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Passive transfer of streptococcus-induced antibodies reproduces behavioral disturbances in a mouse model of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection

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Abstract

Streptococcal infections can induce obsessive-compulsive and tic disorders. In children, this syndrome, frequently associated with disturbances in attention, learning and mood, has been designated pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). Autoantibodies recognizing central nervous system (CNS) epitopes are found in sera of most PANDAS subjects, but may not be unique to this neuropsychiatric subset. In support of a humoral immune mechanism, clinical improvement often follows plasmapheresis or intravenous immunoglobulin. We recently described a PANDAS mouse model wherein repetitive behaviors correlate with peripheral anti-CNS antibodies and immune deposits in brain following streptococcal immunization. These antibodies are directed against group A β-hemolytic streptococcus matrix (M) protein and cross-react with molecular targets complement C4 protein and α-2-macroglobulin in brain. Here we show additional deficits in motor coordination, learning/memory and social interaction in PANDAS mice, replicating more complex aspects of human disease. Furthermore, we demonstrate for the first time that humoral immunity is necessary and sufficient to induce the syndrome through experiments wherein naive mice are transfused with immunoglobulin G (IgG) from PANDAS mice. Depletion of IgG from donor sera abrogates behavior changes. These functional disturbances link to the autoimmunity-related IgG1 subclass but are not attributable to differences in cytokine profiles. The mode of disrupting blood–brain barrier integrity differentially affects the ultimate CNS distribution of these antibodies and is shown to be an additional important determinant of neuropsychiatric outcomes. This work provides insights into PANDAS pathogenesis and may lead to new strategies for identification and treatment of children at risk for autoimmune brain disorders.

Keywords:

autoantibodies; passive transfer; pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection; obsessive-compulsive disorder; Tourette syndrome; autism