



# THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the  
Sri Lanka Medical Association  
Volume 60, No.4, December 2015  
Quarterly ISSN 0009-0875

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## Friendly fire on neurons: antibody-mediated diseases of the nervous system

The unintentional attack during combat on one's own forces, often as a result of mistaken identity, is termed in military jargon as 'friendly fire'. The same occurs within the human body when a specific adaptive immune response is mounted against self-antigens. Since the self-antigen cannot be eradicated, the immune response becomes sustained leading to autoimmune ('friendly fire') disease. Autoimmune diseases of the nervous system can occur as part of a systemic autoimmune response, or as a primary phenomenon where autoimmune responses are specifically directed against neuronal and neuromuscular targets. The immune attack can be mediated by the cellular or the humoral arm of the adaptive immune system, or by the synergistic action of both arms.

Over the last two to three decades an increasing number of neurological disorders have been found to be associated with autoantibodies. However, the mere presence of autoantibodies does not always suggest a direct pathogenic role of the humoral immune response. For example, autoantibodies (Hu, Yo, Ri, Ma2, CRMP5, amphiphysin) in paraneoplastic neurological syndromes are excellent markers of disease, but by themselves do not cause the disease. There are well-established clinical and experimental paradigms to prove the pathogenicity of autoantibodies [1]. The antibodies should be specific to the disease and bind to cell surface targets of the antigen; they should alter the function or number of the target in a manner that explains the clinical phenotype; plasma exchange and other immunotherapies should be clinically effective; and injecting patient plasma or immunoglobulins into experimental animals, and trans-placental transfer of antibodies to offspring, should lead to clinical or electrophysiological evidence of the disease.

The recognition of a pathogenic role of autoantibodies in neurological disorders has transformed the outlook of these diseases from one of passive acceptance to one of active immunological interventions with potential for cure.

### Autoantibody-mediated diseases of the peripheral nervous system

#### *Myasthenia gravis*

Myasthenia gravis (MG) is the commonest neuromuscular disorder and the prototype autoimmune neurological disease. It is characterised by the clinical hallmark of fatiguable muscle weakness. Patients most commonly present with eyelid ptosis and diplopia that in the majority spread to cause bulbar and limb muscle weakness. Some would develop life-threatening respiratory paralysis, the reason to include 'gravis' in its nomenclature. Although the first description of the disease was recorded in 1672 by the

British physician Thomas Willis, it was not until 1960 that it was hypothesised to be mediated by an antibody directed against a neuromuscular junction protein [2]. Acetylcholine receptor antibodies (AChRabs) were first detected in patient serum in 1976, and in subsequent years were shown to fulfil all criteria for pathogenicity [2, 3]. MG thus became the first neurological disease to be identified as being antibody mediated. Although being highly specific for MG, AChRabs are detected in only 85% of patients with generalised MG [3]. It was hypothesised that either there were other autoantibodies causing disease in MG patients seronegative for AChRabs or that the assay was not sensitive enough to detect low-affinity AChRabs. Both these hypotheses were proven to be true. Autoantibodies to another muscle protein that facilitates efficient neuromuscular transmission known as muscle specific tyrosine kinase (MuSKAbs) were identified in 2001, while a more sensitive cell-based assay was able to detect low-affinity AChRabs that were not detectable with previous assays [4,5]. The identification of MuSKAbs led to the recognition of a clinical sub-entity of MG, known as 'MuSK-MG', with predominantly bulbar involvement and poor response to thymectomy and standard immunosuppressive therapy.

Over 90% of Sri Lankan MG patients were found to be seropositive for either AChRabs (85%) or MuSKAbs (6.2%) [6]. The clinical characteristics and occurrence of thymic pathology among Sri Lankan MG patients were similar to other populations except for a male preponderance (1.5:1). Although 42.9% of Sri Lankan MuSK-MG patients had an ocular-bulbar onset, none had facial or tongue muscle wasting as described in some Caucasian patients [6, 7]. MG continues to be most often diagnosed clinically in Sri Lanka because of the ready unavailability of sero-diagnostic assays. However, it has been noted that standard immunosuppressive therapy is often commenced early leading to a less severe disease course [6].

### ***Lambert-Eaton myasthenic syndrome***

Lambert-Eaton (LEMS) is a rare neuromuscular disorder characterised by proximal muscle weakness, diminished tendon reflexes and autonomic dysfunction [8]. Unlike in MG which is characterised by fatigability, in LEMS both muscle strength and tendon reflexes are enhanced by exercise – a phenomenon known as 'facilitation'. LEMS is caused by autoantibodies that bind to presynaptic voltage-gated calcium channels, which inhibits Ca<sup>2+</sup> influx and neurotransmitter release [9]. Malignancy, particularly small cell lung carcinoma, is associated in 50% of patients [8]. Immune-intervention therapies are effective in LEMS with or without tumour, it is imperative to treat the malignancy aggressively.

### ***Other autoantibody-associated Peripheral nervous System disorders***

Although autoantibodies have been identified in several diseases of the peripheral nervous system and although an autoimmune basis is likely in some of them, unlike in MG and LEMS, a pathogenic role of the identified autoantibodies remain unproven.

Guillain-Barre syndrome and Miller-Fisher syndrome are inflammatory demyelinating neuropathies that manifest as acute flaccid paralysis or acute ophthalmoplegic ataxia, which respond to treatment with intravenous immunoglobulins (IVIg) and plasmapheresis [10]. Although autoantibodies are described to various gangliosides, it remains unclear whether these autoantibodies are pathogenic. Similarly, multifocal motor neuropathy (MMN), which is an asymmetrical pure motor demyelinating peripheral neuropathy, is found to be associated with anti-GM1 antibodies in a third of patients. Over 80% of patients with MMN improve muscle strength with IVIg suggesting an autoimmune basis for the neuropathy. Neuromyotonia is a rare condition of peripheral nerve hyperexcitability that originates principally in the distal motor nerves. Some forms of this condition are mediated by autoantibodies directed against CASPR2, a protein complexed with voltage-gated potassium channels, with a good response to plasma exchange. Thymic tumours are found in about 20% of patients with association of other autoimmune diseases and other autoantibodies [11].

### ***Autoantibody-mediated diseases of the central nervous system***

#### ***Autoimmune encephalitis***

The recent discovery of an expanding subset of encephalitides that result from autoantibodies against neuronal cell surface or synaptic proteins, which are potentially treatable, has led to a paradigm shift in the diagnostic approach of encephalitis. Given that the frequency of autoimmune encephalitis has been found in some studies to surpass that of individual viral aetiologies and given its potential for cure if immune intervention is initiated early, it is now recommended that all patients presenting with a clinical syndrome of encephalitis be investigated for an autoimmune aetiology unless there is an alternative aetiology evident in the initial diagnostic work up [12].

There are two major forms of cell surface antibody-mediated autoimmune encephalitis, which may occur in association of tumours or independently, but appear to be treatment-responsive, emphasizing the pathogenic importance of cell surface antibodies.

N-methyl-D-aspartate receptor antibody encephalitis (NMDARE) was first described in 2007 in young women

with ovarian teratomas [13]. With increased recognition, this syndrome is noted to occur in both sexes with female predominance, be more common among children and adolescents with a median age of 21 years, and occur often independent of tumours [14]. NMDARE typically demonstrates a multistage progression with cognitive dysfunction, psychiatric manifestation and seizures developing in the early stage and coma, movement disorders and dysautonomia developing in the late stage [15]. Presentations with incomplete forms of this disorder (“formes frustes”) in which patients develop predominant or apparently isolated psychiatric symptoms, seizures, or movement disorders have been recognised [16]. Neuroimaging remains normal in the majority of patients. Tumour removal, if applicable, and early initiation of immuno-therapy result in substantial improvement in over 80% of patients with NMDARE [17].

Limbic encephalitis (LE) which typically manifests as subacute onset amnesia, behavioural changes, temporal lobe seizures, hyponatraemia and hyper-intense signal in the hippocampi on brain imaging was considered a rare paraneoplastic disorder with a poor prognosis until the discovery of immunotherapy-responsive autoantibody-associated LE in 2001 [18]. Since then, several neuronal cell surface antibody targets have been identified with the commonest being LGI1 (80 - 90%) and CASPR2 (5 - 10%), which are proteins complexed with voltage-gated potassium channels [19].

Autoimmune encephalitis is increasingly recognised in Sri Lanka [20, 21] and in a recent study, 5 of 99 patients presenting with a syndrome of encephalitis to the National Hospital and the Lady Ridgeway Hospital in Colombo were found to have autoimmune encephalitis [unpublished data]. Patients’ age ranged from 1 month to 73 years (median 18 years) with one patient having CASPR2-antibodies, two NMDAR-antibodies and two GABABR-antibodies. If patients were selected based on features of a probable autoimmune aetiology such as multistage progression, movement disorders – particularly orofacial dyskinesia, normal brain imaging and non-diagnostic CSF analysis, the proportion of autoimmune encephalitis would have been higher.

### ***Neuromyelitis optica spectrum disorders***

Neuromyelitis optica (NMO) was first described by Devic and Gault in 1894 as a monophasic disorder characterised by bilateral (or rapidly sequential) optic neuritis and myelitis [22]. Its relapsing nature was noted in the 20<sup>th</sup> century and it was considered a topographically restricted form of multiple sclerosis until the discovery of highly-specific antibodies directed against the main water channels in the central nervous system (CNS) known as aquaporin-4 (AQP4) in 2004, which established NMO as a distinct disease [23]. Furthermore, testing for AQP4 antibodies enabled the recognition of

more restrictive and more extensive forms of NMO, which prompted the broadening of the diagnostic criteria in 2014 to include a wider, but well-characterised clinical spectrum of both optico-spinal and non-optico-spinal syndromes that encompass a unifying diagnosis of ‘NMO spectrum disorders’ (NMOSD) [22]. Treatment strategies used in multiple sclerosis is known to aggravate NMOSD indicating an imperative for accurate diagnosis. The recently revised diagnostic criteria and the characterisation of the clinical syndromes have enabled diagnosis even without antibody confirmation, which has enhanced the recognition of NMOSD in Sri Lanka [24, 25].

### ***Other autoantibody-associated central nervous system disorders***

An increasing number of autoantibodies have been identified in an expanding spectrum of CNS disorders including cognitive impairment, psychiatric manifestations, epilepsy, movement disorders and demyelinating diseases [19]. In many, the pathogenic significance of the associated autoantibody is not known. Although response to immuno-therapy may suggest an autoimmune basis, the associated antibody may not be causative. For example, anti-thyroid antibodies are associated with steroid-responsive Hashimoto encephalopathy, but are unlikely to be involved in the pathogenesis [26]. On the other hand, the antibody may be congruent with the mechanism of disease, but may not fulfil established criteria for pathogenicity described above. For example, glutamic acid decarboxylase (GAD) is the rate-limiting enzyme catalysing the synthesis of GABA, which is the predominant inhibitory neurotransmitter of the CNS, and thus, the clinical manifestations of stiff person syndrome and some forms of epilepsy, cerebellar ataxia and limbic encephalitis can be explained by the impaired CNS inhibition mediated by antibodies against GAD (GADAbs) [27, 28]. However, the pathogenicity of GADAbs remains unproven. Given that GAD is an intracellular protein inaccessible to circulating antibodies, it is likely that GADAbs are part of a wider autoimmune process rather than the disease inciting agent [29, 30].

### **Conclusions**

‘Friendly fire’ is not actually friendly. Autoimmune diseases of the nervous system have the potential to cause devastating neurological sequelae. The identification of autoantibodies directed against cell surface antigens (as opposed to intracellular antigens) in an expanding spectrum of neurological disorders has lent these diseases amenable to treatment, provided that appropriate immunotherapy is initiated early. Furthermore, the understanding of disease mechanisms elucidated by identification of pathogenic autoantibodies is expected to propel development of antigen-specific therapies to avoid the adverse consequences of non-specific immunosuppression and immunomodulation [31, 32].

## Conflicts of interests

There are no conflicts of interest.

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