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Antibody-mediated neuronal cell signaling in behavior and movement disorders

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Abstract

Behavioral and movement disorders may have antibody responses where mimicry and signal transduction may lead to neuropsychiatric abnormalities. In our study, antibodies in pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS) reacted with the neuronal cell surface and caudate–putamen and induced calcium–calmodulin dependent protein (CaM) kinase II activity in neuronal cells. Depletion of serum IgG abrogated CaM kinase II cell signaling and reactivity of CSF was blocked by streptococcal antigen *N*-acetyl-beta-D-glucosamine (GlcNAc). Antibodies against GlcNAc in PANDAS sera were inhibited by lysoganglioside G_{M1}. Results suggest that antibodies from an infection may signal neuronal cells in some behavioral and movement disorders.

Keywords: Streptococci; Chorea; Autoimmunity; Behavior

1. Introduction

Recently, there has been a growing interest in a group of behavior and movement disorders known as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococci (PANDAS). PANDAS is a subset of childhood obsessive–compulsive disorder (OCD) and tic disorders where onset and exacerbation of neuropsychiatric symptoms is preceded by group A streptococcal infection (Swedo et al., 1998b). PANDAS shares common neuropsychiatric symptoms as well as the same proposed infectious etiology with the more well known group A streptococcal sequelae Sydenham's chorea (SC) (Garvey et al., 1998; Swedo, 1994).

SC is the principal neurological manifestation of acute rheumatic fever (ARF) which develops in 10–30% of cases as a result of group A streptococcal pharyngitis (Taranta and Stollerman, 1956). Although SC often occurs in combination with other manifestations of ARF, such as carditis or arthritis, isolated SC has been observed up to 6 months after pharyngitis (Stollerman, 2001; Taranta, 1959). SC is localized to the central nervous system (CNS) and is predominantly characterized by involuntary movements leading to loss of coordination and speech impairment (Marques-Dias et al., 1997). Patients exhibit an array of psychiatric and psychological abnormalities that often predate the onset of the movement disorder by 2 to 4 weeks (Marques-Dias et al., 1997; Swedo et al., 1989). As many as 70% of SC patients develop obsessive–compulsive symptoms which are indistinguishable from OCD (Swedo, 1994; Swedo et al., 1998b). Choreic episodes typically resolve within weeks of onset, however, neuropsychiatric symptoms may persist after resolution of the movement disorder (Asbahr et al., 1998, 1999).

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SC is postulated to result from a cross-reactive, anti-streptococcal antibody response directed against antigens of the basal ganglia, the area of the brain responsible for motor function, suggesting that neurological dysfunction in SC is immunologically mediated (Cunningham, 2000; Swedo et al., 1993). Sera from SC patients reacted with neurons of the basal ganglia and anti-neuronal antibodies correlated with both severity and duration of choreic episodes (Husby et al., 1976). Anti-brain antibodies were absorbed with antigens from rheumatogenic streptococcal strains, indicating that bacterial cell wall components may induce cross-reactive, neuronal antibodies (Bronze and Dale, 1993; Husby et al., 1976).

Volumetric MRI studies have demonstrated enlargement of the basal ganglia in both SC and PANDAS (Giedd et al., 1995, 1996) and immunomodulatory therapies such as plasmapheresis and intravenous immunoglobulin (IVIG) have been effective at ameliorating symptoms associated with SC and PANDAS (Garvey et al., 2005; Perlmutter et al., 1999). Antibodies to basal ganglia have been demonstrated in both SC and PANDAS raising the possibility that development of clinical manifestations in SC and PANDAS are mediated through a similar antibody-mediated mechanism of pathogenesis. However, little is known about the role of streptococcal infection or antibodies in PANDAS (Kurlan and Kaplan, 2004).

Our previous work demonstrated that antibodies from SC recognized brain-derived lysoganglioside G_{M1} and GlcNAc, an epitope of group A streptococcal carbohydrate. SC antibodies reacted with the neuronal cell surface and induced high levels of CaM kinase II activity in human neuroblastoma cells (Kirvan et al., 2003). We tested the hypothesis that antibodies in PANDAS may be associated with a similar antibody-mediated neuronal cell signaling mechanism. The new work reported herein supports the hypothesis that the majority of PANDAS sera contain antibodies which react with lysoganglioside G_{M1} and induce CaM kinase II activation in neuronal cells. Our study is important because it demonstrates antibodies present in movement and behavior disorders which may induce antibody-mediated cell signaling mechanisms in disease.

2. Materials and methods

2.1. Patients samples

PANDAS was identified by clinical criteria of Swedo, et. al., including elevated anti-streptolysin O or DNase B titers

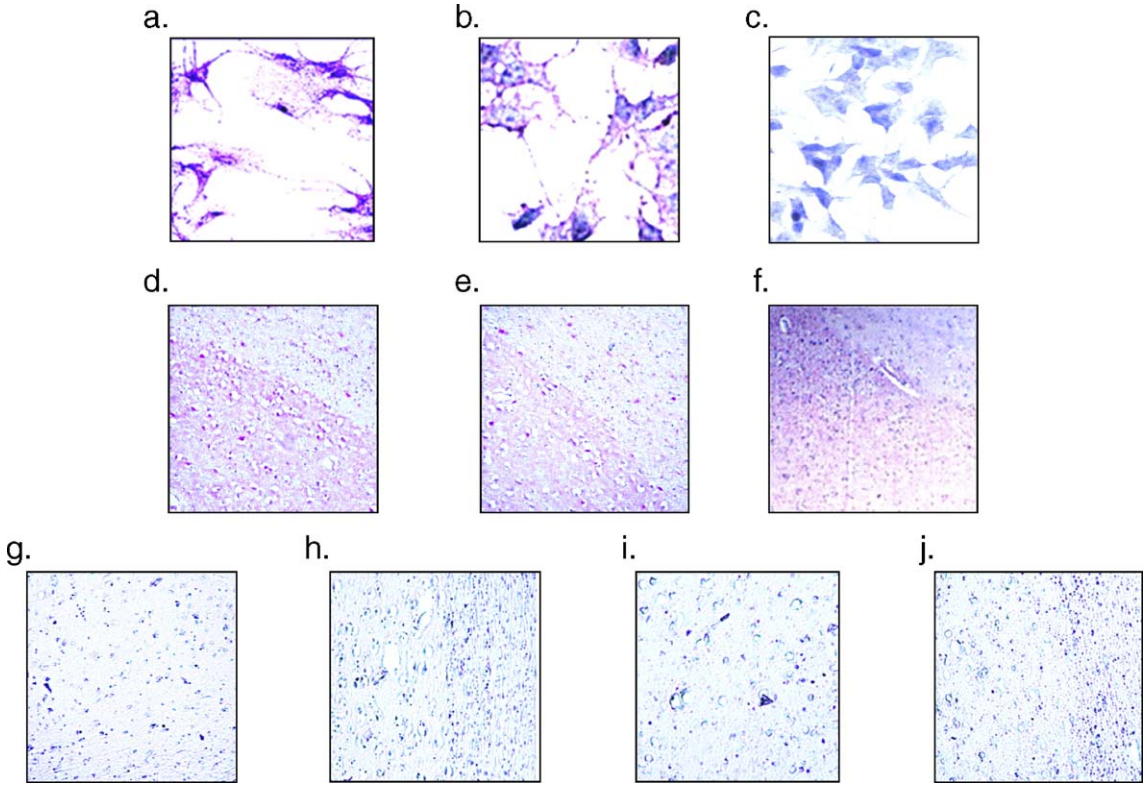

Fig. 1. Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS) antibody recognized neuronal cell surface and human caudate–putamen. (a) Acute PANDAS serum labeled human neuronal cell surface similar to acute Sydenham's chorea (SC) serum (b) Pooled normal human sera showed no reactivity (c). For cell surface immunohistochemistry, a single Sydenham's chorea serum and PANDAS serum samples, and 6 pooled age-matched controls are shown. However, all seven Sydenham's chorea and 16 PANDAS sera demonstrated neuroblastoma cell surface staining (data not shown). PANDAS (d–e) and chorea (f) cerebrospinal fluid (CSF) IgG reacted with human caudate–putamen tissue in a differential staining pattern. Four non-PANDAS control CSF (g–j) showed no binding of caudate–putamen tissue. For CSF staining of human basal ganglia tissue, one Sydenham's chorea, two PANDAS, and four non-PANDAS CSF samples were tested separately.