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CASE REPORT

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Clinical presentation and management of PANDAS Syndrome – Case Report

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Abstract

Autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) are difficult to recognize and diagnose. Symptoms are non-specific, appear suddenly, and may be related to a prior Group A beta-haemolytic streptococcal infection. Limited research complicates treatment. The case is presented of a 10-year-old boy with suspected PANDAS. Symptoms occurred after scarlet fever at the age of 5, which included sudden behavioural changes, decreased attention, and frequent dropping of objects. Over time, there were periods of worsening symptoms, especially during infections and stressful situations. Due to a positive titer of anti-Yo onconeural antibodies, IVIG therapy was initiated. Despite four series of treatment, the neurological symptoms did not significantly decrease. PANDAS remains a diagnostic and therapeutic challenge, requiring further research. It is important to emphasize the need for an interdisciplinary approach and new therapeutic strategies to improve patient outcomes.

Key words

scarlet fever, PANDAS syndrome, Group A Streptococcal Infection, Autoimmune neuropsychiatric disorders, intravenous immunoglobulin (IVIG) therapy

INTRODUCTION

Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) is defined as the acute onset of obsessive-compulsive disorder (OCD) and/or tics in pre-pubertal children, often as a direct consequence of group A streptococcal (GAS) infection. Neuropsychiatric symptoms are usually polymorphic, including emotional lability, severe anxiety, irritability, cognitive regression, motor dysfunction, and micturition disorders [1]. PANDAS negatively affects children's development in many areas, including emotional, social, cognitive, and educational [2]. Although the disease was first described and defined in 1998, there is still a lack of precise epidemiological data on the incidence of PANDAS syndrome in young children [3,4], and making an accurate diagnosis is still controversial. There is also a lack of comprehensive data on the characteristics of the clinical picture. Over the years, disorders associated with PANDAS have been described, including: paediatric acute onset neuropsychiatric syndrome (PANS), acute neuropsychiatric symptoms in children (CANS), and autoimmune neuropsychiatric disorders caused by infections in children (PITAND) [5]. There is also growing evidence for the involvement of neuroinflammatory processes in the pathogenesis of PANDAS. This is supported by imaging studies showing changes in the basal ganglia of the brain [6]. Current main therapeutic strategies, despite the lack of precise recommendations, are based on antibiotic therapy, anti-inflammatory drugs (cyclooxygenase inhibitors, corticosteroids) and immunomodulatory treatment [7].

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CASE REPORT

A 10-year-old boy was born in the 35th week of pregnancy by caesarean section due to bradycardia caused by the umbilical cord wrapping around his hand and head. The post-natal period was uneventful and his further development was normal. The child's vaccinations were carried out according to the vaccination schedule until he was 7 years old, after which they were postponed due to contraindications – autoimmune disorders.

At the age of 5, the boy suddenly developed a fever of 39 °C, and a fine-spotted rash appeared all over his body. The next day his parents took him to the Primary Care Physician, who, due to the lack of enlarged lymph nodes and the presence of typical features accompanying scarlet fever, suggested that the rash could be caused by vascular disease. For the next 3 days, the boy's body temperature remained elevated, which was the reason for another visit to the Primary Care Physician. He recommended that the parents take their son to the Emergency Department. He was diagnosed with dehydration and then discharged home. Nine days after the onset of symptoms, the parents went privately with the boy to the laboratory to perform tests to diagnose scarlet fever, which they themselves suspected. During the visit, it turned out that the child's throat was bright red. On the same day, a visit to the primary care physician took place, where a

diagnosis of scarlet fever was made and antibiotic therapy with penicillin V was initiated. After the symptoms of the disease subsided and a full course of antibiotic therapy was completed, the boy's parents and guardians at school noticed changes in his behaviour – decreased concentration and attention, absent-mindedness, frequent dropping of objects, clearing of the throat, exacerbated stuttering.

Three months later, the boy had type A flu. He reported severe fatigue, lower limb and muscle pain, and a fever. A month later, the patient caught chickenpox from a family member. The infection was mild (single spots on the back and abdomen), thanks to the earlier introduction of acyclovir.

During this time, the obsessions previously noticed by the parents persisted, and the child also began to fear the police and prison. Six months later, he developed abdominal pain, alternating diarrhea and vomiting, severe muscle pain, and irritability. A stool culture revealed pathological bacterial flora and Candida albicans. Penicillin V and nystatin were administered for the infection. After a short break without symptoms, abdominal and muscle pain returned – the boy also began to take a dietary supplement containing a live bacteria strain – Lactobacillus rhamnosus GG. Once the antibiotic therapy had been completed and the reported symptoms had subsided, the child seemed less nervous.

Then, at the age of 6, he began to frequently repeat the words 'I am sorry' and 'Nothing happened'. In ordinary situations, such as leaving something, he asked if he 'wouldn't go to jail' or 'wouldn't die'. His mother had to explain to him that none of these things would happen, otherwise he would start crying. In addition, he constantly picked at his nails, licked a finger and touched various places on his face with it. At a similar time to the beginning of the boy's behavioural changes, the child's father was infected with the SARS-CoV-2 Coronavirus.

Over the course of a year, when the boy was 7 years old, the previously reported symptoms persisted, and even at one point, less than a year after they appeared, they became more troublesome. The boy required constant confirmation that he would not die and would not go to prison. Additionally, he developed separation anxiety towards his mother. The boy became even more irritable – he began to argue with his friends, although he had previously been a non-confrontational person. He began to react to requests and commands by crying and screaming. At the same time as the neurological symptoms intensified, he again began to suffer from abdominal pain. The concerned parents repeated stool tests, which showed the presence of human roundworm in the intestinal flora, for which he received anti-parasitic treatment – mebenzadol, albendazole and pyrantel; there were 2-week breaks between taking each of the drugs. Due to constant gastric problems, the child's mother limited sugar and yeast in his diet. According to her report, he calmed down from then on, and the thoughts that tormented him appeared with less intensity and frequency.

A month later, he had another upper respiratory tract bacterial infection – fever and sore throat, for which he was given penicillin V. Shortly afterwards, he developed a problem with excessive hand washing, which is currently observed to varying degrees of intensity. Another month later, he again began complaining of abdominal pain and additionally constipation, and on an outpatient basis, he visited a paediatric gastroenterologist, where he was tested for: Helicobacter pylori in stool (negative), calprotectin in stool (negative) and antibodies against tissue transglutaminase TGA IgA (negative). The doctor stated that there were no indications for dietary restrictions, due to the negative results of food allergy tests.

When the boy's neurological symptoms intensified, he was referred to a psychologist. The therapy ended after 6 months of meetings which took place weekly at first, then less and less often. According to his parents, it did not produce any immediate results.

The boy then had an outpatient visit to a paediatric neurologist, who ordered an EEG and MRI of the head. The EEG revealed an increased share of theta waves in the parietal-temporal-occipital areas, which may explain the attention and concentration disorders occurring in the child. The MRI revealed a zone of increased signal in the medulla oblongata, which was not confirmed in other sequences of the examination. Additionally, the MRI revealed an enlarged third tonsil.

At a similar time, the patient had an outpatient visit to a child psychiatrist, who, in response to the symptoms presented, diagnosed the occurrence of obsessive-anxiety disorders (F41/F42). Sertraline treatment was started at a dose of up to 50 mg/day, which was discontinued after 4 months due to the lack of noticeable improvement and the occurrence of side-effects in the form of abdominal pain. In the same month, the boy visited the Immunology Clinic, during which diagnostics for paraneoplastic syndromes were performed – a positive titer of onconeural, anticerebellar anti-Yo antibodies was found (+++), which may suggest the occurrence of an inflammatory autoimmune process in the brain. A blood test for the presence of ASO antibodies was also ordered because the immunologist suspected the occurrence of PANDAS syndrome. ASO was detected at a titer of >1,000 and the boy was therefore started on azithromycin, after which the antibody titer dropped to 400 and his obsessions and irritability decreased.

Due to the enlargement of the third tonsil previously detected in the magnetic resonance imaging, an adenoidectomy was performed at the Otolaryngology Department, after which a decrease in the intensity of anxiety symptoms was observed; however, the number of infections in the boy increased – once a month the boy would develop a fever lasting up to 3 days, during which there was a re-exacerbation of behavioural disorders, especially the constant apologizing, licking of fingers. For each such bacterial infection, the boy took azithromycin recommended by the doctor in the event of an acute illness, or in other, milder cases – ibuprofen. After each infection had been cured, the neurological symptoms were weakened. Such situations repeated many times, for another year, on each occasion with a similar course, when the boy was 8-years-old.

At the age of 9, the digestive tract problem reappeared. A stool culture revealed an overgrowth of intestinal bacterial flora – treatment with rifaximin and itraconazole was administered. Less than a month later, due to the deterioration of the neurological condition, another EEG examination of the head was performed and an outpatient visit to a neurologist. The boy began to make sudden, inappropriate movements of the limbs – he had attacks of throwing his arms and legs up. During such episodes, he was tearful and irritable. The EEG recording revealed small changes with a predominance in the frontal-central-temporal areas, spreading to all areas, similar to the previous examination. He was also tested for

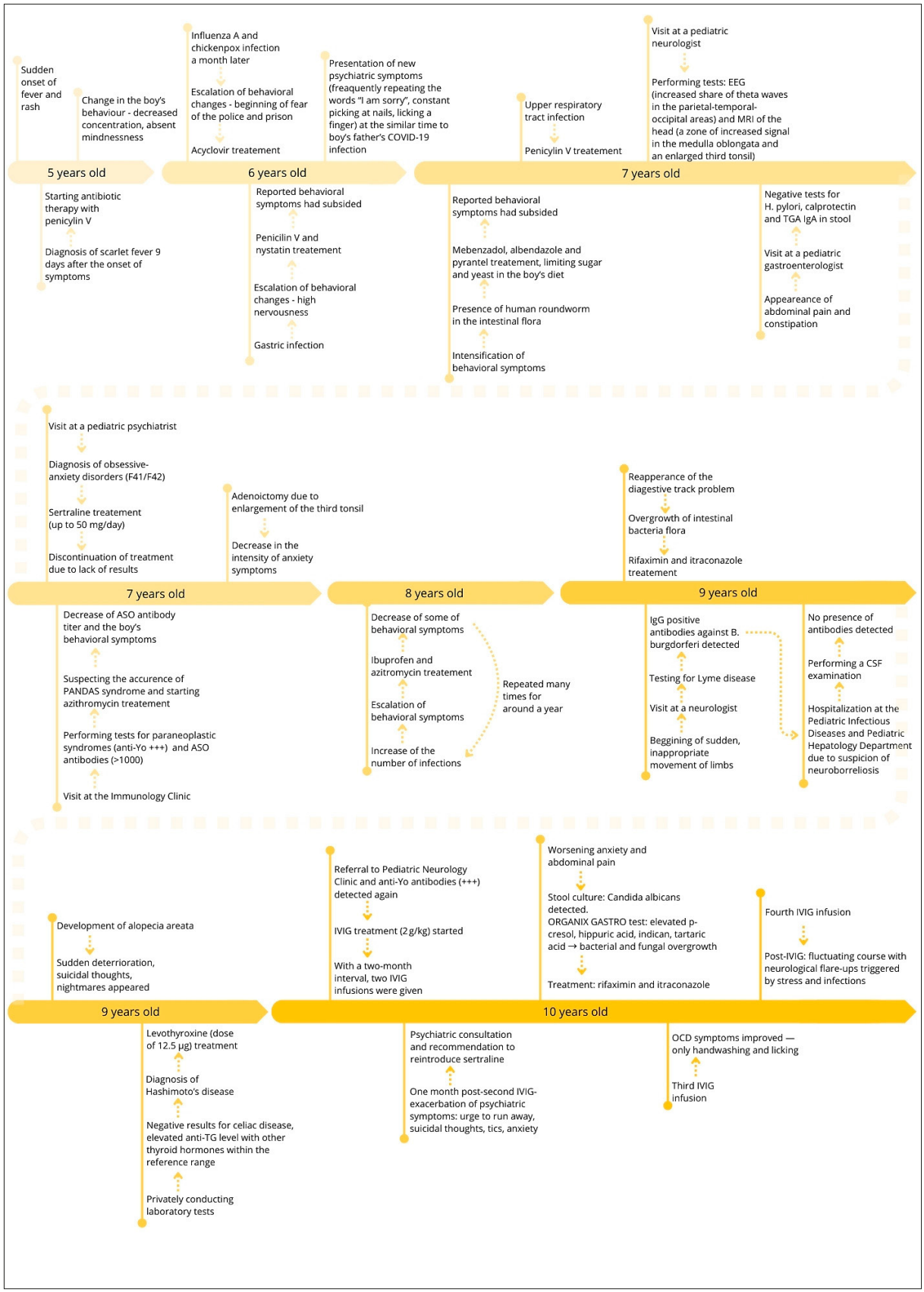

Figure 1. Patient's medical history timeline

Lyme disease: IgM negative and IgG positive antibodies against Borella burgdorferi were detected; Western Blot IgG positive, anti-HSV IgM and IgG negative, toxo IgM and IgG negative.

Positive IgG antibody results against *Borrelia burgdorferi* raised suspicion of neuroborreliosis; therefore, the boy was hospitalized in the Paediatric Infectious Diseases and Paediatric Hepatology Department for further diagnostic evaluation. A cerebrospinal fluid (CSF) culture was performed, which showed no presence of antibodies, ultimately ruling out the initial diagnosis. Additionally, during the hospital stay, an MRI scan of the head was repeated, which showed no abnormalities in the central nervous system. For the next 6 months following the adenotonsillectomy, behavioural disorders were nearly absent. However, a sudden deterioration then occurred – the boy became tearful, developed suicidal thoughts, experienced nightmares, and had frequent urination. Around the same time, he developed alopecia areata, confirmed during an outpatient visit to a dermatologist. Privately conducted laboratory tests ruled out celiac disease and revealed the following results: TSH: 2.47 μIU/ml, FT3: 3.81 pg/ml, FT4: 0.98 ng/dl, Anti-TPO: 4.63 IU/ml – all within the reference range; elevated anti-TG: 69.20 IU/ml. As a result, the parents decided to visit an endocrinologist who diagnosed hypothyroidism due to Hashimoto's disease, and initiated treatment with levothyroxine at a dose of 12.5 μg once daily in the morning.

At the age of 10, the boy was referred to the Paediatric Neurology Clinic, where another panel of onconeural and anti-neuronal antibodies was performed. Once again, an abnormal level of anti-Yo cerebellar antibodies was detected, with a titer of +++. Shortly thereafter, planned treatment with intravenous human immunoglobulin (IVIG) at a dose of 2 g/kg of body weight was initiated in the Paediatric Neurology Department as a therapeutic option. After 2 IVIG infusions, the boy experienced adverse effects, including headaches, elevated body temperature, and weakness. Consequently, the third infusion was withheld. Two months later, the next dose was administered again in the hospital, this time with a slower infusion rate, completing the full 3-dose course, without side-effects.

One month after the second immunoglobulin infusion, during which the anxiety symptoms worsened, the boy had a psychiatric consultation in the Emergency Department of the Children's Hospital At that time, he had thoughts of running away from home, fleeting suicidal thoughts, persistent obsessions and tics, and was highly irritable. He reported that his distressing thoughts intensified when he experienced pain. Ultimately, the physicians determined that there were no absolute indications for hospitalization and recommended scheduling a planned stay in the Child Psychiatry Department for further diagnostic evaluation. Following this episode, the parents took the child for an outpatient visit to a child psychiatrist, who recommended another attempt at treatment with sertraline.

Due to worsening anxiety symptoms and abdominal pain, a stool culture was performed, which revealed *Candida albicans* colonies. The ORGANIX GASTRO test indicated elevated levels of *p*-cresol, hippuric acid, indican, and tartaric acid, suggesting an overgrowth of bacteria and fungi in the intestines. Consequently, the boy was treated again with rifaximin and itraconazole. Additionally, a privately-conducted *Meningitis 9* panel detected the genetic material of *HHV-7*. Following consultation with a physician, observation was recommended.

Two months after the previous IVIG infusion, the boy was re-admitted to the Paediatric Neurology Department for a third IVIG dose. At that time, he was on long-term treatment with levothyroxine, azithromycin (due to an ongoing intestinal infection), and sertraline. His obsessive-compulsive disorder symptoms had improved, manifesting only as frequent hand washing and licking behaviours. The fourth IVIG infusion was administered one month after the third dose. The boy received 3 doses of IVIG, as before. The hospital stay proceeded without complications, and he was subsequently discharged home.

From the time of the fourth IVIG infusion, the course of the disease fluctuated between exacerbations and remissions. Both stress and infections triggered an intensification of neurological symptoms. Throughout this period, the patient remained under psychiatric care. Initially, sertraline caused adverse effects, including abdominal pain. The physician switched the treatment to risperidone, but due to poor tolerance, it was recently replaced with sertraline from a different manufacturer. The effectiveness of this therapy is currently being monitored. The boy continues to be anxious, highly sensitive, and frequently experiences abdominal and headaches. He also remains prone to recurrent upper respiratory tract and gastrointestinal infections, often following exposure to large groups of people, such as at school or in the hospital. He is currently under the ongoing care of a school counsellor, as well as Immunology, Endocrinology, Psychiatry, and Neurology clinics.

DISCUSSION

Effective treatment of any disease relies on thorough diagnostics, accurate pathogen identification, appropriate therapeutic intervention, and careful monitoring of response. In the case of PANDAS syndrome, there is a high risk of diagnostic error at every stage [8].

The literature suggests diagnostic criteria for PANS/PANDAS, which include childhood/adolescent onset of obsessive-compulsive disorder (OCD) or severe restrictive eating behaviours, along with at least 2 of the following symptoms: emotional lability and depression, anxiety disorders, irritability, strongly oppositional behaviour, aggression, developmental and behavioural regression. Other possible symptoms include sensory or motor difficulties, academic decline, sleep disturbances, bed wetting, or increased urinary frequency [7].

There are no clear guidelines for treating this syndrome [7,8]. Case reports suggest significant improvement with intravenous immunoglobulin (IVIG), antibiotics, and therapeutic plasma exchange (TPE). Additionally, NSAIDs and corticosteroids may shorten exacerbations. Tonsillectomy and antibiotic therapy have been shown to prevent recurrent streptococcal infections. IVIG, TPE, NSAIDs, and corticosteroids should be considered in cases with clinical signs of neuro-inflammation [8]. However, steroids, despite alleviating OCD symptoms, may exacerbate tics, leading to their limited use [9].

PANDAS syndrome poses a therapeutic challenge due to its clinical variability. Symptomatic treatment of PANS/PANDAS should include education, behavioural

and supportive therapy, and psychotropic medications. Family and school interventions are also crucial. Therapy should be tailored individually. Mild cases may not require pharmacological treatment, whereas severe cases necessitate it. However, in some patients, immunological treatments and antibiotics may exacerbate symptoms. Additionally, due to potential symptom changes over time (e.g., shifts in emotional state), therapeutic interventions should be adapted accordingly [10].

Given the infectious etiology of PANDAS, antibiotic therapy has been proposed as a treatment approach [7, 9, 11]. Streptococcal infections are treated with amoxicillin, azithromycin, penicillin, and cephalosporins [9]. Murphy et al. demonstrated that antibiotic eradication was effective in resolving OCD symptoms and preventing relapses after acute streptococcal infections [11].

Symptom exacerbation may result from hidden or recurrent streptococcal throat infections. Therefore, in patients with frequent symptom flares, adenoidectomy or tonsillectomy combined with antibiotic therapy is a therapeutic option. Early surgical intervention should also be considered in children for whom medical and behavioural therapies have failed [11, 12].

Studies suggest that immunomodulatory therapies, such as IVIG, may be effective in alleviating symptoms in PANDAS patients [13]. IVIG is particularly beneficial in treatment-resistant neuropsychiatric symptoms caused by PANDAS, with some studies recommending its use from disease onset until remission or significant improvement [14]. However, not all researchers agree on the efficacy of IVIG. Williams et al., in a double-blind study, found that IVIG was no more effective than placebo [13].

Therapeutic plasma exchange (TPE) is recognised as a category II treatment option and can be used as an adjunctive therapy when other methods prove insufficient [15]. This method is reserved for severe cases of PANDAS, showing improvement particularly in OCD, tics, anxiety, and somatic symptoms [16]. However, there are limited clinical studies supporting plasmapheresis, with most showing only short-term symptom relief [7].

Families of children with PANDAS face challenges in obtaining appropriate medical and educational support. Optimal support for children with PANS/PANDAS requires an integrated network of professionals, including teachers, therapists and coaches, who work together to support their development despite the variability of neuropsychiatric symptoms [2].

CONCLUSIONS

PANDAS remains an enigmatic disorder with unclear etiology, posing diagnostic and treatment challenges. Given its strong association with bacterial infections, treatment should be based on antibiotics and immunomodulatory therapy, supplemented with psychotropic drugs for acute psychiatric symptoms. The clinical variability of PANDAS results in the absence of a standardized therapeutic protocol. Further research is needed to better understand the disorder, predict individual differences in disease course and prognosis, and tailor therapeutic options to the specific needs of each child [7,10].

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