Obsessive Compulsive Disorder and DIfferentiation between Non-Autoimmune OCD and the Autoimmune version of the disease called PANDAS

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This article was developed by Dr. Vojdani for patients with OCD, Tourette syndrome, and pediatric autoimmune neuropsychiatric disorder associated with Group A streptococcal infection (PANDAS).

Obsessive Compulsive Disorder is a collection of thoughts and actions that come into your mind without your desire or intention. They usually concern things that make no sense, or fears that have little real basis. They keep replaying, over and over, so that they cannot be shaken from your mind. Their content is frightening because you know it is not normal. As you try and fail to get rid of these unwanted thoughts, a significant level of anxiety is produced, and you feel out of control. To reduce the anxiety created by obsession, a series of characteristic actions or routines, such as washing and cleaning, checking, symmetry, counting, repeating, redoing, hoarding and praying will take place. These actions only temporarily reduce the anxiety created by obsession. Very soon after the action or ritual is completed, the nagging feeling of doubt and dread resurfaces, setting off the whole cycle again. Sometimes there is a meaningful connection between obsession and compulsion; for instance, washing when you feel contaminated. Lady Macbeth's continued washing of her hands ("Out, damned spot!") long after the murder of the royal family comes to mind. But in other instances there is no logical connection between them; for example, wearing certain clothes to prevent the fear of the house catching on fire.

Whether it makes logical sense or not, the compulsion will reduce the anxiety for a brief amount of time; a child with OCD believes that unless he does things a certain way, something bad will happen. But over time his brain builds up a "tolerance" to the rituals' calming effects, and he then has to develop more and more elaborate rituals to get relief from the obsession. With so much anxiety and time consumed by OCD, children are rushed to complete their daily tasks, and, therefore, are even more stressed. Or, often, children with OCD stay up late worrying about how they are going to manage the next day. For this reason they get up hours early in the morning to get their rituals done. As a result, they become sleep-deprived. When they are unable to get the ritual right, children become angry, irritable, and agitated. They may withdraw because their time-consuming rituals rob them of time to socialize. They may slow down to make sure they get things absolutely right, and generally do things more slowly because the rituals are so time-consuming. These rituals can interfere with learning and cause academic difficulties to develop in certain areas. For instance, children with OCD may have stronger verbal skills, but may have relatively weaker nonverbal skills, difficulty in writing, a reduction in processing, speed and efficiency, and impairment in expressive language skills.[1]

Causes and Treatment of OCD

During the past 20 years, research has shifted from seeing OCD as a neurotic condition to understanding its biological basis in the structure and operation of the brain. Dr. J. Schwarz, UCLA researcher, coined the term brain lock to describe how brain structures get caught in a traffic jam during OCD by sending false messages. He states that OCD is associated with a biochemical imbalance and can be treated effectively by behavior therapy.

Drs. Schwarz and Baxter made these discoveries at UCLA by comparing PET scans—which measure the metabolic activity of the brain—of people with and without OCD. They identified specific areas of the brain that are overactive in people with OCD. By performing PET scans on adults with OCD and comparing them with scans of adults without OCD, they showed that the basal ganglia, caudate nucleus, and the orbital frontal regions of OCD patients light up differently and show heightened activity.[2]

The ground-breaking news in this study was that, after successful treatment with either medication or behavior therapy, these abnormalities in brain activities either markedly diminished or disappeared.

Basal ganglia comprise the region of the brain that contains the thought-filtering station and many receptor sites for serotonin. The heightened activity of the basal ganglia in OCD may be the result of elevated serotonin levels. Indeed, in a subgroup of patients with OCD we find a decrease or elevation in the blood and platelet levels of serotonin. Serotonin is a neurotransmitter, a brain chemical whose job is to carry information from one nerve cell to the next. If there is not enough serotonin available, message circuits do not function properly and the message would not stop. Consistent with this, a person who suffers injury to the basal ganglia will develop OCD symptoms. The medications used to treat OCD, such as Prozac, Zoloft, and Paxil, affect serotonin levels. These selective serotonin reuptake inhibitors (SSRIs) target the receptor sites in the basal ganglia, making more serotonin available to direct messages properly. In numerous medication studies, investigators have found that OCD symptoms decrease in response to SSRI treatment, suggesting a strong role for serotonin in OCD.[3]

What Causes OCD?

The exact causes of OCD are not known. As was stated earlier, OCD arises from a biochemical mishap in the brain. In this state, part of the brain sends out a false message of danger without sending it through the proper screening process. As a result, the brain gets stuck in danger mode and is unable to get unstuck. Although we know what areas of the brain are overactive in OCD, it does not mean we understand why some children are washers and some are checkers, or why some of the symptoms change form over time. Sometimes there is a specific stressor that sets off a specific fear; e.g., fear of an infectious disease following the death of someone in school. For many adults with OCD, onset of the illness is associated with increased family responsibilities or change in the health or job status of someone in the

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family. In children, many research studies have described precipitating stressors associated with the onset of OCD. However, many children identified more meaningful triggers such as seeing "The Wizard of Oz" or "The Exorcist," getting poison ivy, or hearing bad news about war, news of terrorist acts, or learning of someone's cancer. Dr. T. Chansky states in her book that many children have described how they were already experiencing low-grade OCD symptoms. But when a major stressful event took place, the symptoms flared into full-blown OCD. It was as if the brain was already primed for OCD and these stressful events tipped the scale.[1]

IS THERE A GENETIC LINK IN OCD?

In a study conducted in 1992 by Dr. D. Rettew and colleagues at the National Institute of Mental Health (NIMH), it was reported that 38 percent of patients or their family members believed a specific event precipitated their OCD behavior, indicating that environmental factors play a role in the development of the disease. On the other hand, it is known that OCD runs in families, which may provide some evidence for the biological roots of OCD. Many studies have documented the greater prevalence of OCD in families where one member has either OCD, tics, or Tourette syndrome.

An NIMH study published in 1990 found that of 46 patients with severe OCD, 17% of the parents and 5% of their siblings met diagnostic criteria for OCD as well. However, in all cases where both parents and child had OCD, the symptoms were dissimilar, i.e., a child with prayer rituals had a parent who compulsively cleaned. Finally, it is important to note that some people develop OCD without any family history of OCD or Tourette syndrome, indicating that there is an important role for the environmental factor in OCD. Additional support for the role of the environment in the OCD puzzle is also provided by pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS).[4]

PEDIATRIC AUTOIMMUNE NEUROPSYCHIATRIC DISORDER ASSOCIATED WITH STREPTOCOCCAL INFECTIONS (PANDAS)

Pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) has been described in children with Obsessive Compulsive Disorder (OCD), anorexia nervosa and/or tic disorders subsequent to streptococcal infections.[5,6]

The acronym PANDAS has been given to a subgroup of pediatric patients who meet five inclusionary criteria:

- Presence of OCD and/or onset of tic disorder
- Pre-pubertal symptoms onset
- Sudden onset or episodic course of symptoms
- Temporal association between streptococcal infections and neuropsychiatric symptoms exacerbation
- Associated neurological abnormalities including antineural antibodies and neuroimmune dysfunction

The unique clinical characteristics of the PANDAS subgroup are the presence of volumetric changes in the basal ganglia, increased titers of antibodies against the Streptococcal M5, M12, and M19 proteins, and their cross-reactive epitope on B-cells (D8/17) and nerve cells, which have been described in a majority of these patients. For an estimated 25-30% of children with OCD, the episode is thought to be triggered or exacerbated by the body's own immune cells, which, while attacking the streptococcus, also begin attacking its own B-cells or the basal ganglia. This ground-breaking discovery may change the course of treatment for a subset of children with OCD. Based on this discovery, elevated serum titers of antibodies against streptococcal antigens and their cross-reactive epitopes on B-cells and nerve cells may require antibiotic and immunomodulatory treatment by the examining physician.[7-14]

However, in relation to streptococcal infections and OCD, several points must be made. Children do not "catch" OCD from streptococcus. Children who have a genetic predisposition for this disorder may have either a first episode or recurrences triggered by a strep infection.

This connection to strep arose from two lines of inquiry: first, the observation that a majority of children with a variant of rheumatic fever

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(Sydenham's chorea) also exhibited OCD symptoms; second, the clinical observation of the presence of strep in the childhood onset of OCD and Tourette syndrome. To understand the mechanism of action, researchers at NIMH took the example of Sydenham's chorea and rheumatic fever and found that these conditions were brought on by antibody attack on the basal ganglia, resulting in a sudden onset of neurological symptoms that include clumsiness and frequent jerky movements. Inspired by "residents" of the nearby zoo, Dr. Susan Swedo and her colleagues coined the acronym PANDAS to describe OCD in this subset of children. PANDAS, which affects children from three years old to puberty, is estimated to account for one third of OCD cases. Children typically develop their first PANDAS episode several months after an acute infection. Subsequent episodes may occur within days to weeks of the strep infection. It is important for parents and clinicians to be informed about PANDAS because even your pediatrician may not be familiar with this syndrome.[9,10]

HOW DOES AUTOIMMUNE OCD (PANDAS) DIFFER FROM NON-AUTOIMMUNE OCD?

Overall, the symptoms of the two conditions are indistinguishable, but by examining the course of the two diseases one may be able to differentiate the two.

- **Non-autoimmune OCD** has a gradual onset, with signs for months or even years before the symptoms become dysfunctional. In contrast, the autoimmune OCD (PANDAS) episodes develop rapidly. Overnight, the changes are dramatic. Parents of children with PANDAS describe these dramatic changes as if their child had gone to bed one night and had awakened as a completely different person who was hard to recognize.

- **A second distinction** is the way symptoms progress. The pattern of OCD symptoms in PANDAS is characterized by sharp ups and downs, which may correlate with the rise and fall of antibody titers against strep antigens and their cross-reaction with B-cell antigens and basal ganglia. In children with non-autoimmune OCD, the ups and downs are not sharp and are more gradual. The symptoms come and go, but without acute exacerbation.

- **A third feature of PANDAS** is the association of the symptoms that come with episodes. Children may have tics, trembling, twitches, grimacing, clumsiness, loss of math skills, sensitivity to touch and clothing tags, poor attention span, distractibility, irritability, impulsivity, separation anxiety, and bedtime fears.

The following guidelines are recommended by NIMH and summarized by Dr. T. E. Chansky in her book, *Freeing Your Child From Obsessive-Compulsive Disorder*. The book will help you to become knowledgeable about the signs and symptoms of PANDAS, as well as the steps to take if you suspect your child or your patient has PANDAS.

Signs and Symptoms of Autoimmune OCD (PANDAS)

- Sudden onset or sharp increase in OCD symptoms
- Presence of tics and/or hyperactivity
- Involuntary and irregular movements of the legs, arms, or face
- Irritability, temper tantrums, mood lability
- Age regression: reverting to younger developmental stage
- Separation anxiety
- Nighttime difficulties
- Severe nightmares and new bedtime fears or rituals

What to do if you suspect PANDAS:

Based on many articles in the scientific journals,[15-21] the following laboratory tests are recommended:

- Do a throat culture for Group A B-Hemolytic Strep
- Do a blood test to check for elevated antibody levels against the following streptococcal, B-cell and brain antigens:

1. Antibodies to the extracellular products of Group A streptococci which collectively are named Streptozyme:
   - ♦ Streptolysin O (SO)
   - ♦ Streptokinase (SK)
   - ♦ Hyaluronidase (SH)
   - ♦ Deoxyribonuclease (DNase)
   - ♦ Nicotinamide Adenine Dinucleotidase (NADase)
2. Antibodies to streptococcal cell components
   - ♦ M5 peptide
   - ♦ M12 peptide
   - ♦ M19 peptide
3. Antibodies to B-cell autoantigen
   - ♦ D8/17
4. Anti-brain antibodies
   - ♦ Myelin basic protein
   - ♦ Ganglioside (Asialoganglioside GM_1)

A PANDAS panel may be ordered from Immunosciences Lab at a 50% discount by practitioners only: 8693 Wilshire Blvd., Suite 200; Beverly Hills, CA 90211; Phone: (310) 657-1077; Fax: (310) 657-1053; Toll Free: (800) 950-4686; www.immunoscienceslab.com

UK Representatives: Nutri-Link Ltd.; Email: eldon@eclipse.co.uk

Differentiation of non-autoimmune OCD from autoimmune OCD (PANDAS) by examining serum reactivity against:

Streptozyme	Streptococcal Peptides	B-Cell AntigensD8/17	Myelin Basic Protein And Ganglioside GM	Medical Condition
–	–	–	–	Optimal
+	–	–	–	Group A streptococcal infection without autoimmune reaction
–	–	+	–	Antibody to B-cell alloantigen and cross-reaction with myosin and tropomyosin
–	–	–	+	Autoimmune neurologic disorder
+	+	–	–	Streptococcal infection with possible PANDAS
+	+	+	–	Streptococcal infection and immune reaction with B-cell alloantigen in PANDAS
+	+	–	+	Streptococcal infection and immune reaction with basal ganglia in PANDAS
+	+	+	+	Streptococcal infection and autoimmune reaction with B-cell alloantigen and basal ganglia in severe PANDAS
–	+	+	+	Old streptococcal infection and autoimmune reaction with B-cell alloantigen and basal ganglia in severe PANDAS

The pattern of these antibodies should be interpreted by the signs and symptoms of PANDAS. Only with the combinations of symptoms plus antibody patterns shown in this table should a final diagnosis of PANDAS be made, and only by your doctor.

Several procedures for the treatment of PANDAS are currently under investigation at the NIMH. These procedures, which were published by Perlmutter et al 1999, Garvey et al 1999, and Murphy and Pichichero 2002, also are summarized in Dr. Chansky's book.[22-24, 1]

In these studies several children were put under daily doses of amoxicillin as a prophylactic measure to control the possibility and severity of strep infection. The effectiveness of this treatment is, as yet, unclear. A second treatment is plasmapheresis for the removal of autoantibodies reacting to B-cell receptors and the cells in basal ganglia. And, finally, intravenous immunoglobulin (IVIG) is used for anti-idiotypic antibodies and regulation of the immune system. These procedures are more invasive and require hospital stays anywhere from several days to two weeks, especially for plasmapheresis, which essentially involves clearing the blood of the antibodies triggering the immune dysfunction and neurological symptoms.

These latter treatments appear to be effective, producing dramatic reductions in symptoms, though they are still under investigation and are not standard medical practice. It is estimated that children will have an average of 1 to 8 infections prior to puberty; at any given time, 5 to 20 percent of school age children have a strep infection. Until there is a vaccine for strep, parents should be vigilant for early signs of strep infection and take preventive measures.

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