What should you know about limbic encephalitis?

O que deve saber sobre encefalites auto-imunes?

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ABSTRACT

Autoimmune encephalitis is an inflammatory disorder characterized by a subacute impairment of short-term memory, psychiatric features and seizures. It is often associated with a variety of other neurological symptoms, and its differential diagnosis is wide, leading to challenges in its recognition. It used to be regarded as a rare disease, usually paraneoplastic and with poor prognosis. However, with the recent recognition of membrane-surface directed antibodies, it is now known that in a substantial proportion of cases there is no association with any malignancy and there is a good prognosis if treated. Hence, early recognition and prompt initiation of immunotherapies are of great importance.

Key words: limbic autoimmune encephalitis, encephalopathy, intracellular antigens, membrane surface antigens, VGKC-complex, LGI1, CASPR2, N-methylaspartate, paraneoplastic syndrome, immunotherapy.

RESUMO

A encefalite autoimune é uma doença inflamatória caracterizada por envolvimento subagudo da memória de curto prazo, presença de sintomas psicóticos e crises epilépticas. Dada a diversidade de sintomas na apresentação, o diagnóstico diferencial é um verdadeiro desafio. Anteriormente, era considerada uma doença rara, de etiologia paraneoplásica e com mau prognóstico. No entanto, com a recente descoberta dos anticorpos dirigidos à superfície da membrana, é atualmente reconhecido que uma grande parte dos casos não tem uma neoplasia subjacente e apresenta um ótimo prognóstico. Assim, o diagnóstico e tratamento imunoterápico precoces são de extrema importância.

Palavras-Chave: encefalite límbica autoimune, encefalopatia, antigénios intracelulares, antigénios da superfície de membrana, complexo VGKC, LGI1, CASPR, N-metilaspartato, síndrome paraneoplásica, imunoterapia.

Limbic encephalitis was firstly described by Brierley in 1960[1] and was characterized as an inflammatory disorder involving the hippocampi, amygdala, frontobasal and insular regions, with a spectrum of symptoms, most commonly characterized by a subacute progressive impairment of short-term memory, psychiatric features and seizures. While in some cases it appears to exclusively involve limbic regions, it has become clear that several clinical features implicate involvement of areas other than the limbic system. For this reason, the authors prefer the term autoimmune encephalitis (AIE).

Once regarded as a rare and paraneoplastic disorder with a poor prognosis, most forms of AIE are now recognised as being non-paraneoplastic and a substantial proportion of them may have a good response to immunotherapy, particularly if it is promptly initiated.

Due to a broad differential diagnosis, the recognition of AIE is frequently difficult and delayed. The aim of this article was to facilitate recognition of the clinical features and to simplify the diagnostic approach, with the ultimate objective of rapid immunotherapy administration.

CLINICAL VIGNETTE

A 52-year-old, right handed, man presented to the Accident and Emergency (A&E) department after two generalized tonic-clonic seizures. He was previously healthy and was the third of four healthy siblings with no problems during development or birth. He was successful at school and worked as a lawyer. There was no previous history of epilepsy, infections of the central nervous system (CNS), trauma, substance abuse or smoking. He was a moderate consumer of alcohol and was taking no medications. There was no relevant family history.

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His spouse noticed that over the last two months he had developed irritability and forgetfulness, which was associated with frequent involuntary jerks of the right side of the face and ipsilateral arm. There was no fever or headache. On examination, he was confused and showed a marked deficit in anterograde memory. After a normal Computerized Tomography (CT) scan, he was treated with acyclovir and phenytoin. Despite this, ongoing jerks were noted.

The differential diagnosis of this case is discussed in the Table 1[2-4] and the results of investigation in Table 2.

Given the subacute history of cognitive decline and the presence of focal seizures (likely faciobrachial dystonic seizures) along with the MRI changes, AIE was suspected[5,6]. Also taking into consideration the age of the patient, a normal CSF and serum hyponatremia, antibodies against the VGKC-complex[7] were requested, and the results were strongly positive. A body CT showed no underlying neoplasm. The patient was treated with high-dose steroids and made a good recovery, returning to work after four months.

The key points for the definite diagnosis were:

(1) subacute history of cognitive decline, irritability and seizures that were refractory to antiepileptic drugs;

(2) presence of faciobrachial dystonic seizures, which are highly characteristic of antibodies against the LGI1 (leucine-rich glioma inactivated 1) subunit of the VGKC-complex;

(3) MRI with medial temporal abnormalities in association with a normal CSF evaluation;

(4) serum hyponatremia without an alternative explanation.

In the next sections, cardinal clinical signs will be presented according to each underlying antibody, and a diagnostic approach will be proposed in order to facilitate the clinical recognition of AIE.

DESCRIPTION

Pathophysiology

For all AIE, a division can be made regarding the location of the causal antigens and, therefore, likely disease mechanisms. Generally, antibodies to intracellular antigens are associated with underlying malignancies and, in contrast, those against membrane antigens usually do not reflect the presence of a tumour. However, some membrane autoantibodies may be associated with tumours (Fig 1). Hence, in all patients presenting with suspected AIE, a comprehensive search for an underlying malignancy is considered.

Antibodies to intracellular antigens (inside the neuron) – Hu, Ma2, CV2, Antiphiphysin, glutamic acid decarboxylase (GAD)

Table 1. Differential diagnosis.

Diagnosis	Possible distinguishing features
Viral encephalitis: commonly Herpes simplex virus	More abrupt onset, fever, headache MRI: typically extensive hippocampal involvement, often with haemorrhagic lesions.
Creudtzfeldt-Jakob disease	Rapidly progressive dementia, myoclonus, visual hallucinations, psychiatric disturbance. MRI: pulvinar and cortical lesions, but may show mesial temporal lobe changes mimicking AIE[2]. EEG: periodic sharp wave complexes.
Metabolic/Toxic encephalopathy	Wernicke-Korsakoff Syndrome: history of alcohol intake and prominent confabulation. Specific MRI features
Tumour	Glioma or primary lymphoma of the CSN. Focal signs are frequent.
Autoimmune meningoencephalopathies	e.g. Sjogrens, SLE, Behçets. Commonly show systemic involvement.
Neurosyphilis	Slow progression, Argyll Robertson pupils. MRI: may show mesial temporal lobe changes[3,4].
Degenerative: Alzheimer disease	Longer course is typical, mostly without seizures.

MRI: Magnetic Resonance Imaging; AIE: autoimmune encephalitis; EEG: Electroencephalogram; CSN: central nervous system; SLE: systemic lupus erythematosus.

Table 2. Results of investigations.

Investigations	Results
Blood analysis	FBC, renal and thyroid function, hepatic enzymes + serological panel for autoimmune disorders: ESR, CRP, complement levels, ANA, dsDNA, ANCA, ACE, SS-A, SS-B, RF, cardiolipin, anti-thyroid antibodies, serum protein electrophoresis – unremarkable. Hyponatraemia 128 mmol/L, urine sodium 60 mmol/L
Cranial computed tomography (CT)	Unremarkable
Cranial magnetic resonance imaging (MRI)	T2 and FLAIR hyperintense lesions in the left medial temporal lobe, without haemorrhagic lesions
Electroencephalogram (EEG)	Mild diffuse slow activity
Cerebrospinal fluid (CSF)	Normal. No inflammatory changes (neither pleocytosis nor oligoclonal bands)

FBC: full blood count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANA: anti- nuclear antibodies; ANCA: anti-neutrophil cytoplasmi cantibody; dsDNA: double-stranded deoxyribonucleic acid; ACE: angiotensin-converting enzyme; SS-A and SS-B: Sjögren's syndrome A and B; RF: rheumatoid factor.

These are usually associated with cytotoxic T cell mechanisms. The neuronal damage seems to be irreversible and the prognosis is usually poor. One exception appears to exist in patients with GAD antibodies: these patients may have AIE, epilepsy or other neurological syndromes, tumours are uncommon, and recovery is possible although patients are often less responsive to immunotherapies[5].

> Antibodies to cell membrane surface antigens – VGKC-complex (LGI1, CASPR2, contactin-2) and the NMDA, AMPA, $GABA_B$ and Glycine receptors

This increasingly recognised category is much less frequently associated with malignancy, and the neurological disease is thought to be mediated by the antibodies themselves. These diseases tend to have a better response to immunotherapy. The first recognised syndrome in this category was the VGKC-complex antibody syndrome[8].

CLINICAL PICTURE

The cardinal signs of AIE are the impairment of short-term memory, usually developing over weeks or months, psychiatric symptoms (irritability, depression and hallucinations) and mesiotemporal seizures[5-9]. Apart from this typical "limbic syndrome", there are other associated neurological features, which often reflect the presence of different associated antibodies.

Antibodies to intracellular antigens

Hu (ANNA-1) – this type can involve any part of the nervous system, including peripheral nerves, dorsal root ganglia and spinal cord. A smoking history is often present as 75% of patients have small cell lung carcinoma (SCLC)[10]. The prognosis is usually poor despite immunotherapy.

Ma2 – the clinical clues are the presence of both hypothalamic (daytime sleepiness, narcolepsy, cataplexy, hyperphagia, hormonal deficits) and brainstem dysfunction (particularly with supranuclear gaze palsy)[11]. It occurs mostly in association with testicular germinal cell tumour in younger males, but in older individuals there may be an underlying non-small cell lung carcinoma or breast cancer[12]. Men with Ma2-antibody encephalitis in whom there is no detectable testicular tumour may have a microscopic tumour below the detection threshold of imaging techniques. For this reason, orchidectomy may be necessary in face of clinical deterioration, *de novo* testicular enlargement, previous cryptorchidism or ultrasound evidence of testicular microcalcification, in the absence of other tumours[8]. MRI may show contrast enhancement[13].

CV2 – the presence of chorea[14] is highly suggestive. It may also occur with involvement of other systems, commonly the visual system (uveitis, optic neuritis). There may be an underlying SCLC, malignant thymoma or other tumours.

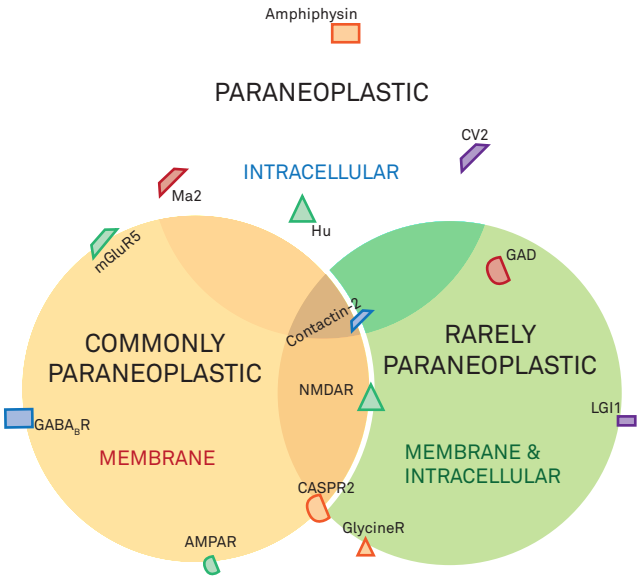


Fig 1. Antibody targets associated with non-paraneoplastic and paraneoplastic syndromes. Although most commonly associated with intracellular antibodies, paraneoplastic syndromes may also be caused by membrane antibodies. Hence, even in the presence of membrane antibodies, a search for an underlying malignancy should be considered.
LGI1: leucine-rich glioma inactivated 1; GAD: glutamic acid decarboxylase

GAD – although GAD is an intracellular enzyme, antibodies directed against this enzyme are usually associated with a non-paraneoplastic AIE[15-17]. It tends to occur in women without any identified tumour. Drug resistant epilepsy is common[15] and GAD-antibodies are also associated with the stiff-person syndrome and ataxia[16]. These antibodies are very common in other autoimmune disorders, typically DM1, often at lower levels[15-18].

Antibodies to cell membrane antigens

The most common syndromes

NMDAR – this appears to be one of the most frequent AIE[19]. It was initially described in young women with ovarian teratomas[20], of which 70% were benign. Nevertheless, it is now known that it also frequently affects men and children[21]. The presence of a tumour is more frequent in black women older than 18 years[19] and rare in paediatric populations. The characteristic clinical picture starts with a psychotic stage (many patients are initially seen by psychiatrists) and seizures, followed by reduction in consciousness, autonomic instability (which includes fluctuation of blood pressure and temperature, tachycardia, bradycardia, cardiac pauses and diaphoresis) and movement disorders, namely dyskinesias. The oral-lingual-facial dyskinesias[19] are the most characteristic, but other abnormal movements, such as opisthotonic postures and a catatonic state[22], may also occur. A curious feature is a dissociative response to stimuli: patients may resist eye opening, but show reduced or absent response to painful stimuli[23]. Invasive ventilation and admission to an intensive care unit are frequently necessary.

Disease relapses may occur in 15–25% of cases, especially in non-paraneoplastic cases without adequate immunotherapy during their previous encephalitic episode[21,24,25]. As far as investigations are concerned, CSF typically reveals an early lymphocytic pleocytosis followed by intrathecal synthesis of antibodies[21,26]. The MRI is frequently normal, however changes can be seen in medial temporal lobes and in white matter[19,21].

VGKC-complex (LGI1, CASPR2, Contactin-2) – it has been recently recognized that VGKC antibodies are directed to particular components of the VGKC-complex, most commonly LGI1, CASPR2 and Contactin-2[5,6,27]. In VGKC-complex associated AIE, most antibodies are directed against LGI1, but a minority have CASPR2 antibodies[5]. Patients show a male:female ratio of 2:1 and are typically older than 40 years[27]. This encephalitis may also present with rapid eye movement sleep behaviour disorder, hypothermia[28], startle syndrome, ataxia and intestinal pseudo-obstruction. A recently described and highly distinctive feature is the presence of faciobrachial dystonic seizures (FBDS), characterized by brief and frequent dystonic paroxysms typically involving the face and ipsilateral arm; these patients consistently have antibodies against LGI1[6]. In VGKC-complex antibody AIE, MRI typically reveals hyperintensity best appreciated in T2 and FLAIR sequences in the mesiotemporal lobes. However, around 40% of cases have a normal MRI[27], and the CSF tends to show the absence of pleocytosis or intrathecal synthesis. Another distinguishing feature is the presence of hyponatremia in around 50% of cases, usually with a SIADH pattern. Only a few VGKC-complex antibody positive patients have tumours, typically SCLC or thymoma[26]. In contrast to NMDAR-antibody positive patients, relapses are unusual in those with antibodies against VGKC-complexes. Patients with an encephalopathy and prominent insomnia, neuromyotonia and dysautonomia are often termed Morvan's syndrome. These patients show high levels of CASPR2-antibodies, often with lower levels of LGI1-antibodies[29]. Morvan's patients have a high risk of an underlying tumour which is usually a thymoma: the majority of patients with a tumour have CASPR2 antibodies[29].

Less frequent syndromes

AMPAR – this antibody has been identified in women with relapsing AIE. Of patients, 64% had an underlying tumour, and the SCLC are the most common[18,30]. CSF typically shows pleocytosis and intrathecal synthesis of antibodies.

$GABA_BR$ – clinically fairly typical apart from early and prominent epileptic seizures[5]. Despite being membrane antibodies, they have been reported to commonly associate with SCLC[31].

GlycineR – patients may present with progressive encephalomyelitis with rigidity and myoclonus (PERM)[24], a rare condition showing limb and axial rigidity, muscle spasms, brainstem signs and hyperekplexia[32-34]. Investigations may show CSF with inflammatory changes, and MRI has been normal in all of the published clinical reports[33,34].

mGluR5 – the two published cases had Hodgkin lymphoma (ophelia syndrome). The clinical picture is reasonably typical, the CSF shows pleocytosis and MRI, apart from limbic involvement, may show parietal and occipital cortex changes[35].

DIAGNOSIS

AIE has a wide differential diagnosis. One way of trying narrow-down the possibilities is to create a rational plan of investigations guided by an accurate clinical history, in an attempt to identify the key points already described.

As far as the diagnosis is concerned, the first step is to consider other treatable disorders, such as viral encephalitis and systemic autoimmune diseases. Secondly, the basic workup includes the following investigations:

(1) MRI – signal changes of medial temporal lobes, best seen in T2 and FLAIR sequences. Often no changes are seen on MRI.

(2) CSF – typically with inflammatory changes as lymphocytic pleocytosis, high protein and oligloconal bands. However, in many conditions, these changes are not present.

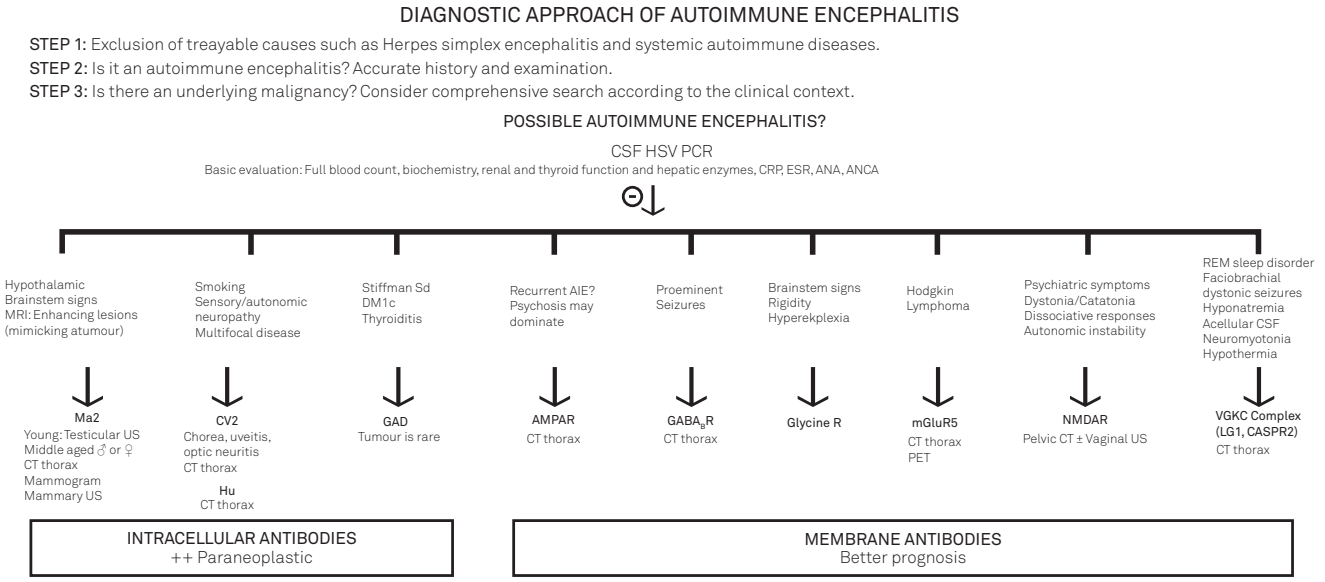
(3) EEG – often showing diffuse slowing and sometimes more focal or epileptiform changes.

(4) A comprehensive investigation to exclude an underlying neoplasm should be considered in all cases.

The combination of the clinical picture and the above laboratory investigations often suggests the diagnosis of AIE, but normal results do not exclude it (particularly normal CSF analysis and MRI). Brain fluorodeoxyglucose PET scan may be useful as it may show hypermetabolic changes in the temporal lobes when the MRI is still normal[21,36].

One should bear in mind that in 60–70% of the paraneoplastic cases, the neurological picture precedes the symptoms related to the cancer. One valuable approach is screening with body imaging such as a CT and/or a PET scan. Additionally, testicular ultrasound in men and mammography/mammary ultrasound in women should be performed when appropriate.

The final step is to detect the autoantibodies either in serum or CSF. In almost all patients, serum shows higher concentrations of antibodies than CSF. It is worth discussing the preferred sample with your diagnostic laboratory as the methods of detection may determine the sample of choice[37]. As there is a constant discovery of new antibodies and an increasing heterogeneity regarding the clinical picture, it may be tricky to decide which antibody to test. Both past medical history and clinical presentation are critical in guiding the optimal approach. There are features that help to distinguish subtypes, for example, hyponatremia *ad initium* (a consequence of the syndrome of inappropriate ADH secretion) and acellular CSF in VGKC-complex antibody mediated encephalitis and the combination of a normal MRI and severe encephalopathy with a movement disorder in NMDAR antibody patients.



CSF: cerebrospinal fluid; GAD: glutamic acid decarboxylase; MRI: magnetic resonance imaging; CT: computed tomography; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANA: anti- nuclear antibodies; ANCA: anti-neutrophil cytoplasmic antibody; US: ultrasound; AIE: autoimmune encephalitis.

Fig 2. Proposed diagnostic approach for autoimmune encephalitis.

Different diagnostic criteria have already been proposed[7,9,38,39] and the aim of the following diagram (Fig 2) was to simplify the diagnostic workup. Its rationale is to firstly exclude alternative treatable conditions (such as herpes simplex encephalitis) and, secondly, to determine which antibody is likeliest given the clinical phenotype.

TREATMENT

When autoimmune encephalitis is considered likely, treatment should be started promptly. Also, a trial of immunotherapy may serve as a valuable "diagnostic test". However, some conditions are typically refractory to initial immunotherapy administration (e.g. NMDAR-antibody encephalitis), and the trial should not be considered definitive proof as to the immune aetiology of the illness.

If there is an identified neoplasm, its removal may be important for the neurological improvement[7,20,21]. However, in traditional paraneoplastic cases associated with intracellular antibodies, there is rarely a favourable response to this approach even with immunotherapies. On the other hand, those cases of AIE associated with membrane antibodies may have a good response to immune interventions, plus tumour removal when indicated[20,26]. IVIg, plasma exchange (PE), corticosteroids, cyclophosphamide and rituximab have all been used with success.

A typical strategy for acute therapy is IV methylprednisolone (1 g IV daily for 3–5 days) with either IVIG (0,4–1 g/kg IV daily for 3–5 days) or PE, usually followed by oral prednisolone. If there is no or only a limited response, some authors advocate second-line therapies[20], such as rituximab and/or cyclophosphamide.

FINAL REMARKS

AIE is a relatively frequent inflammatory disorder with protean clinical manifestations in addition to a typical "limbic syndrome", reflecting the diverse likely causal antibodies. Antibodies against intracellular antigens tend to be associated with underlying malignancies. On the other hand, those directed to membrane antigens are usually not associated with tumours and have a better prognosis. However, such categorization is somewhat artificial, because membrane autoantibodies may also be associated with tumours.

As there are so many associated neurological symptoms, an accurate clinical history is mandatory for the correct investigation of the underlying autoantibody. Many of the clinical and investigation features strongly predict the underlying antibody and hence the association with tumours and potential response to immunotherapies. There are some precious clues, as the presence of hyponatremia and faciobrachial dystonic seizures with VGKC complex antibodies or psychiatric onset, movement disorders and dissociative responses with NMDAR antibodies. The phenotype may help clinicians to make a rational decision regarding antibody testing.

The identification of an encephalopathy with an autoimmune pathogenesis and, therefore, a potential response to immunotherapy is of great importance as successful treatments are possible. Notwithstanding, pharmacological management remains empirical, and prospective studies are needed to determine the optimal drug regimen.

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