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Identification of pyruvate kinase as an antigen associated with Tourette syndrome

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Abstract

Immune responses to β-hemolytic streptococcal infections are hypothesized to trigger tic disorders and early-onset obsessive–compulsive disorder (OCD) in some pediatric populations. Here we identify the M1 isoform of the glycolytic enzyme, pyruvate kinase (PK) as an autoimmune target in Tourette syndrome and associated disorders. Antibodies to PK reacted strongly with surface antigens of infectious strains of streptococcus, and antibodies to streptococcal M proteins reacted with PK. Moreover, immunoreactivity to PK in patients with exacerbated symptoms who had recently acquired a streptococcal infection was 7-fold higher compared to patients with exacerbated symptoms and no evidence of a streptococcal infection. These data suggest that PK can function as an autoimmune target and that this immunoreactivity may be associated with Tourette syndrome, OCD, and associated disorders.
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1. Introduction

Tic disorders, obsessive–compulsive disorder (OCD), and related conditions affect as many as 3% of children and adolescents (Costello et al., 1996; Flament et al., 1988; Kadesjo and Gillberg, 2000; Leckman, 2002; Mason et al., 1998; Valleni-Basile et al., 1994). The factors that contribute to the pathogenesis of these disorders are poorly defined. The hypothesis that infections can modulate the clinical appearance of tic disorders dates from the 1800s (Kushner, 1999). The past decade has seen the reemergence of the hypothesis that post-infectious immune mechanisms account for at least some cases of Tourette syndrome (TS) and OCD.

It is well known that group A β-hemolytic streptococci (GABHS) can trigger immune-mediated diseases (Bisno, 2000; Carapetis et al., 1999; Stollerman, 1997). Rheumatic fever (RF), one of the most well recognized examples of a delayed non-suppurative complication of GABHS infection, usually occurs a few weeks to several months after streptococcal infection among susceptible persons. RF typically involves the heart, joints, and central nervous system. The central nervous system manifestations usually take the form of chorea (Sydenham's chorea). However, some patients with RF also display motor or phonic tics, obsessive–compulsive (OC) symptoms, or features suggesting attention-deficit/hyperactivity disorder (ADHD) (Allen et al., 1995; Mercadante et al., 1997; Swedo et al., 1989). On the basis of these associations, Swedo et al. (1998) proposed that pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) represent a

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distinct clinical entity that includes cases of TS and OCD. This has proved to be a controversial hypothesis (Kurlan and Kaplan, 2004). For example, one study using an administrative regional database of more than 500,000 privately insured individuals linked recent GABHS infections with an increased risk of tic disorders and OCD (Mell et al., 2005). Another study reported that over 90% of TS patients that tested positive for anti-basal ganglia antibodies had serological evidence of a recent streptococcal infection (Church et al., 2003), and two other studies showed that TS patients' sera possessed elevated streptococcal antibody titers (Müller et al., 2001, 2000). However, these results have not been confirmed by other reports (Loiselle et al., 2003; Luo et al., 2004; Morshed et al., 2001; Singer et al., 1998).

It has also been reported that patients with tic disorders and/or OCD have responded positively to antibiotic treatment, antibiotic prophylaxis, and plasma exchange treatment (Mell et al., 2005; Perlmutter et al., 1999; Perrin et al., 2004; Snider et al., 2005). Some children and adults with TS have significantly increased titers of antineural antibodies (Kiessling et al., 1993; Morshed et al., 2001; Singer et al., 1998), and IgG from children with TS bound neurons in the caudate nucleus of human postmortem brains (Singer et al., 1998). A number of proteins of varying size have been identified as possible antigenic target proteins in the sera of tic disorder and early-onset OCD patients. Two studies have identified a protein of 60 kDa as a possible target (Church et al., 2003; Hoekstra et al., 2003), while a third study showed numerous proteins with different molecular weights as contributing to changes in TS antibody repertoires (Wendlandt et al., 2001). Most recently three neuronal glycolytic proteins, pyruvate kinase, aldolase, and enolase have been suggested to be potential autoantigens in a group of patients with post-streptococcal movement and psychiatric disorders (Dale et al., 2006).

Following a series of preliminary studies characterizing the antibodies found in pediatric patients with tic disorders and early-onset OCD, we identified the M1 isoform of the glycolytic enzyme, pyruvate kinase (PK) as a potential target. Anti-PK antibodies reacted with GABHS surface antigens, and antigenic M protein antibodies reacted with PK. These findings suggest that PK may serve as an autoimmune antigen associated with streptococcal infections in patients with TS and associated disorders. To test this hypothesis we screened four sets of patients' sera: (1) symptom exacerbations plus a recently acquired GABHS infection, (2) symptom exacerbations and no GABHS infection, (3) no symptom exacerbations but a recently acquired GABHS infection and (4) no symptom exacerbations and no GABHS infection. Age-matched controls with and without recent GABHS infections were also screened. The results of these studies indicate that GABHS infections in a substantial subset of pediatric patients with a predisposition to tics and OCD symptoms result in the production of antibodies that react with PK.

2. Materials and methods

2.1. Patients

Specimens used in this study were collected from children, aged 7–17 years, with a chronic tic disorder, OCD, or both and healthy children without these disorders who participated in a prospective longitudinal study. A total of 77 children (46 cases and 31 controls) were assessed at baseline and followed prospectively for periods ranging from 4 to 24 months (Leckman et al., 2005; Luo et al., 2004). All patients were followed at the Yale Child Study Center Tic Disorder–Obsessive–Compulsive Disorder Specialty Clinic. Expert clinicians using DSM-IV criteria made all psychiatric diagnoses based on all available information. Exclusion criteria included an intelligence quotient of <75; serious medical illness; major sensory handicaps (e.g., blindness, deafness); major neurologic disease (including a seizure disorder); head trauma resulting in loss of consciousness; current (past 6 months) psychiatric disorder that could interfere with participation, such as major depression; psychosis; and autism or another pervasive developmental disorder. All parents provided written informed consent after the study was described to them in detail. A separate assent form was used to ensure the informed participation of the child and adolescent subjects.

When a family entered the study, information concerning the patient was collected in a two-stage process, as previously described (Findley et al., 2003; Leckman et al., 2005; Lin et al., 2002; Luo et al., 2004). The first stage consisted of the collection of information concerning symptoms associated with TS and OCD according to a self-and-family report (Robertson et al., 1999) based on the tic inventory, ordinal severity scales of the Yale Global Tic Severity Scale (YGTSS) (Leckman et al., 1989), and the symptom checklist and ordinal scales of the Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989; Scahill et al., 1997). The semi-structured interview used to assess and diagnose PANDAS cases was based on that used by the Pediatrics and Developmental Neuropsychiatry Branch of the National Institute of Mental Health Intramural Program (Swedo et al., 1989). In a second stage of assessment, an experienced clinician reviewed these symptom ratings with the child and the parent to ensure their accuracy and validity. Comorbid psychiatric diagnoses were made with all available information, including data collected with the Schedule for Affective Disorders and Schizophrenia for School-Age Children (Kaufman et al., 1997). The Human Investigation Committee at Yale University School of Medicine approved each of these studies, and all parents provided informed consent.

2.2. Ratings of symptom severity

Tic symptom severity was rated with the tic portion of the YGTSS ($YGTSS_{TIC}$). Obsessive–compulsive symptom

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