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Autoimmune Encephalitis

Epidemiology, Clinical Characteristics, and Biomarkers

SONJA KOSEK



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Abstract

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Autoimmune encephalitis (AE) and paraneoplastic neurological syndromes (PNS) are immune-mediated disorders of the nervous system, often associated with neuronal antibodies detectable in blood or cerebrospinal fluid (CSF). Most neuronal antibodies and their associated disorders were identified within the past two decades, substantially improving patient outcomes. This thesis aims to expand our understanding of AE and PNS regarding epidemiology, clinical features, and potential biomarkers.

First, incidence rates of AE and PNS in Healthcare Region Mid Sweden were estimated, and nationwide trends in neuronal antibody testing were analyzed. Between 2015-2019, the annual incidence of AE and PNS increased in parallel with expanding antibody testing, while the proportion of positive results declined slightly. Notably, only about one-third of patients with positive antibody tests fulfilled diagnostic criteria.

Second, clinical features of confirmed AE or PNS cases were characterized. Findings largely mirrored international cohorts, except for an unexpected older age distribution among anti-NMDAR encephalitis cases. Despite hallmark symptoms, diagnoses were often delayed, highlighting the need for greater clinical awareness. Additionally, the onset of non-tumor-related AE primarily occurred during the warm seasons, suggesting a possible seasonal trigger such as viral infections.

Third, a systematic review of studies reporting individual-level brain FDG-PET findings in AE revealed that FDG-PET abnormalities were more frequently detected than MRI abnormalities. Patterns varied by antibody, with medial temporal lobe hypermetabolism typical in some AE subtypes, while others showed complex combinations of hyper- and hypometabolism across multiple anatomical regions. These results underscore the need for refined interpretation strategies, including the selection of appropriate reference regions.

Finally, targeted proteomic profiling of serum and CSF in anti-NMDAR encephalitis revealed distinct, compartment-specific protein signatures involving microglial activation, synaptic dysfunction, and systemic protease activity. Caspase-8 (CASP-8) was significantly elevated in both serum and CSF, particularly in early disease, and dynamic changes correlated with clinical deterioration, suggesting potential utility as a biomarker of disease activity.

In summary, this thesis addresses key challenges encountered in the early stages of identifying a new disease group and contributes to the growing body of knowledge on potential disease biomarkers. The results aim to improve clinical awareness and stimulate further research in AE.

Keywords: paraneoplastic neurological syndromes; encephalitis; neuroinflammation; autoimmunity; proteomics; proximity extension assay; biomarkers

Sonja Kosek, Clinical Neurophysiology, Ingång 85, 3 tr, Akademiska sjukhuset, Uppsala University, SE-751 85 Uppsala, Sweden.

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List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. **Kosek S.**, Persson B., Rodrigues R., Malmeström C., Burman J., Punga A.R. (2023). Antibody-Positive Autoimmune Encephalitis and Paraneoplastic Neurological Syndrome: Epidemiology and Outcome of Neuronal Antibody Testing in Sweden. *Acta Neurologica Scandinavica*, 6993615, 9 pages.
- II. **Kosek, S.**, Burman, J., Punga A. R. (2024). Antibody-positive autoimmune encephalitis and paraneoplastic neurological syndrome: A Swedish case series. *Brain and behavior*, 14(5), e3534.
- III. **Kosek S.**, Kilsved E., Danfors T., Cunningham JL., Pavel R., Punga A.R., Burman J., Fällmar D. (2024) Regional Metabolic Abnormalities in Autoimmune Encephalitis: A Meta-analysis of 498 Cases With Brain FDG PET. *Clinical Nuclear Medicine*, Nov 27.
- IV. **Kosek S.**, Wiberg A., Persson B., Gabrysch K., Burman J., Punga A.R. Targeted Proteomic Profiling of Serum and CSF Reveals CASP-8 as a Candidate Biomarker in anti-NMDA Receptor Encephalitis. (*Manuscript*)

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Abbreviations

AE	Autoimmune encephalitides
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AIDP	Acute inflammatory demyelinating polyneuropathy
CASPR2	Contactin-associated protein-2
CBA	Cell-based assay
CIDP	Chronic inflammatory demyelinating polyneuropathy
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
DPPX	Dipeptidyl-peptidase-like protein-6
EEG	Electroencephalography
FDG-PET	Fluorodeoxyglucose positron emission tomography
FBDS	Faciobrachial dystonic seizure
GABA-B	γ -Aminobutyric acid-B
GAD65	Glutamate decarboxylase isoform 65
HSE	Herpes simplex encephalitis
HSV	Herpes simplex virus
ICU	Intensive care unit
IgLON5	Immunoglobulin-like cell adhesion molecule 5
LGI1	Leucine-rich glioma inactivated 1
LE	Limbic encephalitis
MRI	Magnetic resonance imaging
NMDAR	Anti-N-methyl-D-aspartate receptor
PCD	Paraneoplastic cerebellar degeneration
PNS	Paraneoplastic neurological syndrome
SCLC	Small-cell lung cancer
SIADH	Syndrome of inappropriate anti-diuretic hormone secretion
SPSD	Stiff person syndrome disorders
TBA	Tissue-based assay

Introduction

Autoimmune encephalitides (AE) and paraneoplastic neurological syndromes (PNS) are immune-mediated disorders of the nervous system, characterized by the presence of neuronal antibodies in serum or cerebrospinal fluid (CSF). While neuronal antibodies linked to PNS were first identified in the 1970s, the past two decades have seen remarkable progress with the discovery of numerous new antibodies and their association with AE. This development has transformed clinical practice. AE is now recognized as a treatable form of encephalitis, with many patients responding favorably to immunotherapy. Consequently, the spectrum of neuroimmunological disorders has broadened significantly. This thesis aims to deepen the understanding of this rapidly evolving field, providing insights into epidemiology, clinical characteristics, and biomarkers, with a particular focus on the Swedish context in relation to international findings.

Part 1: The Intricate Interplay of Neuroinflammation and Neurodegeneration

Historical Perspective

Encephalitis, inflammation of the brain parenchyma, can lead to behavioral changes, focal neurological deficits, fever, and epileptic seizures. Several of its infectious causes (e.g., West Nile virus and Herpes Simplex virus) were identified already in the 1930s and 1940s¹⁻³. Subsequently, numerous viruses and other infectious agents were recognized as causes of encephalitis, and the condition was regarded as an infectious disease.

Concurrently, rapidly progressing cerebellar degeneration in patients with carcinoma⁴, without CNS metastasis, was described, and an association between the carcinoma and the nervous disease was hypothesized. This hypothesis was strengthened in 1951 when Brain W.R. et al. published a case series describing subacute degeneration of Purkinje cells in patients with carcinoma⁵. An association between neuropathy and lung cancer had been proposed as early as the late 19th century⁶. The idea that cancer could have a remote effect

on the nervous system, possibly owing to metabolic imbalances, started to spread. The term “paraneoplastic syndrome” had been introduced a decade earlier and was adopted to describe this phenomenon ⁷.

In 1960, Brierley et al. described three patients with inflammation in the medial parts of the temporal lobes, the so-called “limbic system,” with no evidence of viral infection. Two of these patients had a concurrent malignancy ⁸. A few years later, the term “limbic encephalitis” was coined by Corsellis et al., and the association between subacute inflammation in the medial temporal lobes and malignancies was suggested ⁹. This provided an alternative etiology for encephalitis other than infection, namely a paraneoplastic cause. The mechanism by which the malignancy affected the brain remained elusive.

A few years later, another neurological disorder, myasthenia gravis (MG), was linked to thymoma ¹⁰, and an autoimmune etiology in MG was suggested. The breakthrough came in 1976 when Lindstrom et al. described antibodies targeting acetylcholine receptors on skeletal muscles in MG patients (**Figure 1**) ¹¹. That same year, Trotter et al. described a young woman with Hodgkin lymphoma who developed rapidly progressing cerebellar symptoms in whom serum antibodies against cerebellar Purkinje cells were detected (now known as anti-Tr antibodies) ¹². Subsequently, autoantibodies targeting other neuronal antigens were described in patients with various neurological syndromes and cancer (e.g., anti-Yo and anti-Hu antibodies)¹³⁻¹⁷. This sparked theories that the so-called paraneoplastic syndromes, including cases of encephalitis, could have an autoimmune etiology. However, unlike patients with MG in whom immunotherapy was beneficial, those with paraneoplastic neurological syndrome (PNS) rarely responded to treatment ¹⁸.

A breakthrough came in 2007, when Dalmau et al. described 12 young women with encephalitis, all of whom had teratomas. In all cases, antibodies targeting the NMDA receptor (NMDAR) were found in the serum or cerebrospinal fluid (CSF). Most patients experienced significant improvement following tumor resection and immunotherapy ¹⁹. This characteristic distinguished them from previously described paraneoplastic neurological syndromes, which had poor treatment responses. A year later, a larger case series confirmed the diagnosis in patients with and without tumors, most of whom responded to immunotherapy ²⁰. This further supported an autoimmune but not necessarily paraneoplastic etiology in encephalitis. Similar to the acetylcholine receptor (the target of autoantibodies in MG), the NMDA receptor is a cell surface protein. In contrast, the antigens previously described in paraneoplastic neurological syndromes (e.g., Yo, Hu) are all intracellular proteins. This discovery of immune-mediated encephalitis, which, similar to MG,

demonstrated a response to immunotherapy, altered the perception of encephalitis and its causes.

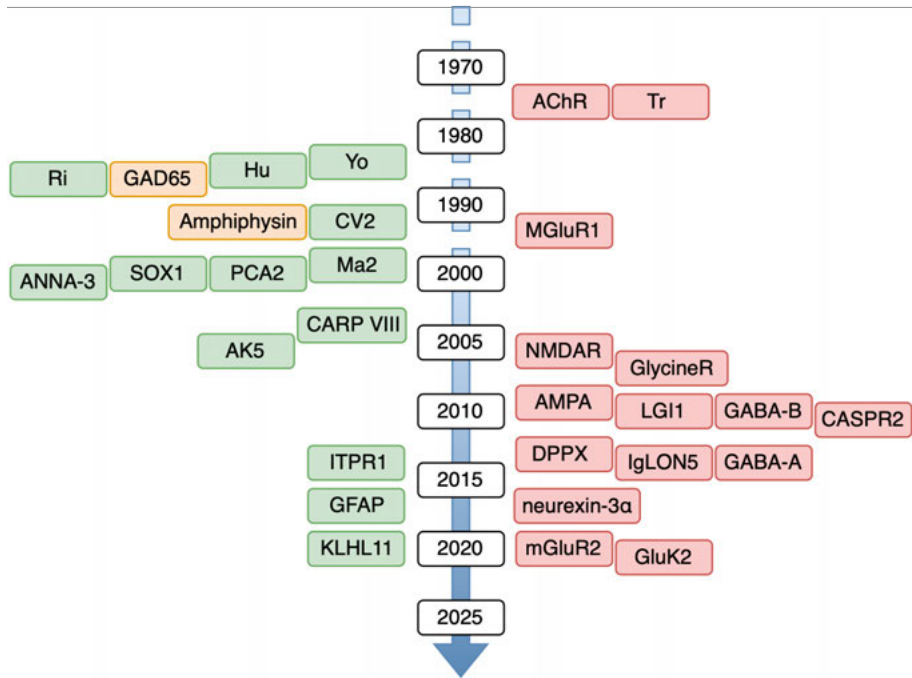


Figure 1. Timeline of neuronal antibody discovery. Antibodies targeting intracellular antigens (onconeural) are presented to the left in green boxes. Antibodies targeting neuronal surface antigens (NSAbs) are presented to the right in red boxes. Antigens with mixed intra- and extracellular characteristics are presented in yellow boxes. The figure is inspired by Segal et al.²¹

In the years to come, additional antibodies targeting neuronal surface proteins were identified, including leucine-rich glioma inactivated 1 antibodies (LGI1)²², contactin-associated protein-2 (CASPR2) antibodies²³, dipeptidyl-peptidase-like protein-6 (DPPX) antibodies²⁴, γ -Aminobutyric acid-B receptor (GABA-B) antibodies²⁵, and antibodies to the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA)²⁶. The proportion of patients with these antibodies having an associated tumor was generally low, with anti-GABA-B antibodies being the exception due to their frequent association with small-cell lung cancer (SCLC).

With new autoantibodies being rapidly discovered, two distinct groups of syndromes based on the antigens targeted started to emerge. Antibodies targeting intracellular structures (also called “onconeural” antibodies) were highly associated with cancer, and the clinical presentation of the patients was often that of classical paraneoplastic neurological syndromes (PNS). These

patients partially responded to tumor treatment but rarely responded favorably to immunotherapy. On the other hand, antibodies targeting neuronal surface proteins were rarely associated with tumors (with a few exceptions), and patients often demonstrated a good response to immunotherapy. This group of syndromes was named autoimmune encephalitides (AE). The characterization of these two new groups of immune-mediated encephalitis provided at least a partial explanation as to why, in previous epidemiological studies, viral etiology could not be confirmed in a significant portion of encephalitis cases ²⁷.

Pathophysiology

Autoantibodies targeting neuronal surface proteins and onconeural (intracellular) antigens are collectively referred to as neuronal antibodies. The term neuronal antibodies has a practical aspect, especially in clinical practice, as will be discussed later. However, merging these two groups of antibodies when discussing their pathophysiology makes little sense, so they will be discussed separately below.

Onconeural antibodies

Onconeural antibodies target intracellular neuronal antigens, such as RNA-binding proteins. These antigens are expressed exclusively in neuronal tissues of healthy individuals, but also in certain tumor cells. For example, the Hu-antigen is expressed by SCLC cells. This, however, does not automatically result in the production of anti-Hu antibodies, as only 17% of SCLC patients have these autoantibodies ²⁸. Furthermore, the presence of anti-Hu antibodies does not always cause neurological symptoms ^{29,30}. This lack of pathogenic effect seems true for all onconeural antibodies, of which several can be detected in patients with tumors without any neurological symptoms ³¹. Consequently, the onconeural antibodies themselves are not sufficient to cause neurological symptoms, as demonstrated in several animal studies ³²⁻³⁴. Rather, the onconeural antibodies appear to be markers for an underlying tumor and the subsequent anti-tumor immune response.

Neurological symptoms in onconeural antibody-associated PNS appear to result from a cellular immune response involving cytotoxic T-cells (**Figure 2**)^{35,36}. Autopsy studies of affected patients have revealed extensive infiltrates of cytotoxic T-cells and neurodegeneration ³⁷⁻³⁹. These T-cells target the same onconeural antigen as the associated onconeural antibody and participate in the body's defense against the tumor. In some individuals, this anti-tumor immune response may misdirect against their own nervous system, where the onconeural antigen is typically present. Consistent with this, patients with onconeural antibodies and cancer often experience slower disease progression

⁴⁰. This heightened T-cell activity is desired when using modern immune checkpoint inhibitors (ICI) in cancer treatment. ICIs disrupt T-cell regulation and, consequently, enhance the T-cell-mediated anti-tumor immune response. For patients with pre-existing PNS, this might result in worsening neurological symptoms, and ICIs may also trigger PNS ⁴¹.

It remains unclear why only some patients with tumors and onconeural antibodies develop neurological symptoms. There are indications of tumors with mutations in the onconeural antigen-encoding genes, which could trigger an immune response targeting the mutated antigen ⁴². To date, this has been sparsely studied, and it is not possible to say whether this is something all onconeural antigens in the context of PNS have in common or not.

Since the neurodegeneration caused by the T-cell-mediated immune response is permanent, immunotherapy has little effect on these patients.

Neuronal surface antibodies

Neuronal surface antibodies (NSAbs) target extracellular neuronal antigens, such as cell surface receptors and ion channels. The immune response in autoimmune encephalitis associated with NSAbs appears to be predominantly humoral, unlike the T-cell-mediated response observed in patients with onconeural antibodies. NSAbs have a direct pathogenic effect, as shown in several *in vitro* and *in vivo* studies ⁴³⁻⁴⁹. The binding of NSAbs to their respective antigens disrupts their normal function, causing altered neuronal signaling and neurological symptoms (**Figure 2**).

The most extensively studied anti-NMDAR antibodies induce cross-linking and subsequent internalization upon bindings of the NMDARs. This reversibly reduces the number of NMDARs on the surface of neurons and alters neuronal signaling⁵⁰. The reversibility explains why many patients have a favorable prognosis if treated promptly ⁵¹. However, over time, the initially reversible antibody-mediated disruption of NMDAR signaling may evolve into more permanent neuronal damage, which leads to glutamate toxicity ⁵².

Clinically relevant anti-NMDAR antibodies are predominantly of the IgG1 subclass, suggesting that complement activation may contribute to disease mechanisms ²⁰. However, findings in this area are conflicting. While CSF samples from patients with anti-NMDAR encephalitis have revealed elevated levels of complement components C6 and C7 ⁵³, autopsy studies have demonstrated deposits of IgG and infiltration of plasma cells in the brain, yet no deposits of complement ^{50,54}.

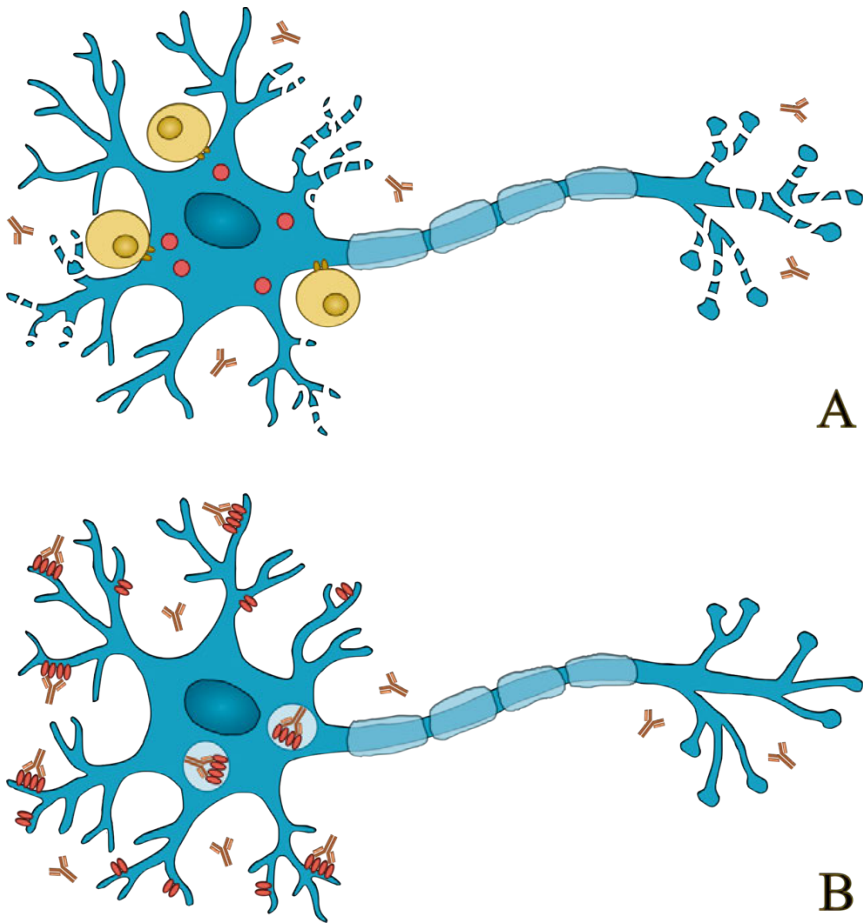


Figure 2 (A) *T*-cell-mediated neurodegeneration associated with onconeural antibodies targeting intracellular antigens (red circles). (B) Antibodies targeting cell surface antigens such as receptors induce cross-linking and internalization, leading to decreased numbers of receptors on the neuronal surface. The figure is inspired by Dalmau et al.⁵⁵

The immune response in anti-NMDAR encephalitis seems to be compartment-specific, with the CNS as the primary site of inflammation. This is evidenced by the intrathecal presence of plasma cells and the frequent detection of antibodies in CSF rather than in serum, pointing to local antibody synthesis⁵⁶. Plasma cells have a longer lifespan compared to other immune cells, which may explain why anti-NMDAR antibodies can be detected in patients long after disease onset and why severe cases might need prolonged immunotherapy^{56,57}. Elevated levels of CXCL13 and T cell-related cytokines in CSF indicate the involvement of both humoral and cellular immunity within the CNS^{58,59}.

Other subtypes of AE associated with NSAbs have been less extensively studied in terms of pathophysiology. Anti-LGI1 antibodies reversibly reduce synaptic AMPA receptors and voltage-gated potassium channels (VGKC) in neuronal cell cultures and mouse models^{60,61}. Anti-LGI1 antibodies are primarily of the IgG4 subclass, which may explain why CSF studies show no complement activation in these patients⁵³.

In contrast to anti-NMDAR encephalitis, the peripheral compartment seems to be the initial site of the immune response in anti-LGI1 encephalitis. Anti-LGI1 antibodies are more easily detected, and levels are higher in serum than in CSF^{62,63}. Although antibody-secreting cells are found in high numbers in the CSF of patients with anti-LGI1 encephalitis, their maturation occurs predominantly in the peripheral compartment⁶⁴. Additionally, the elevation of cytokine levels is less pronounced in the CSF of patients with anti-LGI1 encephalitis⁶⁵, which is consistent with typical unremarkable CSF findings in routine clinical testing⁶³. In contrast to anti-NMDAR encephalitis, patients with anti-LGI1 encephalitis more often present with an abnormal brain magnetic resonance imaging (MRI) and elevated neurofilament light chain (NFL, a marker of neuroaxonal damage) levels in CSF^{66,67}. This aligns with autopsy studies showing neuronal loss³⁷. Patients more often exhibit long-term cognitive dysfunction despite immunotherapy, particularly if not treated early on, implying that neurodegeneration progresses over time⁶⁸.

Markers of inflammation, such as chemokines and cytokines, are increased in the CSF of patients with various AE subtypes. For instance, the CSF levels of chemokines CXCL10, CCL3, and CCL20 are elevated, all of which are important for attracting immune cells to the site of inflammation in the early stages of inflammation⁶⁹⁻⁷². Pro-inflammatory cytokines IL-7 and IFN- γ are also increased^{70,72,73}, as are the anti-inflammatory cytokine IL-10, but with more divergent results^{69-71,74,75}. IL-6, necessary for the differentiation of T helper 17 cells (Th17 cells, a subset of pro-inflammatory CD4+ Th cells), and IL-17A, the signature cytokine of Th17 cells, are elevated in both serum and CSF of AE patients^{74,76}. This is similar to findings in other neuroinflammatory disorders, such as multiple sclerosis (MS), in which Th17 cells are thought to play an important effector role by disrupting the blood-brain barrier (BBB) and activating astrocytes and microglia within the CNS⁷⁷. The function of Th17 cells is regulated by a subgroup of CD4+ Th cells, T regulatory cells (Tregs), which help modulate the immune response. High IL-6 levels promote Th17 cell differentiation and inhibit Treg formation, thereby altering the balance between pro-inflammatory Th17 cells and anti-inflammatory Tregs. This imbalance has been associated with the development of other autoimmune

diseases ⁷⁸, and in some cases has led to treatment development. The knowledge of Treg involvement in AE remains sparse.

The factors that initiate the immune response in AE associated with NSAbs remain unclear. In some cases, the condition is paraneoplastic in origin. The development of NSAbs may be triggered by the ectopic expression of a neuronal antigen by a tumor; for example, ovarian teratomas express NMDAR ¹⁹, and GABA-B antibodies are associated with SCLC in 50% of cases ⁷⁹. Immune checkpoint inhibitors used for cancer treatment may trigger AE ⁸⁰, as may viral infections ^{81,82}. It is presumed that neuronal degeneration due to, for example, herpes simplex virus (HSV) infection leads to neuronal antigen exposure in an inflammatory environment, triggering the production of autoantibodies. Genetic predisposing factors may also be involved. Anti-LGI1 encephalitis is associated with the HLA-DRB1*07:01 allele in approximately 90% of cases, and anti-CASPR2 encephalitis with the HLA-DRB1*11:01 allele in about half of cases ⁸³. Anti-IgLON5 encephalopathy also shows a genetic predisposition, with most patients having the HLA-DRB1*10:01 and HLA-DQB1*05:01 alleles, which are otherwise quite rare in the general population ⁸⁴. Studies have demonstrated that AE coexists with other autoimmune diseases, which might also indicate a genetic predisposition ⁸⁵. In some cases, the existence of thymoma in a patient might explain the occurrence of several autoimmune diseases ⁸⁶, but in most cases, the underlying pathophysiological mechanisms are still unclear. Demyelinating CNS diseases can also coexist with AE, as demonstrated by the overlap of MS and anti-NMDAR encephalitis ⁸⁷.

The exceptions

Unfortunately, the above characterization of onconeural antibodies as being associated with T-cell-mediated permanent neurodegeneration and NSAbs causing antibody-mediated, more reversible inflammatory changes in the nervous system is a simplification. Several neuronal antibodies do not conform to this explanatory model.

Autoantibodies targeting GAD65 are one such example. These antibodies are associated with Stiff-person syndrome disorders (SPSD), cerebellar ataxia, epilepsy, and limbic encephalitis ⁸⁸. GAD65 is an intracellular protein, yet it can be exposed to the extracellular environment during the fusion and reuptake of synaptic vesicles ⁸⁸. It is questioned whether anti-GAD65 antibodies have a direct pathogenic effect or not. Antibodies from patients induce neurological symptoms when injected into rats, indicating a potential direct pathogenic effect of the antibodies and a humoral disease mechanism ⁸⁹. In contrast, other studies have demonstrated a T-cell-mediated immune response ^{88,90}. Brain atrophy in patients with anti-GAD65-associated neurological

syndromes may be caused by cytotoxic T-cell-mediated neuronal loss. For example, patients with limbic encephalitis often develop medial temporal lobe atrophy over time, whereas patients with cerebellar ataxia develop cerebellar atrophy^{91,92}. There is also evidence of complement activation, as elevated levels of activated complement proteins can be detected in CSF, and deposition of activated complement proteins is demonstrated in brain biopsies⁹³. Patients with anti-GAD65-associated neurological syndromes rarely have an underlying tumor; yet, they often have at least one more co-existing autoimmune disease⁹⁴. In summary, the anti-GAD65 antibody targets an intracellular antigen yet is rarely paraneoplastic in origin. The antibodies are possibly pathogenic, but patients show a moderate response to immunotherapy and suffer from irreversible T-cell-mediated neurodegeneration over time⁹⁵.

The interaction between neuroinflammation and neurodegeneration is well exemplified in anti-IgLON5 antibody-associated disease. First described in 2014 by Sabater et al., patients with anti-IgLON5 antibodies demonstrated a more insidious disease progression reminiscent of a neurodegenerative disorder⁹⁶. Neuropathological examination showed atypical tauopathy in the brainstem and hypothalamus⁹⁶. Although patient antibodies target the cell-surface molecule IgLON5, the response to immunotherapy was absent and it was speculated that the antibodies indicate an autoimmune reaction to the neurodegenerative process. Subsequent studies refuted this hypothesis, as anti-IgLON5 antibodies appear to induce neurodegeneration⁹⁷⁻⁹⁹. As more cases of this novel disorder have been described, it has been made apparent that patients can respond to immunotherapy if administered early enough in the inflammatory stage of the disease, prior to neurodegeneration¹⁰⁰.

Part 2: Epidemiology

As many neuronal antibodies were discovered only in the last decades and new antibodies are described almost yearly, epidemiological studies of this continually changing group of syndromes are challenging. This is further complicated by the lack of well-established diagnostic codes and changing diagnostic criteria. Another limitation is uneven regional access to antibody testing. Antibody-negative AE, i.e., patients considered to have immune-mediated encephalitis without any currently known antibody detected, also poses a challenge for patient inclusion in epidemiological studies.

Early epidemiological studies on encephalitis concentrated on hospitalized cases and consistently found that approximately half of the patients had unknown etiologies¹⁰¹⁻¹⁰³. In 2010, Granerod et al. published a study investigating the causes of encephalitis in a prospective cohort in England from 2005 to 2008¹⁰⁴. For the first time, patients with an unknown cause of encephalitis were tested for anti-NMDAR and anti-VGKC antibodies (retrospectively). Antibody-mediated AE accounted for 8% of cases, whereas 37% remained unclassified. The growing recognition of AE became evident in a study by Dubey et al., which tested patients (some retrospectively) for various neuronal antibodies¹⁰⁵. There was a six-fold increase in the incidence rate of antibody-positive AE between the first half of the study period (1995-2005) and the second half (2006-2015).

As the number of discovered neuronal antibodies grew, hospital laboratories tried to keep up with testing. Over time, the number of patient samples tested for neuronal antibodies increased¹⁰⁶, as did the number of positive test results¹⁰⁷⁻¹⁰⁹. More recent epidemiological studies have demonstrated that AE accounts for more than a third of encephalitis cases¹¹⁰. The incidence of AE matches or exceeds that of infectious encephalitis^{105,111}. However, the incidences of both AE and PNS could still be underestimated. For instance, the incidence rates continue to increase annually, and cases are unevenly distributed geographically, with more cases diagnosed close to national reference centers¹¹²⁻¹¹⁵.

The age- and sex distribution differs between AE and PNS. Approximately half of PNS cases are women and the median age is 55-70 years^{112,113,115}. The most common onconeural antibody is anti-Hu (associated with SCLC), followed by anti-Yo (associated with ovarian carcinoma)^{115,116}. AE patients have a bimodal age distribution, with anti-NMDAR being the most common antibody among the young (predominantly female) and LGI1 the most common among the elderly (predominantly male)¹¹⁵. The onset of AE varies according to the season, with most cases occurring during the warm seasons¹¹⁷⁻¹¹⁹.

Part 3: Clinical Characteristics

The work-up of patients with suspected AE or PNS involves a combination of clinical, neuroradiological and neurophysiological examinations, as well as laboratory testing. Detection of the causative neuronal antibody is vital, but as false positive test results occur, testing the right patients is key. Some neuronal antibodies are associated with generic clinical presentations; for example, patients with both anti-Hu and anti-GABA-B antibodies may present with limbic encephalitis, even though one is an onconeural antibody and the other a neuronal-surface antibody. Other neuronal antibodies give rise to distinct clinical presentations that could enable swift diagnosis. Below, some of the more generic and distinct presentations are described. This thesis focuses on syndromes affecting the CNS and therefore, PNS affecting the peripheral nervous system will not be further described.

Symptoms

Limbic encephalitis often causes a triad of symptoms, which typically develop over weeks to months: cognitive deficits, psychiatric symptoms, and epileptic seizures. The hippocampus is part of the limbic system, so short-term memory dysfunction and confusion are common symptoms. Patients often experience amnesia in the acute phase of the disease. Psychiatric symptoms include depression, irritability, anxiety, and psychosis. Epileptic seizures can be both focal and bilateral, and often more than one type of seizure is present in the same individual¹²⁰. Status epilepticus is particularly common in patients with anti-GABA-B encephalitis¹²¹.

At the onset of anti-NMDAR encephalitis, some patients report flu-like symptoms lasting a few days. This is followed by psychiatric symptoms that develop over days to weeks, including behavioral changes, paranoia, hallucinations, and psychosis. The range of psychiatric symptoms can be varied, and characteristics of psychotic and mood disorders are often present simultaneously in the same individual. Speech dysfunction and movement disorders such as dyskinesias and rigidity are often observed. This, in combination with the prominent psychiatric symptoms, may lead to a misdiagnosis of catatonia due to depression or first-time psychosis¹²². However, shortly after the onset of psychiatric symptoms, most patients experience memory dysfunction and epileptic seizures, which help distinguish them from individuals with primary psychiatric disorders. Eventually, the disease may progress to coma, accompanied by life-threatening autonomic dysfunction, including cardiac arrhythmia and hypoventilation necessitating ICU care¹²³.

The onset of anti-LGI1 encephalitis is more insidious, often over several months rather than weeks. In many ways, the presentation is similar to classic limbic encephalitis with memory dysfunction, psychiatric symptoms, and epileptic seizures⁶³. However, there are some defining characteristics. A specific type of seizure, faciobrachial dystonic seizure (FBDS), is seen in around half of cases with anti-LGI1 encephalitis and is considered pathognomonic. These seizures consist of very short episodes with dystonic posturing of the arm and grimacing of the face, sometimes involving the trunk or the leg. They are often unilateral and occur very frequently (up to a hundred times daily), typically preceding the cognitive and psychiatric symptoms¹²⁴. A variety of focal epileptic seizures are also seen in these patients, including paroxysmal dizzy spells and piloerection seizures¹²⁵. Patients with anti-LGI1 encephalitis may also exhibit sleep disturbances such as insomnia and REM sleep disorder¹²⁶.

Several clinical presentations are frequently related to PNS. Limbic encephalitis, subacute cerebellar degeneration, subacute sensory neuropathy, Lambert-Eaton myasthenic syndrome, and dermatomyositis are the most common¹²⁷. Patients with paraneoplastic cerebellar degeneration (PCD) exhibit symptoms of rapidly progressing cerebellar dysfunction over weeks to a few months, including ataxia, dysarthria, dysphagia, and diplopia¹²⁸.

Anti-GAD65-associated disease may present as limbic encephalitis, autoimmune epilepsy, cerebellopathy, and stiff person syndrome disorder (SPSD). Compared with PCD, anti-GAD65-associated cerebellopathy often has an insidious onset, with symptoms progressing over years⁸⁸. PSD presents with muscle rigidity, muscle spasm, and pain.

Anti-IgLON5 encephalopathy may cause a wide variety of symptoms, most frequently sleep disturbance, manifested as obstructive sleep apnea, REM sleep disorder, insomnia, and stridor during sleep. Gait instability, movement disorders (including chorea and parkinsonism), bulbar symptoms, autonomic instability, and cognitive dysfunction may also be part of the clinical picture¹²⁹. The disease has a progressive course, with symptoms developing over months to years with a minority having a subacute onset with symptom development within a month.

Neuroradiology

MRI is the preferred method for visualizing inflammation in the nervous system. In AE, MRI findings can vary significantly based on the associated neuronal antibody and the timing of the examination. Typically, patients with anti-LGI1, anti-GABA-B, and anti-AMPA antibodies who present with limbic encephalitis show unilateral or bilateral hyperintensities on T2-weighted imaging^{67,79,130,131}. Similar MRI findings may appear early in most cases of anti-

GAD65-associated limbic encephalitis, but these cases often progress to atrophy of the medial temporal lobes over time⁹¹. In contrast, patients with anti-NMDAR encephalitis exhibit abnormal MRI scans in only 30-40% of cases, with the abnormalities often appearing as nonspecific T2 hyperintensities¹³². The overlap between anti-NMDAR encephalitis and demyelinating diseases can further complicate the interpretation of MRI images⁸⁷. In anti-IgLON5 encephalopathy, most MRI scans appear completely normal⁸⁴.

For patients with onconeural antibodies, the MRI results largely depend on the clinical syndrome and the timing of the examination. For instance, patients with PCD often have normal MRI scans during the acute phase, but they frequently show cerebellar atrophy on follow-up examinations, irrespective of the associated neuronal antibody^{133,134}. Patients with onconeural antibodies and limbic encephalitis (LE) often cannot be distinguished from patients with NSAbs and LE, as both groups may present with T2 hyperintensities in the medial temporal lobes on MRI¹³⁵. Contrast enhancement and restricted diffusion on diffusion-weighted imaging are uncommon in AE, unlike in herpes simplex encephalitis (HSE), which also shows hemorrhagic lesions in later stages¹³⁶.

Brain FDG-PET

Positron emission tomography (PET) is an imaging technique that utilizes radiotracers to assess physiological functions in the body. The most commonly used radiotracer is fluorodeoxyglucose (FDG), a glucose analog that can be used to detect regional glucose uptake and indirectly measure tissue metabolic activity. In tissues with inflammation, metabolic activity increases, which can then be visualized by FDG-PET examination. As previously mentioned, using MRI to visualize inflammation in the brain of patients with AE can yield very heterogeneous results. Studies indicate that FDG-PET of the brain may have superior sensitivity for detecting abnormalities in patients with AE^{132,137}. The different subtypes of AE may exhibit distinctive metabolic patterns. Anti-NMDAR encephalitis often demonstrates hypermetabolism in the frontal lobes, temporal lobes, and basal ganglia together with hypometabolism in the occipital lobes, and this pattern normalizes with recovery^{138,139}. Anti-LGI1 encephalitis presents with hypermetabolism predominantly in the basal ganglia and occasionally in the medial temporal lobes or cerebellum¹⁴⁰. Patients with PCD can present with hypermetabolism in the cerebellum during the acute stage of the disease, but over time, progress to hypometabolism in the same area, mirroring the cerebellar atrophy seen on MRI¹⁴¹.

Neurophysiology

Electroencephalography (EEG) is a noninvasive method for recording the spontaneous electrical activity of the neurons in the cerebral cortex. Patients with AE often have abnormal, yet nonspecific, EEG findings. Generalized or focal slow-wave activity, occasionally combined with interictal epileptic activity, is the most common finding¹⁴²⁻¹⁴⁵. Several studies have tried to determine whether patients with different subtypes of AE exhibit specific EEG patterns, as this could help differentiate them from other conditions. A few years after the initial description of anti-NMDAR encephalitis, a particular EEG pattern named “extreme delta brush” was suggested to be a specific finding in severe cases¹⁴⁶. However, it has since been established that this pattern can also occur in severe encephalopathy of other causes¹⁴⁷. Patients with FBDS, pathognomonic for anti-LGI1 encephalitis, rarely show any ictal changes on EEG recordings¹⁴⁸. Multifocal seizure activity and interictal epileptic activity are prevalent EEG findings in patients with anti-LGI1 encephalitis, but none of these findings are specific^{148,149}.

Laboratory testing

Peripheral blood sample analyses (i.e., C-reactive protein, erythrocyte sedimentation rate, complete blood count, electrolytes, and liver enzymes) are often normal in both AE and PNS, unless a concurrent malignancy is present. One exception is anti-LGI1 encephalitis, commonly associated with hyponatremia due to the syndrome of inappropriate anti-diuretic hormone secretion (SIADH)¹⁵⁰.

CSF analysis is a routine part of the workup in patients with suspected encephalitis, as identifying and treating differential diagnoses like HSV-1 encephalitis is crucial. In contrast to viral encephalitis, AE may present with normal routine CSF findings (i.e., normal cell counts, protein and glucose levels)¹⁵¹⁻¹⁵³, in particular patients with anti-LGI1 encephalitis and IgLON5 disease^{63,84}. Conversely, anti-NMDAR encephalitis typically causes inflammatory changes in the CSF, characterized by elevated levels of both leukocytes (pleocytosis) and proteins, along with the presence of oligoclonal bands²⁰. These inflammatory CSF findings are often observed in PNS as well¹⁵⁴ and additionally, CSF analysis may provide clues about ongoing neurodegeneration. The level of neurofilament light chain (NFL), a biomarker indicating axonal damage, correlates with disease severity in the acute phase of AE and predicts worse long-term outcomes^{66,155}.

Neuronal antibody testing

Detection of the associated neuronal antibody is crucial for diagnosing AE and PNS. In some cases, the clinical presentation may be characteristic (e.g., FBDS in anti-LGI1 encephalitis), allowing the physician to suspect and test for only one antibody subtype. However, a more generic presentation of limbic encephalitis may be associated with onconeural antibodies (e.g., anti-Hu, anti-Ma2) or NSAbs (e.g., GABA-B, CASPR2). Due to this overlap of clinical presentations, most laboratories offer test panels that include several neuronal antibodies.

Onconeural antibodies are often analyzed using indirect immunohistochemistry on rodent brain tissue, combined with an immunoblot as a confirmatory test¹⁵⁶. However, some laboratories only use commercial immunoblots for simplicity. GAD65 antibodies are usually detected using Enzyme-Linked ImmunoSorbent Assay (ELISA) or radioimmunoassay (RIA). The most widely used method for analyzing NSAbs is fixed cell-based assays (CBA), available as commercial kits. Some specialized laboratories use tissue-based assays (TBA), which provide advantages such as screening for previously uncharacterized antibodies¹⁵⁶.

Expert consensus is that two separate methods, both yielding the same result, are required for a neuronal antibody test to be considered positive^{120,157}. Using only immunoblot to test for onconeural antibodies leads to a high proportion of false-positive results, which can be mitigated by including immunohistochemistry on fixed TBA^{158,159}. The diagnostic accuracy and sensitivity when testing for NSAbs also improve when two different methods are combined, such as a TBA followed by a confirmatory CBA¹⁶⁰⁻¹⁶².

Neuronal antibodies can be analyzed in both serum and CSF. Irrelevant or false-positive results are more common when testing serum samples¹⁶³. Several neuronal antibodies can be positive in sera of patients with other neurological disorders¹⁶⁴⁻¹⁶⁶, but are considered very rare in the normal population¹⁶⁷. For some NSAbs (e.g., anti-NMDAR, anti-GABA-B, anti-AMPA), sensitivity is higher for CSF than serum^{56,79,130}. Anti-LGI1 antibodies are detected more frequently in serum when using only commercial CBAs, but in specialized laboratories using in-house CBAs, the antibodies are detected in serum and CSF equally^{62,168}. Testing for anti-GAD65 antibodies in serum can be especially problematic. Approximately 1% of the general population, 5% of patients with other neurological disorders, and 80% of patients with type 1 diabetes have anti-GAD65 antibodies in serum¹⁶⁹. Patients with neurological syndromes associated with anti-GAD65 antibodies frequently have higher antibody levels than those with type 1 diabetes¹⁷⁰⁻¹⁷². Detection of anti-GAD65 antibodies in CSF is considered more specific¹⁷³. For all neuronal antibodies,

testing of serum and CSF samples simultaneously is recommended ^{120,157}. Repeat testing for neuronal antibodies in patients with suspected AE has not been demonstrated to increase diagnostic yield ¹⁷⁴.

Tumor screening

The risk of underlying cancer is dependent on the detected neuronal antibody. Some antibodies are highly associated with specific tumors (e.g., anti-Yo antibodies and ovarian carcinoma, anti-Hu antibodies and SCLC). Therefore, investigations should be guided by the antibody test result. Usually, basic tumor screening consists of a thoracic and abdominal CT scan, and if this yields nothing, a full-body FDG-PET. In women with anti-NMDAR encephalitis, screening for an ovarian teratoma using ultrasound or MRI is recommended. As the neurological symptoms often precede the cancer diagnosis, repeated tumor screening is advisable ¹⁷⁵.

Diagnostic criteria

In 2004, diagnostic criteria for PNS were proposed to help clinicians report patients more uniformly and facilitate research ¹²⁸. The criteria for “definite PNS” could be met in several ways, involving combinations of clinical presentations, the timing of a concurrent cancer diagnosis, and the detection of onconeural antibodies. In 2021, due to advances in the field such as the discovery of various NSAbs, the criteria were updated with the introduction of the PNS-Care Score ¹⁵⁷. The new criteria are stricter than the previous ones, requiring a classical clinical presentation combined with the detection of consistent “high-risk” autoantibodies and cancer to diagnose “definite PNS” ¹⁷⁶.

There are no diagnostic criteria that encompass all the various subtypes of AE. In 2016, a position paper by Graus et al. proposed a diagnostic algorithm for AE to aid early recognition of the disorder and decrease the time to treatment initiation ¹²⁰. To compensate for the poor availability of neuronal antibody testing worldwide, a diagnosis of AE can be made pending antibody test results. Consequently, this emphasizes the importance of stringent adherence to the proposed algorithm as evidence suggests too lenient inclusion leads to misdiagnosis of AE ¹⁷⁷. The position paper by Graus et al. also included diagnostic criteria for some disorders relevant to this thesis: “definite autoimmune limbic encephalitis” and “definite anti-NMDAR encephalitis”. As previously described, the clinical presentation of AE is broad, and these diagnostic criteria do not fully capture patients with more insidious onset and often normal CSF analysis (e.g., anti-LGI1 encephalitis or anti-GAD65 disease) ^{178,179}. In

such cases, neuronal antibody testing is vital. However, relying too heavily on antibody testing may also lead to misdiagnosis if nonspecific findings are overinterpreted¹⁷⁷.

Given the continued discovery of new neuronal antibodies over the last decades, it is reasonable to assume that several relevant antibodies have not yet been discovered. In the position paper from 2016, criteria for “antibody-negative but probable autoimmune encephalitis” were proposed to identify these patients. This has since been the focus of debate, as the number of published antibody-negative cases has increased. If only a fraction of known neuronal antibodies are tested or if only a serum sample is analyzed, it has been argued that a patient cannot be considered to have antibody-negative AE¹⁸⁰.

Part 4: Treatment and Long-term Outcome

The treatment of AE and PNS often involves a combination of immunotherapy, supportive care, and treating the underlying cause (e.g., malignancy). Due to the rarity of these conditions, there is a lack of clinical trials assessing treatments. Attempts at randomized, placebo-controlled trials have been made, but insufficient recruitment of patients has been an obstacle^{181,182}. Instead, the management of these patients is based mostly on retrospective, observational data and meta-analyses^{183,184}.

Immunotherapy

The immunotherapy regimen is often divided into two stages: acute treatments (first-line immunotherapy), and long-term management (second-line immunotherapy)¹⁸³. First-line therapies include high-dose intravenous corticosteroids, intravenous immunoglobulins (IVIG), and plasma exchange. Second-line therapies include rituximab and cyclophosphamide. In very severe, treatment-refractory cases, additional therapies such as bortezomib and tocilizumab have been tried¹⁸³. Overall, patients with AE have a more favorable outcome if immunotherapy is started early after symptom onset^{185,186}.

First-line treatments are often combined, particularly in severe cases. Evidence suggests that plasma exchange alone, a combination of corticosteroids and IVIG, or all three first-line treatments combined, is associated with a better functional outcome in anti-NMDAR encephalitis¹⁸⁴. Some studies demonstrate that long-term immunotherapy, such as rituximab or repeated IVIG (>6 months), leads to fewer relapses^{184,185}. The indiscriminate use of second-line immunotherapy in anti-NMDAR encephalitis has been questioned, and it is uncertain whether escalation of immunotherapy improves outcomes in all

patients¹⁸⁷. In anti-NMDAR encephalitis associated with a teratoma, and other AEs with paraneoplastic etiology, finding and treating the tumor is crucial. However, tumor treatment alone is insufficient in patients with cell-surface antibodies, who require prompt immunotherapy in combination with oncological treatments¹²⁷.

Patients with anti-LGI1 encephalitis tend to respond better to high-dose intravenous corticosteroids than to IVIG, at least regarding cessation of FBDS¹⁸⁸. When treating anti-LGI1 encephalitis, intravenous corticosteroids are often followed by oral corticosteroids, gradually tapered over several months. In some centers, no additional long-term immunotherapy is given, and most patients have favorable outcomes with few relapses¹⁸⁹. However, there is conflicting evidence, as some studies suggest that patients treated with rituximab experience fewer relapses and less persistent cognitive deficits^{126,185}.

Some subtypes of AE are more challenging to treat. Anti-GAD65-associated encephalitis is often diagnosed late after symptom onset, and the response to immunotherapy is generally limited^{95,185}. Patients with anti-IgLON5 disease show a variable and often limited response to immunotherapy. If immunotherapy is started shortly after symptom onset, in the more inflammatory stage of the disease, some patients improve, or at least disease progression is halted. Late initiation of immunotherapy, when significant neurodegeneration has already occurred, rarely has an effect¹⁰⁰.

The underlying pathology in PNS associated with onconeural antibodies, a T-cell-mediated immune response, means that by the time of diagnosis, the neuronal damage is often irreversible. Most important is finding and treating the underlying malignancy with appropriate surgery or oncological treatments. A trial of at least first-line immunotherapy is usually attempted, but the response is typically poor, especially in severe cases^{190,191}.

Supportive care

Patients with AE require extended hospital stays and are frequently admitted to the ICU, often because of status epilepticus or autonomic dysfunction^{108,192}. Symptomatic medications, such as antiepileptic drugs (AED) and antipsychotics, are frequently prescribed in the acute phase but are not as effective as immunotherapy to control symptoms^{186,193,194}. Few patients with AE develop epilepsy, and AEDs are often discontinued after the acute phase¹⁹⁴. The exception is anti-GAD65-associated limbic encephalitis; these patients commonly develop refractory epilepsy¹⁹⁵.

Long-term outcome

If treated with immunotherapy, AE is generally considered to have a favourable long-term outcome, as assessed by previously established functional outcome scales such as the modified Rankin Score (mRS) ¹⁹⁶. For instance, the vast majority of patients with anti-NMDAR encephalitis and anti-LGI1 encephalitis achieve an mRS of 0-2 (functionally independent in daily life) after a couple of years ^{51,188}. However, initially designed to assess outcome after stroke, mRS is a crude measurement that focuses on motor impairment. Several studies have demonstrated that patients with AE suffer from long-term cognitive and psychiatric sequelae that affect well-being and the ability to return to work, not captured by mRS ^{126,197-199}.

Aims

The overall aim of this thesis was to enhance our understanding of the epidemiology, clinical picture, and the pathophysiological processes involved in AE and PNS.

Specific aims

To estimate the incidence rate of antibody-positive AE and PNS in Healthcare region Mid Sweden from 2015 to 2019, and to describe trends in neuronal antibody testing in that same period (**Study I**).

To describe the clinical characteristics of patients with AE and PNS diagnosed from 2015 to 2019 in Healthcare region Mid Sweden, with a particular focus on the temporal disease course (**Study II**).

To perform a systematic review of all publications describing the presence of brain FDG-PET findings at the individual level in patients with AE and PNS to assess the prevalence and characteristics of regional metabolic abnormalities (**Study III**).

To characterize protein expression profiles in serum and CSF from anti-NMDAR encephalitis patients using targeted proteomics (**Study IV**).

Methods

All studies were conducted in accordance with the Declaration of Helsinki for human studies and were approved by the Swedish Ethical Review Authority (Dnr: 2019-03068) for the AE patients (**Studies I, II, and IV**) and the Regional Ethics Board of Uppsala (Dnr: 2013/278) for the controls (**Study IV**). Written informed consent was obtained for all participants, except for deceased AE patients, for whom consent was presumed (in line with the ethical application).

Study I, II, and IV

Study population

In **Study I**, the study population consisted of the entire Swedish population, with particular focus on Healthcare region Mid Sweden. Sweden had a population of 10,379,295 in 2020, and Healthcare region Mid Sweden (**Figure 3**) had 2,128,642 inhabitants (Statistics Sweden, 2020). In **Study II**, thirty-seven patients from **Study I** were included. Thirty-one of the included patients met the diagnostic criteria for definite AE²⁰⁰ or definite PNS¹⁵⁷. Additionally, five patients with anti-GAD65-associated syndromes (SPSD, encephalitis, or cerebellopathy) and one with anti-IgLON5 encephalopathy were included.

In **Study IV**, eight patients with definite anti-NMDAR encephalitis, identified during data collection in **Study I**, were included together with sixteen symptomatic controls without confirmed neurological disease. Controls were recruited from the Neurology Department at Uppsala University Hospital and presented with nonspecific neurological symptoms (e.g., paresthesia or headache) but had normal clinical and CSF findings. Controls were matched 2:1 to cases by age and sex as closely as possible.

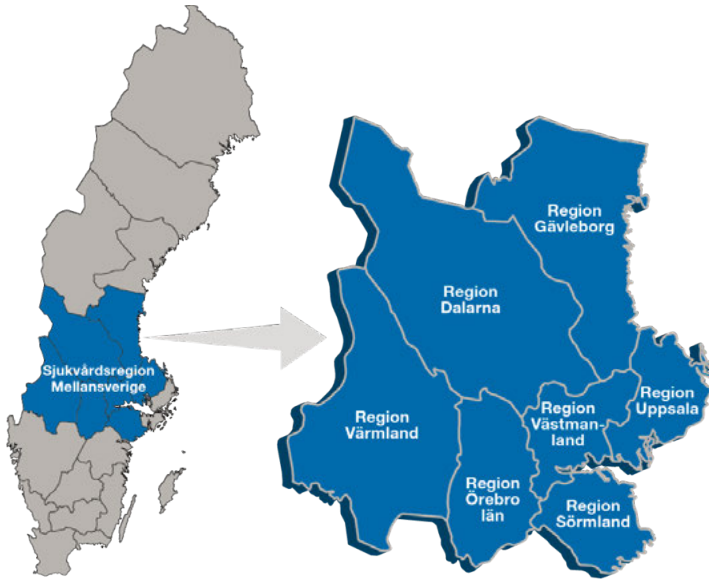


Figure 3. Healthcare region Mid Sweden represented in blue. Image source: <https://www.sjukvardsregionmellansverige.se>

Antibody test results

Neuronal antibody analyses are performed in five Swedish laboratories: four at university hospitals (Uppsala, Karolinska, Sahlgrenska, and Skåne) and one private lab (Wieslab AB). From all five laboratories, test results from 2015–2019 were collected. From Uppsala University Hospital, test results dating back to 2012 were also collected to increase the potential number of cases for **Study IV**. Samples included serum and/or CSF. The data encompassed antibody results (AMPA1/2, Amphiphysin, CASPR2, CV2/CRMP5, DPPX, GABA-B, GAD65, Hu, IgLON5, LGI1, Ma2, NMDAR, PCA-2, Tr, Ri, SOX1, Yo, Zic4), test dates, requesting healthcare region, and patient sex and date of birth. Duplicates were identified based on date of birth and sex and removed, along with repeat positive tests from the same individual. Patients from Healthcare region Mid Sweden with positive test results were invited to participate in case ascertainment. No adjustments were made for potential selection bias due to non-participation.

Antibody testing

All five laboratories used an indirect fixed cell-based immunofluorescence assay (Euroimmun AG, Lübeck, Germany) to detect antibodies against extracellular antigens. One also used immunofluorescence on neuronal tissue for additional screening. For intracellular antigens, a combination of indirect immunofluorescence and immunoblot was required for a positive result, though one

lab relied on immunoblot alone. Most laboratories quantified GAD65 antibodies using ELISA. GAD65 levels >2000 IU/mL in serum or any detection in CSF were considered positive. In one lab that did not quantify serum samples, all positive serum results were included for case ascertainment.

Review of medical records

For **Study I**, medical records of patients with positive antibody test results residing in Healthcare region Mid Sweden (who consented to participate) were reviewed for clinical, laboratory, and imaging data. The following diagnostic criteria were used for case ascertainment: 1) definite PNS (≥ 8 points) according to the PNS-Care Score proposed by Graus et al. 2021¹⁵⁷, or 2) definite autoimmune encephalitis (definite AE) according to Graus et al. 2016²⁰⁰, or 3) definite anti-NMDAR encephalitis according to Graus et al. 2016²⁰⁰. The diagnosis of anti-NMDAR encephalitis was verified in the same way for the cases in **Study IV**.

For **Study II**, a retrospective review of complete medical records was conducted for all patients. The collected data included demographics, comorbidities, presenting symptoms, and evolving symptoms. Diagnostic work-up data included: (a) neuronal antibody testing (serum and CSF), (b) CT scans, (c) whole-body FDG-PET, (d) brain MRI, (e) EEG, and (f) CSF analysis. The review also covered disease course and treatment details: (a) initial department of care, (b) time to diagnosis (days from first contact to antibody detection), (c) time to immunotherapy, (d) type of immunotherapy, (e) duration of hospital and ICU stays, (f) follow-up time (from antibody detection to death or last record review), (g) relapses (defined as symptom recurrence ≥ 3 months after initial improvement, requiring renewed immunotherapy), and (h) month of symptom onset.

Samples

For **Study IV**, serum and CSF samples from anti-NMDAR encephalitis cases were collected in additive-free tubes, stored at 2-8°C for up to 7 days, and subsequently frozen at -20 °C. Serum and CSF from the controls were centrifuged and then snap-frozen at -80°C. All samples underwent a single freeze-thaw cycle and were further aliquoted and randomized into a 96-well plate before analysis.

Proximity Extension Assay

Protein levels in serum and CSF were measured using Proximity Extension Assay (PEA) technology (OLINK Proteomics, Uppsala, Sweden), which

combines antibody-based immunoassays with quantitative PCR (qPCR). Analyses were performed at the Clinical Biomarkers Facility, Science for Life Laboratory, Uppsala University, with sample identities concealed from laboratory personnel.

In PEA, each protein is recognized by a matched antibody-DNA oligonucleotide pair. Upon dual binding, the oligonucleotides hybridize and are extended by DNA polymerase, creating a DNA template that is amplified and quantified by qPCR to determine protein concentration. Results are reported as normalized protein expression (NPX) units on a log₂ scale. A higher NPX values indicate greater protein abundance, and a 1 NPX increase corresponds to a doubling of protein concentration.

Two OLINK panels were used for proteomic profiling: the Target 96 Inflammation panel (comprising 92 proteins related to inflammatory processes) and the Target 96 Neurology panel (containing 92 proteins associated with nervous system function).

Statistical analysis

In **Study I**, the 5-year incidence of AE and PNS in Healthcare region Mid Sweden (2015–2019) was calculated by dividing the number of new ascertained cases by the estimated population over the period, determined as the average of the population at the start of 2015 and the end of 2019, based on Statistics Sweden (SCB) data. Patients meeting the criteria for both definite AE (or anti-NMDAR encephalitis) and definite PNS were included in both subgroup incidence rates. Still, they were counted only once in the composite rate. Yearly crude incidence rates were calculated similarly, using annual average populations. Confidence intervals (95% CI) were calculated assuming a Poisson distribution and using a normal approximation. Antibody test positivity rates were calculated annually as the number of positive results divided by the total number tested, separately for serum and CSF.

In **Study II**, patients were grouped into three groups according to the subtype of neuronal antibody detected: 1) Neuronal surface antibody (NSAbs): Anti-NMDAR, anti-LGI1, anti-CASPR2, anti-GABA-B, anti-IgLON5, anti-AMPA 1/2, anti-DPPX, anti-neurexin-3 α ; 2) Onconeural antibodies: anti-Yo, anti-Hu, anti-Ri, anti-Ma2, anti-CV2, anti-Amphiphysin, anti-SOX1, anti-Zic4, anti-Tr; 3) anti-GAD65 antibodies. All patients were included in the seasonal variation analysis, except those with definite PNS, in whom cancer was considered the primary trigger.

In **Study IV**, all statistical analyses were conducted using NPX values. Group differences in CSF and serum biomarker concentrations between anti-NMDAR encephalitis cases and controls were evaluated using linear

regression, both unadjusted (model 0) and adjusted for age and sex (model 1). Bonferroni correction was applied for multiple comparisons; adjusted p-values below 0.00027 (0.05/182) were considered significant. Principal component analysis (PCA) was performed on the NPX values of all proteins with significant group differences (unadjusted p-value <0.05). Protein correlation between CSF and serum was determined using Pearson correlation coefficients (r). Strengths of correlations were classified according to the British Medical Journal guidelines²⁰¹. Anti-NMDAR cases were stratified by time from symptom onset to sample collection (<1 month vs. >1 month) and compared to controls using one-way ANOVA with Tukey's post hoc test for multiple comparisons.

In **Study I**, descriptive statistics are presented and parametric variables are reported as mean \pm SD. In **Study II**, categorical variables were presented as percentages, and numerical variables were described as mean values with standard deviation or medians with ranges. The Mann-Whitney U test was used for comparisons between two groups, and the Kruskal-Wallis test was used for comparisons between multiple groups. For **Study I-II**, statistical analysis was performed using GraphPad Prism version 9.3.1 for Mac (GraphPad Software, La Jolla, CA, USA; www.graphpad.com). In **Study IV**, graphical visualizations (PCA plots, box plots, and spaghetti plots) were created in GraphPad Prism version 10.4.1 for Mac OS X. All other statistical analyses and figures for **Study IV** were computed in R version 4.4.2 by a biostatistician.

Study III

The literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) under reference number CRD42020192959.

Search strategy

A comprehensive search strategy was developed for PubMed in collaboration with a librarian and subsequently adapted for EMBASE. The intent was to identify all studies, including case series and case reports, that reported at least one clinical case of AE with brain FDG-PET results.

Eligibility criteria

The inclusion criteria were as follows: 1) original publication written in English; 2) reported at least one case of AE (as defined by the authors); 3) provided results from at least one brain FDG-PET.

Selection process

Two authors (SK and EK) separately and independently screened the search results by abstract, if available, or in full text. Disagreement regarding inclusion was resolved with the participation of a third independent reviewer (DF). The excluded records were categorized into three groups: 1) inclusion criteria not met; 2) not original publication; 3) duplicates.

Data extraction

Data was extracted using a predetermined data extraction form. Data items extracted included age, sex, neuronal antibody status, coexisting malignancy, autoimmune disease, viral prodrome, and possible triggering drugs. MRI findings were categorized in two steps. First on a general level (normal, unspecific, specific findings, N/A), and then with a closer classification (type of finding, affected area, uni- or bilateral). PET findings were similarly categorized. First on a general level (normal, generalized hypo/hyper-metabolism or specific abnormal findings), and then with a closer classification (affected areas, hypo- or hypermetabolism, uni- or bilateral).

Statistical analysis

Categorical variables were presented as percentages, and numerical variables were described as medians with ranges. Statistical analysis was performed using GraphPad Prism version 9.3.1 for Mac (GraphPad software, La Jolla, CA, USA; www.graphpad.com).

Results

Study I

Between 2015 and 2019, 525 patients in Sweden (49% female) tested positive for a neuronal antibody (serum and/or CSF). The most common serum antibody was anti-GAD65, followed by anti-Yo and anti-NMDAR. In CSF, anti-NMDAR was most frequent, followed by anti-GAD65 and anti-LGI1.

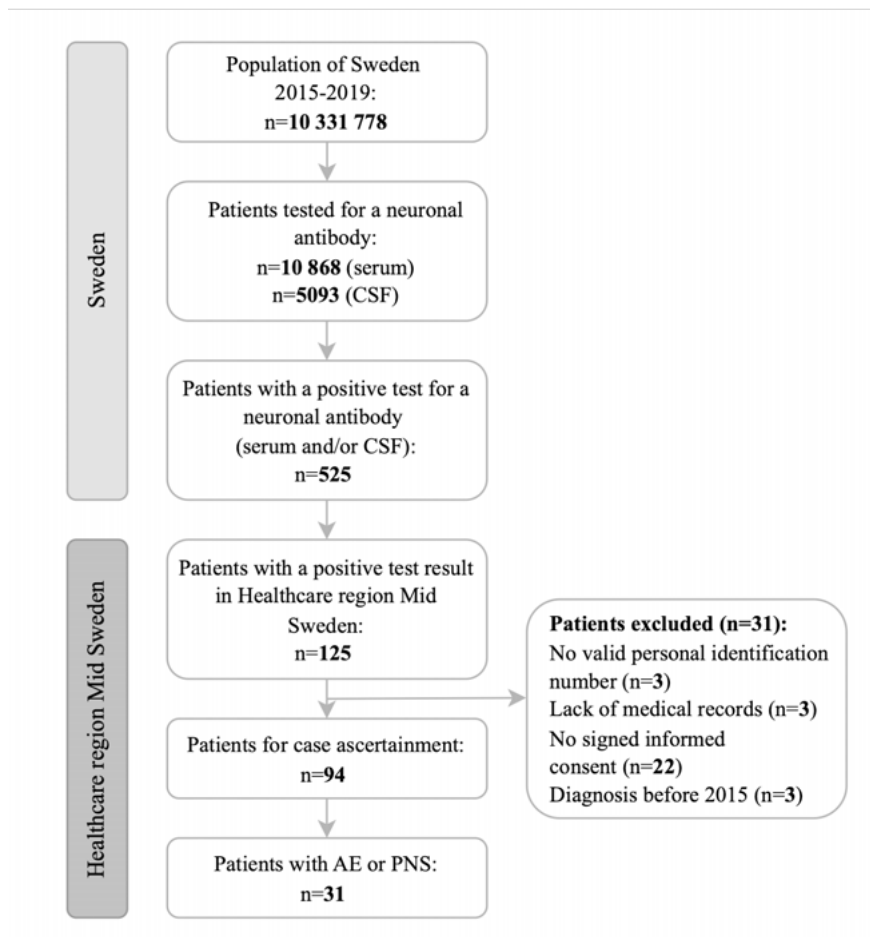


Figure 4. Flowchart of Study I.

Of the 525 patients (**Figure 4**), 125 resided in Healthcare region Mid Sweden, and 94 of them were subsequently included for case ascertainment. Thirty-one fulfilled the diagnostic criteria for definite AE, definite anti-NMDAR encephalitis, or definite PNS.

Anti-NMDAR encephalitis and anti-LGI1 encephalitis were the most prevalent subgroups of AE. Anti-NMDAR patients were predominantly female (83%) with a mean age of 45 ± 22 , while anti-LGI1 patients were mostly male (67%) and older (73 ± 5.2). Among definite PNS cases, 67% were female (mean age 69 ± 8.7).

The crude incidence rate of AE and PNS in the Healthcare region Mid Sweden 2015–2019 was 3.0 per million person-years (CI95% 1.9–4.1). Rates rose from 1.5 in 2015 (95% CI: 0.0–3.2) to 4.3 in 2019 (95% CI: 1.2–7.1; **Figure 5**).

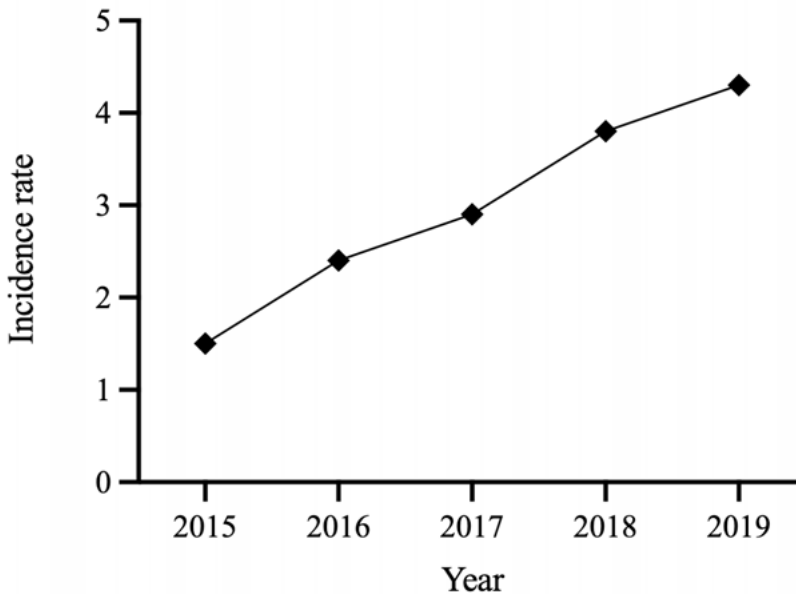


Figure 5. Yearly crude incidence rate of AE and PNS per million person-years.

Nationwide neuronal antibody testing increased annually, with the number of serum samples rising by 34% and CSF samples by 60% between 2015 and 2019 (**Figure 6A**). The proportion of positive tests showed a decreasing tendency over five years, averaging 6.1% for serum (95% CI: 5.5–6.7) and 4.8% for CSF (95% CI: 4.0–5.6; **Figure 6B**). Case ascertainment failed in 63 of 94 included patients (67%). Some of these patients were diagnosed with AE or PNS by their treating physician but did not fulfill the diagnostic criteria

(Figure 7). The rest had various diagnoses, including CNS infections, neuropathies, and movement disorders.

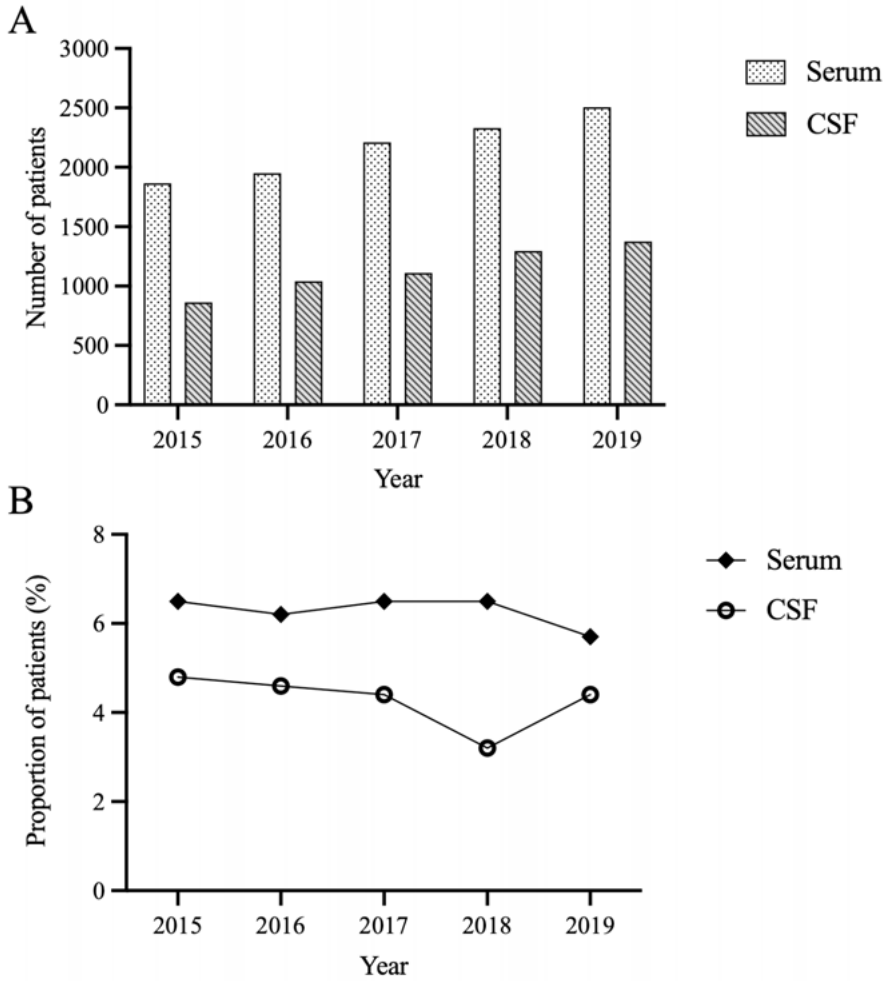


Figure 6. (A) The yearly number of serum and CSF samples tested for neuronal antibodies in Sweden between 2015 and 2019. (B) The proportion of positive test results for serum and CSF samples annually between 2015 and 2019.

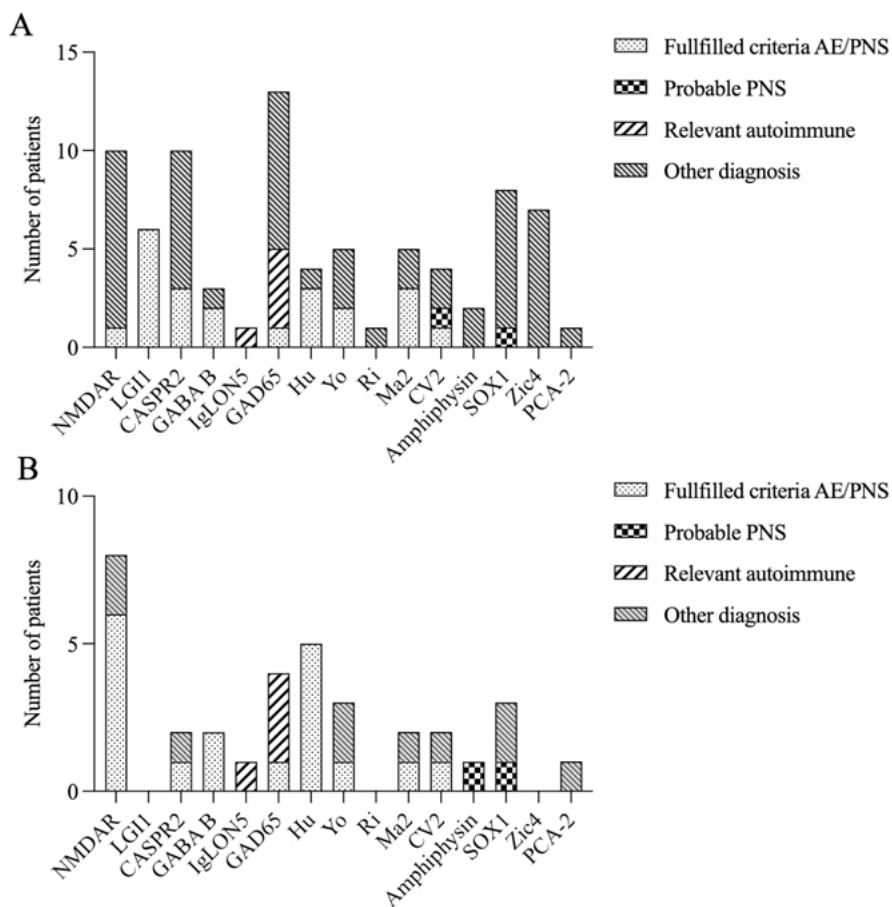


Figure 7. The bars show the number of patients with each antibody in Healthcare region Mid Sweden, divided into subgroups based on whether diagnostic criteria were fulfilled or not. (A) Serum samples. (B) CSF samples. Probable PNS = probable PNS according to the PNS-Care Score. Relevant autoimmune = autoimmune neurological disease consistent with antibody, e.g., anti-IgLON5 disease, GAD65-associated cerebellopathy or SPSD.

The number of patients with positive neuronal antibody tests varied across Sweden's six major healthcare regions. Between 2015 and 2019, the rates (per 1,000,000 inhabitants) were: Mid Sweden 12.7, West Sweden 18.8, North 8.3, South 11.9, Southeast 12.3, and Stockholm 11.3.

Study II

Demographic and clinical characteristics of the 37 patients included in this study are summarized in **Table 1**. Among those with neuronal surface antibodies (NSAbs), the most common were anti-NMDAR (83% female; median age 40 years, range 17–72) and anti-LGI1 (33% female; median age 75 years, range 61–76). Limbic encephalitis (LE) was the predominant clinical syndrome, and the initial manifestations were often psychiatric symptoms or cognitive dysfunction. Nearly half experienced seizures at presentation. Notably, five of six anti-LGI1 patients had FBDS, which was the presenting symptom in all cases.

Among patients with onconeural antibodies, limbic encephalitis was again the most common clinical presentation, followed by paraneoplastic cerebellar degeneration and sensory neuropathy. Compared with patients with NSAbs presenting with LE, those with onconeural antibodies exhibited more cognitive dysfunction and fewer psychiatric symptoms at onset.

Table 1. Abbreviations: LE=Limbic encephalitis, PCD=Paraneoplastic cerebellar degeneration, SPSD=Stiff person syndrome disorder

	NSAbs n=19	Onconeural n=11	GAD65 n=7
Sex, female n (%)	11 (58)	6 (55)	4 (57)
Age, median (range)	69 (17-80)	67 (56-83)	62 (50-75)
Antibody, n (%)	anti-NMDAR 7 (37), anti-LGI1 6 (32), anti-CASPR2 3 (16), anti-GABA B 2 (11), anti-IgLON5 1 (5)	anti-Hu 4 (36), anti-Ma2 3 (27), anti-CV2 2 (18), anti-Yo 2 (18)	anti-GAD65 7 (100)
Clinical presentation, n (%)	LE 17 (89), IgLON5 disease 1 (5), Morvan's syndrome 1 (5)	LE 5 (45), PCD 3 (27), neuropathy 3 (27)	LE 3 (43), SPSD 2 (29), Cerebellopathy 2 (29)

An initial brain MRI performed before the start of immunotherapy was available for 32 patients, and about one-third showed abnormal findings suggestive of encephalitis (**Figure 8**). Follow-up scans were obtained in almost half of the patients, a median of six months after treatment initiation. Among these, complete resolution of abnormalities was rare (6%), while most showed either stable (53%) or partially improved findings (24%). A few patients exhibited new abnormalities on follow-up (12%).

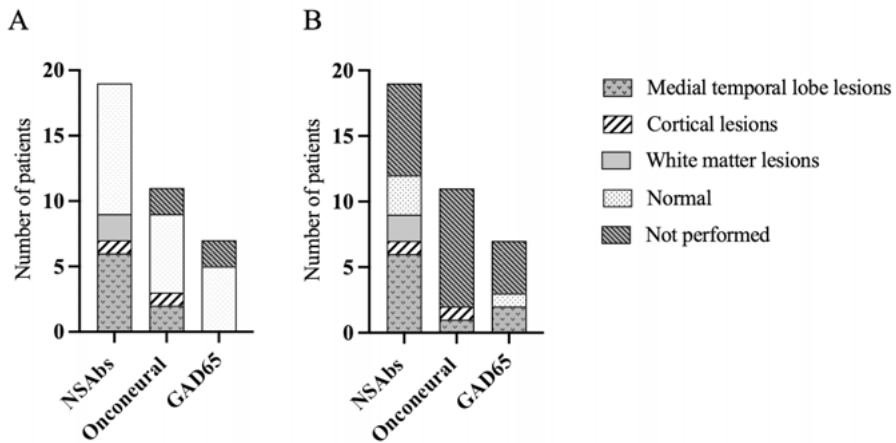


Figure 8. Results of brain MRI. Initial MRI (A) was performed at the onset of neurological symptoms and before the start of immunotherapy, follow-up MRI (B) was performed after the start of immunotherapy.

Lumbar puncture with CSF analysis was performed in thirty-one patients after the onset of neurological symptoms and before the start of immunotherapy (**Figure 9**). In the NSAbs group, only two patients had normal CSF analysis (one case each of anti-LGI1 and anti-CASPR2 encephalitis). Similarly, both the onconeural subgroup and the patients with anti-GAD65 disease had predominantly abnormal CSF findings.

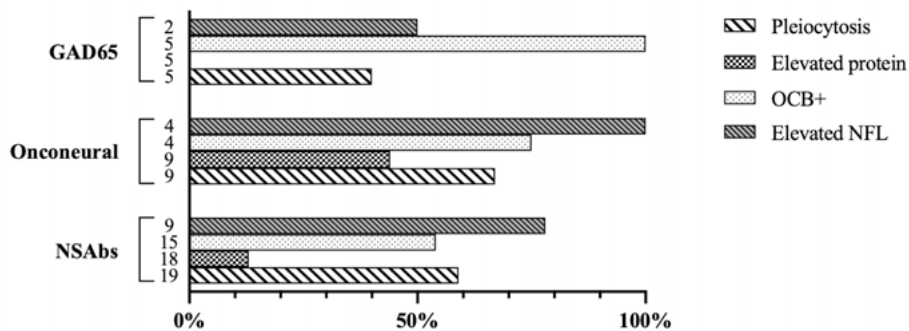


Figure 9. CSF analysis after the start of neurological symptoms and before the start of immunotherapy for each antibody subgroup. Columns show the percentage of patients with pathological results for each CSF analysis. Numbers to the left of columns indicate the number of patients tested for each analysis. Abbreviations: OCB+ = Oligoclonal bands; NFL= Neurofilament light chain.

EEG recordings were obtained from 26 patients after the onset of neurological symptoms but before the initiation of immunotherapy. Among these, about half of the individuals with anti-GAD65 antibodies, roughly a third of those with NSAbs, and none of the patients with onconeural antibodies had electroencephalographic seizures. Except for one patient diagnosed with anti-CASPR2 encephalitis, all EEG recordings showed abnormalities.

Whole-body FDG-PET was carried out in a subset of patients (five with NSAbs, five with onconeural antibodies, and three with anti-GAD65 antibodies). Tumors were identified in nearly half of those examined, and in most of these cases, prior abdominal and thoracic CT scans had shown no evidence of malignancy. Seven patients underwent brain FDG-PET, the majority of whom showed abnormal findings (86%). Only a single patient diagnosed with anti-CASPR2 encephalitis had abnormalities on brain FDG-PET despite a normal brain MRI.

The onset of symptoms showed a seasonal variation in non-paraneoplastic patients with NSAbs and anti-GAD65 antibodies, with most patients (72%) falling ill in the spring or summer (**Figure 10**).

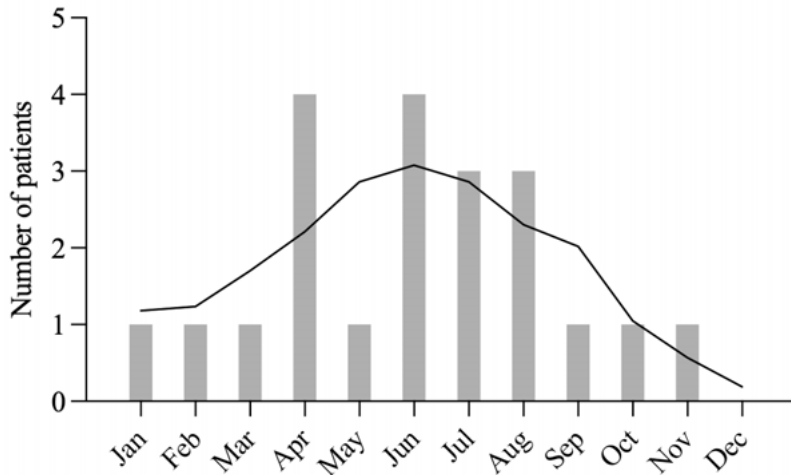


Figure 10. The month of disease onset for patients without malignancy with NSAbs ($n=14$) and anti-GAD65 ($n=4$). Bars indicate the observed number of patients per month. The line is a smoothed curve added to highlight the overall trend (smoothed using GraphPad Prism).

There was no significant difference in time from first contact to the start of immunotherapy between patients with NSAbs, onconeural antibodies, and anti-GAD65 antibodies ($p=0.26$). Among patients with NSAbs, those with an acute onset (anti-NMDAR encephalitis or anti-GABA B encephalitis) received treatment earlier (median 16 days) compared to those with an insidious onset (anti-LGI1 encephalitis, anti-CASPR2 encephalitis, or anti-IgLon5 disease; median 134 days; $p=0.0016$).

All but two patients received first-line immunotherapy. Second-line therapy was administered to 63% of patients with NSAbs, 27% of patients with onconeural antibodies, and 100% of patients with anti-GAD65 antibodies. Among the 16 patients with cancer, two had received treatment before the onset of neurological symptoms. The remaining patients were diagnosed with cancer after the onset of neurological symptoms, and most of them subsequently received cancer treatment (71%).

Study III

The initial search yielded 1303 results, and a total of 234 studies remained at final inclusion, containing 498 individual cases. The inclusion process is visually displayed in a PRISMA flowchart (Figure 11).

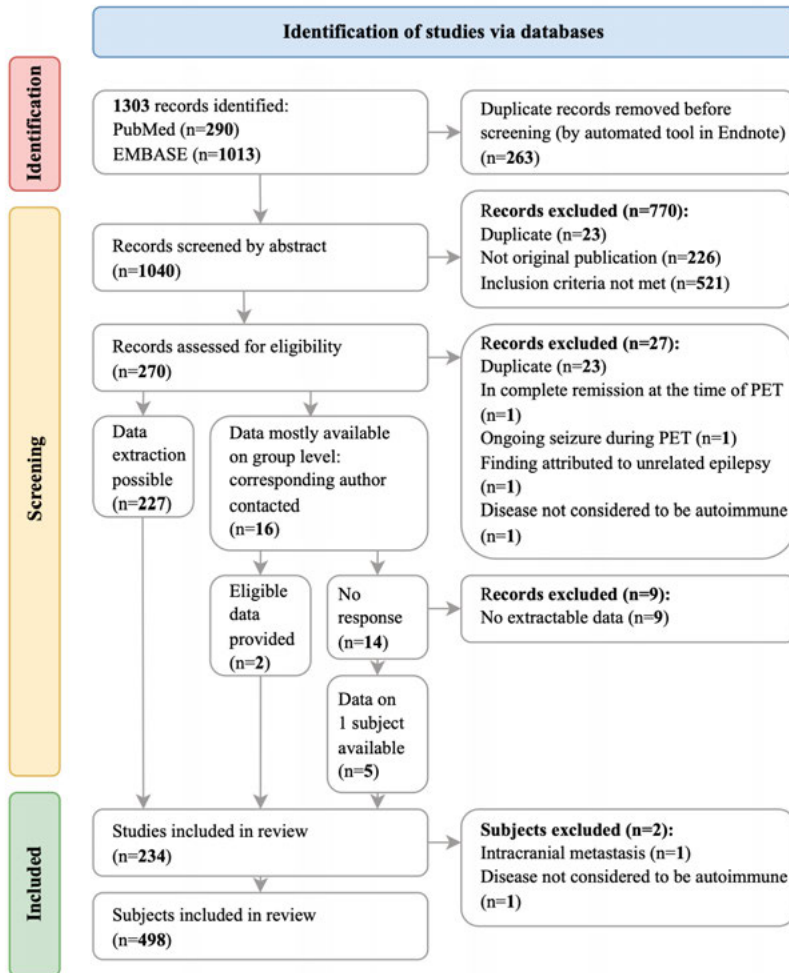


Figure 11. PRISMA flowchart.

There was a fairly even sex distribution in the combined data, with a bimodal age distribution containing peaks around 25 and 61 years. At least one positive test result for neuronal antibodies or thyroid antibodies was reported in 79% of patients.

Of the 498 subjects, most had reported brain MRI results, with roughly half showing abnormalities potentially related to AE. The medial temporal lobe was the most affected region, frequently bilaterally. Details on affected regions in the major antibody-positive groups, along with brain FDG-PET findings, are provided in **Table 2**.

Table 2. *The prevalence of abnormal findings in MRI and FDG-PET for the nine largest subgroups, presented by brain region and antibody. *In most of the older publications, anti-VGKC was reported with an unspecific subtype.*

	n		Any abnormal		Frontal lobe		Insula		Medial temp.	
	MRI	PET	MRI	PET	MRI	PET	MRI	PET	MRI	PET
Anti-NMDAR	107	143	37%	99%	8%	48%	5%	10%	17%	44%
Anti-VGKC*	38	42	64%	95%	5%	29%	2%	2%	52%	52%
Anti-LGI1	79	80	62%	88%	5%	26%	4%	5%	51%	61%
Anti-CASPR2	14	16	50%	88%	6%	50%	-	6%	38%	56%
Anti-GAD	30	30	77%	77%	3%	20%	-	-	63%	37%
Anti-TPO /-TG	16	16	38%	94%	13%	38%	6%	13%	25%	44%
Anti-Hu	16	16	75%	94%	13%	33%	6%	13%	56%	44%
Anti-GABA-B	14	14	50%	79%	7%	7%	-	-	50%	50%
Anti-Ma2	8	8	88%	100%	-	38%	-	-	63%	50%
Total	322	365	55%	93%	7%	36%	3%	7%	39%	49%

<i>(cont.)</i>	Other temp.		Parietal		Occipital		Cerebellum		Basal ganglia	
	MRI	PET	MRI	PET	MRI	PET	MRI	PET	MRI	PET
Anti-NMDAR	6%	50%	3%	44%	4%	63%	3%	39%	5%	33%
Anti-VGKC*	-	45%	-	24%	-	17%	5%	5%	5%	19%
Anti-LGI1	4%	14%	2%	15%	-	8%	-	8%	5%	45%
Anti-CASPR2	6%	25%	-	19%	-	19%	-	-	6%	25%
Anti-GAD	3%	37%	-	30%	-	10%	3%	3%	-	7%
Anti-TPO /-TG	-	19%	6%	19%	-	19%	-	-	6%	13%
Anti-Hu	6%	13%	19%	38%	-	19%	6%	13%	6%	13%
Anti-GABA-B	7%	21%	-	14%	-	7%	-	-	-	7%
Anti-Ma2	-	38%	-	50%	-	25%	-	13%	-	13%
Total	4%	35%	3%	31%	1%	32%	2%	19%	4%	28%

For FDG-PET imaging, the medial temporal lobe remained a common site of abnormality, but other cortical regions, particularly frontal, parietal, and occipital lobes, were more frequently involved than on MRI. In the anti-NMDAR group, FDG-PET abnormalities were prominent in occipital, lateral

temporal, and frontal regions, exceeding the involvement of medial temporal lobes. The discrepancy between MRI and FDG-PET findings varied by antibody type, being the largest for anti-NMDAR and minimal for anti-GAD.

n	Frontal lobe						Insula						Medial temporal						Other temporal						
	Uni		Bi		Any		Uni		Bi		Any		Uni		Bi		Any		Uni		Bi		Any		
	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	
Anti-NMDAR	143	18	7	14	11	32	21	4	2	1	2	5	5	13	8	13	6	30	15	20	7	13	10	33	18
Anti-VGKC*	42	7	5		17	7	21				2		2	17	5	19	12	36	17	10	12	5	21	12	33
Anti-LGI-1	80	1	1	4	16	9	24	1	1		3	1	4	25	5	26	3	53	8	1	1	3	9	4	10
Anti-CASPR2	16		13	6	31	6	42		6				6	38		19		50			6		19		25
Anti-GAD	30	7	7	3	10	3	17							10	13	10	7	17	20	7	10		20	7	30
Anti-TPO/-TG	16		13	13	6	13	19		6			6	13			6	13	6		6		6	13		19
Anti-Hu	16		13	13	25	13	25	13				13		25		31		44		6		6		13	
Anti-GABA-B	14	7				7								29		29		50			7	7		14	7
Anti-Ma2	8	13	13		25	13	38							13	13	25		38	13		13		25		38

n	Parietal						Occipital						Basal ganglia						Global	
	Uni		Bi		Any		Uni		Bi		Any		Uni		Bi		Any		hypo	
	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-	-	
Anti-NMDAR	143	8	8	4	19	11	34	1	9	1	56	1	62	8	1	16	5	27	6	4
Anti-VGKC*	42		7		21		24	2	7		12	2	14	2		17	2	17	2	12
Anti-LGI-1	80		1	1	11	3	14				5	3	5	6	3	34		44	3	6
Anti-CASPR2	16	6	6		6	6	6	6	6		6	13	6	13		13	6	19	6	19
Anti-GAD	30	3	7		20	3	27		10				10	3		3		7		3
Anti-TPO/-TG	16	6	6		6	6	13		6		13		19	6				6		31
Anti-Hu	16	13	13	6	19	19	19	6	6	6	6	13	6		6		6	13		6
Anti-GABA-B	14		14				14				7		7			7		7		21
Anti-Ma2	8		13		38		50				25		25			13		13		

Figure 12. Heatmap table with prevalence (in %) of specific alterations in metabolism. Prevalences above 20/40% are highlighted by a matching background color with low/medium intensity. “Unilateral” and “bilateral” are abbreviated “uni” and “bi”. Some articles did not specify laterality, so the number in “any” may be larger than the sum of uni- and bilat. *In most of the older publications, anti-VGKC was reported with an unspecific subtype.

The detailed patterns of hyper- and hypometabolism by brain region and antibody are shown in **Figure 12**. Overall, medial temporal hypermetabolism was the most prevalent finding, while occipital and parietal hypometabolism was also common, usually bilateral. The frontal lobes showed both increased and decreased metabolism, and basal ganglia involvement was typically bilateral hypermetabolism.

By antibody type, anti-NMDAR cases often exhibited bilateral occipital hypometabolism, frequently alongside hypermetabolism in frontal, temporal, or basal ganglia regions. The classic pattern of medial temporal hypermetabolism (“limbic encephalitis”) was observed in anti-GABA-B, anti-Hu, anti-Ma2, anti-LGI1, and anti-CASPR2 cases, sometimes unilateral. Basal ganglia hypermetabolism was particularly common in anti-LGI1 encephalitis.

Study IV

This case-control study included eight anti-NMDAR encephalitis cases [2 males (25.0%), median age: 34.5 years (IQR 16.3–63.5 years)], and 16 symptomatic controls [3 males (18.8%), median age: 32.5 years (IQR 21.3–62.5 years)], comparable in terms of sex and age distribution. Six patients had paired serum and CSF samples available for testing, while one had only serum and one only CSF. One of the cases had received immunotherapy (IVIG and oral prednisone) three days before sample collection. Five cases had their samples collected within 1 month of symptom onset.

All samples met OLINK's quality control criteria, except for one serum sample and one CSF sample from the anti-NMDAR encephalitis cases in the Inflammation panel, and one CSF sample from a control in the Neurology panel. More than half of the NPX values were below the assay's lower limit of detection (LOD) in 52/182 (29%) of analyzed CSF proteins and 16/182 (9%) of serum proteins. All proteins were included in the linear regression analysis, even those with a high proportion of NPX values below LOD, as they might still provide meaningful relative quantification in this exploratory setting. Unadjusted linear regression analysis (Model 0) yielded similar results to the linear regression analysis adjusted for age and sex (Model 1). Results from the adjusted linear regression analysis (Model 1) are shown as volcano plots for CSF (**Figure 13**) and serum proteins (**Figure 14**).

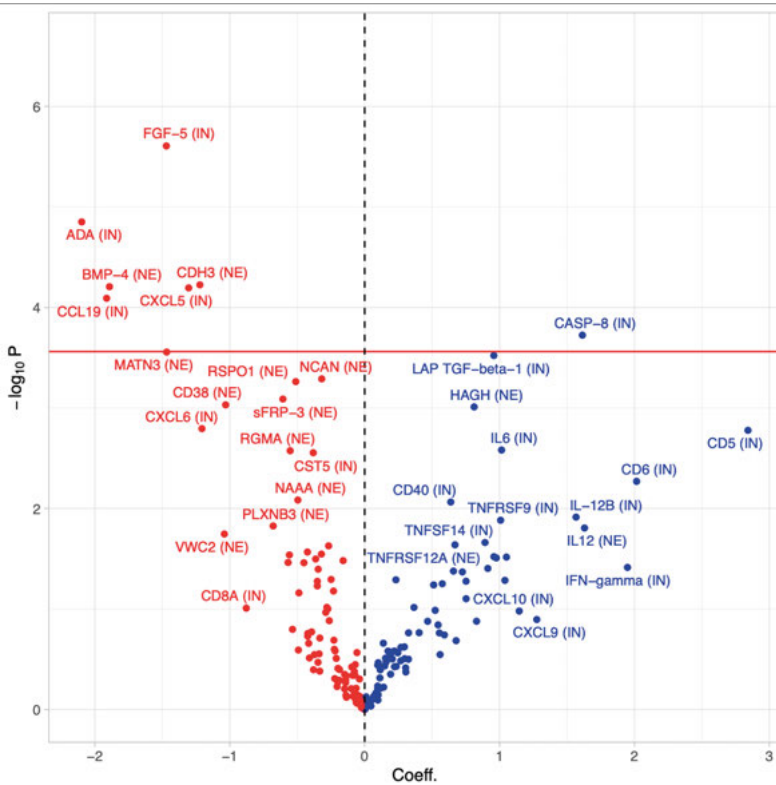


Figure 13. Volcano plot displaying p -values versus linear regression coefficients (Model 1) for differential protein expression in CSF from patients with anti-NMDAR encephalitis compared to controls. The horizontal red line marks the Bonferroni-corrected significance threshold ($p=0.00027$).

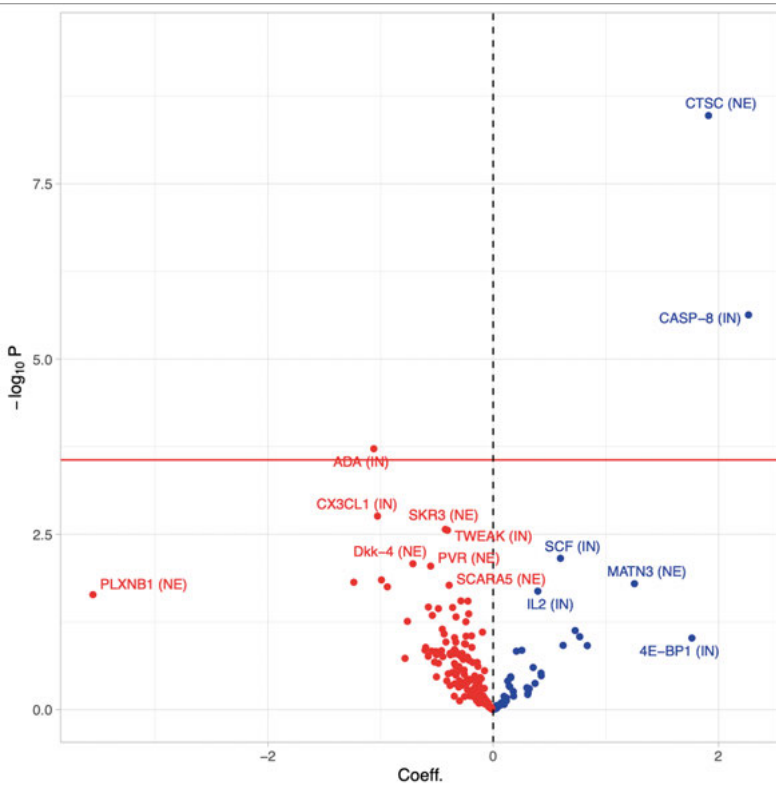


Figure 14. Volcano plot displaying p -values versus linear regression coefficients (Model 1) for differential protein expression in serum from patients with anti-NMDAR encephalitis compared to controls. The horizontal red line marks the Bonferroni-corrected significance threshold ($p=0.00027$).

Levels of six CSF proteins (FGF-5, ADA, CXCL5, CDH3, BMP-4, CCL19) were significantly reduced in anti-NMDAR encephalitis cases compared with controls (Bonferroni-corrected $p < 0.00027$; **Figure 15**), whereas one protein was significantly elevated (CASP-8). In serum, the levels of two proteins (CTSC and CASP-8) were significantly increased, while one protein (ADA) was significantly reduced (**Figure 16**).

Principal component analysis of differentially expressed proteins (CSF proteins $n=47$, serum proteins $n=24$; unadjusted p -value < 0.05), demonstrated clearer separation between anti-NMDAR encephalitis and controls in CSF compared to serum, suggesting compartment-specific alterations (**Figure 17**). There was a larger heterogeneity amongst cases in CSF, with two potential outliers, indicating a variability in the inflammatory response.

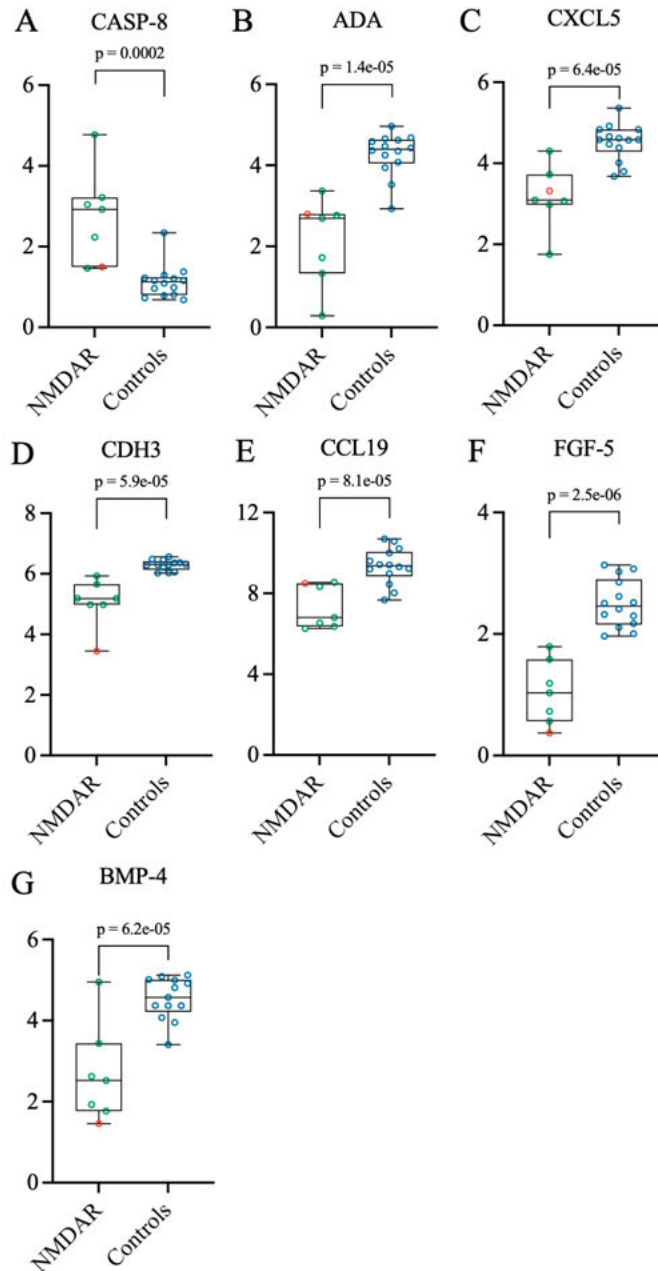


Figure 15. (A-G) Box plots show NPX values for the seven CSF proteins differing significantly between cases and controls. Boxes represent medians with interquartile ranges; whiskers show the full range. Individual cases are shown as green dots (red dot represents the patient who received immunotherapy three days before sampling), and controls as blue dots.

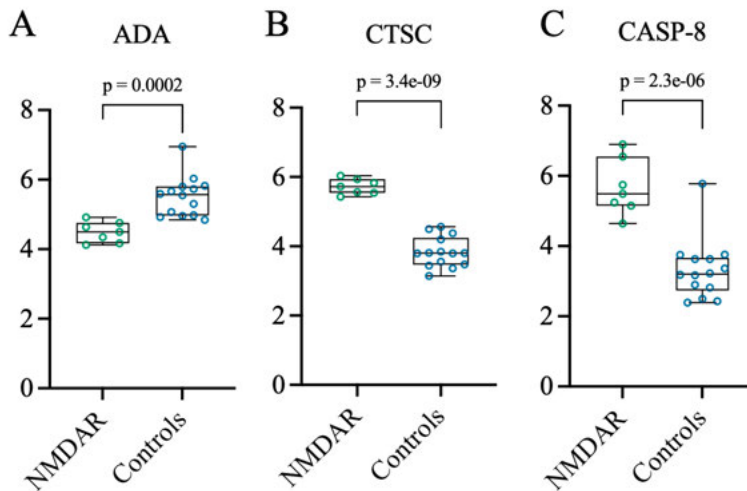


Figure 16. (A-C) Box plots show NPX values for the three serum proteins differing significantly between cases and controls. Boxes represent medians with interquartile ranges; whiskers show the full range. Individual cases are shown as green dots (red dot represents the patient who received immunotherapy three days before sampling, and controls as blue dots).

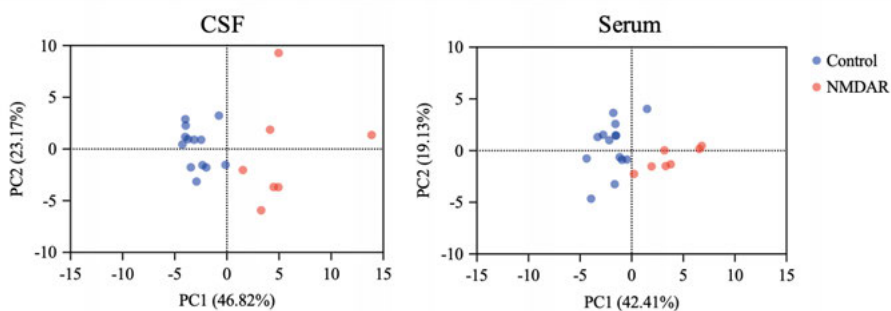


Figure 17. Principal component analysis (PCA) plots based on all proteins with nominally significant group differences (unadjusted $p < 0.05$).

There was a strong to moderate correlation between protein levels in serum and CSF for ADA ($r=0.606$, $p=0.013$) and CASP-8 ($r=0.526$, $p=0.037$), whereas no significant correlation was found for CTSC ($p=0.952$). To explore whether the time from symptom onset to sample collection affected protein levels, anti-NMDAR encephalitis cases were stratified into two groups: <1 month vs. >1 month. Only CSF levels of CASP-8 differed significantly between groups, with higher levels in patients with short symptom duration ($p=0.027$; **Figure 18**).

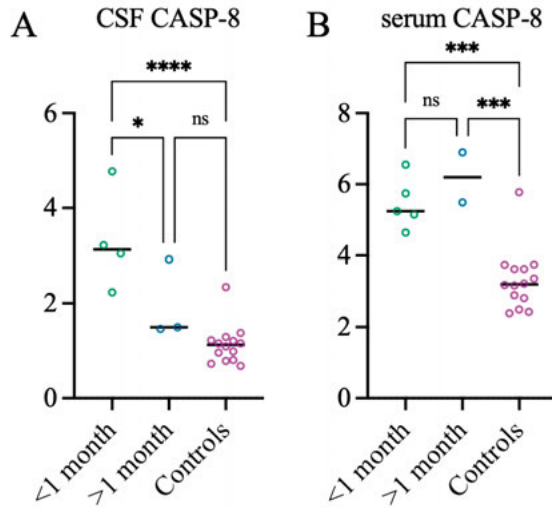


Figure 18. Plots show individual NPX values for anti-NMDAR encephalitis cases, stratified by time from symptom onset to sample collection (<1 month vs. >1 month), and controls. Black lines represent the median. ns=non-significant, * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, **** $p \leq 0.0001$. (A) CSF levels of CASP-8. (B) Serum levels of CASP-8.

Two cases of anti-NMDAR encephalitis had serial samples available; one had paired CSF and serum samples, and one had only CSF samples. A selection of longitudinal protein data from the case with paired samples is presented in **Figure 19**. Initially, CSF levels of CCL19 and CXCL5 were low but rose sharply as the patient's condition worsened and ICU sedation became necessary. CSF CASP-8 levels followed the clinical course, being high at diagnosis, normalizing in the second sample after first-line immunotherapy, and increasing again with deterioration. In serum, CASP-8 and CTSC levels remained consistently elevated, whereas ADA levels stayed low across both time points.

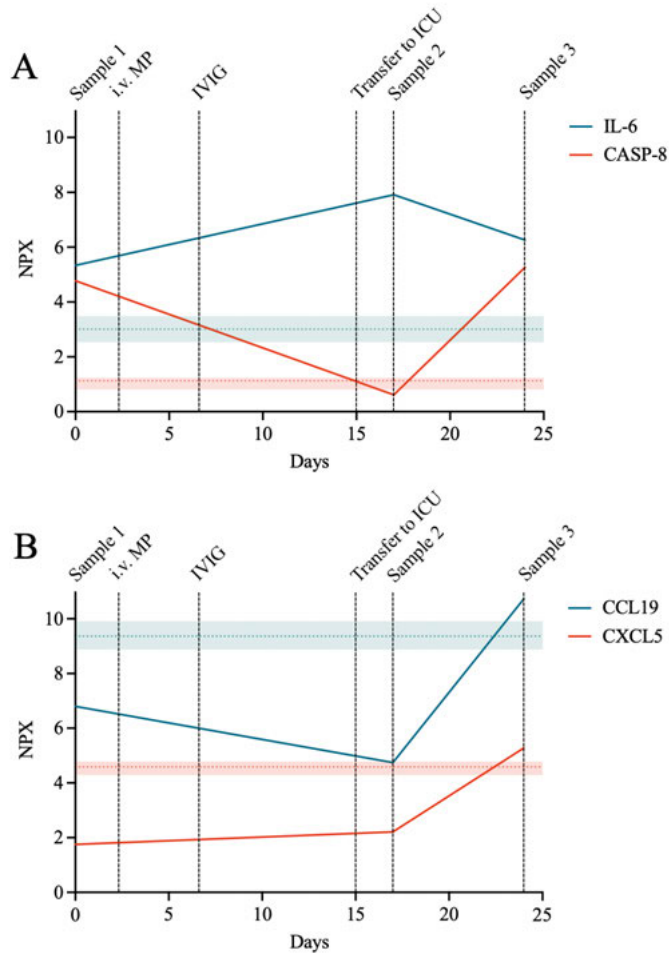


Figure 19. Longitudinal changes in CSF protein levels in a young female with non-paraneoplastic anti-NMDAR encephalitis. Individual longitudinal trajectories of NPX values are shown for IL-6 and CASP-8 (A), and CSF CCL19 and CXCL5 (B), measured across three time points. Shaded horizontal bands indicate the interquartile range observed in healthy controls ($n=14$), and dashed lines indicate the control median. Samples were collected on day 0, day 17, and day 24. At presentation (day -2), the patient exhibited daily focal epileptic seizures, cognitive dysfunction, and dysautonomia. By day 15, her condition had worsened, requiring ICU admission for status epilepticus. On day 17, a third-degree AV block necessitated temporary pacemaker insertion. By day 35, she was discharged from the ICU, and by day 48, she left the hospital seizure-free with mild residual cognitive impairment.

Discussion

The discovery of numerous new neuronal antibodies in the last two decades has established AE as a treatable form of encephalitis. However, with new neuronal antibodies described almost annually, this dynamic field poses many challenges for clinicians trying to keep up with the new knowledge.

Epidemiology

In the context of newly described diseases, epidemiological studies form the foundation. They provide information about the occurrence, affected populations, and potential risk factors, which may guide public health responses. In light of this, **Study I** was an epidemiological study with the primary aim of estimating the incidence rate of AE and PNS in Healthcare region Mid Sweden over a 5-year period. The incidence rate of AE and PNS was 3.0 per million person-years between 2015 and 2019, comparable to previous international studies¹¹⁵. The annual incidence rates increased almost threefold during the study period, most likely indicating increased awareness among clinicians. Although it is fair to call AE a rare disease, it is more common than, for example, HSV-1 encephalitis in Sweden²⁰². Historically, HSV-1 encephalitis has received considerable attention in educational settings, and it is important that AE is likewise recognized and included in these contexts.

Greater awareness of AE is desirable but may also have unintended consequences, such as increased testing for neuronal antibodies in populations with low pre-test probability^{106,177}. In **Study I**, the number of tests for neuronal antibodies increased annually, while the proportion of positive tests tended to decrease over the study period. A low yield is to be expected, and potentially even desired, in such a new and dynamic field, as awareness increases faster than diagnostic precision. However, excessive testing in broad populations with low pre-test probability places high demands on the test's positive predictive value. In Healthcare region Mid Sweden, only a third of patients with a positive test result met diagnostic criteria for AE or PNS. The remaining patients either had an antibody that was nonspecific in this context or a false-positive result. The onconeural antibodies had a particularly high proportion

of failed case ascertainment, and it was associated with the methods used for antibody analysis. The patients in Healthcare region Mid Sweden had their samples analysed in one of two laboratories; one laboratory used only a commercial immunoblot, and one laboratory used a combination of immunoblot and indirect immunofluorescence. The combination of two methods yielded a lower ratio of failed case ascertainment than using only the commercial test (63% vs. 81%), consistent with previous studies^{158,161,162}. However, the overall high proportion of unspecific or false positive test results poses a challenge for clinicians, many of whom have limited experience in this new field. As a result, interpretation of the test result can be difficult, which may lead to misdiagnosis and wrongful treatment¹⁷⁷. It can also create uncertainty about the need for further examinations, such as malignancy screening. When reviewing medical records from **Study I**, several patients with likely false-positive results were found to have undergone CT or FDG-PET scans in search of malignancies. This has several consequences, including unnecessary radiation exposure, inefficient use of healthcare resources, and increased patient anxiety. Therefore, increased knowledge of the clinical characteristics of AE is essential, not only for improving disease recognition but also for the appropriate ordering and interpretation of antibody analyses.

Clinical Characteristics

In view of this, **Study II** was an observational case series that aimed to describe the clinical characteristics of the AE and PNS cases identified in **Study I**. Similar to previously described international cohorts^{112,203}, anti-NMDAR and anti-LGI1 were the most common antibodies in Healthcare region Mid Sweden. The anti-NMDAR subgroup had an older-than-expected age distribution (median 40, range 17-72), which may raise concern about missed diagnoses in younger individuals. However, when examining all patients testing positive for anti-NMDAR antibodies across the entire Swedish population, the age distribution (median 32, range 0-82) was closer to the expected, especially when including only the more specific CSF test results (median 26, range 0-82). Thus, the older-than-expected age distribution in Healthcare region Mid Sweden could reflect random variation due to a small sample size.

As expected, the clinical work-up of the patients in **Study II** revealed predominantly normal findings on brain MRI, and mostly nonspecific abnormalities on EEG and in CSF analyses. A significant diagnostic delay was observed for patients with more insidious onset (e.g., anti-LGI1, anti-CASPR2, anti-IgLON5), with one case of anti-LGI1 encephalitis receiving immunotherapy two and a half years after first healthcare contact. A review of medical records

revealed that clinical investigations (e.g., MRI, CSF analyses) were often performed in close proximity to antibody testing and the initiation of immunotherapy. Thus, the diagnostic delay occurred earlier in the course of disease, with patients frequently presenting to healthcare services multiple times before recognition. For instance, most patients (83%) with anti-LGI1 encephalitis presented with faciobrachial dystonic seizures (FBDS), a symptom considered pathognomonic for this condition, that went unrecognized. The presence of FBDS predicts a more severe disease course ²⁰⁴. Therefore, increasing awareness of the clinical presentations of these disorders is important. Not only neurologists, but also psychiatrists, paediatricians, infectious disease specialists, and geriatricians working in memory clinics need to possess basic knowledge of these conditions.

Epidemiological data can also provide insights into disease pathophysiology, including potential triggers of an autoimmune disease. In the context of AE, a considerable seasonal variation has been previously reported ¹¹⁷⁻¹¹⁹, similar to observations in multiple sclerosis ²⁰⁵. In **Study II**, the majority of patients with non-paraneoplastic AE had onset of symptoms in spring or summer. This may indicate a seasonal influence on disease triggers, such as post-infectious mechanisms following viral respiratory infection in late winter or spring. Viral infections are known triggers of AE, particularly anti-NMDAR encephalitis, which commonly occurs four to six weeks after HSV-1 encephalitis ⁸². It has been hypothesized that viral infections lead to a transient disruption of the blood-brain barrier and subsequent exposure of neuronal antigens in an inflammatory milieu ²⁰⁶. Further investigation of the geographical and temporal distribution of AE subtypes, together with infectious surveillance data, may further elucidate potential disease triggers.

As neuronal surface antibodies initially alter the synaptic function ²², not necessarily cause structural changes in the nervous system, the often normal or nonspecific findings on brain MRI are to be expected. However, this makes it valuable to explore other imaging modalities for both diagnosis and assessment of treatment response. Brain FDG-PET may reveal functional brain anomalies (manifested as regions of increased or decreased glucose metabolism), before structural changes occur. Previous studies have demonstrated that brain FDG-PET has superior sensitivity to MRI when it comes to detecting abnormalities in AE ^{132,207}. Nevertheless, as AE is rare and access to FDG-PET is limited, large studies on brain FDG-PET in AE are difficult to perform. To address this, **Study III** was a systematic review of all publications describing the presence of brain FDG-PET findings at the individual level in patients with AE and PNS to assess the prevalence and characteristics of regional metabolic abnormalities. The results demonstrated that the findings on brain

FDG-PET in AE go beyond the typical “limbic encephalitis” pattern with hypermetabolism in the medial temporal lobes. Many patients showed a more complex pattern, with both hyper- and hypometabolism as well as involvement of several anatomic regions. Different AE and PNS subtypes demonstrated distinct metabolic and anatomical patterns. These observations have important implications for the interpretation of brain FDG-PET in these patients, as the expected pattern of abnormalities must be taken into consideration when, for example, selecting reference regions. If an infratentorial region is used as a reference but is also affected by the disease, this may cause errors of interpretation. It may also confound the interpretation of longitudinal changes, such as treatment response, on serial scans. Further studies characterizing the metabolic and anatomical FDG-PET patterns in different subtypes of AE, and their temporal changes, are needed to establish this method as a reliable diagnostic and monitoring tool.

Biomarkers

Biomarkers found in serum and CSF may serve as valuable tools for diagnosing and assessing the disease prognosis. Accordingly, **Study IV** was an exploratory study using targeted proteomics to characterize protein expression profiles in serum and CSF from patients with anti-NMDAR encephalitis, with the aim of identifying potential biomarker candidates. Anti-NMDAR encephalitis cases demonstrated a distinct, compartment-specific protein signature in both serum and CSF compared to controls. In the CSF, proteins involved in both innate and adaptive immune mechanisms were altered. At the group level, inflammatory proteins ADA, CCL19, and CXCL5 were reduced, whereas longitudinal samples in one patient demonstrated a clear surge in CCL19 and CXCL5 during clinical deterioration. This could indicate that, at the time of CSF sampling, immune regulatory processes were in effect and highlights the importance of temporal information and longitudinal samples in further biomarker studies. In accordance with previous studies⁵³, proteins involved in synaptic maintenance (FGF-5, CDH3, and BMP-4)²⁰⁸⁻²¹⁰ were also downregulated in anti-NMDAR encephalitis cases, potentially contributing to the cognitive deficits observed in the disease. Longitudinal assessment of these proteins alongside serial cognitive testing and functional outcome measures could help determine whether they serve as reliable prognostic biomarkers.

Interestingly, Caspase-8 (CASP-8), a protease involved in the initiation of apoptosis and the regulation of microglia²¹¹, was elevated in both serum and CSF, with a moderate correlation between compartments. Also elevated in the serum of anti-NMDAR encephalitis cases was the protease Cathepsin C

(CTSC), which clustered closely with CASP-8 in hierarchical cluster analysis, indicating co-alteration. Their combined elevation in serum might indicate systemic proteolytic activity and immune activation. Despite the moderate correlation of CASP-8 levels between compartments, the elevation of CASP-8 might reflect different processes in the periphery and the CNS. CTSC was not significantly increased in the CSF, indicating compartment-specific alterations of these proteases. Possibly, increased levels of CASP-8 in the CSF reflect microglial activation rather than mirror the peripheral response. However, a previous proteomics study has shown elevated levels of CTSC together with other proteases in the CSF of patients with anti-NMDAR encephalitis⁵³, indicating that the diverging results could just be due to the small sample size in this study. CSF levels of CASP-8 demonstrated dynamic temporal changes with higher levels in patients with short symptom duration, and increasing levels during clinical worsening in serial samples from one case. A previous study using the same PEA methodology did not find elevated CSF levels of CASP-8 in patients with multiple sclerosis²¹². Taken together, the results from **Study IV** introduce CASP-8 as an interesting biomarker candidate for disease activity that warrants further investigation.

Limitations

This thesis has several limitations. Patients for **Study I**, and consequently also **Study II** and **Study IV**, were identified based on positive antibody test results, thus excluding all antibody-negative cases. As AE and PNS may be challenging to diagnose, it is possible that some true cases were never tested, thus leading to an underestimation of the incidence rate in **Study I**. Varying testing practices at different clinics may also have introduced bias and resulted in geographical variation in case detection. Indeed, among the six major healthcare regions in Sweden, Healthcare region Mid Sweden had 12.7 positive test results per 1000 000 inhabitants between 2015 and 2019, while Healthcare region West Sweden had the highest rate (18.8 per 1000 000), and the Northern healthcare region the lowest (8.3 per 1000 000), indicating regional differences that could have influenced the calculated incidence.

As demonstrated in **Study II**, a diagnostic delay is common, especially in AE with an insidious onset. Consequently, the date of antibody testing may not reflect disease onset, leading to a potential underestimation of cases during a defined time period if testing had not yet been ordered. In contrast, it may lead to overestimation of cases that underwent repeated testing despite an established diagnosis. This limitation was partially mitigated by the review of medical records, as cases with recurrent test results were excluded. The case

ascertainment relied on retrospective review of medical records, making it vulnerable to missing or inaccurate information. Furthermore, only patients who provided written consent to participate in the study were included (75%). This may also have led to an underestimation of the incidence rate, as true cases may have been excluded due to a lack of consent.

Study II was based on a retrospective review of medical records, which makes it susceptible to missing data. This limitation was most evident for patient functional outcomes, which could not be reliably presented in this study due to insufficient documentation. Furthermore, the grouping of patients according to antibody type (NSAbs, onconeural, GAD65) may be questioned, as the groups are still quite heterogeneous. For example, although both anti-NMDAR and anti-IgLON5 antibodies are classified as NSAbs, the clinical presentation of the associated neurological disorders differs substantially, making composite results potentially difficult to interpret. Furthermore, it may limit generalizability.

Although systematic reviews aim to minimize bias, they remain susceptible to both methodological review choices and inherent bias in the publications reviewed. In **Study III**, case series, case reports, and larger cohort studies were included. This probably increased the influence of publication bias, as it is likely that case reports containing abnormal brain FDG PET are published to a larger extent than those with normal findings. Likewise, more spectacular cases are more likely to be published, introducing a selection bias. Cases were grouped based on antibody subtype, but as antibody detection methods were often insufficiently described in the original publications, some degree of misclassification cannot be excluded. A major limitation was the considerable differences in how brain FDG PET findings were reported in the original studies. Differences in imaging acquisition, timing of scans, data processing, reference regions, and interpretation methods (e.g., qualitative or semi-quantitative) make it potentially challenging to distinguish methodological variability from true biological differences. To mitigate these limitations and integrate inconsistently reported data, brain FDG PET findings were categorized into simplified categories according to antibody subtype, anatomical regions, and metabolic pattern (e.g., “hypometabolism” or “hypermetabolism”). This enabled the identification of specific regional or metabolic patterns in different subtypes of AE, despite the variability in the underlying data.

The small sample size in **Study IV** limits generalizability. This was partially addressed by including two matched controls for each case, based on estimates from a pre-analysis power calculation. Another important consideration is the lack of an independent replication cohort and inflammatory controls, which, combined with the small sample size, means the findings should

be regarded as exploratory and hypothesis-generating. Furthermore, pre-analytical variability in sample handling may have influenced protein measurements. Specifically, CSF and serum samples from the anti-NMDAR encephalitis cases were refrigerated for up to seven days before freezing, while control samples were frozen promptly. However, the level of proxy markers used to assess variability in sample handling did not differ between groups²¹³, which, together with low within-group variability, suggests minimal impact of pre-analytical factors.

Conclusions

In **Study I**, it was concluded that the yearly incidence rates of AE and PNS increased during the 5-year study period, as did the number of tests for neuronal antibodies. This likely reflects increased availability of testing and awareness of these conditions. Only a third of patients with a positive neuronal antibody test fulfilled diagnostic criteria for definite AE or PNS, highlighting the challenges physicians face when interpreting test results.

In **Study II**, the similarity in clinical presentation of patients with AE and PNS between Swedish patients and previously described international cohorts was confirmed, except for an older-than-expected age distribution in anti-NMDAR encephalitis cases. Despite presenting with disease characteristic symptoms, the diagnosis was often delayed, underscoring the need for greater clinical awareness. Additionally, the onset of non-tumor-related AE occurred predominantly in the warm seasons, indicating a seasonal trigger such as a viral infection.

In **Study III**, a systematic review of brain FDG-PET in patients with AE revealed complex patterns of hyper- and hypometabolism, highlighting the need to expand the current understanding of FDG PET findings in AE beyond the classical pattern of medial temporal lobe hypermetabolism.

In **Study IV**, targeted proteomic profiling revealed distinct, compartment-specific immunopathological profiles in anti-NMDAR encephalitis, involving both innate and adaptive immune pathways. CASP-8 emerged as a promising candidate biomarker for disease activity and warrants further investigation.

Collectively, these studies contribute to the growing body of knowledge on these emerging neuroinflammatory disorders and highlight the need not only for heightened awareness but also for greater precision in diagnosing and treating them.

Future Perspectives

This thesis provides evidence that the incidence rate of AE is increasing in Sweden, probably due to greater awareness and more frequent testing rather than a true rise in cases. Each year, clinicians order more tests for neuronal antibodies, which raises important questions about patient selection and the testing methods used. As demonstrated in this thesis, a high proportion of patients with positive antibody test results did not fulfill the diagnostic criteria for AE or PNS. This, in turn, could lead to wrongful treatment and unnecessary examinations if un-specific or false positive test results are not interpreted properly. To improve patient selection and increase the pre-test probability of detecting neuronal antibodies, scoring systems such as the APE2 score have been proposed²¹⁴. The APE2 score estimates the likelihood of a positive neuronal antibody in a patient with new-onset encephalopathy or seizures, based on routine clinical features (i.e., brain MRI and CSF findings). An APE2 score ≥ 4 has demonstrated 99% sensitivity and 93% specificity for the detection of neuronal antibodies²¹⁴. Incorporating such scoring systems in clinical practice could reduce broad testing in populations with a low pre-test probability. However, they should be used cautiously since relying too rigidly on a scoring system may lead to underrecognition of AE with atypical or chronic presentations.

Equally important is to review which methods are used for testing neuronal antibodies in Sweden to minimize false-positive results. As demonstrated by this thesis, the proportion of false-positive test results differs between Swedish laboratories. Although all five laboratories use the same commercial test kits for both neuronal surface antibodies and onconeural antibodies, not all of them combine these with a second confirmatory technique, often due to financial limitations. The way test results are reported also varies. Reducing variability between laboratories by standardizing testing methods and reporting practices could therefore lead to higher diagnostic accuracy. Alternatively, this could be achieved by centralizing neuronal antibody testing in Sweden. However, concentrating all testing in a single location increases vulnerability, since the process becomes dependent on only a few individuals who have the required expertise. In addition, Sweden's large geographical area places high demands on logistics, and because rapid test results are important in the context of AE, centralization appears to be a less feasible option.

The rarity of AE and PNS poses challenges not only for treating clinicians but also for conducting research studies. As our understanding of AE grows, it has become increasingly clear that the various subtypes of AE in many respects are completely different diseases, with fundamental differences in clinical presentation, underlying pathophysiology, and treatment response. Grouping AE subtypes in research studies to achieve larger study populations, as done in parts of this thesis, therefore carries the risk of diluting and confounding results. However, refining AE subgroups in studies while still maintaining sufficiently large study populations requires access to even more patients. A newly established national registry for AE and PNS within the Swedish Neuro Registries could facilitate the identification of potential research participants, but its usefulness depends on achieving high national coverage. International cooperation will also be important in future studies to increase the study populations.

Larger study populations would also benefit future biomarker research in AE, and international collaboration could provide much-needed independent validation cohorts. For example, future studies of CASP-8 as a potential biomarker of disease activity in anti-NMDAR encephalitis (and possibly other AE subgroups) should include validation cohorts, inflammatory controls (e.g., neuroinflammatory diseases and infectious encephalitis), and potentially cohorts with other neurological disorders (e.g., neurodegenerative diseases). Careful consideration should be given to the timing of sample collection relative to the clinical disease course, and longitudinal sampling would be ideal. Including both serum and CSF samples would provide more insights into disease mechanisms. However, since this type of multi-centre longitudinal study is challenging and expensive, beginning with a more limited design would be a reasonable first step. For example, high serum levels of CASP-8 have been linked to higher mortality in both malignant middle cerebral artery infarction and sepsis ^{215,216}. A more targeted investigation into whether serum CASP-8 levels in AE patients can predict disease severity could therefore be a practical next step.

Finally, to reliably assess disease severity in AE, the use of functional outcome measures that accurately reflect the clinical manifestations of the disease is essential. The failure to reliably grade the functional outcome of the participants in this thesis, due to insufficient records, highlights the lack of tools available for clinicians. In most research studies, the modified Rankin Scale is still used, despite often failing to capture cognitive sequelae of AE. A scale that assesses disease severity in AE, the Clinical Assessment Scale of Auto-immune Encephalitis (CASE) ²¹⁷, has been proposed and validated in smaller cohorts, and is being incorporated into several ongoing clinical trials ²¹⁸.

Going forward, the consistent use of a limited number of validated functional outcome scales will be important to ensure comparability across studies and clinical registries.

Sammanfattning (Summary in Swedish)

Encefalit, från grekiskans *enképhalos* (hjärna) och suffixet *-it* (inflammation), är en medicinsk term som beskriver tillståndet hjärninflammation. Personer som drabbas av encefalit får ofta symptom såsom förändrat beteende, minnesstörningar och epileptiska anfall. Inflammation i hjärnvävnaden kan orsakas av en virusinfektion, t. ex. herpesvirus eller TBE (fästingburen hjärninflammation). Hos en stor andel av patienter som drabbas av encefalit kan man dock inte påvisa något virus, och historiskt sett har den bakomliggande orsaken ofta varit oklar. Specifik behandling har saknats, med undantag för encefalit orsakat av herpesvirus, och prognosen har därför ofta varit ogynnsam.

Under de senaste två decennierna har forskningen gjort stora framsteg. Man har kunnat visa att en betydande andel av patienterna har en så kallad autoimmun encefalit, vilket innebär att kroppens eget immunförsvar felaktigt angriper friska nervceller och ger upphov till inflammation i hjärnvävnaden. I blod eller ryggmärgsvätska från dessa patienter har man identifierat antikroppar riktade mot proteiner i centrala nervsystemet, vilka benämns neuronala antikroppar. Många olika neuronala antikroppar har beskrivits senaste åren och de är associerade med varierande sjukdomsbilder.

Vissa neuronala antikroppar har en stark koppling till samtidig cancersjukdom hos den drabbade patienten och den neurologiska symptombild som då uppstår benämns paraneoplastiska neurologiska syndrom (PNS). Andra antikroppar har en svag eller obefintlig koppling till cancer, och dessa fall benämns vanligen autoimmun encefalit (AE). Upptäckten att encefalit i många fall orsakas av en autoimmun reaktion har inneburit stora vinster för patienterna, eftersom tillståndet har visat sig svara bra på immunhämmande behandling.

Denna avhandling syftade till att fördjupa vår kunskap om AE och PNS. Som vid alla relativt nyligen upptäckta sjukdomstillstånd är grundläggande epidemiologisk information om vilka och hur många som drabbas av stort värde. Därför kartlades förekomsten av AE och PNS i Sjukvårdsregion Mellansverige i **Studie I**. Resultaten visade att AE och PNS är minst lika vanligt som encefalit orsakat av virus. De årliga incidenstalen för AE och PNS ökade under den femåriga studieperioden, liksom antalet tester för neuronala antikroppar. Detta speglar sannolikt en ökad tillgänglighet till testning samt en större medvetenhet om dessa tillstånd. Endast en tredjedel av patienterna med

ett positivt test för neuronala antikroppar uppfyllde de diagnostiska kriterierna för definitiv AE eller PNS, vilket belyser de utmaningar läkare står inför när de ska tolka testresultaten.

I **Studie II** beskrevs patienter med bekräftad AE eller PNS i Sjukvårdsregion Mellansverige, deras kliniska karakteristika samt deras väg genom sjukvården. Trots att flera patienter tidigt i förloppet uppvisade symtom som är typiska för sjukdomen fördröjdes diagnosen ofta, vilket understryker behovet av ökad klinisk medvetenhet. Dessutom inträffade insjuknandet i AE hos patienter utan cancer huvudsakligen under de varma årstiderna, vilket skulle kunna tyda på en säsongsbunden utlösande faktor, såsom en virusinfektion.

Kännetecknande för AE och PNS är att rutinundersökningar såsom magnetkameraundersökning och analys av ryggmärgsvätska ofta visar normala eller ospecifika resultat, vilket försvarar diagnostiken. Inflammation i hjärnan ökar nervcellernas sockeromsättning, vilket indirekt kan avbildas med en metod som kallas positronemissionstomografi (PET) när man använder ett radioaktivt sockerämne (FDG). FDG-PET av hjärnan vid AE har tidigare visat lovande resultat, men större forskningsstudier är svåra att genomföra då metoden har begränsad tillgänglighet och AE är ovanligt. I **Studie III** utfördes därför en systematisk översikt av publicerade fall av AE där FDG-PET av hjärnan utförts. Resultaten visade att AE ger upphov till komplexa mönster av ökad eller minskad sockeromsättning i hjärnan, och att dessa mönster skiljer sig beroende på vilken typ av neuronal antikropp patienten har. Dessutom påvisade FDG-PET avvikelser i större utsträckning än magnetkameraundersökning, talande för att metoden kan vara ett viktigt komplement i utredningen av dessa patienter.

I **Studie IV** mättes nivåerna av olika proteiner involverade i inflammation och nervsystemets funktion i blod och ryggmärgsvätska hos åtta patienter med en av de vanligaste varianterna av AE, nämligen anti-NMDAR encefalit. 182 olika proteiner analyserades samtidigt med hjälp av en metod som kallas Proximity Extension Assay (PEA). De resulterande proteinprofilerna jämfördes med de från 16 friska kontroller. Resultaten visade att patienter med anti-NMDAR encefalit hade lägre nivåer av vissa proteiner involverade i nervcellernas överlevnad och underhåll, medan några proteiner involverade i reglering av celldöd och inflammation var ökade. Särskilt intressant var ett protein involverat i celldödsreglering och inflammation som heter CASP-8. Det var ökat i både blod och ryggmärgsvätska hos patienter med anti-NMDAR encefalit, mer så hos patienter som hade haft symtom under kort tid. Då denna studie inkluderade få patienter behövs ytterligare studier i framtiden för att bekräfta om dessa proteiner, inklusive CASP-8, skulle kunna vara intressanta markörer för t.ex. sjukdomsaktivitet vid AE.

Sammantaget belyste resultaten från denna avhandling flera av de utmaningar som uppstår tiden närmast efter att en ny sjukdomsgrupp beskrivits. Dessa innefattar både diagnostiska utmaningar, avsaknad av evidensbaserad behandling och behovet av utbildning för ökad medvetenhet kring tillståndet. Förhoppningsvis kan resultaten från denna avhandling bidra till en ökad kunskap om AE och PNS ur ett svenskt perspektiv och underlätta för sjukvårdsplanering och utbildning.

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