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REVIEW

Immune Pathogenesis of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Group A β-Hemolytic Streptococcal Infections (PANDAS)

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ABSTRACT

Pediatric autoimmune neuropsychiatric disorders associated with group A β-hemolytic streptococcal infections or PANDAS, is a well characterized autoimmune disorder that affects the central nervous system producing childhood-onset obsessive-compulsive disorder and tic disorders, and a spectrum of psychiatric comorbidity accompanying exacerbations. Recent advances in the understanding of the postulated pathophysiology had led to effective interventions with immune modulatory therapy. This article reviews the current understanding, diagnosis and management of PANDAS.

Key words: PANDAS; IVIg; Therapeutics

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INTRODUCTION

From 1989 to 1992, Swedo and investigators in the Children Psychiatry Branch of the National Institute of Mental Health (NIMH) in Bethesda, Maryland[1-3] were characterizing the long-term course of children and adolescents with obsessive-compulsive disorders revealing the episodic course of a subgroup characterized by dramatic and acute symptom exacerbations interspersed with long periods of relative symptom quiescence noting that in some, the exacerbations were associated with group A β-hemolytic streptococcal (GABHS) infections. In 1998, Swedo and colleagues[4] described the clinical neuropsychiatric clinical and laboratory features 50 children all of whom met the criteria of prepubertal onset of obsessive compulsive disorder (OCD) or tic disorder, episodic course, and association with GABHS infections and neurological abnormalities. Children with known rheumatic fever, or overt chorea by history and physical examination leading to suspicion of Syndenham chorea, also a known variant of rheumatic fever requiring antibiotic prophylaxis against GABHS, were disqualified from participation. Their studies showed a striking association between the abrupt onset of OCD, tics and comorbid psychiatric symptoms, and a documented GABHS infection and increase in anti-streptococcal titers. Like rheumatic fever, the authors[4] postulated that the pathogenesis of PANDAS was due to exposure of GABHS infection in a genetically and developmentally susceptible host with a resulting central nervous system (CNS) extrapyramidal immune response.

Despite past controversy regarding PANDAS as concerns conflicting epidemiologic studies regarding the risk for behavioral and neuropsychiatric symptoms in affected children[5], the validity of the clinical criteria for PANDAS[6], criticisms of the measurement of antineuronal antibodies and other biomarkers to identify affected patients[7], there has been recent extraordinary progress in the understanding of PANDAS since their report more than fifteen years ago[4], particularly in the role of immune modulatory therapy employing plasma exchange (PE) and intravenous immune globulin (IVIg).

AUTOANTIBODIES

Elevated anti-streptolysin (ASO) antibodies distinguished cases versus non-cases respectively in 59% and 37% (p=0.03) of cases providing evidence of antecedent streptococcal infection, however they are not diagnostic of PANDAS since other factors may mitigate their appearance. Whereas a limited prior exposure to GABHS, hyperlipidemia, treatment with antibiotics and the host ability to mount a strong immune response may lead to false negative titers in a given child[8], sustained high titers result from reinfection, slower rates of the decline in the antibody rise and a more potent immune response may be responsible for inordinately elevated titers providing evidence of repeated exposure[9-11]. A β-cell alloantigen identified by monoclonal antibodies as D8/D17[12] which attaches to the surface of B cells as a susceptibility factor for rheumatic fever, was found in 85% of patients with PANDAS, 89% of those with Syndenham chorea (SC) but in only 17% of controls[13]. The GNcNAc epitope expressed in SC monoclonal antibodies (mAb) is capable of provoking a strong humoral response during active streptococcal infection and in post-infectious sequela[14,15] presumably due to terminal O-linked GLcNAc residues bearing structural similarity to many host glycoconjugates. Experimental animals immunized with GlcNAc mAb leads to T-cell dependent antibody responses and persistently high titers to streptococcal carbohydrate[16]. Lysoganglioside GM1-specific antibodies present in the cerebrospinal fluid (CSF) of patients with active disease blocks SC chorea mAb in acute sera that bind to human caudate-putamen tissue suggested the presence of innate neuronal cell surface determinate capable of altering neuronal physiological homeostasis in SC patients. Anti-ganglioside antibodies affect signal transduction pathways in neuroblastoma cells[17,18] and trigger calcium/calmodulin-dependent protein (CaM) kinase II activation in the catecholamine-secreting neuroblastoma cell line SK-N-Sh[19]. Active but not convalescent PANDA serum IgG reacts with GlcNAc epitope of the streptococcal GAC and lysoganglioside GM1 as in SC, and induces CaM kinase II activity in SK-N-SH human neuroblastoma cells with significant increases in CaM kinase II activity[14] suggesting a role for antibody-mediated neuronal cell signaling in the immunopathogenesis of PANDAS.

IMMUNE MODULATORY THERAPY

The most compelling support for an immune-mediated pathogenesis in PANDAS derives from the results of randomized, placebo-controlled trials (RCT) of IVIg and PE. Both immune modulatory therapies have been associated with significant improvement in neuropsychiatric symptoms severity leading to 45% and 58% reductions respectively, with sustained improvements at one year followup[20]. Among 29 children with OCD and tic disorders randomly assigned five PE over two weeks (10 patients), 1 gram per kilogram daily for two days of IVIg (nine patients), or saline solution placebo (10 patients)[21], there were mean improvement of 45% and 58% respectively following IVIG and PE OCD symptoms on the children's Yale-Brown obsessive compulsive scale score; and a 49% mean improvement in the Tourette syndrome rating scale following PE. These gains were maintained at 1 year, with 14 (82%) of 17 children "much" or "very much" improved over baseline including 7/8 treated by PE and 7/9 children treated by IVIg therapy. A multi-site double-blind placebo-controlled, parallel assignment treatment trial of the efficacy of 2 grams per kilogram of Gamunex over 2 days versus normal saline placebo commenced in PANDAS begun in 2011 at the NIMH (ClinicalTrials.gov identifier NCT01281969) finished recruiting subjects ages 4 to 12 years, and is due to reach primary completion by 2016. In addition to outcome measures of improvement in obsessions, compulsions, and other neuropsychiatric symptoms, the investigators will by exploring the impact of treatment on reduction of titers of cross-reactive antibodies, resolution of basal ganglia inflammation as measured by pre- and post-changes in magnetic resonance imaging (MRI) volumetric scans and inflammatory sequences, and normalization of selected serum and CSF cytokines.

CONFLICT OF INTERESTS

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