Journal of Child Neurology / Vol. 14, March 1999, pages 203-205

Response to the Letter by Dr Gupta Concerning the Treatment of Autistic Children With Intravenous Immunoglobulin

To the Editor: It is important to emphasize that my treatment program using intravenous immunoglobulin for autistic children, as published in this journal,[1] was chronologically the first one in the world's history. The program was conceptualized in 1988 and, as stated in my article, was implemented from August 1989 through November 1990. This predates by several years Dr Gupta's treatment program.[2]

In 1988, as stated in my article, standard protocols for treating children with autoimmune disorders included intravenous immunoglobulin in a dose range of 200 to 400 mg/kg per infusion (Department of Immunology, Hospital for Sick Children, Toronto, Ontario). Since then the dose of intravenous immunoglobulin used for clinical disease processes has increased. Even Dr Gupta's own review article on the use of intravenous immunoglobulin in childhood diseases, published in 1986,[3] cites the following proven effective dosages: 100 to 200 mg/kg per infusion for childhood epilepsy; 200 mg/kg per infusion for myasthenia gravis; and 200 mg/kg per infusion for Sjögren's syndrome.

The Sandoglobulin brand of intravenous immunoglobulin that was used came in lyophilized vials of 6 grams. This was the largest vial size available at the time, and was the most cost effective. Adjusting for body weight, one or two vials were used in each case. This accounts for the range in administered dosages. It was an older, and heavier, autistic child whose dose turned out to be 154 mg/kg per infusion. All the children in the age range up to 6 years received between 300 and 400 mg/kg per infusion.

The serum half-life of intravenous immunoglobulin is 3 weeks. However, the tissue distribution of intravenous immunoglobulin has entirely different kinetics and a more prolonged half-life. For central nervous system disorders such as multiple sclerosis, intravenous immunoglobulin administered every 2 months has been proven to be effective.[4,5] Thus, the treatment schedule that was used in my article of every 6 weeks, to treat a presumptive central nervous system autoimmune disorder (autism), was an appropriate starting point.

The planned treatment program, as clearly stated in my article, was for a total of four infusions. Eight (80%) of the 10 treated children completed the planned program. As stated in my article, two dropped out early purely because of the decision by the parents. In these cases, I strongly recommended that the treatment program be completed, but the parents declined. In the cases that received more than the planned four infusions, as was stated in my article, this was done at the direct request of the parents. In these cases, the parents felt they had seen a mild improvement and wanted more infusions to try to see whether there would be increased clinical responsiveness.

The ages of the children at the start of the intravenous immunoglobulin treatment program were: 4 years (2 cases), 5 years (2 cases), 7 years (1 case), 9 years (2 cases), 13 years (1 case), and 15 years (1 case).

In my report, all of the treatment data results were based on parental reports, school reports, and direct observations by me of the treated children. The results, although they could be considered subjective, were accurate. It must be pointed out that in Dr Gupta's own report of treating autistic children with intravenous immunoglobulin,[2] the presented data were purely subjective in nature, with no quantifiable clinical scale results used (the improvement gradations of 1+, "minimal," to 4+, "striking," were purely subjective ratings).

As was stated in my article, all of the children had quantitative immunoglobulin determinations performed (IgA, IgG, and IgM) and all of these were normal. Immunoglobulin subclasses were not investigated in any of the children.

There have been many published reports of immunologic abnormalities in autism, including several by me.[6,7] However, Dr Gupta is in error when he suggests a uniformity of immunologic findings in autism. For example, entirely normal findings have been reported for CD3+ cell numbers,[6,8,9] CD4+ cell numbers,[6] CD8+ cell numbers,[6,9–11] B cell numbers,[6,7,9,10] and T helper-inducer cell numbers.[10] Even Dr Gupta's report[2] gives inconsistent lymphocyte typing results: the number of CD4+ cells was normal in 13 cases, increased in 5, and decreased in 7; the number of CD8+ cells was normal in 19, increased in 2, and decreased in 4. These results indicate basically normal CD4+ and CD8+ cell numbers, with identical amounts of increased and decreased cell numbers.

As was stated in my article, besides the immunologic results reported from the 10 treated children, 10 other children had the same immunologic work-ups performed and their results were entirely normal. There is nothing to suggest any kind of selection bias in these 20 autistic children.

Dr Gupta's report[2] does not mention the investigation of activation markers. These could be much more important determinants of autoimmune disease status in autism than lymphocyte typing (reviewed in reference 6). Future research protocols investigating autoimmune correlates of autism should include determinations of immunologic activation markers.

My published results[1,6,7] indicate that there is a subset of autistic children whose neurologic disability is due to autoimmune factors. These results are fully in keeping with those of Dr Gupta. My results continue to indicate that intravenous immunoglobulin should not be indiscriminately used to treat autistic patients. As I wrote, intravenous immunoglobulin treatments "can only be used in the context of a formal research protocol."[1] It appears that Dr Gupta agrees with me.

It must not be forgotten that the medical work-up of all children with autism, in clinical practice and in research protocols, should include a sleep electroencephalogram (EEG). Autistic children with unrecognized epileptiform discharges on sleep EEG tracings can have very significant clinical improvement with the use of anticonvulsants.[12]

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References

1. Plioplys AV: Intravenous immunoglobulin treatment of children with autism. *J Child Neurol* 1998;13:79–82.
2. Gupta S, Aggarwal S, Heads C: Dysregulated immune system in children with autism: Beneficial effects of intravenous immune globulin on autistic characteristics. *J Autism Dev Dis* 1996;26:439–452.
3. Gupta S: Current and future uses of intravenous gamma globulin in autoimmune disorders. *Immunol Allergy Prac* 1986;8:370–377.
4. Achiron A, Gilad R, et al: Intravenous immunoglobulin treatment in multiple sclerosis and experimental autoimmune encephalomyelitis: Delineation and usage and mode of action. *J Neurol Neurosurg Psychiatry* 1994;57:S57–S61.
5. Achiron A, Pras E, et al: Open controlled therapeutic trial of intravenous immune globulin in relapsing-remitting multiple sclerosis. *Arch Neurol* 1992;49:1233–1236.
6. Plioplys AV, Greaves A, et al: Lymphocyte function in autism and Rett Syndrome. *Neuropsychobiology* 1994;29:12–16.
7. Plioplys AV, Greaves A, et al: Immunoglobulin reactivity in autism and Rett's syndrome. *Dev Brain Dysfunc* 1994;7:12–16.
8. Marchetti B, Scifo R, et al: Immunological significance of opioid peptide dysfunction in infantile autism. *Brain Dysfunc* 1990;3:346–354.
9. Denney DR, Frei BW, Gaffney GR: Lymphocyte subsets and interleukin-2 receptors in autistic children. *J Autism Dev Dis* 1996;26:87–97.
10. Warren RP, Yonk LJ, Burger RA, et al: Deficiency of suppressor-inducer T cells in autism. *Immunol Invest* 1990;19:245–251.
11. Yonk LJ, Warren RP, Burger RA, et al: CD4+ helper T cell depression in autism. *Immunol Lett* 1990;25:341–345.
12. Plioplys AV: Autism: EEG abnormalities and clinical improvement with valproic acid. *Arch Pediatr Adolesc Med* 1994;148:220–222.