Autoimmune neurological disorders - does the age matter?

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Antibodies binding to central nervous system (CNS) channels, receptors and other synaptic or glial proteins are now recognised as a likely cause of neurological disorders in both adults and children (see Table). Autoimmune encephalopathies are characterized variously by impaired alertness, amnesia, seizures, movement disorders, psychiatric features or autonomic instability, but without focal neurological deficits. The neuronal cell-surface antigens are essential to cellular function or neurotransmission and are generally expressed throughout the nervous system[1]. Autoimmune forms of demyelinating disorders, by contrast, can present as optic neuritis, transverse myelitis or a range of CNS presentations reflecting the site of the lesions. The glial (myelin or astrocyte) cell-surface antigens are widely expressed throughout the CNS. All these patients frequently respond well to immunotherapies, and in some cases the disorders are monophasic and do not require long-term immunosuppression[2]. By contrast, the typical paraneoplastic antibodies are generated against tumour antigens that are shared with the nervous system, and are usually associated with T cell-mediated pathogenic mechanisms; the antibodies represent an epiphenomenon of the disease but can be useful biomarkers for the existence of the appropriate tumour. Unfortunately, patients with the intracellular antibodies often progress relentlessly and do not respond to immunotherapies[3].

The strongest levels of evidence linking identified cell surface antibodies to the pathology of specific disorders are found with AQP4 antibody in neuromyelitis optica spectrum disorder and NMDAR antibody in NMDAR-antibody encephalitis. It is worth appreciating that although initial studies clearly linked the antibodies to the clinical syndromes, the ready availability of commercial and in-house diagnostic assays has led to an expansion of phenotypes to include seropositive patients with only some of the hallmark clinical features, or sometimes with novel features. On the other hand, different antibodies can be associated with similar clinical phenotypes. Most specifically, forms of limbic encephalitis in adults with antibodies to LGI1, GABAbR or AMPAR, may not be clinically distinguishable (see Table).

One intriguing aspect of these newly-described disorders, is the different demographics. As can be seen in the Figure, AQP4 antibodies are not very common in children and the majority of patients are post-puberty females. Antibodies to myelin oligodendrocyte glycoprotein (MOG), however, are more frequent in children than adults, generally presenting with recurrent optic neuritis or ADEM, and with a female to male bias of 2:1. Equally or more common in children is NMDAR-antibody encephalitis which peaks in females between ages 10 and 40. Surprisingly, perhaps, antibodies to leucine-rich, glioma inactivated 1 (LGI1), associated with a now commonly-recognised form of limbic encephalitis in adults, have not been reported in children and they are very rare before the age of 30; the incidence peaks at around 60 years with males dominating.

It was interesting, therefore, to read a case report from Schimmel et al (JPNS et al. XXX) of a 14 year old boy presenting with subacute onset of memory problems, left hippocampal swelling on imaging and positive oligoclonal bands in association with LGI1 antibodies detected at high titre (1:1000) in the serum (but not in the CSF, which is not uncommon with LGI1 antibodies). He developed psychiatric dysfunction but did not demonstrate faciobrachial dystonic seizures[4], although he reported episodes, lasting up to one minute, of half-sided pallor and paraesthesia of the face with ptosis. Although the lack of typical seizures and normal EEG throughout the course of disease is unusual for LGI1-antibody limbic encephalitis, he responded to plasma exchange and immunotherapies with good recovery; some memory problems remained, associated with hippocampal atrophy which is common after LGI1-antibody disease.

Schimmel et al used a commercial cell-based antibody test for LGI1 antibodies, excluding other possible neuronal antibodies in parallel tests. Earlier studies on limbic encephalitis in adults used an immunoprecipitation assay to show antibodies to the whole voltage-gated potassium channel (VGKC) complex, which includes the protein called LGI1. In adults with limbic encephalitis, and sometimes the subsequently defined faciobrachiodystonic seizures, most VGKC-complex antibodies bind to LGI1 or less frequently CASPR2 (the other main cell surface protein in the VGKC-complex). However, VGKC-complex antibodies in children very rarely bind to LGI1 or CASPR2 raising doubts about the pathogenic relevance of "VGKC-complex antibodies" in this age-group. Indeed, in a recent study of 39 children with VGKC-complex-Abs and neuroinflammatory diseases, the antibodies were binding partly or exclusively to intracellular epitopes on the VGKC-complex and were therefore deemed non-pathogenic[5]. Using the right technique for detecting rare antibodies is clearly important and cell-based assays are now widely available and should be used, but it is still important to understand the methodological strengths and weaknesses of the technique.

The gold standard remains the clinical evaluation of the child; this is particularly important when the antibody results are discordant with the characteristic phenotype or when the diagnosis is made in an atypical demographic group. This case suggests that LGI antibodies should be tested in children with subacute onset of memory loss even when presenting with a partial phenotype. Existing small case series, however, have failed to find LGI1-Abs in children with various expression of limbic encephalitis or epileptic encephalopathies, and further systematic studies should be undertaken.

References

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Figure legend:

Figure. Age distributions of patients with different antibodies detected by cell-based assays in one year (2015) by the Oxford diagnostic service. A. White matter/demyelinating disorders: AQP4 (blue) and MOG (green) antibodies are both found in children but MOG antibodies are more common in children, particularly below 10 years, than in adults, whereas this is not the case for AQP4 antibodies. B. Autoimmune encephalopathies: NMDAR (red) antibodies are more common in children and younger females than males particularly below the age of 30. LGI1 (purple) antibodies, by contrast, are typically found in older males with fewer females. Children have not been reported previously. Note that the total number of patients identified with each antibody is not necessarily representative of the population; the numbers have been adjusted to make the age and sex comparisons clearer.

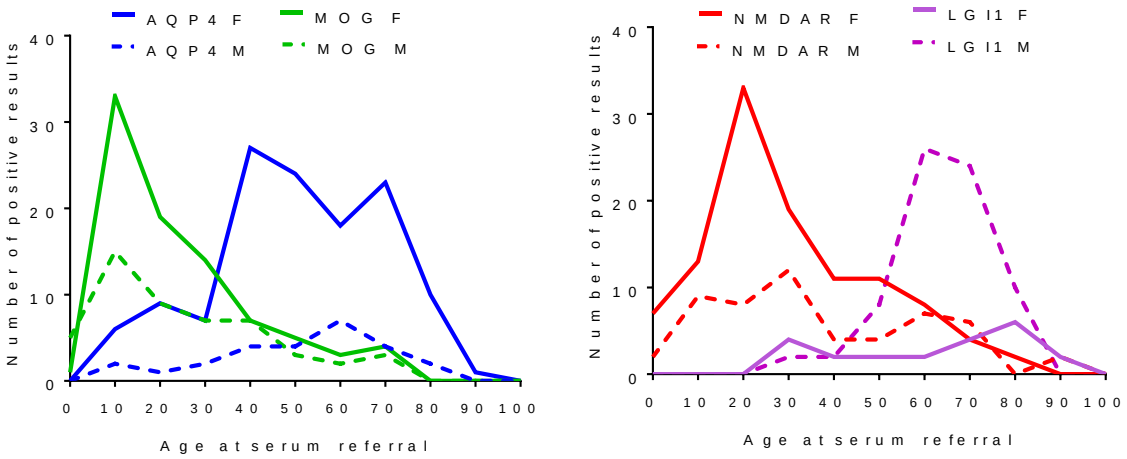

Table. Antibodies of relevance to paediatric neurology

	Main phenotypes in adults	Phenotypes reported in children	Evidence for pathogenicity	Relative frequency in children
NMDAR	Encephalopathy with psychiatric features, movement disorder, seizures and dysautonomia	Similar to adults.	Good	Common, 40% of all patients; F>M
AQP4	NMOSD	Similar to adults	Good	Not common in children; F>M
MOG	Optic neruritis NMOSD	ADS NMOSD Monophasic/recurrent ON ADEM-ON[6]	Increasing	Increasingly identified in acute and relapsing demyelinating syndromes
D2R	No reports	Basal ganglia encephalitis, Sydenham's chorea, Tourette's Syndrome	No evidence in vivo	Found retrospectively in rare cases; not common
GlyR	Progressive encephalomyelitis with rigidity and myoclonus; stiff-person syndrome	Progressive encephalomyelitis with rigidity and myoclonus; autoimmune encephalitis/epileptic encephalopathy	Good in vitro evidence; no in vivo model reports	Not common; F=M
$GABA_AR$	Encephalopathy with refractory seizures and status epilepticus	3/6 patients reported <18yr	Good in vitro evidence; no in vivo model reports	Rare
GAD	Stiff person syndrome	Very rare in children but some patients with limbic encephalitis and refractory seizures	Some in vitro and in vivo evidence, but not complete	Rare
LGI1	Limbic encephalitis	No previous reports	Good in vitro evidence; no in vivo models	No previous reports
CASPR2	Peripheral nerve hyperexcitability; rare Morvan's syndrome	No previous reports	Peripheral nerve hyperexcitability and mechanical allodynia in mice	No reports

Abbreviations: ADEM-ON Acute Disseminated Encephalomyelitis followed by optic neuritis ADS acquired demyelinating syndromes HL Hodgkin lymphoma LE limbic encephalitis NMOSD NMO spectrum disorder PERM progressive encephalomyelitis with rigidity and myoclonus SC Sydenham's chorea TS Tourette's syndrome SPS stiff person's syndrome.