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A REVIEW OF AUTOIMMUNE ENCEPHALITIS.

Neurology

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ABSTRACT

Encephalitis (brain inflammation) is often thought to be mediated by infections (e.g. viral). With the advances in molecular diagnostics, new immunological markers (antibodies) are being discovered in patients presenting with encephalitic syndromes. Thus, research has evoked interest in the 'immune theory' of encephalitis. Limbic encephalitis (LE) was first described in the 1960s and refers to the subacute onset of episodic memory loss, confusion, and agitation. LE is frequently associated with hallucinations, seizures, sleep disturbance, and signal change in the medial temporal lobe and hippocampi on imaging. LE is classically described as being paraneoplastic. We review the clinic- pathological details of Autoimmune Encephalitis in this article.

KEYWORDS

Encephalitis Antibodies Autoimmune VGKC NMDA

Introduction:

Encephalitis (brain inflammation) is often thought to be mediated by infections (e.g. viral). With the advances in molecular diagnostics, new immunological markers (antibodies) are being discovered in patients presenting with encephalitic syndromes. Thus, research has evoked interest in the 'immune theory' of encephalitis [1]. Autoantibody-mediated encephalitis is also known as autoimmune-mediated encephalitis, autoimmune-mediated limbic encephalitis, and autoimmune synaptic encephalitis. How to categorize these syndromes is still in flux: they can be listed by the area of the brain affected, the antibody involved, or the name of the discoverer (eg, Morvan syndrome) [2]. Autoantibodies identified in autoimmune encephalitis fall under two broad categories:

- Those targeting intracellular (intranuclear or intracytoplasmic) antigens; the syndromes they cause are more likely to be paraneoplastic and less responsive to immunotherapy
- Those targeting antigens on the neuronal surface: the syndromes they cause are less likely to be paraneoplastic and are more responsive to immunotherapy [3].

Limbic encephalitis:

Limbic encephalitis (LE) was first described in the 1960s and refers to the subacute onset of episodic memory loss, confusion, and agitation [4]. LE is frequently associated with hallucinations, seizures, sleep disturbance, and signal change in the medial temporal lobe and hippocampi on imaging. LE is classically described as being paraneoplastic [4]. Antibodies to onconeural intracellular antigens which are nuclear or cytoplasmic proteins such as Hu, Ma, and Ri are associated with certain malignancies such as lung cancer and testicular tumours [4,5]. These antibodies are clearly demonstrated by standardised tests, associated with limited subtypes of malignancies, and have a variety of neurological manifestations [5].

The clinical course is usually monophasic and relentlessly progressive with a guarded prognosis, and treatment is directed to the underlying malignancy [6,7]. The antibodies targeting onconeural antigens are believed to be biomarkers of associated tumours rather than being directly pathogenic, and their detection should prompt investigation for an associated underlying malignancy [5,7,8]. Previous studies including passive transfers or active vaccination with the antigen in animal models have failed to reproduce these clinical syndromes, and newly published results have shown that neuronal cell death was due to T-cell mediated cytotoxicity, lending further weight to the contention that this group of antibodies is not directly pathogenic [5,7].

Clinical Features and Diagnosis:

Important clinical clues to suspect autoimmune encephalitis are subacuteonset, fluctuating course, mood and behavior changes, cognitive dysfunction, seizures, dyskinesias and tremors [1]. Patients with limbic encephalitis (such as the patient described in the vignette above) present with symptoms attributed to dysfunction of mesial temporal lobe structures, most notably the hippocampus. Prominent symptoms include short-term memory loss, behavioral disturbances such as agitation and confusion, and psychiatric problems such as depression and psychosis. Recurrent seizures are a salient feature and, not uncommonly, progress to status epilepticus. Multiple antibodies have been linked to the syndrome (Table 1) [2]. The "classic" antibodies initially found in paraneoplastic forms are now generally viewed as nonpathogenic, in part because they are directed against intracellular antigens. Neuronal injury in paraneoplastic limbic encephalitis is believed to be mediated by cytotoxic T lymphocytes, with neuronal autoantibodies being produced after the injury.4 Recently defined antibodies, such as those targeting the N-methyl-d-aspartate (NMDA) receptor and the LGI1 protein, are now understood to be common causes of limbic encephalitis [9,10].

Table 1 :Neuronal antibodies associated with limbic encephalitis [2].

Antigen location	Antibody	Frequency of tumor occurrence	Tumor association	Responsiveness to treatment
Intracellular	ANNA1 (anti-Hu)	> 75%	Small cell lung cancer	Poor
	Anti-CV2 (CRMP)	> 75%	Small cell lung cancer, thymoma	Poor, but longer survival than with ANNA1
	Anti-Ma2	~ 90%	Testicular germ cell tumor	Better than with ANNA1; prognosis is worse with co-occurrence of anti-Ma1
	Anti-GAD65	< 33%	None	Seizure outcome inferior to that in anti-VGKC limbic encephalitis
Cell surface (common)[6,7]	Anti-NMDA receptor	38%	Ovarian teratoma	Very good, but slow recovery
	Anti-LGI1	0	None	Very good, quicker recovery than with NMDA receptor encephalitis
Cell surface (rare)[8,9]	Anti-AMPA receptor	70%	Thymoma, breast, lung	Good
	Anti-$GABA_B$ receptor	47%	Small cell lung cancer	Good

AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANNA1 = antineuronal nuclear antibody 1; CRMP = collapsin-responsive mediated protein; $GABA_B$ = gamma-aminobutyric acid; GAD = glutamic acid decarboxylase; LGI1 = leucine-rich glioma-inactivated protein 1; NMDA = *N*-methyl-o-aspartate; VGKC = voltage-gated potassium channel

Various antibodies along with clinical presentation and a high index of suspicion can guide towards a precise diagnosis. Some of the vital clinical clues are mention in Table -2 [1].

Table – 2: Clues for diagnosis of autoimmune encephalitis [1].

Clues for diagnosis of autoimmune encephalitis
• Subacute onset of memory impairment (short-term memory loss), encephalopthy or psychiatric symptoms
• At least 1 of the following: • Focal neurological deficits • Unexplained seizures • CSF pleocytosis (white blood cell count >5 cells per mm3) • MRI features suggestive of encephalitis
• Exclusion of alternative causes

Clinical Spectrum of Autoimmune Encephalitis:

Most forms of encephalitis associated with antibodies against neuronal surface antigens share a core syndrome of limbic encephalitis (epileptic seizures, short-term memory deficits, behavioural and psychiatric disturbances) with additional features that vary according to the immune response. Antibodies that occur without symptoms of limbic encephalitis include, mGluR1 (cerebellar symptoms), GlyR (spectrum of stiff-person syndrome, encephalomyelitis with rigidity) and dopamine-receptor D2 (basal ganglia encephalitis) [11,12]. In contrast, the clinical picture of anti-NMDA-receptor encephalitis described below defines a new syndrome and is almost pathognomonic. It should not be referred to as limbic encephalitis because the syndrome reflects diffuse encephalitis. About 13 % of patients develop partial forms of the syndrome characterised by predominant psychiatric disturbances, refractory seizures, status epilepticus, or movement disorders. In most of these cases a thorough neurological and neuropsychological examination reveals other features of the syndrome. Truly monosymptomatic manifestations are rare (1 %) [13].

The neurological presentation and the outcome of patients with limbic encephalitis and antibodies against neuronal cell-surface antigens differs from that of paraneoplastic limbic encephalitis in which antibodies are directed against intracytoplasmic targets. Indeed, patients with limbic encephalitis who have antibodies against neuronal cell-surface antigens usually present only with symptoms of limbic encephalitis. By contrast, patients with antibodies directed against intracytoplasmic targets also present with other neurological symptoms. For example, sensory neuronopathy or encephalomyelitis are frequently present in limbic encephalitis with anti-Hu antibodies; anti-Ma2 antibody-associated limbic encephalitis with testicular cancer usually presents with diencephalitis or upper brainstem symptoms;10 and limbic encephalitis with anti-CV2/CRMP5 antibodies is generally associated with neuropathy and small-cell lung cancer [14]. More than 95% of patients with antibodies against intracytoplasmic targets have cancer, and the outcome is poor with limited response to treatment. By contrast, association with cancer seems to be less frequent in patients with antibodies against neuronal cell-surface antigens [14,15].

Anti-NMDA-receptor Encephalitis:
Anti-NMDA receptor encephalitis typically affects women in their 20s and 30s, and about half of patients have an ovarian teratoma. It can also occur in younger patients and in men, in whom it is less likely to be associated with a neoplasm [16]. Typical initial symptoms include striking and often stereotyped neuropsychiatric disturbances manifesting as psychosis, confusion, seizures, and amnesia. After 1 to 2 weeks, new symptoms set in, including reduced consciousness, movement disorders (ranging from orolingualfacial dyskinesia to rigidity and choreoathetosis), autonomic dysfunction, and hypoventilation, often prompting admission to the intensive care unit [17]. Although the outcome is favorable in most cases, recovery, in contrast to VGKC complex antibody-mediated limbic encephalitis, is slow and may take longer than 1 year. Up to a quarter of patients have a relapse, underscoring the importance of maintenance immunotherapy. It is important to undertake an intensive search for possible ovarian and extraovarian teratomas in young women with this syndrome including CT of the pelvis, vaginal ultrasonography, and PET imaging, as removal of the teratoma may be curative [16].

VGKC Complex mediated encephalitis:
Diseases associated with VGKC complex antibodies include limbic encephalitis, epilepsy, neuromyotonia/peripheral nerve hyper excitability and Morvan's syndrome. Limbic encephalitis is the most common syndrome form. The antibodies directed against proteins of the VGKC complex include LGI1, CASPR2, and Contactin-2 [1].

LGI1 Antibodies Encephalitis:
The most frequent neuronal surface antibodies found in patients with limbic encephalitis are LGI1 antibodies [18]. This syndrome affects mostly elder men (m:f 3:1; median 60 years). Myoclonic-like movements have been described in 40 % of the patients and autonomic symptoms occur in around 10 %. Recent studies have shown that the myoclonic-like movements probably correspond to tonic seizures,42 which have also been reported as faciobrachial-dystonic seizures [19]. These types of seizures may precede or occur simultaneously with encephalitis and their prompt recognition and treatment may prevent progression to more severe symptoms. The presence of hyponatremia in 60 % of the patients is also suggestive of this type of autoimmune encephalitis. In addition to classical limbic encephalitis, patients may develop neuromyotonia in rare instances. Many patients with encephalitis associated with LGI1 antibodies have normal or near normal routine CSF studies [20].

Encephalitis with AMPA-receptor Antibodies:
The anti-AMPA-receptor encephalitis has been described mostly in middle-aged women (90 % women, range 38–87 years, median 60 years) with symptoms of classical limbic dysfunction or pure psychiatric manifestations. Patients often respond to immunotherapy, but they tend to relapse (60 %) [20].

Encephalitis with CASPR2 Antibodies:
Patients with CASPR2 antibodies usually develop Morvan's syndrome. This syndrome was first described in 1890 by Augustin Morvan as a syndrome associated with autonomic dysfunction and severe insomnia [21]. Patients with Morvan's syndrome present with a subacute onset of peripheral nerve hyperexcitability (PNH), dysautonomia, and encephalopathy with marked insomnia [22].

Encephalitis with GABA(b)-receptor Antibodies:
The clinical syndrome associated with GABA(b)-receptor antibodies is a limbic encephalitis (memory dysfunction, behavioural abnormalities and seizures) in which seizures and status epilepticus are especially prominent. The patients' median age is 60 years and men and women are affected equally. Most patients with SCLC and limbic encephalitis who are Hu antibody negative, have GABA(B)-receptor antibodies in serum and CSF [20].

Steroid Responsive Encephalopathy with Autoimmunity to Thyroid (SREAT):
This syndrome, previously known as Hashimoto encephalopathy, encompasses a heterogeneous group of clinical syndromes and courses, whose common denominator is the response to immunotherapy and the presence of thyroid antibodies (thyroid peroxidase and thyroglobulin). However, the prevalence of these antibodies is high in the general population (up to 20 %) [23] and the neurological syndrome is poorly defined. The vast majority of published cases have not been tested for all other relevant antibodies [24]. This syndrome should only be considered after exclusion of other autoimmune encephalitis. Most patients diagnosed with Hashimoto's encephalitis have in fact other disorders [24].

Treatment:
Owing in large part to the rarity of autoantibody mediated encephalitides, no randomized trials of therapy have been performed. Treatment at present is guided mostly by case series and expert consensus, which suggest first-line therapy with intravenous immunoglobulin, high-dose corticosteroids, plasmapheresis, or a combination. Different syndromes and antibody-related disorders respond differently to therapy. Syndromes associated with antibodies against intracellular antigens tend to be more resistant to immune therapy than cell surface antigen related syndromes [2].

Conclusion:
- The autoimmune encephalitides comprise a growing group of antibody-mediated disorders with favourable response to immunotherapy.
- Neuroimaging and CSF studies are necessary but their specificity and sensitivity are limited.
- Detection of neuronal antibodies is important for the diagnosis, treatment planning and prognostic evaluation.
- Immunotherapy and if applicable, tumour removal are crucial to expedite neurological improvement and to attain substantial clinical recovery.

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