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 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. Neuro-radiological 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.

Autism spectrum disorder (ASD) is a behaviorally defined disorder, which now affects ~ 2% of children in the United States. Although the standard-of-care for ASD is behavioral therapy, such therapy requires full-time engagement with one or several therapists for many years. In many cases, outcomes are suboptimal and/or incomplete. Thus, medical therapies that can augment behavioral therapy are urgently needed. Recent studies suggest that ASD is associated with a variety of physiological abnormalities including immune system dysfunction. For example, a maternal immune response induced during gestation results in ASD-like behavior in offspring in the maternal immune activation (MIA) rodent and replacing the immune system using bone marrow transplant corrected many symptoms in a mouse model of Rett syndrome, a syndrome closely aligned with ASD6. In individuals with ASD, inflammatory cytokines are elevated in the blood and brain and microglia are active in the brain. Children with ASD have autoantibodies to brain tissue such as myelin basic protein, serotonin receptors, brain endothelium, cerebellar tissue, and glutamic acid decarboxylase (GAD) as well as to non-brain tissue such as the folate receptor alpha (FRα) and mitochondria. Children with autoantibodies are reported to have a more severe form of ASD10–15. The role of autoantibodies during gestation is exemplified by maternal antibodies to fetal brain that have high specificity for the development of ASD in the offspring16 with a relatively more severe phenotype and brain enlargement. Methods: The Institutional Review Board at the University of Arkansas for Medical Sciences (Little Rock, AR) approved the study. Parents of participants provided written informed consent. The study is registered as NCT02003170 on clinicaltrials.gov. All patients evaluated in our ASD multispecialty clinic for AIE were included in this study. The majority of the patients (80/82) were diagnosis with ASD, except for two females, one who was a sibling of a male with ASD and AIE who was treated for severe atypical learning disabilities and attention deficit and one with severe tics and behavioral dysregulation.ASD was diagnosed based upon one of the following criteria: (i) a gold-standard diagnostic instrument such as the Autism Diagnostic Observation Schedule and/or Autism Diagnostic Interview-Revised; (ii) the state of Arkansas diagnostic standard, defined as agreement of a physician, psychologist and speech therapist; and/or (iii) Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis by a physician along with standardized validated questionnaires and diagnosis confirmation by the Principal Investigator (R.E.F.). We have validated that this criteria captures an accurate diagnosis of ASD in our previous studies by re-evaluating a portion of the participants with the ADI-R. Statistical analysis: Statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC) and MATLAB (The Mathworks, Natick, MA). Graphs were produced using Excel version 14.0 (Microsoft Corp, Redmond, WA). To determine whether any significant change occurred in behavior questionnaires with treatment an analysis of variance implemented as a mixed-model regression was utilized. The models included random effect of time (before/during treatment) and intercept to account for individual symptom level. The models tested the a priori hypothesis that a significant change in

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the outcome measure occurred with treatment and used a $\alpha \leq 0.05$. All of the available questionnaire data were used for each participant. There was no imputation for missing data. Participants without questionnaire data both before and after the start of treatment were excluded. The Cohen's d' effect size was calculated for each statistical comparison. Results: NMDA receptor autoantibodies were negative in all of the 34 patients in which it was tested. GAD65 titer elevation was found in three (5%; 13.00, 0.11, 0.07; normal (nl) < 0.02) of the 60 patients in whom it was tested. The PNP was positive for four (6%) of the 63 patients in which it was tested. For the PNP, two of the cases had VGCC autoantibodies (N-type 0.13; nl < 0.03; P/Q-type 0.05, nl < 0.02) and two had striated muscle autoantibodies (1:960 and 1:1920, nl < 1:120). The Cunningham panel was considered to be is positive only when one of the four autoantibody titers was positive in the ELISA AND at the same time autoantibody-mediated CaMKII activation was positive (> 130 above the basal rate of CaMKII in SKNSH human neuronal cell lines as previously described22). In this way, the CaMKII elevation was used as a functional confirmation of the consequence of elevated autoantibodies in the ELISA. In the ELISA, the antineuronal autoantibodies were positive when anti-tubulin was ≥ 2000 titer, anti-lysoganglioside was ≥ 640 titer, anti-D1R was ≥ 4000 titer, and anti-D2R was ≥ 16,000 titer. Endpoint titers were determined at 0.092 cutoff and the titers were determined by routine ELISA as described above. Using our criterion, the Cunningham panel was positive in 44 (57%) of the 77 patients in which it was performed. In 67% of the 33 cases, the Cunningham panel was negative because of a normal CaMKII, whereas it was negative because of normal ELISA autoantibody titers in 30% of the cases and was normal for both ELISA autoantibodies and CaMKII in only one case.

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