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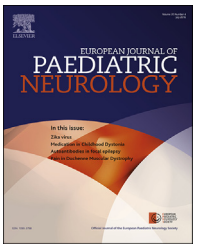

Review article

Principles and approaches to the treatment of immune-mediated movement disorders

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A B S T R A C T

Immune mediated movement disorders include movement disorders in the context of autoimmune encephalitis such as anti-NMDAR encephalitis, post-infectious autoimmune movement disorders such as Sydenham chorea, paraneoplastic autoimmune movement disorders such as opsoclonus myoclonus ataxia syndrome, and infection triggered conditions such as paediatric acute neuropsychiatric syndrome. This review focuses on the approach to treatment of immune mediated movement disorders, which requires an understanding of the immunopathogenesis, whether the disease is destructive or 'altering', and the natural history of disease. Factors that can influence outcome include the severity of disease, the delay before starting therapy, use of multimodal therapy and whether the course is monophasic or relapsing. Although the four main conditions listed above have different pathophysiological processes, there are general themes that broadly apply including: early diagnosis and treatment is better, minimise the severity of disease, escalate treatment if the patient is not responding to initial treatments, and minimise relapse.

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1. Introduction

Neuroimmunological conditions offer an opportunity to change the natural history of disease by using treatments that suppress or modify the inflammatory process affecting the brain. This review aims to reflect upon the current understanding of immune-mediated brain disorders, which have movement problems as a major feature. In a study of acute onset movement disorders in 52 sequential paediatric patients presenting to a single centre, 22 of these 52 patients had an immune-mediated aetiology[1] and a further study on a cohort of encephalitis from the same institution highlighted that autoimmune etiologies were more likely to be associated with movement disorders.[2] This review will describe in brief the clinical syndromes that have been proposed to be 'autoimmune' or immune mediated, with a specific focus on the natural history and the risk of relapse. We review the evidence that neuroinflammation has negative effects on the brain, and that severity and duration of the inflammatory burden often correlates with worse outcomes. Further we discuss the agents used to treat autoimmune and autoinflammatory disorders, and the principles that have evolved in their treatment. Finally we will discuss major questions that exist, and future priorities. After briefly discussing the main syndromes, the review is written in a way that generates general themes about treatment and improving outcomes.

2. Diseases and suspected immunopathogenesis

2.1. *Anti-NMDAR encephalitis*

Anti-NMDAR encephalitis is the prototypic autoimmune encephalitis, with typical clinical features of dyskinesias, agitation, psychosis, aphasia plus other findings[3] (Table 1). Anti-NMDAR encephalitis typically affects previously well individuals, appears to be more common in certain ethnic populations (non-white),[4] and more commonly affects children and young adults. Anti-NMDAR encephalitis is often paraneoplastic in young adult females (associated with ovarian teratomas), but typically non-paraneoplastic in pre-adolescent children.[5] Diagnosis requires presence of CSF or serum NMDAR antibody, with CSF antibody considered to be more specific, and potentially more sensitive. There is clear evidence of NMDAR antibody pathogenicity from *in vitro* and animal models,[11,12] although cytokine and chemokine studies suggest a more complex immune activation.[13,14] New clinical criteria developed by Graus et al.[15] proposed that a clinical diagnosis of probable anti-NMDAR encephalitis can be made when 4 of 6 clinical features are fulfilled along with exclusion of other disorders and either an abnormal electroencephalogram or CSF with pleocytosis or oligoclonal bands. The applicability of these criteria was recently examined in a retrospective cohort of children.[16] The sensitivity of the criteria was 90% and the specificity was 96%, with a median time of 2 weeks from symptom onset to fulfil criteria and very few patients not fulfilling criteria over the period of review.

2.2. *Other autoimmune encephalitis syndromes with movement disorders*

Other autoimmune encephalitis syndromes where movement disorders are dominant features include:

Basal ganglia encephalitis (BGE) is a clinico-radiological syndrome with typical post-infectious dystonia-parkinsonism and associated behavioural change, plus selective restricted inflammatory changes of the basal ganglia. BGE has been associated with autoantibodies against dopamine 2 receptor in some patients.[17]

Stiff person syndrome and related disorders (SPSD)[18] are acquired autoimmune encephalitic syndromes that can be associated with glycine receptor antibodies,[19] anti-DPPX antibodies[20] or other autoantibodies thought to involve inhibitory neurotransmission. Other than encephalopathy, patients have rigidity and stimulus sensitive myoclonus. Antibodies to intracellular GAD can be noted in some cases, serving as a biomarker but not explaining pathogenicity.

There is some evidence that the antibodies associated with these rare syndromes have pathogenic potential, although the literature is significantly smaller than that of NMDAR antibody.

2.3. *Sydenham chorea*

Sydenham chorea remains the prototypic classic post-infectious autoimmune movement disorder, and remains one of the most common causes of acute chorea worldwide. The prevailing hypothesis is that *Streptococcus pyogenes*

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