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Brief Reports

Brief Report: Dysregulated Immune System in Children with Autism: Beneficial Effects of Intravenous Immune Globulin on Autistic Characteristics[1]

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INTRODUCTION

Autism is a syndrome of neurodevelopment associated with behavioral impairments of communication, social interaction, and learning and thinking skills, as well as repetitive and self-injurious behaviors. Although the syndrome of autism was described more than 50 years ago by Kanner (1943), the pathogenesis of autism remains unclear. A number of factors, including genetic, infectious, and immunological factors have been implicated. There is increasing evidence for the presence of immunological abnormalities in children with autism. These have included abnormalities of T cells, B cells, natural killer (NK) cells, and complement system (Stubbs, Crawford, Burger, & Vandebork, 1977; Warren, Foster, & Margaretten, 1987; Warren, Foster, Margaretten, & Pace, 1986; Warren et al., 1990, 1991; Yonk et al., 1990). However, a comprehensive immunological study in the same patient group is lacking. In the present study, we have simultaneously examined T cells, B cells, NK cells, and serum IgM, IgA, IgE, IgG1, IgG2, IgG3, and IgG4 in children with autism. Our data show a markedly dysregulated immune system in children with autism.

Intravenous immune globulin (IVIG) has been used in a number of primary immune deficiency syndrome (as a replacement therapy) and autoimmune and immunoinflammatory disorders (as an immunomodula-

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tory therapy), including demyelinating polyneuropathy, and multiple sclerosis (Donaghy et al., 1994; Dwyer, 1992; Gupta, 1986; Mobine, Sarela, & Ahmed, 1995; Schwartz, 1990). In this preliminary study we treated 10 autistic children with IVIG for the following reasons: (a) IgG subclass deficiency in a subgroup of patients with autism, (b) patients with autism demonstrate autoimmune phenomenon as demonstrated by the presence of antimyelin antibodies (Singh, Warren, Odell, Warren, & Cole, 1993) and cell-mediated response to myelin basic protein (Weizman, Weizman, Szekely, Wijsenbeek, & Livni, 1982), (c) possible association of infectious agents (reviewed in Gillberg & Coleman, 1992) with the development of autism, and (d) presence of high titers of antirubella antibodies in mothers of patients with autism (our unpublished observation). The preliminary results of IVIG treatment show an improvement in many features of autism.

MATERIALS AND METHODS

Subjects

Twenty-five children (ages 3–12 years, 17 male, 8 female) were the subjects of the present study. The diagnosis of autism was established according to criteria of DSM-III-R (American Psychiatric Association, 1987).

Monoclonal Antibodies

FITC-Leu4 (CD3), PE-Leu3 (CD4), PE-Leu2 (CD8), PE-Leu16 (CD20), and PE-Leu11c (CD16) monoclonal antibodies and premixed FITC-IgG1 and PE-IgG2 isotype controls were purchased from Becton-Dickinson, San Jose, CA.

Serum Immunoglobulins

All measurements were done on fresh serum samples. Serum IgG, IgM, and IgA were measured by nephelometry, serum IgG subclasses (IgG1, IgG2, IgG3, and IgG4) were measured by ELISA assay, and IgE was measured by fluorescence polarization immunoassay (Yman, 1991).

Lymphocyte Subsets

Lymphocyte subset study was performed on whole blood samples by dual color flow cytometry. Seven 12 × 75 falcon tubes were labeled as fol-

lows: Tube 1, Leucogate (for gating); Tube 2, IgG1/IgG2 (for isotype control); Tube 3, Leu4 (For CD3 + T cells); Tube 4, Leu4/Leu3 (for CD3 + CD4 + helper/inducer T cells); Tube 5, Leu4/Leu2 (for CD3-CD8 + cytotoxic/suppressor T cells); Tube 6, Leu4/Leu16 (for CD3-CD20 + B cells); and Tube 7, Leu4/Leu11c (for CD3–CD16+NK cells). One hundred microliters of monoclonal antibodies were added to the corresponding tube and then 100 µl of whole blood was added to each tube. Tubes were vortexed and incubated at room temperature in dark for 15 minutes. Two milliliters of 1x FACS lysing buffer (Becton-Dickinson, San Jose, CA) was added to lyse red blood cells. Tubes were vortexed and incubated further at room temperature in the dark for 5 minutes. Tubes were centrifuged, supernatants discarded, and cell pellets were washed with 2 ml phosphate buffer saline. Cell pellets were resuspended in 0.5 ml of 1% paraformaldehyde and then analyzed with FACScan (Becton-Dickinson, San Jose, CA). For each population, 10,000 cells were counted. Data are expressed for both proportions and absolute numbers.

Intravenous Immunoglobulin Therapy

Ten children with autism were given IVIG. Parents were instructed to administer oral Benadryl prior to arrival for infusion. IVIG (400 mg/kg) was started at a rate according to manufacturer's instructions. IVIG treatment was given at 4-week intervals and for at least 6 months. Information was obtained from their speech and behavior therapists and psychiatrists (without their knowledge of the type of treatment) for behavioral, cognitive, and developmental characteristics, some of whom used a number of tests, including Peabody Picture Vocabulary Test, the Vineland Adaptive Behavior Scale, skill evaluation, and preschool language test.

RESULTS

Serum Immunoglobulins (Table I)

A marked abnormality in serum immunoglobulin levels was observed in children with autism when compared to age-matched controls (our laboratory controls). Both serum IgM and IgE levels were increased in 14 of 25 (56%) of patients. Two patients had selective IgE deficiency. Five of 25 (20%) patients had deficiency of serum IgA, 2 had selective IgA deficiency, and the other 3 had low levels of serum IgA. Five of 25 (20%) of patients had low levels of IgG subclasses. IgG subclass deficiency was not

Table I. Serum Immunoglobulins in Children with Autism

Patient	Age (years)	Sex	IgM (mg/dl)	IgA (mg/dl)	IgE (IU)	IgG_1 (mg/dl)	IgG_2 (mg/dl)	IgG_3 (mg/dl)	IgG_4 (mg/dl)
1	3	F	108[b]	<6.6[a]	110[b]	840[b]	223	80	<2[a]
2	3	M	82	21[a]	115[b]	511	69	27	6
3	5	M	109[b]	<7.0[a]	145[b]	1479[b]	199	56	13
4	6	M	170[b]	99	13	769	279	37	113
5	4	M	152[b]	26[a]	147[b]	339	242	37	25
6	6	M	47	[illegible]	[illegible]	640	319	40	97
7	[illegible]	M	102	27	<3[a]	595	90	35	11
8	11	F	171[b]	93	107[b]	810	305	11[a]	74
9	12	M	96	80	919[b]	470	218	58	24
10	5	M	68	91	14	475	164	24	<2[a]
11	3	M	77	99	10	486	34[a]	41	14
12	5	M	198[b]	171[b]	4	753	118	45	49
13	4	M	53	129	7	502	119	29	27
14	5	M	63	86	18[b]	501	178	28	53
15	4	M	141[b]	65	25[b]	511	106	16	33
16	6	F	168[b]	178	8	818	389	75	8
17	11	F	41	64	14	612	201	36	31
18	7	M	93	63	6	870	71	64	37
19	3	M	65	43[a]	16[b]	387	90	27	31
20	12	M	96	123	145[b]	340	28	32	10
21	3	M	111[b]	65	43[b]	270[a]	131	41	27
22	3	F	100[b]	197[b]	15	749	462	145	45

Table I. Continued

Patient	Age (years)	Sex	IgM (mg/dl)	IgA (mg/dl)	IgE (IU)	IgG_1 (mg/dl)	IgG_2 (mg/dl)	IgG_3 (mg/dl)	IgG_4 (mg/dl)
23	6	F	245[b]	93	<3[a]	613	80	22	7
24	4	F	154[b]	70	45[b]	840	209	40	65
25	3	F	103[b]	69	243[b]	526	52	41	26

Normal values (ranges in 95% confidence limit)

Age (years)	IgG_1 (mg/dl)	IgG_2 (mg/dl)	IgG_3 (mg/dl)	IgG_4 (mg/dl)
3–4	280–800	50–440	6–110	2–115
5–6	290–820	60–500	8–130	2–120
7–8	300–1120	60–500	12–130	2–120
9–14	300–1300	70–500	12–130	2–120

Age (years)	IgM (mg/dl)	IgA (mg/dl)
3–5	21–95	54–150
6–8	26–110	53–219
9–11	33–125	61–206
12–15	33–258	69–227

	IgE (IU)
0–13	2–15
14 Yr–over	10–150

[a]Abnormally low levels.
[b]Abnormally high levels.

limited to any subclass, low levels were observed in IgG1 (1), IgG2 (1), IgG3 (1), and IgG4 (2). Two patients had high levels of IgG1.

Lymphocyte Subsets (Table II)

T Cells and T Cell Subsets. The proportions of total T cells (CD3+) were decreased in 4 of 25 (16%) and absolute numbers of CD3 + were decreased in only 1 patient with autism when compared with age-matched controls (Erkeller-Yuksel et al., 1992). In contrast, the absolute numbers of CD3+ T cells were increased in 9 of 25 (36%) of patients with autism. Approximately 64% of autistic children demonstrated abnormality of the proportions of CD3+CD4+ (helper/inducer) T cells and 48% showed abnormal numbers of CD3+CD4+ T cells. Eight of 25 (32%) had decreased proportions and 7 of 25 (28%) had decreased numbers of CD3+CD4+ T cells. Eight of 25 (32%) patients had increased proportions and 5 of 25 (20%) had increased numbers of CD3+CD4+ T cells. The abnormality of the proportions and numbers of CD3+CD8+ (cytotoxic/suppressor) T cells was observed in 64% and 24% of children with autism, respectively. Six of 25 patients (24%) had increased proportions, whereas 10 of 25 (40%) had decreased numbers of CD3+CD8+ T cells when compared to age-matched controls. The absolute numbers of CD3+CD8+ T cells were decreased in 4 of 25 (16%) and increased in 2 of 25 (8%) of patients. The ratio of CD4+/CD8+ T cells was abnormal in 60% of patients increased in 7 of 25 (28%) and decreased in 8 of 25 (32%) of children with autism.

B Lymphocytes. The quantitative abnormality of CD20+ B cells was observed in 60% (for proportions) to 64% (for absolute numbers) of children with autism. Twelve of 25 (48%) had decreased proportions and 3 of 25 (12%) had increased proportions of CD20+ B cells. The absolute numbers of CD20+ B cells were decreased in one and increased in 5 of 25 patients.

Natural Killer Cells. Eleven of 24 children (45%) had decreased and 2 of 25 (8%) had increased proportions of CD3-CD16+ NK cells. The absolute numbers of C3-CD16+ NK cells were decreased in 6 of 24 (25%) and increased in 3 of 24 (12%) children with autism. Five patients showed both decreased proportions and numbers of CD3- and CD16+ NK cells.

Effect of Intravenous Immunoglobulin on Autistic Characteristics (Table III)

Ten patients were given IVIG at 400 mg/kg at 4-week intervals for 6 months and all 10 patients were evaluated throughout this period. The de-

Table II. Lymphocyte Subsets in Children with Autism

Patient No.	Age (years)	Sex	CD3+		CD3+CD4+		CD3+CD8+		CD4/CD8	CD3-CD20+		CD3-CD16+	
			%	Abs. No.	%	Abs. No.	%	Abs. No.	Ratio	%	Abs. No.	%	Abs. No.
1	3	F	58[a]	3712[b]	37	2368[b]	20[a]	1280	1.9[b]	37[b]	2368	5[a]	320
2	3	M	76[b]	4408[b]	42[b]	2436[b]	30	1740	1.4	18[a]	1044	4[a]	232
3	5	M	60	1560	22[a]	572[a]	19[a]	494[a]	0.9[a]	20[a]	520[a]	10	260
4	6	M	76[b]	2888	47[b]	1786	30	1140	1.6	15[a]	570[a]	—[c]	—[c]
5	4	M	79[b]	2765	49[b]	1715	35[b]	1225	1.4	16[a]	560[a]	4[a]	140[a]
6	6	M	66	1914	29[a]	841[a]	29	841	1.0	21	609[a]	6[a]	174[a]
7	3	M	63	2016	29[a]	928[a]	25	800	1.2	25	800	6[a]	192[a]
8	11	F	56[a]	1344[a]	28[a]	672[a]	31	744	0.9[a]	19	456	17	168[a]
9	12	M	78[b]	1950	34	850	32	800	1.1	16	400	8	200
10	5	M	70	2030	30	870[a]	38[b]	1102	0.8[a]	10[a]	290[a]	10	290
11	3	M	68	2244	20[a]	660[a]	49[b]	1617	0.4[a]	24	792	21	693[b]
12	5	M	81[b]	2025	25[a]	625[a]	48[b]	1200	0.5[a]	5[a]	125[a]	8	200
13	4	M	68	2516	38	1406	23[a]	851	1.7	22	184[a]	4[a]	148[a]
14	5	M	57[a]	2166	29[a]	1102	28	1064	1.0	36[b]	1368[b]	4[a]	152[a]
15	4	M	73[b]	4745[b]	51[b]	3315[b]	23[a]	1495	2.2[b]	22	1430	6[a]	390
16	6	F	74[b]	3034[b]	30	1230	27	1107	1.1	20[a]	820	6[a]	246
17	11	F	73[b]	1971	59[b]	1593	13[a]	351[a]	4.5[b]	11[a]	297[a]	9	243
18	7	M	67	2010[b]	24[a]	720	63[b]	1890[b]	0.4[a]	14[a]	420[a]	21[b]	630[b]
19	3	M	70	1820	43[b]	1118	22[a]	572[a]	1.9[b]	17[a]	442[a]	12	312
20	12	M	71	2982[b]	32	1344	44[b]	1848[b]	0.7[a]	16	672[b]	17[b]	714[b]

Table II. Continued

Patient No.			CD3+		CD3+CD4+		CD3+CD8+		CD4/CD8	CD3-CD20+		CD3-CD16+	
Age (years)		Sex	%	Abs. No.	%	Abs. No.	%	Abs. No.		%	Abs. No.	%	Abs. No.
21	3	M	78[b]	3432[b]	56[b]	2464[b]	20[a]	880	2.8[b]	19[a]	836	5[a]	220
22	3	F	51[a]	1836	31	1116	23[a]	828	1.3	35[b]	1260	11	393
23	6	F	64	3776[b]	44[b]	2596[b]	12[a]	708[a]	3.6[b]	25	1475[b]	8	472
24	4	F	61	2623	39	1677	19[a]	817	2.0[b]	27	1161	6[a]	258
25	3	F	60	3060[b]	32	1632	25	1275	1.3	13[a]	663[a]	11	561

Normal values (ranges)

Age group	CD3+	CD4+	CD8+	CD4/CD8[d]	CD20+	CD16+
1–6						
%	62–69	30–40	25–32	1.0–1.6	21–28	8–15
Abs. No.	1800–3000	1000–1800	800–1500		700–1300	200–600
7–17						
%	66–76	33–41	27–35	1.1–1.4	12–22	9–16
Abs. No.	1400–2000	700–1100	600–900		300–500	200–300

[a]Abnormally low values.
[b]Abnormally high values.
[c]Not determined.
[d]CD4/CD8 ratio range.

Table III. Effect of Intravenous Immune Globulin on Autistic Characteristics

Patient Age (years)	Sex	Degree of improvement[a]	Characteristic changes following 6 months of infusion
3	M	+++	Very calm, better eye contact, counting numbers, painting X-mas cards, responding "normal for age"
4	M	+++	Speech dramatically improved (400+ nouns, 300+ verbs), plays appropriately, good eye contact, stims only when under stress, regular school with speech therapy
4	M	+	No hyperactivity, speaking full sentences, more articulate speech, more aware of surrounding, good eye contact, more social
3	M	+++	Increased eye contact, improved attention span, speech improved, however not always coherent speech, calmer behavior, much more independent and expressive
5	M	+	Calmer, sleeps well, increased verbal expression, improved and appropriate behavior, better eye contact
4	M	+++	Verbalizing, much calmer, no stimming, good eye contact. Curently in kindergarten with tutor
5	M	+	Better eye contact, more aware of surroundings, much calmer, no echolalia, still no spontaneous speech, however speech is articulate
3	M	++++	Speech almost normal, behavior normal, good eye contact, more social, attending regular school
3	M	+	Improved focus, better eye contact, more verbal, much calmer, improved awareness of surroundings
6	F	+	More initiative and appropriate physical play, calmer affect, better eye contact

[a] + = minimal, ++ = modest, +++ = marked, ++++ = striking.

gree of improvement was given arbitrary symbols of + to +++ for improvement ranging from mild to striking. A consistent (although variable) change was observed in calmer and improved social behavior, better eye contact, loss of echolalia, and response to commands. The speech was improved in terms of better articulation and improved vocabulary; however, little effect was observed on spontaneous meaningful speech in most patients. One of the patients almost completely recovered speech and another had marked improvement in speech. These two patients are attending regular school.

DISCUSSION

In this preliminary study a marked abnormality of immune parameters was observed in children with autism when compared to age-matched controls. This included abnormalities of various lymphocyte subsets and serum levels of various immunoglobulin classes and subclasses. Furthermore, intravenous immunoglobulin treatment resulted in improved autistic features.

Abnormalities of T cell and T cell subsets have been described in autism. Yonk et al., (1990) reported lower numbers of CD2+ (total) T cells in patients with autism (age range 3–31 years, M = 11.0). However, no data were provided for individual patients and it is unclear from their study how many patients had decreased T cell numbers. In the present study of children (age range 3–12 years, M = 6), 4 of 25 patients had decreased proportions and 9 of 25 had increased proportions of CD3+ T cells. Nine of 25 patients had increased numbers and only 1 had decreased number of CD3+ T cells. This discrepancy between our present study and that of Yonk et al. could be due to the different age groups of the patients and different monoclonal antibodies used to define total T cell subsets. Yonk et al. also reported decreased proportions and numbers of CD4+ T cells in a group of patients with autism. In the present study, 7 of 25 patients had decreased proportions and numbers of CD3+CD4+ T cells. Furthermore, a quantitative decrease in CD4+CD45RA+ naive cells has also been reported in patients with autism (Menage, Thibault, Barthelemy, Lelord, & Bardos, 1992; Warren et al., 1990). We observed that the proportions and numbers of CD8+ cells were increased or decreased in children with autism. Yonk et al. (1990) also observed deceased numbers of CD8+ T cells in 4 of 25 patients. In the present study we demonstrated a marked abnormality of CD4+/CD8+ T cell ratios. The decrease in CD4+ T cells in autism may explain decreased T cell-mediated response to mitogens (Stubbs et al., 1977; Warren et al., 1986), and increased colo-

nization with *Candida albicans*, whereas increased-CD4+ T cells may explain an enhanced immune response to brain antigens (Weizman et al., 1982) and antimyelin antibodies in autism (Singh et al., 1993). In our study, antimyelin antibodies were present in 6 of 25 patients (data not shown).

Natural killer (NK) cells are large granular lymphocytes that appear to play an important role in defense against virus-infected cells and tumor cells (Herberman & Ortaldo, 1981). Warren et al. (1987) reported decreased NK activity in 12 of 31 (38%) of patients with autism; however, they found no correlation with the proportions of Leu 11+ (CD16+) cells. No data were given as to how many of their patients had abnormality of CD16+ cells. In the present study, we observed that 11 of 25 (45%) patients had decreased proportions, and 6 of 24 (24%) had decreased absolute numbers of CD3-CD16+ NK cells. Our quantitative results of NK cells differ from those of Warren et al. (1987); however, (a) Warren et al. gave no data on individual patients or how many patients had low NK cells (only mean values for entire group was given); (b) patient group (ages 3–28 years) had an unspecified number of children which were also compared with healthy adults; (c) no dual color analysis of CD3 and CD16 was used to exclude CD3+ CD16+ cells. Taking together the functional data of Warren et al. and our quantitative data, it appears that a sizable proportion of children with autism have a deficiency of NK cell numbers and functions. This deficiency may play a role in increased susceptibility to various virus infections that in turn may play a role in the pathogenesis of autism.

CD20+ B cells were decreased in a large number of children with autism. This observation is in agreement with Yonk et al. (1990) who also reported lower numbers of CD20+ B cells; however, these investigators did not provide data on individual patients. The decreased CD4+ T cells and decreased B cells could be responsible for decreased specific antibody response in autism (Stubbs, 1976).

A marked imbalance of various immunoglobulins classes and subclasses was observed. Two patients (8%) had selective IgA deficiency and another 3 (12%) had low levels of serum IgA. This is an unusually high frequency of selective IgA deficiency, which occurs in the general population with a frequency of 1 in 700–1000. Patients with selective IgA deficiency are more prone to develop allergies and autoimmune phenomena (Chapel & Haeney, 1993). This selective IgA deficiency, with or without high frequency of elevated serum IgE levels observed in this study, may explain an increased incidence of allergies in children with autism. Furthermore, imbalance of immunoregulatory T cell subsets and increased selective IgA deficiency may account for autoimmune phenomena of antibrain and antimyelin antibody responses observed in autism (Singh et

al., 1993; Weizman et al., 1982). A high frequency of elevated serum IgM may suggest a presence of persistent antigenic stimulation in vivo. Approximately 20% had deficiency of one of the subclasses of IgG which could put a subgroup of patients with autism in high risk for infections, especially sinopulmonary infections. Two patients had selective IgE deficiency. The significance of selective IgE deficiency is presently unclear.

An increase in serum immunoglobulins observed in the present study and reported and depressed cell-mediated responses (Stubbs et al., 1977; Warren et al., 1986) in autism may suggest a shift in the T helper cell population from T_H1 to T_H2 type (Romagnani, 1995) in a subset of patients with autism.

Intravenous immunoglobulin has been used as a replacement therapy in a number of primary and secondary immune deficiency states and as an immunomodulatory therapy in a number of autoimmune and immunoinflammatory disorders, including chronic demyelinating polyneuropathy, multiple sclerosis, and Guillain-Barre syndrome (Donaghy et al., 1994; Dwyer, 1992; Gupta, 1986; Mobini et al., 1995; Schwartz, 1990; Van der Meche & Schmitz, 1992). Interestingly, both the patients with Guillain-Barre syndrome and autism have serum antimyelin antibodies (Koski, 1987; Singh et al., 1993). The present study was initiated in patients who had IgG subclass deficiency and/or high titers of maternal rubella antibody titers. We theorized that the high titers of rubella antibody (>1,280 vs. normal <320) present in mothers of children with autism would be transplacentally transferred and may also persist for a prolonged period in the child. When such a child gets MMR immunization, rubella antigen may complex with preexisting antibodies and such complexes might play a role in the pathogenesis of autistic features. Furthermore, intravenous immune globulin is known to remove immune complexes. However, when children with autism who did not have IgG subclass deficiency or high maternal rubella antibody tiers were treated with IVIG, similar results were obtained.

In this preliminary study, 6 months of IVIG infusion resulted in marked improvement in a number of autistic characteristics, including eye contact, calmer behavior, speech, echolalia, and so forth. The earliest effect is observed on calmer behavior and better eye contact. Speech is slow to improve and spontaneous speech improvement appears to develop last. In a few patients, discontinuation of IVIG after 6 months resulted in the reappearance of features of autism. These patients were improved when IVIG was restarted. Two patients were evaluated for 5 months prior to and 5 months following IVIG infusion. In both patients no significant changes were observed, positive or negative, prior to IVIG; however, significant changes were observed following IVIG therapy with regard to spontaneous conversational speech, thinking and processing, oral reading, and

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An increase in serum immunoglobulins observed in the present study and reported and depressed cell-mediated responses (Stubbs et al., 1977; Warren et al., 1986) in autism may suggest a shift in the T helper cell population from T_H1 to T_H2 type (Romagnani, 1995) in a subset of patients with autism.

Intravenous immunoglobulin has been used as a replacement therapy in a number of primary and secondary immune deficiency states and as an immunomodulatory therapy in a number of autoimmune and immunoinflammatory disorders, including chronic demyelinating polyneuropathy, multiple sclerosis, and Guillain-Barre syndrome (Donaghy et al., 1994; Dwyer, 1992; Gupta, 1986; Mobini et al., 1995; Schwartz, 1990; Van der Meche & Schmitz, 1992). Interestingly, both the patients with Guillain-Barre syndrome and autism have serum antimyelin antibodies (Koski, 1987; Singh et al., 1993). The present study was initiated in patients who had IgG subclass deficiency and/or high titers of maternal rubella antibody titers. We theorized that the high titers of rubella antibody (>1,280 vs. normal <320) present in mothers of children with autism would be transplacentally transferred and may also persist for a prolonged period in the child. When such a child gets MMR immunization, rubella antigen may complex with preexisting antibodies and such complexes might play a role in the pathogenesis of autistic features. Furthermore, intravenous immune globulin is known to remove immune complexes. However, when children with autism who did not have IgG subclass deficiency or high maternal rubella antibody tiers were treated with IVIG, similar results were obtained.

In this preliminary study, 6 months of IVIG infusion resulted in marked improvement in a number of autistic characteristics, including eye contact, calmer behavior, speech, echolalia, and so forth. The earliest effect is observed on calmer behavior and better eye contact. Speech is slow to improve and spontaneous speech improvement appears to develop last. In a few patients, discontinuation of IVIG after 6 months resulted in the reappearance of features of autism. These patients were improved when IVIG was restarted. Two patients were evaluated for 5 months prior to and 5 months following IVIG infusion. In both patients no significant changes were observed, positive or negative, prior to IVIG; however, significant changes were observed following IVIG therapy with regard to spontaneous conversational speech, thinking and processing, oral reading, and

attention span. At this stage it is unclear how long IVIG is indicated in autism. Because of the small sample and only one female in this trial of IVIG, the effect of age and gender on the responsiveness to IVIG treatment cannot be ascertained; however, it appears that younger children respond earlier (after 2–3 infusion) as compared to older children (after 4–5 infusions). The mechanisms of beneficial effects of IVIG in autism are presently unknown. However, several possibilities could be entertained. These include its role in correction of underlying antibody deficiency, modifying abnormal immunoregulatory functions and molecular mimicry via an idiotypic–antiidiotypic network, and/or possibly remyelination in the brain. It has been suggested that autoimmunity may be initiated by molecular mimicry in which antibodies or T cells generated in the response to an infectious agent cross-react with self-antigens (e.g., myelin basic protein). Antiidiotypic antibodies (antibodies against epitopes in variable domain of immunoglobulin) present in IVIG manipulate the immune system via idiotype–antiidiotype interactions in three ways. First, they can neutralize an autoantibody; second antiidiotypic antibodies may bind and down-regulate the B cell receptor for antigen, thus decreasing autoantibody production and; third, regulatory T cells may recognize antiidiotypic antibody or a complex of idiotype-antiidiotypic antibodies, and thereby regulate the production of cytokines from such cells.

A controlled double-blind, placebo-controlled multicenter study is being planned to extend the observations of the present preliminary study, to develop a profile of patients that are most likely to respond significantly to the treatment with IVIG, and to examine the effect of IVIG on dysregulated immune functions in autism.

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