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


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. 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. 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. 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. 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. In some cases, obsessions, compulsions, and tics may also be mediated by post-streptococcal autoimmunity. Several studies have shown crossreactive antimicrobial 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. The subgroup shares a unique clinical course and is identified by the acronym PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections).

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. 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. Steroid therapy was not a viable treatment option for our study, because tics and OCD may worsen during steroid administration. 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...
infection-triggered exacerbations of OCD.\textsuperscript{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;\textsuperscript{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);\textsuperscript{18} 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).\textsuperscript{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,\textsuperscript{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,\textsuperscript{20–22} children's Yale-Brown obsessive compulsive scale,\textsuperscript{23} global assessment scale,\textsuperscript{24} clinical global impression scales of symptom severity and change,\textsuperscript{25} and the National Institute of Mental Health rating scales for global functioning, anxiety, and depression.\textsuperscript{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 irritible, 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.
Rating scores for symptom severity

<table>
<thead>
<tr>
<th>Symptom</th>
<th>IVIG (n=9)</th>
<th>Plasma exchange (n=10)</th>
<th>Placebo (n=10)</th>
<th>p for difference between placebo and active treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessions and compulsions</td>
<td>26 (7-5)</td>
<td>14 (7-0)</td>
<td>14 (7-0)</td>
<td>0.006</td>
</tr>
<tr>
<td>Tics</td>
<td>6 (8-2)</td>
<td>5 (5-7)</td>
<td>5 (5-7)</td>
<td>0.005</td>
</tr>
<tr>
<td>Global impairment</td>
<td>8 (7-0)</td>
<td>7 (7-0)</td>
<td>6 (7-0)</td>
<td>0.009</td>
</tr>
<tr>
<td>Psychosocial functioning</td>
<td>56 (9-7)</td>
<td>64 (7-12)</td>
<td>64 (7-12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (8-2)</td>
<td>7 (7-0)</td>
<td>7 (7-0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>5 (4-1)</td>
<td>6 (2-5)</td>
<td>6 (2-5)</td>
<td>0.002</td>
</tr>
<tr>
<td>Emotional lability</td>
<td>6 (2-2)</td>
<td>4 (2-4)</td>
<td>4 (2-4)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 1: Symptom severity at baseline and 1 month after treatment
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 followup
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<0·05) 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

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

| Rating score for symptom severity | IVIG (n=9) | | | | Plasma exchange (n=8) | | | | p for difference | | | between groups |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Obsession and compulsions | 267·5 (5·9) | 147·1 (10·8) | 113·3 (15·5) | 58* | 229·9 (14·9) | 95·9 (10·1) | 69·9 (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.

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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.
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). One 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 followup
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 liability, 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. 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 paraesthesia, 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. 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. 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 recurrences 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. 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 neuropsychiatric 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. 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 so as 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 draft first of the paper. Susan L. Libman was co-principal investigator of the study, and contributed to data acquisition, analysis, and interpretation, and to the preparation of the paper. M. Jarred Gavey was medically responsible for the first year of the study, and contributed to data acquisition and interpretation. Susan H. Amburger and E. L. 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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