

Autoantibody Associated Disorders of the CNS in Children: The List Keeps Growing

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In this issue of the Canadian Journal of Neurological Sciences, Wong-Kisiel et al draw timely attention to some autoimmune (AI) etiologies for “encephalopathies” and epilepsies in children (the term will be used to include adolescents).¹ Timely, because of the explosion of knowledge in this field, the potential for treatment, and the association with malignancies.

Seminal observations in the first half of the 20th century, contributed to the recognition of autoimmunity and AI diseases.² Autoimmune diseases affect 4%-8% of the population in some western countries,^{3,4} and may now be the third leading cause of morbidity and mortality in the industrialized world.⁵

Experimental and clinical observations over the past 50 years have identified the essential roles of genetic, gender, immunologic and environmental factors in the occurrence of AI diseases; 78% of those affected are women, and individuals and families often have more than one AI disorder.^{4,10} Infection is a well recognized environmental trigger. Decline in infectious diseases and improvements in hygiene, have been postulated (“The hygiene hypothesis”) to explain the apparent increase in AI disorders in developed countries, but other factors may also be responsible.¹¹

The term “autoimmunity” is generally used when the inflammatory response is due to a specific adaptive immune response against host antigens, associated with specific auto-reactive lymphocytes or antibodies. Autoimmunity may be ‘physiological’ or ‘pathological’, and the mere presence of circulating antibodies is not proof of AI disease.¹² Hence, criteria (“Witebsky’s postulates”) modelled on Koch’s postulates, were proposed to classify AI diseases into three categories: those with direct, indirect and circumstantial evidence for autoimmunity respectively, a position endorsed by Drachman.^{13,14} In the Neurosciences, Myasthenia Gravis is the best example of the first, Multiple Sclerosis of the second, with almost all of the remaining AI disorders falling into the third category.

Immune-mediated inflammation, not necessarily AI, can occur in some CNS conditions, for reasons that are often not clear, neurometabolic disorders like adrenoleukodystrophy and neuronal ceroid lipofuscinoses being examples. In others, such as the Aicardi-Goutieres syndrome which has some similarities to familial chilblain lupus, a genetic defect may predispose to an abnormal immune-mediated inflammatory response.¹⁵ The distinction between non AI and AI mechanisms may be difficult in clinical practice, and both phenomena may be responsible for some disorders.

The terms, paraneoplastic, parainfectious and idiopathic,¹ describe sub-groups rather than primary etiologies, for entities such as opsoclonus-myoclonus syndrome, limbic encephalitis associated with voltage gated potassium channel complex

(VGKC), and Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. As the subsequent paragraphs suggest, the potential list of AI disorders keeps growing like the many-headed Hydra of Greek mythology.

Wong-Kisiel et al have addressed the complex relationship between seizures and AI mechanisms, as have Vincent’s group.^{1,16,17} Recently, Suleiman et al reported a four-month-old female infant who presented with intractable epileptic spasms and developmental delay; the cerebrospinal fluid showed elevated neopterin and mirrored oligoclonal bands, prompting the testing for autoantibodies; VGKC antibodies were elevated.¹⁸ Thus, AI mechanisms can affect very young children.

The neurological manifestations of *Mycoplasma pneumoniae* may have an immunological basis.¹⁹ NMDAR encephalitis was associated with evidence of acute *Mycoplasma pneumoniae* in four of ten adults and children in the California encephalitis project, an association that lends further support to the contribution of infectious agents to AI disease.²⁰ In a prospective study of 203 adults and children with encephalitis from England, 21% had an immune-mediated etiology.²¹ Hence, immune-mediated encephalitides should be included in the differential diagnosis of children presenting with fever and coma.²² The occurrence of psychotic symptoms, sleep disturbances and dyskinesias in such a setting is strongly suggestive of NMDAR encephalitis.

Pathological autoimmunity, triggered by infection in a genetically predisposed individual, may be responsible for several syndromes (with intriguing eponyms such as AERRPS, AESD, DESC, NORSE, FIRES) associated with acute, often intractable seizures and impaired consciousness, as well as entities such as hemorrhagic shock and encephalopathy syndrome and acute necrotizing encephalopathy.²³⁻³⁰ Elevated VGKC antibodies were found in a boy with fever-induced refractory epileptic encephalopathy in school-age children (FIRES).³⁰ However, a genetically determined inflammatory cascade, rather than an autoantibody mediated disorder, seems likely in most of these cases.

Voltage gated potassium channel complex antibodies may not actually bind to the potassium channel but rather to synaptic proteins closely bound to VGKC. Lai et al have shown that the limbic encephalitis attributed to VGKC antibodies, is actually associated with LGI1 (leucine-rich, glioma-inactivated) antibodies and should be considered an AI synaptic encephalopathy.³¹

Autoantibodies (NMO-IgG) targeting the water channel aquaporin-4 (AQP4) are biomarkers for neuromyelitis optica (NMO). Several studies in adults and children have shown that the manifestations of NMO go beyond optic neuritis and transverse myelitis, to include seizures, ophthalmoplegia, ataxia

and co-existing AI disorders.³² Neuromyelitis optica is therefore now referred to as “NMO spectrum disorder.” Aquaporin-4 autoimmunity may be mistakenly diagnosed as multiple sclerosis in children. The spectrum of neurological syndromes associated with glutamic acid decarboxylase (GAD) antibodies is also widening, although stiff-person syndrome and cerebellar ataxia remain the most common.³³ However, it is not clear whether GAD antibodies will prove to be important and pathogenic; GAD is an intracellular antigen, and antibodies should not have access to GAD unless there is disruption of the cell membrane.

Clinicians dealing with children must consider the possibility of immune-mediated CNS disorders in a bewildering variety of acute and chronic clinical scenarios,¹ especially if the child is female. In addition to a high degree of clinical suspicion, biomarkers in the blood and cerebrospinal fluid can aid in diagnosis.³⁴ The presence of fever or suggestion of an infective etiology does not exclude a triggered or concomitant immune process. Magnetic resonance imaging may suggest a demyelinating process, but is often normal or non-specifically abnormal on T1- or T2- weighted imaging in many AI CNS diseases. The diagnosis of an AI disorder is important, as malignancies may be responsible for some cases. In addition, prompt ‘immune-therapy’, albeit based on observational studies, to which Wong-Kisiel et al allude,¹ may improve outcome.

The clinical manifestations of AI disorders of the nervous system continue to unfold. It is very likely that as yet unrecognized autoantibodies will explain several currently unexplained conditions. New assays are likely to employ ‘cell based’ approaches that present the antigen in its conformational state. Many autoantigens are likely to be important cell surface receptors or synaptic proteins involved in neurotransmission. We may be able to correlate the type of autoantibody with response to immunotherapy.

As Vincent et al suggest,³⁵ recent advances in the field of AI disorders in general and AI CNS disorders in particular, have created a pressing need for a rational universally accepted current classification that will assist clinicians and researchers. In addition, there is equal urgency to clarify the significance of antibodies in clinical situations. The European Federation of Neurological Societies has developed guidelines for the diagnosis and management of NMO.³⁶ A similar consensus is needed for the entire group of AI and suspected AI CNS disorders in adults and children.

Shashi S. Seshia

University of Saskatchewan, Saskatoon, Saskatchewan, Canada
E-mail: sseshia@yahoo.ca

Russell C. Dale

University of Sydney and the Children's Hospital at Westmead
Westmead, New South Wales, Australia

Fenella J. Kirkham

UCL Institute of Child Health, London, UK
Southampton General Hospital, Southampton, UK

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NOTE

We have provided some simple definitions:

Biomarker: A “substance” that is objectively measured and evaluated as an indicator of normal or pathogenic processes, or pharmacologic responses to a therapeutic intervention. It may have a causal role or be secondary to the disease.

Autoantibody: An antibody directed against ‘self’ i.e., against a component of one own’s tissue.

Autoantigen: Normal protein or protein complex against which autoantibody is formed.

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