



Autoimmune Encephalitis

**A comparison of patients with anti-GAD and anti-NMDAR
antibodies**

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**Thesis for the degree of Bachelor of Science
University of Iceland
Faculty of Medicine
School of Health Science**



HÁSKÓLI ÍSLANDS

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Abstract

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Introduction: Autoimmune encephalitis (AIE) comprises a group of disorders characterized by rapidly progressive short-term memory deficits, psychiatric symptoms and/or epileptic seizures. They are generally considered to be caused by immunological mechanisms, including autoantibodies directed against different neuronal antigens. The clinical presentation, effect of treatment and long-term outcome of these patients is variable and may differ between antibody groups. Results from recent studies indicate that early diagnosis and treatment may result in better recovery. In this study we compare AIE patients with anti-glutamic acid decarboxylase (GAD) antibodies and patients with anti-N-methyl-D-aspartate receptor (NMDAR) antibodies.

Materials and Methods: Three follow-up periods were established; onset, a baseline visit and 12 months from the baseline visit. Onset was defined as the date of onset of symptoms and the associated hospital visit and baseline visit as the closest date of return for each patient (median: 86 days after onset, range: 4-435). Clinical data and lab results were collected retrospectively for these periods. Scores on the Karnofsky performance scale and the modified Rankin scale as well as ability to work were used to assess a patient's state and recovery. Fisher's exact test was performed with JMP for associations and Mann-Whitney U test was used to compare median values with RStudio.

Results: Out of 41 AIE patients treated at Sahlgrenska University Hospital, five had anti-GAD antibodies, three had anti-NMDAR antibodies and one had both. These patients were subsequently classified into three groups, for comparison. The median age at disease onset was 38 years (range: 18-65), 78% were female (n=7). No patient was correctly diagnosed with AIE or given appropriate treatment measures at onset, making all of them return for the baseline visit. At that time, both groups had more severe symptoms and anti-NMDAR patients were more likely to have personality changes than patients with anti-GAD antibodies (p=0,0179). There were non-significant trends for anti-GAD patients to have AIE related abnormalities on brain magnetic resonance imaging (p=0,1964) and to respond better to immunosuppressive treatment (IST) (p=0,1964) compared to anti-NMDAR patients.

Conclusions: The results of this study indicate that anti-GAD patients might respond better to IST than patients with anti-NMDAR encephalitis, as opposed to earlier published findings. However, our patient group was very small and data was collected retrospectively. Therefore, this investigation should be repeated prospectively, in a larger patient group, over a longer period of time. The way our results differ from earlier findings, as well as the fact that none of these patients got correctly diagnosed at onset, emphasises the need for further research of these different groups of AIE.

Ágrip

Heilabólga af völdum sjálfsofnæmis

Samanburður á sjúklingum með anti-GAD og anti-NMDAR mótefni

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Inngangur: Heilabólga af völdum sjálfsofnæmis (AIE) er fjölbreyttur hópur sjúkdóma sem einkennist af hraðversnandi nærminnstruflunum, geðrænum einkennum og/eða flogum. Þeir eru taldir geta orsakast af breytingum á ónæmiskerfinu, einna helst með myndun fjölda sjálfsmótefna gegn mótefnavökum í taugavef. Hvernig klínísk birtingarmynd sjúklinganna er, hvernig þeir svara meðferð og hversu vel þeim farnast er misjafnt og getur það tengst því hvaða mótefni á í hlut. Nýlega birtar greinar gefa til kynna að snemm greining og viðeigandi meðferð geti bætt batahorfur. Í þessari rannsókn berum við saman tvo undirhópa AIE sjúklinga, þá með anti-glutamic acid decarboxylasa (GAD) mótefni og þá með anti-N-methyl-D-aspartate viðtaka (NMDAR) mótefni.

Efni og aðferðir: Þrjú uppvinnslutímabil voru ákveðin; upphaf, grunnheimsókn og 12 mánaða eftirfylgni frá grunnheimsókninni. Upphaf var skilgreint sem upphaf einkenna og tilheyrandi sjúkrahúsheimsókn og grunnheimsóknin var fyrsta endurkoma hvers sjúklings á spítala (miðgildi: 86 dögum eftir upphaf, spönn: 4-435). Klínískum gögnum og rannsóknarniðurstöðum var safnað með afturvirkum hætti fyrir þessi tímabil. Stigun á mælikvarða Karnofskys fyrir getu og á breytta Rankin mælikvarðanum sem og færni einstaklinganna til vinnu voru notuð til að meta ástand sjúklings og bata. Fisher's exact próf var notað fyrir samanburð á tengslum milli hópanna tveggja með forritinu JMP en miðgildi voru borin saman með Mann-Whitney U prófi með RStudio.

Niðurstöður: Af 41 sjúklingi með AIE sem hefur fengið meðferð á Sahlgrenska Háskólasjúkrahúsinu voru fimm með anti-GAD mótefni, þrír með anti-NMDAR mótefni og einn sjúklingur með bæði. Þeim var í kjölfarið skipt í þrjá mismunandi hópa. Miðgildi aldurs sjúklinganna við upphaf var 38 ár (spönn: 18-65), 78% voru konur (n=7). Enginn sjúklinganna var greindur með AIE eða fékk viðeigandi meðferð við upphaf, sem olli því að allir komu aftur í það sem var kallað grunnheimsókn. Á þeim tímapunkti voru báðir hóparnir með alvarlegri einkennum. Anti-NMDAR sjúklingarnir voru líklegri til að vera með persónuleikabreytingar heldur en sjúklingar með anti-GAD mótefni (p=0,0179). Tilhneiging, þó ómarktæk, sást til að anti-GAD sjúklingarnir væru frekar með AIE tengda afbrigðileika á segulómun á heila sem og að þeir svöruðu ónæmisbælandi meðferð betur en sjúklingar með anti-NMDAR mótefni.

Ályktun: Niðurstöður þessarar rannsóknar gefa til kynna að anti-GAD sjúklingar gætu svarað ónæmisbælandi meðferð betur heldur en sjúklingar með anti-NMDAR mótefni, þvert á niðurstöður annarra rannsókna. Þó skal því haldið til haga að sjúklingahópurinn í þessari rannsókn hafi verið lítil og gögnunum safnað með afturvirkum hætti. Þessa rannsókn ætti að endurtaka með framvirkum hætti, fyrir stærri sjúklingahóp og yfir lengri tíma. Munurinn á þessum niðurstöðum og niðurstöðum annarra rannsókna sem og að enginn þessara sjúklinga hafi fengið rétta greiningu við upphaf, endurspeglar mikilvægi þess að halda áfram að rannsaka þessa mismunandi sjúklingahópa AIE.

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Abbreviations

AIE	Autoimmune Encephalitis
ANS	Autoimmune Neurological Symptoms
Anti-GAD	Anti-Glutamic Acid Decarboxylase Antibodies
Anti-NMDAR	Anti-N-Methyl-D-Aspartate Receptor Antibodies
BBB	Blood-Brain Barrier
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DPP	Double-Positive Patient
ELISA	Enzyme-Linked Immunosorbent Assay
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
GABA	Gamma-Aminobutyric Acid
GAD	Glutamic Acid Decarboxylase
GFAP	Glial Fibrillary Acidic Protein
GG	Anti-GAD Patient Group
ICA	Islet Cell Cytoplasmic Antibodies
IDDM	Insulin-Dependent Diabetes Mellitus
IgG	Immunoglobulin G
IST	Immunosuppressive Treatment
IVIG	Intravenous Immunoglobulin
KPS	Karnofsky Performance Scale
LE	Limbic Encephalitis
LP	Lumbar Puncture
MoCA	The Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
MRS	The Modified Rankin Scale
NFL	Neurofilament Light Chain
NG	Anti-NMDAR Patient Group
NSAS	Neuronal Surface Antibody Syndromes
PNS	Paraneoplastic Neurological Syndromes
PET	Positron Emission Tomography
PLEX	Plasma Exchange
SCLC	Small-Cell Lung Carcinoma
SE	Status Epilepticus
SUH	Sahlgrenska University Hospital
TIA	Transient Ischemic Attack
T2-FLAIR	T2-Weighted Fluid-Attenuated Inversion Recovery
T-tau	Total Tau Protein
US	Ultrasound

1 Introduction

1.1 Autoimmune Encephalitis

Autoimmune encephalitis (AIE) comprises a group of disorders generally considered to be caused by immunological mechanisms, including autoantibodies against different neuronal antigens, which can result in severe inflammation of different parts of the brain [1, 2]. It is often characterized by rapidly progressive short-term memory deficits, psychiatric symptoms or seizures as the most prominent symptoms with most patients having sleep dysfunctions as well. These are just a few of the possible symptoms and many patients end up with multiple differential diagnoses before the right one is made [3-5]. One possible reason for these multiple and diverse symptoms is that there are numerous different antineuronal antibodies that can cause damage to the central nervous system (CNS), either directly or indirectly [6]. Many of them affect glutamate (excitatory) or gamma-aminobutyric acid (GABA) (inhibitory) channels, either directly or by inactivating transmitters essential for their functions [7]. This interference disrupts the synaptic plasticity needed for learning, cognition and memory, which might explain some of the main symptoms seen in patients with AIE [8]. Furthermore GABA channel abnormalities play an important role in epilepsy, possibly explaining the prominent seizures in patients with AIE [9].

The different autoantibodies known to cause AIE can be further classified into groups [6]. One classification is based on the biochemical function of the causative antibody; 1) Antibodies against intracellular agents, 2) antibodies against synaptic receptors and 3) antibodies against ion channels and other cell-surface proteins [2]. Another common classification refers to the specific syndromes they cause; 1) Limbic encephalitis (LE), 2) anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis or 3) other syndromes and autoantibodies to cell surface antigens or synaptic receptors [5]. (A further overview of these antibodies can be seen in appendix 1, page 31).

Sometimes the formation of these autoantibodies is preceded by an infection, believed to trigger synaptic autoimmunity, while others can sometimes be preceded by tumours [5, 10]. Pruss et al. [11] found that approximately 30% of herpes simplex virus encephalitis patients also had anti-NMDAR antibodies. The association with neoplasms has been known for long and some antibodies are even classified as well-characterised onconeural antibodies, meaning that a definite paraneoplastic neurological syndrome (PNS) can be diagnosed even if the tumour itself is not found [12].

For a definitive diagnosis it is helpful to find specific autoantibodies, which can be troublesome [2]. Identifying a neuronal cell-surface antibody (such as anti-NMDAR) requires many different tests and strategies depending on each of their distinctive properties [2]. Onconeural and anti-glutamic acid decarboxylase (GAD) antibodies that attach to intracellular proteins are easier to detect with standard tests like immunoblotting or enzyme-linked immunosorbent assay (ELISA) [2].

1.1.1 Anti-NMDAR Encephalitis

In 2005, four female patients with ovarian teratomas had developed seizures, memory deficits, decreased levels of consciousness, central hypoventilation and cerebrospinal fluid inflammatory

abnormalities all in a short period of time [13]. They all turned out to have autoantibodies against hippocampal neuronal antigens. These cases revealed a connection between antibodies against NMDAR and encephalitis in 2007 [14]. The NMDAR are excitatory glutamate receptors containing two GluN1 subunits and two GluN2/3 subunits and the antibodies causing anti-NMDAR associated AIE most likely bind to the amino terminal domains of a GluN1 subunit, which studies show is necessary and sufficient for these antibodies recognition [15, 16]. These antibodies are therefore classified as antibodies against synaptic receptors [2].

The majority of patients with anti-NMDAR encephalitis have headache or fever preceding a rapid change in behaviour, occurring within a few days or weeks. The possible presenting symptoms include anxiety, insomnia, aggression, hallucinations (both visual and auditory), mania and psychosis [5, 17]. Many of the patients are initially referred to psychiatrists because of the prominent psychiatric symptoms, and even though some also have other symptoms such as short-term memory loss, it is often underestimated and not discovered until later [18]. Anti-NMDAR encephalitis can affect people of all ages, but the disease usually occurs in young adults and children, predominantly women [5]. According to data that Dalmau et al. [17] have collected, anti-NMDAR encephalitis appears to be the most common type of paraneoplastic encephalitis in human beings known to date. This makes anti-NMDAR patients the most studied of all AIE patients but it is uncertain how much of this knowledge can be applied to other subgroups [5]. However, humans are not the only species affected. Recent evidence implies that anti-NMDAR encephalitis might also affect animals. A post-mortem histological examination of the polar bear Knut has lead to scientists believing that he suffered from anti-NMDAR encephalitis, which caused a seizure that lead to him drowning [19]. This raises the question of whether we can learn from animal AIE cases in the future.

1.1.2 Anti-GAD Encephalitis

Anti-GAD encephalitis is a chronic non-paraneoplastic form of LE that does not respond well to treatment [20]. GAD is an important enzyme for the secretion of GABA, the major inhibitory neurotransmitter of the CNS, from neurons and pancreatic cells [7, 21]. Anti-GAD antibodies are classified as antibodies against intracellular agents [2]. Disrupting GABAb receptors in rodents using antibodies, results in prominent seizures, memory deficits, increased anxiety and mood dysregulation [7]. The same symptoms are often seen in patients with anti-GAD mediated AIE. The disease usually starts with prominent seizures, followed by the same symptoms of memory deficits and anxiety, and occurs predominantly in young individuals, especially females [20]. As for prior mentioned subtypes, symptoms of anti-GAD AIE can vary. Today it is believed that the so-called stiff-person syndrome and cerebellar ataxia, might be direct consequences of anti-GAD mediated AIE and that anti-GAD antibodies even occur more frequently in patients with these syndromes than in patients diagnosed with LE [2, 22]. Anti-GAD encephalitis is still, however, considered being a subclass of LE and anti-GAD antibodies are often found in association with anti-GABAb antibodies (also a form of LE) [1, 2]. It is important to note that only high titres of anti-GAD antibodies found in serum are associated with AIE, since low titres are important markers for patients with insulin-dependent diabetes mellitus (IDDM) and can even be found, in rare cases, in healthy people [1, 20, 23]. But in cerebrospinal fluid

(CSF) the antibody titres can be up to 40-fold lower than those found in serum and still indicate a possible AIE [20].

1.2 Criteria for Diagnosis

In 2016 Graus et al. [2] proposed new criteria for the diagnosis of different types of AIE, since the older criteria were considered too reliant on antibody testing and response to immunotherapy, which usually delayed diagnosis. The authors point out that if early diagnostic criteria include antibody status it may take up to several weeks to diagnose a patient and start the correct treatment. Having more advanced and specialised criteria for each case would result in a quicker diagnosis and limit treatment delay [2]. According to the new criteria, a diagnosis of AIE can be made when three standard criteria are met. The patients need to have a subacute onset of symptoms (working memory deficits, altered mental status or psychiatric symptoms) developing in less than 3 months. Secondly, the patients must have a new focal CNS finding, unexplained seizures, CSF pleocytosis or an abnormal magnetic resonance imaging (MRI) with features suggesting encephalitis. Finally, alternative causes must be excluded [2]. In the same article, the authors set specific criteria for each known subtype of AIE, where LE diagnosis requires symptoms suggesting limbic system involvement as well as bilateral medial temporal lobe abnormalities on T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) MRI. For a probable diagnosis of anti-NMDAR mediated encephalitis, however, patients need to meet the aforementioned AIE criteria in addition to presenting with rapid onset of four out of 6 so-called major groups of symptoms; 1) abnormal psychiatric behaviour or cognitive dysfunction, 2) speech dysfunction, 3) seizures, 4) movement disorders, 5) decreased levels of consciousness or 6) autonomic dysfunction or central hypoventilation [2]. But for a definitive anti-NMDAR encephalitis diagnosis, the antibodies need to be found as well as having one of these major symptoms [2].

1.2.1 CSF Parameters

When measured at symptom presentation, 80% of autoimmune encephalitis patients have mild-to-moderate pleocytosis of lymphocytes in CSF, 30% have mild-to-moderate increase of protein concentration and 50-60% have oligoclonal bands, which confirm the presence of intrathecal immunoglobulin synthesis [5, 24]. Neurofilament light chain (NFL) and total tau protein (T-tau) are important CSF markers of neuronal damage and glial fibrillary acidic protein (GFAP) of glial damage and even if these markers are not specific to autoimmune neurological disorders they still indicate neuronal or axonal damage and thus help when setting up differential diagnoses [25-27].

1.2.2 Brain MRI

Brain MRI alone could never be sufficient for diagnoses of AIE [28]. But in cases such as LE, a combination of assessment of a patient's symptoms and MRI results might suffice in setting a probable or definite diagnosis of AIE, since many of these patients have limbic system abnormalities on brain MRI [2, 29]. Usually, there is an increased T2-FLAIR signal from one or both temporal lobes, similar to changes seen in patients with herpes simplex viral encephalitis or medial temporal lobe seizures, but with the addition of other criteria a correct diagnosis can still be made [5]. Brain MRI

abnormalities are not as common in many other forms of AIE, where they tend to be either inconclusive or even appear normal [28]. One study even showed that approximately 67% of patients with anti-NMDAR encephalitis have normal MRI scans [28].

1.3 Paraneoplasia

PNS are neurological symptoms occurring with cancer, so long as other causes can be excluded and the cancer is associated with the symptoms and not a coincidence [12]. PNS are thought to be immune-mediated and many are associated with so-called onconeural antibodies. PNS can occur without any identified antibodies just as the antibodies can occur without causing a neurological syndrome. This can cause difficulties differentiating PNS from a plain neurological syndrome in a patient with a coexisting malignancy [12]. LE is one out of 8 syndromes defined as "classical PNS" and may be associated with cancer even if no antibodies are found in either CSF or serum [10]. Anti-GAD encephalitis is an exception to other diseases classified as LE as it is tumour free in 75% of cases [2]. On the other hand, tumour occurrence in patients with anti-NMDAR antibodies is quite high, especially in women older than 18 years. The occurrence is dependent on age, sex and ethnicity and the most prevalent tumour is ovarian teratoma [5, 17]. This difference between patient groups, but still common association with cancer, makes thorough screening for malignancies even more important, especially considering that PNS usually appear before any malignancy is detected [30]. It is recommended to screen AIE patients with computed tomography (CT) of thorax and abdomen followed by a colonoscopy (in patients over 50 years old) and sex-specific examinations, such as pelvic ultrasound (US) and mammography for females and testicular US for men. If other tests are negative, a fluorodeoxyglucose-positron emission tomography (FDG-PET) is also recommended, to avoid missing a possible tumour. Even if all test results are negative it is recommended to repeat screening in three to 6 months and after that every 6 months up till four years [30].

1.4 Treatment

Concrete treatment guidelines for all AIE patients do not exist as patients can be in very different states, have distinct symptoms as well as responding differently to treatment [5]. As an example, anti-NMDAR patients appear to respond well to immunotherapy, while patients with anti-GAD encephalitis can be more difficult to treat [20, 28]. But giving immunotherapy shortly after the patient's initial episode can help in reducing the amount of relapses of symptoms [31]. In addition to getting treatment for the causal mechanisms of the disease, patients may need symptomatic treatment for optimal recovery. For patients with classic limbic encephalitis it is recommended to start treatment with high-dose corticosteroids or intravenous immunoglobulin (IVIG), followed by plasma exchange (PLEX), rituximab or cyclophosphamide, when needed, as a second-line therapy [32]. Patients with anti-NMDAR mediated AIE and associated tumours respond faster to immunotherapy after tumour reduction, than those without any tumours to begin with [17]. The importance of removing any possible tumour for a patient's outcome can not be overemphasized, but it is also important that patients with other symptoms, such as epileptic seizures or psychiatric symptoms, get suitable symptomatic treatment to be able to recover and regain their former state and way of living [32]. As mentioned by

Kayser et al. [33], NMDAR patients often have persistent psychiatric symptoms that can be difficult to treat, even though they respond well to immunotherapy.

1.5 Outcome

To assess the outcome of patients with AIE many physicians use the so-called modified Rankin scale (MRS) [28]. MRS is a modified version of a scale created by John Rankin and is often used in the assessment of stroke patients' handicap [34, 35]. This scale measures the degree of disability of a patient and is therefore also suitable when assessing disabilities caused by other neurological diseases. Patients are graded from the score of zero to 6, where zero equals no symptoms and 6 equals death (see appendix 2, page 32).

Little is known about long-term outcomes of patients with AIE in general which made Titulaer et al. [28] collect data and describe different factors of long-term outcome in patients with anti-NMDAR encephalitis. According to their findings most of these patients have a maximum MRS score of 5 (scoring 6 would indicate death) as well as needing intensive care. Yet many of these patients improved within 4 weeks after beginning immunotherapeutic treatment and during the first 24 months approximately 80% of the patients achieved a favourable outcome (no need for intensive care and a MRS scoring of 0-2) while approximately 6% died. Worse outcomes were more associated with patients not receiving immunotherapy or tumour removal, when applicable.

Another study by many of the same authors showed that anti-NMDAR encephalitis patients over 44 years old usually have a less severe disease but still a poorer outcome than the younger patients [36]. But as they state, this difference in outcome might be in part due to late diagnosis of older patients and therefore delay until starting immunosuppressive treatment (IST). Patients that appear to have fully recovered can have a relapse, and sometimes several. Relapses might occur in 12-24% of anti-NMDAR encephalitis cases, some even many years after the initial symptoms and treatment, with only a few of them resembling the typical syndromes of anti-NMDAR encephalitis and most of them being less severe [28, 31].

In another study with 16 patients with LE (half of which had a positive anti-Hu antibody while the other half had no identifiable antibody) 9 patients died, three from a progression of the associated small-cell lung carcinoma (SCLC) but the other 6 because of the neurological disorder associated with the anti-Hu antibody [37].

1.6 The Importance of Further Research

Knowledge of whether symptoms, suitable treatments and/or recovery may differ between groups can be of value since autoimmune encephalitis is a growing group of diseases but even more because they are generally considered to respond favourably to immunotherapy [1]. Further knowledge and understanding of possible differences between these groups might aid in getting each patient the optimal treatment for their form of the disease and adjusting new guidelines to improve the speed and specificity of treatment and boost recovery. Getting diagnosed with encephalitis early on is crucial so that the right treatment can be started as soon as possible [38]. As an example more than 75% of all

patients documented with anti-NMDAR recover progressively in association with the decline of antibody titres following the right treatment [17].

Most data known today about AIE has been collected from patients with anti-NMDAR encephalitis and it would be desirable for future diagnosis of any kind of AIE to see how much of the knowledge about this specific patient group can be applied to others as well [5]. Comparisons of other antibody groups to a NMDAR group could help in that direction, by finding differences and similarities in clinical presentation, efficacious treatments, associations to other diseases and whether other groups of patients recover as well when starting treatment early.

2 Aim

The aim of this study is to compare patients from different subgroups of autoimmune encephalitis with respect to symptoms, diagnostic procedures, treatment and outcome to find possible differences or similarities between groups. These kinds of comparisons can hint at something new and unknown about these diseases and encourage further research in that matter.

3 Materials and Methods

3.1 Ethics

This study is retrospective, based on data from medical records and lab results in Melior (the database of Sahlgrenska University Hospital (SUH) in Gothenburg) and was approved by the Regional Ethical Board at the University of Gothenburg.

3.2 Patients

The patients in this study were selected from a list of patients with diverse autoimmune neurological symptoms (ANS) earlier reported in a publication by Constantinescu et al. [25]. In the same article they described thoroughly how they identified patients with ANS during a search in patient files from year 2000 to 2015 in Melior and which inclusion criteria they used for selecting patients. For this study, only patients with antibodies against GAD, NMDAR or both measured in CSF, serum or both, were selected from the list for further comparison.

3.3 Data Collection

All data was collected from patient files and lab results in Melior and by subsequently filling out special sheets and forms created by Radu Constantinescu (see Appendix). The data from the handwritten forms was then added both to an Excel sheet (for statistical analysis) and tables in this thesis. Details critical for correct registration of a patient to a certain patient ID were registered on the first sheet (Appendix 3, page 33) as well as the different diagnoses of each patient from onset and until correctly diagnosed with AIE. In addition, if available in the data, all other known autoimmune diseases were noted as well. Three different follow-up periods were defined for further comparison; onset of symptoms, a baseline visit and 12 months from the baseline visit (12-month follow-up). Onset was defined as the date registered in Melior of a patient's first appearing of symptoms and the associated hospital visit. The baseline visit was defined as the closest date of return because of the same or more severe symptoms (a median of 86 days (range: 4-435) from onset). The 12-month follow-up date used in this study was defined as the description entry of each patient closest to 12 months from the baseline visit (12 ± 3 months). Each patient's medical record was thoroughly read covering the period from onset up until this 12-month follow-up.

3.3.1 Measurement of Antibodies

Sheet 2 (Appendix 4 A-C, pages 34-36) was used to obtain any antibody data (positive or negative) available in the lab results section of Melior, or in some cases in medical records, from each patient's onset and until March 2017. When multiple test data was available, multiple sheets were used for comparison of antibody titres between time periods and when possible, assessed whether the antibody titre had increased or regressed.

3.3.2 Symptoms and Outcome

Symptoms and outcome of each patient was recorded on sheets 3-5 (Appendix 5-7, pages 37-40) at times of onset, at baseline visit and at 12-month follow-up. General descriptions of each patient were used to assess all possible symptoms and descriptions of level of care, hospitalization and possible death, were used together with Appendix 1 and 8 (pages 31 and 41) to assign each patient a suitable score on both MRS and the Karnofsky performance scale (KPS) for each time period. Each patient's score on both scales as well as ability to work or study was used to assess worsening and recovery, as well as the patient's final outcome at 12-month follow-up.

3.3.3 Brain MRI

A special tab in Melior keeps all MRI data of a patient together with a radiologist's original assessment. MRI scans from the date of onset until 12-month follow-up were collected on sheet 6 (Appendix 9, page 42) together with the radiologist's conclusion, which was used for further classification. For comparison, the first MRI taken for each patient after onset (either taken at onset, the baseline visit or within a month from the baseline visit) was classified as "the first MRI" and every additional MRI after that was used for assessment of possible changes. A radiologist's statement of improvement, deterioration or unchanged status between MRI scans was also noted, be using multiple sheets 6 for each patient. For some patients the last MRI available was taken around 12-month follow-up, but for others around 6 months from the baseline visit.

3.3.4 Malignancies

All data available about a patient's different malignancy investigations was collected on sheet 7 (Appendix 10, page 43). Malignancy examinations at interest were CTs of abdomen, pelvis and thorax, high- or low-dose (PET-CT) and CSF-immunophenotype as well as sex-specific examinations. Final conclusions from all examinations, except from the sex specific examinations, were grouped together in a separate tab of Melior and recorded for each patient from onset until the 18th of April 2017. Data regarding sex specific examinations had to be collected from medical records for each patient, being gynaecological examinations and mammographies for female patients and US of testis for male patients. This was done from each patient's onset of symptoms until the 12-month follow-up.

3.3.5 Cerebrospinal Fluid Analysis

Sheet 8 (Appendix 11, page 44) was used for collecting lab results from CSF analysis, available in a separate tab in Melior. The first lumbar puncture (LP) performed after onset, with complete data, was used for this comparison and when available, the next LP, taken within the study period. A patient was considered having a CSF inflammation if he had any of the following abnormalities in CSF: pleocytosis ($> 3 \times 10^6$ mononuclear cells/L), high IgG index ($> 0,63^1$), high IgM index (0,060) or CSF specific oligoclonal immunoglobulin G (IgG) bands (> 1 CSF-selective band). Blood-brain barrier (BBB) disruption was defined as either an increased blood:CSF albumin ratio (18-45 years: $> 6,8$; 45-90 years: $> 10,2$) or increased CSF albumin (18-45 years: > 320 mg/L; 45-90 years: > 420 mg/L) [39].

¹ CSF IgG index is calculated as following: $[\text{CSF IgG} / \text{CSF albumin}] / [\text{serum IgG} / \text{serum albumin}]$, and is provided in the laboratory results

Measured values of the neuronal damage markers NFL, GFAP and T-tau were also recorded for comparison. In June 2010, the methods for measuring NFL in LP in Sweden were changed so the same method as Constantinescu et al. [4] used to convert older NFL-levels (where NFL old/ NFL new = 0,32) were used to be able to compare the values of all patients [26, 40]. The same reference values as Constantinescu et al. [25] used for NFL, GFAP and T-tau were used, as they were given in the laboratory results. Reference values for CSF-NFL: <30 years: <380 ng/L; 30-40 years: <560 ng/L; 40-60 years: <890 ng/L; >60 years: 1850 ng/L. Reference values for CSF-GFAP: <20 years: <175 ng/L; 20-60 years: <750 ng/L; >60 years: <1250 ng/L. Reference values for CSF-T-tau: <18 years: <250 ng/L; 18-45 years: <300 ng/L; >45 years: <400 ng/L.

3.3.6 Treatment Data

To compare the different treatments each patient received (both IST and symptomatic treatments) during the first 12 months from the baseline visit, all medical records from onset until 12-month follow-up were reviewed thoroughly. All treatments, including daily doses and number of treatment days, with start and end dates, were recorded on sheets 9 and 10 (Appendix 12 A-B and 13 A-B, pages 45-48). Furthermore, if mentioned in the medical records, all information on efficacy and side effect of each IST was also documented on the backside of sheet 9.

3.3.7 Precise Diagnosis

All collected data was used together to give each patient a fitting diagnosis according to Graus et al.[2] recommended criteria for autoimmune encephalitis and Graus et al.[12] recommended criteria for paraneoplastic syndromes. The criteria used for these diagnoses can be seen in Appendix 14 A-B and 15 (pages 49-51). When available, further MRI and lab results, not taken during the follow-up period of this study, were used for this proper diagnosis.

3.4 Statistical Analysis

Statistical comparison for associations (present or absent) was performed with Fisher's exact test, using JMP version 13.0.0 from SAS Institute Inc. Mann-Whitney U test was performed for comparison of median values as appropriate, using RStudio version 1.0.136 from RStudio Inc. Two-tailed p-values of $\leq 0,05$ were considered statistically significant.

4 Results

4.1 Demographics

Out of 41 patients (14 males/ 27 females), five patients had anti-GAD antibody titres, three had anti-NMDAR antibodies and one patient had both making a total of 9 patients in this study. 18 other patients in the database had no detectable antibody in either serum or CSF, two had not yet been tested and the final 12 patients had very diverse antibody combinations that were not included in this study. The 9 patients in this study were subsequently classified into three groups, respectively: GG (anti-GAD group) and NG (anti-NMDAR group), for comparisons, and DPP (double-positive patient). 78% were female (n=7) and the median age at disease onset was 38 years (range: 18-65). A further comparison of the groups is available in table 1 (page 13).

Table 1
Patient demographics before onset

Patient group	GG	NG	p-values*	DPP
Patients, n	5	3		1
Female, n (%)	4 (80%)	2 (67%)	1,0000	1 (100%)
Age at onset, median, range [years]	38 (23-45)	26 (18-40)	0,4534	65 (65)
Prior diagnosis of autoimmune disease, n (%)	3 (60%)	0 (0%)	0,1964	1 (100%)
Work percentage, median, range [%]	100 (50-100)	100 (100)	0,6056	0 (0)
KPS, median, range [%]	100 (80-100)	100 (100)	0,6056	70 (70)
MRS, median, range [0-6]	0 (0-2)	0 (0)	0,6056	2 (2)
Antidepressants, n (%)	2 (40%)	0 (0%)	0,4643	0 (0%)
Antiepileptic drugs, n (%)	1 (20%)	0 (0%)	1,0000	0 (0%)
IST, n (%)	0 (0%)	0 (0%)		0 (0%)

The table shows the demographics of each group as well as patients general status before onset of AIE symptoms. The patient's age at onset is presented as the median value of each group and range and the patient's general status (work percentage, KPS and MRS scores) are presented in the same way. The rest of the categories are presented with the number of patients (n) in each group fitting the criteria and the percentage from the total population of the group (n= number, % = percentage of total in group).

*Two-tailed p-values for comparisons between GG and NG

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group, DPP = double-positive patient, KPS = the Karnofsky performance scale, MRS = the modified Rankin scale and IST = immunosuppressive treatment.

4.2 Additional Autoimmune Disorders

Table 2
Comparisons of other autoimmune diseases

Patient group	GG	NG	p-values	DPP
Patients, n	5	3		1
Other autoimmune disease, n (%)	4 (80%)	0 (0%)	0,1429	1 (100%)
Hypothyroid*, n (%)	4 (80%)	0 (0%)	0,1429	1 (100%)
Type I diabetes*, n (%)	2 (40%)	0 (0%)	0,4643	0 (0%)
Sjögren's syndrome*, n (%)	1 (20%)	0 (0%)	1,0000	0 (0%)

The table shows the number of patients from each group (n= number, % = percentage of total in group), with other autoimmune diseases in addition to their AIE.

*Two-tailed p-values for comparisons between GG and NG

*Was recorded as the patients' different autoimmune disorders

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group and DPP = double-positive patient.

Prior to onset of AIE, four patients (all with an anti-GAD antibody, 3 from GG and the DPP) were hypothyroid on an autoimmune basis and one more patient (from GG) had his hypothyroid disease discovered during the follow-up period of this study. In addition to having an AIE and being hypothyroid, two of these patients also developed a type I diabetes and a third developed Sjögren's syndrome. While 4/5 GG patients ($p=0,1429$) and the DPP had other autoimmune diseases in addition to their AIE, no patient from NG had any additional autoimmune disorders. A detailed view of these disorders and differences between groups can be seen in table 2 (page 13).

A similar view was seen in comparisons of additional autoantibodies. Two GG patients had islet cell cytoplasmic antibodies (ICA) in addition to the anti-GAD antibodies and two other GG patients and the DPP had anti-TPO antibodies (and were hypothyroid) and one of these GG patients had anti-TG as well. Meanwhile the NG patients had no additional antibodies discovered. Out of the 9 patients in this study, 6 patients had CSF and serum antibody data available in SUH's bio-bank for confirmation but for the other three patients there were only notes in their medical records, and no values accessible. When using both sources, all 9 patients had positive antibody titres measured in CSF at some point but only 7/9 patients had positive antibody titres in serum. Only one patient, from NG, had a total regression of anti-NMDAR antibodies in CSF between two different tests, but not all patients had multiple test results.

4.3 Diagnostic Delay

Table 3
Differences in diagnostic delay

Patient group	GG	NG	p-values*	DPP
Patients, n	5	3		1
Days from onset until baseline visit, median, range	86 (6-249)	7 (4-435)	0,7857	262 (262)
Days from onset until first neurologic contact, median, range	25 (8-267)	11 (0-441)	0,7857	0 (0)
Days from onset until diagnosis, median, range	93 (14-3116)	28 (13-443)	0,5714	357 (357)
Days between first neurologic contact and diagnosis, median, range	14 (5-2849)	2 (2-28)	0,2302	357 (357)

The table shows the median value (plus range) of the number of days it took for patients of each group from onset until the baseline visit, to first meet a neurologist, to get correct diagnosis and number of days passing between the latter two.

*Two-tailed p-values for comparisons between GG and NG

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group and DPP = double-positive patient.

It took a median of 93 days (range 13-3116 days) for a correct diagnosis of AIE to be made for the 9 patients, with patients of NG having a non-significant lower median value than GG, as seen in table 3 (page 14). All of the patients got other initial diagnoses. Four patients were originally diagnosed with having had a one-time seizure, one a severe anxiety attack, one having fainted due to a vasovagal problem, one was diagnosed with an astrocytoma, one with a pulmonary embolism and the final patient was diagnosed schizophrenic. There was a median of 86 days (range: 4-435) from disease onset until the baseline visit. Most patients had to wait several days for their first neurologic contact, with a median of 16 days (range 0-441) from onset. In 5 out of 9 cases the correct diagnosis was made within the first month from the patients' first neurologic contact (all three patients from NG and two of the patients from GG) with a median of 14 days (range 2-2849) for all 9. Notably, no patient got the correct diagnosis neither at onset of symptoms nor before having met with a neurologist.

4.4 Symptoms

Table 4
Epileptic seizures

Time period	Onset				Baseline visit				12-month follow-up			
Patient group	GG	NG	p-values*	DPP	GG	NG	p-values*	DPP	GG	NG	p-values*	DPP
Patients, n	5	3		1	5	3		1	5	3		1
Epileptic seizures*, n (%)	5 (100%)	3 (100%)		1 (100%)	5 (100%)	3 (100%)		1 (100%)	4 (80%)	0 (0%)	0,1429	0 (0%)
Status epilepticus, n (%)	0 (0%)	0 (0%)		0 (0%)	1 (20%)	2 (67%)	0,4643	1 (100%)	0 (0%)	0 (0%)		0 (0%)
Involuntary movements ^Δ , n (%)	2 (40%)	1 (33%)	1,0000	0 (0%)	3 (60%)	2 (67%)	1,0000	1 (100%)	0 (0%)	0 (0%)		0 (0%)
Intervals of hallucinations ^Δ , n (%)	1 (20%)	1 (33%)	1,0000	0 (0%)	0 (0%)	1 (33%)	0,3750	0 (0%)	2 (40%)	0 (0%)	0,4643	0 (0%)
Intervals of diminished concentration ^Δ , n (%)	2 (40%)	1 (33%)	1,0000	1 (100%)	2 (40%)	0 (0%)	0,4643	0 (0%)	1 (20%)	0 (0%)	1,0000	0 (0%)

The table shows how many patients (n= number, % = percentage of total in group) from each group had any kind of epileptic seizure at onset, baseline visit and 12-month follow-up and what their main symptoms of epileptic seizures were.

*Two-tailed p-values for comparisons between GG and NG

*Any kind of epileptic seizure

^ΔDescribed as the patients' main symptoms of epileptic seizures. At 12-month follow-up, one patient from GG (20%) had unexplained symptoms that were still considered as being epileptic. This patient described short seizures of hot rushes and getting weak afterwards (p = 1,0000). This occurred several times a day.

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group and DPP = double-positive patient.

Table 5
Psychiatric symptoms

Time period	Onset				Baseline visit				12-month follow-up			
Patient group	GG	NG	p-values*	DPP	GG	NG	p-values*	DPP	GG	NG	p-values*	DPP
Patients, n	5	3		1	5	3		1	5	3		1
Psychiatric symptoms, n (%)	3 (60%)	3 (100%)	0,4643	0 (0%)	4 (80%)	3 (100%)	1,0000	1 (100%)	3 (60%)	0 (0%)	0,1964	0 (0%)
Depression/anxiety*, n (%)	3 (60%)	1 (33%)	1,0000	0 (0%)	4 (80%)	2 (67%)	1,0000	1 (100%)	3 (60%)	0 (0%)	0,1964	0 (0%)
Personality change*, n (%)	0 (0%)	2 (67%)	0,1071	0 (0%)	0 (0%)	3 (100%)	0,0179	1 (100%)	0 (0%)	0 (0%)		0 (0%)
Hallucinations*, n (%)	1 (20%)	2 (67%)	0,1429	0 (0%)	1 (20%)	3 (100%)	0,1429	0 (0%)	1 (20%)	0 (0%)	1,0000	0 (0%)

The table shows how many patients (n= number, % = percentage of total in group) from each group had any form of psychiatric symptom at onset, baseline visit and 12-month follow-up and what their main psychiatric symptoms were.

*Two-tailed p-values for comparisons between GG and NG

*Described as the patients' main psychiatric symptoms.

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group and DPP = double-positive patient.

As seen in tables 4-6 (pages 15-16) all patients had some kind of epileptic seizure at onset, and almost all showed psychiatric symptoms or signs of cognitive abnormalities. At this point there was no significant difference between groups, but patients of GG appeared to have a tendency of being more likely to have memory disturbances, while NG patients showed signs of hallucinations and personality

changes. Furthermore, all patients had sleep dysfunctions at some point during the study period, mostly due to difficulties of falling asleep or waking up in the middle of the night. At the baseline visit the symptoms were, in general, more severe and occurring more frequently. At this point four out of the 9 patients had status epilepticus (SE), of which three needed intensive care (one from each group, GG, NG and the DPP). Also at this point, the patients of NG were significantly more likely to show personality changes ($p=0,0179$) while both groups now had a similar percentage of patients with cognitive abnormalities. At 12-month follow-up, only two patients from NG still showed any abnormal symptoms, both having memory disturbances, while a fairly equal amount of GG patients showing the same symptoms as at onset, but most of them now less frequently.

Two patients (one from GG and one from NG) had a confirmed infection within one month before onset. The NG patient had an unusually fierce viral cold, with ear locks, vomiting and sleep dysfunctions, which resulted in a fever at onset. While a urinary bacterial infection was recorded for the GG patient, but there was no mentioning of fever at onset. For the rest of the patients ($n=7$), no infection was recorded for three of the patients within one month before onset, while four patients either could not remember, or were not asked. None of these 7 patients had a fever at onset.

Table 6
Cognitive abnormalities

Time period	Onset				Baseline visit				12-month follow-up			
Patient group	GG	NG	p-values*	DPP	GG	NG	p-values*	DPP	GG	NG	p-values*	DPP
Patients, n	5	3		1	5	3		1	5	3		1
Cognitive abnormalities, n (%)	5 (100%)	1 (33%)	0,1071	1 (100%)	4 (80%)	3 (100%)	1,0000	1 (100%)	4 (80%)	2 (67%)	1,0000	1 (100%)
Memory disturbance*, n (%)	4 (80%)	0 (0%)	0,1429	1 (100%)	3 (60%)	2 (67%)	1,0000	1 (100%)	4 (80%)	2 (67%)	1,0000	0 (0%)
Disorientation*, n (%)	3 (60%)	0 (0%)	0,1964	0 (0%)	3 (60%)	0 (0%)	0,1964	0 (0%)	0 (0%)	0 (0%)		1 (100%)
Expression disorder*, n (%)	0 (0%)	1 (33%)	0,3750	0 (0%)	1 (20%)	1 (33%)	1,0000	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Diminished concentration*, n (%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	1 (33%)	0,3750	0 (0%)	0 (0%)	1 (33%)	0,3750	0 (0%)

The table shows how many patients (n = number, % = percentage of total in group) from each group had any form of cognitive abnormality at onset, baseline visit and 12-month follow-up and what abnormalities they were showing.

*Two-tailed p-values for comparisons between GG and NG

*Mentioned as the patients' different cognitive abnormalities. At onset one patient from GG had a clear dysarthria as well ($p = 1,0000$) and at 12-month follow-up one NG patient complained about brain tiredness, getting exhausted very quickly when needing to think a lot ($p = 0,3750$).

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group and DPP = double-positive patient.

4.5 Brain MRI

Out of the 9 patients in this study, 6 patients had a pathologic first MRI. As seen in table 7 (page 17), GG patients had a non-significantly ($p=0,4643$) higher occurrence of pathologic MRI scans than NG. Three GG patients and the DPP had their first MRI pathology regarded as related to AIE with a

T2/FLAIR signal increase from the left hippocampus, or bilaterally, as well as from the left temporal lobe, mostly from the uncus or amygdala regions. Comparison between groups regarding pathology related to AIE and improvement on a later MRI were the ones closest to being statistically significant ($p=0,1964$) showing a tendency in favour of GG.

The two patients with other abnormalities at the first MRI (one patient from GG and one from NG) were both described as having an "almost normal" MRI with slight abnormalities in different parts of the brain. The NG patient had a slight cystic alteration, frontally in centrum semiovale on the right side, with no other parenchymal changes, without any relation to AIE and no signs of BBB disruption. The GG patient had a few dot formed signal changes in the left cerebrum, believed to be widened vascular spaces and very discrete signal changes frontally, cortically in the left gyrus. The hippocampi had no signs of atrophy or signal changes and there was no clear relation to AIE. This same GG patient had another MRI after the follow-up period of this study, were there were new abnormalities and these were considered related to AIE.

The NG patient mentioned to have a deterioration between MRI scans in table 9, had a normal first MRI but was at one later instance diagnosed with a slight volume reduction in the right hippocampus, but without any relations to an AIE. However, at the following MRI this patient was considered to have no abnormality again.

Two patients improved from having abnormal MRI scans to having normal. One GG patient went from having clear AIE related pathologies visible on brain MRI at the first and several other MRI scans to having a completely normal brain MRI at 12-month follow-up. The NG patient with an abnormality to begin with (not related to AIE) improved and had a normal MRI at a later instance. So when looking at the last MRI results available for each patient during this follow-up period, five patients had normal MRI scans, all three NG patients and two GG patients, but the other four still had abnormalities.

Table 7
Comparisons of brain MRI

Patient group	GG	NG	p-values*	DPP
Patients, n	5	3		1
Pathologic first MRI, n (%)	4 (80%)	1 (33%)	0,4643	1 (100%)
Pathology related to AIE, n (%)	3 (60%)	0 (0%)	0,1964	1 (100%)
Normal first MRI, n (%)	1 (20%)	2 (67%)	0,4643	0 (0%)
Improving MRI, n (%)	3 (60%)	0 (0%)	0,1964	0 (0%)
Worsening MRI, n (%)	1 (20%)	1 (33%)	1,0000	1 (100%)
Unchanged MRI, n (%)	1 (20%)	2 (67%)	0,4643	0 (0%)

The table shows the number of patients (n= number, % = percentage of total in group) with a pathologic or normal MRI and whether it gets improved, worsens or remains unchanged at later stage. It also shows whether abnormalities were taken under consideration in relation to AIE or not.

*Two-tailed p-values for comparisons between GG and NG

Abbreviations: MRI = magnetic resonance imaging, GG = anti-GAD patient group, NG = anti-NMDAR patient group, DPP = double-positive patient and AIE = autoimmune encephalitis.

4.6 Malignancies

One, out of the 9 patients in this study, had a malignancy in the form of a cancerous tumour in the left adrenal gland, which recurred and had metastases in different parts of the abdomen and the other adrenal gland. A breast tumour had been removed from the same patient just a few days before onset

of diagnosis. All patients but one from the GG group had a full body FDG-PET scan, which was later repeated for two patients, the DPP patient (with a malignancy) within one year from removal of the tumour and one GG patient three years after the first scan. In addition all but one of the GG patients (n=8) had CT scans of thorax and abdomen, which was later repeated for four of the patients. Furthermore, one patient from GG had a full sex-specific examination (US testes) and two other patients had either gynaecological examination or a mammography. All the NG patients had some type of sex-specific examination performed, with one female missing a mammography. As for the DPP she had only a mammography showing post op abnormalities but nothing cancerous. Only one patient had a CSF-immunophenotype done, which was negative.

4.7 CSF Parameters

Table 8
Comparison of CSF parameters

Patient group	GG	NG	p-values*	DPP
Patients, n	5	3		1
CSF inflammation, n (%)	5 (100%)	3 (100%)		1 (100%)
BBB disruption, n (%)	1 (20%)	1 (33%)	1,0000	0 (0%)
Abnormal (high) NFL, n (%)	3 (60%)	3 (100%)	0,4643	1 (100%)
Abnormal (high) GFAP, n (%)	1 (20%)	0 (0%)	1,0000	1 (100%)
Abnormal (high) T-Tau, n (%)	2 (40%)	2 (67%)	1,0000	1 (100%)
Later LP improved, n (%)	1 (20%)	2 (67%)	0,4643	1* (100%)
Later LP worsened, n (%)	0 (0%)	1 (33%)	0,3750	1* (100%)
A later LP not taken, n (%)	4 (80%)	0 (0%)	0,1429	0 (0%)

The table shows the number of patients (n= number, % = percentage of total in group) with an abnormality in CSF parameters in the first complete LP accessible in the database. It also shows whether an LP was repeated later within the study period and then its comparison to the first one (when applicable).

*Two-tailed p-values for comparisons between GG and NG

*For this patient some parameters got better while others got worse.

Abbreviations: CSF = cerebrospinal fluid, GG = anti-GAD patient group, NG = anti-NMDAR patient group, DPP = double-positive patient, BBB = blood-brain barrier, NFL = neurofilament light chain, GFAP = glial fibrillary acidic protein, T-Tau = total tau protein and LP = lumbar puncture.

As seen in table 8 (page 18), all patients had at least one LP taken, but four patients from GG were the only ones not having any additional LP taken during the study period (p = 0,1429) and therefore impossible to assess whether they had improved or worsened. Out of the five patients with a later LP, three show clear signs of improvement, one is clearly worsened and one is improving in some values but worsening in others. At the first LP, all patients had a CSF inflammation and one patient from both NG and GG had a BBB disruption as well. The only GG patient with a later LP during the follow-up period had an improvement and had only an elevated NFL as an abnormality at the later LP, but no longer had any sign of CSF-inflammation, BBB-disruption or other elevated values. One NG patient got lower values but still had CSF inflammation, another had much lower values and had no further signs of BBB disruption but still had CSF inflammation and the final NG patient got worse with much higher values of NFL, GFAP and T-tau and kept his CSF-inflammation. The DPP had a lowering of almost all values, and therefore what could seem as an improvement, but had an increased value of blood/CSF albumin ratio and was therefore diagnosed with a new BBB disruption at this time and therefore as both improved and deteriorated.

4.8 Treatment

Table 9

Comparisons of immunosuppressive treatment during the follow-up period

Patient group	GG	NG	p-values*	DPP
Patients, n	4	3		1
First treatment efficacious, n (%)	3 (75%)	0 (0%)	0,1964	1 (100%)
First treatment efficiency questionable, n (%)	1 (25%)	1 (33%)	1,0000	0 (0%)
More than one treatment method, n (%)	2 (50%)	3 (100%)	0,1964	1 (100%)
A later treatment efficacious, n (%)	2 (50%)	2 (67%)	1,0000	1 (100%)
Questionable efficiency of a later treatment, n (%)	0 (0%)	1 (33%)	0,3750	0 (0%)
Side effects of treatments, n (%)	1 (25%)	1 (33%)	1,0000	0 (0%)
Treatment still after 12-months, n (%)	2 (50%)	0 (0%)	0,4643	1 (100%)
Corticosteroid pulse an effective method*, n (%)	3 (75%)	0 (0%)	0,1964	1 (100%)

The table shows how the immunosuppressive treatment worked for the different groups (n= number, % = percentage of total in group). For one patient of GG, due to the late discovery of the disease, the patient started IST several years after the follow-up period of this study and could therefore not be included in this comparison. Hence n(GG) = 4.

*Two-tailed p-values for comparisons between GG and NG

*Shows only the number of patients who had a clear positive effect of a corticosteroid pulse treatment, the fourth patient from the GG and one NG patient had unclear effects of this treatment. If both are counted, the corticosteroid pulse was effective in four GG patients (100%) and one NG (33%) (p=0,4643).

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group, DPP = double-positive patient and IST = immunosuppressive treatment.

Table 10

Comparisons of symptomatic treatments during the follow-up period

Patient group	GG	NG	p-values*	DPP
Patients, n	5	3		1
Any anti-epileptic medication, n (%)	5 (100%)	3 (100%)		1 (100%)
More than one type of anti-epileptic medication tried, n (%)	3 (60%)	3 (100%)	0,4643	1 (100%)
Any anti-depressants or anti-anxiety medication, n (%)	4 (80%)	3 (100%)	1,0000	0 (0%)
Any sleeping medication, n (%)	3 (60%)	3 (100%)	0,4643	0 (0%)
Epileptic treatment still after 12-months, n (%)	4 (80%)	2 (67%)	1,0000	1 (100%)

The table shows an overview of the different symptomatic treatments that each patient received (n= number, % = percentage of total in group).

*Two-tailed p-values for comparisons between GG and NG

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group and DPP = double-positive patient.

As seen in table 9 (page 19), only four out of the five GG patients were available for comparison of IST. The final GG patient was not diagnosed until several years after the follow-up period of this study and did not receive any IST until then. This patient is therefore unavailable for this comparison. Notably, no patient received IST at the first visit date. Most of the other 8 patients received IST within one month from the baseline visit, except for one GG patient, which was diagnosed at around 6 months from the baseline visit and started treatment then.

6 out of these 8 patients in this study got corticosteroid pulses (Solumedrol, 1g intravenous for three-five days) as their first IST, which had a clear positive effect on three GG patients, no effect on one NG patient and unclear effect on two patients, one GG patient and one from NG. The GG patient with the unclear effect received oral steroid treatment immediately after the last pulse, and when the patient got better, the physicians could not tell whether the pulses or the oral steroids caused the progression. The NG patient with unclear effect got IVIG straight after the pulse. Both treatments had questionable effect and when they were repeated, they had no effect. For the GG patients, either the

corticosteroid pulses were repeated monthly, for the period of 6-months, or the patients were given oral steroids with scheduled lowering of doses, too maintain the recovery. Two out of the four GAD patients were still receiving IST at the 12-month follow-up of this study, one due to late onset of treatment and the other due to relapse.

The NG patients, on the other hand were more difficult to treat. Two of them started out with corticosteroid pulses and then got IVIG immediately after, one with the questionable efficiency and the other did not respond to this treatment. Furthermore, the third NG patient got IVIG to begin with and then corticosteroid pulses, both without effect. One NG patient got better following a change in epileptic treatment, while the other two needed further treatment measures. One responded positively to two doses of Rituximab and then got corticosteroid pulses for two months with positive effect, while the other had a PLEX, immediately followed by per oral steroids, which had a positive effect. The NG patients improved with later treatment measures and at 12-month follow-up, none of them were in need of continuing IST.

The DPP received oral steroids in the beginning with positive effect, together with one set of corticosteroid pulses and then continued with oral steroids with scheduled lowering of doses. The patient required steroids during the whole follow-up period.

Few patients had side effects of the treatment, as seen in table 9 (page 19) and the only side effects presented were night sweats, weight gaining and headaches. The diabetics got help controlling their blood-glucose levels during treatments by endocrinologists.

All patients got some sort of symptomatic treatment, as seen in table 10 (page 19). All got anti-epileptic medication and most of them also sleeping pills and/or anti-depressants/anti-anxiety medication. There was no tendency of one drug working better than others but most patients had to try multiple different anti-epileptics (carbamazepine, lamotrigine, levetiracetam (Keppra®) and fenatone to name a few) before finding the one with the best effect and least side effects. In fact, for one patient of NG, the lowering of Keppra doses probably resulted in improvement. At 12-month follow-up all patients, except for one from GG and one from NG, still needed epileptic treatment.

4.9 Outcome

Shortly after onset of symptoms all patients scored similarly or equally on both MRS and KPS as before disease onset, as well as keeping their work or study percentage in the same amount. Out of the four patients being admitted to hospital at this point all were discharged shortly after. On the other hand, after the baseline visit, where the patients presented with more severe symptoms (see 4.4 Symptoms, pages 15-16), they had subsequently lower scorings on both scales as well as most patients needing a sick leave from work or studies. Patients of GG scored a median of 10 points lower on KPS and 1 point higher on MRS (both indicating worsening of states), while NG scored a median of 50 points lower and 2 points higher, respectively on each scale. This made a difference on median values on KPS of 40 points between the groups and 1 point on MRS (both in favour of GG). At this point, all but two patients, both from GG, were admitted to hospital and while four were discharged shortly after, three patients (one from GG and two from NG) needed to be kept in hospital for more than one month.

At 12-month follow-up most patients had improved greatly (except for two GG patients, one without diagnosis and suitable treatment and the other diagnosed 6 months after baseline visit and starting treatment later). The three remaining GG patients had a better functional recovery than the NG-patients, returning to work or study as before onset. This resulted in the patients of GG scoring a median of 10 points higher on KPS (being able to work) than the patients of NG. One NG patient, with 100 on KPS and 0 on MRS (fully recovered) was unemployed but looking for a job, while the other two NG patients were still on a sick leave. As for the DPP she had a worse recovery and was in need of additional home care support. She died approximately three years after onset, being the only one out of the 9 patients not alive when this thesis was written.

Table 11
Outcome

Time period	Onset				Baseline visit				12-month follow-up			
Patient group	GG	NG	p-values*	DPP	GG	NG	p-values*	DPP	GG	NG	p-values*	DPP
Patients, n	5	3		1	5	3		1	5	3		1
KPS, median, range [%]	90 (80-90)	90 (70-90)	0,6056	70 (70)	80 (40-90)	40 (40-70)	0,1638	40 (40)	80 (70-90)	70 (70-100)	0,7570	50 (50)
MRS, median, range [0-6]	1 (1-2)	1 (1)	0,6056	2 (2)	2 (1-3)	3 (2-3)	0,2069	4 (4)	2 (1-2)	2 (0-2)	1,0000	4 (4)
Admitted, n (%)	2 (40%)	1 (33%)	1,0000	1 (100%)	3 (60%)	3 (100%)	0,4643	1 (100%)	3 (60%)	1 (33%)	1,0000	1 (100%)
Discharged, n (%)	2 (40%)	1 (33%)	1,0000	1 (100%)	2 (40%)	1 (33%)	1,0000	1 (100%)	3 (60%)	1 (33%)	1,0000	1 (100%)
Hospitalised, n (%)	0 (0%)	0 (0%)		0 (0%)	1 (20%)	2 (67%)	0,4643	0 (0%)	0 (0%)	0 (0%)		0 (0%)
Working, n (%)	5 (100%)	3 (100%)		0 (0%)	3 (60%)	0 (0%)	0,1964	0 (0%)	4 (80%)	0 (0%)	0,1429	0 (0%)
Work percentage, median, range [%]	100 (50-100)	100 (100)	0,6056	0 (0)	50 (0-100)	0 (0)	0,1685	0 (0)	50 (0-100)	0 (0)	0,0765	0 (0)

The table shows the outcome of each patient group at onset, baseline visit and 12-month follow-up as median values of their KPS and MRS scoring and work percentage (with the range) when being discharged, as well as showing how many patients (n= number, % = percentage of total in group) from each group had to be admitted to hospital and how many were discharged shortly after or had to stay in hospital.

*Two-tailed p-values for comparisons between GG and NG

Abbreviations: GG = anti-GAD patient group, NG = anti-NMDAR patient group, DPP = double-positive patient, KPS = the Karnofsky performance scale and MRS = the modified Rankin scale.

4.10 Final Diagnosis

In this study the DPP had a definite paraneoplastic syndrome, all NG patients had definite anti-NMDAR encephalitis and 4 GG patients had a definite autoimmune limbic encephalitis (with bilateral abnormalities on MRI). The final patient from GG had a completely different disease presentation, with years of depression and then a rapid onset of hallucinations followed by epileptic seizures half a year later, which was thought to be due to changes in epileptic medication. This patient is more difficult to give a definite diagnosis using recommended criteria, with positive anti-GAD antibodies in CSF and serum but a normal MRI and no clear rapid progression of symptoms.

5 Discussion

5.1 Summary

At onset the symptoms were similar between patient groups, although GG showed a non-significant trend towards having more memory disturbances while NG had hallucinations and personality changes. At baseline visit there was again no great difference in symptom presentation between the groups, except for NG being significantly more likely to have personality changes ($p=0,0179$). However, at this point, four out of 9 patients had SE, where three of them needed intensive care. Also both groups had lower median scorings on both KPS and MRS and all but two patients were admitted. This shows that in general, the patients were in worse states at the baseline visit than at symptom onset.

All patients, except for one from GG, received IST during the follow-up period. All the other four GG patients responded to treatment right away and started showing progress, but all NG patients needed further treatment measures. In the same manner the MRI scans improved for three out of five GG patients. Then at 12-month follow-up, the NG patients were close to symptom free (two out of three still showing memory disturbances but not any seizures or psychiatric symptoms) while all but one GG patient had similar symptoms as at onset, only not as frequent and with less severity. Although this could suggest that the NG patients had a better outcome, the patients of GG scored a median of 10 points higher on KPS and were in a greater amount returning to work, while none of the NG patients had started working.

5.2 Multiple Autoantibodies

In some cases, a specific antibody-test analysis, either positive or negative, was only recorded in the medical records without the test results themselves or their values. The missing data may be explained by the fact that some tests were shipped abroad while others were examined in other parts of Sweden. Even if some test records stated that the tests were done at SUH or a regional hospital close to SUH, many of them were still inadequate. A diagnosis of AIE and follow-up is also quite a new term and therefore partly still in development [2]. Patients in this study were therefore differently assessed, with different work-up and although some had many CSF tests, with clear screening for many autoantibodies and adequate data, others were just diagnosed one time for a positivity of a certain antibody.

Many of the anti-GAD patients in this study had more than one kind of auto-antibody, which is quite common and there is a possibility that even more antibodies are yet to be discovered for them as well as for the other patients of this study [1].

5.3 Clinical Presentation and Symptoms

Results from the comparisons of psychiatric symptoms and cognitive abnormalities hint at anti-NMDAR patients having more immense psychiatric symptoms and especially personality changes (significantly different between groups with $p=0,0179$), while anti-GAD patients might have more

prominent cognitive abnormalities. However, before jumping into any conclusions it is important to think about what Dalmau et al. [18] reported on anti-NMDAR patients. In that paper, the anti-NMDAR patients did not show short-term memory deficits partly because of interference of more prominent psychiatric symptoms during memory assessment. This might explain why only one patient from the NG in this study was diagnosed with a cognitive abnormality at onset but all three of them at the baseline visit. The patients' prominent psychiatric symptoms could have interfered with further assessment of other possible symptoms to begin with, but as they improved, there was room for assessment of further symptoms and abnormalities, which led to the discovery of their cognitive abnormalities.

5.4 MRI Results

Examination of results from MRI demonstrated that four out of five GG patients, and the DPP patient, had visible brain abnormalities, but only one of the three NG patients. Moreover, only three of the abnormalities discovered in the MRI, and all three were cases in the GG group, were related to AIE.

These results show that patients of GG had a higher tendency of having pathologies visible on MRI and that those abnormalities were linked to AIE, than patients of NG. Furthermore, it is also noteworthy that the patients of GG improved on MRI during the follow-up period while the only patient from NG that had multiple MRI scans available became worsened. It would have been interesting to see whether the other two patients from NG would also deteriorate, but data regarding these patients happened to be very restricted (either not done or done at another hospital and therefore not available for this study). This resulted in no possibility to compare these groups in regard to later MRI scans.

Even though this study had a low number of patients and thus a low statistical power, these results might give a slight hint about how each patient group appears on a MRI scan. Moreover, our results are in good correlation with the results published by Titulaer et al. [28] where they showed that a mere 33% of 540 anti-NMDAR patients had an abnormal MRI, which is the same percentage as in this study (one out of three patients of NG). On the other hand, our results on the anti-GAD patients did not agree with the results reported by Malter et al. [20]. Malter's results showed that all anti-GAD patients had increased T2/FLAIR signalling of amygdala or hippocampal regions while only 60% (3/5) in this study showed that phenotype on the first MRI.

Considering that two of the GG patients were diagnosed at later stages than around the baseline visit, one a couple of months and the other several years later, there is a possibility that they just had a slower progression of the disease and that at their first MRI examination they had not yet suffered an inflammation pathology. As a matter of fact, one of these patients did have an abnormal MRI after 6 months from the baseline visit, where the pathology was considered possibly related to AIE, and at a later MRI the relation was clear. While the other GG patient had no abnormal MRI in the database. As mentioned before, it would have been interesting to compare the patient groups in regard to later MRI results as well, but due to a lot of missing data for the patients of NG this could not be completed. Nevertheless, these results give a good hint at what could be expected and what might have been the

results if the groups had been bigger. Maybe then, there would have been some statistically significant differences in MRI abnormalities between the groups.

5.5 Malignancies

While most patients in this study had multiple screening examinations and all but one patient, a patient from GG, were subsequently scanned with FDG-PET, no patient got all examinations recommended by Titulaer et al. [30] and the examinations done were not repeated as often as recommended either. Still these malignancy investigations led to discovery of a malignancy in one patient, the DPP.

This patient, a female patient, had just been operated for removal of breast cancer, only days before her onset of symptoms and during the follow-up period of this study, a FDG-PET scan showed a tumour in one of her adrenal glands. Neither of these two tumour types are classified as the most common tumours associated with anti-NMDAR encephalitis, with the most common tumour being ovarian teratoma, according to Dalmau et al. [17]. It is therefore difficult to speculate which of these two tumours might be associated with her neurological symptoms, and in that way, classify it as a PNS.

Keeping in mind that not all recommendations of screening as put forth by Titulaer et al.[30] were being followed, there is a slight risk of a malignancy getting by unnoticed. Still, it is known that anti-GAD antibodies are rarely associated with cancer, which might confirm that there is no tumour being missed in the patients of GG [2]. On the other hand tumour occurrence is more common in patients with anti-NMDAR antibodies and mostly in female patients [17]. A further follow-up and screening for malignancies is recommended and should be repeated on all patients of this study, especially the female patients with anti-NMDAR antibodies.

5.6 CSF Parameters

While all NG patients and the DPP had multiple LPs taken during the follow-up period, only one out of five GG patients had multiple LPs, with the other four only having one LP taken. This difference in number of tests made for each group could possibly be explained by the fact that the NG patients had a tendency of being in a worse state, with more severe symptoms than patients of GG (see 4.4 Symptoms and 4.9 Outcome, pages 15-16 and 20-21). When a patient is not responding to treatment and not showing any signs of improvement it is quite understandable that more tests are taken, compared to for patients that are clearly improving. Since all anti-GAD patients that received IST responded well (see 4.8 Treatment, pages 19-20), the physicians probably did not feel the need for further tests.

5.7 Outcome

The fact that no patient got the correct diagnosis until after meeting a neurologist clearly states the importance of having a neurologist's assessment of these patients. So far autoimmune encephalitis is fairly rare, and maybe not the first diagnosis that comes in mind during general examination by the

common physician. However, with more acquired knowledge of the disease, and its diverse symptoms, hopefully a physician might recognise symptoms and seek a neurologist's consultation sooner. This would hopefully result in an earlier diagnosis as well as helping the patients to get suitable treatment earlier on. The fact that each of these 9 patients got sent home at onset and needed to return for the baseline visit of this study is not acceptable.

According to the literature, patients with anti-NMDAR encephalitis are more likely to improve and have fewer relapses if immunotherapy is started early after onset of symptoms [28, 31]. The results of this study, however, indicate that there was no clear difference in outcome between patients getting an early diagnosis and treatment compared to other patients. There was much rather a difference in outcome between the two patient groups, NG and GG, without regard to how early treatment was started. Patients from GG scored, non significantly, a median of 10 points higher on KPS than NG because they had more functional recovery, being able to return to work or study at 12-month follow-up, as before disease onset.

This is contradictory to the literature where anti-GAD mediated encephalitis is generally regarded as a difficult form of AIE to treat, while patients with anti-NMDAR antibodies are more likely to recover, especially if treatment is started early [20, 28]. One possible reason for why the GG patients of this study had a better outcome than those of NG could be due to the fact that they responded better to IST than the NG patients. The GG patients did not need additional treatment measures and they appeared to recover soon after starting initial treatment. However, even this is contradictory to what Malter et al. [20] described, where anti-GAD patients did not respond well to treatment.

Before drawing any conclusions, it is important to note that this study only covered the time of onset, the baseline visit and up until 12 months from the baseline visit. There is a possibility that patients in both groups could be more or less likely to have a relapse later on. Notably, one GG patient had already had a relapse, not as severe, but still a relapse and therefore started treatment again. Furthermore, even though the patients of GG had a tendency of being more functional (being able to get back to work) and therefore scoring higher on KPS, they still showed symptoms of epileptic seizures and psychiatric symptoms, which the NG patients did not. Keeping this in mind, there is no easy way to say that one patient group had a better recovery than the other.

5.8 Advantages and Disadvantages of the Study

5.8.1 Advantages

The establishment of onset, the baseline visit and the 12-month follow-up from the baseline visit as time points for comparison, gave a good view of symptoms and outcome for these patients. Using the baseline visit shows how many patients were sent home with their original symptoms, only to return later in a worse state. If only onset and 12-month follow-up dates had been selected and viewed many patients would probably not have been considered as sick, and since most patients were in a better state at onset compared to at 12-month follow-up there is also a risk that they would have appeared to have worsened during the first year. However, by taking into consideration the patients' states at the baseline visit, it was possible to get a better view of the severity of their disease as well as to assess how much the treatment did for each patient. This baseline visit helped in all further comparisons

between the groups, which may also help in clinical practice. These results give a clear indication that there is a risk that these patients may be misdiagnosed at onset of their symptoms and even get sent home without further follow-up, only to return in a worse state.

The very thorough and comprehensive analysis of all records for every single patient gives this study the opportunity to take into account all relevant decisions or judgements made by either the physician, or the health care professionals that examined the patient. Furthermore, since one and the same person analysed all of the files for all patients, the risk for a bias in the way that data was collected was reduced.

Another advantage of this study was the use of KPS in addition to MRS. Since many authors use MRS to compare the progression and outcome of AIE patients, it was also used in this study [28]. However, during the collection of data, MRS often did not give as good of a picture of the patient as the KPS scale. This might be due to the fact that the MRS is created around and applied to correctly diagnose the outcome of stroke patients and their handicap. This scale is therefore very focused on the patients' ability to walk, but walking was not the biggest issue for the patients in this study, except for one who had a prior stroke diagnosis [35]. With the help of KPS it was possible to properly show which group had a greater functional ability and therefore give a more detailed view of each patient's outcome. As seen in 4.9 Outcome (pages 20-21), both groups had the same median value on MRS but different on KPS, without this second scale, it would have been more difficult to present this difference.

In addition, another advantage of this study was the design, i.e. to compare different groups of AIE patients. One group containing patients with the probably most common AIE antibody, anti-NMDAR patients [17], one with another less known antibody group and then the third being a double positive patient (having both antibodies). Even though there was only one double positive patient the data from this patient could often give a good view as of being somewhere in between both groups and could aid in assessing whether any symptoms were more common in one group than the other. In brief, all comparison data collected with this study design can help (especially in a identical study with more patients and higher statistical power) determining how much of the information from anti-NMDAR patients is applicable to other AIE patients [5].

5.8.2 Disadvantages

According to the literature anti-NMDAR based encephalitis often appears after a recent infection. In one study approximately 70% of anti-NMDAR patients had headache or fever at onset [5]. Therefore, it would have been interesting to have more information on patients' infections within at least a month before onset. Nevertheless, the information of the temperature at onset, that was available for 8/9 patients, made it possible to assess a possible fever at onset. This only patient with no data regarding the temperature at onset was also one out of two patients with a diagnosed infection close to onset and it would have been interesting to know if this patient had a fever or not.

Only one patient was examined with The Montreal Cognitive Assessment (MoCA) test to assess memory disturbance. In addition, there was no clear evidence of psychiatric tests being made, or at least not enough results to build on and compare between groups. Since the data was acquired by reading patient files retrospectively, without any significant test results, and then used to determine

possible cognitive and psychiatric abnormalities, the assessment of these symptoms was quite subjective. However, if this had been a prospective study with every single patient examined with the same tests for these abnormalities, the results might have given a clearer and more reliable comparison between groups. On the other hand, since the same person collected and analysed all data for this thesis, the researcher bias was reduced.

Assessment of symptoms was done without regard to possible medications that each patient was receiving. It was thought better to describe symptom presentation exactly as noted in the medical records instead of assuming that the patients might have presented differently if they had no symptomatic treatments.

One unfortunate imperfection of the medical records was the lack of information on patients' medication history. Most commonly the only available information to use was a limited notification from doctors planning a treatment or sometimes information on patient receiving medications during nursing at hospital. This resulted in a lot of research time wasted in double-checking day to day in all records to find a possible change in medication or side effects. This also made it difficult to assess the value of the different treatment methods. Reading every detail about these treatments was a time consuming process, which could have been better spared for looking up data for more patients. In the same manner, the medical records only contained limited information on antibody quantification, usually also without stating antibody titres, whether other antibodies were checked or even sometimes whether the antibodies were measured in serum or CSF.

Another reason for the incomplete data found in the medical records was that every time a patient was originally registered in a hospital near SUH and later admitted to SUH for further treatments, only a part of the data was transferred and became viewable in Melior. This was the case for two patients of this study, and unfortunately both were from NG (two out of three NG patients). The author had access to all the medical records for these patients but not to all lab results and diagnostic work-ups. Moreover, sometimes if a special examination was claimed to have been performed at another hospital there was no way to obtain the results, at least not in Melior. This was one of the reasons for the restricted comparison between groups in this study and could have created a bias in data evaluation. This restriction to data also raises the question of whether other diagnostic work-up data might have been missed.

The fact that two patients got delayed diagnoses and were both from GG, might have affected the results. One of these patients was not diagnosed until years after the follow-up period and could therefore not be used for comparison of IST. The other was diagnosed around 6 months after the baseline visit and therefore started treatment later than the other patients of this study. This affects the comparisons at 12-month follow-up. The GG patient not diagnosed during this study period, kept all the same symptoms as well as work percentage (50%) and KPS and MRS scores throughout the entire follow-up period and had a normal MRI without deterioration. However, the GG patient, with the diagnosis around 6 months from the baseline visit, responded well to treatment and was on the road of recovery. However, having started IST later than the other patients, this patient went from working at onset and baseline visit to being the only GG patient not working at 12-month follow-up and was also the only GG patient with a worsening between MRI scans.

From my own point of view, with my experience now and all the knowledge I have gained during this work, I would perhaps have started this project differently. Gone faster through some medical record data while putting more emphasis on other fields, which could be useful for this thesis. I would also try to find a similarity between groups earlier and not assess so many different symptoms, treatments and everything in this great detail and rather spend more time collecting data about more patients for comparison (other antibody groups). There was also much time consumed looking for data that could be interesting for comparison but was not available. Some examples have already been mentioned, but it can be added that if there had been a better collection of electrolytes for each patient at each visit it would have been possible to compare electrolyte disturbances between patient groups. This could in turn maybe have given a clue as to whether electrolyte changes were common or not in patients with AIE and if so, what types are most occasionally seen. But electrolyte status was only available for a few patients, most of them having some abnormalities, but when there was no more data to be found for the other patients, this collection was skipped all together.

5.9 Conclusions

This thesis gives no ground breaking results with only one statistically significant difference, that patients with anti-NMDAR antibodies are more likely to show personality changes than patients with anti-GAD antibodies ($p=0,0179$). Still it manages to show a slight difference in tendencies between the groups, which gives an idea about differences that might have been statistically significant if the groups were larger. While most of these differences are similar to recent studies, one is contrary to earlier findings. In this study, patients with anti-GAD antibodies appear to respond better to IST than do patients with anti-NMDAR antibodies and even though they appear to have more symptoms at 12-month follow-up than patients with anti-NMDAR antibodies, the anti-GAD patients seem to be more functional and have a greater possibility of going back to work, or studies, as prior to their disease onset. However, our patient group was very small and data was collected retrospectively. Therefore, this investigation should be repeated prospectively, in a larger patient group, over a longer period of time. The way our results differ from earlier findings, as well as the fact that none of these patients got correctly diagnosed at onset, emphasises the need for further research of these different groups of AIE.

5.10 Next Steps

The next step for this study would be to add the other subgroups of the 41 patients in Melior and assess in a similar way for a greater comparison. Even though adding such small patient groups probably wont result in something statistically significant, it could further deepen our knowledge about the diversity of these syndromes.

Furthermore, there is a work in progress to create a separate database for all patients with AIE in Sweden. The goal is to make data regarding each of these patients more available, to ease in future comparisons and research, as well as setting up standard procedure methods so that each new case of AIE will have a similar prospective follow-up.

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Appendix

Appendix 1

A detailed overview of some known autoantibodies and their classification as put forth by Graus et al. [2].

	Syndrome	Diagnostic assay	Frequency of cancer	Main type of cancer
Antibodies against intracellular antigens				
Hu (ANNA1) ^{8*}	Limbic encephalitis	Western blot	>95%	Small-cell lung carcinoma
Ma2 ⁹	Limbic encephalitis†	Western blot	>95%	Testicular seminoma
GAD ¹⁰	Limbic encephalitis‡	Radioimmunoassay	25%§	Thymoma, small-cell lung carcinoma
Antibodies against synaptic receptors				
NMDA receptor ¹¹	Anti-NMDA receptor encephalitis	Cell-based assay	Varies with age and sex	Ovarian teratoma¶
AMPA receptor ¹²	Limbic encephalitis	Cell-based assay	65%	Thymoma, small-cell lung carcinoma
GABA _B receptor ¹³	Limbic encephalitis	Cell-based assay	50%	Small-cell lung carcinoma
GABA _A receptor ¹⁴	Encephalitis	Cell-based assay	<5%	Thymoma
mGluR5 ¹⁵	Encephalitis	Cell-based assay	70%	Hodgkin's lymphoma
Dopamine 2 receptor ¹⁶	Basal ganglia encephalitis	Cell-based assay	0%	..
Antibodies against ion channels and other cell-surface proteins				
LGI1 ¹⁷	Limbic encephalitis	Cell-based assay	5–10%	Thymoma
CASPR2 ¹⁸	Morvan's syndrome or limbic encephalitis	Cell-based assay	20–50%	Thymoma**
DPPX ¹⁹	Encephalitis††	Cell-based assay	<10%	Lymphoma
MOG ²⁰ ‡‡	Acute disseminated encephalomyelitis	Cell-based assay	0%	..
Aquaporin 4 ²¹ ‡‡	Encephalitis	Cell-based assay	0%	..
GQ1b ²²	Bickerstaff's brainstem encephalitis	ELISA	0%	..

GAD=glutamic acid decarboxylase. LGI1=leucine-rich glioma inactivated 1. CASPR2=contactin associated protein 2. DPPX=dipeptidyl-peptidase-like protein-6. MOG=myelin oligodendrocyte glycoprotein. *Amphiphysin or CV2 (CRMP5) antibodies instead of Hu antibodies in a few patients with limbic encephalitis and small-cell lung carcinoma. †Limbic encephalitis frequently associated with hypothalamic and mesencephalic involvement. ‡GAD antibodies occur more frequently in patients with stiff person syndrome and cerebellar ataxia. The association with cancer preferentially occurs in patients with limbic encephalitis. §Tumours found more frequently in men older than 50 years.²³ ¶Ovarian teratoma usually found in young women aged 12–45 years. ||Morvan's syndrome usually has a more chronic clinical course, but might present with predominant cognitive and behavioural symptoms fulfilling criteria of possible autoimmune encephalitis. **Thymoma associated with Morvan's syndrome rather than limbic encephalitis. ††Encephalitis associated with diarrhoea and hyperekplexia. ‡‡Mostly restricted to children.

Table: Antibodies in the diagnosis of autoimmune encephalitis

Appendix 2

MRS is a modified version of a scale created by John Rankin and is often used in the assessment of stroke patients' handicap. This scale measures the degree of disability of a patient and is therefore also suitable when assessing disabilities caused by other neurological diseases. Patients are graded from the score of zero to 6, where zero equals no symptoms and 6 equals death [34, 35].

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

Appendix 3

The first sheet used for extraction of data.

Autoimmune encephalitis

Date (<u>dd-mm-yyyy</u>):	Patient ID:
	Doctor's ID:

|

Patient <u>study ID</u>		
Date of birth (YYYY-MM-DD)		
Gender		
<u>Diagnosis</u>		
	Start date	Stop date
I <u>Onset diagnosis</u>		
II		
III		
IV		
V		

Comments:

Appendix 4 A:

The second sheet used for extraction of data, on three pages (A-C).

Date (dd-mm-yyyy):	Visit number:	Patient ID:
		Doctor's ID:

ANTINEURONAL ANTIBODIES IN CSF			
CSF sample date:	<input type="checkbox"/> Same as visit date <input type="checkbox"/> Other date: <u> </u>		
CSF antibodies (conclusion)	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal <input type="checkbox"/> Impossible to assess		
Group	Tested antibodies		
CSF Antibodies (summary)	<input type="checkbox"/> Complete <input type="checkbox"/> Not complete	Results	Exact value
Neuronal surface antibodies	AMPA1	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	AMPA2	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	CASPR2	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	GABA _A receptors	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	GABA _B receptors	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Glycine receptors	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	LGI1	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	mGluR5	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	NMDA receptors	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Other (specify!): <u> </u>	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
<input type="checkbox"/> Onconeural antibodies	Amphiphysin	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	CV2/CMPR5	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Ma1	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Ma2/Ta	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Hu	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Yo	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	

Appendix 4 B:

Autoimmune encephalitis

Date (dd-mm-yyyy):	Visit number:	Patient ID:
		Doctor's ID:

	Ri	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Other (specify!):	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
Other specified antibodies	<input type="checkbox"/> GAD	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	<input type="checkbox"/> Other (specify!):	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	

ANTINEURONAL ANTIBODIES IN SERUM			
Serum sample date:	<input type="checkbox"/> Same as visit date <input type="checkbox"/> Other date:		
Serum antibodies (conclusion)	<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal <input type="checkbox"/> Impossible to assess		
Group	Tested antibodies		
Serum Antibodies (summary)	<input type="checkbox"/> Complete <input type="checkbox"/> Not complete	Results	Exact value
Neuronal surface antibodies	AMPA1	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	AMPA2	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	CASPR2	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	GABA _A receptors	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	GABA _B receptors	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Glycine receptors	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	LGI1	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	mGluR5	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	NMDA receptors	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Other (specify!):	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	

Appendix 4 C:

Autoimmune ~~encephalitis~~

Date (dd -mm- yyyy):	Visit number:	Patient ID:
		Doctor's ID:

<input type="checkbox"/> Oncone uronal antibodies	Amphiphysin	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	CV2/CMPR5	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Ma1	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Ma2/Ta	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Hu	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Yo	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Ri	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	Other (specify!); www	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
Other specified antibodies	<input type="checkbox"/> GAD	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	
	<input type="checkbox"/> Other (specify!):	<input type="checkbox"/> Positive <input type="checkbox"/> Negative <input type="checkbox"/> Impossible to assess	



Appendix 5

The third sheet used for extraction of data.

Autoimmune encephalitis

Date (dd-mm-yyyy):	Visit number: 0	Patient ID:
		Doctor's ID:

Y. SYMPTOM(S) ONSET

Symptom onset date	<input type="checkbox"/> Unknown		
First symptom(s) at onset (1-6)	<input type="checkbox"/> Epileptic seizures <input type="checkbox"/> Status epilepticus <input type="checkbox"/> Psychiatric symptoms <input type="checkbox"/> Cognitive problems <input type="checkbox"/> Movement disorders <input type="checkbox"/> Sleep disorders <input type="checkbox"/> Impairment of consciousness <input type="checkbox"/> Autonomic symptoms <input type="checkbox"/> Focal neurologic symptoms <input type="checkbox"/> Other ... <input type="checkbox"/> Unknown		
Infection (within one month before onset)	<input type="checkbox"/> Yes <input type="checkbox"/> Viral <input type="checkbox"/> Bacterial <input type="checkbox"/> Other	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
Date for prodromal infection	<input type="checkbox"/> Unknown		
Symptoms for infection	<input type="checkbox"/> Nasal <input type="checkbox"/> Throat <input type="checkbox"/> Respiratory <input type="checkbox"/> Muscular pain <input type="checkbox"/> Abdominal <input type="checkbox"/> Other....	<input type="checkbox"/> Rhinitis <input type="checkbox"/> Laryngitis <input type="checkbox"/> Myalgia <input type="checkbox"/> Urinary <input type="checkbox"/> Coughing	
Fever at onset	<input type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Unknown
Date for fever	<input type="checkbox"/> Unknown		
Date for first medical contact	<input type="checkbox"/> Unknown		
Date for admission in hospital	<input type="checkbox"/> Unknown		
Date for first neurologic contact	<input type="checkbox"/> Unknown		
<input type="checkbox"/> Impossible to perform			
<input type="checkbox"/> Completed		<input type="checkbox"/> Not completed	

Radu Constantin ... 14/6/2016 16:19
Comment [1]: Minst ett kryss i varje rad nedan, annars Not ~~completed~~ alt. Impossible to perform. Specify if possible.

Radu Constantin ... 8/2/2017 10:58
Comment [2]: If YES, then specify (depression, psychosis, anxiety, personality disturbance, etc.)

Radu Constantin ... 8/2/2017 10:59
Comment [3]: If YES, then specify (memory disturbance, disoriented, ~~dyscognitive~~ disorder, diminished concentration, etc.)

Radu Constantin ... 8/2/2017 11:09
Comment [4]: If YES, then specify (coma, confusion)

Radu Constantin ... 8/2/2017 11:01
Comment [5]: If YES, then specify (cardiac, blood pressure, sweating, urinary, bowel, etc.)

Radu Constantin ... 8/2/2017 11:07
Comment [6]: If YES, then specify (paresis, sensory disturbance, etc.)

Appendix 6 A

The fourth sheet used for extraction of data, on two pages (A-B).

Autoimmune encephalitis

Visit date (dd-mm-yyyy):	Visit number:	Patient ID:
Symptom onset date: ...	Doctor's ID:	
Days from Treatment Day 1: ...		

15. SYMPTOMS FROM CORE CLINICAL DOMAINS

				Onset date
1) Epileptic seizures	Epileptic seizures ¹	<input type="checkbox"/> YES	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
	Status epilepticus	<input type="checkbox"/> YES	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
	Number of all seizures/week ²	<input type="checkbox"/> ... <input type="checkbox"/> Not known		
2) Psychiatric symptoms	Psychiatric symptoms	<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
	Specify symptoms			
3) Cognitive problems	Cognitive abnormalities	<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
	MOCA	... <input type="checkbox"/> Not performed		
4) Movement disorders		<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
5) Sleep disorders		<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
6) Impairment of consciousness		<input type="checkbox"/> YES	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
	Confusion	<input type="checkbox"/> YES	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
	Coma	<input type="checkbox"/> YES	<input type="checkbox"/> NO <input type="checkbox"/> Impossible to assess	
Number of affected clinical domains (0-6)		<input type="checkbox"/>		

¹ Any kind of epileptic seizure.

² Average number of all seizures per week (based on past month)

Radu Constanti... 8/2/2017 11:15
Comment [1]: Specify when possible

Appendix 6 B

Autoimmune encephalitis

Visit date (dd-mm-yyyy):	Visit number:	Patient ID:
Symptom onset date: ...	Doctor's ID:	
Days from Treatment Day 1: ...		

Autonomic symptoms	<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO	
Focal neurologic symptoms	<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO	
Peripheral neurologic symptoms	<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO	
Electrolyte disturbances	<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO	
Fatigue/Psychasthenia	<input type="checkbox"/> YES	<input type="checkbox"/> NO	
Other significant symptoms	<input type="checkbox"/> YES (specify)	<input type="checkbox"/> NO	

Radu Constant... 8/2/2017 11:17
Comment [2]: E.g. hyponatremia, etc.

Radu Consta... 19/8/2016 09:24
Comment [3]: Specify

Appendix 7

The fifth sheet used for extraction of data.

Autoimmune encephalitis

Date (<u>dd-mm-yyyy</u>):	Visit number:	Patient ID:
		Doctor's ID:

<u>Outcome</u>	
<u>Karnofsky Performance Status Scale</u>	
<u>Modified Rankin Scale (mRS)</u>	
<u>Work</u>	<input type="checkbox"/> Sick leave <input type="checkbox"/> Working <input type="checkbox"/> Part time %..... <input type="checkbox"/> Full time <input type="checkbox"/> Retired <input type="checkbox"/> Age <input type="checkbox"/> Sickness
<u>Marriage</u>	<input type="checkbox"/> Single <input type="checkbox"/> Married <input type="checkbox"/> Partnership <input type="checkbox"/> Divorced <input type="checkbox"/> Widowed
<u>Level of care</u>	<input type="checkbox"/> At home <input type="checkbox"/> without help <input type="checkbox"/> help from kin <input type="checkbox"/> help from social services <input type="checkbox"/> Nursing home <input type="checkbox"/> Personal assistants <input type="checkbox"/> 100% (day and night) <input type="checkbox"/> Day only <input type="checkbox"/> % / hours per day
<u>Hospitalization</u>	<input type="checkbox"/> Still in hospital <input type="checkbox"/> Discharged at date:
<u>Death</u>	<input type="checkbox"/> Yes Date of death: <input type="checkbox"/> No

Appendix 8

The Karnofsky performance scale (KPS) is a scale developed for assessment of a patient's health and functional status. The scale runs from zero to 100 points with 10-point intervals. Zero is the lowest score and equals death while 100 is the highest and equals a patient without any complaints or symptoms of disease. KPS works better or equally well as the Activities of daily living and the Instrumental activities of daily living scales for predicting a patient's outcome and is more reliable for classification of patients into high- and low-risk groups [41].

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Appendix 9

The sixth sheet used for extraction of data.

Date (dd-mm-yyyy):	Visit number:	Patient ID:
		Doctor's ID:

BRAIN MRI

Brain MRI (conclusion)	<input type="checkbox"/> Normal <input type="checkbox"/> <u>Abnormal</u> <input type="checkbox"/> Impossible to <u>assess</u>
Comparison with previous visit	<input type="checkbox"/> Improvement <input type="checkbox"/> Deterioration <input type="checkbox"/> Unchanged <input type="checkbox"/> Not applicable

ABNORMAL BRAIN MRI

	Hippocampus	Temporal lobe	Other location (specify below)
Pathology present	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No
T2/FLAIR signal increase	<input type="checkbox"/> Left <input type="checkbox"/> Right	<input type="checkbox"/> Left <input type="checkbox"/> Right	<input type="checkbox"/> Left <input type="checkbox"/> Right
Atrophy	<input type="checkbox"/> Left <input type="checkbox"/> Right	<input type="checkbox"/> Left <input type="checkbox"/> Right	<input type="checkbox"/> Left <input type="checkbox"/> Right
Other pathology	<input type="checkbox"/> Left <input type="checkbox"/> Right	<input type="checkbox"/> Left <input type="checkbox"/> Right	<input type="checkbox"/> Left <input type="checkbox"/> Right
Related to AIE ¹	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unclear

Other location for pathology (other than hippocampi and temporal lobes)	<input type="checkbox"/> Focal <input type="checkbox"/> Multifocal <input type="checkbox"/> Diffuse
	<input type="checkbox"/> <u>Supratentorial</u> <input type="checkbox"/> <u>Infratentorial</u>
	<input type="checkbox"/> Meninges <input type="checkbox"/> Ventricles <input type="checkbox"/> Gray matter <input type="checkbox"/> <u>White matter</u>
	<input type="checkbox"/> Frontal <input type="checkbox"/> Parietal <input type="checkbox"/> Occipital <input type="checkbox"/> Insula <input type="checkbox"/> <u>Basal ganglia</u> <input type="checkbox"/> Thalamus <input type="checkbox"/> Brainstem <input type="checkbox"/> Cerebellum <input type="checkbox"/> Spinal cord

Comments:

Appendix 10

The seventh sheet used for extraction of data.

Date (dd-mm-yy):	Visit number:	Patient ID:
		Doctor's ID:

Malignancy investigations		
Malignancy investigation	Date	Conclusion
CT abdomen and pelvis		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy ◊ Other abnormality <input type="checkbox"/> Impossible to assess
CT thorax		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy ◊ Other abnormality <input type="checkbox"/> Impossible to assess
Gynecological examination		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy ◊ Other abnormality <input type="checkbox"/> Impossible to assess <input type="checkbox"/> Not relevant (male)
Mammography		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy ◊ Other abnormality <input type="checkbox"/> Impossible to assess <input type="checkbox"/> Not relevant (male)
Ultrasound testis		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy ◊ Other abnormality <input type="checkbox"/> Impossible to assess <input type="checkbox"/> Not relevant (female)
PET-CT <input type="checkbox"/> High dose CT <input type="checkbox"/> Low dose CT		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy ◊ Other abnormality <input type="checkbox"/> Impossible to assess
CSF-immunophenotype		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy (lymphoma) ◊ Other abnormality <input type="checkbox"/> Impossible to assess <input type="checkbox"/> Not relevant
Other (specify)...		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy ◊ Other abnormality <input type="checkbox"/> Impossible to assess
Conclusion		<input type="checkbox"/> Normal <input type="checkbox"/> Abnormal ◊ Malignancy (specify) ◊ Other abnormality <input type="checkbox"/> Impossible to assess <input type="checkbox"/> Not completed

Radu Constanti, 8/2/2017 11:38

Comment [1]: When repeated, fill in a new form each time.

Appendix 11

The eighth sheet used for extraction of data.

Date (dd-mm-yyyy):	Visit number:	Patient ID:
		Doctor's ID:

CEREBROSPINAL FLUID				
CSF inflammation (YES on any of the following)		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
				<i>Exact value</i>
<u>Pleocytosis</u>	<3 cells/ <u>ul</u>	<input type="checkbox"/> Yes <input type="checkbox"/> Monocytes <input type="checkbox"/> Lymphocytes <input type="checkbox"/> Neutrophils	<input type="checkbox"/> No	Monocytes....
				Lymphocytes....
				Neutrophils....
High <u>IgG</u> index ¹	>0,63	<input type="checkbox"/> Yes	<input type="checkbox"/> No	...
High <u>IgM</u> index	>0,060	<input type="checkbox"/> Yes	<input type="checkbox"/> No	...
<u>Oligoclonal</u> bands	>1 band	<input type="checkbox"/> Yes	<input type="checkbox"/> No	...
Blood-brain barrier disruption (YES on any of the following)		<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Increased blood/CSF albumin ratio (18-45 years: >6.8; 45-90 years: >10.2)		<input type="checkbox"/> Yes	<input type="checkbox"/> No	...
Increased CSF albumin (>320 mg/L)		<input type="checkbox"/> Yes	<input type="checkbox"/> No	...

Neuronal damage markers	Normal	Abnormal (high)	Exact value
NFL			
GFAP			
T-Tau			
β-amyloid			

Appendix 12 A

The ninth sheet used for extraction of data, on two pages (A-B).

Autoimmune encephalitis

Date (dd-mm-yyyy):	Visit number:	Patient ID:
		Doctor's ID:

Immunomodulatory treatment

	Immunotherapy	Start date	Stop date	Daily dose	No. of treatment days per treatment cycle	No. of treatment cycles
0	<input type="checkbox"/> No immunotherapy			NA	NA	NA
1	<input type="checkbox"/> Corticosteroid pulse					
2	<input type="checkbox"/> Peroral steroids				NA	NA
3	<input type="checkbox"/> IVIG ¹					
4	<input type="checkbox"/> Plasma exchange (PLEX) ²			NA		
5	<input type="checkbox"/> Cyclophosphamide [^]					
6a	<input type="checkbox"/> Rituximab ^{^^} (first)					
6b	<input type="checkbox"/> Rituximab ^{^^} (second)					
6c	<input type="checkbox"/> Rituximab ^{^^} (third)					
6d	<input type="checkbox"/> Rituximab ^{^^} (fourth)					
7	<input type="checkbox"/> Azathioprine ^{^^^}				NA	NA
8	<input type="checkbox"/> Methotrexate				NA	NA
9	<input type="checkbox"/> Other					
10	<input type="checkbox"/> Other					

¹ = intravenous immunoglobulins

² = plasmaferes

[^] = Sendoxan

^{^^} = Mabthera

^{^^^} = Imurel

NA = not applicable

Appendix 12 B

Autoimmune encephalitis

Date (dd-mm-yyyy):	Visit number:	Patient ID:
		Doctor's ID:

	Immunotherapy	Efficacious	Not efficacious	Questionable efficacy	Side effects/adverse events
0	<input type="checkbox"/> No immunotherapy				
1	<input type="checkbox"/> Corticosteroid pulse				
2	<input type="checkbox"/> Peroral steroids				
3	<input type="checkbox"/> IVIG ¹				
4	<input type="checkbox"/> Plasma exchange (PLEX) ²				
5	<input type="checkbox"/> Cyclophosphamide [^]				
6a	<input type="checkbox"/> Rituximab ^{^^} (first)				
6b	<input type="checkbox"/> Rituximab ^{^^} (second)				
6c	<input type="checkbox"/> Rituximab ^{^^} (third)				
6d	<input type="checkbox"/> Rituximab ^{^^} (fourth)				
7	<input type="checkbox"/> Azathioprine ^{^^^}				
8	<input type="checkbox"/> Methotrexate				
9	<input type="checkbox"/> Other				
10	<input type="checkbox"/> Other				

Appendix 13 A

The tenth sheet used for extraction of data, on two pages (A-B).

Autoimmune encephalitis

Date (dd-mm-yyyy):	Visit number:	Patient ID:
		Doctor's ID:

Symptomatic treatments

	Start date	Stop date	Notes
Antiepileptic drugs			
<u>Carbamazepine</u>			
<u>Valproate PO (tablets)</u>			
<u>Valproate IV</u>			
<u>Fenatoin PO (tablets)</u>			
<u>Fenatoin IV</u> (ProEpanutin*)			
<u>Levetiracetam</u> (Keppra*) PO			
<u>Levetiracetam</u> (Keppra*) IV			
<u>Lacosamid (Vimpat*)</u> PO			
<u>Lacosamid (Vimpat*)</u> IV			
<u>Topiramate</u> (Topimax*)			
<u>Clonazepam</u> (Iktorivil*) IV			
<u>Clonazepam</u> (Iktorivil*) PO			
Deep anesthesia for status epilepticus			
Deep anesthesia for status epilepticus			
Deep anesthesia for status epilepticus			
Deep anesthesia for status epilepticus			
Deep anesthesia for status epilepticus			
Deep anesthesia for status epilepticus			

Appendix 13 B

Autoimmune encephalitis

Date (<u>dd-mm-yyyy</u>):	Visit number:	Patient ID:
		Doctor's ID:

<u>Psychopharmaca</u>			
Antidepressants			
<u>Tranquilizants</u> (anti-anxiety)			
Antipsychotics			
Sleeping pills			
Other			

Appendix 14 A

Three panels with diagnostic criteria for AIE as put forth by Graus et al. [2], on two pages (A-B).

Panel 1: Diagnostic criteria for possible autoimmune encephalitis

Diagnosis can be made when all three of the following criteria have been met:

- 1 Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms
- 2 At least one of the following:
 - New focal CNS findings
 - Seizures not explained by a previously known seizure disorder
 - CSF pleocytosis (white blood cell count of more than five cells per mm³)
 - MRI features suggestive of encephalitis†
- 3 Reasonable exclusion of alternative causes (appendix)

*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

Panel 2: Diagnostic criteria for definite autoimmune limbic encephalitis

Diagnosis can be made when all four* of the following criteria have been met:

- 1 Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
- 2 Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
- 3 At least one of the following:
 - CSF pleocytosis (white blood cell count of more than five cells per mm³)
 - EEG with epileptic or slow-wave activity involving the temporal lobes
- 4 Reasonable exclusion of alternative causes (appendix)

*If one of the first three criteria is not met, a diagnosis of definite limbic encephalitis can be made only with the detection of antibodies against cell-surface, synaptic, or onconeural proteins. †¹⁸F-Fluorodeoxyglucose (¹⁸F-FDG) PET can be used to fulfil this criterion. Results from studies from the past 5 years suggest that ¹⁸F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal-appearing medial temporal lobes.^{44,45}

Appendix 14 B

Panel 4: Diagnostic criteria for anti-NMDA receptor encephalitis

Probable anti-NMDA receptor encephalitis*

Diagnosis can be made when all three of the following criteria have been met:

- 1 Rapid onset (less than 3 months) of at least four of the six following major groups of symptoms:
 - Abnormal (psychiatric) behaviour or cognitive dysfunction
 - Speech dysfunction (pressured speech, verbal reduction, mutism)
 - Seizures
 - Movement disorder, dyskinesias, or rigidity/abnormal postures
 - Decreased level of consciousness
 - Autonomic dysfunction or central hypoventilation
- 2 At least one of the following laboratory study results:
 - Abnormal EEG (focal or diffuse slow or disorganised activity, epileptic activity, or extreme delta brush)
 - CSF with pleocytosis or oligoclonal bands
- 3 Reasonable exclusion of other disorders (appendix)

Diagnosis can also be made in the presence of three of the above groups of symptoms accompanied by a systemic teratoma

Definite anti-NMDA receptor encephalitis*

Diagnosis can be made in the presence of one or more of the six major groups of symptoms and IgG anti-GluN1 antibodies,† after reasonable exclusion of other disorders (appendix)

*Patients with a history of herpes simplex virus encephalitis in the previous weeks might have relapsing immune-mediated neurological symptoms (post-herpes simplex virus encephalitis). †Antibody testing should include testing of CSF. If only serum is available, confirmatory tests should be included (eg, live neurons or tissue immunohistochemistry, in addition to cell-based assay).

Appendix 15

One table with diagnostic criteria for PNS as put forth by Graus et al. [12].

Table 4 Diagnostic criteria for paraneoplastic neurological syndromes (PNS)

Definite PNS

1. A *classical* syndrome and cancer that develops within five years of the diagnosis of the neurological disorder.
2. A non-classical syndrome that resolves or significantly improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission.
3. A non-classical syndrome with onconeural antibodies (well characterised or not) and cancer that develops within five years of the diagnosis of the neurological disorder.
4. A neurological syndrome (classical or not) with well characterised onconeural antibodies (anti-Hu, Yo, CV2, Ri, Ma2, or amphiphysin), and no cancer.

Possible PNS

1. A classical syndrome, no onconeural antibodies, no cancer but at high risk to have an underlying tumour.
 2. A neurological syndrome (classical or not) with partially characterised onconeural antibodies and no cancer.
 3. A non-classical syndrome, no onconeural antibodies, and cancer present within two years of diagnosis.
-