

CASE REPORT

Infection-Induced Autoimmune Encephalopathy: Treatment with Intravenous Immune Globulin Therapy. A Report of Six Patients

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ABSTRACT

OBJECTIVE: To present illustrative patients with infection-induced autoimmune encephalopathy (IIAE) who manifest symptoms and signs of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) and are successfully treated with an anti-infective and immune modulatory protocol.

METHODS: Six children age 5 to 17 years with the diagnosis of IIAE associated with various infections and comorbid conditions including humoral immunodeficiency and Autism Spectrum Disorder (ASD) are described. Pertinent literature from 1958 to the present is reviewed. Antimicrobial and high dose (1 gram per kilogram total body weight) intravenous immune globulin (IVIg) therapy was administered every 8 weeks according to an established anti-infective and immune modulatory protocol. Informed consent by the parents and legal authorization was obtained in all cases. Neuroradiological testing was not performed in any of the cases.

RESULTS: The combination of antimicrobial medication followed by IVIg in this cohort was well-tolerated leading to improvement in symptoms and signs of IIAE allowing tapering or discontinuation of maintenance medications.

CONCLUSION: IVIg is a safe and beneficial therapy in IIAE,

PANDAS and ASD impacting favorably on underlying humoral immune deficiency and infectious-induced CNS autoimmunity in this small and highly selected cohort. The present findings are awaiting further replication by other investigators and should be further explored relative to the optimal dose and duration of therapy.

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Key words: Infection; Autoimmune; Encephalopathy; Intravenous; Intravenous treatment

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INTRODUCTION

Infection-induced autoimmune encephalopathy (IIAE) is a designation applied to the abrupt onset of a neuropsychiatric disorder after acute infection. Studies at the Children Psychiatry Branch of the National Institute of Mental Health (NIMH) in Bethesda, Maryland reported high rates of OCD and motor tics behaviors in children with group A β -hemolytic streptococcus (GABHS)^[1,2] similar to Sydenham's chorea^[3-5]. Subgroups of children with OCD and tic-onset and preceding GABHS infection not meeting the criteria for Sydenham chorea were also described. A prospective study later confirmed the association of acute GABHS tonsillopharyngitis to neuropsychiatric manifestations of PANDAS that included OCD and motor tic behaviors, with responsiveness to antibiotic therapy of the sentinel episode^[6]. Other affected children with PANDAS in association with non-GABHS infections such as Mycoplasma and Borrelia species, with or without humoral immunodeficiency, defined as a deficiency in all or some classes of serum immunoglobulins, has suggested a broader etiopathogenesis for IIAE.

Children with IIAE experience OCD, motor tics, separation anxiety, regressive behaviors, irritability, rage, sensory sensitivity, deterioration in learning ability, and anorexia. The onset can be so debilitating as to cause near catatonic behaviors while others function marginally at school, later deteriorating for hours on end necessitating full-time care at home. After initial stabilization and improvement with acute and suppressive antimicrobial therapy, reinfection carries the risk of perpetual and precipitous worsening for weeks, months or longer.

The limited benefit of conventional anti-infective treatment in PANDAS prompted investigations into the role of immune modulatory therapy targeting increased titers of pathogenic autoantibodies employing intravenous immune globulin (IVIg) and plasma exchange^[7, 8]. Such treatments were associated with sustained improvement in severe OCD and motor tics respectively in the Yale-Brown Obsessive Compulsive Scale and the Tourette Syndrome Rating Scale scores with non-disabling side effects including nausea, vomiting, headaches, and dizziness. We report six children with IIAE due to PANDAS associated with GABHS and non-GABHS infections, concomitant humoral immune deficiency, and autism. The observed benefited from short courses of immune modulatory therapy leading to periods of unprecedented improvement suggesting an even wider application for IVIg therapy. There is a recent review of the advances in the current understanding, diagnosis and management of PANDAS^[9].

PATIENT REPORTS

PATIENT 1

At age 9 years, a 17-year-old girl was noted to have ritualistic, oppositional, and defiant behaviors refusing to leave the house, go to school, or interact with friends. There were intrusive thoughts, severe mood swings, depression, forgetfulness, hyperactivity and insomnia. She had difficulty concentrating and impoverished reading comprehension. There were tactile and sensory disturbances, urinary frequency, and bilateral severe knee pain. A history of recurrent episodes of GABHS infection, sinusitis and bronchitis confirmed the diagnosis of PANDAS with concomitant laboratory evidence of humoral immunodeficiency and Lyme disease. The patient received intravenous cefotaxime, oral azithromycin, hydroxychloroquine, and doxycycline followed by two courses of high-dose (1.6 grams per kilogram) IVIg over 2 days every 8 weeks. After two months of IVIg therapy there was improvement of neuropsychiatric symptoms. Although well-tolerated, IVIg therapy was associated with heightened occurrence of migraine headaches and fatigue.

PATIENT 2

A 12-year-old boy had a several year history of recurrent pyelonephritis, chronic sinusitis, allergic rhinitis, moderate persistent asthma, and vocal tics. The diagnosis of PANDAS was established with an association of preceding recurrent GABHS infection and there was concomitant humoral immune deficiency. Amoxicillin and clavulanate potassium and anti-asthma medication was followed by two courses of high-dose IVIg treatments over four months. After the second infusion, there was near total resolution of anxiety and vocal tics for four years. When anxiety and vocal tics returned there was an immediate and sustained response to reinstitution of IVIg.

PATIENT 3

A 7-year-old girl was noted to have separation anxiety, clothing

sensitivity, ritualistic hand washing, temper tantrums, visual hallucinations, hoarding behaviors, and aggressive intrusive thoughts. There was hyperactivity in school and urinary frequency with nocturnal enuresis, and joint arthralgia. There was a several year history of recurrent sinusitis, pneumonia and bronchitis and preceding GABHS infection. Laboratory investigation showed GABHS, Lyme disease and humoral immune deficiency. The patient was treated with amoxicillin and clavulanate potassium followed by high-dose IVIg therapy for a total of four courses. The first IVIg infusion was followed by immediate improvement in neuropsychiatric symptoms that was sustained throughout the course of therapy.

PATIENT 4

At 2 years of age this presently 5-year-old boy with ASD developed new-onset sleep disturbance, pica, and separation anxiety. There was a history of recurrent GABHS infection, otitis media, sinusitis, gastroesophageal reflux, hypothyroidism, and Crohn's disease. Humoral immune deficiency was noted on laboratory investigation. In December 2010 the patient was treated with an anti-infective regimen followed by high-dose IVIg therapy for two days each month alternating every 8 weeks for two years. Although well-tolerated, there were a few occasions of heightened agitation, fearful and combative behavior. There was marked improvement in language and social interactions followed by gains in learning and memory retention. Off of IVIg therapy and with sustained benefit in cognition, the patient is able to take a bus to school on his own.

PATIENT 5

Beginning at age 13 years, a 16-year old girl had recurrent GABHS pharyngitis and sinus infections in association with OCD and vocal tics with new headaches and joint pains. She was high functioning and had made academic achievement in high school. The diagnosis of PANDAS was established with concomitant humoral immunodeficiency. She was given amoxicillin and clavulanate potassium followed by two courses of high-dose IVIg treatment over four months after leading to resolution of vocal tics without further GABHS infection after which therapy was discontinued. One year later neuropsychiatric symptoms returned commensurate with a positive Lyme serology and she was treated with amoxicillin and clavulanate potassium and azithromycin followed by further courses of high-dose IVIg therapy with near-complete resolution of OCS and vocal tics. She is now attending college with minimal symptoms.

PATIENT 6

At age 5 years, a 9-year-old boy had a tick attachment with a migratory rash suggesting active Lyme borreliosis and subsequently developed progressive psychosis, paucity of spoken language, and OCD behaviors. There was a history of recurrent GABHS infection. Laboratory studies demonstrated elevated anti-streptolysin O, DNase B titers, and increased Bartonella henselae and Babesia duncani IgM antibody titers by immunofluorescent assay, with concomitant humoral immunodeficiency, without conclusive evidence of Lyme. The diagnosis of IIAE was made and the patient was given oral azithromycin, clindamycin and atovaquone followed by high-dose IVIg. After the first two treatments there was significant and sustained improvement in language and social engagement with reduced OCD and motor tic behaviors.

DISCUSSION

Six children age 5 to 17 years were diagnosed with IIAE and PANDAS, and underlying humoral immunodeficiency, two of whom had preceding or former autistic behaviors. High-dose IVIg therapy given after an anti-infective protocol aimed at treating underlying GABHS infection and other precipitating infectious agents led to observable clinical benefit of PANDAS symptomatology with few side effects suggesting a direct impact on primary humoral immune deficiency and other mechanism related to IIAE. In some instances, neuropsychiatric medications were successfully tapered or discontinued.

The beneficial effects of IVIg on IIAE is attributed to immune modulation and down-regulation of pathogenic host IgG antibodies that target sites in the basal ganglia. Measurable reductions in titers of cross-reactive antibodies, resolution of basal ganglia inflammation as measured by pre- and post-changes in magnetic resonance neuroimaging volumetric scans and inflammatory sequences, and normalization of selected serum and CSF cytokines in responsive patients with PANDAS have likewise been attributed to the objective immune modulatory benefit of IVIg in affected children (ClinicalTrials.gov identifier NCT01281969).

The basis for improved outcome measures of obsessional behaviors associated with PANDAS after IVIg is more speculative due to the speculative neuroanatomic basis of psychiatric behaviors associated with PANDAS. Surgical procedures and deep brain stimulation for the treatment of refractory psychiatric behaviors including OCD have focused on disrupting thalamocortical loops in the region of the ventral anterior capsule and ventral striatum^[10] and nucleus accumbens rostral to the preoptic area of the hypothalamus. Trials of deep brain stimulation targets focusing in these neural networks in refractory tics and OCD in Tourette syndrome that showed benefit in affected patients^[11] suggest that there may be shared regions for the origin of OCD in Tourette syndrome as in PANDAS. There is limited data in neuroimaging employing nuclear medicine cerebral perfusion (brain) single photon emission computerized tomography (SPECT) or functional magnetic resonance imaging (MRI) in Sydenham chorea and PANDAS that demonstrate inconsistent findings precluding any firm conclusions^[12]. None of our cases underwent SPECT or functional MRI which may have provided interesting insights into the pathophysiology and correlation with their response to IVIg. However, there were logistic reasons including lack of insurance coverage and exposure to anesthesia to sedate the children.

The association of underlying humoral immunodeficiency in four patients suggests that IVIg should be considered on that basis alone in affected children with non-GABHS forms of PANDAS and ASD. The small number of patients in our study cohort makes it all the more important to have corroboration of our findings to determine the most appropriate dose and duration of IVIg treatment.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1. Swedo SE, Rapoport JL, Leonard HL, Lenane M, Cheslow D. Obsessive-compulsive disorder in children and adolescents: clinical phenomenology of 70 consecutive cases. *Arch Gen Psychiatry* 1989; 46: 335-341.
2. Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J, Dubbert BK. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *Am J Psychiatry* 1998; 155: 264-271.
3. Chapman AH, Pilkey L, Gibbons MJ. A psychosomatic study of eight children with Sydenham's Chorea. *Pediatrics* 21:582-595, 1958.
4. Freeman JM, Aron AM, Collard JE, Mackay MC. The emotional correlates of Sydenham's Chorea. *Pediatrics* 35:42-29, 1965.
5. Grimshaw L. Obsessional disorder and neurological illness. *J Neurol Neurosurg Psychiatry* 27:229-231, 1964.
6. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). *Arch Pediatr Adolesc Med* 156:356-361, 2002.
7. Snider LA, Swedo SE. PANDAS: current status and directions for research. *Molecular Psychiatry* 2004; 9: 900-907
8. Perlmutter SJ, Leitman SF, Garvey MA, Hamburger S, Feldman E, Leonard HL, Swedo SE. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorders in childhood. *Lancet* 1999; 354: 1153-1158.
9. Younger DS, Bouboulis DA. Immune Pathogenesis of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Group A -Hemolytic Streptococcal Infections (PANDAS). *International Journal of Neurology Research* 2015; 1: 5-7.
10. Tye SJ, Frye MA, Lee KH. Disrupting disordered neurocircuitry: Treating refractory psychiatric illness with neuromodulation. *Mayo Clin Proc* 2009; 84:522-532.
11. Sturm V, Lenartz D, Koulousakis A, Treuer H, Herholz K, Klein JC, Klosterkötter J. The nucleus accumbens: a target for deep brain stimulation in obsessive-compulsive- and anxiety-disorders. *J Chem Neuroanat* 2003; 26:293-299.
12. Citak EC, Cucuyener K, Karabacak NI, et al. Functional brain imaging in Sydenham's chorea and streptococcal tic disorders. *J Child Neurol* 2004; 19:387-390.

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