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ORIGINAL ARTICLE

# Improvement in children with autism treated with intravenous gamma globulin

MARVIN BORIS, MD[1], ALLAN GOLDBLATT, PA-C[2] & STEPHEN M. EDELSON, PHD[3]

[1]*New York University School of Medicine, New York, New York, USA,* [2]*Truro College, New York, New York, USA, and* [3]*Autism Research Institute, 4182 Adams Ave, San Diego, CA 92116, USA*

**Abstract**

*Purpose.* Immune dysfunction has been associated with children with autism. One study found a beneficial response of intravenous gamma globulin (IVIG) therapy in autistic children. The present study further evaluated the administration of IVIG to these children.

*Design.* This report shows the response of 26 autistic children who received IVIG over a 6 month period.

*Materials and methods.* In documented autistic children, 400 mg kg$^{-1}$ IVIG was administered each month for 6 months. Baseline and monthly Aberrant Behavior Checklists were completed on each child in order to measure the child's response to IVIG.

*Results.* The participants' overall aberrant behaviors decreased substantially soon after receiving their first dose of IVIG. Further analysis of the total scores revealed decreases in hyperactivity, inappropriate speech, irritability, lethargy and stereotypy. However, 22 of the 26 children regressed to their pre-IVIG status within 2–4 months of discontinuing the IVIG.

*Conclusions.* Significant improvement occurred in autistic children receiving monthly IVIG. There is a reasonable rationale considering the risk/reward ratio to utilize IVIG therapy in children with autism. A well-controlled placebo double-blind study would be important to further clarify the use of IVIG in autism and its duration of benefits.

**Key words:** *Autism, intravenous gamma globulin, autoimmunity, Aberrant Behavior Checklist*

## Introduction

Autism is a psychiatric syndrome manifested by impairments in social interaction, communication, and restricted repetitive and stereotyped patterns of behavior, interests and activities with onset prior to age 3 years. The underlying biomedical etiologies in children with autism await further investigation. Genetic disorders possibly associated with epigenetic and transposon activity may lead to an increased incidence of multiple system disease in these children. One association has been the high incidence of immunological abnormalities and autoimmune disease in a subset of children with autism [1–3]. Based on

Correspondence: Marvin Boris, 77 Froehlich Farm Blvd, Woodbury, NY 11797, USA. Tel: 516 921 3456. Fax: 516 364 1844. Email: mboris@pol.net

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the immunological abnormalities, a number of trials of intravenous gamma globulin (IVIG) have been utilized in autistic children.

Gupta et al. [1], in an open clinical trial, administered IVIG to 10 children aged 3–12 years at a dose of 400 mg kg$^{-1}$ at 4 week intervals for 6 months. Evaluations from the intravenous infusion nurse, physician, parents, behavioral and speech therapists showed clinical improvement in most of the patients. Younger patients had greater improvement. Plioplys [2] treated 10 ASD children with IVIG. Their ages ranged from 4 to 17 years. The dose administered was 200–400 mg kg$^{-1}$ every 6 weeks, four times. In four children there was mild improvement, in five children no improvement and in one child a marked benefit. Plioplys stated that a certain subset of autistic children might benefit from IVIG.

DelGuidice-Asch et al. [3] administered 400 mg kg$^{-1}$ monthly for 6 months to five children with autism. Using 10 assessment scales, only one subscale of the Ritvo-Freeman scale, the sensory response, showed a clinically meaningful response. Therefore, this small open pilot study did not suggest IVIG to be helpful in this group of patients with autism.

A group of autistic children in our practice who failed to improve for at least 1 year with dietary elimination of dairy and gluten, vitamin and mineral supplementations, and behavioral educational therapies were treated with and evaluated for the possible efficacy of IVIG.

## Methods

### *Participants*

In total, 27 children and adolescents participated in this study. All of them lived near or in Long Island, New York. The study had IRB approval. Informed consents were obtained from the parents. All participants received a diagnosis of autism from an independent psychologist, neurologist, psychiatrist or developmental pediatrician and met the DSM IV criteria for autism. The children's ages ranged from 3 to 17 years, with an average age of 6.77 years. There were 21 males and six females. Parents were also asked to estimate the onset of their child's regression. The age of onset of regression ranged from 11 to 30 months, with an average age of 17 months. All the children in this study were considered by history to have regressive autism.

Prior to receiving IVIG, this group of children failed to show any significant improvement during at least the previous year with a gluten- and casein-free diet, early intervention therapies, applied behavioral treatment, speech and occupational therapy. During the course of IVIG therapy, all educational interventions continued as during the previous year.

### *Design and procedure*

The participants received IVIG injections 4 weeks apart, for a total of six injections. There were only five exceptions – one participant received IVIG 2 weeks after his first injection and two participants received IVIG 8 weeks and one received IVIG 10 weeks after their fifth injection. One child received only five infusions and was not included in the results.

The IVIG preparation used was Gammagard. The dose administered was 400 mg kg$^{-1}$ over a 2–3 hour period.

Parents completed the Aberrant Behavior Checklist (ABC) 2–4 weeks prior to their child receiving their first IVIG injection (baseline) and within 1 week following each of the six IVIG injections. The ABC contains 58 questions that are divided into five subscales. The subscales are: hyperactivity, inappropriate speech, irritability, lethargy, and stereotypy.

Validity and reliability studies have shown the ABC to be an appropriate questionnaire to assess treatment effectiveness [4]. Questions are rated on a four-point scale: 0='not a problem', 1='the behavior is a problem but slight in degree', 2='the problem is moderately serious', and 3='the problem is severe in degree', A one-way analysis of variance (ANOVA) with repeated measures was performed on the total aberrant behavior score and on each of the five subscale scores. The ABC forms were rated by the psychologist (SE) associated with the study.

## Results

The routine laboratory evaluation of a new patient included a complete blood count (CBC), platelet count, serum metabolic assay (SMA), erythrocyte sedimentation rate (ESR), ammonia, lactate, pyruvate, plasma amino acids, urinary organic acids, serum myelin basic protein, serotonin, thyroid antibodies, immunoglobulins GAME, IgG subclasses, anti-streptococcal antibodies, metylenetetrahydrofolate reductase genetic enzyme variants. Patients with a significant history of symptoms of inflammatory bowel disease were colonoscoped and biopsied. The CBCs and SMAs were consistently normal. The other data in the 26 retrospectively analyzed children are presented in Table I.

The participants' overall aberrant behaviors decreased substantially soon after receiving their first dose of IVIG. Further analysis of the total score revealed decreases in hyperactivity, inappropriate speech, irritability, lethargy and stereotypy.

Figures 1–6 present the mean and standard error of the mean for the total aberrant behavior score and the five subscale scores. The results show that the mean baseline scores were relatively high for the total aberrant behavior score and the five subscale scores. Following the first injection of IVIG, all of the mean scores for the total and subscale scores were much lower than the baseline scores. A comparison of the baseline and first post-assessment scores showed a decrease of 37% for the total score, 39% for hyperactivity, 25% for inappropriate speech, 42% for irritability, 35% for lethargy, and 28% for stereotypy. Furthermore, there was a gradual decrease in the total and subscale scores over the subsequent five assessment periods.

The results from the ANOVA were all statistically significant. They were: total aberrant behavior score ($F_{(6,150)}=33.346$, $p<0.001$), hyperactivity ($F_{(6,150)}=33.840$, $p<0.001$), inappropriate speech ($F_{(6,150)}=3.259$, $p<0.01$), irritability ($F_{(6,150)}=25.032$, $p<0.001$), lethargy ($F_{(6,150)}=19.867$, $p<0.001$), and stereotypy ($F_{(6,150)}=12.550$, $p<0.001$).

Another ANOVA with repeated measures was used to analyze the estimated age of onset in relation to the total and five subscale scores. None of the results was statistically significant.

## Discussion

This open retrospective study analyzed 26 children with autism who received IVIG. All five subscales and their total score on the ABC significantly improved. The duration of the improvement after cessation of IVIG treatments remains to be defined in further studies, even though through observation, 22 of these 26 children regressed within 2–4 months.

The biomedical abnormalities observed in the study group were extensive. The increased platelets in 62% and ESR in 54% are non-specific indicators of inflammatory or immunological problems. More specifically, the incidence of 65% autoantibodies to myelin basic protein, 31% thyroid antibodies, 62% confirmed biopsies for colitis, 23% low

Table I. Abnormalities in the intravenous gamma globulin study group.

| Patient | ↑ Platelets | ↑ ESR | ↑ Ammonia | ↑ Lactate | ↑ Pyruvate | ↑ Myelin basic protein | ↑ Serotonin | ↑ Thyroid Abs | Colitis | ↓ Ig antibodies | ↑ ASLO, DNASE | MTHFR + |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ✓ | ✓ | ✓ | ✓ | | ✓ | | | ✓ | | ✓ | ✓ |
| 2 | | | ✓ | | | | ✓ | | | | | ✓ |
| 3 | ✓ | ✓ | | | | | | | ✓ | | | ✓ |
| 4 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | |
| 5 | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ |
| 6 | ✓ | ✓ | ✓ | | | ✓ | | | | | | ✓ |
| 7 | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 8 | ✓ | | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 9 | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | | |
| 10 | | ✓ | | | | | | | | | | ✓ |
| 11 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| 12 | ✓ | | | | | | ✓ | | | | | ✓ |
| 13 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | ✓ | ✓ |
| 14 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | | ✓ |
| 15 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ |
| 16 | | | | | | | | | | | | ✓ |
| 17 | | | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| 18 | ✓ | | ✓ | | | | | | | | | ✓ |
| 19 | ✓ | ✓ | | | | | ✓ | | | | | ✓ |
| 20 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 21 | | ✓ | | | | ✓ | | | | | | ✓ |
| 22 | ✓ | | | | | | ✓ | | ✓ | | | ✓ |
| 23 | | | ✓ | ✓ | ✓ | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| 24 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | | | ✓ |
| 25 | | | | | | | ✓ | | | | | ✓ |
| 26 | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| Total(%) | 16 (62) | 14 (54) | 17 (65) | 13 (50) | 11 (42) | 17 (65) | 14 (54) | 8 (31) | 16 (62) | 6 (23) | 9 (35) | 24 (92) |

ESR, erythrocyte sedimentation rate.

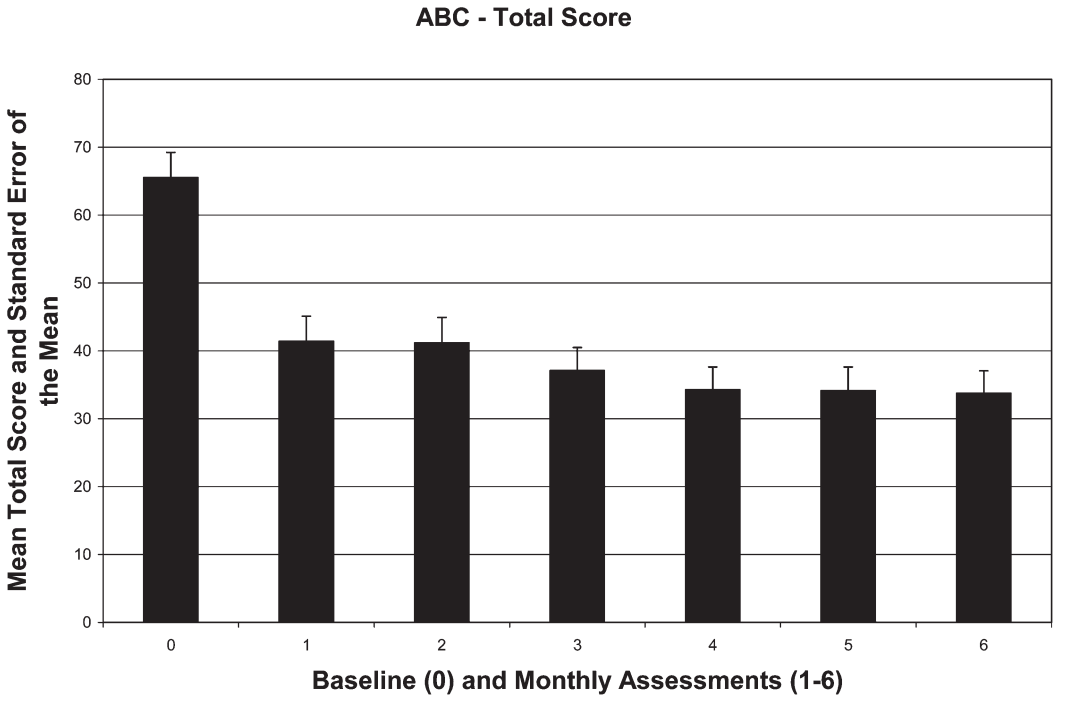


Figure 1.

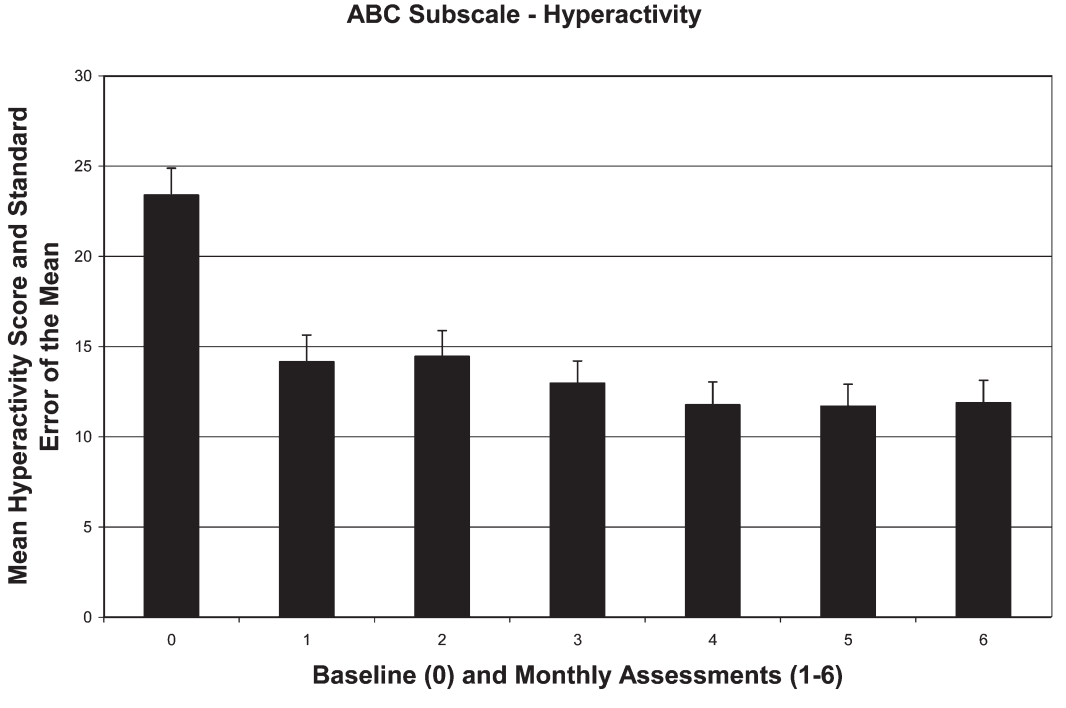


Figure 2.

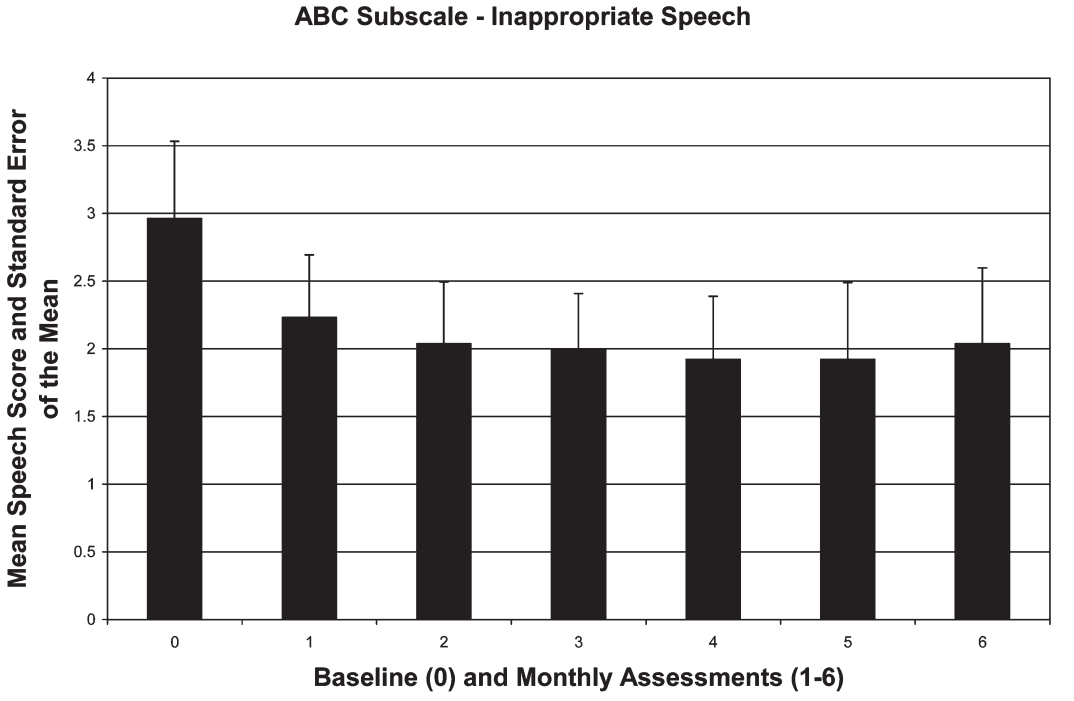


Figure 3.

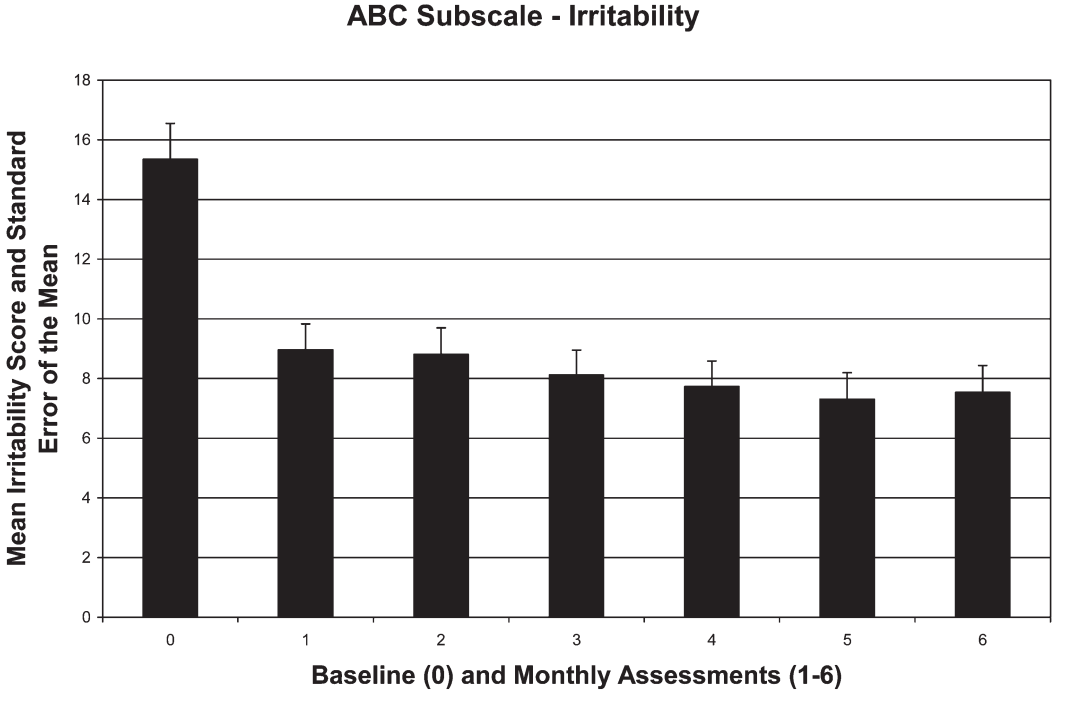


Figure 4.

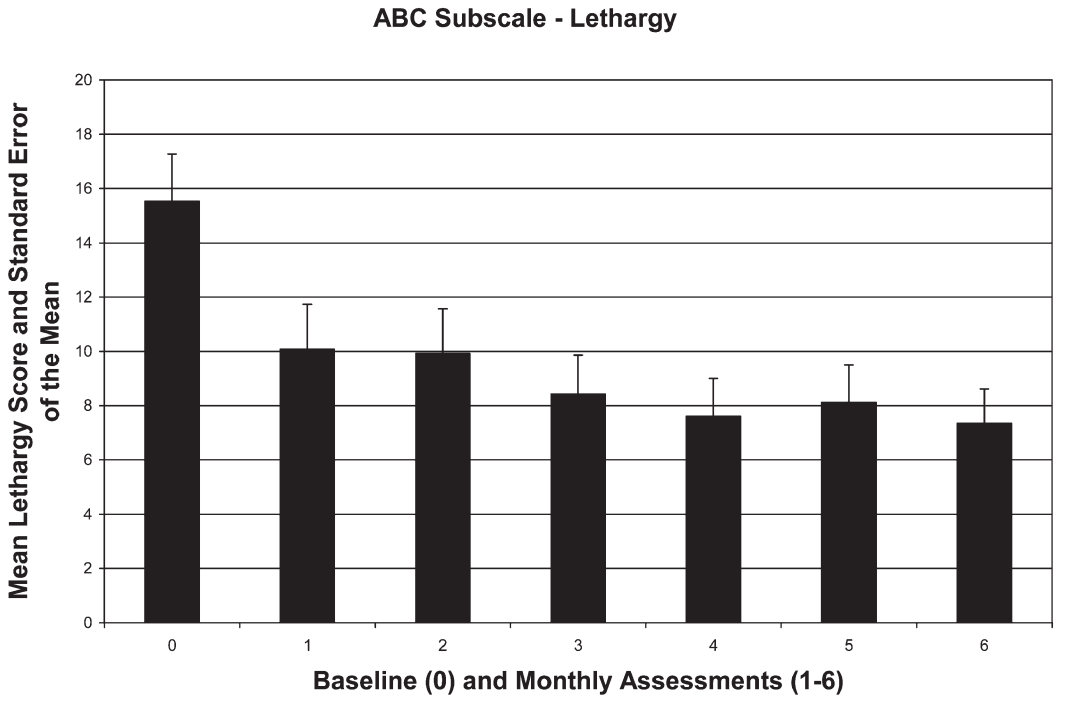


Figure 5.

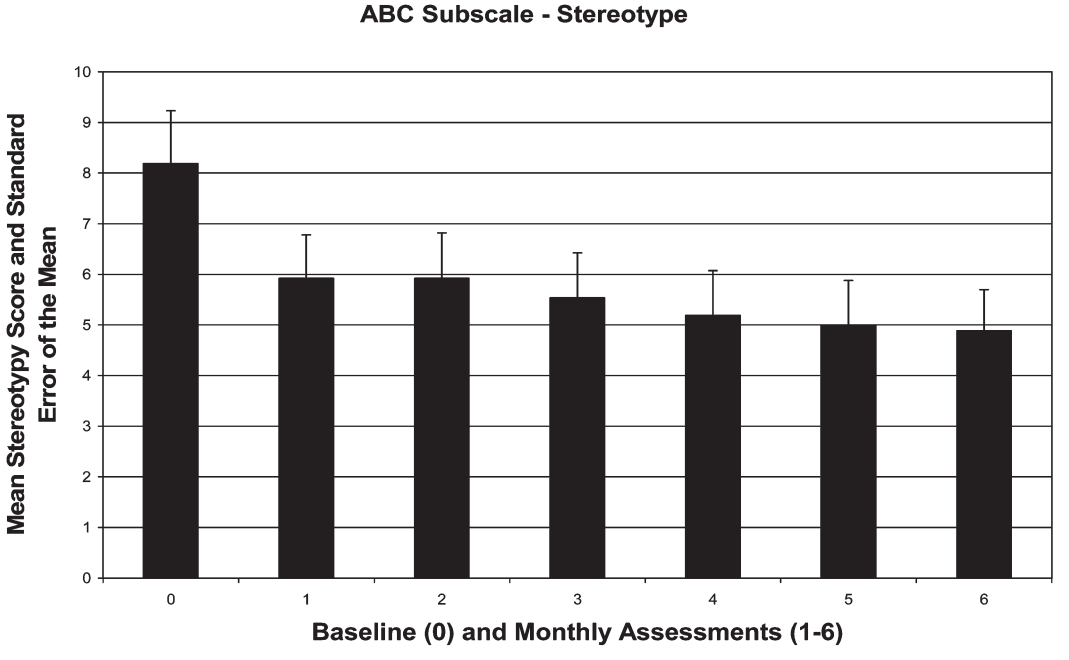


Figure 6.

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immunoglobulin levels, and 35% with high anti-DNASE and anti-streptolysin O titers are indicative of autoimmune disease. Indicators of metabolic dysfunction in these children include high ammonia in 65%, high lactate in 50%, high pyruvate in 492% and a positive genome abnormality of methylenetetrahrofolate reductase (either heterozygous or homozygous) in 92% [5].The reasons for these abnormalities require further investigation.

IVIG is a potent immunological therapy. A NIH Consensus Statement [6] asserted that the risks involved in the use of IVIG are minimal. A review article on IVIG [7] again confirmed their safety. After nearly two decades of experience, the safety of IVIG has been established. For any potential recipient, the small risk of adverse reactions must be weighed against the likelihood of significant benefit. The small number of children in this trial did not exhibit any side-effects of IVIG, but the number was not sufficient for an analysis of any side-effects.

Latov et al. [7] reported that IVIG is used in the treatment of immunological diseases that affect the entire neuroaxis, including the brain, spinal cord, peripheral nerves, muscles, and neuromuscular junction. The panel reviewed the available literature on the use of IVIG in order to evaluate the efficacy of this therapy in neuroimmunological diseases. In prospective, rigorously controlled, double-blind clinical trials, IVIG was found to have proven efficacy in Guillain–Barre syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, dermatomyositis, and Lambert–Eaton myasthenic syndrome. It was found to probably be effective in myasthenia gravis and polymyositis, and possibly effective in several other neuroimmunological diseases. Comi et al. [9] observed clustering of autoimmune disorders in autism.

Further studies are needed to evaluate the use of IVIG for neuroimmunological diseases in which its efficacy is suspected but not proven and to elucidate its mechanisms of action.

In summary, studies have shown a role of immunological disorders in children with autism. This retrospective study showed significant improvement in 26 children with autism treated with IVIG. Risk factors for IVIG are minimal. Autism is a long-term disease with substantial impact on patients and their families. There is a reasonable rationale considering the risk/reward ratio to utilize IVIG therapy in children with autism. A well-controlled placebo double-blind study is needed to further clarify the use of IVIG in ASD.

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