exceeding cutoff scores in two out of three symptom domains) that the symptomatology of the AA group was less severe than that of the CA group as attested by the lower average CARS score. This cannot be explained by a difference in age at diagnosis since this difference was found to be nonsignificant. Note that the symptom profile of the AA group differed from that of the CA group (see Table V). The AA subjects were more likely not to reach cutoffs in the domain of Repetitive behavior and stereotyped patterns of interest than on the Social and Communication impairment domains. A study of the classification of autism spectrum disorders with the ADI-R has led Tanguay, Robertson, and Derrick (1998) to conclude that "requiring that all persons with autism spectrum disorder have a symptom from the "restrictive, repetitive, and stereotypic" list may need to be reconsidered." (p. 271).

The level of intelligence was significantly higher in the AA group than in the CA group. Also, the male:female ratio was higher in the AA than the CA group, although the difference was not statistically significant. This is in accordance with the notion that in moving from a more severe end of the autistic spectrum towards a less severe symtomatology, one would expect to find higher levels of intelligence and accordingly higher male:female ratios (Bailey, Philips, & Rutter, 1996; Fombonne, 1998; Wing, 1993). The diagnostic category of Atypical autism as defined by the ICD-10 was created to provide for the group of severely retarded subjects who show some autistic features (Rutter, 1989). The narrow definition of Atypical autism used in the present study recruited an altogether different group.

Clinical studies may tend to oversample lower functioning subjects compared with higher functioning ones (Bristol *et al*., 1996; Volkmar, Szatmari, & Sparrow, 1993). The data from the present study seem to support this conclusion in the younger cohort, with only 5% of children diagnosed with IA/CA falling into the normal or near normal category of IQ/DQ 70 or above. This finding should predict a low male:female ratio. However, on the contrary, this ratio (3.6) is what one would expect to find in population-based research (Fombonne, 1998). There is the possibility that selecting the IQ/DQ measures closest to the date of diagnosis may skew the distribution of IQs/DQs toward the retarded range in children diagnosed at 3 years of age or younger. In the younger cohort, 18 of 37 subjects with Childhood autism were tested at age 3 or younger. All of these were given the Bayley Scales of Infant Development. Research has indicated that many autistic children tested with the Bayley scales at such a young age show large increases when tested with other instruments at an older age (Lord & Schopler, 1989). A follow-up of this group with reassessment of intellectual levels might answer this question.

The high rate of mental retardation in the IA/CA group of the younger cohort is difficult to explain in full. Three tentative explanations have been advanced which may explain part of the difference between the cohorts. First, clinical studies may oversample mentally retarded subjects. Second, the early testing with the BSID may explain part of the difference. Third, a part may be explained by the "second wave" of referrals mentioned above (i.e. children older than 7 referred from special schools for the mentally handicapped because of increased sensitivity to autistic symptomatology in these schools).

Since this study focused on the extreme end of the autism spectrum, it is of interest to examine the two PDD categories that are most likely to go unnoticed,

that is, Rett syndrome (RS) and Disintegrative disorder (DD). No cases of ICD-10 Rett syndrome were found in the present study. The prevalence of RS has been estimated at 1 in 10,000 to 15,000 girls (Hagberg, 1995). Given a prevalence of 1 per 15,000, the probability of finding one or more cases of RS amongst the 41,896 girls of the two birth cohorts of the present study was calculated at 94%. The authors made an additional informal survey by contacting professionals in key positions in the health care system inquiring about girls with RS born in the two periods 1974–1983 and 1984–1993. This search produced no additional cases. The possibility that cases of RS may have been missed cannot be excluded. However, a geographical variability in the prevalence of RS is also a possible explanation (Hagberg & Hagberg, 1997). Two cases of Disintegrative psychosis (diagnosed by ICD-9 criteria) were found in the older cohort of the present study. The resulting estimate of prevalence for the two cohorts amounts to 0.23 per 10.000. Pooling the two cohorts of the present study with Magnússon's (1977) 1964–1973 cohort (total 128,761 subjects), where four cases of Disintegrative psychosis were found, results in a prevalence of 0.46 per 10,000. Burd, Fisher, and Kerbeshian (1987) reported 0.11 per 10,000.

The case register method is conventionally considered to underestimate prevalence (Bristol *et al*., 1996; Bryson *et al*., 1988). There may be uncertainty of having found all settings and some settings may be unwilling to participate in an epidemiological study. In the present study, cases of autism were collected from the registers of two centers (DCAP and SDCC), the only ones in Iceland specialized in the diagnosis of autism. This minimizes the effects of the limitations mentioned above. It is, however, quite possible that some cases, especially high-functioning ones, may have gone undetected in the primary and secondary level of services and hence not have been referred to the specialized centers. Another potential problem of missing cases is when autism is associated with another medical condition (Gillberg & Coleman, 1996; Nordin & Gillberg, 1996; Rutter, Bailey, Bolton, & Le Couteur, 1994). A case in point is that no instance of autism comorbid with Down syndrome (DS) was found in this study, but the comorbid occurrence of autism and DS has been found to be at least 7% of DS subjects in a recent study (Kent, Evans, Paul, & Sharp, 1999).

The possibility of false positives is obviously present, especially since the earliest diagnosis was selected as the case diagnosis and most of the subjects were diagnosed at an early age, almost half of them at age 3 or younger. This possibility is minimized by the fact that the present authors and their co-workers were involved in the follow-up of all individuals who received diagnoses of autism in the cohorts studied. This follow-up consisted of counseling for parents and professionals involved in the care of the autistic subjects and reevaluations when questions arose regarding the diagnosis and/or the course of the disorder in individual cases. At the present date, none of the reevaluations have resulted in a change of diagnosis from autistic to nonautistic. This is in accordance with research showing stability of diagnosis even at the age of 2–3 years (Lord, 1995; Stone *et al*., 1999). No cases of transition between the two categories of CA and AA were found in the study. This may be due to the fact that reevaluations were only conducted when questions arose, whereas systematic reassessment of the whole group might have revealed such transitions.

The reasons for the increased prevalence of autism found in the younger cohort of this study are unclear. The data show that this increase cannot be explained by migration. There is no clear evidence of changes in the availability of services that should lead to more cases being found, although this has not been formally studied. On the other hand, there are obvious changes in classification schemes and in diagnostic practices, which have been dealt with above. The latter are likely to make case detection more efficient. Also, there is some evidence for increased awareness of autism spectrum disorders as attested by a "second wave" of referrals of individuals belonging to the younger cohort who had already been diagnosed with mental retardation. The results of the study do not allow any conclusions as to a genuine change in incidence.

In spite of the limitations of the case register method in epidemiological research, this method may still be useful in monitoring changes in prevalence of severe developmental disorders when the total population is small, when the service system is efficient in finding such disorders, and when many birth cohorts are studied. In order to find high-functioning individuals with autism who may have been missed in the present study, a community-based methodology is needed. A further survey of autistic symptoms in individuals with mental retardation is in preparation.

The increased number of individuals receiving diagnoses of autism has already created a crisis in the provision of services in Iceland, as the system has not developed to cope with the increased demand. This crisis is particularly pronounced in the youngest age groups. The results of the present study provide a baseline for the reorganization of the service system.

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II

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Autism Diagnostic Interview-Revised and the Childhood Autism Rating Scale: Convergence and Discrepancy in Diagnosing Autism

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The agreement between the Autism Diagnostic Interview–Revised (ADI-R) and the Childhood Autism Rating Scale (CARS) was investigated in the diagnostic assessment of 54 children aged 22–114 months referred for possible autism. The observed agreement between the two systems was 66.7% (Cohen's kappa = .40) when the ADI-R definition for autism was applied (i.e., scores reaching cutoff in three domains on the ADI-R), but increased considerably with less stringent criteria; that is, scores reaching cutoffs in two domains and in one domain on the ADI-R. As predicted, the CARS identified more cases of autism than the ADI-R. Children classified as autistic according to both instruments had significantly lower IQ/DQ and more severe autistic symptomatology than those classified with the CARS only.

KEY WORDS: Autism; diagnosis; Autism Diagnostic Interview–Revised; Childhood Autism Rating Scale.

INTRODUCTION

Diagnostic instruments for autism usually rely on two main sources of information; that is, descriptions of caregivers of the course of development and current behavior patterns and information from direct observation of behavior (Le Couteur, Rutter, Lord, Rios, Robertson, Holdgrafer, & McLennan, 1989; Lord, 1991). These instruments may be developed for different purposes and at different times and, therefore, may or may not be based on the same conception of autism. Data on the concordance of diagnostic instruments are important for clinical practice as well as for research on autism.

The Autism Diagnostic Interview–Revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) is a standardized instrument that provides an algorithm for the ICD-10 (World Health Organization [WHO], 1993) and DSM-IV (American Psychiatric Association [APA], 1994) diagnoses of autism. The Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988) was developed to meet the administrative and research needs of the TEACCH program in North Carolina. It is based on a pre-ICD-10/DSM-IV conception of autism (Lord & Risi, 1998). Both of these instruments are widely used, but data on their agreement are sparse.

A search of the literature revealed only two studies comparing the ADI-R and the CARS (Lord 1995; Pilowsky, Yirmiya, Shulman, & Dover, 1998). Lord (1995) used a prospective approach to study the stability of diagnoses in 30 children referred for possible autism at the age of 2 years. She investigated how these instruments scored at this age predicted group membership for autism and nonautism compared with an independent clinical diagnosis at age 3. Both instruments were overinclusive for children with a mental handicap or delayed language at the age of 2 years, but to a lesser

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extent at the age of 3 years. The ADI-R was more accurate than the CARS with nonautistic children; the CARS overdiagnosed mentally handicapped children as having autism (Lord, 1997). If a cutoff of 32 points were used, instead of the classic 30, the accuracy of the CARS increased in that it classified nonautistic children more often correctly. "Agreement between the ADI-R and CARS was in fact quite high; the difference was whether a simple total or thresholds across several areas (i.e., social reciprocity, communication, restricted and repetitive behaviors) were required for a diagnosis" (Lord, 1997, p. 463).

The agreement of the ADI-R and the CARS has also been studied in a larger and more heterogeneous sample by Pilowsky *et al.* (1998), who assessed 70 individuals with both the ADI-R and the CARS. The age range for this group was 2 to 34 years of age ($M = 12.2$ years). Participants diagnosed as having autism based on only one instrument were significantly younger in age than those receiving diagnoses based on both instruments. No gender differences in symptoms of autism were revealed on either instrument. These authors found an overall percentage of observed agreement, of 85.7%, but the Cohen's kappa coefficient was .36. This discrepancy was considered to result from poor agreement on cases classified as nonautistic. The authors suggested that disagreement between these diagnostic instruments might be attributed to differences in sources of information.

Research indicates that, of the diagnostic systems used for the classification of autism in the last decades, DSM-III (APA, 1980) provides the narrowest approach, whereas the DSM-III-R (APA, 1987) provides the broadest, with the ICD-10 (WHO, 1993) intermediate, paralleling the clinicians' patterns of diagnosis (Volkmar, Cicchetti, Bregman, & Cohen, 1992; Volkmar *et al.,* 1994). The CARS may be either on a par with the DSM-III-R in diagnosing autism or represent a broader concept of autism than the DSM-III-R (Sevin, Matson, Coe, Fee, & Sevin, 1991; Van Bourgondien, Marcus, & Schopler, 1992). Sponheim (1996) found excellent agreement between the ICD-10 and the CARS (kappa = .83) in a clinical sample, where the same clinician rated according to four systems in a fixed order. However, according to Lord's (1997) review of diagnostic instruments, research findings suggest that the CARS "probably identifies more children as having autism" (p. 473) than the three-domain diagnostic frameworks; that is, ICD-10 and DSM-IV.

The objectives of this study were to gather information on the agreement of the ADI-R and the CARS in a young clinical sample and to study the characteristics of the children who were classified as autistic or nonautistic with these two instruments. It was predicted that the CARS would diagnose more cases with autism than the ADI-R.

METHOD

Participants

The sample comprised 54 children, aged 22 to 114 months, referred for possible autism to the daycare unit of the State Diagnostic and Counseling Center (SDCC) during a 42-month period (October 1993 through March 1997). Included in the study were all children referred for possible autism that were assessed with both the ADI-R and the CARS during the child's stay at the SDCC. The mean age of this sample was 45.4 months ($SD = 15.9$) and consisted of 47 boys and seven girls, a ratio of 6.7 to one. The mean IQ/DQ was 62.7 ($SD = 18.0$; range 16–96), with 22% tested in the severely retarded range (<50), 35% in the mildly retarded range (50–69), and 43% in the normal range (≥70).

Excluded from the study were four children (three boys and one girl) who were not subjected to the full diagnostic program carried out at the SDCC. None of these children were diagnosed with autism during this initial assessment, but later, all of them were diagnosed with an autistic spectrum disorder.

Measures

Diagnostic Instruments

The ADI-R is a standardized, semistructured, investigator-based interview for caregivers of individuals with autism, which provides a diagnostic algorithm for the ICD 10 and the DSM-IV definitions of autism. Reliability and validity have been shown to be adequate (Le Couteur *et al.,* 1989; Lord *et al.,* 1994; Lord, Pickles, McLennan, Rutter, Bregman, Folstein, Fombonne, Leboyer, & Minshew, 1997; Lord, Storoschuck, Rutter, & Pickles, 1993). An ADI-R diagnosis of childhood autism requires reaching or exceeding cutoffs in all three ICD-10 symptom domains; that is, impairment in reciprocal social interaction (SI), communication (CO), and repetitive behaviors and stereotyped patterns (RB), given that abnormality of development is evident at or before 36 months. All scores of three points from the protocol were converted to two points on the algorithm sheet (1993 revision). Different algorithms were applied according to the chronological age (<4 years; ≥4 years) of the participants for

the SI domain. Different cutoffs were applied in the CO domain according to whether the participants were verbal (8 points) or nonverbal (7 points), as proposed in the ADI-R algorithm for the ICD-10. "Verbal," according to the ADI-R protocol, means "functional use of spontaneous, echoed or stereotyped language that, on a daily basis, involves phrases of 3 words or more that at least sometimes include a verb and is comprehensible to other people" (Rutter, Lord, & Le Couteur, 1990, p. 27). The ADI-R has been translated into Icelandic and back into English. The backtranslation was reviewed by one of the authors of the ADI-R and, subsequently, appropriate alterations were made to the Icelandic translation to ensure equivalence of the two versions.

The CARS was originally developed as an observational instrument (Prizant, 1992). It consists of 15 items, which are scored on a 7-point Likert scale, and all the items contribute equally to the total score. According to the CARS manual, autism is defined by a score of $\geq$30 points. The interval from 30 to 36.5 points defines mild to moderate autism, and scores of 37–60 define severe autism. This instrument has been shown to have a high degree of internal consistency, interrater, and test-retest reliability, as well as high criterion-related validity and good discriminant validity (DiLalla & Rogers, 1994; Eaves & Milner, 1993; Garfin, McCallon, & Cox, 1988; Lord, 1995; Nordin, Gillberg, & Nydén, 1998; Schopler *et al.,* 1988; Sevin *et al.,* 1991). The CARS has been used in Iceland since 1989. A pilot study has been carried out on the validity and reliability of an Icelandic translation, which had previously been backtranslated into English (Einarsdóttir & Haraldsdóttir, 1992).

The conceptual difference between the CARS and the ICD-10/DSM-IV definition of autism is reflected in the fact that the CARS total score employs no weighting of different items, whereas the three-threshold approach of the current diagnostic frameworks accords extra weight to the area of social deficits (Lord & Risi, 1998; Prizant, 1992). Furthermore, the CARS assesses some areas of nonspecific difficulties, for example, mental retardation, language delay, and activity level, that are not included in the ICD-10 or the DSM-IV definition of autism (Lord & Risi, 1998; Prizant, 1992).

Cognitive Tests

The same clinical psychologist who applied the CARS in each case carried out the cognitive testing at the SDCC. The tests employed were the two editions of the Bayley Scales of Infant Development (BSID; Bayley, 1969; Bayley, 1993), the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989), the Wechsler Intelligence Scale for Children (WISC; Hannibalsson, 1971; Wechsler, 1949), and the Leiter International Performance Scale (LIPS; Arthur, 1952; Levine, 1982). If the child had valid WPPSI-R results ($n = 21$), they are reported. One participant was given the WPPSI-R, even though he exceeded the upper age limit by 4 months, and the WISC was administered to one participant. In the rest of the sample ($n = 32$), the BSID results were used to determine developmental quotients (DQs). Of those children tested with the two editions of the BSID, some did not receive raw scores that converted into standard scores above 50, and some exceeded the upper age limits of the BSID. For the sake of consistency in the data, ratio DQs were derived from all BSID raw scores. In addition, the LIPS was administered unless the BSID results clearly indicated that a LIPS baseline would not be reached (13%).

Procedure

There are two tertiary service centers in Iceland in the field of developmental disorders: the SDCC and the Department of Child and Adolescent Psychiatry, University Hospital (DCAP). During the study period, the majority (78%) of Icelandic children with possible autism were referred to the SDCC for diagnostic purposes, with a minority referred to the DCAP. The SDCC serves mainly preschool children (85% of new referrals at the time of the study). It receives referrals from primary and secondary health, social and educational services, and pediatricians and other professionals in private practice.

During the evaluation period, which lasted from 1 to 8 weeks (mean stay = 21 days), the CARS and the ADI-R were given as well as tests of cognitive, language, and sensory-motor development. A physical examination, including a neurological examination, was conducted, and a thorough diagnostic work-up was carried out during or following admission, which included a hearing test, auditory evoked potentials, electroencephalogram, neuro-imaging, chromosomal analysis, and blood and urine metabolic studies. The diagnostic process was concluded with the meeting of an interdisciplinary team, which made the final diagnosis and proposed a treatment plan.

In this study, the second author (P. M.) a clinical psychologist, interviewed all parents. He received appropriate training in the use of the ADI-R at the Institute of Psychiatry, London. Of the five clinical psychologists at the SDCC who were responsible for

the scoring of the CARS, the first author scored the CARS in 74% of the cases. The scoring was based on observations and video-recordings of the children in both structured and nonstructured situations and took from 30 to 60 minutes for each child.

The CARS was given prior to the ADI-R, usually 3 to 4 weeks earlier, but the age of diagnosis was based on the date when the ADI-R was applied. The sources of information for the two instruments were totally separate: the ADI-R ratings depended on information from parents, whereas the scoring of the CARS was based solely on observations of the child's behavior. The clinicians applying the ADI-R and the CARS were blind to each other's results.

Design and Statistical Analyses

In studying the agreement between the ADI-R and the CARS, three conditions were defined according to the number of symptom domains where cutoffs were reached or exceeded on the ADI-R (i.e., cutoffs reached in all three domains, cutoffs reached in two domains, and cutoff reached in one domain). The first is the ADI-R definition of autism as specified in the ICD-10. The two other conditions may correspond to ICD-10 classifications (e.g., Asperger's syndrome or Atypical autism), but without specific guidelines.

Alpha coefficients for the ADI-R were calculated for different groups according to chronological age and verbal status for each symptom domain. Missing values within each domain were replaced by the series mean. In the RB domain, item 70 (Circumscribed Interests) was excluded from the analysis. This item was not applicable to children younger than 10 years in the 1993 revision of the algorithm, so data for this item were not consistently gathered.

One-way analyses of variance (followed up by Scheffé post hoc tests) were conducted with groups satisfying criteria for autism on both the ADI-R and the CARS, on the CARS only, or on neither instrument, as the independent variable. Dependent variables were age at diagnosis, IQ/DQ, CARS total scores, ADI-R domain scores, and ADI-R total score. In the analysis of symptom severity, the CO symptom domain on the ADI-R was split into verbal and nonverbal groups. The chi-square test was used to compare categorical data.

RESULTS

Medical Examinations

None of the 54 children tested positive for a chromosomal disorder, was hearing impaired, or had a metabolic disorder. Of the 36 children classified as autistic by either or both diagnostic instruments, three (8%) had medical conditions with suspected etiologic relationship with autism. One had prenatal macrocephaly (head circumference above 2 *SD* above the mean) and suspected Sotos overgrowth syndrome. Magnetic resonance imaging of the brain showed occipital polymicrogyria. Another child suffered a prenatal vascular accident, which caused atrophy of the left hemisphere; as a result, he had hemiplegia, a seizure disorder, and a visual field defect. The third child had epilepsy with normal brain imaging. Other significant medical findings included postnatal macrocephaly in five children and severe myopia and cleft soft palate, each in one child. Nine children (25%) had a history consistent with autistic regression before 3 years of age. Three children (8%) had a positive family history of autism; one of them had a sibling with autism.

Significant medical findings in the nonautistic group included two children with brain abnormalities, one of whom had a subarachnoidal cyst in the temporal area and the other signs of mild posterior periventricular white-matter injury. One child was born prematurely (35 weeks of gestation), and four children in this group had postnatal macrocephaly.

Internal Consistency of the ADI-R and the CARS

Cronbach's alpha was calculated for both instruments. For the ADI-R, only nine (three subgroups and three symptom domains) of 12 coefficients were computed, as one group (nonverbal children older than 4 years of age) only consisted of two cases. For the SI domain, the alpha coefficients ranged from .79 to .85; for the CO domain, from .80 to .83, and for the RB domain, from .35 to .61. The lowest RB coefficient was for verbal children older than 4 years of age, but the highest was for nonverbal children less than 4 years old.

For the CARS, the corrected item-total correlations showed coefficients ranging from .42 to .90 for all items but one (Level and Consistency of Intellectual Response), which had a negative correlation. The alpha coefficient for the 15 items was .94.

Agreement between the Instruments

Significant correlations ($p < .001$, one-tailed test) were found between the CARS total score and the ADI-R domain and total scores: CARS, SI = .81; CARS, CO = .60; CARS, RB = .69; CARS, ADI-R total = .81. The differences between the CARS and the ADI-R domain scores correlations were tested with Steiger's

method of comparing correlation coefficients of the same correlation matrix (Steiger, 1980, as cited in Howell, 1992). The only significant difference [$t(51) = 2.88$, $p < .01$] was between the CARS, SI and CARS, CO correlations. However, this difference disappeared when the data were analyzed separately for groups with different verbal status.

Further results of the agreement between the two instruments are presented according to the classification of autism or nonautism under three conditions defined by different domain thresholds on the ADI-R with the 30+ points definition of the CARS held constant (Table I). The observed agreement between the two instruments increased steadily from the most stringent condition (scores reaching cutoffs in three domains on the ADI-R) to the least stringent condition (scores reaching cutoff on one domain on the ADI-R). The chance-corrected agreement varied accordingly from moderate to almost perfect agreement (Landis & Koch, 1977, as cited in Lilienfeld & Stolley, 1994).

The change from the first to the second condition resulted in increased agreement in the diagnosis of autism between the instruments, whereas the diagnosis of nonautism remained practically constant. One child changed status from nonautism to autism according to the ADI-R (a 33-month-old boy with a language disorder who tested in the normal range and received 25.5 points on the CARS). The change from the second to the third condition still increased the concordance between the two instruments with one additional child who moved to the ADI-R-only group (a 49-month-old boy with a language disorder who tested in the normal range and received 24.5 points on the CARS). The only child left in the CARS-only group under the third condition was a 50-month-old boy who tested in the severely retarded range and who received 32 points on the CARS.

Table I. Agreement between the Autism Diagnostic Interview–Revised (ADI-R) and the Childhood Autism Rating Scale (CARS) in the Diagnosis of Autism According to Different Conditions Defined by the ADI-R (Cutoffs Reached or Exceeded in Three, Two or One Symptom Domains)

ADI-R conditions	CARS ≥ 30	CARS < 30
Condition one[a]		
3 domains	18	0
2, 1, 0 domains	18	18
Condition two[b]		
3, 2 domains	28	1
1, 0 domains	8	17
Condition three[c]		
3, 2, 1 domains	35	2
0 domains	1	16

[a] Observed agreement = 66.7%; Cohen's kappa = .40.
[b] Observed agreement = 83.3%; Cohen's kappa = .66.
[c] Observed agreement = 94.4%; Cohen's kappa = .87.

Comparison between Groups

The groups compared were the ones defined by the first condition described above (i.e., cutoffs reached or exceeded in three domains on the ADI-R) and CARS scores ≥ 30 points. The Pearson chi-square revealed no differences between the groups on verbal versus nonverbal status [$\chi^2(2, N = 54) = 3.15$, $p = .21$] or gender [$\chi^2(2, N = 54) = 2.3$, $p = .32$]. A one-way ANOVA did not reveal a significant difference between groups for age at diagnosis [$F(2,51) = 0.838$, $p = .438$]. Significant differences emerged for IQ/DQ [$F(2,51) = 13.94$, $p < .001$]. The Scheffé post hoc test only revealed a difference in cognitive status between the ADI-R/CARS group on the one hand and the CARS-only and the nonautistic groups on the other (see Table II). No difference emerged between the two latter groups.

For the ADI-R symptom domains (SI, CO, RB) and total scores, the ANOVAs showed significant differences between groups: for SI, $F(2,51) = 30.01$, $p < .001$; CO, $F(2,51) = 34.49$, $p < .001$; RB, $F(2,51) = 38.15$, $p < .001$; and total scores, $F(2,51) = 67.08$, $p < .001$. For further analysis of CO domain scores, the groups were split according to verbal status. For both the verbal and nonverbal subjects, the difference between groups was still significant; that is, verbal $F(2,27) = 33.88$, $p < .001$, and nonverbal $F(2,21) = 32.16$, $p < .001$. Post hoc comparisons revealed progressively less severe autistic symptomatology from the ADI-R/CARS group to the nonautistic group for SI, CO verbal subjects, and total scores. This was not true for CO nonverbal subjects and the RB domain, as significant differences were not found between the CARS-only group and the nonautistic group (see Table III). The one-way ANOVA showed a significant difference between groups for the CARS [$F(2,51) = 62.19$, $p < .001$], and all post hoc comparisons between pairs of groups were significant as well.

ADI-R/CARS Autism versus CARS-Only Autism

Further comparison of the characteristics of the two autistic groups revealed both similarities and differences. The male: female composition of the ADI-R/CARS group showed the characteristic ratio of 3.5:1 usually found in autism, whereas the CARS-only group showed a greater preponderance of boys (17:1).

Table II. Mean Age at Diagnosis and Mean IQ/DQ According to Classification of Autism and Nonautism by the Autism Diagnostic Interview–Revised (ADI-R) or the Childhood Autism Rating Scale (CARS)

	Autism			Nonautism
	ADI-R + CARS ($n = 18$)	ADI-R only ($n = 0$)	CARS only ($n = 18$)	Neither ($n = 18$)
Age (months)				
M	42.72_a	0	44.17_a	49.28_a
SD	15.71	0	9.42	20.70
Range	22–91	0	23–61	25–114
IQ/DQ				
M	49.50_a	0	63.11_b	75.50_b
SD	17.55	0	14.88	11.21
Range	16–87	0	42–83	54–96

Note. Means in a row sharing subscript letters are not significantly different ($p < .05$).

The ADI-R/CARS group contained more nonverbal subjects (61%) than the CARS-only group (33%), although this difference did not reach statistical significance.

In the ADI-R/CARS group, seven (39%) participants reached baseline on the LIPS ($M = 91$; $SD = 17.05$), but in the CARS-only group, 12 (67%) reached this baseline ($M = 100.92$; $SD = 12.62$). The categorical distribution of the number of children who reached baseline on the LIPS revealed no statistical significance [$\chi^2(1, N = 36) = 2{,}786$, $p = .095$].

The difference between the mean IQ/DQ of the two groups is also apparent in their respective IQ/DQ distributions. For the ADI-R/CARS group, this distribution was 50% (<50), 39% (50–69), and 11% (≥70). For the CARS-only group, this distribution was quite different, at 17% (<50), 39% (50–69), and 44% (≥70).

In the CARS-only group, 10 subjects (56%) reached cutoff scores in two ADI-R domains, with the most common combination being SI + CO. Only one subject had another combination (CO + RB).

Table III. Mean Scores and Standard Deviations of Groups Classified as Autistic and Nonautistic on the Basis of the Autism Diagnostic Interview–Revised (ADI-R) Symptom Domains[a] or the Childhood Autism Rating Scale (CARS)

	Autism						Nonautism	
	ADI-R + CARS ($n = 18$)		ADI-R-only ($n = 0$)		CARS-only ($n = 18$)		Neither ($n = 18$)	
Instruments	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
ADI-R/SI	16.44_a	4.22	0		10.61_b	4.88	6.0_c	2.76
ADI-R/CO: verbal[b]	17.0_a	1.63	0		11.42_b	4.29	5.36_c	1.36
ADI-R/CO: nonverbal[b]	11.45_a	2.07	0		7.33_b	1.86	3.71_b	2.06
ADI-R/RB	4.0_a	1.19	0		1.83_b	1.20	0.94_b	0.80
ADI-R/Total	34.05_a	5.56	0		22.50_b	7.54	11.67_c	3.63
CARS/Total	42.69_a	6.60	0		35.30_b	2.71	26.53_c	2.44

Note. Means in a row sharing subscript letters are not significantly different ($p < .05$).

[a] ADI-R Cutoffs: Social Impairment (SI) = 10; Communication (CO) = 7 (nonverbal), Communication (CO) = 8 (verbal); Repetitive Behavior (RB) = 3.

[b] CO verbal status: ADI-R + CARS verbal, $n = 7$; nonverbal, $n = 11$. CARS-only verbal, $n = 12$; nonverbal, $n = 6$; nonautism verbal, $n = 11$; nonverbal, $n = 7$.

DISCUSSION

The sample studied comprised the great majority of children referred for possible autism at the tertiary level of services in Iceland during the time of study. Associated medical conditions were found in 8% of the children diagnosed with autism, compared with 10–15% reported in a recent study as the prevalence of medical conditions with suspected etiological relationship with autism (Barton & Volkmar, 1998).

Significant correlations were found between the ADI-R domains and total score and the CARS total score, which supports the concurrent validity of the two instruments. All the correlation coefficients remained significant when the sample was split according to verbal status (verbal versus nonverbal) or age at diagnosis (<48 versus ≥ 48 months).

As predicted, the CARS classified more cases with autism than the ADI-R when they were compared on the basis of the 30-point cutoff score on the CARS and the requirement of reaching or exceeding cutoffs in the three symptom domains of the ADI-R. The agreement between the instruments increased progressively when the number of thresholds required for diagnosis on the ADI-R was changed from three to two, and then to one. Thus, autism as defined by the three thresholds on the ADI-R seems to be more restrictive than the category of autism as defined by the CARS. This is in line with Lord's (1995, 1997) results comparing the accuracy of the ADI-R and the CARS in a group of children followed from age 2 to age 3 years. In contrast, results from the Pilowsky *et al.* (1998) study of a group with a wider age-range (2–34 years) did not show a clear trend in this respect.

Unfortunately, the results of these two studies are not directly comparable with the results of this one as to the agreement between the instruments. In Lord's (1995) study, the focus was on the stability of diagnosis based on the ADI-R and clinical diagnosis, but not on the agreement of the ADI-R and CARS as such, and the kappa coefficients that could be compared with the present study were not reported. In the Pilowsky *et al.* (1998) study, the observed agreement was 85.7% but the chance-corrected agreement was less acceptable (kappa = .36). Although in the present study the observed agreement was lower, the kappa coefficient was similar. It is difficult to interpret this comparison because of the different age groups of the two samples.

Lord *et al.* (1994) reported alpha coefficients for the three symptom domains of the ADI-R that were higher than those found in the present study. In both studies, the coefficients were lowest for the domain of repetitive and stereotyped behaviors. It has proved problematic to construct a scale tapping repetitive and stereotyped behaviors with equal diagnostic differentiation for severely retarded individuals on the one hand and those that are higher functioning on the other (Berument, Rutter, Lord, Pickles, & Bailey, 1999). This is reflected in the lower alpha coefficients for the RB domain. In the present study, the alpha coefficient was highest for nonverbal children less than 4 years old, but lowest for verbal children older than 4 years of age. In general, stereotyped and repetitive motor mannerisms and sensory abnormalities are more likely to be seen in significantly impaired individuals, but circumscribed interests and verbal rituals are more likely to be seen in higher-functioning individuals (Berument *et al.,* 1999; Waterhouse, Morris, Allen, Dunn, Fein, Feinstein, Rapin, & Wing, 1996). In this study, one item in the RB domain (Circumscribed Interests) was excluded a priori from the statistical analysis because of inconsistent scoring caused by changing criteria during the study period. Omitting an item that covers behaviors that are more likely to be present in higher-functioning individuals may affect the internal consistency of the RB scale in this group.

The internal consistency of the CARS was high and in line with that reported by the authors (Schopler *et al.,* 1988). Only one item (Level and Consistency of Intellectual Response) had a negative corrected item-total correlation. This result parallels findings reported in other studies (Garfin *et al.,* 1988; Nordin *et al.,* 1998).

Post hoc comparisons between the groups revealed lower cognitive abilities in the ADI-R/CARS group than in the CARS-only group and the nonautistic group. Autistic symptomatology was more severe in the ADI-R/CARS group than in the CARS-only group and, in turn, more severe in this latter group than in the nonautistic group (see Table III). The ADI-R/CARS group contained more girls and more nonverbal subjects than the CARS-only group. Although these latter differences were not significant, the total picture is in line with what might be expected in the light of recent research findings, that in moving from the more severe end of the autistic spectrum toward less severe symptomatology, one would expect to find higher levels of intelligence and higher male: female ratios (Bailey, Philips, & Rutter, 1996; Fombonne, 1998; Wing, 1993). In the CARS-only group, 10 subjects reached cutoffs in two ADI-R domains. The most frequent two-domain

combination on the ADI-R was the SI domain and the CO domain. Only one subject had another combination (CO + RB). Similar findings have been reported in other studies (e.g., Pilowsky *et al.,* 1998; Tanguay, Robertson, & Derrick, 1998). This may be seen as support for a certain independence between the RB domain vis-à-vis the SI and the CO domains. Stella, Mundy, and Tuchman (1999) arrived at a parallel conclusion on the basis of the analysis of the factor structure of the CARS.

Not reaching cutoff in the RB domain does not mean, however, that the individual is symptom free in this respect. Of the nine children in the CARS-only group, who reached cutoffs in the SI and CO domains but who had subthreshold scores in the RB domain, seven had a score of two points, and two children had a score of one point. Of those with a score of two points in the RB domain in this group, four were 48–61 months of age. On consulting the ADI-R protocols, only one of these might have scored positive on item 70 (Circumscribed Interests) in the RB domain. If the whole CARS-only group is considered, there were only two children who received a score of zero in the RB symptom domain. Only six children in the nonautistic group were symptom free in this domain according to the ADI-R.

In their study of the stability of a diagnosis of autism between the ages of 20 to 42 months, Cox, Klein, Charman, Baird, Baron-Cohen, Swettenham, Drew, & Wheelwright (1999) reported that symptoms of RB were less frequent at age 20 months than at 42 months, at which age they were reported in most autistic individuals. These researchers studied the effects of adjusting the cutoff scores in the RB domain of the ADI-R from 3 to 2 points. In their study, this increased the number of children correctly classified with autism and PDD at 20 months, but had no effect at 42 months. In the sample of the present study this adjustment increased the observed agreement between the ADI-R and the CARS from 66.7% to 81.2% and the chance-corrected agreement from .40 to .63.

Lord (1995, 1997) suggested an adjustment of the CARS cutoff in very young children from 30 to 32 points, which increased the number of children classified correctly in the sample studied. When a cutoff of 32 points on the CARS was introduced in this study for children younger than 3 years of age, together with the three-threshold definition of autism on the ADI-R, there was no change in the concordance of the two instruments in diagnosing autism. However, it is impossible to draw any definite conclusions regarding this modification because only 13 children (24%) were younger than 3 years of age when they were seen at the SDCC.

A few methodological shortcomings deserve mentioning. First, the clinical sample in this study was small, with a narrow age range, and one should be careful in extrapolating these findings to the use of the instruments with older individuals. However, the narrow age range may be an asset in view of the possibly different constellation of symptoms and differing expression of autistic symptomatology over the lifespan. Second, only one professional conducted all the ADI-Rs, and no inter-rater reliability check was built into the study. We refer, however, to this rater's initial training at the Institute of Psychiatry, where reliability was established with a consensus group. Third, there was no inter-rater reliability check made for the scoring of the CARS, where the same professional was responsible for scoring in the majority of cases.

Given the discrepancy between the two diagnostic instruments, the question may arise: Which is more correct and valid, the CARS or the ADI-R? The data of this study do not allow a definitive answer to this question. The ADI-R quantifies three symptom domains of autism as defined by the ICD-10 and the DSM-IV, with special weight on social impairment, whereas the CARS relies on a unidimensional concept of autism with no weighting of specific symptom domains and one cutoff. Thus, the two instruments establish diagnostic boundaries based on different premises. Our data indicate that the two diagnostic instruments recruit somewhat different groups of autistic subjects, the ADI-R/CARS group having more severe symptomatology and being more intellectually impaired than the CARS-only group. This is in line with the results reported by Waterhouse *et al.* (1996), who came to the conclusion that current diagnostic systems "identify a higher symptom count/lower IQ group as core autism" (p. 80). Whether one diagnostic instrument is closer to a "gold standard" than the other cannot be determined from the present study. The question might, however, be resolved by a study including independent evaluation of "caseness" by experts.

The CARS was designed as an aid in the initial assessment and classification of autism. Studies concur in finding that the CARS has good reliability and validity, even when used by raters who are relatively naïve to autistic spectrum disorders. The results of this study indicate that the CARS represents a broader diagnostic concept of autism than the ADI-R, at least for the age groups studied. This has led us to encourage the use of the CARS in primary and secondary health

care and educational settings in Iceland, where it can be used as a screening tool to facilitate decisions about referral to the tertiary level of services.

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ORIGINAL PAPER

Follow-up of Children Diagnosed with Pervasive Developmental Disorders: Stability and Change During the Preschool Years

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Abstract Forty-one children with pervasive developmental disorders (PDDs) receiving eclectic services were assessed twice during their preschool years. Measures were compared over time for the whole group and for diagnostic subgroups: Childhood autism (CA group) and Other PDDs group. The mean intelligence quotient/developmental quotient (IQ/DQ) of the whole group was stable ($P = 0.209$) and scores on the Childhood Autism Rating Scale (CARS) decreased ($P = 0.001$). At time 2, the CA group was more impaired than the other PDDs group: autistic symptoms were more severe ($P = 0.01$), adaptive behavior scores were lower ($P = 0.014$), and a trend for lower IQ/DQs ($P = 0.06$). Children in this study seemed to fare better than reported in previous follow-up studies on children with autism.

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Introduction

When a child is diagnosed with autism, information on the outcome of this neuro-developmental disorder is of importance to parents as well as clinicians and service providers. Accurate information can be crucial for parents in their effort to come to terms with the diagnosis, to develop effective coping strategies (Howlin, Goode, Hutton, & Rutter, 2004), and to seek appropriate services. The field of autism is undergoing constant development that calls for new data on outcome in autism and other pervasive developmental disorders (PDDs). The changing epidemiology of autism is indicative of the need to revise knowledge regarding outcome. The increase in the prevalence of autism found in recent studies is not confined to milder forms of autistic symptomatology but is apparent for Childhood autism as well as other PDD categories (see Fombonne, 2003; Wing & Potter, 2002; for reviews). There are indications that recently diagnosed cohorts may be less impaired and show a better outcome than cohorts diagnosed previously (Seltzer et al., 2003). More children are now diagnosed with autism at an early age than one to two decades ago (Chakrabarti & Fombonne, 2001; Howlin & Moore, 1997; Magnússon & Saemundsen, 2001). Earlier detection makes earlier intervention possible and practicable, which may improve the overall functioning of children with autism and thus affect their outcome (Dawson & Osterling, 1997; Lord & McGee, 2001, Rogers, 1998; Smith,

1999). If more children with PDDs are diagnosed, and at an earlier age, more information is needed on outcome during the preschool years. The present follow-up study provides data on stability and change in preschool children diagnosed with PDDs according to the ICD-10 classification scheme (World Health Organization [WHO], 1992, 1993).

Several studies have shown that the diagnosis of autism tends to be reliable and stable over time. This applies even though the diagnosis is made at a young age (Cox et al., 1999; Eaves & Ho, 2004; Lord, 1995; Moore & Goodson, 2003; Sigman & Ruskin, 1999; Stone et al., 1999). Expert clinicians are reliable and accurate in differentiating between PDD and non-PDD children using the ICD-10 or DSM-IV criteria (APA, 1994), but differentiating between autism and PDD-NOS or atypical autism remains problematic (Buitelaar, Van der Gaag, Klin, & Volkmar, 1999; Mahoney et al., 1998). Although diagnostic status tends to be stable over time, and impairments extend into adulthood for most people (Howlin et al., 2004), certain behavioral features may change (Cox et al., 1999; Eaves & Ho, 1996; Fecteau, Mottron, Berthiaume & Burack, 2003; Lord, 1995; Moore & Goodson, 2003; Seltzer et al., 2003; Starr, Szatmari, Bryson, & Zwaigenbaum, 2003; Stone et al., 1999). Improvement in cognitive functioning among a subset of children does not seem to affect changes in diagnosis (Sigman & Ruskin, 1999).

In general, cognitive measures have played an important role in predicting outcome in autism, where a combination of intelligence quotient/developmental quotient (IQ/DQ) and language scores has provided the best prediction of later functioning (DeMyer, Hingtgen, & Jackson, 1981; Freeman, Ritvo, Needleman, & Yokota, 1985; Gillberg & Steffenburg, 1987; Lotter, 1978; Venter, Lord, & Schopler, 1992). Reviews of earlier follow-up studies show that cognitive measures are stable over time for children with autism as a group, with the majority scoring in the mentally retarded range (DeMyer et al., 1981; Lotter, 1978). Later follow-up studies of children with autism have confirmed this and also demonstrated that there are changes within the group, both in direction and amount (Eaves & Ho, 1996, 2004; Freeman et al., 1991; Lord & Schopler, 1989a; Sigman & Ruskin, 1999; Venter et al., 1992; Yang, Jong, Hsu, & Chen, 2003).

Stability and predictability of IQ test scores generally increase after children have reached their fifth year of age. Consequently, such scores have to be treated with caution before 5 years of age. However, there is more stability between infant test scores and childhood IQs for children with developmental disabilities than for children without such disabilities (Sattler, 2001).

Studies particularly examining stability and change in preschool age children with autism have demonstrated that cognitive testing of those children older than 4 years of age gives more stable measures compared with the testing of younger children. The greatest changes in IQ/DQ occur when the children are 3 years or younger when initially tested (Freeman et al., 1985; Lord & Schopler, 1988, 1989b). Such changes may be related to developmental level and the tests employed, as well as intervention (Harris & Handleman, 2000; Lord & Schopler, 1989b; Magiati & Howlin, 2001). Children diagnosed with PDDs other than autism are more likely to demonstrate higher cognitive functioning and have milder symptoms than children diagnosed with autism (Baird et al., 2000; Chakrabarti & Fombonne, 2001). There are indications that different diagnostic categories predict different outcomes, and children who, as a group, have milder forms of autism may fare better than those diagnosed with ''core'' autism (Smith, Groen, & Wynn, 2000; Szatmari et al., 2000). To our knowledge, few studies have been published on the outcome of children with ICD-10 PDD diagnoses during the preschool years (Cox et al., 1999; Szatmari et al., 2000).

The purpose of the present study was to describe stability and change of preschool children in Iceland with any ICD-10 PDD diagnosis where services and educational and treatment methods were based on an eclectic approach, and to contribute to the accumulation of data on outcome in autism. Diagnostic subgroups are described with regard to autistic symptoms, verbal status, and standardized measures of cognition and adaptive behavior. We report on the follow-up of children born during a 4-year period (1992–1995) who were diagnosed during preschool age with PDDs and were subsequently evaluated again before starting elementary school between 5 and 6 years of age.

Method

Participants

The source of data was the files of the State Diagnostic and Counseling Center (SDCC) of all children (n = 89) in Iceland born during the years 1992–1995 who were diagnosed with PDD according to the ICD-10 before January 1, 2004. Participants for the present study were selected from this group based on the following criteria: (a) a diagnosis of a PDD according to the ICD-10 diagnostic criteria (WHO, 1992, 1993) during the preschool period, both at the time of the initial diagnosis (time 1), and at follow-up before starting

elementary school around the age of 6 (time 2); (b) a minimum of 1 year between evaluations where eclectic treatment and services were provided; (c) a diagnosis based on the autism diagnostic interview-revised (ADI-R; Lord, Rutter, & Le Couteur, 1994) and a formal observation of behavior with the Childhood Autism Rating Scale (CARS; Schopler, Reichler, & Renner, 1988) at time 1; (d) evaluation with at least one of these diagnostic instruments at time 2; (e) the use of standardized tests at both times to assess cognitive ability.

Forty-one children met these criteria, seven girls and 34 boys (1:4.8). Their mean age at time 1 was 41.43 months (*SD* = 9.06; range 22–59 months) and 69.14 months (*SD* = 4.14; range 61–79 months) at time 2. Of the 48 children who were excluded, one had an incomplete assessment at time 1; two moved abroad shortly after the initial diagnosis; two were not diagnosed with a PDD at time 2; four were participating in an intensive behavioral intervention study and thus receiving more treatment hours and parent and staff training and supervision than was normally provided; and 14 children were referred late in the preschool period and therefore had only one evaluation. Six of these late referrals were clients of the SDCC from early childhood and had received other neuro-developmental diagnoses, but their behavior aroused suspicion of a possible autism spectrum disorder when they came in for their routine reevaluation before starting elementary school. One child moved to Iceland with incomplete diagnostic workup and in one case parents resisted for some time bringing their child for evaluation. The remaining six children who were referred late during their preschool years had a relatively high-cognitive level and had mild or unclear autism spectrum behavioral characteristics. Twenty-five children were not diagnosed with PDD until after the preschool period.

Procedure

The Service System

The SDCC has a legal responsibility in case of suspicion of serious neuro-developmental disorders that are likely to result in a handicap. As such, the institution receives referrals from the whole country. During the study period, children with suspected autism were referred to the SDCC. Referrals came from primary and secondary health care, social, and educational services, from professionals in private practice, and from another tertiary institution for child and adolescent psychiatry. Diagnosis and assessment were carried out by an interdisciplinary team consisting of developmental pediatricians, clinical child psychologists, social workers, speech and language pathologists, occupational therapists, and a special education teacher. The composition of the team varied in each individual case, but always included at least the first three professions mentioned.

At time l, all the children had a physical examination, including a neurological evaluation. A thorough diagnostic work-up was carried out which included a hearing test, auditory evoked potentials, ophthalmologic evaluation, electroencephalogram, neuro-imaging, chromosomal analysis, and blood and urine metabolic studies. The ADI-R and the CARS were administered as well as developmental tests. In all cases the ADI-R was administered to parents by experienced clinicians who had established reliability with a consensus group led by the authors of this instrument. The diagnosis was based on the results of diagnostic instruments and developmental tests combined with medical data and clinical observations from team members. At time 2, the children were seen again by a team of clinicians. The ADI-R was only repeated in ten cases, mostly related to tentative diagnosis at time 1, but otherwise the procedure was largely similar to that taking place at time 1, except that medical tests were seldom repeated. At time 2, however, there was obviously access to a greater amount of information, including all relevant data derived from the initial diagnosis at time 1, plus data on the development of the child between time points, and clinical examination, developmental measures and the application of the CARS at time 2.

Following the diagnostic procedure at time 1, the parents were informed of the results as were the professionals involved, including the preschool staff. Reading material was suggested to the parents and professionals and courses on autism were provided as well as courses and workshops on the education and treatment of children with autism. As a rule, all children who received a PDD diagnosis were offered a comprehensive follow-up assessment before entering elementary school. The exception was if the child had been referred and assessed within ~1 year before starting elementary school, which was the case for some of the children who were excluded from the study.

In general, children in Iceland are eligible for preschool from the age of 1–2 years. The preschool is run at the community level and is not compulsory. Normally the preschool terminates during the summer of the year in which the children become 6 years of age and start elementary school. The legislature has

provided children with handicaps the right to services at the preschool level. Thus, for the great majority of children with autism, the preschool becomes the natural focus of education and treatment, which was the case for all the participants in the present study.

All the participants were assigned an aide or a special educator in the preschool and these aides received counseling from SDCC autism specialists, usually in collaboration with professionals at the local level. The special education and treatment was a combination of one-to-one instruction and participation with an aide in a group setting with typically developing peers. The children received eclectic treatment that was a combination of special educational methods and personal experiences. The special education was to some extent inspired by the Treatment and Education and Related Communication Handicapped Children (TEACCH) approach (Lord, Bristol, & Schopler, 1993), and for some of the younger children in our sample also by the principles of Applied Behavior Analysis (ABA) (Lovaas et al., 1981; Maurice, Green, & Luce, 1996). Quality control was not available on the application of these specialized methods for the children in this study. Some of the children received additional treatments that were individually selected for each child, such as speech and language therapy, physical therapy, pharmacotherapy, and occupational therapy. Respite care in some form became a regular part of additional services at some point during the preschool period for the majority of the families. Data were gathered on the scope, content and intensity of services received by each individual child and his/her family by administering questionnaires to the parents, going through the children's files at the SDCC, as well as progress reports from the preschools.

Diagnostic Classification

For diagnosing PDDs the ICD-10 classification system was used (WHO, 1992, 1993). The ICD-10 divides PDDs into eight subcategories (see Table 1).

In the present study, no child had a diagnosis of Rett's syndrome (F84.2), Other childhood disintegrative disorder (F84.3), or Overactive disorder associated with mental retardation and stereotyped movements (F84.4). The remaining five categories were, however, all used for diagnostic purposes (F84.0, F84.1, F84.5, F84.8, and F84.9). In the ICD-10 there are clear specifications for the diagnosis of Childhood autism (F84.0) and some diagnostic guidelines for Atypical autism (F84.1), Asperger's syndrome (F84.5), and PDD, unspecified (F84.9), but no guidelines for Other PDDs (F84.8). At the SDCC the F84.9 category was used as an undifferentiated PDD category, especially for young children (<3 years) and when the clinical picture was unclear and/or the diagnostic instruments gave conflicting results and criteria for other F84 codes could not be met. Hence, this particular category was mostly reserved for a tentative or suspected diagnosis of PDD. The F84.8 category was used as a residual category when the child's symptoms did not fulfill diagnostic criteria for Childhood autism, Atypical autism or Asperger's syndrome but these symptoms were clearly on the autism spectrum and caused considerable impairment of functioning.

Table 1 ICD-10 diagnostic classification of pervasive developmental disorders, F84

F84.0	Childhood autism
F84.1	Atypical autism
F84.2	Rett's syndrome
F84.3	Other childhood disintegrative disorder
F84.4	Overactive disorder associated with mental retardation and stereotyped movements
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified

Note: The DSM-IV PDD categories Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, and Asperger's Disorder may roughly be considered parallel to the corresponding ICD-10 PDD categories (F84.0, F84.2, F84.3, and F84.5). The DSM-IV PDD-NOS category includes three of the ICD-10 categories (F84.1, F84.8, and F84.9). The ICD-10 F84.4 category does not have any correspondence with the DSM-IV

Measures

Diagnostic Instruments

The ADI-R (Lord et al., 1994) is a standardized, semi-structured investigator-based interview for caregivers of individuals with suspected autism. It provides a diagnostic algorithm for the ICD-10 and the DSM-IV definitions of autism where behavioral symptoms are classified into three domains: qualitative abnormalities in reciprocal social interaction, qualitative abnormalities in communication, and restricted, repetitive and stereotyped patterns of behavior, all with specified cutoffs. For direct assessment of behavior the CARS (Schopler et al., 1988) was used. The CARS consists of 15 items, which are scored on a seven-point scale with all the items contributing equally to one total score. The cutoff for autism

is ≥ 30 points. The interval from 30 to 36.5 points defines mild-moderate autism, and scores of 37–60 define severe autism. There is considerable experience in using these instruments for diagnosing PDDs in Iceland (Magnússon & Saemundsen, 2001; Saemundsen, Magnússon, Smári, & Sigurdardóttir, 2003). The behavior of all but two of the children was evaluated with the CARS at time 1, and all the children at time 2.

Developmental Tests

Cognitive test results were obtained with the Bayley Scales of Infant Development-Second Edition (BSID-II; Bayley, 1993), and the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989). Decisions about which test to use were based on the child's age and developmental level at the time of administration. The majority of the children received the BSID-II at time 1 and the WPPSI-R at time 2 (see Table 2).

US norms were used for the above-mentioned tests, since Icelandic norms were not available at the time of the study. There has been no validation study of the BSID-II in Iceland. A validation study on a previous edition of the WPPSI (Wechsler, 1967) in a group of 70 four-year-old Icelandic children indicated an acceptable reliability of the three total scores (Gudmundsson, Grétarsson, Kristjánsdóttir, & Jónsdóttir, 1993). Another study on the reliability and validity of the Icelandic standardization of the Test of Language Development (TOLD-2P; Símonardóttir, 1996, unpublished data) showed substantial correlation (0.73–0.82) between individual subtests of TOLD-2P and the language part of WPPSI-R in a group of children with developmental disabilities.

For the WPPSI-R, deviation standard scores were obtained and for the BSID-II ratio DQs were used for all children. This was done to obtain comparable measures across children and times since some of them scored below standardization values on the BSID-II and in other cases chronological age exceeded the age specific norms. Also, since all the children receiving the BSID-II at time 2 exceeded the 42 months upper age limit of this test, it was decided not to use the Naglieri extrapolation method (Naglieri, 1981; Robinson & Mervis, 1996) because it would create more problems than it solved by increasing diversity in the data. It may be added that a ratio DQ calculated from the BSID (Bayley, 1969), when the upper age limit is exceeded, is a good predictor of later IQ on the Stanford–Binet test in young children with disabilities (Atkinson, 1990a; Goldstein & Sheaffer, 1988).

Table 2 Number of children evaluated with same or different cognitive tests at times 1 and 2

Tests	*N*
BSID-II–BSID-II[a]	12
WPPSI-R–WPPSI-R[b]	9
BSID-II–WPPSI-R	20
Total	41

[a] The Bayley Scales of Infant Development-Second Edition

[b] The Wechsler Preschool and Primary Scale of Intelligence-Revised

The Vineland Adaptive Behavior Scales, Survey Form (VABS; Sparrow, Balla, & Cicchetti, 1984) were used to assess adaptive behavior in communication, daily living skills, socialization, and motor skills. Information was obtained in interviews with parents at time 2. Results are reported in standard composite scores that are based on US norms.

Classification of Language Abilities

Language abilities were classified into three categories based on the ADI-R definition of overall level of language: (1) fewer than five words total and/or no use of speech on a daily basis; (2) words but no phrases; no functional use of three word phrases in spontaneous, echoed or stereotyped speech, but use of speech on a daily basis with at least five different words in the last month; (3) phrases; functional use of spontaneous, echoed or stereotyped language that, on a daily basis, involves phrases of three words or more that at least sometimes include a verb and is comprehensible to other people. Categories 1 and 2 define non-verbal status, while category 3 defines verbal status. Two specialists, a clinical psychologist and a speech and language pathologist, classified the children's language abilities independently of each other, based on all available information and data in the their files. Their observed agreement was 97.5%.

Data Analysis

At both times 1 and 2 the participants were divided into two diagnostic groups when analyzing measures, i.e., children diagnosed with Childhood autism (F84.0: CA group) and Children diagnosed with other PDDs (F84.1, F84.5, F84.8, F84.9: Other PDDs group). Diagnostic groups (CA and Other PDDs) at time 2 were used as independent variables. The dependent variables at both times were IQ/DQ, verbal status, and CARS total scores, and in addition the ADI-R domain scores at time 1 and VABS total scores at time 2.

Non-parametric statistical tests were used because of the few participants (n = 41) and because the data

were not normally distributed. The Mann–Whitney *U* was used to test differences between the two diagnostic groups. The Wilcoxon matched-pairs signed-ranks test was used to analyze continuity in time (IQ/DQ and CARS). Spearman's rho was used to assess correlation between variables. When calculating chi-square, Fisher's exact test was used. Since age at time1 as well as the period between assessments varied between participants, the need arose to control for these variables. Thus, age at time 1 was used as a covariate for analyses at time 1, and age at time 1 and the period between times 1 and 2 as covariates for analyses at time 2. As the distribution of these dependent variables deviated from normality, a logarithmic transformation was applied before univariate analyses were run.

Results

Of the 41 children with PDDs, seven (17%) had medical conditions with a suspected etiologic relationship with autism based on the categorization used by Barton and Volkmar (1998). One girl had Turner's syndrome and one boy had Soto's syndrome associated with a minor brain malformation (occipital polymicrogyria). One child was microcephalic, one had suffered herpes meningitis in infancy, and three children had epilepsy with normal brain imaging. Six of these seven children were diagnosed with CA. Other significant medical findings included visual defects in two children who both had CA; one had severe myopia and the other severe hyperopia. Five children had postnatal macrocephaly (four of them were diagnosed with CA) and one child in the Other PDDs group was born with a cleft soft palate. Autistic regression, such as temporary loss of words or other skills, was reported in 33.3% of the children in the CA group and 27.3% in the Other PDDs group. The rate of all PDDs for children born during 1992–1995 according to the population registry was 48/10,000 (95% CI, 37.9–58.0).

The mean period of time between times 1 and 2 was 27.71 months (*SD* = 9.47; range 12–50 months). The children attended preschool for an average of 36.56 h per week (*SD* = 6.95; range 20–45), and there was no difference between the CA group ($n = 30$) and the Other PDDs group ($n = 11$), $U = 154.0$, $P = 0.717$. Within the preschool, the children received special education and support for an average 29.37 h per week (*SD* = range 8–45). Children in the CA group received more hours of special education per week ($M = 30.97$, $SD = 9.96$) than the Other PDDs group ($M = 25.0$, $SD = 9.22$), $U = 97.5$, $P = 0.038$. In most cases the intervention was inspired by the TEACCH approach, and in one-fourth of the cases diffuse ideology was reported. In two-thirds of the cases the aide had a professional background, and the same proportion had attended courses on autism and autism education. Some of the children received additional treatments outside the preschool. Respite care ranged from 12 h per month and up to 6 days per month, usually over week-ends. Besides attending service team meetings at the preschool, many of the parents received parental counseling that was mainly provided by private practitioners. Two-thirds of the parents attended special training courses provided by the SDCC on autism education (see Table 3).

All but two of the children diagnosed with PDD at time 1 still had a PDD diagnosis at time 2. These two children (excluded from the study) had cognitive scores in the moderate mental retardation (MR) range that remained stable over time. Of the total group, 13 children (32%) changed diagnostic category at time 2. Most of the changes between times came from the undifferentiated diagnostic category. Over 90% of the children who received a CA diagnosis at time 1 stayed

Table 3 Services received between times 1 and 2 by diagnostic group

	CA[a] $n = 30$	Other PDDs[b] $n = 11$	All $N = 41$ (%)
Preschool			
Counseling by autism specialists	30	11	41 (100)
Aide attended autism courses	23	8	31 (75.6)
Aide had a professional background	23	8	31 (75.6)
Special education per day ≥ 6 h	26	6	32 (78.0)
Educational and treatment methods			
TEACCH inspired	18	5	23 (56.1)
TEACCH and ABA combined	6	1	7 (17.1)
ABA integrated with other methods	1	0	1 (2.4)
No well-defined method for autism	5	5	10 (24.4)
Other treatments in addition to preschool			
Speech and language therapy	18	6	24 (58.5)
Physical therapy	11	2	13 (31.7)
Pharmacotherapy	11	0	11 (26.8)
Occupational therapy	6	1	7 (17.1)
Parents and family			
Lectures and courses on autism	21	5[c]	26[c] (65.0)
Parental counseling	17[d]	3	20[d] (51.3)
Training courses on intervention methods	21[c]	6[c]	27[d] (69.2)
Respite care	23	5	28 (68.3)

[a] *CA* Childhood autism

[b] *Other PDDs* Other pervasive developmental disorders

[c] Data missing for one child

[d] Data missing for two children

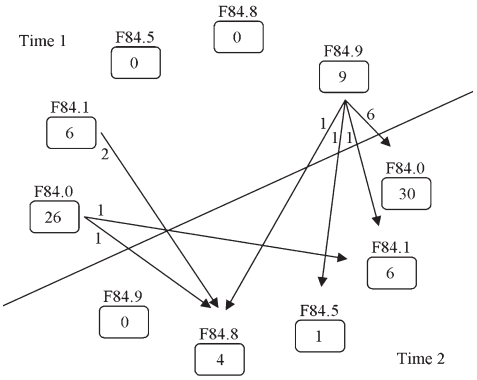

Fig. 1 Changes in ICD-10 diagnostic classification from times 1 to 2 ($n = 41$)

in the same diagnostic category at time 2 (see Fig. 1). Diagnostic stability was similar between the 11 children diagnosed under 3 years of age and the 30 children diagnosed over 3 years of age, $\chi^2(1, n = 41) = 0.151$, $P = 0.719$.

ADI-R results, only available for the whole group at time 1, showed as expected more severity of symptoms for the CA group than the Other PDDs group in one of three symptom domains, SI: $U = 62.5$, $P = 0.002$; CO: $U = 130.5$, $P = 0.306$; RB: $U = 100.5$, $P = 0.051$. According to the CARS scores, autistic symptoms decreased from times 1 to 2 for the total group, $z = 3.21$, $P = 0.001$. The mean paired change ($n = 39$) between times amounted to 2.41 points. There was also a significant change in mean scores for the CA group, $z = 2.48$, $P = 0.013$. Change in mean scores for the Other PDDs group was not significant, $z = 1.64$, $P = 0.101$. In spite of great individual differences over time (± 12.5 points), there was a strong correlation between the CARS measures at times 1 and 2, $r_s = 0.71$, $P < 0.001$. Not surprisingly, the children in the CA group had more severe autistic symptoms on the CARS than children in the Other PDDs group, whether on time 1 ($U = 49.0$, $P = 0.002$) or 2 ($U = 64.5$, $P = 0.003$) as can be seen in Table 4. This difference remained significant when age at time 1 and period between assessments were used as covariates, time 1: $F(1, 36) = 6.42$, $P = 0.016$; time 2: $F(1, 37) = 7.28$, $P = 0.01$.

Mean cognitive performance for the whole group ($N = 41$) was stable ($z = 1.26$, $P = 0.209$) with a strong correlation between measures over time, $r_s = 0.81$, $P < 0.001$. Most stability was seen in the IQ/DQ groups scoring 70 or higher and lower than 35. Most change proportionally over time was apparent in the 35–49 IQ/DQ group, where almost half of the children moved to a lower IQ/DQ range and the other half

Table 4 Comparison of means of children's standardized test scores by diagnostic group and time

	CA ($n = 30$)		Other PDDs ($n = 11$)		Total ($N = 41$)	
	M	*SD*	M	*SD*	M	*SD*
ADI-R[a]						
Social Interaction	14.90	4.88	9.45**	3.21	13.37	5.06
Communication	11.20	3.61	9.82	3.22	10.83	3.53
Repetitive Behavior	2.70	1.53	1.64	1.36	2.41	1.55
CARS[b]						
Time 1	38.83 [c]	6.12	33.20[d]*	1.99	37.39[e]	5.89
Time 2	36.88	7.03	29.64**	4.23	34.94	7.13
IQ/DQ[f]						
Time 1	53.97	18.06	64.27	13.56	56.73	17.43
Time 2	55.53	25.38	75.73	13.66	60.95	24.41
VABS[g]						
ABC	51.24[c]	11.09	61.73*	10.53	54.13[h]	11.80

[a] *ADI-R* Autism Diagnostic Iinterview-Revised (only available at time 1)

[b] *CARS* Childhood Autism Rating Scale

[c] $n = 29$

[d] $n = 10$

[e] $n = 39$

[f] *IQ/DQ* Intelligence quotient/developmental quotient

[g] *VABS/ABC* Vineland Adaptive Behavior Scales/adaptive behavior composite score (only available at time 2)

[h] $n = 40$

* $P < 0.05$

** $P < 0.01$

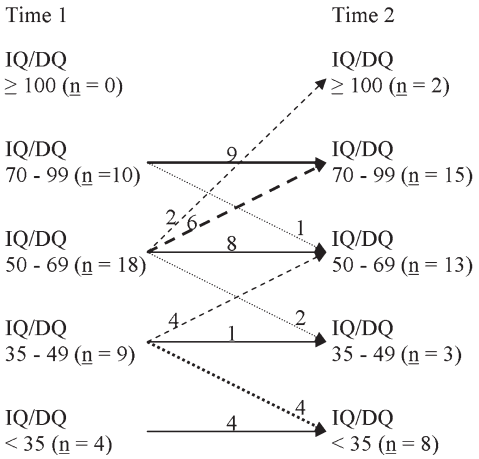

Fig. 2 Stability and change in intelligence quotient/developmental quotient (*IQ/DQ*) from times 1 to 2

moved to a higher IQ/DQ range. Considerable change was also seen in the 50–69 IQ/DQ group over time, where two children scored above 100, six children scored above 70 and two below 50 (see Fig. 2).

At time 1, 24.4% of the whole group was above IQ/DQ of 70 compared with 41.5% at time 2. At time 2, 30% of the CA group had IQ/DQ scores above 70, but 72.7% of the Other PDDs group. No difference was found between the CA group and the Other PDDs group on cognitive measures at time 1 ($U = 111.0$, $P = 0.112$), but at time 2 the Other PDDs group performed better, $U = 85.0$, $P = 0.018$ (see Table 4). However, when age at time 1 and the period between assessments were used as covariates, this difference was not significant, although there was a trend, $F(1, 37) = 3.75$, $P = 0.06$. There was a strong association between cognitive status and autistic symptoms on the CARS, where higher cognitive status and milder symptomatology were interrelated, both at times 1 ($r_s = -0.73$, $P < 0.001$) and 2, $r_s = -0.83$, $P < 0.001$.

Children who were 3 years and younger at time 1 did not show significant gains in IQ/DQ over time compared with children who were older than 3 years at time 1, $U = 126.5$, $P = 0.257$. IQ/DQ scores for children under 3 years at time 1 did not differ from the IQ/DQ scores of children diagnosed over 3 years, at either time 1 ($U = 131.5$, $P = 0.324$) or 2 ($U = 129.0$, $P = 0.289$). Also, no difference was found between the age groups in CARS scores, either at time 1 ($U = 119.0$, $P = 0.274$) or 2 ($U = 113.0$, $P = 0.126$).

There was no relationship between the number of hours in special education per week and change in scores from times 1 to 2, whether in IQ/DQ scores ($n = 41$, $r_s = -0.09$, $P = 0.586$) or CARS scores, $N = 39$, $r_s = 0.06$, $P = 0.726$. When looking specifically at children in the CA group, no relationship was found between the amount of time spent in special education and change in scores from times 1 to 2, in IQ/DQ scores ($n = 30$, $r_s = -0.05$, $P = 0.789$) or CARS scores, $n = 29$, $r_s = 0.14$, $P = 0.482$.

According to the ADI-R definition of verbal status, about half (46.3%) of the total group had phrased speech/were verbal at time 1 while 70.7% had phrased speech at time 2. In the CA group, 11 children had phrased speech at time 1 and 18 at time 2. The corresponding figures for the Other PDDs group were 8 and 11. Comparison between groups at time 2 revealed differences, with 60% of the CA group having phrased speech, while in the Other PDDs group all the children had phrased speech, $\chi^2(1, n = 41) = 6.22$, $P = 0.018$.

Measures of adaptive behavior were available for all but one child at time 2. Children in the CA group ($n = 29$) had, on average, a lower adaptive behavior composite score (ABC) than the Other PDDs group ($n = 11$) on the VABS, $U = 78.5$, $P = 0.014$ (see Table 4). This difference remained significant when age at time 1 and period between assessments were controlled for, $F(1,36) = 5.01$, $P = 0.031$. VABS results for the whole group in the present study were lower than the results of cognitive tests at time 2, $z = 3.09$, $P = 0.002$.

Discussion

All the participants ($N = 41$) in this study attended preschool and received eclectic intervention on the average about 30 h per week. The mean cognitive performance of the whole group was stable but autistic symptoms decreased from times 1 to 2, as measured by the CARS. When the study group was split according to diagnostic groups at time 2, outcome measures at time 2 showed more impairment for the CA group than for the Other PDDs group: autistic symptoms were more severe, ABC scores were lower, and a trend for lower IQ/DQs. At time 2, 30% of the CA group had IQ/DQ scores of ≥ 70 and 60% had phrased speech according to the ADI-R definition, while the respective figures for the Other PDDs group were 73 and 100%.

The great majority of the children diagnosed with CA at time 1 received the same diagnosis at time 2, which reflects the stability of the diagnosis of autism (Cox et al., 1999; Lord, 1995; Moore & Goodson, 2003; Stone et al., 1999). A third of the children changed

diagnostic category between times. Most of the changes may be explained with movement from the undifferentiated category (see Fig. 1). Tentative diagnosis reflected the reality facing clinicians, as sometimes it is difficult to diagnose autism in young children, for instance when they also have a substantial developmental delay and/or a medical condition/syndrome, and/or when the results of diagnostic instruments do not converge (Lord, 1995; Nordin & Gillberg, 1996; Rasmussen, Börjesson, Wentz, & Gillberg, 2001). It has been suggested that in cases of suspected autism no children below 3 years of age should receive other than a tentative PDD diagnosis, which should be reviewed when they are 5–6 years of age (Szatmari, 2003).

On average, CARS scores decreased from times 1 to 2 with a mean change of –2.41 point. Other investigators have reported a drop of three points on the CARS in school-aged children (Eaves & Ho, 1996; Mesibov, Schopler, Schaffer, & Michal, 1989). It has been suggested that such a decrease in scores represents both a statistically and a clinically significant change (Van Bourgondien & Mesibov, 1989). On the other hand, Eaves and Ho (2004) did not replicate this finding in a younger sample of children with autism where the CARS scores remained unchanged between mean ages 2 years 9 months and 4 years 11 months. At first glance, the most plausible explanation of the different results found in the present study and that of Eaves and Ho (2004) is that their study group was more cognitively impaired, allowing for less change between times on a group level.

One way of describing the change in the CARS scores in the present study is to look at the position of mean scores for the diagnostic groups according to the classification of autistic symptom severity. According to the CARS classification of symptom severity, at time 1 the mean score for the CA group classified them as having ''severe autism'' (range 37–60), while the mean score for the Other PDDs group classified them as having ''mild to moderate autism'' (range 30–36.5). At time 2 the respective CARS means classified the CA group at the boundaries of ''severe autism'' and ''mild to moderate autism'', while the Other PDDs group were classified at the boundaries of ''non autistic'' and ''mild to moderate autism''. However, there were great individual differences, reflected by the maximum of a 12.5 point change in either direction. The child who presented with the largest increase in CARS scores (37.5–50) showed a decrease in DQ score on the BSID-II from 47 to 21. The raw score was almost the same at both times, indicating no measurable progress in cognitive development. This child did not show evidence of regression and did not have epilepsy or other known cerebral involvement. Nevertheless, the child had developed severe anxiety and challenging behaviors. The child whose CARS score showed the largest decrease (33.5–21) had an increase in IQ score on the WPPSI-R from 65 to 100. This increase was explained by a gain of 40 points on the verbal scale of the test while the performance IQ score remained virtually unchanged.

There was stability in cognitive measures from times 1 to 2 for the study group as a whole, which is in general what has been reported for children with autism (Eaves & Ho, 1996; Freeman et al., 1985; Lord & Schopler, 1989b; Sigman & Ruskin, 1999; Venter et al., 1992). The stability and change that were observed in the groups which initially had IQ/DQ scores at or above 70 and below 30 were consistent with the results of other studies (Eaves & Ho, 1996; Lord & Schopler, 1989b; Venter et al., 1992). The change in IQ/DQ scores from times 1 to 2 seen in this study exemplifies the need to interpret the initial results of cognitive tests with caution in this age group. For instance, eight children who tested in the mild MR range (50–69) at time 1 scored higher than 70 at time 2, and two of them actually scored above 100. Similarly, five children scoring in the moderate MR range (35–49) at time 1 received scores in the severe to profound MR range (below 35) at time 2. The stability observed in the small group who initially had an IQ/DQ score below 35 offers quite a challenge in terms of education and treatment. A study of the effects of behavioral treatment on preschool children with severe MR and PDDs showed that although intensively treated children achieved clinically meaningful gains and a higher mean IQ than a comparison group receiving minimal treatment, they remained considerably delayed, with the majority still scoring in the severe MR range (Smith, Eikeseth, Klevstrand, & Lovaas, 1997).

As previously stated, the CA group showed the expected rate of MR in autism, i.e., 70% of the children scored below the IQ/DQ limit of 70 at time 2. If, However, all PDD diagnoses are considered, 59% had IQ/DQ scores below 70 at time 2, which is in line with recent epidemiological data on preschool children showing a decrease in the average rate of MR for all PDDs (Baird et al., 2000; Chakrabarti & Fombonne, 2001). Nevertheless, the rate of MR in this clinic-based group was higher than that found in geographically defined multi-stage epidemiological studies.

Previous studies of young children with autism have shown that most changes in IQ/DQ scores over time occur in groups of children who are under 3 years of age when initially tested, as compared to older

children. Change over time in IQ/DQ test scores in very young children has been attributed to several factors, such as the difficulty in testing many of the young children, better test behavior at follow-up related to direct and indirect treatment effects, and the use of different tests at different times (Freeman et al., 1985; Lord & Schopler, 1988, 1989b; Magiati & Howlin, 2001). Our study did not replicate the above findings, since the IQ/DQ scores of children who were under 3 years of age at time 1 were as stable over time as the scores of children who were older. Since there were only 11 children under 3 years of age, comparison with the above-mentioned studies is difficult.

The mean ABC score on the VABS for the CA group in the present study was similar to the weighted mean of mute and verbal children with autism below 10 years of age in the study of Carter et al. (1998) which provides supplementary norms for individuals with autism, i.e., $M = 51.24$ ($SD = 11.09$) and $M = 51.02$ ($SD = 14.68$), respectively. Comparable norms for the Other PDDs group were not available to our knowledge. The Other PDDs group scored higher on the VABS than the CA group at time 2. For both groups, ABC scores were lower than the IQ/DQ scores, a result, which is consistent with several previous studies of children with autism (Eikeseth, Smith, Jahr, & Eldevik, 2002; Freeman et al., 1991; Lord & Schopler, 1988; Venter et al., 1992). Different patterns have also been reported and may be related to age, cognitive status and type of intervention of the groups studied (Eaves & Ho, 2004; Smith et al., 2000; Stone, Ousley, Hepburn, Hogan, & Brown, 1999). For the CA group, this difference did not meet requirements for a significant and real underlying difference between adaptive functioning and intelligence as demonstrated by Atkinson (1990b), but it did for the Other PDDs group. This indicates that despite relatively high IQs, these children may experience difficulties in adaptive functioning in their daily lives. Furthermore, it has been shown that large increases in IQ have only modest effects in increasing social skills and daily living skills for children with autism (Schatz & Hamdan-Allen, 1995). Thus, it is important to measure adaptive skills in the more cognitively able PDD group, as well as to target those skills especially in intervention and training programs.

For our group as a whole ($N = 41$), almost 30% remained non-verbal at time 2, but a different picture emerged when considering subgroups, with 40% of the children in the CA group being non-verbal but none of the children in the Other PDDs group. Previous studies on children with autism have shown that the percentages of non-verbal children have dropped from around 50% (Greenfeld & Lockyer, 1967; Kobayashi, Murata, & Yoshinga, 1992) to 15–30% (Chakrabarti & Fombonne, 2001; Eaves & Ho, 1996; Freeman et al., 1991; Lord & Schopler 1988). Comparison between studies is difficult because of different definitions of non-verbal status, age at the time of study and diagnostic subgroups. We used the ADI-R definition of overall level of language where non-verbal status includes both children who have fewer than five words and children who have words, but no use of three word phrases. Chakrabarti and Fombonne (2001), who used an identical definition, reported that 30% of their group of children with autism and other PDDs had no functional use of language. When subtypes were considered, the same was true for 69% of the children with autism. This high proportion of non-verbal children can possibly be explained by the young age of their study group (mean age 41 months). The corresponding figure for our CA group at time 1 was 63% when their mean age was also 41 months. If we narrow our definition of non-verbal status and only include those children who had fewer than five words, then 23% of the children in the CA group met this criterion at time 2. This is similar to the definition used by Eaves and Ho (1996), who reported that 20% of their study group were non-verbal when their average age was 7 years.

Of the 87 children in the four birth cohorts (1992–1995) in Iceland with a PDD diagnosis on January 1, 2004, 39 were diagnosed late in the preschool period or later (>6 years of age). There are many reasons why children are diagnosed ''early'' or ''late'', some reflecting factors concerning the child, some reflecting family factors, and some reflecting factors in the service system. For instance, the children diagnosed early may be more severely cognitively impaired and/or have more severe autistic symptomatology than the children diagnosed late (Eaves & Ho, 2004). If children have previously received neuro-developmental diagnoses other than PDDs, it may delay the diagnosis of an autism spectrum disorder. The socioeconomic status of parents and geographical location may affect how early children are referred and how early the children are assessed. At this stage, it is a reasonable hypothesis that the group in the present study, which was diagnosed relatively early in the preschool period, may have had more severe symptoms of autism and have been more severely cognitively impaired than those children excluded from the study because of late diagnosis. Comparison of the ''early group'' and the ''late group'' is the subject of a separate study.

The services that the children in the study received have been referred to as eclectic services. This implies

that the intervention methods within the preschool setting were not entirely based on well-defined methods of education or treatment developed for children with autism, but rather on several different approaches and personal experiences of the preschool staff. It was disconcerting to find that time spent in special education in preschool did not affect change in outcome measures. Neither did Eaves and Ho (2004), whose study group also received a wide variety and amount of intervention, find a relationship between time spent in intervention and change in scores (VIQ; PIQ; CARS; ABC). Although quantity, or time spent in intervention, is an important variable in affecting outcome of children with autism and related developmental disorders, this variable alone is not sufficient to produce significant gains. The nature of the treatment and education and its quality is also important in this respect, as well as the characteristics of the children themselves (Howard, Sparkman, Cohen, Green, & Stanislaw, 2005; New York State Department of Health, 1999; Sallows & Graupner, 2005; Smith, 1999). Thus, the importance of offering these children a comprehensive, well-defined and evidence-based program cannot be underestimated. The present results can perhaps be used as a baseline to compare the outcome of well-defined methods of education and treatment for children with PDDs in Iceland in our effort to improve their progress and well-being.

Albeit a small sample, one of the strengths of this study was that it was comprised of 64% of all children born in 1992–1995 who were diagnosed with ICD-10 PDD during the preschool period in a confined geographical area. In addition, many of the parameters used to describe clinical and epidemiological samples seem to add credibility to the sample. Nevertheless, the study was clinic based and as such it has a more limited generalizability than if the sample had been drawn from a larger group as defined by two- or multi-stage surveys of PDDs. Since the follow-up of the study group was based on ongoing services, the children were referred at different ages so that the period between times 1 and 2 was not fixed, although a certain minimum was defined. This may have led to an underestimation of the potential of some of the children who were diagnosed relatively late during the preschool period and received services for only a year before they were reassessed before entry into elementary school. Another limitation of this study is that the clinicians reassessing the children were not blind to their former diagnostic status or to the results of diagnostic instruments and cognitive tests. Hence, the changes described here between times 1 and 2 may have been confounded to some extent by the knowledge of the children's previous development and diagnostic practices. Furthermore, the cognitive tests and the measure of adaptive behavior were not standardized in Iceland, which may limit the comparability of our results to other studies. Data were only available for three measures at both times 1 and 2: IQ measures, the CARS, and verbal status. Information on the child's family, such as socioeconomic status, might have added strength to the study.

In future follow-up studies of preschool children with PDDs, we would suggest that, besides cognitive measures at both times, more comprehensive measures on autism symptomatology be included, such as the ADI-R (Rutter, Le Couteur, & Lord, 2003) and the ADOS (Lord, Rutter, DiLavore, & Risi, 2001), as well as appropriate language tests, measures on adaptive behavior (Sparrow, Cicchetti, & Balla, 2005) and socioemotional functioning (e.g. Achenbach & Rescorla, 2000). Also, given adequate number of participants we would suggest that in the future follow-up of preschool children with PDDs, at least three subgroups should be retained, Childhood autism, Atypical autism, and Asperger's syndrome (Chakrabarti & Fombonne, 2001, 2005).

In sum, children diagnosed with PDDs according to the ICD-10 in this study seemed to fare better as a group regarding IQ/DQ and overall level of language than reported in previous follow-up studies on children with autism. However, our children diagnosed with Childhood autism made more modest gains over time than children diagnosed with other PDDs, and they remained cognitively and behaviorally impaired. It is important to monitor the development of preschool children diagnosed with PDDs. Reassessment at the end of the preschool period may increase the likelihood that individual children will be provided with suitable educational placement. Finally, it would be prudent to take diagnostic subgroups into consideration when predicting outcome and designing and interpreting research on treatment efficacy.

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IV

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Autism Spectrum Disorders in Children With a History of Infantile Spasms: A Population-Based Study

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The objective of this article is to describe autistic spectrum disorders in children diagnosed with infantile spasms in the first year of life. The source of data was the records of all 3 pediatric departments in Iceland. Twenty children born between 1981 and 1998 who had infantile spasms were invited to participate. When appropriate, the parents of these children were asked to complete the Social Communication Questionnaire. Children scoring 10 points or higher on the questionnaire were selected for further examination using the Autism Diagnostic Interview–Revised and either the Autism Diagnostic Observation Schedule or the Childhood Autism Rating Scale. All participants were given appropriate cognitive tests or measures of adaptive behavior. The parents of 17 children (10 boys, 7 girls) agreed to participate in the study. Age at assessment ranged from 5 to 19 years with a mean age of 11 years and 6 months. Fourteen children had at least one neurodevelopmental disorder. Six (6/17), or 35.3%, were diagnosed with autism spectrum disorder (3 boys, 3 girls), five of these had a history of symptomatic infantile spasms, and four were profoundly mentally retarded (IQ/DQ<20). If the diagnosis of autism spectrum disorder was restricted to children with a developmental age of 24 months or more (3 cases), the prevalence was 17.6%. The estimates found in this study exceed the estimated prevalence of autism spectrum disorder in the general population.

Keywords: infantile spasms; autism spectrum disorder

Infantile spasms occur primarily in infants and young toddlers.[1-3] In the great majority of cases, the onset is in the first year of life, with a peak incidence between 3 and 8 months of age.[4] Clinical manifestations are characterized as flexor or extensor spasms. The most common EEG pattern associated with infantile spasms is hypsarrhythmia. Infantile spasms are associated with many prenatal, perinatal, and postnatal factors. When such factors are present, patients are classified as symptomatic. When there is no prior developmental deviance or related factors, the patient is classified as cryptogenic[5] or idiopathic.[6] A distinction between symptomatic and cryptogenic etiology is of importance for outcome studies because the cryptogenic group has a better prognosis.[1,2] The average incidence of infantile spasms is approximately 0.31 per 1000 live births, with higher rates associated with higher geographical latitudes.[1] In a review of 67 studies with an average follow-up period of 31 months, the mortality of infantile spasms cases was 12%, and only 16% of infantile spasms cases had normal development.[1]

Autism is a neurodevelopmental disorder with a strong genetic component, although the genetic mechanisms are not known.[7] Autism spectrum disorder is an umbrella term for life-long developmental disorders of brain function, with autism representing the more severe end of the spectrum.[8] The prevalence of autism and other autism spectrum disorders has been rising since the early 1990s (see Fombonne[9] for a review), and the estimated prevalence of all autism spectrum disorders is now on the order of 0.6% in the youngest age groups with a sex ratio of 4 to 5 boys for every girl.[10,11] Studies in Iceland have shown a similar trend of increased prevalence of autism[12] and other autism spectrum disorders.[13] Numerous medical conditions have a possible etiological relationship with autism,[14,15] including infantile spasms.[16]

The association between infantile spasms and autism was studied in a sample of 192 surviving children, born between 1960 and 1976, who had been examined or treated for infantile spasms in 3 main pediatric hospitals in Helsinki, Finland.[16] A 13-point scale was used in screening for autistic

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symptoms followed by a chart review or clinical examination. Twenty-four children (12.5%) were diagnosed with autism based on Rutter's criteria.[17] A more recent Swedish study showed similar results, reporting 9% with autism (diagnostic criteria not reported) in a cohort of 57 infantile spasms cases.[6] The present study's objective was to describe the association between infantile spasms and autism, in light of evolving definitions of autism, using currently accepted diagnostic instruments.

Method

Patient Population and the Study Group

Twenty-five individuals born in Iceland between 1981 and 1998 were diagnosed with infantile spasms in the first year of life. The case-finding procedures have been described previously.[5] Index cases were identified in 2 ways. Initially, all medical records of children with convulsive disorders at all 3 pediatric departments in Iceland were reviewed to identify children with infantile spasms. Subsequently, staff pediatricians at the 3 hospitals were contacted in an attempt to identify additional cases. All index cases were identified by search of the medical records, and no new cases were added by interviewing pediatricians.[5] Ascertainment bias is considered minimal because infantile spasms is the most common catastrophic epilepsy in childhood[18]; thus, cases of infantile spasms are unlikely to go unnoticed or not to be referred for specialized services.

When data gathering for the present study, which began in 2004, 3 individuals had since died, and 1 lived abroad. Another child died before entering the study. Of the 20 potential participants, 17 agreed to participate (10 boys and 7 girls) in the investigation on autistic behaviors. Age at assessment ranged from 5 to 19 years with a mean age of 11 years and 6 months (standard deviation, 4 years and 5 months).

The 3 children who did not take part in the investigation on autistic behaviors were all classified as cryptogenic (2 boys and 1 girl) and were diagnosed with infantile spasms before 1989.

Measures

Social Communication Questionnaire.[19] This is a screening measure for autistic behaviors developed from the Autism Diagnostic Interview–Revised (see below). It contains 40 items that require yes and no responses from parents. There are 2 versions—a lifetime version and a current version. In the present study, the lifetime version was used, which " . . . is completed with reference to the individual's entire developmental history and produces results that are pertinent to referral for more complete diagnostic workup."[19(p1)] A score of 15 points is the recommended cutoff to distinguish between autism spectrum disorders and other diagnoses.

Autism Diagnostic Interview–Revised.[20] This is a standardized, semistructured, investigator-based interview for caretakers of individuals with suspected autism. For a diagnosis of autism, cutoffs must be reached or exceeded in all 3 symptom domains: (a) impaired social interaction, (b) impaired communication, and (c) stereotyped and repetitive actions, given that abnormality of development is evident at or before 36 months. In this study, the proposed algorithm for the International Classification of Diseases, 10th revision (ICD-10), revised October 1994, was used.

Autism Diagnostic Observation Schedule.[21] This is a semistructured, standardized assessment of social interaction, communication, and repetitive behaviors developed to accompany the Autism Diagnostic Interview–Revised when autism or autism spectrum disorders are suspected. The Autism Diagnostic Observation Schedule consists of 4 modules, which selection depends on the verbal status and age of the individual to be assessed. This instrument provides algorithms and cutoffs both for autism and autism spectrum disorder.

Childhood Autism Rating Scale.[22] This scale was developed as an observational measure and consists of 15 items that are scored on a 7-point scale, where all items contribute equally to a total score. The proposed cutoff for autism is the score of 30 points.

Cognitive tests. Various cognitive tests were used for the participants in this study, including the Bayley Scales of Infant Development, first and second editions,[23,24] the Wechsler Preschool and Primary Scale of Intelligence–Revised,[25] and the Wechsler Intelligence Scale for Children, third edition.[26] The cognitive tests were used to obtain deviation standard score or intelligence quotient (IQ). When chronological age exceeded the age specific norms on the Bayley scales, a ratio developmental quotient (DQ) was calculated as a substitute for IQ.

Vineland Adaptive Behavior Scales–Survey Form.[27] This form is a general assessment of adaptive behavior. It consists of 4 scales or domains that assess information regarding communication skills, daily living skills, socialization, and motor skills. The adaptive behavior composite is a standard score summing up the performance of the above scales. The manual also provides "age equivalents" corresponding to domain raw scores.

Procedure

The parents of all potential participants were contacted by letter, followed by a telephone call, and in this way informed of the study objectives. Those who agreed to participate gave their written informed consent. When deemed appropriate, the parents were given the Social

Communication Questionnaire as an initial test of autistic behaviors. A score of 10 points was chosen as the cutoff in order to minimize the likelihood of missing cases with milder symptomatology and/or high functioning individuals with autism spectrum disorder. In 7 cases, it was considered inappropriate to ask the parents to complete the Social Communication Questionnaire because the children were all nonambulatory with profound mental retardation and 5 had severe cerebral palsy. Instead, these children were seen by one of the authors (E.S.) in their schools, and their current level of adaptive functioning was documented using the Vineland scales in an interview with a special education teacher who knew the child well.

Diagnostic instruments were applied for those reaching or exceeding the cutoff of 10 points on the Social Communication Questionnaire. In 1 case, the diagnosis of autism had already been established by an interdisciplinary team (see below), and in 1 case, the Social Communication Questionnaire was considered inappropriate, but upon school visit, the Childhood Autism Rating Scale was applied, followed by the Autism Diagnostic Interview–Revised. Specialists in autism affiliated with the State Diagnostic and Counseling Center applied the diagnostic instruments in all cases; this tertiary center has been described previously.[12,13] Those applying the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observation Schedule had been trained in their application at sites recognized by the authors of the instruments. Use of the Childhood Autism Rating Scale does not require special training, but there was considerable experience using this instrument.[28] The clinical diagnosis of an autism spectrum disorder was based on ICD-10[29,30] and made by an interdisciplinary team in 2 cases and in 4 cases by one of the authors (E.S.). When such diagnosis was given, the results were presented to the parents and a joint decision made on a written re-referral to the State Diagnostic and Counseling Center, where the new diagnosis was informally reviewed.

The children (n = 14) known at the State Diagnostic and Counseling Center had received various developmental tests at the institution, including cognitive tests when applicable, and this group had been followed to age 5 or 6 years. If recent test results existed, they were not repeated within the study (2 participants). Also, for the purpose of this study, cognitive tests were not repeated for the most severely handicapped children. Instead the Vineland scales were used to estimate their level of functioning, thus confirming their classification as being profoundly mentally retarded (IQ < 20). For these children, the Vineland scales were also used to determine mental age for classification purposes (mental age, < 24 months or ≥24 months). When recent results were available, the Vineland scales were not reapplied (2 participants).

Children were classified as cryptogenic if they had normal neurological and developmental history, normal neurological examination results, no known associated etiological factor, and negative diagnostic evaluation findings. All other cases were classified as symptomatic.[5] Active epilepsy was defined as 1 or more epileptic seizures during 5 years preceding the assessment.[31] The prevalence was calculated as the percentage of cases in the group studied and the exact 95% confidence intervals found assuming binomial distribution.[32]

The study was reported to the Data Protection Authority, and the National Bioethics Committee approved the procedures of the study.

Results

Of the study group (N = 17), 13 children were classified as symptomatic and 4 as cryptogenic. All the symptomatic children had at least 1 neurodevelopmental disorder (other than autism spectrum disorder). Two had relatively mild disorders, 1 with a specific learning disability and another with general developmental delay. Eleven were mentally retarded (IQ < 70), of whom 10 were profoundly mentally retarded (IQ < 20), and of these, 5 had severe forms of cerebral palsy and 6 had active epilepsy (Table 1). Three of the 4 cryptogenic children had IQs above 100 and functioned well educationally.

Altogether, 6 children (6/17) were diagnosed with autism spectrum disorder, or 35.3% (95% confidence interval, 14.2-61.7), 5 were symptomatic, and 1 was cryptogenic. The gender distribution of these children was 3 boys and 3 girls.

The diagnosis of childhood autism was made in 4 cases, and in 2 cases, atypical autism was diagnosed, all but 1 being ambulatory (Table 2). Of the children with autism, 4 were profoundly mentally retarded, 1 had severe mental retardation (IQ of 20 to 34), and 1 was not mentally retarded. In 4 cases the question of autism had been raised at different times during their life, but only 1 had a formal evaluation of autism. The scores of the autistic group on the Social Communication Questionnaire ranged from 13 to 23 points, whereas the cutoff used in the present study was 10 points. Restricting diagnosis of autism spectrum disorder in this study to individuals with a mental age of 24 months or higher leaves 3 applicable cases (patients 3, 9, and 11) with a prevalence of 17.6% (95% confidence interval, 3.8-43.4).

One child who scored above the cutoff of 10 points on the Social Communication Questionnaire did not receive a diagnosis of autism spectrum disorder. This child had dysgenesis of the white matter and was a classic case of severe nonverbal learning disability (verbal IQ, 107; performance IQ, 56).[33] The Autism Diagnostic Interview–Revised picked up some symptoms of social and communication impairment, but the cutoffs were not reached. However, cutoff was reached in the repetitive behavior domain. The same was true for the Autism Diagnostic Observation Schedule, which primarily picked up repetitive behaviors. This child

Table 1. Characteristics of the Study Group[a]

Case No.	Sex	Causal Factors	Classification	Age (Years, Months)	Active Epilepsy	Cerebral Palsy	IQ/DQ	MA ≥24 Months	SCQ Total
1	Boy	Perinatal asphyxia	Sympt	15, 8	Yes	Yes	<20	No	NA
2	Boy	None	Crypt	13, 7	No	No	120	Yes	0
3[a]	Girl	Tuberous sclerosis	Sympt	16, 10	Yes	No	<20	Yes	13
4	Boy	Idiopathic MRI	Sympt	13, 5	No	No	<20	No	NA
5	Boy	Idiopathic MRI	Sympt	19, 0	No	No	<20	No	17
6	Girl	None	Crypt	18, 10	No	No	111	Yes	8
7	Girl	Subdural hemorrhage	Sympt	7, 11	Yes	No	<20	No	NA
8	Boy	Perinatal asphyxia	Sympt	11, 9	No	Yes	<20	No	NA
9	Boy	None	Crypt	13, 0	No	No	77	Yes	14
10	Girl	Prenatal asphyxia	Sympt	12, 5	No	No	78	Yes	13
11	Boy	Down syndrome	Sympt	10, 0	No	No	28	Yes	23
12	Boy	Perinatal asphyxia	Sympt	5, 2	No	No	75	Yes	8
13	Boy	Neonatal seizure	Sympt	7, 8	Yes	Yes	<20	No	NA
14	Girl	Aicardi syndrome	Sympt	9, 8	Yes	Yes	<20	No	NA
15	Girl	Focal seizures	Sympt	7, 8	No	No	<20	No	22
16	Girl	Hypertensive encephalopathy	Sympt	5, 3	Yes	Yes	<20	No	NA
17	Boy	None	Crypt	7, 2	No	No	113	Yes	1

NOTE: MRI = magnetic resonance imaging; Sympt = symptomatic; Crypt = cryptogenic; IQ/DQ = intelligence quotient/developmental quotient; MA = mental age; SCQ = Social Communication Questionnaire; NA = not applied.
a. Six questions were left unanswered for this participant.

Table 2. Results of Diagnostic Instruments and Diagnostic Classification of the Autistic Group

Case No.	Verbal Status	ADI-R			ADOS		CARS Total	ICD-10 Class
		SI	CO	RB	SI	CO		
3	+	21	20	4	NA	NA	34.5	F84.0
5	–	28	14	4	NA	NA	38.5	F84.0
7	–	26	14	4	NA	NA	46	F84.0
9[a]	+	5	7	4	7	2	NA	F84.1
11[b]	–	10	7	2	4	9	NA	F84.1
15[b]	–	15	14	5	12	6	NA	F84.0

NOTE: Verbal status = ADI-R definition of verbal (+) and nonverbal (–); ADI-R = Autism Diagnostic Interview–Revised; SI = social impairment (cutoff = 10); CO = communication (cutoffs: nonverbal = 7 and verbal = 8); RB = repetitive behaviors (cutoff = 3); ADOS = Autism Diagnostic Observation Schedule; CARS = Childhood Autism Rating Scale; ICD-10 classification: F84.0, childhood autism; F84.1, atypical autism; NA = not applied.
a. Received ADOS-3.
b. Received ADOS-1.

was being treated for general anxiety. Two children had a score on the Social Communication Questionnaire that was close (8 points) to the cutoff used in this study. One was an 18-year-old girl with an IQ of 111 who had been classified as cryptogenic. She was doing well educationally but had some social problems due to nonreferred anxiety. The other was a 5-year-old boy who had been classified as symptomatic. He was born prematurely, and magnetic resonance imaging showed changes compatible with periventricular leukomalacia.

Discussion

The results of this study underline the poor prognosis of individuals who have infantile spasms during the first year of life in which 82.4% (14/17) of the study group had a neurodevelopmental disorder and the majority had profound mental retardation. Three of the 4 participants classified as cryptogenic had normal cognitive and educational performance. However, a more thorough neuropsychological assessment might have revealed mild cognitive deficits in these cases as described by Gaily and coworkers.[34] The prevalence of autism spectrum disorder in the present study was 35.3%, but considering the wide 95% confidence interval, we cannot conclude that it is higher than the prevalence of 9% to 12.5% reported in previous studies.[6,16] If only individuals with a mental age of 24 months or higher are included in the present study, the prevalence of autism spectrum disorder is 17.6% with a 95% confidence interval, which includes the figures in the previous studies.[6,16] These 2 previous studies used different definitions of autism, and their

results may not be comparable with those of this study. However, the prevalence found far exceeds the estimate (0.6%) reported in the youngest age groups of the general population.[10,11]

In light of increased risk of autism in individuals with mental retardation, it is important to consider the possibility that the association between infantile spasms and autism simply reflects the severity of cognitive impairment in infantile spasm groups. In a recent study on the prevalence of pervasive developmental disorders according to the DSM-IV-TR in children and adolescents with mental retardation, the figure of 16.7% was suggested as the most reliable and well-founded estimate of pervasive developmental disorders in a large population-based sample.[35] In line with previous research in mentally retarded populations, there was, however, a much higher prevalence (26.1%) of pervasive developmental disorders in individuals with an IQ ≤ 50 than the prevalence (9.3%) for individuals with an IQ of 51 to 70 (based on the DSM-IV-TR IQ classification). When children and adolescents with an IQ < 50 also have active epilepsy, the prevalence of autism spectrum disorders (or pervasive developmental disorders) may increase still.[31] Given how severely impaired our study group was, we would have expected a high frequency of autism spectrum disorder. In fact, 5 of our mentally retarded group (n = 11) were diagnosed with autism. Because of the small size of the sample, it is not possible to conclude whether the frequency of autism represents an increased risk due to infantile spasms alone or whether it reflects the low cognitive status of the group, which in turn is indicative of the seriousness of the underlying neurological condition. Research on autism in tuberous sclerosis complex lends some support to a suggested causal role of infantile spasms in the development of autism.[36]

This study highlights the difficulties clinicians and researchers face in diagnosing autism in severely handicapped individuals. For instance, when an individual has a severe form of cerebral palsy and profound mental retardation, the additional diagnosis of autism may carry little weight regarding intervention or service planning. However, this does not preclude that autism diagnosis in profoundly retarded individuals may be meaningful and useful to parents and professionals. Diagnostic instruments tend to overdiagnose autism in young retarded children,[37] and the same is true for some older individuals who are severely cognitively impaired.[38] In the manual of the Autism Diagnostic Interview–Revised,[39] it is specified that the interview is appropriate if the individual concerned has a mental age above 24 months because " . . . most of the features that are regarded as diagnostic of autism do not clearly manifest until after the age of 2 years."[39(p3)] The ICD-10[29,30] and the DSM-IV[40] classification schemes do not resolve this issue because they do not provide clear guidelines as to the diagnosis of autism in the most impaired population. In light of this uncertainty and the lack of consensus in diagnosing autism in individuals with profound mental retardation and/or with mental ages below 24 months, it seems important to report the level of mental age of participants in research involving autism spectrum disorder.

Some limitations of this study must be mentioned. From the outset, it was clear that it would be difficult to apply the same methods across all participants because the group had a large age range and contained neurologically intact children, as well as children with severe forms of cerebral palsy, profound mental retardation, some with weak or no response to visual and/or auditory stimuli, and some receiving all food through gastrointestinal tubes. The Social Communication Questionnaire was chosen as an initial test for autism because it was available in the Icelandic language in the context of other research, not because it had been carefully selected from among other theoretically available tests for this purpose. During the study, it was not possible to apply the diagnostic instruments in such a way that the clinical specialists involved were blind to the results of other diagnostic instruments.

In conclusion, this study is population-based, and the autism diagnoses are founded on well-documented diagnostic instruments and clinical judgment. The results show a high prevalence of autism spectrum disorder among children with infantile spasms, and this disorder is ascertained after the children had catastrophic epilepsy in their first year of life. It is not known whether infantile spasms may be contributing to this disorder of the developing brain or whether these conditions have common etiology. The results indicate that at least all ambulatory children with previous symptomatic infantile spasms should be clinically investigated or assessed for the possible development of ASD. The implication for research is that autism spectrum disorder should be reported in relation to mental age, and the cutoff of 24 months is suggested. Further studies should penetrate the association of epilepsy with autism.

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Autism Spectrum Disorders in Children with Seizures in the First Year of Life—A Population-based Study

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Summary: *Purpose:* To describe autistic spectrum disorders (ASDs) in a cohort of children with history of unprovoked seizures other than infantile spasms in the first year of life.

Methods: The source of data was computer records from all the three pediatric departments in Iceland. Children diagnosed 1982–2000 with unprovoked seizures with onset between 28 days and 12 months of age (N = 102) were invited to participate in a study. Children with known developmental disorders and those whose parents had concerns regarding their child's development or behavior were investigated for possible ASD. Parents were asked to complete the Social Communication Questionnaire and children scoring 10 points or higher were further examined with the Autism Diagnostic Interview-Revised and observational measures.

Results: Eighty-four children (82.4%), 28 boys and 56 girls, participated in the study and 36.9% (31/84) were investigated for possible ASD. Twenty-four (28.6%) had at least one neurodevelopmental disorder, 14.3% had mental retardation (MR), and six (7.1%) were diagnosed with ASD, all of whom also had MR and three of whom had congenital brain abnormalities.

Conclusion: These results suggest that the estimated prevalence of ASD is higher in children with history of seizure in the first year of life than it is in the general population. There are indications that support the view that children with ASD and history of seizure in the first year of life have higher prevalence of congenital brain abnormalities and are more often female, than other children with ASD. **Key Words:** Epilepsy in infancy—Autism spectrum disorder—Social Communication Questionnaire—Autism Diagnostic Interview-Revised.

A high frequency of seizure disorder was an important factor in demonstrating that autism had a neurobiological etiology (Barton and Volkmar, 1998). According to one review (Tuchman and Rapin, 2002), the data on reported frequency of epilepsy in autism ranges widely (5%–38.3%). Schain and Yannet (1960) were probably first to provide data that supports this association; in their study, 21 of 50 severely impaired autistic participants had a history of one or more seizures. Of those, 10 had their seizure onset in the first year of life, and three were diagnosed with infantile spasms. In a more recent study of 246 children with autism spectrum disorder (ASD), the majority of those who also had epilepsy (13 of 16) had their seizure onset in the first year of life, and four had infantile spasms (Wong, 1993). Further evidence indicates a peak incidence of seizures in early childhood in individuals with ASD (Olsson et al., 1988; Volkmar and Nelson, 1990; Steffenburg et al., 2003; Danielsson et al., 2005).

Studies on the prevalence of ASD in children with epilepsy are scarce (Steffenburg et al., 1996, 2003; Clarke et al., 2005). Steffenburg and colleagues (2003) studied children aged 6–13 years (N = 90; 47 males, 43 females) with mental retardation (MR) and active epilepsy. This group was severely impaired; over 60% had an IQ <50 (Steffenburg et al., 1996). Diagnosis was standardized with multiple sources of information, including clinical examination, semistructured interviews, and behavioral checklists. The prevalence of ASD in their study was 38% (20 males, 14 females). Of ASD cases, 35% had onset of epilepsy in the first year of life. Clarke and colleagues (2005) looked for ASD in a group of children with epilepsy aged 2–18 years (N = 97; 59 males, 38 females) who were followed in a tertiary care epilepsy clinic. Assessment of probable ASD was done by having parents respond to the Autism Screening Questionnaire (Berument et al., 1999). Thirty-one children (32%) scored 15 points or above, the recommended cutoff indicative of ASD, but only nine had a previous diagnosis of ASD. Diagnostic assessment was

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not part of the study design and the cognitive level of the participants was not known.

Infantile spasms constitute a significant minority of unprovoked seizures and epilepsy with onset in the first year of life (Hrachovy and Frost, 2003; Olafsson et al., 2005). Infantile spasms are in several studies found to be associated with autistic behaviors (Riikonen and Amnell, 1981; Sidenvall and Eeg-Olofsson, 1995; Askalan et al., 2003; Saemundsen et al., in press), and the most recent one was done in the same population as the present study (Saemundsen et al., in press). Unprovoked seizures with onset in the first year of life, excluding infantile spasms, consist of various epileptic syndromes, classified as generalized or partial, with or without secondary generalization (Cavazutti et al., 1984; Kramer et al., 1997). It is unknown whether such seizures with onset in the first year of life present a risk for developing ASD.

Thus we considered it of interest to study the prevalence of ASDs in a population-based group of children with unprovoked seizures (excluding infantile spasm) with onset in the first year of life, using diagnostic instruments and appropriate cognitive tests.

METHODS

The present study is a part of a larger research project on the outcome of children who had seizures in the first year of life during the period between January 1, 1982 and December 31, 2000. The primary source of data was computer and paper hospital records from the Landspitali University Hospital and the Landakotsspitali, both in Reykjavík, and the Regional Hospital in Akureyri, which were the only pediatric inpatient facilities in the country during the study period.

Inclusion criteria were at least one unprovoked seizure during the age range between 28 days and 12 months (based on gestational age). Included in the study group were all cases with a convincing description of an epileptic seizure by an eyewitness, or a description of a seizure in the presence of other supportive evidence, i.e., epileptiform changes on EEG, CNS infection, stroke, or other cerebral pathologies known to be related to seizures, or a family history of seizures in the first year of life in a first-degree relative. Febrile seizures and infantile spasms were excluded. Altogether 357 children were found in the hospital records to have discharge diagnoses of convulsions, seizures, or fits in the first year of life (International Classification of Diseases-Ninth Revision (ICD-9) no. 345.0–345.9 and 780.3; International Classification of Diseases-Tenth Revision (ICD-10) no. G40.0–G40.9, G41.0–41.9, and R56.8). After a careful chart review, 102 were considered to have had unprovoked seizures fulfilling the criteria of the study. The other 255 either had febrile seizures, other nonepileptic fits, or infantile spasms. The parents of 84 children (82.4%) agreed to participate in the ASD study.

In a telephone interview, parents were asked several questions regarding the child's seizures, development, and behavior. Children with a known neurodevelopmental disorder or parental concern regarding developmental skills or behavior were contacted again by mail, followed by a telephone call, and asked to participate in a further study on autistic behaviors. As an initial test of autistic behaviors, parents were asked to complete the Social Communication Questionnaire (SCQ) (Rutter et al., 2003a), except in the cases of severely handicapped children.

The SCQ, previously named Autism Screening Questionnaire (ASQ) (Berument et al., 1999), is a screening measure for autistic behaviors developed from the ADI-R (see below). It contains 40 items that require yes or no responses from parents. There are two versions, a lifetime version and current version. In the present study, the lifetime version was used, which ". . .is completed with reference to the individual's entire developmental history and produces results that are pertinent to referral for more complete diagnostic workup" (Rutter et al., 2003a, p. 1). A score of 15 points on the SCQ is the recommended cutoff to distinguish between ASDs and other diagnoses. However, in order to minimize the possibility of missing ASD in cases with milder sympomatology or in high functioning individuals, a score of 10 points was chosen as cutoff in this study. Diagnostic instruments were applied when behavioral scores reached or exceeded this cutoff.

The Autism Diagnostic Interview-Revised (ADI-R) (Lord et al., 1994) is a standardized, semistructured, investigator-based interview for caregivers of individuals with suspected autism. For a diagnosis of autism, abnormality in development has to be evident at or before 36 months and the cutoff must be reached or exceeded in all three symptom domains: (a) impaired social interaction, (b) impaired communication, and (c) stereotyped and repetitive actions. In this study, the proposed ADI-R algorithm for ICD-10, revised October 1994, was used. The Autism Diagnostic Observational Schedule (ADOS) (Lord et al., 2001) is a semistructured, standardized assessment of social interaction, communication, and repetitive behaviors, developed to accompany the ADI-R when autism or ASDs are suspected. ADOS provides algorithms and cutoffs for both autism and ASD. It consists of four modules, the selection of which depends on the verbal status and age of the individual to be assessed. The psychologists administering ADI-R and ADOS had been trained in their application at sites recognized by the authors of the instruments. The Childhood Autism Rating Scale (CARS) (Schopler et al., 1988) was also used for rating autistic behaviors. CARS was developed as an observational measure and consists of 15 items that are scored on a seven-point scale, with all items equally weighted in the total score. The proposed cutoff score for autism is 30 points.

All the participants investigated for ASD were also assessed with an appropriate cognitive test. Various tests were used, including the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) (Wechsler, 1989), the Wechsler Intelligence Scale for Children-Third Edition (WISC-III) (Wechsler, 1992), and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997). The cognitive tests were used to obtain deviation standard score or intelligence quotients (IQ), i.e., verbal IQ, performance IQ, and full scale IQ. If the child had been recently or repeatedly tested, those test results were accepted as valid and not repeated for the purpose of the study. In the case of severe handicap ($n = 4$), the Vineland Adaptive Behavior Scales-Survey Form (VABS) (Sparrow et al., 1984) was used to estimate the level of cognitive functioning. The VABS is a general assessment of adaptive behavior. It consists of four scales or domains that assess information regarding communication skills, daily living skills, socialization, and motor skills as well as a standard score, the adaptive behavior composite, which sums up the performance in the four domains. The VABS manual also provides "age equivalents" corresponding to domain raw scores.

ASD is an umbrella term for life-long developmental disorders of brain function with autism representing the more severe end of the spectrum (Tuchman and Rapin, 2002). This term was deemed more suitable for the purpose of the present study than the more encompassing term pervasive developmental disorder, which includes Rett's syndrome and other childhood disintegrative disorders. Otherwise, the ICD-10 (World Health Organization, 1992, 1993) was used for classification, except in the case of attention-deficit hyperactivity disorder (ADHD). The subclassification of mental retardation based on measured IQ was as follows: mild 50–69, moderate 35–49, severe 20–34, and profound below 20. Epilepsy was defined as recurrent episodes of unprovoked, paroxysmal seizure activity (Cowan, 2002). Active epilepsy was defined as seizure within 5 years or still on antiepileptic medication. Children were classified cryptogenic if they had normal neurological and developmental history, normal neurological examination, no known associated etiological factor, and negative diagnostic evaluation. All other cases were classified as symptomatic. All diagnoses presented in this study are subsumed under the term "neurodevelopmental disorder" (NDD), which is used for genetic or acquired developmental disorders affecting the nervous system at the time of rapid development and causing various forms of neurological dysfunction.

Age at assessment ranged from 4 to 20 years with a mean age of 11 years and 1 month (standard deviation 6 years and 1 month). The clinical diagnosis of a major NDD was made by an interdisciplinary team at a tertiary center specialized in developmental disabilities. Other NDDs were diagnosed by pediatricians and psychologists. All diagnoses were reviewed for the purpose of the study. Prevalence was calculated as the percentage of cases in the studied group and the exact 95% confidence intervals were found assuming binomial distribution (Armitage and Berry, 1991). Pearson chi-square was used for categorical data and Fisher's exact test when a cell had an expected count of less than five. For the calculation of sensitivity and specificity of the SCQ, the Wilson's method was used (Altman, 2003). For the Wechsler IQ data, a one-sample *t*-test was used to test the deviance from the mean of 100, and the Wilcoxon test for comparing paired verbal and performance measures, because the dispersion of test scores was not of normal distribution.

All the parents gave their written informed consent, as did the older and more able children. The study was approved by the Data Protection Authority and the National Bioethics Committee in Iceland.

RESULTS

One hundred two children (42 boys and 60 girls) had experienced at least one unprovoked seizure in the first year of life during the period under study. Of those, consent was given for 84 children (82.4%), composed of 28 boys and 56 girls. The gender proportion is similar among the participants as among the total sample of children with seizure in the first year of life. Seventy-two participants (85.7%) had had more than one seizure. Fifty-three children were without parental concern regarding development or behavior and 31 had parental concern and were investigated for possible ASD (Fig. 1). Twenty-four children, or 28.6% (24/84), had at least one NDD: MR 14.3%; cerebral palsy (CP) 8.3% (6.0% dual diagnosis MR and CP); ADHD 6.0%; disorders of scholastic skills 3.6%; and receptive language disorder 2.4% (Table 1). More boys than girls had NDD (32.1% vs. 26.8%), although the difference was not statistically significant ($p = 0.608$).

Of the 31 children (12 boys and 19 girls) who were investigated for possible ASD, all but two (cases no. 8 and 20) had more than one seizure. Seventy-one percent (22/31) of these children were classified as cryptogenic. Twenty-nine parents answered the SCQ, but in two cases the parents were not asked to complete the SCQ because the children had severe CP and profound MR. Twelve children scored at or above the cutoff of 10 points on the SCQ. The SCQ was incompletely filled out by the parent of case no. 2 but this child was included in the diagnostic stage because, in conversation with the parent, it was clear that the child would have scored above the cutoff. Hence, 13 children were examined further for ASD. One was tested with ADOS without being further considered suspect of ASD. All the others received ADI-R ($n = 12$) and ADOS ($n = 10$), and/or CARS ($n = 5$) testing.

Six (6/84) children including four girls and two boys or 7.1% (95% confidence interval 2.7–14.9) were diagnosed

TABLE 1. *Characteristics of the 31 children investigated for possible ASD*

Case No.	Gender	Associated causal factors	Classification	Neurodevelopmental disorder	SCQ Total	Verbal IQ	Perform IQ
1	F	No	Crypt	No	8	86	99
2	M	No	Crypt	Aut, MR	8	50	55
3	F	No	Crypt	RLD	13	71	94
4	M	No	Crypt	RLD	7	63	96
5	M	No	Crypt	No	1	111	101
6	F	Cong. toxopl.	Sympt	Aut, MR	24	58	– [c]
7	F	No	Crypt	No	23	108	121
8	F	No	Crypt	SRD	4	– [a]	106
9	M	No	Crypt	No	4	109	113
10	F	No	Crypt	No	5	111	105
11	F	CVD	Sympt	CP	2	100	116
12	F	No	Crypt	No	1	117	113
13	M	No	Crypt	No	9	108	92
14	F	No	Crypt	MR	5	64	74
15	F	No	Crypt	ADHD	16	82	75
16	F	Trisomy 21	Sympt	Aut, MR	19	<20	<20
17	M	No	Crypt	SRD	15	104	115
18	M	No	Crypt	SRD	5	116	103
19	F	No	Crypt	ADHD	6	98	119
20	F	Septicemia	Sympt	CP	5	74	77
21	F	Cerebral cyst	Sympt	CP, MR	Na	<20 [b]	<20
22	F	Cerebral cyst	Sympt	Aut, CP, MR	19	52	45
23	M	No	Crypt	Aut, MR	26	68	72
24	F	No	Crypt	Aut, MR	24	<20 [b]	<20
25	F	Cort. dysplasia	Sympt	CP, MR	1	82	62
26	M	Sturge-Weber	Sympt	CP, MR	10	50	47
27	M	Lissencephaly	Sympt	CP, MR	Na	<20 [b]	<20
28	M	No	Crypt	MR	4	74	63
29	F	No	Crypt	ADHD	14	89	88
30	F	No	Crypt	MDSS	4	88	85
31	M	No	Crypt	ADHD	12	90	101

F, female; M, male; Cong. toxopl., congenital toxoplasmosis; CVD, cerebral vascular disease; Cort. dysplasia, cortical dysplasia; Crypt, cryptogenic; Sympt, symptomatic; Aut, autism; MR, mental retardation; RLD, receptive language disorder; SRD, specific reading disorder; CP, cerebral palsy; ADHD, attention-deficit hyperactivity disorder; MDSS, mixed disorder of scholastic skills; Na, not applied.

[a] Missing.

[b] With mental age below 24 months.

[c] Blind.

with ASD, according to ICD-10 (Table 2). All were mentally retarded: two had mild MR, two had moderate MR, and two had profound MR. Three of the children with ASD had congenital brain abnormalities: one had a porencephalic cyst, malformation of the cerebellum, and spastic hemiplegia; one had congenital toxoplasmosis and blindness; and one had trisomy 21. Cases no. 2, 6, and 16 received their ASD diagnosis within the study, but cases no. 22, 23, and 24 had been diagnosed previously. In view of the principles of use in the ADI-R manual that the interview is appropriate for individuals of mental age above 24 months (Rutter et al., 2003b), one of the children (case no. 24) should be excluded. With this restriction, the prevalence of ASD becomes 6.0% (95% confidence interval 2.0–13.4).

The number of seizures in the first year of life (1 vs. >1) did not seem to be associated with ASD ($p = 0.587$). At the time of follow-up 14 children had active epilepsy and of the six children with ASD, three had active epilepsy. Twenty-one children were known to have benign infantile familial convulsions and none of these had ASD. Electroencephalogram (EEG) was performed at least once in 77 children (91.7%), either at the time of the first seizure or later. Of these, 12 (15.6%) were abnormal. Of the children later diagnosed with ASD, five had EEG, four of which were abnormal (generalized epileptiform: 1; focal epileptiform: 2; epileptiform but unknown if focal or generalized: 1). Of the non-ASD children, 72 had EEG, eight of which were abnormal (nonspecific slowing: 1; generalized epileptiform: 1; focal epileptiform: 6).

Of the 13 children examined for ASD, seven did not receive an ASD diagnosis. Their SCQ scores ranged from 10 to 23. The lower cutoff score of 10 points on the SCQ applied in this study did not give additional cases of ASD. The child with the lowest SCQ score had CP and MR. The child with the highest score on the SCQ was the only child in this group who exceeded the cutoff without neurodevelopmental diagnosis. Developmental history and the family background were complicated and this child had subclinical attention deficit, a history of difficulties learning to read, and perfectionist tendencies. Of the children with intermediate scores on the SCQ (12–16 points), three had

TABLE 2. *Results of diagnostic instruments and diagnostic classification for the participants who were clinically examined for ASD*

Case no.	Verbal status	ADI-R			ADOS		CARS total	ICD-10 class
		SI	CO	RB	SI	CO		
2[a]	+	11	8	4	6	2	Na	F84.1
6[a]	+	10	7	2	7	2	Na	F84.1
16	–	11	12	4	Na	Na	30.5	F84.0
22[b]	+	21	10	4	6	4	34.5	F84.0
23	+	13	15	7	Na	Na	35	F84.0
24	–	22	14	4	Na	Na	46	F84.0
3[a]	+	1	2	0	4	2	Na	Not-aut
7[a]	+	3	1	0	0	0	Na	Not-aut
15[a]	+	6	8	1	4	1	Na	Not-aut
17[c]	+	0	0	2	0	0	Na	Not-aut
26[b]	–	9	8	1	4	0	31	Not-aut
29[a]	+	Na	Na	Na	1	0	Na	Not-aut
31[c]	+	2	0	1	0	1	Na	Not-aut

Verbal status, verbal (+) or nonverbal (–) according to ADI-R definition; ADI-R, Autism Diagnostic Interview-Revised; SI, social impairment (cutoff = 10); CO, communication (cutoffs nonverbal = 7, and verbal = 8); RB, repetitive behaviors (cutoff = 3); ADOS, Autism Diagnostic Observation Schedule; CARS, Childhood Autism Rating Scale; Na, not applied; ICD-10 classification: F84.0, childhood autism, F84.1, atypical autism; Not-aut = not autism.

[a]Cases no. 2, 3, 6, 7, 15, 29 received ADOS-module 3.

[b]Cases no. 22, 26 received ADOS-module 1.

[c]Cases no. 17, 31 received ADOS-module 4.

ADHD, one had a receptive language disorder, and one had a specific reading disorder. Counting the case with an incomplete SCQ as negative and using the cutoff of 10 points on the SCQ resulted in seven false positives with sensitivity of 0.83 and specificity of 0.70. Using the recommended cutoff of 15 points resulted in unchanged sensitivity but higher specificity of 0.87.

Scores for those tested with the Wechsler intelligence tests (27/31) deviated significantly from 100 in the negative direction for both the verbal (mean = 85.50; p = 0.002) and the performance (mean = 89.88; p = 0.031) scales. No difference was found between mean verbal and mean performance scores in either direction for the group as a whole (p = 0.396). The same was true for the children (18/31) who tested in the normal range (≥70) and had a mean full scale IQ of 98.28 (p = 0.191).

DISCUSSION

To our knowledge, this is the first population-based study on ASD in children who had unprovoked seizures with onset in the first year of life, other than infantile spasms. The prevalence of ASDs found in this group was 6.0%–7.1%, depending on the inclusion of one participant with mental age below 24 months (Rutter et al., 2003b). The lower 95% confidence limits for both figures (2.0 and 2.7) exceed the estimated 0.6%–1% prevalence of ASDs in the general population (Chakrabarti and Fombonne, 2005; Baird et al., 2006). Our results are not directly comparable with the study of Steffenburg and colleagues (2003), since all their participants were mentally retarded and had active epilepsy, but only 14.3% of the children in the present study had MR. Neither are the results of Clarke and colleagues (2005) comparable with our results, since diagnostic assessment and cognitive measures were not part of their study design.

In the present study, all of the children with ASD were mentally retarded and had previously received the diagnosis of epilepsy. Three had congenital brain abnormalities, and three were without known associated neurological factors. It is interesting to note that previously, the prevalence of associated medical conditions with known or suspected etiologic relationship with autism has been estimated at 10%–15% (Barton and Volkmar, 1998; Kielinen et al., 2004). Hence, children who have epilepsy in the first year of life and who later develop ASD may constitute a subgroup with higher frequency of congenital brain abnormalities than reported for the group of other children with ASD (Olsson et al., 1988).

A recent review of prevalence surveys of autism found that the mean gender ratio was more than four males to every female (Fombonne, 2003). Conversely, the autistic group of the present study comprised two boys and four girls, which reflects the gender ratio of all participants and those investigated further for possible ASD. Thus, the

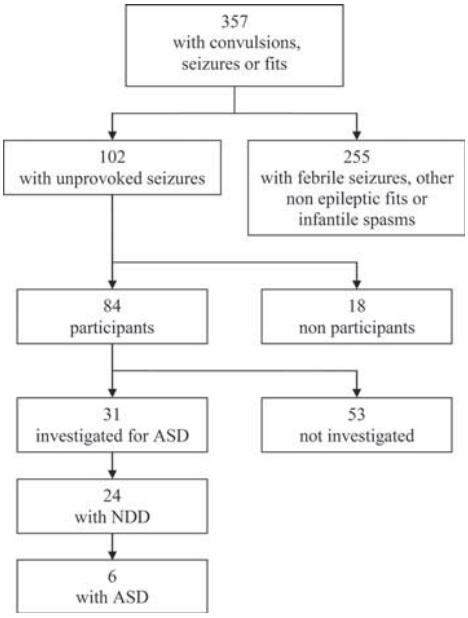

FIG. 1. Overview of the number of participants with neurodevelopmental disorder (NDD) and the number of participants with autism spectrum disorder (ASD).

gender ratio of the autistic group in the present study may be regarded as additional evidence supporting the view that children with ASD who had epilepsy in the first year of life may differ as a group from other children with ASD. Other studies have concluded that severe cognitive impairment and ASD are associated with epilepsy and the female gender (Tuchman et al., 1991; Elia et al., 1995; Danielsson et al., 2005).

A notable portion of children diagnosed with ASD and having a history of epilepsy did have their seizure onset in the first year of life (Wong, 1993; Steffenburg et al., 2003; Danielsson et al., 2005). This is not unexpected, as the age-specific incidence of epilepsy in childhood is highest during a child's first year (Tsuboi, 1988; Hauser et al., 1993; Sidenvall et al., 1993; Camfield et al., 1996; Olafsson et al., 2005). Epilepsy with onset in the first year of life is more often considered symptomatic than epilepsy with onset later in childhood (Czochańska et al., 1994; Kramer et al., 1997; Kramer, 1999; Datta and Wirrell, 2000). If symptomatic seizures in the first year of life are associated with MR (Cavazzutti et al., 1984, Kramer et al., 1997) and MR is associated with ASD (Nordin and Gillberg, 1996; Fombonne, 2003; de Bildt et al., 2005), it follows that there is an association between symptomatic seizures in the first year of life and ASDs (Olsson et al., 1988; Askalan et al., 2003; Pavone et al., 2004).

The association between epilepsy, MR, and ASD is complicated and the existence of a common causal factor or factors is of course a possibility (Elia et al., 1995; Steffenburg et al., 2003; Pavone et al., 2004). However, since the epilepsy is often found prior to diagnosis of ASD and MR, as is the case in present study, the temporal requirement for possible causation is met, and thus the influence of seizures themselves on the developing brain seems likely (Tuchman and Rapin, 1997; Asano et al., 2001; Clarke et al., 2005).

This study does have limitations. First, although the material is population based only children with known NDD or parental concern received the SCQ as an initial test of autistic behaviors. A stronger design would have been to give the SCQ to all those willing to participate ($N = 84$), and then take a random sample from the group that scored below the cutoff for diagnostic assessment, in view of possible adjustment of the prevalence found. Second, it was not possible to keep the professionals who were engaged in the diagnostic process blind to the results of the SCQ or other sources of information.

The study has five principal strengths. First, the data on seizure cases was collected prior to the diagnosis of ASD and independently of it, which minimizes the possibility of case-ascertainment bias. Second, the use of data from the comprehensive health care system in Iceland to identify children with seizures in the first year of life through a 19-year period ensured the inclusion of seizure cases and the recognition of epilepsy cases. Third, the systematic use of SCQ as the initial step in the search for autistic behaviors helped in the ascertainment of ASD cases. Fourth, the diagnosis of ASD was based on current diagnostic instruments, which take age into consideration, and clinical judgment, by trained and experienced professionals, ensuring reliable diagnosis. Fifth, the systematic use of ICD-10 minimizes misclassification of the NDD diagnoses.

In conclusion, the results of the present study suggest that the estimated prevalence of ASD in children with a history of seizure in the first year of life exceeds that of the general population. All the children with ASD had MR and epilepsy. There are indications that support the view that children with ASD and history of seizure in the first year of life have higher prevalence of congenital brain abnormalities and are more often female, than other children with ASD. The clinical implication is that a history of seizures in the first year of life should alert health care service providers to the possibility of accompanying NDD, which should generally become apparent during the preschool years if not already detected, and if MR is a concomitant feature of the seizures, the possibility of ASD should be evoked. Further research on the association between seizures in the first year of life and the risk of developing ASD should be investigated according to different types of epilepsy.

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VI

Risk of autism spectrum disorders after infantile spasms: a population-based study nested in a cohort with seizures in the first year of life

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Key words: Epilepsy in infancy; infantile spasms; symptomatic seizures; autism spectrum disorders

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Summary: *Purpose:* No population-based study has investigated the risk of autism spectrum disorders (ASDs) in children after unprovoked seizures with onset in the first year of life. Our objective was to determine whether infantile spasms were related to risk of ASD as compared to unprovoked seizures with onset in the first year of life after adjusting for symptomatic origin of seizures.

Methods: This is a population-based case-control study nested in a cohort of children with seizures in the first year of life. The cohort comprised 95 children, 34 boys and 61 girls. Cases were defined as children with ASD and exposure was a history of infantile spasms. The Mantel-Haenszel test and logistic regression were used to calculate the odds ratio (OR) and 95% confidence intervals (CI).

Results: The crude OR for ASD risk among cases and controls was 5.53 (95% CI 1.25-23.06) for children with infantile spasms as compared to other children. Stratification on age and gender did not change the OR. The OR for ASD associated with infantile spasms adjusted for symptomatic seizures was 1.55 (95% CI 0.33-7.37), while the OR for ASD associated with symptomatic seizures adjusted for infantile spasms was 8.73 (95% CI 1.88-40.54). Restriction to mental age 24 months or higher yielded higher ORs.

Discussion: Infantile spasms predicted high risk for ASD, but this was to a large extent explained by the association of ASD with symptomatic origin of seizures.

Key words: Epilepsy in infancy; infantile spasms; symptomatic seizures; autism spectrum disorders

Introduction

A recent review cited a number of studies that found increased rates of epilepsy (5% to 38.3%) in individuals with autism and autism spectrum disorders (ASDs) (Tuchman & Rapin, 2002). It is well documented that in some cases seizures are present prior to the diagnosis of ASD (Olsson et al., 1988; Wong, 1993; Steffenburg et al., 2003; Danielsson et al., 2005). This sequence is particularly evident in infantile spasms, since their onset is during the first year of life in 94% of cases (Hrachovy & Frost, 2003), but ASD is rarely diagnosed until after 2 years of age.

Population-based studies on infantile spasms that have reported on the prevalence of ASDs show a considerable range in their results (9% to 35%) (Riikonen & Amnell, 1981; Sidenvall & Eeg-Olofsson, 1995; Saemundsen et al., 2007a). A recent population-based study on the association between seizures in the first year of life (other than infantile spasms) and ASDs reported a relatively high prevalence of ASD (7%) (Saemundsen et al., 2007b). According to the above-mentioned studies, the prevalence of ASDs among both children with infantile spasms and those with other unprovoked seizures in the first year of life seems to exceed the prevalence of ASDs in the general population, which ranges from 0.5% to 1% in recent studies (Chakrabarti & Fombonne, 2005; Baird et al., 2006; Fombonne et al., 2006; Ellefsen et al., 2007; Jonsdottir et al., 2007).

Infantile spasms may indicate a more serious encephalopathy leading to more severe cognitive impairment than other seizures in the first year of life, and thus increasing the risk of ASD, since intellectual disability (ID) and ASDs are closely related (de Bildt et al., 2005). However, children with cryptogenic origin of infantile spasms have a better outcome in general than those with symptomatic origin (Hrachovy & Frost, 2003). This inevitably generates the hypothesis that it is the

etiology of early seizures that is associated with ASD, not the seizure type as such (Olsson et al., 1988; Askalan et al., 2003).

Previous electroencephalography (EEG) studies have suggested that the risk of autism and ASD in children with infantile spasms is increased when there is a history of epileptiform temporal lobe focus, both in case series with mixed etiologies and among cases with tuberous sclerosis complex (Riikonen & Amnell, 1981; Bolton et al., 2002).

Our objective was to determine whether infantile spasms were related to risk of ASD as compared to unprovoked seizures with onset in the first year of life, after adjusting for symptomatic origin of seizures.

Methods

This is a population-based case-control study nested in a cohort of children with unprovoked seizures in the first year of life. It is based on two studies of Icelandic children, one on children with infantile spasms in the first year of life detected during the period 1981-1998 and the other on children with unprovoked seizures in the first year of life, other than infantile spasms, detected during the period 1982-2000. As the definitions of the groups and the estimation of the prevalence of ASDs have been reported previously (Saemundsen et al., 2007a; Saemundsen et al., 2007b), a brief summary will be given. The cohort in the present study is based on the overlapping period in both groups, from 1 January 1982 to 31 December 1998. Altogether 121 children made up this cohort, 25 children having a history of infantile spasms in the first year of life and 96 children having had other unprovoked seizures with onset in the first year. Of these, five had died and one lived abroad. The parents of the remaining 115 children were invited into a study of possible ASDs, of which 95

(82.6%) children participated, 34 boys and 61 girls. A girl with unprovoked seizures during the first year of life was discovered after the publication of these studies (Saemundsen et al., 2007a; Saemundsen et al., 2007b). She was included in the present study, and later found to be with ASD.

All the parents gave their written informed consent, as did the older and more able children. The study was approved by the Data Protection Authority and the National Bioethics Committee in Iceland.

As an initial test of autistic behaviors, the Social Communication Questionnaire (SCQ) (Rutter et al., 2003a) was used for all children with a known neurodevelopmental disorder or parental concern about the development or behavior of the child. The diagnostic instruments consisted of the Autism Diagnostic Interview-Revised (Lord et al., 1994), the Autism Diagnostic Observation Schedule (Lord et al., 2001), and the Childhood Autism Rating Scale (Schopler et al., 1988). For a diagnosis of autism, autistic behaviors must be present to a certain degree in three symptom domains: a) impaired social interaction, b) impaired communication, and c) stereotyped and/or repetitive behavior. In addition, abnormality in development has to be evident at or before 36 months according to the International Classification of Diseases-Tenth Revision (ICD-10) (WHO, 1993).

Epilepsy was defined as recurrent episodes of unprovoked, paroxysmal seizure activity (Cowan, 2002). Seizures were classified as non-symptomatic (cryptogenic) if the children had normal neurological and developmental history, normal neurological examination, no known associated etiological factor, and negative diagnostic evaluation. All other cases were classified as symptomatic (Ludvigsson et al., 1994). Electroencephalogram (EEG) was not performed systematically; however, 89 children out of 95 had EEG and of these, 28 were considered abnormal. We looked at the type

of EEG pattern recorded during the first year of life and classified the EEG tracings as ever epileptiform right temporal focus, and ever epileptiform left temporal focus.

Statistical analysis

The incidence estimate of unprovoked seizures in the first year of life was based on data from Statistics Iceland using the official population on 31 December of each year of the inclusion period of the cohort 1982 to 1998 (Statistics Iceland, 2007). Total person years of observation were 74,043. Incidence per 100,000 was calculated and 95% confidence intervals (CI) were found assuming Poisson distribution (Armitage & Berry, 1991).

History of infantile spasms, the exposure variable, was compared for cases and controls stratified separately on age (born 1990 and earlier, or later) and gender, using the method of Mantel-Haenszel. If the expected values were less than five, the Fisher exact test was used to calculate 95% CI and this was completed in Epi-Info 6. A multivariate case-control analysis was performed using a logistic regression analysis. The adjusted odds ratio (OR) and exact computation of 95% CI were calculated using the SPIDA software package (Gebski et al., 1992). Infantile spasms versus seizures other than infantile spasms were treated as a dichotomous variable. Year of birth was treated as a continuous variable expressed in years and gender as a dichotomous variable. The classification of seizures into symptomatic and non-symptomatic (cryptogenic) was treated as a dichotomous variable. A restriction was applied to cases and controls with mental age 24 months or higher, as the diagnosis of autism based on the ADI-R is of constrained validity in individuals with mental age less than 24 months (Rutter et al., 2003b).

Results

Altogether over the 17-year inclusion period, 121 children had unprovoked seizures, regardless of type, during the first year of life. The incidence of all unprovoked seizures in the first year of life was 163.4 per 100,000 person years (95% CI 135.6-195.3).

Among the participants of this study (N=95), 17 or 17.9% had infantile spasms, and 78 or 82.1% had other types of seizures. The majority of the children had epilepsy (more than one unprovoked seizure) or 87.4%. Most of the seizures were classified as non-symptomatic (76.8%). Females outnumbered males by 1.8 to one. One-fourth (24/95) of the sample had ID. Thirteen children, eight females and five males, (13.7%; CI 7.5-22.3) had ASD, either childhood autism (ICD-10: F84.0) or atypical autism (ICD-10: F84.1). Six of the children with ASD had infantile spasms, and seven had other types of epilepsy (Table 1). All but one of the children with ASD had ID and six had profound ID (intellectual quotient < 20). The distribution of the EEG classification is also shown in Table 1.

The crude OR for ASD associated with infantile spasms was 5.53 (95% CI 1.25-23.06). The Mantel-Haenszel OR for ASD associated with infantile spasms was 5.52 (95% CI 1.24-22.30) stratified on year of birth (born 1990 and earlier or later), and 5.88 (95% CI 1.26-27.02) stratified on gender. The OR for ASD associated with infantile spasms adjusted for year of birth and gender was 5.81, (95% CI 1.52-22.25), so the differences between crude, stratified, and adjusted estimates were minor. Thus, age and gender were not adjusted for in the remainder of the regression analysis.

The OR for ASD associated with infantile spasms in the regression analysis, unadjusted, was 5.53, (95% CI 1.57-19.54). The OR for ASD associated with

symptomatic origin of seizures in the regression analysis, unadjusted, was 10.93 (95% CI 2.95-40.53).

Table 2 shows the adjusted OR taking into account whether the seizures were of symptomatic origin. The OR was 1.55 (95% CI 0.33-7.37) for children with infantile spasms compared to those without infantile spasms, adjusted for symptomatic origin of seizures. The OR was 8.73 (95% CI 1.88-40.54) for children with symptomatic origin of seizures compared to those with non-symptomatic seizures, adjusted for infantile spasms.

Table 3 shows the results after restriction to cases and controls with mental age 24 months or higher. The OR was 2.59 (95% CI 0.34-19.96) for children with infantile spasms compared to those without infantile spasm, adjusted for symptomatic origin of seizures. The OR was 18.00 (95% CI 3.33-97.29) for children with symptomatic origin of seizures compared to those with non-symptomatic seizures, adjusted for infantile spasms.

Excluding from the calculations the girl who was discovered later, the crude OR for ASD associated with infantile spasms was 6.45 (95% CI 1.41-28.49). The exclusion of this case did not materially affect the estimates of the ORs or the confidence limits in the other analyses.

Discussion

The incidence of all unprovoked seizures of 163.4 per 100,000 person years in the first year of life was somewhat higher than the estimate reported in a prospective study in the population with the same geographical definition but a different time frame, where the incidence was 130.2 per 100,000 person years (95% CI 77.1-205.7) (Olafsson et al., 2005). The similarity of these incidence estimates, found with

different surveillance methods, supports the view that our cohort reflects the status in the population.

Our calculations show a significant association between seizures of symptomatic origin and risk of ASD adjusted for whether the seizures were infantile spasms or not. The OR was high and the 95% confidence intervals did not include unity. The association between infantile spasms and risk of ASD adjusted for symptomatic seizures was not statistically significant, although the ORs were 1.55 or higher in the analyses. The observed association is supported by evidence from other studies (Bolton et al., 2002; Askalan et al., 2003), suggesting a causal association of ASD with neuropathological phenomena rather than the seizures themselves. The results are also in agreement with a recent study on children with active epilepsy and ID, where no difference in the distribution of infantile spasms was found between groups with or without ASDs (Steffenburg et al., 2003).

The restriction in this study to those with mental age 24 months or higher was made to increase the diagnostic accuracy of ASD. After the restriction, the ORs for symptomatic seizures and infantile spasms were higher, further strengthening the association between ASD and symptomatic origin of seizures and infantile spasms.

All the cases had epilepsy, so in this study it was not possible to evaluate the role of epilepsy in association with ASD. As EEG is clinically indicated in epilepsy, and the EEG pattern is often found abnormal in epilepsy, introducing EEG tracings into the multivariate analysis would automatically invite circular reasoning.

The primary information through a 17-year period on children with seizures in the first year of life, including the seizure type (i.e. whether infantile spasms or not, and whether symptomatic or not), as well as the EEG tracings, was obtained from the comprehensive health care system in Iceland, ensuring the inclusion of seizure cases

and the recognition of epilepsy cases. Through a cross-sectional study with an 83% participation rate, the SCQ was systematically used as the initial step in the search for autistic behaviors. Ascertainment and diagnosis of ASD, according to ICD-10, were based on current diagnostic instruments and clinical judgment by trained and experienced professionals, ensuring reliable diagnosis and diminishing the risk of misclassification of cases and controls (Saemundsen et al., 2007a; Saemundsen et al., 2007b). The use of the comprehensive population register in Iceland enabled us to ascertain the vital and emigration status, and the addresses of the children in the study. The data on the exposure variable in this study, i.e. whether the seizures were infantile spasms or not and whether the seizures were symptomatic or not, were obtained from the medical records of the cases and the controls. The medical records were noted before and unrelated to the formulating of the hypothesis of the present study and diagnosing of the cases, which eliminates the possibility of recall bias concerning the exposure variable.

The present study has some limitations. First, although the material is population-based, only children with known neurodevelopmental disorders or parental concern regarding developmental skills or behavior of the child received the SCQ as an initial test of autistic behaviors. A more thorough approach would be to test the whole cohort with the SCQ. Second, it was not possible to keep the professionals who were engaged in the diagnostic process blind to the results of the SCQ or other sources of information. Third, there was no formal reliability check between the different professionals who applied the diagnostic instruments, although all of them had undergone proper training in their use (Saemundsen et al., 2007b).

To our knowledge, this is the first population-based case-control study of ASD among children with seizures in the first year of life, adjusted for whether

symptomatic in origin or not. Our results indicate that seizures of symptomatic origin may be a causative factor in ASD. We cannot conclude on the possible role of infantile spasms in the etiology of ASD, as in this study, infantile spasms were not an independent risk factor for ASD.

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Disclosure of Conflicts of Interest

The authors have nothing to declare.

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Table 1. Characteristics of cases and controls

	Cases n = 13 (%)	Controls n = 82 (%)
Infantile spasms	6 (46.2)	11 (13.4)
Symptomatic seizures	9 (69.2)	14 (17.1)
Epilepsy (> 1 seizure)	13 (100)	70 (85.4)
Males	5 (38.5)	29 (35.4)
Born 1990 or earlier	6 (46.2)	36 (43.9)
Mental age < 24 months	4 (30.8)	8 (9.8)
EEG recorded	12 (92.3)	77 (93.9)
Abnormal EEG	11 (91.7) [a]	17 (22.1) [a]
Epileptiform, right TL [b]	1 (8.3) [a]	3 (3.9) [a]
Epileptiform, left TL [b]	4 (33.3) [a]	4 (5.2) [a]

[a)] Percentages of those with EEG

[b)] TL= temporal lobe

Table 2. Adjusted odds ratios and 95% confidence intervals (CI) from logistic regression of autism risk among cases and controls according to infantile spasms and symptomatic origin of seizures

	Cases n = 13	Controls n = 82	Odds ratio[a]	95% CI
Not infantile spasms	7	71	1	Reference
Infantile spasms	6	11	1.55	0.33-7.37
Non-symptomatic seizures	4	68	1	Reference
Symptomatic seizures	9	14	8.73	1.88-40.54

[a] Data have been calculated in unique multivariate analysis, taking into account simultaneously all the variables.

Table 3. Adjusted odds ratios and 95% confidence intervals (CI) from logistic regression of autism risk among cases and controls according to infantile spasms and symptomatic origin of seizures after restriction to individuals with mental age at or above 24 months

	Cases n = 9	Controls n = 74	Odds ratio[a]	95% CI
Non-infantile spasms	6	69	1	Reference
Infantile spasms	3	5	2.59	0.33-19.96
Non-symptomatic seizures	3	68	1	Reference
Symptomatic seizures	6	6	18.00	3.33-97.29

[a] Data have been calculated in unique multivariate analysis, taking into account simultaneously all the variables.