Obsessive-Compulsive Disorder, Tics, and Autoinflammatory Diseases: Beyond PANDAS

Presenters: Blanca Garcia-Delgar, MD¹ and Astrid Morer, MD, PhD^{1–3}

Discussants: Maxwell J. Luber, BA⁴ and Barbara J. Coffey, MD, MS⁴

Chief Complaint and Presenting Problem

A. WAS A 15-year-old BOY with a history of persistent tics, obsessive-compulsive disorder, and recurrent episodes of vague physical symptoms referred for consultation regarding the diagnosis of Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS).

History of the Present Illness

Parents reported that since A. was diagnosed with mononucleosis at age 10, he had been experiencing recurrent episodes of low-grade fever, asthenia, arthralgia, headache, concentration difficulties, and abdominal pain. These episodes occurred every 1–2 months, lasted 2–3 weeks, and did not have an obvious trigger. During the episodes of illness, A. was so exhausted that he could not attend school or meet his friends, but he was able to resume his daily activities as soon as symptoms remitted.

Since the beginning of the present condition, A. had been referred to a variety of specialists. After ruling out the most common medical conditions, A. was evaluated by a team of rheumatologists who diagnosed chronic fatigue syndrome. However, A.'s parents did not consider fatigue to be the main problem and made an appointment with an internist for a second opinion. Guided by gastrointestinal manifestations (abdominal pain occasionally accompanied by diarrhea and weight loss), the doctor ordered an endoscopy and serologic tests to screen for celiac disease. Results were negative, except for identification of villous atrophy and Periodic Acid-Schiff (PAS)-positive macrophages in the duodenal biopsy. With suspicion of Whipple disease, A. was started on trimethoprim/sulfamethoxazole and subsequently switched to doxycycline for leukopenia. After a 4-month trial with doxycycline, gastrointestinal symptoms persisted, so antibiotics were discontinued.

Soon after A. was diagnosed with mononucleosis, he started exhibiting obsessive-compulsive symptoms. At that time, he needed the TV volume to be set at a specific number and avoided touching surfaces that were not completely clean. At age 14, obsessive-compulsive symptoms started impacting his daily life, so his parents made an appointment with a psychiatrist who diagnosed obsessive-compulsive

disorder (OCD). Given A.'s difficulties engaging in a structured cognitive-behavioral therapy due to his medical condition, medication was initiated. A. was started on sertraline 50 mg once a day and gradually titrated to 100 mg bid. He tolerated the medication well, without any side effects. Obsessive-compulsive symptoms partially remitted and persisted during the following episodes of illness.

In addition to obsessive-compulsive symptoms, A. also exhibited motor tics. Parents reported that A. developed the onset of tics at age 9, soon after the family returned home from living abroad for 1 year. A. recalled the return as a sad and stressful period in his life. Initially, A. developed eye and facial movements and gradually went on to have other tics involving his limbs. Parents reported that A. also used to sigh repeatedly. Retrospectively, this was probably his first vocal tic, but it was not recognized as such at the time. Motor tics persisted and increased during the following year, so A. was referred to a neurologist who diagnosed chronic motor tic disorder. At that time, no therapy was started as tics were not impacting A.'s functioning. By the age of 14, his tics increased and the psychiatrist started risperidone 0.5 mg bid. A.'s tics improved subsequently and by the time of the evaluation, A. was only exhibiting eye blinking. Despite the positive response to medication, his tics tended to worsen with fatigue, particularly during the episodes of illness, and eye movements were occasionally so intense that botulinum toxin injections were required.

In addition to tic exacerbation, A. also reported concentration difficulties during the episodes of illness. A. did not show symptoms of attention-deficit/hyperactivity disorder, but he was started on short-acting methylphenidate during an episode of illness to help maintain academic performance. This medication had to be discontinued immediately due to an allergic reaction (orofacial edema).

Given the episodic course of his psychiatric symptoms, A. was referred to a specialized clinic in tics and Tourette's disorder for consultation regarding a question of PANDAS.

Developmental History

A. was born full term by vaginal delivery with a birth weight of 3.4 kg. Pregnancy was uncomplicated except for gestational diabetes that was controlled by diet. A. had newborn streptococcal

¹Department of Child and Adolescent Psychiatry and Psychology, Institute of Neurosciences, Hospital Clínic, Barcelona, Spain.

²Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.

³Centro de Investigación en Red de Salud Mental (CIBERSAM), Instituto Carlos III, Madrid, Spain.

⁴Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York.

septicemia and bronchiolitis at age 6 months that required treatment with antibiotics.

A. met all of his developmental milestones on time. He was reported to be an easy, sociable child with a tendency to be self-demanding and perfectionistic.

Educational History

A. received regular education. He had always attended the same school except for one academic year during which he moved abroad with his family. During that year, A. had no difficulties adjusting to the new school. A. had generally done well academically until the year before the present evaluation, when he had shown a decline in his school performance due to his absences during the episodes of illness.

Social History

A. lived with his biological parents and his 18-year-old brother. A. had a good relationship with his family, but parents reported that he had gradually become more oppositional at home since the beginning of the present illness. A. had always been very sociable and friendly, but at the time of evaluation, he was having problems in maintaining his social life due to his illness.

Family History

Paternal grandmother had an episode of depression after her divorce that was successfully treated with psychotherapy and psychopharmacology. Mother had traits of obsessive-compulsive personality disorder, which were notable in other relatives of her immediate family. None of them had required treatment.

Father had recurrent streptococcal pharyngitis during childhood and an episode of tuberculosis at the age of 30 that responded to antibiotic treatment. He also reported recurrent self-limited episodes of mild arthralgia that were never evaluated. There was no other known history of infections or autoimmune diseases in the family.

Medical History

A. had a history of numerous infections during childhood. At age 6, he had a urinary tract infection treated with antibiotics. At age 11, he was diagnosed with mononucleosis and atypical pneumonia caused by *Mycoplasma pneumoniae*. Throughout A.'s childhood, he also exhibited recurrent pharyngitis that required use of antibiotics.

A. had a history of allergic reactions to medications. He developed orofacial edema on methylphenidate and leukopenia on trimethoprim/sulfamethoxazole. A. also had lactose and gluten intolerance for which he was on a special diet.

Growth and development were described as healthy, although A. had lost weight during a time when episodes of illness were occurring more often.

Mental Status Examination

Mental status examination revealed a cooperative adolescent, with no dysmorphic features. A. exhibited motor tics (eye blinking) that did not interfere with his daily life. No other abnormal movements were noticed. During the interview, A. established eye contact and was oriented in time, day, and place. His memory and attention were intact, although he described concentration difficulties during his episodes of illness. A. reported concerns about his health problems, which were appropriate in the context of his

medical history. A. described his mood as irritable, but denied other depressive symptoms, such as hopelessness or suicidal ideation. There was no evidence of thought disorder or hallucinations during the interview. Judgment and insight appeared intact for his age. A. was interested in undergoing new procedures and trying new medications that could help with his recovery.

His neurological examination was within normal limits.

Treatment Course

During consecutive episodes of illness, blood tests and throat cultures were conducted to examine a potential relationship between clinical symptoms and streptococcus infections. Antinuclear antibody (ANA) and neuronal antibody titers were also requested to screen for systemic lupus erythematosus and autoimmune encephalitis. Results were repeatedly normal, except for a positive ANA at low titers (1:40) and neutropenia (neutrophils $1100/\text{mm}^3$; normal range: $1500\text{--}7000/\text{mm}^3$). Low white cell count had also been detected in previous episodes, but it had been related to the use of trimethoprim/sulfamethoxazole.

Given the abnormalities in the blood test and the history of multiple infections, a genetic test was conducted to study diseases characterized by episodic fever and leukopenia, such as cyclic neutropenia. While results were pending, A. suffered a new episode with low-grade fever, odynophagia, headache, arthralgia, peri-orbital edema, and facial rash. With suspicion of an immunological condition, A. was started on prednisone 10 mg bid. Two days later, fever and odynophagia remitted, but other symptoms such as arthralgia and headache persisted.

Three weeks later, a mutation in the gene encoding the TNF receptor superfamily member 1A (variant R92Q) was detected, a finding suggestive of tumor necrosis factor receptor-associated autoinflammatory syndrome (TRAPS). This diagnosis was confirmed after repeating the genetic test with A.'s parents, who were found to be heterozygotes for the same mutation.

A. was then referred to a specialized clinic in autoimmune diseases, where a biologic drug, anakinra, was started at 100 mg/day. On that medication, episodes of illness became less frequent and severe, so prednisone was discontinued 2 weeks later. Psychiatric symptoms (tics and OCD) also improved. One year after anakinra was started, risperidone was reduced from 0.5 mg bid to 0.5 mg qd and sertraline from 100 mg bid to 100 mg qd. As A.'s medical condition improved, he was able to resume social and leisure activities.

Brief Formulation

In summary, A. was a 15-year-old boy with a history of persistent motor tics and OCD in the context of recurrent episodes of vague physical symptoms. Motor tics had persisted for more than 1 year and were accompanied by at least one vocal tic, so the diagnosis of Tourette's disorder was made. Given that psychiatric symptoms did not show a clear exacerbation during episodes of illness, and laboratory tests were negative for streptococcus infections, PANDAS diagnosis was ruled out. In the context of his health problems, A. developed depressive symptoms, such as irritability and oppositional behaviors, which remitted as soon as the physical symptoms improved, meeting criteria for adjustment disorder.

From a biological perspective, A. had a genetic predisposition to affective disorders because of a family history of depression on the paternal side. Moreover, he also had a personal and family predisposition to immunological disorders that guided clinicians to further investigate genetic immune conditions such as TRAPS.

That said, A. had many strengths, including strong family support and solid academic performance, which allowed him to continue with his academic activity despite missing school during the episodes of illness.

Multiaxial Diagnoses

Axis I: Tourette's disorder
Obsessive-compulsive disorder
Adjustment disorder, past
Axis II: Deferred
Axis III: Tumor necrosis factor receptor-associated autoinflammatory syndrome (TRAPS)
Methylphenidate allergy, lactose and gluten intolerance
Possible severe adverse reaction to trimethoprim/sulfamethoxazole
Axis IV: Other psychosocial problems: long period with a severe undiagnosed condition
Axis V: Global Assessment of Functioning score at baseline: 40
Global Assessment of Functioning score at follow-up: 75

Discussion

This case represents an interesting interface of psychiatric and immunological disorders. To our knowledge, this is the first report of psychiatric symptoms in an adolescent with TRAPS.

TRAPS is a rare genetic disease with an estimated prevalence of one per million (Lainka et al. 2009). It is caused by mutations in the gene encoding the TNF receptor superfamily member 1A (*TNFRSF1A* gene), a key structure in the immune system (McDermott et al. 1999). TRAPS was formerly known as familial Hibernian fever as it is characterized by recurrent episodes of fever that typically occur every 5–6 weeks and last for 7–14 days (Lachmann et al. 2014). During these episodes, subjects usually exhibit other symptoms such as myalgia, abdominal pain, skin rash, and eye manifestations (conjunctivitis or periorbital edema) (Cantarini et al. 2012; Lachmann et al. 2014). Episodes usually occur spontaneously, but in a small minority, specific triggers can be identified (i.e., stress, sex hormonal changes, fatigue, exercise, infections, and vaccinations) (Lachmann et al. 2014). Episodes of fever can begin at any age, but most people have their first episode in childhood (Lachmann et al. 2014).

A. exhibited a mild TRAPS phenotype that led to misdiagnosis and inadequate management for 5 years. Delays in the diagnosis are particularly common in subjects with A.'s mutation, the R92Q variant, as it has been related to a lower proportion of familial disease, more headaches, and fewer rash and eye manifestations (Lachmann et al. 2014). The low penetrance of the R92Q variant may also explain why A.'s parents did not develop features of TRAPS despite being carriers of the mutation. TRAPS is inherited in an autosomal dominant pattern, so one mutated gene is sufficient to develop the disease (McDermott et al. 1999).

Central nervous system symptoms such as headache, seizures, and vertigo have been reported in patients with TRAPS (Minden et al. 2004; Lachmann et al. 2014), but psychiatric symptoms have not been described to date. However, OCD and tics have been related to several other immunological conditions. One of the first investigators to suggest the relationship between immune and psychiatric symptoms was Dr. Susan Swedo, who described a case series of 50 prepubertal children with acute onset of tics and OCD in association with streptococcal infections (Swedo et al. 1998). This clinical presentation was named Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) and is defined by the following diagnostic criteria: (1) presence of

lifetime diagnostic criteria for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) (American Psychiatric Association 1994) OCD and/or tic disorder; (2) onset between age 3 and the beginning of puberty; (3) episodic course of symptom severity, characterized by abrupt onset or dramatic symptom exacerbation; (4) temporal association between symptom onset and/or exacerbation and group A beta-hemolytic streptococcus (GABHS) infection, as documented by positive throat culture and/or elevated anti-GABHS antibody titers; and (5) association with neurological abnormalities during symptom exacerbation, such as tics, or choreiform movements, but not chorea *per se* (Swedo et al. 1998). A. met diagnostic criteria #1, 2, and 5, but psychiatric symptoms did not show a clear exacerbation during the episodes of illness (criteria #3). However, taking into consideration the complexity of the case, further laboratory studies were conducted to examine a potential association between psychiatric symptoms and streptococcus infections (criteria #4).

In terms of treatment, evidence of therapy for patients with TRAPS relies on retrospective cohorts or small prospective studies. Nonsteroidal anti-inflammatory drugs have been reported to be beneficial in relieving symptoms, but they have not shown to be effective in terminating inflammatory episodes (Ter Haar et al. 2013). On the other hand, corticoids have been reported to be effective for terminating inflammatory episodes, but they have only been recommended as acute treatment due to serious adverse effects and resistance related to their long-term use (Ter Haar et al. 2015). Although therapeutic options for severely affected patients are not yet standardized, therapy with biological agents is necessary in some cases. Among biological agents, IL-1 blockade agents such as anakinra seem to be a first-line treatment (Ter Haar et al. 2015). Etanercept, an anti-TNF agent, can also be effective in some patients, but positive effects with this medication have been reported to decline over time (Drewe et al. 2003; Bulua et al. 2012). Biological agents can be used on demand, but in cases with frequent attacks and/or subclinical inflammation between attacks, maintenance therapy is recommended to limit the exposure to corticosteroids and minimize the risk of long-term complications of TRAPS, such as amyloidosis (Ter Haar et al. 2015).

In A.'s case, anakinra was used with an excellent response. Psychiatric symptoms also showed a remarkable improvement, but the extent to which his favorable course was related to the use of biological medications remains unknown. Recent studies have described increased levels of proinflammatory markers in children and adolescents with neuropsychiatric disorders, including OCD and tics (Mitchell and Goldstein 2014; Gariup et al. 2015). Studies have also reported higher levels of serum TNF- α during periods of tic exacerbation (Leckman et al. 2005; Parker-Athill et al. 2015). Although the correlation between tic severity and high cytokine levels does not imply causation, it seems plausible to hypothesize that psychiatric symptoms could attenuate with the remission of inflammation. Caution is needed in supporting this hypothesis, as A.'s OCD and tic improvement could also be related to a reduction in stress after the TRAPS diagnosis (Conelea et al. 2011) or the natural history of tics, which tend to improve with age (Bloch et al. 2006).

More studies about the relationship between immunity and neuropsychiatric disorders are needed to find new therapeutic interventions that can improve patients' prognosis.

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Address correspondence to:
 Barbara J. Coffey, MD, MS
 Icahn School of Medicine at Mount Sinai
 One Gustave L. Levy Place, Box 1230
 New York, NY 10029

E-mail: barbara.coffey@mssm.edu