The General Practice Guide to Autoimmune Diseases

Edited by Y. Shoenfeld and P. L. Meroni

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Autoimmune encephalitis

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1 Introduction

Until recently, autoimmune encephalitis was restricted to the syndrome described as paraneoplastic limbic encephalitis (LE), an infrequent paraneoplastic neurological syndrome (PNS) mainly associated with lung cancer [1]. Paraneoplastic LE used to run a severe clinical course that rarely improved despite removal of the tumour and intensive treatment with immunotherapy. However, in the last five years, the characterization of different antibodies against neuronal surface antigens has led to the identification of different types of LE and other encephalitic syndromes. These are important to recognize because they usually improve with immunotherapy and some of them are associated with tumours that can be diagnosed at an early stage when the chances of cure are highest. Taken together, these encephalitides are not as unusual as previously believed. In a retrospective analysis of encephalitis of unknown origin admitted to an intensive care unit, 1 % were finally identified as autoimmune.

2 Diagnostic measurements for experts

In a patient with suspected autoimmune encephalitis, the first step is to identify if the symptoms and imaging studies are compatible with LE [2]. LE presents with a diversity of symptoms including confusion, depression, agitation, anxiety, memory disturbance, and dementia. The typical picture is the subacute onset of confusion with markedly poor short-term memory. Seizures are not uncommon and may be the presenting symptom. Brain MRI shows bilateral high intensity lesions in the amygdala and hippocampus in FLAIR sequences that rarely enhance after gadolinium administration (Fig. 1). In any patient with the diagnosis of LE, detection of anti-neuronal antibodies is critical to support the possibility of a paraneoplastic origin and guide the work-up for the detection of the underlying tumour [3]. Onconeural antibodies Hu (ANNA-1), CV2 (CRMP5) and amphiphysin are associated with lung cancer, almost always small cell lung cancer (SCLC). Anti-Ma2 antibodies indicate the presence of an underlying testicular

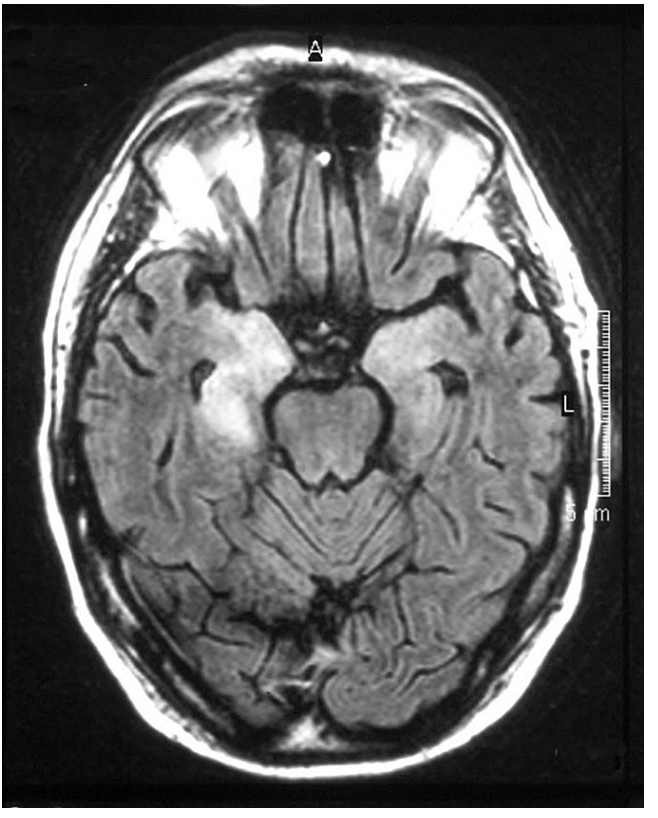

Figure 1. Brain MRI of a patient with LE, Hu antibodies and SCLC: Diffuse hyperintensities in FLAIR sequences along bilateral mesial temporal lobes.

Table 1. Onconeuronal antibodies and paraneoplastic LE.

Antibody	Tumour	Antibody positive patients without cancer*	Frequency in cancer without LE*
Hu (ANNA1)	SCLC	2 %	16 %
CV2 (CRMP5)	SCLC, thymoma	4 %	9 %
Amphiphysin	SCLC	5 %	1 %
Ma2	Testicular	4 %	0 %

* For review see reference [2].

seminoma (Table 1). Antibodies against neuronal surface antigens are reported in patients with LE but they do not indicate if the LE is paraneoplastic. At least 50 % of LE patients with antibodies against AMPA or GABA receptors have SCLC. Anti-AMPAR are also seen in patients with LE and breast cancer. Lastly, in patients with antibodies against proteins of the potassium channel-complex (LGI1, and less frequently CASPR2) or with anti-GAD antibodies, the LE is almost never paraneoplastic (Table 2) [4]. It is important to emphasize that the presence of circulating anti-neuronal antibodies is not necessary for the diagnosis of LE but a work-up to rule out an underlying cancer is mandatory in every patient with LE even in the absence of anti-neuronal antibodies [2].

A severe, but treatment-responsive encephalitis has been associated with antibodies to NR1, a crucial subunit of the NMDA receptors [5]. Most patients are children or young women who do not develop the classical picture of LE. They are initially seen by or admitted to psychiatric wards for acute anxiety, behavioural change, or psychosis, followed in a few days by seizures, decline of consciousness, aphasia, and abnormal movements. Patients may develop hypoventilation and autonomic imbalance that requires admission to intensive care units. The encephalitis is paraneoplastic in some patients who have an ovarian teratoma. The frequency of ovarian teratomas is higher (56 %) in women older than 18 years than girls under the age of 14 years (9 %).

Table 2. Antibodies against neuronal surface antigens in LE.

Antibody	Tumours (%)	CSF pleocytosis (%) /IT synthesis	Comments
LGI1*	none	41/no	Male predominance; Associated rapid eye movement (REM) sleep behaviour disorder; frequent hypernatremia (> 70 %)
NMDA receptor	Ovarian teratoma (9–56)	91/yes	Female predominance; MRI normal in 45 %, frequency of tumour higher in patients >18 years old. Relapses in 20 %.
AMPA receptor	SCLC, breast, thymoma (70)	90/yes	Female predominance; frequent relapses (60 %)
$GABA_B$ receptor	SCLC (47)	80/yes	Seizures in 86 %. Concurrent GAD antibodies in 3 patients

* Fewer than 5 % present CASPR2 antibodies instead of LGI1 antibodies.

3 Requirements for family practitioners

Autoimmune encephalitides are unusual but many of them are potentially treatable. Therefore, a high degree of awareness is important in order to detect the patients at an early stage and to start treatment as soon as possible. The possibility of an anti-NMDA receptor encephalitis must be raised in children and young women who rapidly develop psychiatric symptoms that cannot be classified as typical psychosis, particularly if the patient develops associated seizures, dyskynesias, or language dysfunction characterized by dramatic drop in verbal output and dysarthria. A normal brain MRI does not rule out the diagnosis as it may be normal in up to 50 % of patients. However, CSF examination is almost always abnormal showing variable degrees of pleocytosis [5].

The possibility of an LE must be suspected in young men (who are at risk of LE associated with Ma2 antibodies and testicular cancer) and older patients of both sexes who rapidly develop an amnestic syndrome characterized by short-term memory loss and variable degrees of confusion, behaviour problems and seizures [2]. Seizures may be the predominant symptom in LE associated with GAD or GABAR antibodies. Idiopathic LE associated with antibodies against proteins of the potassium channel-complex (LGI1, and less frequently CASPR2) is more prevalent in men and usually presents as a classical picture of LE. Rapid eye movement sleep behaviour disorder develops at the onset of LE and is rarely reported unless the physician specifically addresses the issue. Hyponatraemia is a frequent finding whereas CSF analysis shows mild pleocytosis in only 41 % of the patients. Some patients may develop prominent myoclonus and the syndrome can sometimes be misdiagnosed as Creutzfeldt-Jakob disease.

4 Follow up

Clinical observations

Autoimmune encephalitides run a subacute clinical course and patients must be admitted in hospital for vital support, to perform a brain MRI, whole body CT or PET scan to look for an underlying tumour, lumbar puncture and analysis of anti-neuronal antibodies in serum and CSF, and to start immunotherapy.

Blood tests

In patients with LE and positive onconeural antibodies, there is no need to repeat the antibody studies because the antibody levels do not correlate with the clinical evolution. In patients with encephalitis associated with antibodies against surface antigens the level of the antibodies tends to decrease in association with the clinical recovery. However, low levels may persist for years. At present, there are no

guidelines for the clinical value of repeated evaluation of antibody levels in these encephalitides.

Expectations

Prognosis will depend of the type of encephalitis. Patients with LE, positive onconeural antibodies and cancer rarely improve but the LE stabilizes, usually with severe deficits, after several weeks despite appropriate immunotherapy and treatment of the tumor. Patients with encephalitis associated with antibodies against surface antigens, that are probably responsible for the syndrome, usually improve with immunotherapy. Clinical recovery is particularly significant in patients with idiopathic LE associated with anti-LGI1 antibodies and with anti-NMDA receptor encephalitis provided early treatment is started and the underlying ovarian teratoma, if present, removed [4, 5]. In patients with LE associated with anti-AMPAR antibodies or with anti-NMDA receptor encephalitis, relapses are not uncommon particularly in patients without cancer.

5 Management

Early detection and treatment of the underlying tumour is the approach that offers the greatest chance for neurological improvement or symptom stabilization. Therefore, a work-up for cancer must be done in every patient with suspected autoimmune encephalitis. In patients with LE and onconeural antibodies, where the chances of an underlying cancer are highest, imaging studies must include a whole body PET scan if other studies are negative. In patients with Ma2 antibodies elective orchyectomy and serial examination of the testicle to rule out in situ carcinomas is indicated in patients at high risk of testicular cancer such as those with calcifications or undescended testicle(s). In women with anti-NMDA receptor encephalitis, the ovarian teratomas are frequently small and asymptomatic. Although oophorectomy is not recommended if the tumour screening is negative, any small cystic and persistent lesion of the ovary must be viewed with a high index of suspicion and its removal is recommended.

There are no firm guidelines as to which kind of immune therapy should be used in these patients. However immunotherapy should be started early while the screening of the tumour is conducted and without waiting for the results of the antibody determinations. Many patients are initially treated with one or more of the following, intravenous immunoglobulin, corticosteroids or a combination of them. Patients with onconeural antibodies rarely improve with these therapies but some stabilize. Whether these patients require more aggressive immunotherapy is questionable and should depend on the functional status of the patient at the time. Up to 80 % of patients with encephalitis associated with antibodies against neuronal surface antigens respond to first line treatment. For non-responders, second-line

immunotherapy, with rituximab, cyclophosphamide or both, is recommended by experts. There is no data on the value of long-term immunotherapy to prevent relapses in anti-NMDA receptor encephalitis.

6 Diagnostic tests

Onconeural antibodies (Ma2, Hu (ANNA-1), CV2 (CRMP5) and amphiphysin) are detected by immunoblot of purified recombinant antigens. Several commercial assays are available. These antibodies may be seen in patients with cancer without PNS. Therefore, a positive result must be put in the context of the clinical picture. Conversely a negative result does not rule out the possibility of a paraneoplastic LE.

Anti-GAD antibodies are detected by RIA. Only high levels support that the neurological syndrome, in this case LE, is related to the antibody. Low levels of GAD antibodies are present in patients with type I diabetes mellitus and autoimmune polyendocrine syndromes without associated neurological syndromes.

Antibodies against neuronal surface antigens are detected by immunofluorescence on HEK293 cells transfected with the appropriate antigen. There is currently a commercial kit that allows the simultaneous measurement of antibodies against NMDAR, GABAR, AMPAR, LGI1, and CASPR2. In patients with anti-NMDA receptor encephalitis, antibodies may be present in the CSF when the serum is negative. Conversely, in patients with non-paraneoplastic LE LGI1 antibody levels are usually higher in the serum and they may be negative in the CSF.

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