case report

Wien Med Wochenschr
https://doi.org/10.1007/s10354-020-00779-6

wmw
Wiener Medizinische Wochenschrift

Tourette syndrome or PANDAS—a case report

Rhea Singh · Nataliya Nekrasova · Dmytro Butov

Received: 26 March 2020 / Accepted: 12 August 2020

Summary Tourette syndrome (TS), a relatively common disorder, has been gaining more attention during the past two decades because of an increased number of reports. Nevertheless, it is still not completely understood. Furthermore, a clinical entity called "pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections" (PANDAS) has been introduced, which describes a tic disorder, accompanied by psychiatric disorders such as obsessive compulsive disorder (OCD), after a streptococcal infection in childhood. We present a case report of a 19-year-old adolescent Ukrainian female, with a history of anxiety disorder and OCD, who, despite TS remission during childhood, presented with new-onset motor and phonic tics after 1 month of severe tonsillitis. Blood and cerebrospinal cultures showed *Streptococcus pyogenes*, with magnetic resonance imaging revealing hypo-intense changes in the caudate nucleus on both sides. Treatment with clonazepam and fluoxetine, along with behavioral therapy, have improved the severity of her condition. This report presents a case of TS reemergence against the background of immunological reaction or PANDAS with a late adolescent onset.

R. Singh · Prof. Dr. of medical sciences D. Butov, MD, PhD, ScD (✉)
Kharkiv National Medical University, Kharkiv, Ukraine
dddimed@gmail.com

R. Singh
rheasingh@yahoo.com

Prof. Dr. of medical sciences N. Nekrasova, MD, PhD, ScD
Neurology department №2, Kharkiv National Medical University, Kharkiv, Ukraine
Limka.nno@gmail.com

Keywords Adolescent female · Obsessive-compulsive disorder (OCD) · Streptococcal infections · New-onset tics · Anti-neuronal antibodies

Introduction

Gilles de La Tourette syndrome (TS), first described in 1885 and thought to be a rare disorder at the time, now affects approximately 1% of children and adolescents. It is more often seen in males than in females [1]. It involves at least one vocal and multiple motor tics, lasting for at least 1 year. The syndrome is found to be more prevalent in people with autistic spectrum disorders, learning disabilities [2], and psychiatric disorders such as attention deficit hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD). It is broadly thought to be caused by a disturbance in the striato-thalamo-cortical pathway, but the exact mechanism is unknown. More and more research is being carried out on this topic because of an increased number of reports on children between the age of 5 and 16 presenting with TS accompanied by psychiatric disorders, who require behavioral therapy for condition improvement [3]. Adult-onset TS has not been very commonly reported and most people with TS have a history of tic disorders in their childhood [4]. In the case of childhood-onset TS, the occurrence and severity of tics decline as the child approaches adolescence [5]. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) has been a subject of debate as a clinical identity for many years because of a lack of sufficient evidence [6]. We present a case report of a 19-year-old female patient presenting with new-onset tic disorders accompanying OCD and anxiety disorder after a bout of severe tonsillitis (Table 1).

Published online: 21 September 2020

Table 1 Unique case points

What is known	What is new
Approximately 96% of the cases of TS present at 8–13 years	Female patient presented with re-emergent TS at the age of 19, after suffering from severe tonsillitis, or PANDAS in adolescence?
The usual period of PANDAS onset is pre-pubertal	The patient suffers from premorbid OCD and anxiety disorders

Case history

A 19-year-old female patient presented to the Neurology Department of Kharkiv National Medical University, Ukraine, from December 2019 to June 2020 (and ongoing). During her first visit, she described a 1-month history of sudden-onset involuntary body movements involving twitching of the facial muscles and leg jerks with episodic vocalizations involving hissing sounds and echolalia. The symptoms started acutely within 3 days. The symptoms were of a waxing and waning nature without any remission and started simultaneously. These involuntary movements increased during periods of emotional stress. Her parents were 45 and 49 years old, of a rigid and strict personality.

Anamnesis

The patient was born full term via normal delivery without any complication. She had no siblings. Early childhood development was on par with age standards, although she was a shy child. She had a history of tic disorder involving shoulder shrugs and blinking and humming for a brief period of 14 months at the age of 11 years, which resolved spontaneously without treatment. The symptoms were not preceded by a streptococcal infection. She also had a history of chickenpox at the same age (11 years) and pneumonia at 13. Moreover, she started suffering from social stress, anxiety disorder, and OCD starting from the age of 16, which had worsened since the start of the presenting symptoms. There was no history of other infectious diseases such as tuberculosis, measles, and sexually transmitted diseases. She had only a few friends and was currently studying geology and lived in a hostel. Since the beginning of the tics, her performance in her studies declined slightly with occasional irritable episodes. There was no history of drug or alcohol abuse. One month prior to the beginning of the tics, she suffered from severe tonsillitis. She took oral penicillin (prescribed for 10 days) after 2 weeks of onset, which resulted in its remission.

Physical examination

On initial physical examination, consciousness was clear, although the patient kept fidgeting and trying to dust and arrange her dress, clenching and unclenching her hands repetitively. While answering the questions, the presenting complaints were observable facial twitching, hissing vocalizations, and involuntary leg movements (tics). The patient tried to control her echolalia, but it was observed a few times during examination. The tics were quite frequent and severe. The respiratory, cardiovascular, digestive, urinary, and musculoskeletal system were unremarkable.

Neurological status

Meningeal signs (nuchal rigidity, Kernig's sign, Brudzinski's sign, lethargy) were absent, oromandibular dystonia and hemifacial spasms were present; increased tendon reflexes on the right side ($S \leq D$) and asymmetry of abdominal reflexes ($S \geq D$) were observed. No pathological signs, sensory disorders, or disturbance in balance and coordination were observed. All cranial nerves were intact. Occasional mild–moderate headaches were reported. Sonography of the neck and head vessels revealed no signs of occlusion and hemodynamic stenosis. Magnetic resonance imaging (MRI) of the head showed hypointense changes in the region of the caudate nucleus on both sides; however, no signs of trauma or encephalitis were detected. Blood tests revealed *Streptococcus pyogenes* and high anti-streptolysin titer. Lumbar puncture was done, with an opening pressure of 25 cm of water. It revealed high a white blood cell count of 150 cells/mm^3, low glucose level (1.8 mmol/l), and an elevated protein level (5 g/l). The cerebrospinal fluid (CSF) culture was positive for *Streptococcus pyogenes*. Anti-neuronal antibodies against the caudate nucleus were also detected. However, the Cunningham panel (detection of autoantibodies against dopamine D1 receptor, dopamine D2 receptor, lysoganglioside GM1 and tubulin and activation of calcium-dependent calmodulin protein kinase II [CaM-Kinase II]) was not used. She was prescribedofloxacin-200 (400 mg/day) for 14 days and continued on clonazepam with a daily divided dose ranging between 0.1 and 0.25 mg/day and fluoxetine (10 mg/day). She had been advised to undergo behavioral therapy. Blood culture results following 1-month treatment with ofloxacin, were negative for *Streptococcus pyogenes*. The severity of the tics had decreased in the following follow-up visits, although to date there is still not complete remission.

Discussion

Tourette syndrome is a neuropsychiatric disorder characterized by tics, often accompanying other disorders such as OCD and ADHD, depression, autistic spectrum disorders, and learning disabilities [7]. Motor tics can be simple or complex and observable in any part of the body. Vocal tics are involuntary sounds such as sniffing, clearing the throat, coughing, shouting, echolalia, and coprolalia. These tics can worsen with emotional stress or excitation. Although previ-

ously thought to become unnoticeable during sleep, some studies suggest that the tics can persist even during sleep [8]. The onset of the disease is typically between the age of 3 and 8 years, manifesting by the age of 11, with a waxing and waning course [9]. Idiopathic adult-onset TS is rarely reported, most of which can be attributed to recurrent childhood disorders; apart from this, the adult onset can be brought on by encephalitis, trauma, and other conditions [10]. Recent estimates predict TS to be found in 1% of children. Its prevalence is more in men than in women with a ratio of 3:1 [2]. In children, mental retardation and growth development disorders may be present, not due to TS itself but due to the disorders that often accompany it. The precise pathogenesis is unknown but it is reported to be due to defects in the cortico-striato-thalamo-cortical pathway that is responsible for cognition, emotions, and sensorimotor functions [11]. It is hypothesized, although not exactly known how, that neurotransmitters such as dopamine [12], GABA, acetylcholine, serotonin, norepinephrine [13], and glutamate [14] play a role in the pathophysiology of TS. Thinning of the cortex and the shrinking of the caudate nucleus represent the most evident neuroanatomical abnormality [15]. On MRI of our patient, hypo-intense changes were visible, showing the caudate nucleus was affected.

The etiology of TS is complex including various environmental factors and underlying genetic abnormalities [16] The genes most commonly implicated in TS are SLITRK1, NTN4, DRD2, DRD4, and AADAC [17, 18]. There is a genetic and familial link between OCD and TS [19]. People with TS accompanying OCD generally show high levels of psychosocial stress. Also, raised stress levels increase the severity of OCD, but evidence for the converse is lacking [20]. Patients with comorbid psychiatric disorder have decreased self-concept and symptoms of social and affective anxiety are most common [21]. Patients with TS and OCD are more prone to self-harming behaviors [22].

Also, it has been hypothesized in studies that there could be an immunological basis to TS. The cross-reaction between basal ganglia antigens and anti-neuronal antibodies found in these patients could be the cause of the onset of tics [23].

The significance of PANDAS as a clinical entity is often debated because the data provided by different types of studies cannot be interpreted together. The foremost criteria for PANDAS are: (a) the presence of OCD and/or a tic disorder; (b) onset during childhood; (c) a periodical nature of symptom severity; (d) association with streptococcal infections; (e) association with neurological abnormalities [24]. Some authors believe that there is a connection between prior streptococcal infections and the onset and expression of TS via an immune-mediated pathway similar to Sydenham's chorea [25–27]. Some have described anti-neuronal antibodies to play a role in the pathogenesis of PANDAS [28]. An immunological dysfunction in PANDAS has strongly been advocated by a controlled trial in which intravenous immunoglobulins and plasma exchange helped improve the conditions of the patients [29]. A clear relationship between TS and streptococcal infections is yet to be established as different studies have selected varying cohorts of patients, and thus the data are misleading [9, 24]. Our patient has shown symptoms that match the criteria of PANDAS, except the adolescent age of onset, although the patient suffered from TS during childhood and was in remission until the presentation.

The treatment options are limited: Dopamine antagonists, monoamine-depleting drugs such as tetrabenazine, α_2-adrenergic agonists such as clonidine and guanfacine, behavioral interventions, and habit reversal therapy are some of the treatments used. Haloperidol considerably reduces the symptoms of this syndrome [30]. Our patient is showing improvement in tic severity with clonazepam, fluoxetine, and behavioral therapy. In addition, ofloxacin was used against *Streptococcus pyogenes*. The negative blood culture results after medication proved its efficacy.

Our 19-year-old female patient presented with acute-onset tic disorder with a waxing and waning course, with preceding streptococcal infection, with premorbid psychiatric conditions such as OCD and anxiety that worsened since the start of the tics. Despite the treatment given to treat tonsillitis, which resulted in its remission, on blood analysis, *Streptococcus pyogenes* could still be detected with high ASO titers. Anti-neuronal antibodies were detected and the CSF cultures revealed *Streptococcus pyogenes*. Changes in MRI were also detected. This could point to the reemergence of TS due to immunological reaction or PANDAS with a late adolescent onset. Environmental factors and social stress could also be an underlying factor in our patient.

Despite the increasing awareness of TS and the numerous studies being performed, many symptoms such as ocular tics, tics that mimic asthma, persistent coughing and blinking often go misdiagnosed [31]. Furthermore, the complex autoimmune mechanism behind TS associated with OCD, anxiety at an older adolescent age with prior streptococcal infection, or PANDAS is still not fully understood. These are topics that need further research. This will increase the efficiency of medical care given to children and adolescents who suffer from these diseases.

Our case report provides a source of interesting information for clinicians, delivering an educational message for novice doctors to help improve their diagnostic skills in such rare cases.

Acknowledgements We want to thank all the personnel involved with this case.

Compliance with ethical guidelines

Conflict of interest R. Singh, N. Nekrasova and D. Butov declare that they have no competing interests.

Ethical standards The clinical case was approved by the Ethics Committee of the Kharkiv National Medical University, Kharkiv, Ukraine.

References

1. Meoni S, Macerollo A, Moro E. Sex differences in movement disorders. Nat Rev Neurol. 2020;16:84–96.
2. Robertson MM, Eapen V, Singer HS, Martino D, Scharf JM, Paschou P, et al. Gilles de la Tourette syndrome. Nat Rev Dis Primers. 2017;3:16097.
3. McGuire JF, Ricketts EJ, Scahill L, Wilhelm S, Woods DW, Piacentini J, et al. Effect of behavior therapy for Tourette's disorder on psychiatric symptoms and functioning in adults. Psychol Med. 2019; https://doi.org/10.1017/S0033291719002150.
4. Thenganatt MA, Jankovic J. Recent advances in understanding and managing Tourette syndrome. F1000Res. 2016; https://doi.org/10.12688/f1000research.7424.1.
5. Groth C, Debes NM, Rask CU, Lange T, Skov L. Course of Tourette syndrome and comorbidities in a large prospective clinical study. J Am Acad Child Adolesc Psychiatry. 2017;56(4):304–12.
6. de Oliveira SKF, Pelajo CF. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS): a controversial diagnosis. Curr Infect Dis Rep. 2010;12(2):103–9.
7. Gorman DA, Thompson N, Plessen KJ, Robertson MM, Leckman JF, Peterson BS. Psychosocial outcome and psychiatric comorbidity in older adolescents with Tourette syndrome: controlled study. Br J Psychiatry. 2010;197(1):36–44.
8. Hanna PA, Jankovic J. Sleep and tic disorders. In: Chokroverty S, Hening Walters A, editors. Sleep and movement disorders. Woburn, MA: Butterworth-Heinemann; 2003. pp. 464–71.
9. Jankovic J. Tourette's syndrome. N Engl J Med. 2001;345(16):1184–92.
10. Chouinard S, Ford B. Adult onset tic disorders. J Neurol Neurosurg Psychiatry. 2000;68(6):738–43.
11. Leckman JF, Peterson BS, Anderson GM, Arnsten AFT, Pauls DL, Cohen DJ. Pathogenesis of Tourette's syndrome. J Child Psychol Psychiatry. 1997;38(1):119–42.
12. Singer HS, Szymanski S, Giuliano J, Yokoi F, Dogan AS, Brasic JR, et al. Elevated intrasynaptic dopamine release in Tourette's syndrome measured by PET. Am J Psychiatry. 2002;159(8):1329–36.
13. Pogorelov V, Xu M, Smith HR, Buchanan GF, Pittenger C. Corticostriatal interactions in the generation of tic-like behaviors after local striatal disinhibition. Exp Neurol. 2015;265:122–8.
14. Singer HS. The neurochemistry of Tourette syndrome. In: Davide Martino, James F. Leckman, editors. Tourette Syndrome. Oxford: Oxford University Press; 2013. https://doi.org/10.1093/med/9780199796267.003.0013
15. Robertson MM. The Gilles de la Tourette syndrome: the current status. Arch Dis Child. 2012;97(5):166–75.
16. Pagliaroli L, Vető B, Arányi T, Barta C. From genetics to epigenetics: new perspectives in tourette syndrome research. Front Neurosci. 2016;10:277.
17. Yuan A, Su L, Yu S, Li C, Yu T, Sun J. Association between DRD2/ANKK1 TaqIA Polymorphism and Susceptibility with Tourette Syndrome: a meta-analysis. PLoS ONE. 2015;10:6.
18. Bertelsen B, Stefánsson H, Jensen LR, Melchior L, Debes NM, Groth C, et al. Association of AADAC deletion and Gilles de la tourette syndrome in a large European cohort. Biol Psychiatry. 2016;79(5):383–91.
19. Pauls DL. The genetics of obsessive compulsive disorder and Gilles de la Tourette's syndrome. Psychiatr Clin. 1992;15(4):759–66.
20. Lin H, Katsovich L, Ghebremichael M, Findley DB, Grantz H, Lombroso PJ, et al. Psychosocial stress predicts future symptom severities in children and adolescents with Tourette syndrome and/or obsessive-compulsive disorder. J Child Psychol Psychiatry. 2007;48(2):157–66.
21. Silvestri PR, Chiarotti F, Baglioni V, Neri V, Cardona F, Cavanna AE. A preliminary examination of self-concept in older adolescents and young adults with Gilles de la Tourette syndrome. Eur J Paediatr Neurol. 2017;21(3):468–74.
22. Stafford M, Cavanna AE. Prevalence and clinical correlates of self-injurious behavior in Tourette syndrome. Neurosci Biobehav Rev. 2020; https://doi.org/10.1016/j.neubiorev.2020.03.022.
23. Morer A, Lázaro L, Sabater L, Massana J, Castro J, Graus F. Antineuronal antibodies in a group of children with obsessive-compulsive disorder and Tourette syndrome. J Psychiatr Res. 2008;42(1):64–8.
24. Orefici G, Cardona F, Cox CJ, Cunningham MW. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). In: Streptococcus pyogenes: basic biology to clinical manifestations. University of Oklahoma Health Sciences Center; 2016. https://www.ncbi.nlm.nih.gov/books/NBK333433/.
25. Allen AJ, Leonard HL, Swedo SE. Case study: a new infection-triggered, autoimmune subtype of pediatric OCD and Tourette's syndrome. J Am Acad Child Adolesc Psychiatry. 1995;34(3):307–11.
26. Kurlan R, Johnson D, Kaplan EL. Streptococcal infection and exacerbations of childhood tics and obsessive-compulsive symptoms: a prospective blinded cohort study. Pediatrics. 2008;121(6):1188–97.
27. Mell LK, Davis RL, Owens D. Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. Pediatrics. 2005;116(1):56–60.
28. Loiselle CR, Wendlandt JT, Rohde CA, Singer HS. Antistreptococcal, neuronal, and nuclear antibodies in Tourette syndrome. Pediatr Neurol. 2003;28(2):119–25.
29. Snider LA, Swedo SE. Antibiotic prophylaxis against group A beta-hemolytic streptococci with azithromycin or penicillin for childhood-onset neuropsychiatric disorders. Pediatr Res. 2004;55(4):69A.
30. Erenberg G, Rothner AD. Tourette syndrome: a childhood disorder. Cleve Clin Q. 1978;45(1):207–212.
31. Singer HS. Current issues in Tourette syndrome. Mov Disord. 2000;15(6):1051–63.