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ESSENTIALS Autoimmune limbic encephalitis—typical presentation is with acute or subacute onset of short-term memory loss, seizures, and dis- orientation. MRI characteristically shows striking abnormalities in the hippocampus. Antibodies against cell-surface proteins that are components of voltage-gated potassium channel complexes are found in a high proportion and are probably pathogenic. Aside from supportive care, treatment is with immunosuppression, often com- prising corticosteroids with intravenous immunoglobulin and/or plasma exchange. Morvan’s syndrome—a very rare condition presenting with varying degrees of neuromyotonia, memory loss, confusion, sleep disturb- ance, and autonomic features, also with antibodies to voltage-gated potassium channel-complex proteins, in about 90% of patients. Autoimmune encephalopathy with antibodies to N-methyl-D- aspartate receptor (NMDAR)—a neuropsychiatric illness, often affecting young women who may have an associated ovarian tera- toma. Prompt treatment with immunosuppression can lead to good outcomes but there is a 5% mortality rate and delayed diagnosis is common in patients with less typical presentations. Autoimmune limbic encephalitis with VGKC-complex antibodies Epidemiology Since its first recognition in 2001, hundreds of patients have been identified with autoimmune limbic encephalitis (LE) associated with antibodies that immunoprecipitate voltage-gated potassium channel (VGKC)-complex proteins. Preliminary epidemiology sug- gests that it is more common in men (2:1) and that the median age at onset is

65 years. The phenotype has been recognized mainly in patients over the age of 18 years at onset. Clinical features The classic presentation is with subacute onset of short-term memory loss, seizures, disorientation, with psychological disturb- ance or hallucinations. Additional features that may occur are sleep disturbance, autonomic dysfunction, and neuromyotonia, but these would be more typical of Morvan's syndrome (see next). The most striking feature on examination is the profound disorientation and memory loss, leading to poor performance on bedside cognitive tests such as the Mini-Mental State Examination. Neuromyotonia (see Chapter 24.19.3) may be evident, but often the examination is otherwise unremarkable. Some patients develop only one aspect of the syndrome (e.g. isolated memory loss or isolated temporal or frontal seizures), but are otherwise similar to those with the full syndrome. Some patients report an influenza-like illness one to two weeks earlier. Recently, an increasing number of patients with immunotherapy-responsive brief frequent dystonic seizures (termed faciobrachial dystonic seizures), that often precede the limbic disturbance by days to months, have been recognized. Investigations Hyponatraemia is present in 80% of patients, usually accompanied by a low plasma and urine osmolarity. Other routine blood tests are normal. The cerebrospinal fluid is often normal but may show a mild pleocytosis. VGKC-complex antibody titres are character- istically very high in these patients (more than 400 pmol/litre and often more than 1000 pmol/litre (normal range less than 100 pmol/ litre)), and higher than the titres commonly found in patients with neuromyotonia (usually less than 400 pmol/litre) (Fig. 24.24.1b). MRI shows striking abnormalities in 70% of patients and it is often these that lead the clinician to suspect the diagnosis and request the confirmatory serological test (Fig. 24.24.1a). The most classic change is high signal restricted to the hippocampus (either uni- laterally or bilaterally), best seen on T2-weighted or FLAIR (fluid- attenuated inversion recovery) sequences, with associated swelling of the affected area. A few patients have more widespread areas of increased signal in the medial temporal lobes and amygdala. LE associated with VGKC antibodies can occasionally (<10%) be a paraneoplastic disorder and so all patients should undergo appro- priate imaging to detect any underlying malignancy (e.g. thymoma or small-cell lung cancer). VGKC-complexes are extracted from brain tissue and include the Kv1 shaker-type VGKCs in a multiprotein complex that includes leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2). The antibodies can be identified by 24.24 Autoimmune encephalitis
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section 24 Neurological disorders 6394 immunoprecipitation of VGKC-complexes, or by binding to the individual proteins by cell-based assays. In LE and faciobrachial dystonic seizures, they are most often directed to LGI1; CASPR2 antibodies are found in neuromyotonia and Morvan's syndrome. However, VGKC-complex antibodies without LGI1 or CASPR2 re- activity may not be helpful in achieving a diagnosis, and their sig- nificance needs further research. Treatment Initially patients often require fluid restriction to manage the hyponatraemia, antiepileptic drugs for their seizures, antipsychotic drugs to control paranoid ideation, and corticosteroids with plasma exchange or intravenous immunoglobulin for acute immuno- suppression. The choice of antiepileptics is complicated by the hyponatraemia, which can be profound. Often the seizures do not respond well to antiepileptics alone and do not start to reduce in fre- quency until immunosuppression has been established. There have been no randomized controlled trials to determine the most effective immunosuppressive regimens in these patients and currently the protocols are similar to those used to treat pa- tients with autoimmune disorders of the neuromuscular junction (see Chapter 24.18). Corticosteroids appear to be a particularly im- portant

component because longer-term follow-up suggests that those treated with intravenous immunoglobulin alone respond less well than those treated with intravenous immunoglobulin and ster- oids. Although early treatment is recommended, as it appears to be associated with improved prognosis, even late introduction of ster- oids and other immunosuppression can be beneficial. Differential diagnosis Acutely, the differential diagnosis lies mainly with infectious causes of LE, the most common being herpes simplex encephalitis (HSE), and most patients will have a cerebrospinal fluid polymerase chain reaction for HSE performed on admission, particularly if they have a high fever and severe headache. Korsakoff's pyschosis can present similarly and so an accurate alcohol history and suggestive blood tests, such as liver function tests and mean cell volume, should be performed. The other main differential lies with paraneoplastic LE, so all pa- tients need imaging to detect associated tumours and, in the right context, it may be appropriate to look for the particular antibodies seen with these disorders (see Chapter 24.23). Other forms of po- tentially immunotherapy-responsive LE are now being recognized, some of which are associated with antibodies to other neuronal surface antigens (e.g. N-methyl-D-aspartate receptor, see next and Chapter 24.23) and can be nonparaneoplastic. Table 24.24.1 sum- marizes the most useful antibodies and associated syndromes. Morvan's syndrome, although very rare, can present similarly to LE but requires sleep disturbance (mainly insomnia) and is also distin- guished by additional peripheral and autonomic features (see next), that can go unrecognized. In addition (as with the autoimmune disorders of the neuromuscular junction), there are patients with a similar clinical phenotype who respond to immunomodulatory therapies, but in whom no antibody is detectable by current methods, although new diagnostic tests will undoubtedly emerge. Pathogenesis VGKC-complex LE is probably an immune-mediated disorder given the time course of patients' clinical, serological, and radiological re- sponses to immunosuppression. VGKC is a transmembrane protein that is densely expressed in the hippocampus and elsewhere in the brain, where it is complexed with LGI1, CASPR2, and other proteins. Genetic mutations in VGKC can cause seizures both in mice and in humans and, as the channel is involved in stabilizing the membrane potential, its dysfunction will result in neuronal hyperexcitability. There is evidence that LGI1 antibodies are pathogenic; they disrupt the role of LGI1 in modulating VGKC function in hippocampal cul- tures. Less is known about CASPR2 antibodies. NMT LE −100 0 100 200 300 400 1000 2000 3000

> 4000 VGKC antibody (a) (b) Fig. 24.24.1 (a) T2-weighted coronal MRI of the brain with the red circles highlighting the abnormal high signal bilaterally in the hippocampi of a patient with limbic encephalitis (LE) associated with voltage-gated potassium channel (VGKC) complex antibodies. (b) VGKC-complex antibody levels in patients with LE compared with those in patients with neuromyotonia. The horizontal line denotes the cut-off for healthy individuals. LE patients with these antibodies usually have values more than 400 pmol/litre, these are common and up to 1000 pM/litre in the rare Morvan's syndrome (not shown), whereas they tend to be lower titre and absent in >60% of patients with neuromyotonia.

 Morvan's syndrome This is a very rare condition in which patients present with varying degrees of neuromyotonia, central nervous

system symptoms such as memory loss, confusion and sleep disturbance, and add- itional autonomic features such as constipation and cardiac ar- rhythmias. Few cases have been described, but the majority have VGKC-complex antibodies, usually at levels intermediate between neuromyotonia and VGKC LE; these are directed more often to CASPR2 than to LGI1. Thymoma is more common than in VGKC LE or neuromyotonia (c.50%), and can be aggressive, but most pa- tients do well with thymectomy, if appropriate, and immunosup- pression, and some appear to have a self-limiting disease. Autoimmune encephalopathy
with NMDAR antibodies Epidemiology Patients with a neuropsychiatric disorder associated with antibodies that immunoprecipitate the NMDA receptor were first identified in 2007. Preliminary epidemiology suggests that it is more common in women (4:1) and that the median age at onset is 21 years. 25% of cases occur in children and the illness is uncommon in those over 45 years (<5%). It appears to be more common in Asian and African patients. Up to 40% of young women with the antibodies will have an ovarian teratoma which can be bilateral. Clinical features Patients can present with a wide variety of neuropsychiatric symp- toms, but prominent features usually include headache, movement disorders, behavioural disturbance, psychosis, seizures, catatonia, mutism, autonomic disturbance, and altered consciousness. Central hypoventilation, profound autonomic neuropathy, catatonia, and coma often necessitate management on the intensive care unit. The most striking feature on examination is the movement disorder which classically involves the perioral musculature but can affect any muscles, but it is not usually present at first presentation. In add- ition, there is often dystonic posturing and increased tone. Speech impairment is common and patients may become mute. Many cases presenting as a relapse following herpes simplex virus encephalitis have been described, particularly in children. Investigations Routine blood tests are usually normal. The cerebrospinal fluid often reveals a lymphocytosis, which can be marked (>400 cells/ul), espe- cially in the early phase of the illness. NMDAR antibodies can be detected in serum and in cerebrospinal fluid, but titres are higher in serum. MRI may be normal in up to 50% of patients but there can be T2 hyperintensity in various brain regions, most commonly the brainstem or limbic areas. Some patients have white matter signal change which is unexplained. Electroencephalography frequently demonstrates profound slowing and there may be electrographic evidence of seizure activity. Treatment Initially patients require antiepileptic drugs for their seizures, anti- psychotic drugs for behaviour, benzodiazepines for catatonia, and corticosteroids with plasma exchange for acute immunosuppres- sion. Any associated teratoma should be promptly surgically re- moved. Second line immunosuppression is generally with rituximab or cyclophosphamide. The role of ‘steroid-sparing agents’, such as azathioprine or mycophenolate, remains uncertain. Table 24.24.1 The most useful antibodies and their associated syndromes Antigen Demographics Most common clinical phenotypes/tumours N-methyl-D-Aspartate receptor (NMDAR) 80% females Age range: <12 months to 85 years (median 21 years) Whole brain encephalopathy (initial psychiatric symptoms, seizures, memory, and language deficits, followed by movement disorders, autonomic instability, and decreased level of consciousness); ovarian tumours in young adult women VGKC-complex associated protein: leucine-rich glioma-inactivated 1 (LGI1) 65% males Age range: 30 to 80 years old (median 60 years) Limbic encephalitis. Faciobrachial dystonic seizures; thymus and lung rare. VGKC-complex associated protein: contactin-associated protein-like 2 (CASPR2) 85% males Age range: 46 to 77 years (median 60 years) Limbic encephalitis Neuromyotonia. Morvan’s syndrome including insomnia, autonomic features, and neuromyotonia. Idiopathic ataxia; thymoma in up to 50% α-amino-3-hydroxy-5-methyl-4- isoxazolepropionic acid receptor (AMPAR) 75% females Age range: 23 to 87 years (median 60 years) Limbic encephalitis (prominent psychiatric manifestations); lung,

thymoma, and breast tumours γ-aminobutyric acid B receptor (GABAbR) 50% females Age range: 24 to 75 years (median 62 years) Limbic encephalitis (prominent seizures); small-cell lung cancer most common γ-aminobutyric acid A receptor (GABAaR) Not yet clear Age range wide Status epilepticus or limbic features without clear-cut syndrome; no clear tumour association Glycine receptor (GlyR)

> 50% males Age range: wide Progressive encephalomyelitis with rigidity and myoclonus, stiff person syndrome, or related features; thymoma, lymphomas, breast <20%

section 24 Neurological disorders 6396 Differential diagnosis Acutely the differential diagnosis includes limbic encephalitis (see earlier), systemic lupus erythematosus, a primary psychiatric dis- order, or metabolic causes including toxins. New central nervous system autoantibodies and associated clinical syndromes are continually being described and are proving clinically useful in identifying patients who may respond to immunomodu latory treatments (see Table 24.24.1). Guidelines for recognition of autoimmune forms of encephalitis have been published. FURTHER READING Buckley C, et al. (2001). Potassium channel antibodies in two patients with reversible limbic encephalitis. Ann Neurol, 50, 73–8. Graus F, et al. (2016). A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol, 15, 391–404. Irani SR, et al. (2010). Antibodies to Kv1 potassium channel- complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain, 133, 2734–48. Irani SR, et al. (2011). Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol, 69, 892–900. Irani SR, et al. (2012). Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol, 72, 241–55. Irani SR, et al. (2014). Cell-surface central nervous system autoanti- bodies: clinical relevance and emerging paradigms. Ann Neurol, 76, 168–84. Titulaer MJ, et al. (2013). Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor en- cephalitis: an observational cohort study. Lancet Neurol, 12, 157–65. Vincent A, et al. (2004). Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form
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