Editorial

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PANDAS: overview of the hypothesis

PANDAS: visão geral da hipótese

The "PANDAS Hypothesis": Basal ganglia dysfunction due to an aberrant immune response that is triggered by streptococcal infection, underlies the pathogenesis of an emerging group of neuropsychiatric disorders of which Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS) is an example.

Basal ganglia dysfunction has various manifestations, all of which fall into a relatively well defined symptom complex or syndrome. It is difficult to rely purely on the clinical manifestations to making an aetiological diagnosis in disorders due to basal ganglia dysfunction. Although a particular phenotype is typically associated with specific disease entities, 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, typically presents with chorea, but is associated with a wide spectrum of other movement disorders, which includes both hyper- and hypo-kinetic movement disorders. Therefore it would be appropriate to use a biomarker, in addition to the clinical features, to define this emerging group of disorders.

Sydenham's chorea (SC) is the prototype of this group of disorders with the first report of anti-basal ganglia antibodies (ABGA) dating back to the mid seventies.[1] Despite current methodological issues concerning the detection of ABGA, recent studies have confirmed this earlier result and have extended the spectrum of disorders associated with the presence of ABGA. ABGA were originally found using immunofluorescence microscopy. Currently both immunofluorescence microscopy and Western immunoblotting are being used to detect ABGA.[1] In addition to SC, subjects with PANDAS, TS, obsessive-compulsive disorder (OCD), adult-onset tic disorders, dystonia and post-encephalitic Parkinsonism have now been described in association with ABGA.[2]

Methodological problems in relation to different Western immunoblotting techniques currently being used by different laboratories may explain the differences in the reported prevalence of ABGA in these disorders. These include 1) problems with non-specific or low affinity binding, a common problem when using enhanced chemiluminescence to detect autoantibodies, 2) standardisation of the basal ganglia antigen source and how it is prepared, and 3) optimising electrophoretic methods and conditions.[3-4] These methodological issues will hopefully be resolved if the results of the recent identification of the candidate autoantigens[5] can be reproduced.

To establish whether or not these disorders fulfil Witesbsky's criteria for defining a disease as autoimmune, it will be necessary to establish an appropriate animal model using candidate autoantigens. Interestingly, a disease with features similar to rheumatic and SC has been induced in animals by inoculating the animal with rheumatogenic strains of streptococci. Whether

or not a SC-like illness can be induced by the passive transfer of ABGA has not been established. Therefore, SC in which the temporal and aetiological relationship with recent streptococcal infection is beyond doubt fulfils at least two out of four of Witesbsky's criteria for being an autoimmune disease.

The apparent overlap between the clinical phenotype of SC, PANDAS, TS and OCD, and the finding of serological evidence of recent streptococcal infection and ABGA in these disorders, suggests that they may therefore represent one disease entity. For example, patients with PANDAS usually have psychiatric features and frequently have choreaiform movements. Patients with SC often have tics and OCD and patients with OCD often have tics and other subtle movement disorders. If PANDAS, TS and OCD are the same disease as SC why don't patients with these disorders have rheumatic fever? This latter issue 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 autoantigens have been confirmed and further categorised and the antigenic epitopes compared to those that are presumably shared with streptococcal antigens. The latter assumes that molecular mimicry underlies the immunopathogenesis of these disorders.

In conclusion, the PANDAS hypothesis is plausible, particularly if you accept the similarities between ABGA positive patients with PANDAS, TS, OCD and SC. The current working hypothesis is that antibodies induced in response to streptococcal infection cross-react with antigenic determinants in the basal ganglia resulting in basal ganglia dysfunction. Although the experimental evidence is incomplete, i.e. we have yet to confirm identified putative autoantigens, create appropriate animal models and reproducibly transfer disease with the passive transfer of autoantibodies. Despite this deficiency in experimental evidence there is now a compelling case to accept 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.

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References

1. Husby G, van de Rijn I, Zabriskie JB, Abdin ZH, Williams RC Jr. Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. J Exp Med. 1976;144(4):1094-110.

2. Martino D, Giovannoni G. Antibasal ganglia antibodies and their relevance to movement disorders. Curr Opin Neurol. 2004;17:425-32.

3. Singer HS, Hong JJ, Rippel CA, Pardo CA. The need for caution in considering the diagnostic utility of antibasal ganglia antibodies in movement disorders. Arch Dis Child. 2004;89(7):595-7.

4. Giovannoni G, Dale R, Church A. Anti-basal ganglia antibodies in movement disorders [letter]. Arch Dis Child 2004. Available from: http://adc.bmjjournals.com/cgi/eletters/89/7/595#1116.

5. Dale RC, Candler PM, Church AJ, et al. Glycolytic enzymes on neuronal membranes are candidate autoantigens in post-streptococcal neuropsychiatric disorders. Mov Disord. 2004; 19(Suppl 9);S33.