Autoimmune Encephalitis
Pathophysiology, Diagnosis and Treatment

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Autoimmune encephalitis is a family of similar neuropsychiatric diseases presenting with a range of symptoms including subacute dysfunction in memory, decreased cognition, psychosis, refractory seizures, and encephalomyelopathy. During the initial investigation, infectious and medical causes of encephalitis must be ruled out and autoimmune aetiologies explored. Patients will often have a characteristic clinical history and findings, CSF pleocytosis, MRI T2-FLAIR, especially in temporal lobes and limbic system, and EEG changes. Specific autoantibodies can be detected using commercial laboratory tests with high sensitivity and specificity. The diseases can largely be broken down into group I encephalitides with autoantibodies against intracellular synaptic proteins, and group II encephalitides with autoantibodies against neuronal surface proteins. When a diagnosis is suspected, patients should receive first-line steroids and IVIG. If this fails, second-line immunotherapies rituximab and cyclophosphamide are recommended. The majority of autoimmune encephalitides have an association with various tumours and are therefore paraneoplastic syndromes in many patients. Comprehensive screening for cancer should be carried out in all patients, focusing on the specific cancer association, and appropriate cancer treatment can help ease neurological symptoms. Outcomes vary by disease and recovery is usually slow. This is a relatively newly recognised disease and new research is vital to increase recognition and form treatment strategies to best deal with this underdiagnosed condition. This is a review of the literature on the pathophysiology, diagnosis and treatment of autoimmune encephalitis.

Introduction

Autoimmune encephalitis is a family of similar neuropsychiatric diseases with different pathophysiology. It is important to identify the exact type of disease in order to best diagnose and treat a patient. Often the diagnosis can be challenging as many of the symptoms overlap, and many autoimmune, and even infectious encephalitides may be confused. While clinical presentations vary, in general, there is a subacute dysfunction in memory and decreased cognition. Certain types are often associated with underlying malignancy and therefore are paraneoplastic conditions, while others are seen without cancer in the body. Paraneoplastic forms are comparable to more well-known diseases such as Lambert-Eaton myasthenic syndrome (LEMS) where antibodies are formed against presynaptic voltage-gated calcium channels leading to muscles weakness. Like many of the autoimmune encephalitides, LEMS is often seen on a background of small cell lung cancer (Petty, 2007).

Autoimmune encephalitis was first described in 1968 as a paraneoplastic syndrome causing damage and inflammation of the temporal lobe and limbic structures with progressive memory loss seen in some patients with lung cancer (Corsellis, Goldberg, & Norton, 1968). Later in 1988, when brain imaging became widely available, this inflammation could be picked up using MRI to visualise T2-weighted hyperintense regions in the limbic system and temporal lobes on a patient by patient basis (Kohler, Hufschmidt, Hermle, Volk, & Lücking, 1988). Larger studies were done, and a pattern began to emerge of similar T2-FLAIR signal changes, and diagnostic criteria were established in 2000. In 2007 these criteria were altered to include the non-paraneoplastic forms of limbic encephalitides (Tüzün & Dalmau, 2007). Josep Dalmau can almost be considered 'the father' of autoimmune encephalitis for his discoveries in this field and many of the papers referenced in this review include him as a lead or co-author. In 2016, many of the world leaders in this field came together to publish updated guidelines. They felt the need for more widely usable criteria, as antibody testing is frequently initially outside the reach of many hospitals. They describe the criteria for possible autoimmune encephalitis if a patient has all 3 of the following:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, altered mental status, or psychiatric symptoms.

2. At least one of the following:

   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than five cells per mm3)
   - MRI features suggestive of encephalitis

3. Reasonable exclusion of alternative causes (Graus et al., 2016).

Groups of Autoimmune Encephalitis

Autoimmune encephalitides can be grouped based on the antibody present. Group I autoimmune encephalitides have antibodies to intracellular antigens, like anti-Hu. They are most often paraneoplastic, mediated by cytotoxic T-cells and have a limited response to treatment. For this reason, and the fact that the neuronal damage tends to be irreversible, they have worse clinical outcomes than group II encephalitides. As the damage is largely caused by T-cells, the antibody levels are less correlated with disease severity but may be useful as tumour markers (Dalmau & Bataller, 2006). Focusing on anti-Hu encephalitis, it was discovered in 1985 in two patients with subacute sensory neuronopathy (a form of polyneuropathy due to neural degeneration (Zuberbuhler et al. 2015)) with a previous diagnosis of small cell lung cancer (SCLC). This is an aggressive neuroendocrine lung cancer which metastasises early and is associated with various paraneoplastic syndromes. An immune response is generated when Hu proteins are expressed on cancer cells such as SCLC. Hu protein is normally only found in the nuclei of neurons of the central and peripheral nervous system, i.e. immune privileged environments. T cells are activated and anti-Hu antibodies are produced (Bernal et al. 2002). Studies have shown that T-cells are central mediators of the disease and are present at higher levels in the CSF of patients with anti-Hu encephalitis than controls with SCLC without neurological disease (De Jongste et al. 2013). CD8+ T cells infiltrate affected tissue and are found in close proximity to damaged neurons at autopsy (Jean et al. 1994). These results suggest that T cells are central to the immune response in the CNS.

Group II diseases have antibodies which target cell surface neuronal antigens such as anti-NMDAr encephalitis. They are less likely to be paraneoplastic, more responsive to therapy and have antibodies as the central mediator of their pathogenicity (Bien et al., 2012). Due to this direct link between antibody titre and disease activity, the levels can sometimes be monitored for treatment response, severity and recurrence. Patients with this group of antibodies may have systemic autoimmune disease, experience symptoms following viral infection or vaccination, or have an idiopathic aetiology (Glaser et al., 2003). Focusing on anti-NMDAr encephalitis, it is mediated by IgG1 and IgG3 antibodies against the GluN1 subunit of the NMDAR (Dalmau et al. 2008). These antibodies have been shown to be pathogenic and crosslink the NMDAR

causing its internalisation. This leads to less receptor at the synapse and less NMDA mediated signalling. Secondly, they also directly antagonise signalling at the receptor, similar to pharmacological antagonists PCP and ketamine (Moscato et al. 2010). They have been shown to be pathogenic when passively transferred into the brains in rodent experiments (Planagumà et al. 2015). An ovarian teratoma can express the onconeural antigen NMDAR, and antibodies can be formed and subsequently cross the BBB and cause neural damage. However in one study only 45% of women with anti NMDAR encephalitis were found to have an ovarian teratoma (Florance et al. 2009). Therefore, there must be another mechanism of antibody production.

Diagnosis

Clinical

Symptoms can be generalised or patient specific. Generally, symptoms include loss of cognition, memory (especially anterograde) or consciousness, and psychiatric symptoms such as mood swings, psychosis, compulsive behaviours and hallucinations. In some cases, more idiosyncratic symptoms can appear, such as ocular symptoms in anti-Ma associated encephalitis (Rosenfeld, Eichen, Wade, Posner, & Dalmau, 2001). Certain encephalitides may present within a syndrome of symptoms. For example, some cases of Morvan's syndrome are caused by anti-Caspr2 antibodies, a subtype of anti-VGKC encephalitis. This presents as neuromyotonia, neuropsychiatric features, autonomic dysfunction and neuropathic pain (Josephs et al., 2004). Anti-Caspr2 antibodies also cause some cases of Isaacs syndrome which presents as peripheral nerve hyperexcitability, twitching, stiffness and cramps (Irani et al. 2010). Table 1 shows key features which may (or may not) be visible in the presentation of each type of autoimmune encephalitis.

The collection of symptoms, along with the medical history focusing on any cancers, as well as the age and sex of the patient can help to guide the laboratory and radiologic tests which should be ordered. If a patient has not been previously diagnosed with a solid tumour, a full screen with CT, MRI or PET is recommended as many of the diseases are paraneoplastic. Children have more motor symptoms and fewer psychiatric symptoms than adults, and thus chorea or other movement disorders may be seen in this cohort (Armangue et al., 2013).

Laboratory

From a biochemical perspective, blood and CSF samples are often sent for analysis. A full blood count performed along with a lumbar puncture and subsequent CSF differential cell count. Common CSF findings in autoimmune encephalitis can help to reach a diagnosis. A mild lymphocytic pleocytosis (<100 WBC/µL) is seen in 80% of patients. A raised protein count (<150 mg/dL), normal glucose and an elevated IgG with oligoclonal bands

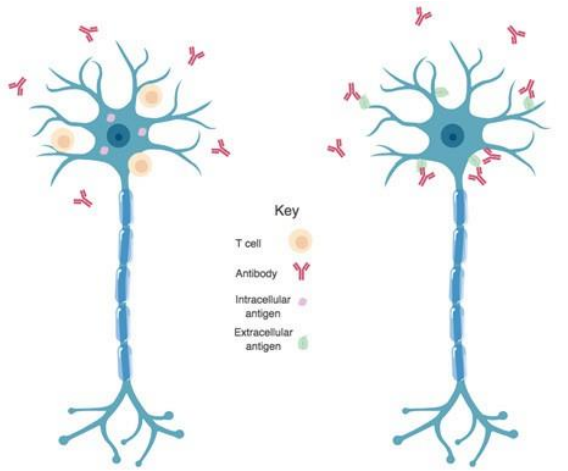

Figure 1: (left) T cell and antibody activity to intracellular antigen in group I autoimmune encephalitis. (right) Antibody attack on extracellular antigens in group II autoimmune encephalitis.

are also seen frequently (Tüzün & Dalmau, 2007).

With suspected AI encephalitis, an antibody panel is requested. In recent years, tests have improved in specificity and sensitivity for the detection of specific intracellular and neuronal surface antibodies. It is important to detect the antibody early in order to characterise the disease and to determine management strategies. Broad-spectrum commercial tests for relatively common antibodies should be carried out before specific tests for rarer antibodies, if the former is negative. Both the serum and CSF of the patient must be tested, with clinical justification based on the fact that in 14% of anti-NMDAR encephalitis patients the serum is negative for specific antibodies which are found to be present in the CSF (Gresa-Arribas et al., 2014). Only testing serum would give a false negative for this group. On the other hand, patients with positive serum and negative CSF may have degenerative or psychiatric pathologies (Zandi et al., 2015). When antibodies are found in both CSF and serum, titres can be used to estimate intrathecal production levels.

Antibody tests are central to the classification of these diseases, but results have to be analysed carefully and positive findings do not always equate to a diagnosis. In group II encephalitides such as anti-NMDAR encephalitis, IgG antibodies are pathogenic and diagnostic whereas IgM or IgA are seen in other psychiatric diseases and even in up to 10% of the healthy population (Jearanaisilp, Sangruji, Danchaivijitr, & Danchaivijitr, 2014). While it may be presumed that antibody titres correlate with disease severity and treatment response in other AI conditions, this is rarely the case here. In most of the diseases the only occasions they are useful is when comparing a single patient's CSF antibody titres over the disease course, to analyse treatment response or relapse. However, clinical wellbeing of the patient is still a better measure of the disease (Gresa-Arribas et al., 2014). Furthermore, testing for an antibody that is known to be pathogenic does not mean that it is pathogenic in every positive case. Looking at anti-GAD antibodies, a positive result can mean 3 things. The antibodies may be pathogenic and cause SPS, encephalitis or cerebellar degeneration. They may be found together with anti-GABA-B receptor antibodies which are actually the pathogenic antibody. Or lastly, they may be found in T1DM in patients without neurological disease (Tohid, 2016).

Group I		Group II	
Encephalitis Antibody	**Symptom**	**Encephalitis Antibody**	**Symptom**
Hu	Sensory neuronopathy	NMDAR	Prodrome + psychosis
Ma	Ophthalmoplegia	VGKC	REM sleep disorder
CV2/CRMP5	Sensorimotor neuropathy	GABAr	Seizures
SOX1	LEMS	AMPAr	Psychosis
GAD	T1DM + Stiff person syndrome (SPS)	GlyR	Motor/SPS

Table 1: Types of autoimmune encephalitis (named by antibody produced) and their distinguishing symptoms often seen uniquely in patients with this form of AI encephalitis

Neuroimaging

MRI is the primary imaging modality used in patients with suspected AI encephalitis. MRI changes are frequent but can often be similar to changes seen in other encephalitic causes like Herpes Simplex Virus (HSV) and so may be nonspecific (Sili, Kaya, & Mert, 2014). Findings vary by type of encephalitis as highlighted by Kelley et al. published in the American Journal of Neuroradiology (Kelley et al., 2017). Most classically seen are T2-FLAIR (fluid-attenuated inversion recovery) hyperintense lesions in temporal lobes and limbic structures. It is important to note that a negative MRI does not exclude the diagnosis of autoimmune encephalitis.

Electroencephalogram (EEG) is an alternative neuroimaging test used to aid diagnosis. EEG can help to exclude other causes of symptoms like seizures and diagnose and aid prognosis of certain types of autoimmune encephalitis. In classic limbic encephalitis, EEG can detect epileptic foci in one or both temporal lobes, or focal or generalised slow activity (Lawn, Westmoreland, Kiely, Lennon, & Vernino, 2003). When EEG detects an extreme delta brush pattern it can be suggestive of anti-NMDAR encephalitis and prompt antibody testing (Schmitt et al., 2012). EEG can also be used to determine the aetiology of refractory epilepsy or status epilepticus in which no response is seen to anti-epileptic treatments. Anti-GABAr encephalitides are the most heavily linked autoimmune encephalitis to seizure activity (Lancaster et al., 2010).

Exclusion of other diseases

As autoimmune encephalitis is a rare diagnosis, more common diseases must be considered and ruled out. Many forms of encephalitis, along with other similar pathologies, can present with comparable features and there are various tests which must be done to elicit the aetiology of these symptoms. Firstly, as infectious causes of encephalitis are prevalent, patients will likely be screened for Herpes simplex virus (HSV) encephalitis, the most common cause of viral encephalitis. This test is done by PCR of CSF and has 94% sensitivity and 98% specificity but only after 24 hours of onset (Weil, Glaser, Amad, & Forghani, 2002). For this reason, patients may be empirically started on acyclovir. Other viral causes which may be screened for include Varicella zoster, Enterovirus, West Nile virus, and Japanese encephalitis (Venkatesan, 2015). Bacterial causes include Listeria, Streptococcus, Syphilis, Lyme disease, and Tuberculosis. Fungal causes include Cryptococcus and Aspergillus and are found more commonly in immunocompromised patients (Venkatesan, 2015). As some of these causes are endemic in certain regions and depend on the host being immunocompromised in most cases, gaining a comprehensive medical and travel history from the patient is important. These infectious agents can be detected through PCR, serology for antigen or antibody, or culture. To effectively test for many agents at once, next generation sequencing techniques have been developed. These methods, like metagenomics deep sequencing of CSF, can screen for 100s of pathogens at once and speed up the diagnosis of the infectious agent (Wilson et al., 2014). Interestingly, 20% of patients with HSV encephalitis develop antibodies to the NMDAR (Armangue et al., 2015). This explains the previously mysterious condition of relapsing neurologic symptoms post HSV encephalitis which occur as psychiatric, cognitive or movement symptoms a few weeks after acyclovir treatment. This is a now well-established link showing a CNS viral infection triggering an autoimmune encephalitis. The mechanism behind this is likely to be inflammatory damage by the virus exposing the NMDAR to immune cells and stimulating an inflammatory response. This presentation likely occurs in the deep cervical lymph nodes which receive antigens from the CNS (Ransohoff & Engelhardt, 2012).

As well as infectious causes, other medical and autoimmune causes must also be excluded. Wernicke's encephalopathy, mostly seen in alcoholics, can mimic autoimmune encephalitis. If this is likely, thiamine supplementation will be carried out without waiting for lab results as fast treatment is necessary to avoid long term damage (Lallas & Desai, 2014). Other medical diseases which can present similarly are serotonin syndrome, and neuroleptic malignant syndrome. There are certain autoimmune diseases, which are not autoimmune encephalitides, that can present similarly. These include multiple sclerosis, encephalomyelitis, and neuropsychiatric lupus seen in the form of antiphospholipid syndrome. These will likely have other symptoms present, and so a full history and examination is important. They will also have different findings on MRI (Lancaster, 2016).

Treatment

Timely treatment is hugely important in these diseases to prevent further deterioration and long-term damage. When autoimmune encephalitis is strongly suspected or confirmed, empiric treatment will be commenced, often before any specific antibodies are detected. First-line treatments usually include steroids and/or intravenous immunoglobulin (IVIG). Steroids help to reduce the cerebral inflammation in AI as well as other causes of encephalitis. However, steroid do carry the risk of systemic side effects and are contraindicated in certain patients due to conditions such as peptic ulcers, hypertension, osteoporosis and diabetes mellitus (Kopera, 1993). IVIG also reduces inflammation by blocking Fas-mediated cell death, increasing the expression of the inhibitory Fc receptor on APCs, and shortening the half-life of autoreactive antibodies (Nimmerjahn & Ravetch, 2007). If the disease is suspected

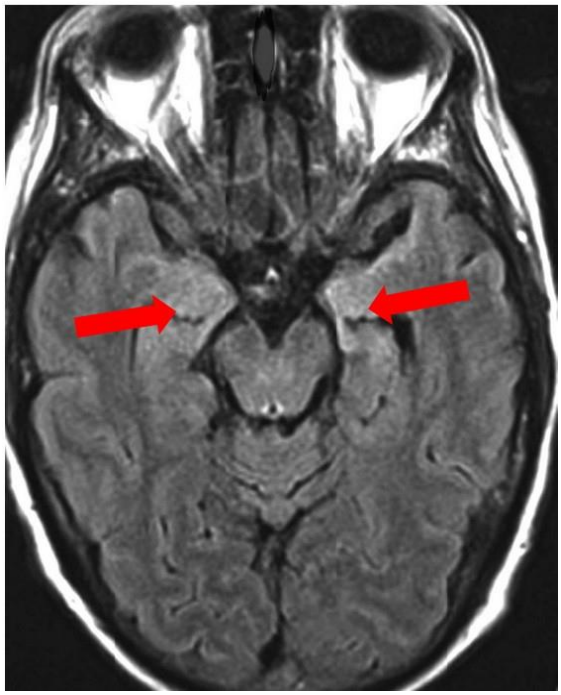

Figure 3: MRI of a patient with NMDAR encephalitis showing increased signal intensity bilaterally in the medial temporal lobes and hippocampi. Image taken from (Zhang et al. 2013)

to be a group II encephalitis, plasmapheresis is sometimes carried out to remove the pathogenic antibodies. IVIG and plasmapheresis are unlikely to worsen the disease if it turns out to be infectious (Lancaster, 2016). One major problem with these first-line treatments is that they do not reduce intrathecal antibody production (Furneaux, Reich, & Posner, 1990). First-line immunotherapy such as steroids have been shown to be limited in their efficacy in autoimmune encephalitis (Shin et al., 2018). At least half of patients are put on second line agents for this reason.

Second-line treatments are employed in patients unresponsive to first-line treatments. These include the immunotherapies of anti-B cell monoclonal antibody rituximab, or the anti-T cell drug cyclophosphamide (Lancaster, 2016). If a tumour is already diagnosed or newly detected it will be removed if at all possible. This usually helps to stabilise the disease aggressiveness (Alamowitch et al., 1997). Second-line treatments also share the problem of not targeting intra-thecal antibody production. Rituximab targets CD20 on B-cells to eliminate these cells, but the mature plasma cells within the CNS do not express CD20 and are therefore resistant (Martinez-Hernandez et al., 2011). Blood brain barrier (BBB) penetration of these second-line therapies is also limited (Dalmau, Geis, & Graus, 2017).

As previously mentioned, patients presenting with autoimmune encephalitis are likely to have a concurrent tumour. For this reason, a full cancer screen should be carried out, targeted to the diagnosis, e.g. ultrasound of testicles for Anti-Ma associated encephalitis. This should be done at presentation, and at follow-ups over the next 24 months, as tumours may be undetectable initially. It is vitally important to detect and address the cancer at the onset of treatment for a number of reasons. Firstly, treating the tumour may help the neurological symptoms. Secondly, coordination between tumour therapy and immune therapy may be important. Lastly, treatments with some immunotherapy agents may delay or complicate the diagnosis of certain cancers like lymphoma (Lancaster, 2016). For group I encephalitides, detection of the antibody may occur in certain cancers in the absence of encephalitis. If the antibody is detected by chance, or when investigating another disease, tumour screens should still be carried out. For group II encephalitides, presence of the antibody in the CSF usually indicates neurological disease, and likewise, the relevant tumour tests should be performed. On the other hand, patients with likely autoimmune encephalitis or cerebellar degeneration without identifiable antibodies should still be broadly screened for cancer (Lancaster, 2016).

More research is needed into many aspects of the treatment of autoimmune encephalitis. Further clarifying the pathophysiology of the specific types of autoimmune encephalitis will allow more targeted therapies and improve responses, especially for group I encephalitides. RCTs comparing individual first and second-line treatments are also needed to produce evidence bases guidelines for physicians attempting to treat these diseases. For now, prompt initiation of first-line therapies with appropriate monitoring and transfer to second-line drugs, along with tumour identification and resection, is the best treatment strategy.

Concluding Remarks

Autoimmune encephalitis is a relatively novel but important consideration on the list of potential diagnoses for a patient presenting with a range of neurological or psychiatric symptoms. It is not one disease but a family of similar diseases within two major groups. Many of the types are paraneoplastic or can occur in the absence of cancer, but careful tumour screening is usually warranted at presentation and at later follow-ups. The diagnosis relies on the initial clinical history and examination, laboratory findings and neuroimaging. Many other diseases, like infectious and medical encephalitides can present in similar ways and must be excluded. While the diagnosis of autoimmune encephalitis is frequently overlooked, early recognition and treatment is key to effective management in these patients. Current treatments consist of first-line steroids, IVIG and plasmapheresis, moving onto second-line immunotherapies, but this varies with aetiology and health of the patient.

New research in the last 5 years has identified many new autoantibodies and this is predicted to continue in coming years. This allows the correct identification of many diseases with previously unknown aetiologies as autoimmune. There is a need for new research into treatments, especially those which target the intrathecal synthesis of autoantibodies, as well as treatments to improve outcomes for the encephalitides with antibodies to intracellular antigens. For these group I encephalitides, better understanding of the role of T cell autoimmunity is needed to develop and utilise anti-T cell therapies in these diseases. Further large studies are needed to improve the classification of individual types of autoimmune encephalitis to allow for better diagnostic guidelines within the field. Currently, there are 7 clinical trials ongoing or recruiting into various aspects of autoimmune encephalitis listed on clinicaltrials.gov, and these will only help to improve understanding and outcomes in these relatively novel but devastating diseases.

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