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Supplementary webappendix

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APPENDIX

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Syndromes at the frontier of autoimmune encephalitis (AE)

Morvan syndrome

Morvan syndrome is a rare CNS disorder (less than 100 patients described) affecting mostly men, and characterized by a constellation of peripheral and CNS symptoms. The clinical course of Morvan syndrome is usually chronic and the median duration of symptoms by the time of diagnosis is approximately one year. In general, the episodes of confusion, agitation, and hallucinations that may suggest a possible AE are preceded by symptoms of neuromyotonia, dysautonomia, and sleep dysfunction which should lead to the diagnosis of this disorder.[1]

The full-blown syndrome includes peripheral nerve hyperexcitability with neuromyotonia and neuropathic pain, dysautonomia (mostly hyperhidrosis), encephalopathy with confusion, agitation, and hallucinations, and a characteristic sleep disorder called agrypnia excitata.[2] CSF, brain MRI, and neuropathological studies are usually normal or with nonspecific findings. Thymoma is found in approximately 20-50% of the patients and ~75% of them have CASPR2 antibodies.[3] These antibodies are not specific for Morvan syndrome because they also occur in patients with isolated neuromyotonia or LE.[4] However, in the appropriate clinical setting they are an important clue for the diagnosis.

Primary angiitis of the CNS (PACNS)

This is a rare disorder that results from inflammation of CNS vessels without evidence of involvement of systemic vessels. Obligatory diagnostic criteria include the demonstration of angiographic or histological evidence of angiitis within the CNS (Table 5S).[5] Comprehensive reviews of the disorder in adults and children have been published.[6,7] In adults, symptoms include headache, and diffuse or focal neurological deficits, along with CSF lymphocytic pleocytosis and MRI showing multiple bilateral ischemic foci. Stroke and transient ischemic attacks involving multiple vessels occur in 30-50% of the patients.[6] In children the clinical picture of small vessel PACNS more frequently resembles that of AE.[7] The differential diagnosis with AE is complicated at early stages when children present with headache, cognitive dysfunction, learning difficulties, or behavioral changes before developing seizures or stroke symptoms. The combination of headache and multifocal inflammatory lesions in the MRI, are very common in childhood PACNS (cPACNS) and less frequent in AE.[7] For example, one the most frequent AE, anti-NMDAR encephalitis, often occurs with normal MRI or findings different from those in PACNS. Serum inflammatory markers such as C-reactive protein, C3 complement, erythrocyte sedimentation rate, and von Willebrand-factor antigen are commonly elevated in small vessel disease; this is contrast to most AE in which these serological markers are not elevated. Non-progressive cPACNS is commonly treated with a three month course of corticosteroids in addition to antithrombotic therapy, while progressive large vessel cPACNS and small vessel cPACNS mandate a combination of steroids and cyclophosphamide, followed by mycophenolate.[8,9]

Rasmussen encephalitis and other epileptic syndromes of possible autoimmune origin

Rasmussen encephalitis (RE) is a chronic inflammatory disease characterized by intractable focal onset seizures, and deterioration of neurological functions associated with progressive atrophy of the affected hemisphere.[10] Although initially reported in children, it can also affect adolescents and adults. The pathogenesis of the disease is unclear, but the current prevailing theory is a cytotoxic T-cell autoimmune mechanism.[11] The most effective treatment with regard to seizures is hemispherectomy. Important diagnostic clues that differentiate this disorder from most AE are the symptom chronicity, unilateral hemispheric functional and structural involvement, and refractoriness to immunotherapy.[10]

Another devastating epileptic syndrome often considered in the differential diagnosis of AE is febrile infection-related epilepsy syndrome (FIRES).[12] This syndrome is characterized by the onset of seizures in previously healthy children in the setting of a febrile episode. Seizures rapidly evolve to status epilepticus and pharmacoresistant epilepsy. When seizures improve, patients present an important cognitive deterioration. Paraclinical studies have failed to demonstrate a viral or autoimmune origin. CSF analysis does not show pleocytosis nor oligoclonal bands. Brain MRI is usually normal at onset of the syndrome but the subsequent studies show bilateral temporal atrophy a few months after the onset of the disease.[12]

Other epileptic syndromes include idiopathic hemiconvulsion hemiplegia and epilepsy syndrome (IHHE) and a syndrome similar to FIRES, predominantly reported in Asia: acute encephalitis with refractory, repetitive partial seizures (AERRPS).[12,13] Several confounding factors with AE occur at initial stages of these disorders where the MRI may show FLAIR/T2 medial temporal lobe abnormalities due to seizures, and the CSF mild pleocytosis. On the other hand several antibody-associated AE can present with severe seizures and status epilepticus. To date none of the treatment-refractory epileptic syndromes mentioned above have been linked to relevant autoantibodies.

Table 1S: Differential diagnosis in patients with possible autoimmune encephalitis

Disorder
CNS infections[14]
Septic encephalopathy[15]
Metabolic encephalopathy[16]
Drug toxicity*
Cerebrovascular disease[17]
Neoplastic disorders[18]
Creutzfeldt-Jakob disease[19]
Epileptic disorders[12]
Rheumatologic disorders (e.g., lupus, sarcoidosis, other)[20]
Kleine-Levin[21]
Reye syndrome (children)[22]
Mitochondrial diseases[23]
Inborn errors of metabolism (children)[24]

*Including use of illicit drugs, direct neurotoxic effect of prescribed drugs or through induction of seizures, posterior reversible encephalopathy, idiosyncratic reaction (e.g. neuroleptic malignant syndrome), drug interaction (e.g. serotoninergic syndrome) or drug withdrawal.

Table 2S: Limbic encephalitis and systemic disorders of presumably autoimmune pathophysiology*

	Bilateral involvement of medial temporal lobes in MRI FLAIR sequences	CSF pleocytosis	Distinctive features	Diagnostic tests
Systemic lupus erythematosus[25]	Yes	Yes	Systemic and serological abnormalities	Lupus criteria
Sjögren's syndrome[26]	Unilateral	Unknown	Systemic symptoms (sicca syndrome)	SS-A, SS-B antibodies; salivary gland biopsy
Kikuchi-Fujimoto disease[27]	Yes	Yes	Cervical lymphadenopathy; MRI abnormalities beyond the temporal lobes	Lymph node biopsy showing histiocytic necrotizing lymphadenitis
Behçet' disease [28]	Yes	Yes	Systemic symptoms (recurrent attacks of oral, genital ulcers, uveitis, polychondritis)	Behçet criteria
X-linked lymphoproliferative disease[29]	Yes	Yes	MRI abnormalities beyond the temporal lobes	Genetic confirmation

* These diagnoses are associated rarely with LE, we acknowledge that causation is unclear and the underlying diagnosis may just be a comorbidity or epidemiological risk factor

Table 3S: Differential diagnosis of autoimmune limbic encephalitis

Disorder	Bilateral involvement of medial temporal lobes in MRI FLAIR sequences	CSF pleocytosis	Distinctive features	Diagnostic tests
Herpes simplex virus encephalitis (HSE)[30]	Yes	Yes	Fever (>38ºC). MRI hemorrhagic lesions, beyond medial temporal lobes	HSV DNA in CSF. This test can be negative if done too early (≤24 hours) or too late (after 10-14 days). Consider determination of intrathecal HSV antibody synthesis for atypical or protracted cases.
HHV-6 encephalitis[31]	Yes	Occasional	Most common in immunosuppressed patients	HHV-6 DNA in CSF
Glioma[32]	Almost always unilateral	No	Contrast enhancement common	Biopsy
Status epilepticus[33]	Bilateral	Unknown	More common in children and young adults. MRI abnormalities beyond temporal lobes	None. Reversible evolution of MRI findings sometimes leading to atrophy
Neurosyphilis[34]	Variable	Yes	Symptoms and MRI findings beyond medial temporal lobe involvement	CSF treponemal antibody tests
Whipple[35]	Yes	Yes	Systemic symptoms (polyarthralgia and intermittent diarrhea), oculomasticatory myorhythmia). Symptoms and MRI findings beyond medial temporal lobe involvement.	*T whipplei* DNA in CSF
HIV[36]	Yes	Yes	Low CD4 cell count	Positive HIV serology

Table 4S: Clinical clues and comorbidities that associate with antibodies related to subtypes of limbic encephalitis[37]

ANTIBODIES THAT OFTEN OR PREDOMINANTLY ASSOCIATE WITH LIMBIC ENCEPHALITIS	
Hu (ANNA1)	Usually affect older subjects with history of smoking or SCLC; rarely associated with pure LE; frequently accompanied by encephalomyelitis or sensory neuronopathy
Ma2	Usually affect men younger than 45 years, with germ-cell tumor of the testis. The tumor is frequently microscopic. In older men and women a variety of other tumors have been reported. The syndrome develops as LE, upper brainstem or diencephalic encephalitis. Symptoms may include failure of the hypothalamic-pituitary axis, narcolepsy-cataplexy, or severe rigidity with hypokinesis.
LGI1	Frequently occurs in patients older than 50 years, with mild male predominance. In most cases the clinical picture is a typical LE; 60% of the patients develop hyponatremia. Symptoms of LE may be preceded or associated with bradycardia sometimes leading to pacemaker placement or short-lasting myoclonic-like movements described as facio-brachial dystonic seizures. In some patients the presentation mimics a rapidly progressive dementia (e.g., Creutzfeldt-Jakob)
GABAbR	Usually affect adults; 50% have an underlying SCLC or neuroendocrine tumor. The syndrome presents as typical LE with early and prominent seizures. Some patients develop cerebellar ataxia. As with AMPAR antibodies (see below), the GABAbR antibodies may occur with co-existing tumor-related antibodies.
AMPAR	Mildly predominates in women. About 50% of the patients present with LE; the rest develop LE combined with other symptoms. Some cases present with pure psychosis or RPD. About 65% of the patients have an underlying tumor (mainly SCLC, thymoma). These antibodies may co-exist with onconeuronal antibodies, other neuronal cell surface, thyroid, or tumor-related antibodies (SOX1, VGCC) reflecting a propensity to autoimmunity.
GAD	May occur as pure or predominant LE. In these cases the syndrome is often paraneoplastic and screening for an underlying tumor is recommended. However, regardless of the neurological syndrome, the co-existence of GAD antibodies and cell surface neuronal antibodies (e.g., AMPA or GABAbR) frequently associate with an underlying cancer, and tumor screening is also recommended. Many patients with anti-GAD associated neurological symptoms have type I diabetes mellitus or other endocrinopathies.
ANTIBODIES THAT RARELY ASSOCIATE WITH LIMBIC ENCEPHALITIS	
CV2 (CRMP5)	Similar demographics and tumor association as for Hu antibodies, but some patients may have thymoma or other tumors. Rarely associated with pure LE. Accompanying features may include uveitis, retinopathy, optic neuropathy, chorea, and peripheral neuropathy.
Caspr2	Rarely present as classical LE. Associate more frequently with Morvan syndrome; in these cases the presence of an underlying thymoma should be investigated. The occurrence of history of neuropathic pain or neuromyotonia suggest Morvan syndrome.
DPPX	Patients often have gastrointestinal dysfunction, diarrhea, and loss of weight preceding the neurological syndrome (psychiatric manifestations, confusion, seizures, tremor, myoclonus, nystagmus). Hyperekplexia is frequent, and patients may develop a syndrome resembling progressive encephalomyelitis with rigidity and myoclonus. Most patients do not have a tumor. Presentation as classical LE is unusual.
GABAaR	Patients present with multifocal (cortical-subcortical FLAIR MRI changes) or diffuse encephalitis, with prominent seizures and status epilepticus, often requiring induced coma. If antibodies are only detected in serum the syndrome association is broad. Presentation as classical LE is unusual. Most patients do not have a tumor; some have thymoma.
mGluR5	Patients present with non-focal encephalitis, and a clinical picture suggesting involvement beyond the limbic system. Most patients have Hodgkin's lymphoma.
Adenylate-kinase 5	Patients present with isolated severe short-term memory loss. No seizures. No association with cancer. Poor response to immunotherapy.

Table 5S: Diagnostic criteria of primary vasculitis of the CNS[38]

1. A newly acquired focal or diffuse neurological deficit and/or psychiatric symptoms
2. Demonstration of classic angiographic or histopathological features of vasculitis in the CNS.
3. No evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disorder.

References

1. Abou-Zeid E, Boursoulian LJ, Metzer WS, Gundogdu B. Morvan syndrome: a case report and review of the literature. J Clin Neuromuscul Dis. 2012;13(4):214-27.

2. Provini F, Marconi S, Amadori M, et al. Morvan chorea and agrypnia excitata: when video-polysomnographic recording guides the diagnosis. Sleep Med. 2011;12(10):1041-3.

3. Irani SR, Pettingill P, Kleopa KA, et al. Morvan syndrome: clinical and serological observations in 29 cases. Ann Neurol. 2012;72(2):241-55.

4. Lancaster E, Huijbers MG, Bar V, et al. Investigations of caspr2, an autoantigen of encephalitis and neuromyotonia. Ann Neurol. 2011;69(2):303-11

5. Hajj-Ali RA, Calabrese LH. Diagnosis and classification of central nervous system vasculitis. J Autoimmun. 2014;48-49:149-52.

6. Salvarani C, Brown RD Jr, Hunder GG. Adult primary central nervous system vasculitis. Lancet. 2012;380(9843):767-77.

7. Benseler SM. Central nervous system vasculitis in children. Curr Rheumatol Rep. 2006;8(6):442-9.

8. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. Lancet Neurol. 2011;10(6):561-72.

9. Broussalis E, Trinka E, Kraus J, McCoy M, Killer M. Treatment strategies for vasculitis that affects the nervous system. Drug Discov Today. 2013;18(17-18):818-35.

10. Varadkar S, Bien CG, Kruse CA, et al. Rasmussen's encephalitis: clinical features, pathobiology, and treatment advances. Lancet Neurol. 2014;13(2):195-205.

11. Bien CG, Bauer J, Deckwerth TL, et al. Destruction of neurons by cytotoxic T cells: a new pathogenic mechanism in Rasmussen's encephalitis. Ann Neurol. 2002;51(3):311-8.

12. Nabbout R. FIRES and IHHE: Delineation of the syndromes. Epilepsia. 2013 Sep; 54 Suppl 6:54-6.

13. Sakuma H, Awaya Y, Shiomi M, et al. Acute encephalitis with refractory, repetitive partial seizures (AERRPS): a peculiar form of childhood encephalitis. Acta Neurol Scand. 2010;121(4):251-6.

14. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis. 2013;57(8):1114-28.

15. Gofton TE, Young GB. Sepsis-associated encephalopathy. Nat Rev Neurol. 2012;8(10):557-66.

16. Frontera JA. Metabolic encephalopathies in the critical care unit. Continuum (Minneap Minn). 2012;18(3):611-39.

17. Amin OS, Shwani SS, Zangana HM, Hussein EM, Ameen NA. Bilateral infarction of paramedian thalami: a report of two cases of artery of Percheron occlusion and review of the literature. BMJ Case Rep. 2011 Mar 3;2011. pii: bcr0920103304.

18. Chaturvedi S, Pant I, Kushwaha S, Jha DK. Intravascular lymphoma: an unusual cause of rapid cognitive decline and the role of brain biopsy. BMJ Case Rep. 2014 Aug 21;2014. pii: bcr2014205835.

19. Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking creutzfeldt-jakob disease. Arch Neurol. 2008 Oct;65(10):1341-6.

20. Fanouriakis A, Boumpas DT, Bertsias GK. Pathogenesis and treatment of CNS lupus. Curr Opin Rheumatol. 2013;25(5):577-83.

21. Arnulf I, Rico TJ, Mignot E. Diagnosis, disease course, and management of patients with Kleine-Levin syndrome. Lancet Neurol. 2012;11(10):918-28.

22. Pugliese A, Beltramo T, Torre D. Reye's and Reye's-like syndromes. Cell Biochem Funct. 2008 ;26(7):741-6.

23. Gieraerts C, Demaerel P, Van Damme P, Wilms G.Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome mimicking herpes simplex encephalitis on imaging studies. J Comput Assist Tomogr. 2013;37(2):279-81.

24. Brusilow SW, Maestri NE. Urea cycle disorders: diagnosis, pathophysiology, and therapy. Adv Pediatr. 1996;43:127-70.

25. Stübgen JP. Nervous system lupus mimics limbic encephalitis. Lupus. 1998;7(8):557-60.

26. Collison K, Rees J. Asymmetric cerebellar ataxia and limbic encephalitis as a presenting feature of primary Sjögren's syndrome. J Neurol. 2007;254(11):1609-11.

27. Guéguen A, Sené T, Maillart E, Gout O. Encephalitis and CSF increased level of interferon-α in Kikuchi-Fujimoto disease. BMJ Case Rep. 2012;2012. pii: bcr0120125579.

28. Kumar N, Leep Hunderfund AN, Kutzbach BR, Pulido JS, Miller GM. A limbic encephalitis MR imaging in a patient with Behcet disease and relapsing polychondritis. AJNR Am J Neuroradiol. 2009;30(7):E96.

29. Verhelst H, Van Coster R, Bockaert N, et al. Limbic encephalitis as presentation of a SAP deficiency. Neurology. 2007;69(2):218-9.

30. Solomon T, Michael BD, Smith PE, et al. Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012;64(4):347-73.

31. Seeley WW, Marty FM, Holmes TM, et al. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology. 2007;69(2):156-65.

32. Athauda D, Delamont RS, Pablo-Fernandez ED. High grade glioma mimicking voltage gated potassium channel complex associated antibody limbic encephalitis. Case Rep Neurol Med. 2014;2014:458790.

33. Chevret L, Husson B, Nguefack S, Nehlig A, Bouilleret V. Prolonged status epilepticus with early and persistent restricted hippocampal signal MRI abnormality. J Neurol 2008;255:112-6.

34. Scheid R, Voltz R, Vetter T, Sabri O, von Cramon DY. Neurosyphilis and paraneoplastic limbic encephalitis: important differential diagnoses. J Neurol. 2005;252(9):1129-32.

35. Blanc F, Ben Abdelghani K, Schramm F, et al. Whipple limbic encephalitis. Arch Neurol. 2011; 68(11):1471-3.

36. Scriven J, Davies S, Banerjee AK, Jenkins N, Watson J. Limbic encephalitis secondary to HIV seroconversion. Int J STD AIDS. 2011;22(4):236-7.

37. Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. Ann N Y Acad Sci. 2015;1338:94-114.

38. L.H. Calabrese, J.A. Mallek. Primary angiitis of the central nervous system. Report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore), 1988; 67(1):20-39.