EDITORIAL

Insights into Autoimmune Movement Disorders in Children: Echoes of the 14th Congress of the Portuguese Neuropaediatrics Society

Perspectivas sobre Doenças do Movimento Autoimunes em Crianças: Ecos do 14º Congresso da Sociedade Portuguesa de Neuropediatria

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Last February, the city of Porto hosted the 14th Congress of the Portuguese Neuropaediatrics Society, which was focused on movement disorders in children. One of the most participated sessions was dedicated to autoimmune movement disorders, particularly to their clinical and therapeutic peculiarities. The spectrum of autoimmune movement disorders in children consists of encephalitic syndromes like anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, post infectious syndromes such as Sydenham's chorea (SC), movement disorders accompanying systemic autoimmune disorders like systemic lupus erythematosus (SLE) and infection-triggered movement disorders with a putative immune mediated basis, such as paediatric acute neuropsychiatric syndrome (PANS).

Since the description of anti-NMDAR antibodies with an evolving, multi- symptom encephalitis syndrome in 2007,[1] our understanding of this specific disorder has grown so that we now understand it as disorder of mainly children and young adults. Movement disorders and seizures seem to be more common presenting features in children, whereas psychiatric features are commoner at presentation in adults.

The clinical phenomenology of movement disorders in anti-NMDAR encephalitis is complex, consisting of a mixture of perseverative behaviour, stereotypies and other hyperkinetic movements and sometimes hypokinetic movements in adolescents, young adults or later stage of the disease. Recognition of this phenomenology has been instrumental not only in the diagnosis of this disorder in many cases, but also the recognition of herpes simplex encephalitis triggering autoimmune encephalitis in children.[2] Even though several disorders have biomarker associations (**Table 1**), these may not always be accessible in all settings or the turnaround times may be long. The importance of clinical phenomenology, along with supporting initial investigations has been recognised leading to the proposal of diagnostic criteria for various autoimmune encephalitis syndromes,[3] which was validated on a retrospective paediatric cohort showing high sensitivity and specificity for anti-NMDAR encephalitis.[4] Some other clinical syndromes can point towards particular antibody or disease associations. Pure chorea with mood lability, with or without the full accompaniment of other features of acute rheumatic fever points towards SC and less commonly can be due to SLE or as a part of anti-NMDAR or autoimmune basal ganglia encephalitis (BGE). SC remains the most common cause of acute onset of chorea in many countries and second after cerebrovascular incidents in other countries. Alternative clinical phenomenology such as myoclonus or rigidity may point towards other syndromes (**Table 1**).

Antibodies to the NR1 subunit of the NMDA receptors fulfil the now accepted cell surface paradigm in autoimmune neurological disorders and these can be a valuable diagnostic

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Table 1. Autoimmune movement disorders presented by syndrome, movement disorder, other features and diagnostic features.

Group	Syndrome	Movement disorder	Other features	Diagnostic features
Encephalitis syndromes	NMDAR antibody encephalitis	Stereotypical hyperkinetic movements, perseverative movements, chorea, dystonia, rigidity	Encephalopathy, agitation and psychosis, aphasia, seizures, dysautonomia, sleep dysregulation	CSF and serum anti-NMDAR antibodies to the NR1 subunit MRI normal in 70% of cases EEG changes are non-specific, but an extreme delta brush pattern or extreme spindles can be a clue
	Autoimmune basal ganglia encephalitis	Dystonia, akinesia	Emotional disorders	MRI basal ganglia T2W hyperintensities, serum anti-D2R antibodies
	Stiff-person spectrum disorder	Myoclonus, rigidity, hyperekplexia PERM	Encephalopathy, seizures	Anti-GlyR antibodies (can have limbic T2W hyperintensities on MRI) Anti-DPPX antibodies (recent weight loss and diarrhoea are a clue) Rare associations: Anti-amphiphysin Anti-LGI1 Anti-GABA A Anti-GABA B Anti-GAD65 antibodies in high titres
Post infectious syndromes	Sydenham chorea	Chorea	Emotional disorder	Recent streptococcal infection, rheumatic carditis
	Opsoclonus-myoclonus-ataxia	Opsoclonus, myoclonus, ataxia		Post infectious cases have MRI changes in the brainstem or cerebellum Rare antibody associations: Anti-GQ1B Anti-GABA-A Anti-DPPX Anti-Glutamate receptor ∂2 Anti-Hu Anti-GAD65
Paraneoplastic syndromes	Opsoclonus-myoclonus-ataxia	Opsoclonus, myoclonus, ataxia	Sleep disturbance, irritability	Clinical syndrome, neural crest tumour
	Anti-NMDAR encephalitis	#as above	#as above	Ovarian teratoma in adolescent females
Infection triggered syndromes	Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS) and PANS	Infection associated relapsing-remitting tics	Emotional lability, obsessive-compulsive disorder	Clinical syndrome
Movement disorders associated with systemic autoimmune disease	Neuropsychiatric SLE	Chorea, parkinsonism	Emotional disorder, psychosis, cognitive deficits, seizures	Lupus autoantibodies Anti-phospholipid antibodies
	Anti-phospholipid syndrome	Chorea	Emotional disorder, psychosis, cognitive deficits, seizures	Anti-phospholipid antibodies
	Hashimoto encephalopathy	Chorea, dystonia, ataxia	Encephalopathy, psychiatric features, seizures	Anti-thyroid antibodies, likely cell surface antibodies (NMDAR antibodies)
	Coeliac disease	Ataxia, chorea, other	Seizures, cognitive, psychiatric features	Coeliac autoantibodies Anti-TTG antibodies, intracranial calcifications

Abbreviations: CSF=cerebrospinal fluid, D2R=dopamine receptor D2, DPPX=dipeptidyl-peptidase-like protein 6, EEG=electroencephalogram, GlyR=glycine receptor, GABA=gamma amino butyric acid, GAD=glutamic acid decarboxylase, GQ1B=ganglioside Q1B, LGI1=leucine-rich glioma inactivated 1, MRI=magnetic resonance imaging, NMDAR=N-methyl-D-aspartate receptor, PANS=paediatric acute neuropsychiatric syndrome, PERM=progressive encephalomyelitis with rigidity and myoclonus, SLE=systemic lupus erythematosus, TTG=tissue transglutaminase.

biomarker of disease.[3,5] Molecules like anti-glutamic acid decarboxylase (GAD) antibodies and many paraneoplastic antibodies bind to intracellular nuclear antigens, such as anti-Hu and anti-Yo. These antibodies that bind to denatured intracellular antigens are useful biomarkers of a paraneoplastic or autoimmune process, but are not considered to be strictly pathogenic and do not induce disease in animal models. In terms of diagnostic use, the use of validated assays that pick-up disease-specific antibodies is important, as is choice of the correct samples (**Table 1**). Other investigation modalities can help provide evidence for diagnosis, such as ancillary blood or cerebrospinal fluid (CSF) biomarkers, electroencephalogram (EEG) changes and presence or absence of magnetic resonance imaging (MRI) abnormalities. Neuroimaging is often normal or non-specific in the majority of children with autoimmune movement disorders syndromes (**Table 1**), but can sometimes point towards specific disorders such as BGE or anti-GABA A (Gamma-Aminobutyric Acid-A) receptor encephalitis, where multifocal or diffuse cortical and subcortical T2 weighted hyperintensities are reported.[5]

The recognition of autoimmune movement disorders is important, as these are treatable conditions where outcomes can be modified significantly by timely use of immune therapies. Nevertheless, despite the many advances that have been made in understanding the pathophysiology of these conditions, the therapeutic approach is somewhat simplistic and not targeted.[6] Since these diseases are characterized by the existence of active neuroinflammation, the use of systemic corticotherapy is perfectly justified. These drugs have broad anti-inflammatory properties and exert effects on the permeability of the blood-brain-barrier, contributing to the reduction of oedema. Intravenous methylprednisolone is the most used drug, but oral prednisolone, dexamethasone and also adrenocorticotrophic hormone (ACTH) may be considered, in specific situations. A very broad mechanism of action is also recognized to intravenous immunoglobulin (IVIg), which can contribute to the removal of pathogenic antibodies from the bloodstream, as well as other molecules and immune active constituents. Although more invasive, plasma exchange uses the same principles, offering the opportunity to remove, by physical means, those same pathogenic molecules.[6,7]

The remission of this type of disease is not achieved immediately, so the maintenance of immunosuppressive therapy over time can be an issue, particularly if we consider the long-term adverse effects of corticosteroids in children. The concept of steroid-sparing immune suppression gains, thus, prominence, and there are some drugs with the potential to take on this role. Rituximab, a monoclonal antibody that depletes CD20-positive cells from the blood, is one of the most frequently used. By eliminating antibody-producing cells from circulation, its effects have also an impact on the activity of T and natural killer cells, so the therapeutic benefit can be broader than initially considered.[8] Cyclophosphamide is an antineoplastic agent and a potent immunosuppressant that can be used for the same purpose as rituximab. Both drugs have a relatively rapid onset effect, so the induction of a state of remission can be an advantage associated with their use. Nevertheless, maintaining this same remission can be a issue in children, given that the adverse effects associated with these drugs can have profound implications, at an early stage of life. Therefore, as a maintenance strategy, drugs such as mycophenolate mofetil, methotrexate and azathioprine may be used.[6] Even so, it is important to consider that there are refractory and complex cases, which can thus be more difficult to control, in clinical terms. In line with the knowledge that has been acquired from other medical areas, therapeutic targets have been identified that could motivate a more specific prescription, in the future. It is possible that drugs such as interleukin-6 antagonists, tumour necrosis factor-alpha antagonists, or Janus kinase blockers may become an option for treating children affected by immune-mediated movement disorders.[6]

In addition to immunotherapy, there may be a need to consider some specific interventions, depending on the precise diagnosis to be made. In paraneoplastic syndromes, the removal of the underlying tumour may be relevant for treatment success and, in PANS, some antibiotics (such as azithromycin) have been reported to have beneficial implications in the control of some features of the clinical syndrome.[9] Moreover, the myriad of clinical manifestations that may be associated with the diagnosis of an immune-mediated movement disorder may justify

the use of several groups of drugs, only for symptomatic control. Benzodiazepines, L-dopa, antipsychotics, antiepileptic drugs, antidepressants and analgesics are just some of the pharmacological classes that could be mentioned in this context.[6]

Scientific knowledge about immune-mediated diseases, even in groups as specific as children, is substantially growing. This naturally puts the burden of continuous updating on the clinician, but it is also a very challenging stimulus. We live in a difficult time for congresses and face-to-face meetings. But science brings us closer and its universal language made this article possible, a reflex of a past medical congress, in an effort shared between Portugal and Australia. ■

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