Original Article

Intravenous Immunoglobulin Treatment of Children With Autism

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ABSTRACT

Since autism has been associated with immunologic abnormalities suggesting an autoimmune cause of autistic symptoms in a subset of patients, this study was undertaken to investigate whether intravenous immunoglobulin (IVIg) would improve autistic symptoms. Ten autistic children with immunologic abnormalities, demonstrated on blood tests, were enrolled in this study. Their ages ranged from 4 to 17 years, with two girls and eight boys. Eight children (1 female and 7 male) historically had undergone autistic regression. Intravenous immunoglobulin, 200 to 400 mg/kg, was administered every 6 weeks for an intended treatment program of four infusions. In five children, there was no detectable change in behavior during the treatment program. In four children, there was a mild improvement noted in attention span and hyperactivity. In none of these children did the parents feel that the improvement was sufficient to warrant further continuation of the infusions beyond the termination of the program. Only in one child was there a very significant improvement, with almost total amelioration of autistic symptoms over the time period of the four infusions. Once the treatment program was completed, this child gradually deteriorated over a 5-month time period and fully reverted to his previous autistic state. In this treatment program, five children had no response to intravenous immunoglobulin. In the four children who showed mild improvements, those improvements may simply have been due to nonspecific effects of physician intervention and parental expectation (ie, placebo effect). However, in one child there was a very significant amelioration of autistic symptoms. There were no distinguishing historic or laboratory features in this child who improved. Given a positive response rate of only 10% in this study, along with the high economic costs of the immunologic evaluations and the intravenous immunoglobulin treatments, the use of intravenous immunoglobulin to treat autistic children should be undertaken only with great caution, and only under formal research protocols. (*J Child Neurol* 1998;13:79–82).

Autism is a syndrome characterized by social and communicative deficits of early onset accompanied by abnormal behaviors. There are many biomedical causes underlying autistic symptomatology.[1] However, in the majority of autistic patients no clear etiology is ascertained.

Immune system abnormalities have been associated with autism. These have included inhibition of macrophage migration in response to human myelin basic protein,[2] reduced mitogen-induced lymphocyte blastogenesis[3,4] decreased numbers of T-lymphocytes with altered ratios of helper to suppressor T-cells,[4] decreased helper T-cell and B-cell numbers,[5] deficiency of suppressor-inducer T-cells,[6] decreased natural killer cell activity,[7] and the demonstration of circulating antibodies to serotonin receptors.[8] In another study of 14 patients with autism, eight had an abnormal lymphocyte proliferative response to mitogens and to autologous lymphocytes and monocytes.[9]

Further immunologic abnormalities in autism have been delineated by the author.[10,11] In a study of 17 autistic children, there was an abnormally increased percentage of DR+ (activated) T-lymphocytes in 11 patients. With increasing age, there was a decreasing percentage of DR+ lymphocytes. No patient had interleukin-2 (IL-2) receptor+ cells. These results suggested "incomplete" activation, a finding seen in autoimmune diseases. The decrease in activated cells with increasing age suggested that there may be an autoimmune process that is more active earlier in life in a subset of autistic patients.[10]

Received July 11, 1996. Received revised Nov 27, 1996. Accepted for publication Nov 30, 1996.

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In a further investigation of autistic children, when serum samples were tested against Western blots prepared from normal, human cerebellar tissue, there was an increased incidence of anti-210K neurofilament subunit reactivity with an overall incidence of 88% (23% in controls; $P < .001$).[11] Those results suggested the possibility of anticerebellar immunoreactivity playing a role in the genesis or modification, or both, of cerebellar circuitry in autism.

Given the immunologic abnormalities in autistic children, immunomodulatory treatments may be appropriate for selected individuals. Intravenous immunoglobulin (IVIg) is a highly effective treatment for a wide variety of systemic inflammatory diseases including inflammatory diseases of the peripheral nerves (Guillain-Barré syndrome),[12] myasthenia gravis,[13] and inflammatory myopathies.[14] Intravenous immunoglobulin has also been reported to be effective in the treatment of central nervous system disorders such as intractable epilepsy[15] and multiple sclerosis.[16]

In 1989, a clinical trial of intravenous immunoglobulin for autistic children was undertaken and completed in 1990. Given the current widespread interest in the use of intravenous immunoglobulin for autism, and recent pronouncements of its curative nature in the lay literature, the author feels compelled to publish these results as a strong cautionary word against the growing indiscriminate use of intravenous immunoglobulin in treating autistic children.

MATERIALS AND METHODS

There were a total of 10 children enrolled in the treatment program. There were eight males and two females. The age range was from 4 years and 3 months to 15 years and 7 months with a mean age of 8 years. The diagnosis of autism conformed to the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed revised (*DSM-III-R*) criteria for autism.[17] Each child underwent a thorough review of the medical history, a physical and neurologic examination. Eight children (7 male and 1 female) historically had undergone autistic regression (previously entirely normal development until loss of neurologic and developmental functioning occurred). The age of onset of regression ranged from 6 months to 3 years with a mean of 21 months. In one child, seizures and autistic regression occurred at the age of 6 months, 2 days following a second diphtheria-pertussis-tetanus (DPT) immunization. This child presumably suffered a reaction to pertussis immunization, which left him with autism. In no other child was there a biomedical cause of autism detected. In each child the physical examination and neurologic examinations were entirely normal.

Only one child had a concomitant medical illness: epilepsy. A 15-year-old boy had generalized, tonic-clonic seizures that had been well controlled with carbamazapine. His last seizure was 2 years prior to being enrolled in this program. In nine families, review of the family history was entirely normal. In one family, three family members (the mother, an aunt, and an uncle) had ankylosing spondylitis. There was no suggestion in the child taking part in the study of the presence of this, or any other, rheumatic disease.

In each child, the following investigations were performed and yielded normal results: complete blood count, chemistry screen (including electrolytes, renal function tests, and liver function tests), T_3, T_4, TSH, lactate, pyruvate, amino acids, and ammonia levels, chromosome studies (including cultures for the fragile-X chromosome abnormality), quantitative immunoglobulin studies (IgG, IgA, and IgM), sedimentation rate, audiometric screening, and vision screening. Three children had both visual evoked responses and auditory brainstem responses performed and in all cases the results were normal. Six children had brain imaging performed (computed tomographic [CT] or magnetic resonance imaging [MRI] scans). The results of the scans were normal in five children, and in one (the 15-year-old with epilepsy) mild, compensated ventriculomegaly was detected. Nine children had electroencephalograms (EEG) performed. In eight the results were entirely normal, whereas in the 15-year-old with epilepsy, independent bitemporal spikes and spike and wave complexes were detected.

In addition, immunologic investigations were performed in all of the children. In six cases, these were performed at the American Medical Laboratories in Fairfax, Virginia, in three cases at the clinical immunology laboratories of the Hospital for Sick Children in Toronto, Canada, and in one case at SmithKline Beecham clinical laboratories in Staten Island, New York. The normative data from the respective laboratories was similar. For the purposes of this investigation, the normative data was used according to the American Medical Laboratories. In all 10 cases CD19 (pan-B-cell marker), CD3 (pan-T-cell marker), CD4 (T helper marker), CD8 (T suppressor marker) and calculated CD4/CD8 ratios were entirely normal. In three cases, assays were also performed for natural killer cells, T helper-inducer cells and T suppressor-inducer cells and all of these results were normal.

In all 10 cases, lymphocytes were assayed for the activation DR marker. In five cases, there was an abnormally increased percentage of lymphocytes expressing the DR antigen (the elevated values were 26%, 26%, 27%, 28%, and 30% with normative values being from 4% to 23%). Likewise, in five cases there was an increased percentage of T-lymphocytes that expressed the DR antigen (DR+/CD3+) (elevated values were 2.2%, 2.4%, 3%, 3%, and 7% with normative values being < 1.5%). The presence of interleukin-2 receptor expression (CD25) on lymphocytes was assayed in 7 cases. In all cases, abnormalities were detected. CD25 expression on all lymphocytes gave the following elevated values: 2%, 4%, 5%, 6%, 6%, 10%, and 11% (normal values were < 1.5%). The absolute count of CD25+ lymphocytes was also elevated (assays were performed in 6 cases): 58, 116, 144, 199, 208, and 410 cells/μL (normal values being < 30 cells/μL). In six cases, CD25 expression was assayed on T-lymphocytes (CD25+/CD3+) and in all cases elevated values were obtained: 2%, 3%, 4%, 4%, 5%, and 6% (normal values being < 1.5%).

Only children who had a demonstrated abnormality in immune parameters were allowed to enter this study. During the process of evaluation, approximately 10 additional children underwent the screening procedures and normal immunologic laboratory results were obtained. They were not allowed to enter into the program. No one with a deficiency of IgA was entered into this program.

At the time of entry into the program, only one child was taking a medicine: the 15-year-old with epilepsy was taking carbamazepine (with therapeutic blood levels). None of the other nine children were taking any medicines.

In all cases, informed parental consent was obtained prior to entry into the treatment program. The intent of the treatment program was to use 200 to 400 mg/kg of intravenous immunoglobulin per treatment, every 6 weeks for a total of four intravenous administrations. The dosage and scheduling of the intravenous immunoglobulin infusions was in accordance with standard protocols for treating childhood inflammatory autoimmune disorders that were in use at that time by the Department of Immunology, Hospital for Sick Children, Toronto, Canada. The costs of the intravenous immunoglobulin preparations and administration were billed to insurance carriers. In all cases the intravenous immunoglobulin preparation used was obtained from Sandoz Pharmaceutical Company (Sandoglobulin).

The actual dose administered ranged from 154 mg/kg to 375 mg/kg per dose with a mean of 270 mg/kg per administration. The number of infusions given ranged from one to six. Six children had the planned 4 infusions, and one child each had 1, 3, 5, and 6 infusions. In the child who received six infusions, two were administered by the author and four by local physicians in Colombia. In the patient who received five infusions, the fifth infusion was given at the request of the parents. The children who had only one or three infusions were withdrawn from the treatment program by the parents due to apparent lack of effectiveness. Each infusion was given over 1½ hours. Prior to starting the infusion, 4 children needed to be sedated with rectal pentobarbital, 3 with oral chloral hydrate, and 3 did not require any sedation. There were no adverse events associated with sedation or with the administration of the intravenous immunoglobulin.

The infusions were administered during 1989 at the Autism Clinic in Washington, DC, and in 1990 at Michael Reese Hospital in Chicago. The first infusions for the first patient occurred on August 12, 1989 and the final infusion in the last patient was on November 9, 1990.

RESULTS

Compliance with the treatment program was excellent. In only two cases were less than the planned four intravenous immunoglobulin infusions given. In these cases the number of infusions given were one and three. Discontinuation from the program took place because the parents did not see any effectiveness. In two cases more than four infusions were given (5 and 6 infusions, respectively). This was done at the request of the parents because they wanted to maximize potential improvement.

In five cases, no clinical improvement was seen from the intravenous immunoglobulin infusions. In four cases, the parents reported mild improvement in attention and hyperactivity. However, in those cases the basic autistic symptoms remained unchanged. The improvements reported by parents in those cases could not be independently confirmed by the author or by teacher and school reports.

Even though a degree of effectiveness was seen in these four cases, none of the families elected to continue further intravenous immunoglobulin treatments. The parents felt that the costs and inconvenience involved in using intravenous immunoglobulin outweighed the slight improvements seen.

One child did have a remarkable improvement in autistic symptoms. He was 5 years 2 months old at the time of entry into the study. He was treated with 375 mg/kg of intravenous immunoglobulin for a total of four infusions. The first infusion was on August 12, 1989 and the final one on December 2, 1989. His clinical history was unremarkable other than the fact that he was entirely normal until he underwent an autistic regression between 16 and 18 months of age. When first seen, he was severely withdrawn with no evident social interactions, even with the parents. He was totally noncommunicative, saying no words and appearing to understand no spoken expressions, not even his own name. He engaged in hand-flapping behaviors, was mesmerized by spinning objects such as wheels on a toy car, and refused to allow anyone to touch his face. He did not play with toys and did not engage in any imaginative activities. His immunologic evaluation revealed the following abnormalities: 4% of all lymphocytes were CD25+ (normal, < 1.5%), the count of CD25+ lymphocytes was 116/μL (normal, < 30/μL), and the CD25+/CD3+ percentage of lymphocytes was 4% (normal, < 1.5%). The remainder of his immunologic and general medical laboratory tests were entirely normal.

After each intravenous immunoglobulin infusion he had gradual clinical improvement that occurred in a stepwise fashion. Each improvement started to take place 7 to 10 days after an infusion and would peak after 3 weeks. Then there was a gradual deterioration, but he did not return to his previous baseline at the time of the next intravenous immunoglobulin infusion. There was gradual overall improvement to the point that after the third infusion, he was speaking words, using short sentences, and had a 20 to 30 word vocabulary. He also became much more sociable and enjoyed interactions with his parents, teachers, and siblings. The special education program in which he was enrolled reevaluated him as no longer being autistic and informed the parents that he would not be allowed to continue in that school for the following academic year. After the fourth and last infusion, clinical improvement continued. Due to a family tragedy which resulted in loss of income and loss of medical insurance, further intravenous immunoglobulin treatments could not be arranged. The clinical improvement lasted for 2 months after the last infusion, with a subsequent gradual deterioration over the following 3 months. He eventually returned to the same severe autistic condition that he presented prior to the start of the treatment program.

DISCUSSION

Autism is a clinically defined syndrome characterized by social and communicative deficits accompanied by abnormal behaviors. Although there are many biomedical causes of autism, the majority of affected patients do not have a defined etiology. It is possible that an autoimmune process may be pathogenically involved in a subset of autistics since previous studies have demonstrated a variety of immune abnormalities in autism. The published literature and the

previously reported investigations by the author support this hypothesis.

Intravenous immunoglobulin is a safe and well tolerated immunomodulatory treatment. It is of benefit in a number of inflammatory diseases, peripheral nervous system disorders and central nervous system diseases. This treatment program was undertaken to investigate whether clinical improvement could be seen in autistic children who had evidence of immunologic abnormalities on blood test results.

Overall the results were disappointing. In five cases there was no suggestion of any clinical improvement. In four cases the mild improvement that was reported by the parents could not be confirmed by school teachers, or by the author. Those cases of mild improvement can be simply attributed to the placebo effect.

It was in only one case that a substantial and dramatic improvement took place. The time course of this improvement is compatible with the tissue distribution of intravenous immunoglobulin. After each infusion the improvement became noticeable after 7 to 10 days, which corresponds to the extravascular tissue distribution equilibrium time of intravenous immunoglobulin. The improvement persisted for 4 weeks, and then gradually declined. This observation corresponds to the 3 to 4 week half-life of intravenous immunoglobulin. After the final infusion, clinical improvement persisted for 2 months and then gradually deteriorated to baseline autistic symptoms over 3 months.

In reviewing this case in detail, there were no distinguishing features on clinical history, physical examination, or laboratory testing that would have separated this child from the nonresponders. There were some minor differences, however. In context of the entire study population he was of a young age, 5 years 2 months old, at the start of the program. However, there were two other 4-year-olds and one other 5-year-old enrolled in the program who did not have a significant improvement. He also had the highest dosage of intravenous immunoglobulin administered (375 mg/kg for each infusion). However, four other children had infusion amounts that ranged from 300 to 333 mg/kg per infusion who did not improve significantly.

The results with this one child suggest that there is a small subset of autistic children in whom an autoimmune process may be a pathogenic one in causing autistic regression and the symptoms of autism. However, the clinical history and available laboratory tests did not distinguish this child from the nine nonresponders. Given the inconvenience and high economic cost of these infusions, the use of intravenous immunoglobulin in treating autistic children cannot be advocated on a clinical basis. This can only be done in the context of a formal research protocol.

Recently, a tremendous amount of excitement has been generated by claims of almost universal improvement with the use of intravenous immunoglobulin in improving symptoms of autism. Those claims have led to widespread parental demands for this treatment approach. The results from the author's study should be a strong cautionary word to avoid the indiscriminate use of intravenous immunoglobulin in autistic children.

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