

# Therapeutic Response to Plasmapheresis in Four Cases with Obsessive-Compulsive Disorder and Tic Disorder Triggered by Streptococcal Infections

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## Abstract

The acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) has been assigned to a subgroup of patients experiencing pediatric onset obsessive-compulsive symptoms and tics as a result of autoimmune response to group A  $\beta$ -hemolytic streptococcal infection. It has been hypothesized that an immune process initiated by infection affects the basal ganglia and causes neuropsychiatric symptoms. In cases with severe neuropsychiatric symptoms, the use of treatment strategies that interrupt the autoimmune process responsible for the pathogenesis of PANDAS, such as therapeutic plasmapheresis or intravenous immunoglobulin, has been proposed. In this paper, we discuss the effect of plasmapheresis treatment in 4 adult cases of obsessive-compulsive disorder and tic disorder triggered by streptococcal infections.

**Key Words:** Obsessive-compulsive disorder, tic disorder, plasmapheresis, streptococcal infection, autoimmunity

## INTRODUCTION

In recent years, the cluster of neuropsychiatric symptoms composed of pediatric onset obsessive-compulsive symptoms and tics caused by an autoimmune response to group A  $\beta$ -hemolytic streptococcal (GABHS) infection, has gained recognition as a distinct disorder. Researchers refer to this clinical picture observed in children as pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) (Swedo et al., 1997). The National Institute of Mental Health (NIMH) has determined the following diagnostic criteria for this disease: 1) Presence of obsessive-compulsive disorder (OCD) and/or a tic disorder; 2) Pediatric onset of symptoms (age 3 years to puberty); 3) Episodic course of symptom severity; 4) Temporal association of symptom onset or exacerbation with GABHS infection; 5) Association with neurological abnormalities (motoric hyperactivity, choreiform movements) (Snider and Swedo, 2003). Along with OCD or tic disorder, other symptoms, such as mood instability, impulsivity, and attention deficit, have also been observed in these patients (Gimzalı et al., 2002).

Even though PANDAS is a pediatric disorder by definition, adult onset OCD or tic disorder patients associated with GABHS have been classified as adult onset PANDAS (Bodner et al., 2001, Church and Dale). Nevertheless, NIMH has a tendency to describe the adult onset form of the clinical picture as immune mediated OCD (NIMH, 2006).

Because it is thought that PANDAS is caused by an autoimmune process, treatments with the potential to interrupt this process have been suggested for use. As a result, the use of immunoglobulins, prednisolone, and plasmapheresis has been considered (Leonard and Swedo 2001; Perlmutter et al., 1999). Additionally, the use of antibiotics for the prevention of streptococcal infections, which aggravate the neuropsychiatric symptoms in PANDAS cases, is reported to be beneficial (Garvey 1999, Snider 2005). Nevertheless, there are no reports on the use of the afore-mentioned approaches in adult cases, which exacerbate after a streptococcal infection. In this paper the effects of plasmapheresis treatment in 4 adult cases with OCD and tic disorder, triggered by streptococcal infections and diagnosed according to the DSM-IV diagnostic criteria are discussed.

## Case I

VT, a 21-year-old unemployed, single male completed only one year of high school. He presented to our outpatient clinic with the following complaints: anxiety, thoughts about impending bad events, repetitive behaviors (such as taking his clothes off and putting them back on, and closing the doors at home and re-opening them), spending a very long time in the bathroom to wash his body, social withdrawal, not leaving home, being afraid and involuntary movements.

His complaints began at the age of 9 years and have followed an undulating course, which gradually became more severe. Meaningless repetitive behaviors, primarily involuntary body movements, were increasing, especially after throat infections. He had received medications for these complaints from various other hospitals; however, he had not benefited adequately from any of the medications and did not remember their names. He received various treatment combinations consisting of haloperidol 3 mg/day<sup>-1</sup>, sertraline 50 mg day<sup>-1</sup>, and carbamazepine 400 mg day<sup>-1</sup> during his outpatient follow-up period (10 months) with us, but did not respond. Subsequently, he was admitted to our inpatient clinic at 2004, and he was diagnosed with major depressive disorder, OCD, and tic disorder. During clinical follow-up his treatment consisted of quetiapine 600 mg day<sup>-1</sup>, valproic acid 1000 mg day<sup>-1</sup>, clonazepam 2 mg day<sup>-1</sup>, and fluvoxamine 200 mg day<sup>-1</sup> at various points in time, and he was discharged with partial recovery in terms of obsessive-compulsive and tic symptoms. He was again admitted to the inpatient ward due to the reappearance of the symptoms mentioned above.

Patient history did not reveal any findings, except for frequent throat infections. None of his relatives had a psychiatric disorder. During the mental status examination during his second hospital admission, his shoulders were drooped, his grooming was poor, his affect was blunt, he appeared shy, his participation during the interview was reluctant, and he made eye contact only when he was called by name. Orientation and memory were intact. Spontaneous attention was normal, voluntary attention was diminished. His speech was succinct and his associations were normal. He had contamination, doubting, and religious obsessions. His mood was euthymic. He had washing and control compulsions. He also had sudden motor tics, such as head movements and shrugging of the shoulders. Although the patient's insight was good, during the hospitalization it was observed that the patient's insight was sometimes poor. Judgment, abstract

thought, and intelligence were normal. The neurological examination did not reveal any pathology, except for increased activity of the deep tendon reflexes and motor tics. All biochemical and hematological tests were normal, except for increased antistreptolysin O (ASO) (1250 IU ml<sup>-1</sup>) on the first day of the second hospitalization. Electroencephalograph (EEG) and cranial magnetic resonance imaging (MRI) results were normal.

## Case II

ŞT, an 18-year-old unemployed single male. He presented to the outpatient clinic with the following complaints: compulsively tidying up, correcting the position of objects, preoccupations about impending bad events that might happen to himself or his family, involuntary limb movements, diminished concentration, forgetfulness, and closing his mouth continuously. The patient's academic results had gradually deteriorated after the onset of these complaints, which began when he was 9-10 years old. He had become a stubborn, defiant, irritable, and introverted person, whereas he had previously been an extroverted and cooperative child. Upon presentation, he was diagnosed with OCD and tic disorder, and was given such treatments as haloperidol 2 mg day<sup>-1</sup>, risperidone 1 mg day<sup>-1</sup>, sertraline 50 mg day<sup>-1</sup>, and fluoxetine 20 mg day<sup>-1</sup> at different times within a span of 2 years. EEG conveyed middle amplitude slow wave discharges over the left frontotemporal region, and mild neuronal hyperexcitability over the occipital regions bilaterally. MRI revealed a 4 × 3-cm arachnoid cyst in the anterior part of the left temporal lobe. Based on the MRI findings the patient was started on valproic acid 750 mg day<sup>-1</sup> and was referred to the department of neurosurgery for regular follow-up. Even though after the initiation of valproic acid treatment the patient's complaints of introversion and irritability had improved, when his complaints were taken as a whole, none of the treatments offered significant improvement of his symptoms. He was then admitted to the inpatient service due to an exacerbation of his symptoms, which began one month earlier following an upper respiratory tract infection.

Patient and family medical histories were unremarkable. The findings of his mental status examination were as follows: personal hygiene was good, his answers to questions were succinct, he made regular eye contact, and he willingly cooperated. His speech and his associations were normal. Although his mood was euthymic, he was observed to be anxious, from time to time. His thought content revealed contamination, symmetry, and aggressive obsessions. He had control, symmetry, and arrang-

**Table I.** ASO, YBOCS, YGTSS, and CGI values before and after plasmapheresis.

	Case I		Case II		Case III		Case IV	
	BP	AP	BP	AP	BP	AP	BP	AP
ASO (IU ml <sup>-1</sup> )	1250	122	756	151	384	76	743	136
YBOCS	31	9	35	16	33	16	29	8
YGTSS								
Motor tics total score	10	5	12	6	20	9	20	7
Vocal tics total score	0	0	0	0	15	9	0	0
General impairment score	10	5	15	5	45	20	40	15
Total score	20	10	27	11	80	38	60	22
CGI (severity)	5	3	4	2	6	3	5	2

BP: Before plasmapheresis. AP: After plasmapheresis.

ing compulsions. He had motor tics, such as stretching his fingers, eye movements, and fixing his hair with his hands. Judgment, abstract thinking, insight, and intelligence were normal. Neurological examination did not reveal any pathology, except for motor tics. Hematological and biochemical analyses did not reveal any pathology, except for an increase in ASO (756 IU ml<sup>-1</sup>).

### Case III

AO, a 35-year-old married male healthcare worker presented to our outpatient clinic with the following complaints: thoughts about harming his wife and children, lack of concentration, increased psychomotor activity, anxiety, coprolalia, obscene gestures, involuntary movements, and excessive talking. His complaints began when he was 6-7 years old with involuntary limb, shoulder, and head movements, vocal tics, and increased psychomotor activity. In time, complaints, such as persecutory thoughts, lack of concentration, anxiety, excessive talking, increased psychomotor activity, inability to sit still during class, and touching or tapping objects unnecessarily, were added to the list of existing symptoms. His complaints, which would exacerbate after throat infections, had a tendency to improve spontaneously. Because of these symptoms the patient had received diagnoses of Tourette's disorder, OCD, major depressive disorder, bipolar disorder, and PANDAS, and had received various pharmacological treatments at different doses for varying periods of time (sertraline, mianserine, fluoxetine, risperidone, olanzapine, quetiapine, lithium, haloperidol,

clonazepam, carbamazepine, pimozide, etc.) He reported that he had partially benefited from these treatments; however, the duration of these improvements had been short. He was hospitalized 4 times, 2 of which had been in our hospital, but he never improved completely. He was hospitalized in our department for the third time after an exacerbation of his symptoms, which emerged during the course of 10 days following a throat infection.

His medical history revealed that he had attempted suicide by jumping from a window due to his depressive episode. As a result, he was hospitalized for 4-5 months in the department of orthopedics due to a fractured femur. There was no family history of psychiatric disease. The mental status examination revealed that his grooming was good, and he willingly cooperated. Orientation and memory were intact. Spontaneous attention was natural, voluntary attention was impaired. His associations were natural. His mood was depressive, anhedonic, and anxious. He had doubting, aggressive, religious, and sexual obsessions. These thoughts turned into over-valued ideas. The patient had compulsions of control, need to ask or confess, and repeating certain words or prayers in his mind. He masturbated impulsively and had motor and vocal tics, coprolalia, and copropraxia. His intelligence, judgment, and abstract thoughts were intact. Even though his insight at the time of the initial interview was unimpaired, during last hospitalization period it was observed that his judgment and insight tended to impair. Neurological examination revealed impaired

ability in cerebellar tests, which was more prominent on the left side. Motor and vocal tics were observed. Cranial MRI and EEG were normal. ASO level was high (384 IU ml<sup>-1</sup>). It was noted that his ASO level had also been high (473 IU ml<sup>-1</sup>) during his previous hospitalization.

#### Case IV

SA, an 18-year-old single, unemployed male dropped out of school when he was in the eighth grade and was living with his parents. He presented to our outpatient clinic due to distressing thoughts about himself and his family, doing things according to a particular order, frequently checking the doors and windows, lack of concentration, increased psychomotor activity, forgetfulness, irritability, and involuntary movements. His complaints began when he was 11 years old. He had distressing thoughts, such as thinking that his mother was a beggar, or thinking that there was sputum in his food. While drinking tea, he would think that the glass was not clean and would suddenly want to throw the glass away, which he sometimes did. While walking he would experience an urge to hit people on the street; when his friends were with him, he would hit them. Because of these behaviors his personal relationships deteriorated significantly. He then began to take off his clothes and put them back on again. He began to have the feeling of having missed a part of something or of having made a mistake, even though he was trying to be very meticulous in everything he did. He was checking his belongings, questions on an exam or whether he had extinguished the burning objects at home as he was going out, over and over again. He was sometimes shaking his head, blinking quickly, suddenly kneeling down, and touching his knees. Sometimes these behaviors would become less frequent. The patient had been treated with risperidone 1 mg day<sup>-1</sup>, pimozide 1 mg day<sup>-1</sup>, and fluoxetine 20 mg day<sup>-1</sup> at our outpatient clinic; however, he did not respond. The patient was hospitalized because of a lack of response to treatment and an increase in feelings of guilt and suicidal ideation.

The patient's medical history was free of any significant diseases, except for a history of 2 febrile convulsions when he was a baby. His family medical history was unremarkable. The mental status examination revealed that he was a lean looking patient whose appearance matched his age. His grooming was good, he made regular eye contact, and willingly participated in the interview; however, he did look anxious. Cognitive abilities were intact. Thought content included obsessions, such as doubting contamination, losing things, and intrusive images of

violence. His affect was anxious, his mood was depressive. There was an increase in psychomotor activity. There were impulsive behaviors, compulsions of control and cleaning, and repetitive rituals. He had both simple and complex tics. The patient's intelligence, judgment, abstract thought, and insight were normal. Neurological examination revealed a slight disability in the left upper cerebellar tests, along with simple and complex motor tics. MRI revealed hyperintense areas in multiple regions within the basal ganglia. EEG was normal. ASO level at the time of his hospitalization was 743 IU ml<sup>-1</sup>.

#### Diagnose, Treatment, and Clinical Course

All the cases were evaluated according to the DSM-IV TR. For case I, diagnoses of OCD and tic disorder were confirmed. For case II, the diagnoses of OCD, chronic motor tic disorder and personality change due to a general medical condition (arachnoid cyst), were considered. For case III, the patient met the criteria of OCD and Tourette's disorder according to the DSM-IV TR criteria. Case IV was diagnosed with OCD and tic disorder. Because the DSM-IV diagnostic system does not include the diagnosis of PANDAS, all the patients were evaluated according to the NIMH diagnostic criteria for PANDAS. 1) All 4 cases had both OCD and a tic disorder; 2) Even though all the cases were  $\geq 18$  years old, the onset of symptoms had occurred during the pre-adolescent period; 3) All the patients described dramatic exacerbations during the course of the disorder; 4) The relatives of cases I, II and III clearly described exacerbations following throat infections; however, this was not as clearly stated for case IV. All the cases had been hospitalized during an exacerbation of symptoms and high ASO levels within 4-6 weeks of symptom exacerbation confirmed the history of recent GABHS infection. Church and Dale (2002) suggested that an ASO level of 270 IU ml<sup>-1</sup> as the threshold value for adult PANDAS patients; 5) All the cases presented with positive neurological examination findings (tics) at the time of symptom exacerbation.

Therapeutic plasmapheresis is a form of therapeutic apheresis. Therapeutic apheresis is a term used to describe processes, such as decreasing the amount of a patient's blood cells, changing the blood components (plasma, erythrocyte), modifying the blood components, or autologous peripheral stem cell harvesting, performed to achieve clinical benefit. Removal of a major part of the plasma, which has been separated from the cellular components of the blood, and its substitution by colloid, crystalloid solutions, or by artificial plasma with simi-

lar physical properties with that of the removed plasma, (e.g. pH and viscosity) is called plasmapheresis. The aim of this procedure is to remove the patient's auto-antibodies that were produced against the patient's own tissues. After the procedure, the cellular elements are returned to the circulation. The estimated plasma volume is 40 ml kg<sup>-1</sup> (3000-4500 ml) and through this procedure 60% of the plasma can be changed. The number and frequency of plasmapheresis sessions are determined empirically, based on the disease and response. In order to ensure a balance between the circulation and tissues, plasmapheresis is conducted at intervals of a few days. Generally, within 10-15 days a total of 5-7 sessions are carried out. The optimum change tables are not precisely known for various diseases. For the majority of patients, 4%-5% albumin solutions are preferred for substitution. Albumin use carries no risks of viral contamination or allergic reactions. With the current techniques, plasmapheresis has mild side effects, which include hypotension, paleness, dizziness, nausea, vomiting, paresthesia, and muscle cramps. When side effects are severe, the procedure can be temporarily terminated. Due to problems of adaptation, the procedure may require anesthesia, especially with children (El-Ghariani and Unswort, 2006; Perlmutter et al., 1999; Sadhasivam and Litman, 2006).

Prior to plasmapheresis all the patients in the presented study received consultations from the hematology, infectious diseases, and dermatology departments. When all the counter-indications were excluded, written consent was received, both from the patients and their first-degree relatives, after which plasmapheresis was carried out. The patients received subclavian catheters one day before the initial session, which remained in place until the last plasmapheresis session. Based on previous studies, plasmapheresis treatment of 5 sessions within 15-20 days was planned for all the patients (Perlmutter et al., 1999). One patient, however, underwent only 4 sessions of treatment due to a hemorrhage in the subclavian region, whereas the remainder of cases received 5 sessions of treatment within the preplanned time period. Plasmapheresis was carried out in the department of hematology under the supervision of a doctor and a nurse. With the exception of a single case, the patients all reported short-term dizziness and nausea.

The Yale-Brown Obsession Compulsion Scale (YBOCS) (Tek et al., 1995), Yale Global Tic Severity Scale (YGTSS) (Zaimoglu et al., 1995), and Clinical Global Impression Scale (GCIS) (Guy 1976) were given to all of the cases before the first plasmapheresis and one week after the last plasmapheresis session. ASO, YBOCS,

YGTSS, and CGI values before and after treatment are given in Table I. As predicted (based on previous studies) (Denys et al., 2004), when patients with a  $\geq 35\%$  decrease in YBOCS total score were classified as responders, it was observed that all the patients had responded to the treatment, in terms of obsessive-compulsive symptoms. The mean change in YBOCS scores was 62%. When the patients' changes in tic severity were globally assessed, it was noted that all the patients had a  $\geq 50\%$  decrease in tic severity. Mean change in total YGTSS score was 56%. The elation of mood was observed after the 2nd or 3rd session, which lasted for 1, or 2 days in the patients. All the patients were discharged with a significant reduction in obsessive-compulsive symptoms and tics. The patients and their relatives described the level of recovery as that which had not been previously achieved.

Cases I-IV began treatment with and were discharged with the following, respectively: Case I: quetiapine 600 mg day<sup>-1</sup> and fluvoxamine 200 mg day<sup>-1</sup>; Case II; fluoxetine 20 mg day<sup>-1</sup> and carbamazepine 400 mg day<sup>-1</sup>; Case III: olanzapine 10 mg day<sup>-1</sup> and escitalopram 10 mg day<sup>-1</sup>; Case IV: fluoxetine 20 mg day<sup>-1</sup> and risperidone 1 mg day<sup>-1</sup>. The improvement observed in cases I-III continued during the 6-month post discharge follow-up period. Case I experienced an exacerbation of complaints at the sixth post discharge month. The patient had an upper respiratory tract infection before the onset of symptoms and his ASO was elevated (532 IU ml<sup>-1</sup>). Similarly, case IV experienced an exacerbation of complaints at the sixth post discharge week following an upper respiratory tract infection. His ASO level at the time was elevated (673 IU ml<sup>-1</sup>). Plasmapheresis was planned for both of these cases based on the request of the patients and their relatives; however, due to a change of government regulations concerning medical treatment reimbursement, this plan was not carried out. Based on the consultation received from the department of infectious diseases, both of the patients began to receive monthly prophylactic depot penicillin treatment.

## DISCUSSION

In this paper, the efficiency of plasmapheresis in 4 cases with OCD and tic symptoms triggered by streptococcal infections were discussed. Although the patients and their relatives reported that the onset of symptoms occurred during the pre-adolescent period, because evidence of streptococcal infections acting as triggers was not completely reliable and because PANDAS is a pediatric diagnose, the classification of the patients as PANDAS was avoided.

In all 4 cases plasmapheresis treatment resulted in significant improvement in both obsessive-compulsive symptoms and tics. The present study is the second largest of its kind, following Perlmutter et al., (1999) who reported 10 pediatric cases. This paper is the first to describe the use of plasmapheresis in adult cases of streptococcal-triggered OCD and tic disorder. Perlmutter et al., in their placebo-controlled study, applied plasmapheresis to 10 PANDAS patients, intravenous immunoglobulin treatment to 9 patients and placebo treatment to 10 patients. They reported significant improvement in obsessive-compulsive symptoms, depressive symptoms, anxiety, and general functionality in the treatment arm as compared to the placebo, at the end of the first month. Plasmapheresis treatment was superior to placebo in terms of tic symptoms, whereas, there was no significant difference between immunoglobulin treatment and placebo. Perlmutter et al. reported a 58% decrease in the severity of obsessions and compulsions with plasmapheresis treatment at the end of the first month, and a 49% decrease in the severity of the tics, globally. In the present study the rates of decrease were similar (62% on YBOCS, 56% on YGTSS). Perlmutter et al. reported that the improvement was still present in more than 80% of the patients at the end of the first year.

When other methodologies targeting autoimmune processes were compared to plasmapheresis, they were found to be less reliable. Perlmutter et al. reported more side effects with immunoglobulin treatment and suggest that plasmapheresis is a safer and more tolerable treatment. Furthermore, the side effects of plasmapheresis tend to be short-lived and reversible upon cessation of treatment (El-Gharani and Unswort, 2006). Steroid treatment, which is frequently used to treat autoimmune diseases, is not promoted due to the risk of an increase in obsessive-compulsive symptoms and side effects caused by the treatment (Jonasson et al., 1993; Perlmutter et al., 1999).

Anti-streptococcal antibodies produced during a GABHS infection are involved in a cross reaction in the nervous system and through an autoimmune pathway

effect the basal ganglia (Swedo et al., 1994). The function of plasmapheresis treatment is to remove the anti-streptococcal antibodies involved in this cross reaction in the nervous system from the body. The presence of these auto-antibodies and the fact that they target the basal ganglia were demonstrated in various studies (Hallet et al., 2000; Kiesling et al., 1993; Singer et al., 1999). Perlmutter et al. (1999) linked the gradual increase in improvement rates following each plasmapheresis session directly to the increase in the rates of antibody removal. The efficiency of plasmapheresis has not only been limited to clinical evaluations, it has also been shown in case reports with careful volumetric measurements demonstrating that increases in basal ganglia volume reverse in response to plasmapheresis treatment (Elia et al., 2005; Giedd et al., 1996).

Psychopharmacological treatments targeting obsessive-compulsive symptoms and tics triggered by streptococcal infections work by reversing the neuronal effects of the antibodies responsible for the symptoms (Swedo et al., 2001). Plasmapheresis treatment aims to remove these antibodies. As observed in 2 of our cases, due to intervening infections these auto-antibodies can re-emerge and the symptoms can exacerbate. Nevertheless, the mechanism of action of plasmapheresis targets a point within the disease pathogenesis, which is one step earlier than that targeted by psychopharmacological treatments. Plasmapheresis removes the agents causing the neuronal damage and its effect starts sooner than that of pharmacological intervention. Plasmapheresis seems to be an appropriate choice for non-responders to pharmacological treatment and severe cases. Since there is always the risk of an exacerbation of symptoms due to intervening infections, penicillin prophylaxis can be suggested following plasmapheresis. The invasiveness of the procedure, the long duration of the sessions, and the side effects limit the use of plasmapheresis in pediatric and adolescent patient groups.

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