Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood

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Summary

Background In children, exacerbations of tics and obsessive symptoms may occur after infection with group A β-haemolytic streptococci. If post-streptococcal autoimmunity is the cause of the exacerbations, then children might respond to immunomodulatory treatments such as plasma exchange or intravenous immunoglobulin (IVIG). We studied whether plasma exchange or IVIG would be better than placebo (sham IVIG) in reducing severity of neuropsychiatric symptoms.

Methods Children with severe, infection-triggered exacerbations of obsessive-compulsive disorder (OCD) or tic disorders, including Tourette syndrome, were randomly assigned treatment with plasma exchange (five single-volume exchanges over 2 weeks), IVIG (1 g/kg daily on 2 consecutive days), or placebo (saline solution given in the same manner as IVIG). Symptom severity was rated at baseline, and at 1 month and 12 months after treatment by use of standard assessment scales for OCD, tics, anxiety, depression, and global function.

Findings 30 children entered the study and 29 completed the trial. Ten received plasma exchange, nine IVIG, and ten placebo. At 1 month, the IVIG and plasma-exchange groups showed striking improvements in obsessive-compulsive symptoms (mean improvement on children's Yale-Brown obsessive compulsive scale score of 12 [45%] and 13 [58%], respectively), anxiety (2·1 [31%] and 3·0 [47%] improvement on National Institute of Mental Health anxiety scale), and overall functioning (2·9 [33%] and 2·8 [35%] improvement on National Institute of Mental Health global scale). Tic symptoms were also significantly improved by plasma exchange (mean change on Tourette syndrome unified rating scale of 49%). Treatment gains were maintained at 1 year, with 14 (82%) of 17 children "much" or "very much" improved over baseline (seven of eight for plasma exchange, seven of nine for IVIG).

Interpretation Plasma exchange and IVIG were both effective in lessening of symptom severity for children with infection-triggered OCD and tic disorders. Further studies are needed to determine the active mechanism of these interventions, and to determine which children with OCD and tic disorders will benefit from immunomodulatory therapies.

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Introduction

Obsessive-compulsive disorder (OCD) and tic disorders are common in childhood, affecting 1–2% of school-aged children and adolescents. The obsessional thoughts and compulsive rituals of OCD are generally chronic and disabling, and cause serious psychological distress and lifelong impairment of social and occupational functioning.[1] Treatment with serotonin reuptake blocking drugs, behaviour therapy, or both, helps more than 75% of patients, but most show only a partial response, and relapse when medication is discontinued. Tic disorders, including Tourette syndrome, have a more variable course than OCD, since the severity of symptoms waxes and wanes. About two in three of these patients will have complete or partial remission of symptoms during adolescence.[2] Medications such as neuroleptics can reduce tic severity, but do not eliminate them.

The cause of OCD and tic disorders is unknown, although the two disorders may have a common cause that is a combination of genetic and environmental factors.[3] Post-streptococcal autoimmunity has been postulated as one possible environmental trigger, and Sydenham's chorea, the neurological manifestation of rheumatic fever, has been proposed as a potential model of pathophysiology.[4]

Molecular mimicry is thought to play a part in the aetiology of Sydenham's chorea, through a process in which antibodies against group A β-haemolytic streptococci crossreact with neuronal cells to produce inflammation in the central nervous system (particularly within the basal ganglia), resulting in chorea, muscle weakness, and emotional lability.[5,6] In some cases, obsessions, compulsions, and tics may also be mediated by post-streptococcal autoimmunity. Several studies have shown crossreactive antistreptococcal antibodies in children with OCD and tic disorders, and a marker of susceptibility to rheumatic fever has been shown in a subgroup of these patients.[7–9] The subgroup shares a unique clinical course and is identified by the acronym PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).[10]

The pathophysiology proposed for Sydenham's chorea suggests that treatments that interrupt the autoimmune process might lessen the severity of symptoms. Preliminary results for a controlled trial of plasma exchange and intravenous immunoglobulin (IVIG) in patients with Sydenham's chorea showed efficacy of both treatments.[11] We hypothesise that if the aetiology of PANDAS is similar to that in Sydenham's chorea, then immunomodulatory therapies might also be effective treatments for exacerbated neuropsychiatric symptoms.[12] Steroid therapy was not a viable treatment option for our study, because tics and OCD may worsen during steroid administration.[13] Plasma exchange and IVIG were chosen as the active treatments because of their record of safety and effectiveness in several childhood and adult immune-mediated diseases, as well as anecdotal reports of symptom improvement in patients with

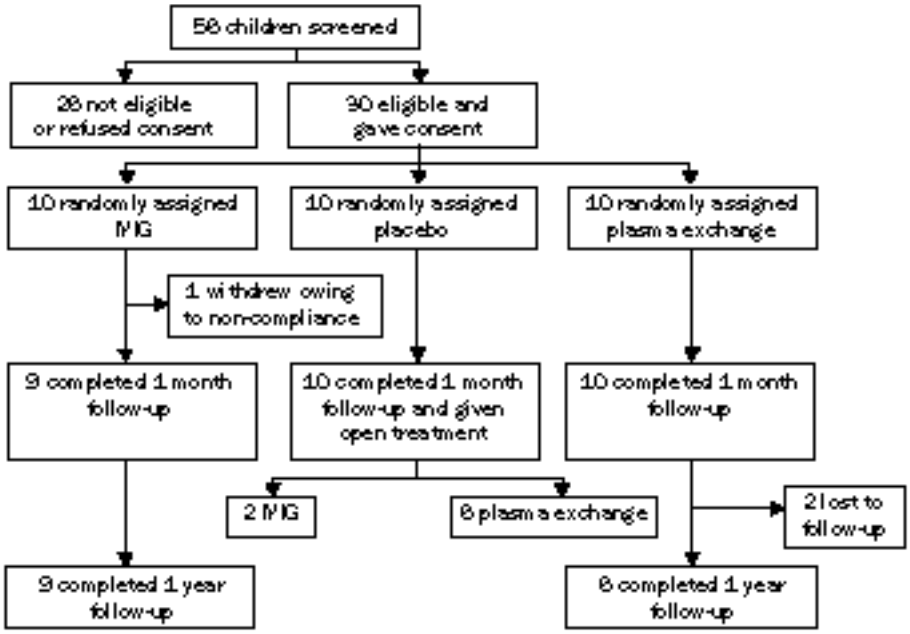

Figure 1: **Trial profile**

infection-triggered exacerbations of OCD.[12,14–16] We aimed to show whether plasma exchange and IVIG would be better than placebo in decreasing neuropsychiatric symptoms in children with infection-triggered exacerbations of OCD and tic disorders.

Patients and methods

Patients

Children aged 5–14 years were recruited nationwide over 4 years via letters to paediatricians, neurologists, and psychiatrists. Referrals were screened by telephone interview to assess study eligibility. Those parents who were interested in the treatment protocol and whose children fitted our criteria were assessed at the National Institute of Mental Health outpatient clinic. Eligibility criteria were: a tic disorder, obsessive compulsive disorder, or both, that met definitions in the Diagnostic and Statistical Manual of Mental Disorders;[17] onset of neuropsychiatric signs and symptoms before puberty; a history of sudden onset of signs and symptoms, or an episodic course characterised by abrupt exacerbations and periods of partial or complete remission; evidence of and association between streptococcal infection and onset or exacerbation of signs and symptoms (requirements for the PANDAS subgroup);[10] and current exacerbation severe enough to cause significant distress and interfere with the child's social functioning in at least two spheres (home, school, social relations).

Children were excluded from the study if they had a history of Sydenham's chorea or rheumatic fever, autism, schizophrenia or other psychotic disorder, a neurological disorder other than a tic disorder, an autoimmune disorder, or other medical illness. Immunoglobulin concentrations were measured and children were excluded from the study if they had IgA deficiency (a contraindication to IVIG administration).[18]

At initial assessment, most children were taking neuropsychotropic medications, including serotonin reuptake inhibitors for OCD symptoms, and clonidine or neuroleptic medications for tics. These medications were continued at constant dose for 1 month, after which time dose could be adjusted as needed by each child's physician. Oral penicillin or erythromycin was given during follow-up according to American Heart Association guidelines for prophylaxis against rheumatic fever, to protect against streptococcal infections.

The study protocol was approved by the institutional review board at the National Institute of Mental Health, Bethesda, MD, USA. Each parent and child gave consent or assent, respectively, for the investigation.

Study design

Children who met criteria for study entry underwent baseline medical, neurological, and psychiatric assessment. This assessment included a structured psychiatric interview,[19] echocardiography, and laboratory studies, including antistreptolysin-O test, antistreptococcal deoxyribonucleic B titres, and throat culture. We measured severity of neuropsychiatric signs and symptoms with the Tourette syndrome unified rating scale,[20–22] children's Yale-Brown obsessive compulsive scale,[23] global assessment scale,[24] clinical global impression scales of symptom severity and change,[25] and the National Institute of Mental Health rating scales for global functioning, anxiety, and depression.[26] The latter scales were used as a template for a new measure, the National Institute of Mental Health emotional lability scale, which we used to rate irritability and emotional lability on a scale from 0 (no irritability) to 4 (very irritable, oppositional behaviour daily). The global assessment scale is a global assessment of functioning in which high scores show better psychosocial functioning and low scores show greater impairment. On all the other rating scales, scores decrease as symptoms improve.

After baseline assessment, children were randomly assigned plasma exchange, IVIG, or placebo (saline solution) by randomisation chart. Investigators and study participants were unaware of whether the child received IVIG or placebo, but were aware of who received plasma exchange. Children randomly assigned IVIG or placebo received 1 g/kg IVIG (Gammagard, Hyland Division, Baxter Healthcare, Deerfield, IL, USA) or the same amount of saline solution daily for 2 consecutive days. To maintain double masking, the bottles and tubing were shielded from view, and all patients were treated with diphenhydramine and paracetamol (acetaminophen) to lessen the occurrence of side-effects (nausea, vomiting, headache), which might have revealed the active treatment.

Plasma exchange was done in the Department of Transfusion Medicine of the National Institute of Health Clinical Center. One plasma volume (45 mL/kg bodyweight) was exchanged in each procedure, and five or six procedures were done, once a day or on alternate days, to complete a course in 10–12 days. Exchanges were done by use of a Spectra apheresis device (Cobe, Lakewood, CO, USA) with citrate anticoagulant (acid citrate dextrose formula A, ratio 13:1). 80% of the replacement fluid was 5% albumin, and the remainder was normal saline. External jugular venous access with a double-lumen central venous catheter was used in seven children; in the other three children, bilateral antecubital veins were used. Symptoms shown during apheresis were recorded as mild, moderate, or severe adverse effects depending on degree of discomfort and ability to continue with the procedure.

Medication	Plasma exchange (n=10)	IVIG (n=9)	Placebo (n=10)
None	3	4	4
Serotonin reuptake inhibitor	2	3	2
Serotonin reuptake inhibitor plus antidepressant	0	1	3
Neuroleptic	2	0	1
Neuroleptic plus serotonin uptake inhibitor	3	1	0

Table 1: **Medication use at baseline in each study group**

Treatment outcome was assessed at 1 month and 1 year after start of therapy. Because of differences in treatment duration (2 days for IVIG, 10–12 days for plasma exchange), the first follow-up assessment was 2–4 weeks after cessation of therapy. This assessment consisted of a standardised neurological examination and the same ratings of symptom severity were used to assess baseline status. After symptom ratings at 1 month were completed, the IVIG/placebo masking was broken. If the child had received placebo and had no improvement in symptoms, open treatment with IVIG or plasmapheresis was offered according to protocol requirements—thus, 1-year follow-up ratings are not available for the placebo group.

Statistical analysis

To measure differences between groups at baseline and after treatment, we used repeated-measures ANOVA on each of the symptom-severity ratings by use of the SAS statistical programme (version 5). We used Duncan post-hoc analysis to analyse significant findings ($p \leq 0{\cdot}05$ throughout). Differences in baseline severity and degree of symptom change were assessed by ANOVA, χ^2 test of homogeneity, or paired *t* test, as appropriate. We used Pearson product-moment correlations to assess relations between baseline variables and outcome measures. Results are presented as mean (SD).

Results

Baseline characteristics

We screened more than 200 children by telephone; 58 underwent face-to-face screening in our clinic. 28 children did not meet eligibility criteria or were unwilling to participate in the randomised trial. 30 children (19 boys, 11 girls) were enrolled in the study (figure 1). One girl (IVIG group) left the study in the first week because of non-compliance; the other 29 completed the ratings at 1 month (ten plasma exchange, ten placebo, nine IVIG). Two children in the plasma-exchange group were lost to follow-up (at 4 and 6 months, respectively) before the assessment at 1 year.

At baseline, the three study groups were similar in age, primary diagnosis, duration of exacerbation, use of psychotropic medications, and presence of antistreptococcal titres. There were no differences in mean age at study entry (plasma exchange 10·3 years [SD 2·8]; IVIG 9·1 [2·4]; placebo 9·4 [2·3], p=0·8), or in the mean duration of acute illness or exacerbation before study entry (plasma exchange 29·1 weeks [49·4]; IVIG 12·3 [6·4]; placebo 10·5 [4·0], p=0·3). Medication use was similar in each group (table 1). The number of children who had started or increased medication dosage less than 2 months before study entry was also similar among the three groups (p=0·8). Treatment groups had similar numbers of children with a primary diagnosis of tic disorder (IVIG, two; placebo, three; plasma exchange, five) or OCD (IVIG, seven; placebo, seven; plasma exchange, five; p=0·3). The plasma exchange and placebo groups each had six children with OCD and tics, two with OCD alone, and two with tics alone. The IVIG group had four children with OCD and tics, and five with OCD alone. At baseline, symptom severity was similar among the three groups for all measures (table 2), except tic severity, which was greatest in the plasma-exchange group (p=0·02).

Throat cultures were negative at baseline in all subjects. Titres of antistreptolysin-O were similar among the three groups (plasma exchange: three negative, seven positive, mean 458 [SD 229]; IVIG: five, four, mean 517 [290]; placebo: five, five, mean 350 [147]). Antistreptococcal deoxyribonucleic B titres were also similar among the three groups (plasma exchange: five negative, five positive, mean 452 [SD 278]; IVIG: two, seven, mean 780 [434]; placebo: three, seven, mean 546 [391]). There was no correlation between baseline titres and degree of treatment response for any group, or for the study population as a whole.

Response to treatment

Of the ten children randomly assigned plasma exchange, all succesfully completed the planned course of five (n=6) or six (n=4) procedures. Children's weight ranged from 22 kg to 61 kg (mean 38·9 kg). The mean plasma volume exchanged per procedure was 1667 mL [SD 552]. Whole blood flow rates ranged from 24–56 mL/min, depending on the child's weight and citrate tolerance. Time to completion of the procedures ranged from 85 min to 121 min (mean 101 min [11]). A 10% decrease in packed-cell volume was observed during the course of the exchanges; the platelet count did not change.

Adverse reactions (pallor, dizziness, nausea) occurred in seven patients, two of whom also had vomiting. Significant bradycardia or hypotension did not occur, and no patients had paraesthesia or muscle cramping. Three children also complained of feeling anxious and were restless during the procedures, but none required medication. Reactions were most common during the first procedure, and tended not to recur during subsequent exchanges. Treatment consisted of postural manipulation and temporary cessation of the

Rating scores for symptom severity	IVIG (n=9)			Placebo (n=10)			Plasma exchange (n=10)			p for difference between placebo and active treatment
	Baseline	1 month	% change	Baseline	1 month	% change	Baseline	1 month	% change	
Obsessions and compulsions	26·7 (5·9)	14·7 (10·8)	45*	23·0 (13·6)	22·1 (13·1)	3	22·5 (13·4)	9·5 (10·1)	58*	0·006
Tics	6·8 (9·2)	5·5 (7·7)	19	11·0 (9·5)	9·7 (9·1)	12	21·7 (14·7)	11·0 (9·2)	49*	0·005
Sum of obsessions, compulsions, and tics	33·4 (10·2)	20·2 (14·3)	40*	34·0 (7·3)	31·8 (8·9)	6	44·2 (15·2)	20·5 (12·0)	54*	0·001
Global impairment	8·7 (1·0)	5·8 (1·9)	33*	7·7 (1·6)	7·7 (1·6)	0	8·0 (2·7)	5·2 (2·3)	35*	0·0009
Psychosocial functioning	56·0 (9·7)	67·4 (12·1)	20	58·3 (10·5)	59·9 (11·4)	3	56·0 (13·1)	73·0 (15·3)	30	0·2
Anxiety	6·8 (1·2)	4·7 (1·6)	31*	6·2 (2·4)	6·0 (2·3)	3	6·4 (2·8)	3·4 (1·8)	47*	0·001
Depression	5·4 (2·1)	4·0 (2·1)	26*	6·2 (2·5)	6·3 (3·0)	2	5·2 (2·2)	2·9 (17)	44*	0·002
Global severity	4·7 (0·8)	3·4 (1·2)	26*	4·8 (0·4)	4·8 (0·5)	1	5·0 (0·9)	3·2 (1·0)	36*	0·0001
Emotional lability	6·2 (2·2)	4·4 (2·4)	29*	6·5 (2·6)	6·6 (2·6)	2	6·3 (2·1)	4·1 (1·8)	35*	0·001

Data are mean (SD) or %. *% changed from baseline to 1 month follow-up in which paired *t* tests were significant at p<0·05.

Table 2: **Symptom severity at baseline and 1 month after treatment**

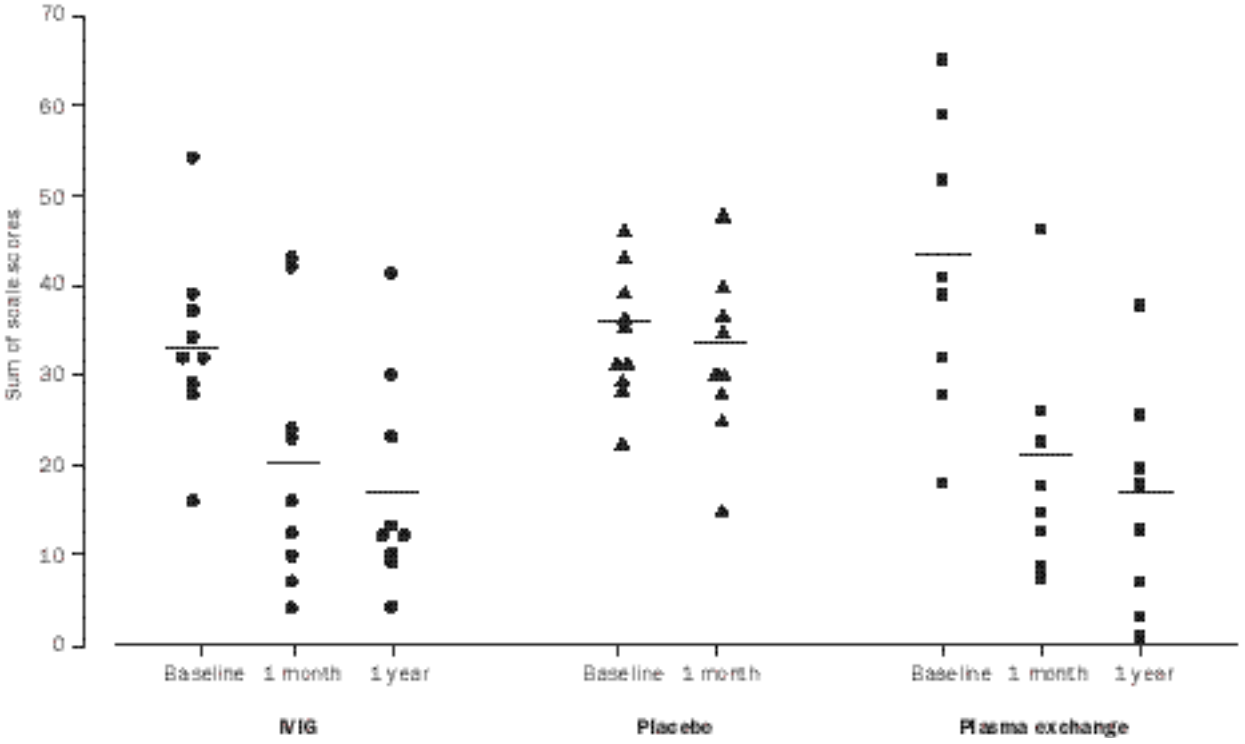

Figure 2: **Change in obsessive-compulsive disorder and tic severity at 1 month (all three groups) and 1 year (plasma exchange, IVIG)**
Scores are sum of Yale-Brown scores and Tourette syndrome unified rating scale scores. Horizontal bars are means.

procedure; no procedure had to be stopped prematurely due to an adverse event. There was no correlation between the occurrence of vasovagal, citrate, or hyperanxiety reactions and the type of venous access used (central *vs* peripheral).

In the IVIG group, the range of children's weight was 18·0 kg to 42·8 kg, and the range of infusion was 18–43 g/day (360–860 mL). Six children had adverse effects of mild to moderate severity, including nausea and vomiting (five), mild to moderately severe headache (three), and low-grade fever (four). These symptoms tended to occur during the second day of the infusion, and were relieved by hydration and additional doses of paracetamol and diphenhydramine. None was of sufficient severity to preclude completion of the IVIG infusion.

In the placebo group, the children's weight ranged from 16·9 kg to 49·5 kg, and the infusions ranged from 340 mL to 1 L. Two children experienced mild adverse effects of the infusion: both had stomachache (without nausea or vomiting), and one had mild headache. The symptoms were treated with paracetamol or diphenhydramine and did not interfere with completion of the placebo infusion.

1 month follow-up

At 1 month after treatment, the plasma exchange and IVIG groups showed striking improvements in obsessive-compulsive symptoms, anxiety, depression, emotional lability, and global functioning (table 2). Ratings done 1 month after treatment showed significant differences ($p \leq 0{\cdot}05$) from baseline in the plasma exchange and IVIG groups for the children's Yale-Brown scale, the National Institute of Mental Health scales of anxiety, depression, emotional lability, and global function, and the clinical global impression severity scale. The plasma exchange group showed significant improvements in tic severity over placebo but the IVIG group did not, perhaps because baseline ratings were highest in the plasma exchange group. No group had significant improvements in global assessment scale (table 2).

At 1 month, global change scores for children in the plasma exchange and IVIG groups were improved by 48% and 41%, respectively (clinical global impression change 1·9 [SD 1·1] for plasma exchange and 2·4 [1·1] for IVIG). By contrast, placebo produced no change in overall symptom severity (change 4·1 [0·6]) or in specific symptom severity (table 2).

In the plasma-exchange group, symptom improvement usually occurred near the end of the first week of treatment, whereas in the IVIG group improvement was not usually seen until at least the third week after treatment. The plasma-exchange group appeared to have greater symptom relief than did the IVIG group (figure 2), with particularly

Rating score for symptom severity	IVIG (n=9)				Plasma exchange (n=8)				p for difference between groups
	Baseline	1 month	1 year	% change from baseline	Baseline	1 month	1 year	% change from baseline	
Obsession and compulsions	26·7 (5·9)	14·7 (10·8)	11·3 (5·5)	58*	22·9 (14·9)	9·5 (10·1)	6·9 (7·9)	70*	0·88
Tics	6·8 (9·2)	5·5 (7·7)	5·8 (8·7)	15	18·9 (14·0)	11·0 (9·2)	8·9 (9·6)	53*	0·06
Sum of obsessions, compulsions, and tics	33·4 (10·2)	20·2 (14·3)	17·1 (11·9)	49*	41·8 (16·0)	19·8 (12·3)	15·8 (12·5)	62*	0·29
Psychosocial functioning	56·0 (9·7)	67·4 (12·1)	70·6 (7·3)	26*	56·3 (14·6)	73·0 (15·3)	82·5 (12·9)	47*	0·28
Global severity	4·7 (0·8)	3·4 (1·2)	3·4 (0·7)	26*	5·0 (1·1)	3·2 (1·0)	2·8 (1·4)	45*	0·26

Data are mean (SD) or %.*% changes from baseline to 1 year in which paired *t* tests were significant at p<0·05.

Table 3: **Symptom severity at baseline and 1 year after treatment**

striking individual improvements in obsessive-compulsive symptoms (table 2).

The lack of placebo response was not the result of treatment resistance, since the children in the sham IVIG group showed improvement after open treatment with IVIG (two children) or plasma exchange (eight children). 1 month after active treatment, the mean clinical global impression change score for the ten children in the group was 2·6 (SD 1·3), with most children reported to be "very much improved". Obsessive-compulsive symptoms had decreased by 40% on average (mean Yale-Brown score decreased from 22 to 13·3) and tics by 17·5% (mean Tourette syndrome unified rating scale improved from 9·7 to 8·0). Overall functioning had also improved, as measured by the global assessment scale (14% increase from 60 to 68) and the clinical global impression scale (decreased from 4·8 to 3·7). Only two children failed to respond to active treatment (one given IVIG, one given plasma exchange). Both had tics without OCD, but this pattern was not associated with a lack of response among children in the plasma exchange and IVIG groups.

1 year follow-up

At 1 year after treatment, 17 children initially assigned active treatment were reassessed (plasma exchange, eight; IVIG, nine). Three children had had a second course of immunomodulatory therapy in the intervening months. One child in the plasma-exchange group was retreated with plasma exchange for a symptom exacerbation 10 weeks after initial treatment, one was treated with IVIG at 4 months, and one in the IVIG group had a second IVIG treatment at 2 months. At the time of their symptom exacerbations, all three children had a history of streptococcal exposure and increased antistreptococcal titres despite prescription of oral penicillin prophylaxis.

At baseline, 13 children (plasma exchange, six; IVIG, seven) used psychotropic medications for symptom relief. At 1 year's follow-up, six of these children (plasma exchange, two; IVIG, four) were taking an equivalent or higher dosage of medication, but seven (plasma exchange, four; IVIG, three) were on a lower dosage. Two of the 13 children had been able to discontinue medication because of symptom remissions.

Symptoms remained improved from baseline on all measures at the 1-year follow-up assessment. The most clinically meaningful improvements occurred in obsessive-compulsive symptoms, tic severity, and global measures of symptom severity and psychosocial functioning (table 3). Our clinical impression after 1 year's follow-up was that plasma exchange was better than IVIG, particularly for treatment of symptoms of OCD. The symptom rating confirmed these impressions (table 3, figure 2).

The change in global assessment scale scores from baseline to 1 year follow-up (table 2) shows a striking improvement in psychosocial function. In general children who previously had "symptom impairments in several social areas" now had "good functioning in all areas". These improvements were also shown by the clinical global impression change score: the IVIG group was rated as "much improved" (score 2·3 [SD 1·1], 53%) and the plasma-exchange group was "very much improved" (1·75 [0·9], 70%). 14 (82%) children had symptom reductions of at least 50%. Parents commonly reported that "my child's back to his old self again" and children reported that "things are a lot easier now".

Discussion

Plasma exchange and IVIG were both better than placebo in the treatment of exacerbations of neuropsychiatric symptoms in children with OCD and tic disorders. Both active treatments gave rapid and sustained improvements in global functioning, depression, emotional lability, and obsessive-compulsive symptoms, whereas placebo had little or no effect. The lack of a placebo effect is not surprising, given the number of studies in which placebo has failed to relieve obsessive-compulsive symptoms.[27] However, the lack of placebo response is still of note in our trial because the invasive nature of therapies might have led to a robust placebo effect. The adverse effects of IVIG treatment could have served to break the blinding in the IVIG and placebo groups. All children were aware of the potential for nausea, vomiting, and headache in association with IVIG treatment, and children who did not have these side-effects may have concluded that they had received placebo. The data did not reveal such a pattern—there was no relation between degree of adverse effects and symptom improvement in either the IVIG group or the placebo group. Without evidence of efficacy, the potential risks of sham apheresis were not justifiable in paediatric research, so some of the benefits seen in the plasma-exchange group might have been due to the placebo effect of a presumed high-technology intervention. If that were the case, however, the benefits should have waned over time, but they did not, and the plasma-exchange group continued to show striking improvements 1 year after the apheresis procedures.

Acute adverse effects of plasma exchange were frequent, but mild. Although most patients had dizziness or nausea, none developed paraesthesias, muscle spasm, hypotension, or bradycardia. We could not easily determine whether these symptoms were vagal in origin or due to citrate-induced hypocalcaemia. In all cases, symptoms resolved rapidly with postural manipulation and transient interruption of the apheresis procedure. Overall, the safety profile of apheresis in these children was excellent. The children appeared to tolerate plasma exchange better than IVIG, since the side-effects of IVIG (nausea, vomiting, headache) persisted for 12–24 h whereas those related to apheresis were brief and limited to the procedure period.

More than 80% of the patients who received IVIG or plasma exchange remained "much" or "very much" improved at 1 year, and their symptoms were in the subclinical range of severity. These results are particularly striking when compared with previous reports of the intractable nature of paediatric OCD and tic disorders; long-term outcome studies in OCD have shown that less than one third of patients had clinically meaningful symptom improvements.[28]

It is intriguing that a single course of IVIG or plasma exchange gave such sustained treatment effects. The original hypothesis of our study was that both IVIG and plasma exchange would reduce symptom severity by blocking (IVIG) or removing (plasma exchange) the antistreptococcal antibodies that were cross-reacting with neuronal tissue.[4–6] A single treatment course would therefore give lasting benefits if streptococcal infections were prevented by antibiotic prophylaxis. The hypothesis suggests that the rate of improvement with plasma-exchange treatment should be directly proportional to the rate of antibody removal. This improvement occurred in a few instances, with symptoms beginning to improve at about the time of the third exchange, and additional benefits shown after the fourth and fifth treatments.

However, most of the children did not have such a direct response, and showed the greatest improvement in the days and weeks following cessation of the apheresis procedure. This pattern could also be predicted by the hypothesis, since the inflammatory changes caused by the autoantibodies would take some time to resolve. The model is unable to explain why symptom recrudescences occurred so rapidly after streptococcal infections (since titre rises appear to occur more slowly), or to explain the mechanism by which peripheral effects of IVIG and plasma exchange could be translated across the blood-brain barrier to give volumetric changes in basal ganglia structures.[30] The actions of IVIG and plasma exchange are too broad to be helpful in delineating the nature of the improvements or in determining the pathophysiology of the neurospychiatric symptoms. Trials with more selective and specific immunomodulatory agents may answer the questions raised by our study, and may give information about the types of patients who will respond to immunomodulatory therapy.

Our results suggest that plasma exchange and IVIG are highly beneficial to a subgroup of patients with tics and obsessive-compulsive symptoms, but the study does not support the routine use of immunomodulatory agents in OCD and tic disorders. The children who we studied are not likely to be representative of typical paediatric patients with OCD or tic disorders, since they were selected from a much larger group of children on the basis of a history consistent with PANDAS.[10] Given the specificity of the entry criteria, the results cannot be extrapolated to all patients with OCD and tics. Because the mechanism of action of the therapeutic response is unknown, the additional groups of patients that might benefit from treatment with IVIG or plasma exchange is not clear. To assess this issue, the eligibility criteria have been modified to allow study of a broader cross-section of patients with OCD and tic disorders. These trials will attempt to assess whether IVIG and plasma exchange are effective in treating symptom exacerbations that are not triggered by streptococcal infections, and whether the treatments can benefit patients with chronic symptoms.

Contributors

Susan Perlmutter was responsible for patient care during the second and third years of the study, participated in data analysis and interpretation, and prepared the first draft of the paper. Susan Leitman was co-principal investigator of the study, and contributed to data acquisition, analysis, and interpretation, and to preparation of the paper. Marjorie Garvey was medically responsible for the first year of the study, and contributed to data acquisition and interpretation. Susan Hamburger and Elad Feldman had primary responsibility for data analysis and presentation. Henrietta Leonard was co-principal investigator of the study, involved in study design, and data interpretation. Susan Swedo was the principal investigator for the study, responsible for study design and direction of data acquisition, analysis, and interpretation. She prepared the final paper and revision.

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