

Anti-Basal Ganglia Antibodies and their Clinical Relevance

Basal ganglia dysfunction due to an aberrant post-streptococcal autoimmune response against neurones in the basal ganglia is the proposed pathogenesis of an emerging group of movement and neuropsychiatric disorders. Sydenham's chorea is the prototype of this group of disorders. Anti-basal ganglia antibodies (ABGA) are found in the majority of subjects with Sydenham's chorea.^{1,2} More recently other neuropsychiatric disorders or phenotypes have also been associated with ABGA. These include Tourette's syndrome,³ adult-onset tic disorders,⁴ obsessive-compulsive disorder (OCD),⁵ paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS),^{6,7} dyskinesias,⁸ dystonia,⁹ post-streptococcal acute disseminated encephalomyelitis (ADEM),¹⁰ myoclonus¹¹ and post-encephalitic Parkinsonism or encephalitis lethargica.¹² The proposal that these disorders are mediated by autoimmune mechanisms is controversial and not widely accepted.¹³ Reasons for conflicting results in this field and issues concerning the detection of ABGA have been highlighted recently.¹⁴ Differences in Western immunoblotting methods may explain the differences in the reported prevalence of ABGA in these disorders.^{15,16} Studies are currently being undertaken to reconcile these differences. The identification of the candidate autoantigens will obviously aid this process.

The association between a specific neuropsychiatric disorder and ABGA does not necessarily imply that these disorders are autoimmune. To establish a disorder as being autoimmune one needs to apply Witebsky's criteria of autoimmunity (Table 1).¹⁷ To do this it will be necessary to confirm the results of recent studies that have identified candidate autoantigens in these disorders^{18,19} and to establish the specificity and sensitivity of antigen-specific autoantibody assays. Kirvan et al. identified a monoclonal antibody from a subject with Sydenham's chorea with specificity for both mammalian lysoganglioside and N-acetyl-beta-D-glucosamine (GlcNAc), a dominant carbohydrate epitope of group A streptococci.¹⁸ Their human anti-lysoganglioside monoclonal antibody from a subject with Sydenham's chorea and sera from subjects with active Sydenham's chorea bind to the surface of human neuronal cells and induce calcium/calmodulin-dependent protein (CaM) kinase II activity. Convalescent sera and sera from other streptococcal diseases in the absence of chorea did not activate the kinase.¹⁸ This implicates antibody-mediated neuronal cell signalling in the pathogenesis of Sydenham's chorea. Dale and colleagues have identified aldolase C (40 kDa), non-neuronal and neuronal specific enolase (45 kDa doublet) and pyruvate kinase M1 (60 kDa) as possible autoantigens.¹⁹ These glycoytic enzymes are expressed on the surface of neurones and streptococci and are homologous with each other, which raises the possibility that ABGA are induced by molecular mimicry. Human non-neuronal enolase has previously been proposed as a candidate auto-antigen in autoimmune diseases related to streptococcal infection including rheumatic fever.²⁰ Appropriate animal models using candidate autoantigens will have to be established to build the case for autoimmune mediated mechanisms. Of note, Poynton, Paine and Holmes, between 1901 and 1903, were able to induce a disease in rabbits with features similar to rheumatic fever and Sydenham's chorea by inoculating the animals with "rheumatogenic" strains of streptococci.²¹ Three studies have used a passive transfer model by studying the effects of infusing serum con-

taining anti-neuronal antibodies from subjects with Tourette's syndrome into the striatum of rats. Two studies showed a significant increase in either oral stereotypies or episodic utterances in rats receiving higher-titre sera from subjects with Tourette's syndrome as compared to rats infused with lower-titre sera from subjects with Tourette's syndrome or controls.^{22,23} The third study using a similar methodology did not confirm these results.²⁴

In support of contemporary findings in relation to encephalitis lethargica a number of early investigators, including von Economo, detected streptococci or diplococci in the throats of patients with encephalitis lethargica during the 1917-1928 epidemic;²⁵ the gram positive organism was dismissed as being the primary aetiological agent of encephalitis lethargica as it was never isolated from the brain of terminal cases. Remarkably, an encephalitis lethargica-like illness was induced in dogs after vaccination with streptococcal isolates from patients with encephalitis lethargica.²⁵

Basal ganglia dysfunction has various manifestations, all of which fall into a relatively well-defined symptom complex or syndrome.²⁶ It is difficult to rely on the clinical manifestations to make an aetiological diagnosis in disorders due to basal ganglia dysfunction. Although a particular phenotype is typically associated with a "specific" disease entity, for example chorea or tics in Sydenham's chorea and Tourette's syndrome respectively, one would expect from applying basic principles that immune mediated basal ganglia dysfunction should result in the full spectrum of movement and emotional disorders that have been attributed to basal ganglia pathology. Huntington's disease and Wilson's disease, well-defined genetic disorders with a predilection for the basal ganglia, are associated with the full spectrum of both hyper- and hypo-kinetic movement disorders. Therefore using a biomarker, in addition to specific clinical features, would seem appropriate in defining this group of disorders.

The apparent overlap between the clinical phenotype of Sydenham's chorea, PANDAS, Tourette's syndrome and OCD, and the finding of serological evidence of recent streptococcal infection and ABGA in these disorders, suggests that they may represent one disease entity. For example, patients with PANDAS usually have psychiatric features and frequently have choreiform movements. Patients with Sydenham's chorea often have tics and OCD and patients with OCD often have tics and other subtle movement disorders. If PANDAS, Tourette's syndrome and OCD are the same disease as Sydenham's chorea why don't patients with these disorders have associated rheumatic fever? A detailed cardiac evaluation of 60 subjects with PANDAS did not reveal evidence of rheumatic carditis.²⁷ Whether or not subjects with ABGA have subtle cardiac involvement has yet to be investigated systematically. One could speculate that the current strains of streptococci that induce neuropsychiatric disease are different to those that are capable of inducing rheumatic carditis. These issues and others will hopefully be resolved once the putative autoantigens have been confirmed and further categorised.

In conclusion, immune-mediated basal ganglia dysfunction is plausible, particularly if you accept the clinical similarities between ABGA positive patients with PANDAS, Tourette's syndrome, OCD and Sydenham's chorea. At present the experimental evidence to categorise these disorders as autoimmune is incomplete, i.e. we have yet to confirm identified putative autoantigens



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and create appropriate animal models. Despite this deficiency in the experimental evidence there is a case to acknowledge immune mediated basal ganglia dysfunction as an emerging clinical entity. This is important as it has potentially major implications for the diagnosis and treatment of patients with basal ganglia dysfunction.

Table 1. Modified Witesbsky's Criteria⁷

1. The presence of auto-reactivity, i.e. an antibody or T cell which is self-reactive.
2. Recognition of the specific autoantigen.
3. Induction of the disease in animal model.
4. Passive transfer of the disease to the animal.*

* Criterion 4 applies to auto-antibody mediated human disease only. It is not possible to transfer a human autoimmune disease to animal via the passive transfer of autoreactive T cells as they have to by definition see their 'autoantigen' in the context of the correct MHC molecule.

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