

Evaluation of a Neuropsychiatric Disorder: From PANDAS to PANS and CANS



Muharrem Burak BAYTUNCA¹, Tuğba DONUK², Serpil ERERMIŞ³

SUMMARY

PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections) syndrome is a disorder that presents itself before adolescence with an abrupt onset of obsessive-compulsive disorder symptoms and/or tics. This disorder is related to Group A streptococcal (GAS) infection with neurological findings, such as motor hyperactivity and choreiform movements. The progress of the disorder may be described as wax-and-waning apart from abrupt onset and this remitting and relapsing course is associated with exacerbating infections, according to the creators of PANDAS syndrome. The ruling out of rheumatoid fever and Sydenham's chorea is necessary for making a proper diagnosis. Since the recognition of this syndrome, clinicians have encountered many children who did not fulfill all 5 criteria for PANDAS classification, which must be met for diagnosis. Since literature findings show a lack or absence of strong evidence for a major role of GAS, the newly-defined categories PANS (Pediatric Acute-onset Neuropsychiatric Syndrome) and CANS (Childhood Acute Neuropsychiatric Syndrome) were created to encompass non-PANDAS patients who "almost meet" the criteria. PANS and CANS include significant psychiatric symptoms that associate with abrupt onset of OCD symptoms and/or tics but do not require identification of any infection agents, immune dysfunctions, or environmental precipitants. In this paper, we aimed to discuss the diagnosis of PANS/CANS on the basis of a case in which the patient developed an abrupt onset of anxiety, obsessions, and vocal tics following an infection. The progress of PANDAS classification criteria and the diagnosis category whereby patients 'almost meet' the criteria for PANDAS diagnosis are discussed.

Keywords: Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections, Obsessive-Compulsive Disorder, streptococcal infections, tic disorders

PANDAS syndrome was first identified by Swedo and colleagues in 1998 after they noted a different group that presented with atypical features (abrupt onset and fluctuating course) and neuropsychiatric symptoms among prospectively followed children suffering from Obsessive Compulsive Disorder (OCD). Cases were required to meet all proposed criteria to elucidate the mechanism of the disorder (which is hypothesized to be an autoimmune disorder) to create an etiologically homogenous group to perform scientific research on these patients (Chang et al. 2014). Hence, patients that have been clinically very similar but do not meet all criteria have been excluded from the classification. The authors

that proposed the criteria for PANDAS noticed caveats to the weaknesses of classification system, which failed for encompassing patients that most of but not all the criteria. Therefore, they suggested the classification of PANS (Pediatric Acute onset Neuropsychiatric Syndrome) and aimed to classify adolescent and vague cases, which did not meet all the PANDAS criteria (Swedo et al. 2012). Later, the classification of CANS (Childhood Acute Neuropsychiatric Syndrome) was introduced into the literature (Singer et al. 2012). Interestingly, both new classification systems show significant differences among the criteria for diagnosis, but classify OCD symptoms and tic disorders with other psychiatric findings such as

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^{1,2}MD, ³Prof., Ege University, School of Medicine, Child and Adolescent Psychiatry, İzmir, Turkey.

e-mail: baytunca@yahoo.com

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anxiety, emotional lability, and irritability. Moreover, PANS and CANS have been used to encompass the childhood age group (under 18 years of age) and a larger patient population by excluding the 'being pre-adolescence' requirement for PANDAS. In addition, PANS and CANS do not require the identification of infection agents, such as GAS or environmental precipitants. The definition of PANS suggests that restricted food intake or dietary behavior change can compensate for the criteria and identification of OCD and/or tics alone (Swedo et al. 2012). Recognition of new classification systems will provide better treatment of these types of cases according to their relevant diagnosis category.

Case

A 6 year 8 month old girl patient presented to our clinic with an urge to swear, wishing harm to her parents, fear of being harmed by others, repeated throat clearing, and restricted food intake. Upon reviewing the history of the patient, we observed that she was born at term with normal weight and no notable disorders or trauma in her medical history. No psychosocial stressors (divorce, domestic violence, etc.) were reported by the mother. No psychiatric disorder was found in the family history including OCD and Tourette syndrome. The patient's pediatric neurological examination at admission was normal. Her psychiatric examination revealed aggressive obsession, anxiety, irritability, vocal tics, sleep disorder, motor hyperactivity, impulsivity, and emotional lability. However, choreiform movements were not reported by the family and were not found during follow-up. The patient was rated as "markedly ill" on the Clinical Global Impression Scale and her score on the Yale Brown Obsessive Compulsive Scale was observed as 14. The scale score indicated mild OCD findings due to the absence of compulsions. After interviewing the mother, it was reported that these symptoms emerged the same day following a cryptic tonsillitis attack, which was one week prior to the psychiatric referral. Although the patient's fever and symptoms of tonsillitis notably regressed after the amoxicillin treatment 40 mg/kg started by pediatrician, her psychiatric symptoms and restricted food intake were

reported to continue at the same level for a period of one week. Following an interview with her teacher, it was documented that there was an increase in her mobility in the classroom. This finding was interpreted as increased motor activity. After these data were collected, we checked her family history for documented autoimmune disorders but we did not confirm any autoimmune disorder. In the light of the decision taken with the pediatric neurology department, Anti-streptolysin O (ASO), Anti-DNase B, Rheumatoid Factor, Complement C3 and C4, C-reactive protein, hemogram, and biochemistry panel tests were ordered for the diagnosis of PANDAS and her throat culture was sent to laboratory. Since the patient had been receiving antibiotic treatment for the last 1 week, throat culture test resulted as negative. The ASO level was found 86.5 IU-ml and other laboratory results were found within the normal range. The patient was diagnosed with PANS according to sudden and severe psychiatric symptoms (anxiety, emotional lability, irritability, obsession, increased motor activity, and restricted food intake) that presented with mild OCD and vocal tics, which started before adolescence. This was diagnosed after ruling out other disorders such as Sydenham's chorea and Rheumatic Fever by the pediatric neurology department. She administered fluoxetine (10 mg/day) and risperidone (0.5 mg/day) for treatment of the OCD symptoms and vocal tics. During the follow-up period (over four years), the vocal tics and motor hyperactivity notably regressed in the first two months; however, alleviation of the OCD symptoms took longer time. Full recovery and complete disappearance of her symptoms were achieved in the 3rd year of the treatment regime. Although the patient developed several an upper respiratory tract infections at different times throughout the follow-up period, no deterioration/exacerbation/relapse signs were observed in her disorder. The patient's final score on the Yale Brown Obsessive Compulsive Scale (Goodman et al. 1989) was 0, and she was considered to be 'much improved' according to the Clinical Global Impression Scale (Guy 1976).

Table 1. Comparison of the features of the neuropsychiatric disorders with abrupt onset

CANS	PANS	PANDAS
*Symptoms of OCD with rapid onset before 18 years of age	* Symptoms of OCD with rapid onset and/or severe restricted food intake	* Presence of tics and/or OCD symptoms
* Accompanying psychiatric symptoms (anxiety, psychosis, regression, sensitivity to sensory stimulus, emotional lability etc.)	* Accompanying psychiatric symptoms (anxiety, emotional lability, irritability, regression, decrease in school performance, sensory-motor anomalies, enuresis, sleep disorders, etc.)	* Onset before adolescence
*Motor symptoms (tics, dysgraphia, clumsiness, hyperactivity)	*Ruling out of neurological and medical disorders (Sydenham's chorea, Tourette etc.)	* Acute symptom onset and episodic course
		* Relation between GAS infection and appearance/ exacerbation of symptoms
		*Neurological abnormalities (motor hyperactivity, choreiform movements, etc.)

PANS (Pediatric Acute-onset Neuropsychiatric Syndrome), CANS (Childhood Acute Neuropsychiatric Syndrome)

DISCUSSION

PANDAS syndrome was first identified by Swedo and colleagues in 1998 when sudden OCD symptoms and/or tics were observed following a GAS infection (Swedo et al. 1998). It was proposed that the disorder may become evident through the production of antibodies, resulting from the similar antigenic structure of Group A streptococcus to neuronal proteins, which mistakenly initiates an auto-immune response. However, researchers over the years found that the level of suspected antibodies (such as Anti-streptolysin O, Anti-DNase B) in the blood did not increase by recurrent exacerbation of the disorder in patients with PANDAS syndrome, which is a shortfall of the theory and has been supported by many studies (Leckman et al. 2011). Obligation of the presence of a waxing and waning course (which is a requirement for making diagnosis of PANDAS) was not observed in many studies like our case. Recent studies suggested that there may not be a relationship between GAS infection and exacerbation of the disorder (Leckman et al. 2011, Gabbay et al. 2008). Although OCD symptoms of our patient followed a chronic course, her disorder did not relapse after attacks of tonsillitis. Exclusion of possible medical conditions is important for all three disorders (PANDAS, PANS, and CANS), and special attention must be paid to Sydenham's chorea and Rheumatic Fever to rule out these disorders. The absence of these findings in the neurological examination of our patient was another supportive factor for PANS. When the three disorders were considered, the lack of symptom exacerbation in our patient (even she had throat infection during follow-up and no fluctuating course) led us to move away from PANDAS. On the other hand, existence of the restricted food intake among the PANS description (which is lacking in CANS and PANDAS criteria) facilitated the diagnosis in favor of PANS. Furthermore, the term of "childhood" in CANS classification does not cover adolescent patients and further prioritized the PANS classification above CANS. Consistent with this, researchers who identified PANDAS syndrome preferred the PANS classification instead of CANS upon updates and consensus made in 2014 (Chang et al. 2014).

In a recently published study, PANS cases frequently showed symptoms of anxiety and emotional lability; and findings such as sleep disorders, decreased school performance, attention problems, irritability, and increased motor activity were observed more frequently than other symptoms (Murphy et al. 2014). Emotional lability, symptom of anxiety of being harmed, decreased school performance, sleep pattern disturbance, and increased irritability were newly developed psychiatric findings of our patient. Other symptoms, which may be observed in PANS patients that were not presented in our case, are generalized anxiety disorder, panic disorder, school phobia, handwriting deterioration, physical complaints, thoughts of suicide, sensory abnormalities, urinary

incontinence, hallucinations, psychotic symptoms, mydriasis, anorexia, and visual-spatial disorders. OCD symptoms and tics are core symptoms described for all three disorders. It was observed that obsessions such as fear of getting dirty/contamination or harming oneself as well as compulsive behaviors (including ordering and/or arranging and symmetry) are frequently seen in PANS patients (Murphy et al. 2014). Aggressive obsessions such as wishing harm to her parents were presented in our patient. However, these obsessions had not reached the compulsive level. In addition, our patient also had new-onset vocal tics that appeared after tonsillitis. Although the average age of onset for OCD in children is 10.3 years (Geller and March 2012), PANS patients have OCD/tic symptoms at earlier ages. A recent study found the average age of onset for OCD in PANS patients as 7.8 year old (Murphy et al. 2014). As in our case, the observed OCD findings and vocal tics for a 6 year old differed from the routine OCS properties and were more compatible with PANS. Interestingly, patients that present with tic disorders and restricted food intake show lower life quality findings and have more school problems than those who do not present with these symptoms; both issues were found in our case report.

In conclusion, PANS and CANS are updated versions of the classification for PANDAS. These two newer classification systems are novel descriptions for encompassing the vague patients that do not meet all criteria for PANDAS in order to create a homogenous group for scientific research. PANS is a more general and practical classification when compared to CANS since it includes eating behavior changes and covers all age groups below 18-year-old that may be observed in clinical practice. PANS patients frequently present psychiatric symptoms such as emotional lability and anxiety in association to symptoms of OCD and/or tics and show OCD symptoms at an earlier age compared to classic forms of childhood OCD. Moreover, symptoms such as psychotic findings, hallucinations, mydriasis, choreiform movements, and anorexia may be observed in patients with PANS syndrome. It is possible to classify vague PANDAS cases under PANS with this updated classification.

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