High Dose Intraveneous Immunoglobulin Improves Symptoms in Children with Autism Presented at The International Symposium on Autism

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ABSTRACT: Although autism is likely a multifactorial disorder with diverse etiologies, evidence is accumulating that a combination of genetic predisposition, an environmental insult, and resulting alterations in immunity lead to the development of autoimmunity in many of the children who have a period of normal development and then develop autistic symptoms. The children's ages ranged from 2.7-10.9 years (mean=5.8) with 10M and 3F. Twelve had normal immunoglobulin levels while one 9-year-old girl had borderline low IgG3 of 17 and a low IgA of 6. Nine of the 11 children who had antibodies to Myelin Basic Protein (MBP) measured were positive (82%) and of the 9 who had antibodies to Neuron-Axonal Filament Protein (NAFP) measured, 7 were positive (78%). The immunoglobulin dosage used has ranged from 1 to 2 gm/kg of IVIG given monthly. Four children have received one dose to date with limited follow up. Nine children have received multiple doses: 4 doses in 3 patients and 3 doses in 6 children. Eight of the 9 have made significant gains in language based on both the observations of the families and by improvements noted by therapists, teachers and the treating physician. Two of the children had been nonverbal and currently are speaking spontaneously. All children have been noted to make gains in relatedness and interaction. Improvements were found in the children negative for anti-MBP and/or anti-NAFP as well as in the children with demonstrable autoantibodies. One child, a 5-year-old boy who was verbal but had marked autistic features, normalized after one dose of 2 gm/kg and 3 doses of 1.5 gm/kg and is now considered a typical child and has been accepted into regular school. A 9-year-old boy who received 3 doses of 1 gm/kg now appears normal to his family with significant gains in language and social awareness. High dose IVIG appears to ameliorate the symptoms of children with autism at a higher rate than previous trials using lower doses. The positive results found in this open label trial of 1-2 gm/kg IVIG in children with autism should lead to a controlled trial in the future.

Immunological treatments for autism. J Autism Dev Disord 2000 Oct;30(5):475-9 Gupta S. Division of Basic and Clinical Immunology, Medical Sciences I, University of California, Irvine 92697, USA. sgupta@uci.edu

Several investigators, including ourselves, have reported significant changes in various immune responses in children with autism. These changes demonstrate dysregulation of the immune system (deficiency in some components of the immune system and excesses in others). In addition, certain genes in the major histocompatibility complex (that

regulates immune responses) appear to be involved in autism. Based upon immunological abnormalities, various treatment modalities have been applied to children with autism. In this brief review, these immunological changes and various biological therapies are analyzed and summarized.

Treatment of children with autism with intravenous immunoglobulin. J Child Neurol 1999 Mar;14(3):203-5 Gupta S.

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).
Leonard HL, Swedo SE.
Int J Neuropsychopharmacol 2001 Jun;4(2):191-8
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The evidence to date, both published and unpublished, which addresses the validity of the proposed unique subgroup of children with early and abrupt onset of obsessive--compulsive disorder (OCD) and/or tic disorders subsequent to streptococcal infections was reviewed. The aetiology of OCD and tic disorders is unknown, although it appears that both disorders may arise from a variety of genetic and environmental factors. Post-streptococcal autoimmunity has been postulated as one possible mechanism for some. The acronym PANDAS (for paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) has been given to a subgroup of paediatric patients who meet five inclusionary criteria: presence of OCD and/or tic disorder, pre-pubertal symptom onset, sudden onset or episodic course of symptoms, temporal association between streptococcal infections and neuropsychiatric symptom exacerbations, and associated neurological abnormalities. The proposed model of pathophysiology provides for several unique treatment strategies, including the use of antibiotic prophylaxis to prevent streptococcal-triggered exacerbations, and the use of immunomodulatory interventions (such as intravenous immunoglobulin or therapeutic plasma exchange) in the treatment severe neuropsychiatric symptoms. For the latter study group, long-term (2--5 yr) follow-up revealed continued symptom improvement for the majority of patients, particularly when antibiotic prophylaxis had been effective in preventing recurrent streptococcal infections. In addition, the episodic nature of the subgroup's illness provides for opportunities to study brain structure and function during health and disease, as well as allowing for investigations of the aetiologic role of anti-neuronal antibodies and neuroimmune dysfunction in both OCD and tic disorders. Although much research remains to be done, an increasing body of evidence provides support for the postulate that OCD and tic disorders may arise from post-streptococcal autoimmunity. The unique clinical characteristics of the PANDAS subgroup, the presence of volumetric changes in the basal ganglia, and the dramatic response to immunomodulatory treatments, suggest that symptoms arise from a combination of local, regional and systemic dysfunction. Ongoing research is directed at understanding the nature of the abnormal immune response, as well as identifying at-risk children, in order to provide for novel strategies of prevention and treatment.

The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy.
J Clin Immunol 2000 Mar;20(2):94-100
Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J.

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To compare the efficacy of immunoglobulin replacement therapy given intravenously versus subcutaneously to prevent infections in patients with primary antibody deficiency syndromes, an international, multicenter, open label, crossover study was designed. Forty patients were randomized to receive either subcutaneous or intravenous immunoglobulin replacement therapy for 1 year. In the second year, patients were switched to the alternative treatment, enabling patients to act as their own controls. Equivalent doses were given by both routes. Ethical approval was obtained from the review boards of the hospitals in which the patients were seen and written consent obtained from each patient. Patients with a primary antibody deficiency syndrome, either common variable immunodeficiency or IgG subclass deficiency or specific antibody deficiency, who required immunoglobulin replacement therapy were included in the study. Patients were excluded if they had significant thrombocytopenia (defined as platelets less than 50 x 10(9)/liter), had high levels of anti-IgA antibodies (defined as greater than 1:8192), or had severe adverse reactions to a blood product within the last 2 years. The primary end point was the number of infections and their severity (moderate and major) during the two treatment periods. Secondary end points were adverse reactions, length of infections, days lost from school or work due to infections, and acceptability of treatment regimens to the patients. Based on the assumption that it was difficult to prove equivalence of therapies statistically in crossover studies, an arbitrary number of 40 patients was selected on the basis that this might be achievable in 2 years. There are no significant differences in efficacy or adverse reaction rates between immunoglobulin replacement therapy given subcutaneously or intravenously.

Proinflammatory and regulatory cytokine production associated with innate and adaptive immune responses in children with autism spectrum disorders and developmental regression.
J Neuroimmunol 2001 Nov 1;120(1-2):170-9
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We determined innate and adaptive immune responses in children with developmental regression and autism spectrum disorders (ASD, N=71), developmentally normal siblings (N=23), and controls (N=17). With lipopolysaccharide (LPS), a stimulant for innate immunity, peripheral blood mononuclear cells (PBMCs) from 59/71 (83.1%) ASD patients produced >2 SD above the control mean (CM) values of TNF-alpha, IL-1beta, and/or IL-6 produced by control PBMCs. ASD PBMCs produced higher levels of proinflammatory/counter-regulatory cytokines without stimuli than controls. With

stimulants of phytohemagglutinin (PHA), tetanus, IL-12p70, and IL-18, PBMCs from 47.9% to 60% of ASD patients produced >2 SD above the CM values of TNF-alpha depending on stimulants. Our results indicate excessive innate immune responses in a number of ASD children that may be most evident in TNF-alpha production.

Abnormal Measles Serology and Autoimmunity in Autistic Children
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Singh, VK & Courtney Nelson
Immune factors such as autoimmunity may play a causal role in autism. We recently showed that many autistic children have autoantibodies to brain myelin basic protein (MBP) as well as elevated levels of measles virus antibodies. To extend this research further, we conducted a serological study of measles virus (MV), mumps virus (MuV), rubella virus (RV), cytomegalovirus (CMV), human herpesvirus-6 (HHV-6), measles-mumps-rubella (MMR), diptheria-pertussis-tetanus (DPT), diptheria-tetanus (DT) and hepatitis B (Hep B) and studied correlations with MBP autoantibodies. Antibodies were assayed in sera of autistic children (n=125) and normal children (n=92) by ELISA or immunoblotting methods. We found that autistic children have significantly (p=0.001) higher than normal levels of MV and MMR antibodies whereas the antibody levels of MuV, RV, CMV, HHV-6, DPT, DT or Hep B did not significantly differ between autistic and normal children. Immunoblotting analysis showed the presence of an unusual MMR antibody in 60% (75 of 125) of autistic children, but none of the 92 normal children had this antibody. Moreover, by using MMR blots and monoclonal antibodies, we found that the specific increase of MV antibodies or MMR antibodies was related to measles hemagglutinin antigen (MV-HA), but not to mumps or rubella viral proteins, of the MMR vaccine. In addition, over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a causal association between MMR and brain autoimmunity in autism. Stemming from this evidence, we suggest that an "atypical" measles infection in the absence of a rash but with neurological symptoms might be etiologically linked to autoimmunity in autism.

Immunoglobulin subclass concentration in preterm infants treated prophylactically with different intravenous immunoglobins.
Am J Perinatol 1995 Sep;12(5):306-9
Amato M, Huppi P, Imbach P, Llauto A, Burgi W.

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The most immature infants have critically low concentrations of all immunoglobulin G (IgG) subclasses, associated with a higher risk for pyogenic, respiratory, and meningeal infection. Selective IgG subclass deficiency is an established indication for intravenous immunoglobulin (IVIG) substitution. However, considering that therapeutic efficacy of IVIG is dependent on its pharmacokinetics, we studied peak and trough IgG subclass serum levels during the neonatal period (28 days) in a group of 34 healthy preterm babies (30.2 +/- 2 weeks gestational age (GA) and 1065 +/- 210 g birthweight (BW) treated prophylactically with three daily standard doses of two different IVIG preparations: Sandoglobulin (SG) (0.5 g/kg/day) and Pentaglobin (PG) (5 mL/kg/day). IgG subclass

levels were assayed by radioimmundiffusion (RID) before treatment (day 1) and at days 3, 5, 7, 14, and 28 of life. Statistical analysis was performed by paired t test. In the first week of life only (days 3, 5, 7), for both IVIG preparations, subclass levels were higher than pretreatment values: IgG1, 4.6 +/- 1.7 versus 5.6 +/- 1.6 g/L; IgG2, 1.6 +/- 0.8 versus 2.1 +/- 0.6 g/L; IgG3, 0.2 +/- 0.7 versus 0.3 +/- 0.1 g/L; IgG4, 0.3 +/- 0.1 versus 0.9 +/- 0.1 g/L ($p < 0.05$). During this time (7 days) IgG2 levels were higher in the SG group and IgG4 was higher in the PG group ($p < 0.05$). This study shows pretreatment IgG subclass levels 14 days after treatment and different patterns, depending on the used preparation. We conclude that prospective clinical trials should include the study of target serum levels and timing of IVIG administration not only for IgG but also for IgG subclasses.

[Intravenous immunoglobulins in bronchial asthma: a therapeutic alternative?]
Infusionsther Transfusionsmed 1993 Apr;20 Suppl 1:141-4; discussion 145
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Treatment of severe bronchial asthma usually requires the use of steroids. Given the known side effects of steroid treatment, potential alternative therapeutical strategies are currently evaluated; among others, intravenously administered immunoglobulins (ivIg) may be considered. In one study of 5 children with bronchial asthma and IgG subclass deficiency, an improvement of asthma was demonstrated in 4 out of the 5 patients under ivIg treatment over several months. In another study on ivIg treatment in 8 immunocompetent children with steroid-dependent asthma, there also was an improvement of asthma, leading to a reduction in the required steroid dose; furthermore, there was a diminution in skin prick test reactivity. At present, only speculations can be made about the possible mechanisms of action.

Successful immunoglobulin treatment in a patient with neuromyotonia.
Clin Neurol Neurosurg 2000 Sep;102(3):173-5
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Neuromyotonia is characterized by spontaneous and continuous muscle fibre activity leading to muscle cramps, pseudomyotonia, myokymia and weakness. Electromyographic recordings show typical findings. An auto-immune mechanism has been suggested in at least a subset of patients. Various therapies have been tried with different outcome. A patient with neuromyotonia responding well to high-dose immunoglobulin treatment is presented.

Serum IgG subclass concentrations before and after administration of intravenous immunoglobulin in common variable immunodeficiency.
J Clin Lab Immunol 1992;38(1):29-39
Ozawa T, Motoyoshi F, Kato Y, Kondo N, Orii T.
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IgG subclass levels were measured before and after administration of intravenous immunoglobulins (IVIGs) in patients with common variable immunodeficiency (CVI). Six patients were treated with IVIG at the dose of 100-150mg/kg to maintain a trough level of 200mg/dl every 4 or 5 weeks, except for patient 5 who was given IVIG only 3 or 4 times per year. Three kinds of IVIGs, polyethylene-glycol (PEG)-treated IVIG, alkylated IVIG and sulfonated IVIG were used for replacement therapy. Although serum IgGl levels were low before administration of IVIGs, they increased to the normal levels after each administration of IVIGs in four patients. IgG2 preserved normal levels before and after administration of IVIGs in all patients. IgG3 was present at low normal concentration in patient 1, low concentration in patients 2, 3 and 6, and undetectable in patients 4 and 5 before infusion. Although increases in IgG3 levels were shown after infusion of PEG-treated IVIG, there were no increases after infusion of sulfonated or alkylated IVIG. However, there have been several reports that IgG3 is detected in sulfonated or alkylated IVIG preparations by another method. IgG4 levels were somewhat low before administration, but four patients achieved normal serum levels with treatment. In light of the above results of replacement therapy with IVIGs, we should consider the IgG subclass levels for patients such as CVI or selective IgG subclass deficiency.

New and controversial uses of intravenous gamma-globulin.
Pediatr Infect Dis J 1988 May;7(5 Suppl):S34-6
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During the last few years the use of intravenous immunoglobulin (IVIG) has attracted increasing interest for the treatment of patients who do not have a classical humoral antibody deficiency syndrome. In certain situations this approach has revolutionized medical management, e.g. in immune thrombocytopenia. In other areas, such as in Kawasaki's syndrome, IVIG therapy have been shown to be highly beneficial in preventing long term disease sequelae by some investigators, but the field remains controversial. Conditions under which IVIG therapy has been shown to be of potential benefit are: (1) intractable childhood epilepsy; (2) autoimmune diseases, e.g. myasthenia gravis, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, idiopathic neutropenia and aplastic anemia; (3) atopic allergy with IgG subclass deficiency including bronchial asthma; (4) in severe infections in combination therapy with antibiotics and as an antipyretic; (5) in Kawasaki's disease; (6) in multiple myeloma and chronic lymphocytic leukemia. Oral and intraventricular administration of IVIG have also been tried, the former for severe diarrhea and the latter to try to rescue the central nervous system from damage by a pathogen. Carefully controlled clinical trials are needed to establish the efficacy of gamma-globulin therapy in these and other conditions.