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Tremor and Other Hyperkinetic Movements

In Response to:
Helm CE, Blackwood RA. Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS): Experience at a tertiary referral center. Tremor Other Hyperkinet Mov. 2015; 5. doi: 10.7916/D8348JCX

Editorials

PANDAS: The Need to Use Definitive Diagnostic Criteria

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"The truth is rarely pure and never simple."

Oscar Wilde (1854–1900), The Importance of Being Earnest, 1895, Act I

The entity pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) was initially proposed in 1998.[1] The formal diagnosis required that the affected individual meet five specific criteria: prepubertal onset, obsessive compulsive disorder (OCD) and/or a tic disorder, the dramatic sudden explosive onset of symptoms, a relapsing and remitting course of symptoms that are temporally associated with Group A beta-hemolytic streptococcal (GABHS) infection, and the presence of other neuropsychiatric abnormalities (hyperactivity, emotional lability, anxiety, or piano-playing choreiform movements). Since that original report, the PANDAS hypothesis has remained controversial on the basis of both clinical grounds and failure to confirm a definitive immune process.

In their report,[2] Helm and Blackwood describe their experience with PANDAS from the perspective of a pediatric division of infectious disease. The authors' conclusion, that the majority of patients (76%) referred with a pre-diagnosis of PANDAS did not fulfill diagnostic criteria, confirms that described in other reports.[3] Hence, one logical outcome, as stated in their manuscript, is the need to improve the "current deficit in physician knowledge" about this diagnosis. All are in agreement that the misdiagnosis of PANDAS has the potential to lead to the unnecessary use of various treatments (antibiotics, Intravenous immunoglobulin (IVIG), and plasmapheresis) and needs to be rectified.

That said, what about the five children that were said to fulfill the criteria for PANDAS? An important question is whether there is sufficient data available to support the diagnosis in these individuals. Granted, the authors were not the primary caregivers, but in any controversial disorder, it is essential that all core information be available. In four of the five described PANDAS cases, the explosive onset included tics, but were they pre-existing symptoms? Some have suggested that the presence of prior tics should exclude the diagnosis of PANDAS. Others, recognizing the often variable nature of tics, have excluded them as a major diagnostic category in the broadened PANS (pediatric acute-onset neuropsychiatric syndrome) criteria.[4] Similar questions can be raised about the two reported children with Attention Deficit Hyperactivity Disorder (ADHD). In a multicenter longitudinal study of children with PANDAS, tic/OCD exacerbations were not associated with an increase in the severity of psychiatric comorbidity, including motoric hyperactivity, emotional lability, intense anxiety, cognitive deficits, or oppositional behaviors.[5]

Moving to criterion 5 (other "neuropsychiatric abnormalities"), Helm and Blackwood do not provide information about the presence or absence of piano-playing choreiform movements. In the original published PANDAS cohort, no individual had "overt chorea," but all

except one had choreiform movements and 50% had "marked choreiform" movements.[1] Admittedly, the absence of choreiform movements does not negate the possibility of PANDAS, recognizing that two differing subgroups of children fulfilling the original proposed criteria for PANDAS have been reported: 1) the original cohort, displaying choreiform piano-playing movements (PANDAS-choreiform), and 2) a PANDAS-chronic tics and OCD cohort that includes children with at least two prior acute fulminant episodes of tics or OCD in a temporal association with a GABHS infection, but lacking piano-playing movements.[6] This distinction may actually be very significant, recognizing that the PANDAS-choreiform cohort has biomarkers very similar to Sydenham's chorea (elevated anti-dopamine 1 receptor (D1R) and anti-dopamine 2 receptor (D2R) immunoglobulin (Ig)G levels and possibly elevated anti-lysoganglioside-GM1), whereas the PANDAS-chronic tics and OCD group has normal levels of antibodies to tubulin and D2R, and control group-dependent alterations of anti-D1R and lysoganglioside-GM1, i.e. unchanged compared to a large (n=70) multicenter control but differing from a smaller (n=15) previously published control group.[6]

The essential characteristic of PANDAS is the temporal association between the onset and exacerbation of tic or OCD symptoms and a GABHS infection. Is there sufficient information in the 5 Helm and Blackwell case's confirming the recurrence of symptoms within several weeks of a new GABHS infection? In four out of five, there was "at least one documented elevated anti-streptococcal titer," but what levels were considered elevated? This is important, since levels of these antibodies are normally higher among school age children than adults.[7] Additionally, as noted by the authors, 56% of those misdiagnosed as PANDAS also had elevated anti-streptococcal titers. Prior investigators have emphasized that the use of single-point-in-time assessments of anti-streptococcal antibodies is unacceptable and that a new infection should be confirmed by a significant rise (0.2 log) in anti-streptolysin O (ASO) and/or anti-DNAse B titers.[8] Further, did any individuals with repeat positive GABHS throat cultures have streptococcal typing to confirm they were not carriers? As should be obvious by this time, diagnosing a new streptococcal infection may not be straightforward.

Helm and Blackwood also raise the suggestion that a documented response to antimicrobial treatment (present in three out of five patients with PANDAS) might be an additional diagnostic clue. Perhaps this could have been supported by providing comparable data for children in the misdiagnosed group. Although the point is interesting, it is physiologically unclear how an acute clinical improvement can occur following the administration of an antibiotic in a disorder proposed to be secondary to elevated anti-neuronal antibodies.

In conclusion, this report raises a number of interesting issues and serves to further our knowledge about a controversial topic. It also shows that full knowledge about the details of the utilized diagnostic criteria and the results of obtained clinical investigations are required in order to further advance our understanding of this entity.

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