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Paediatric autoimmune neuropsychiatric syndrome in recurrent acute bacterial pharyngitis – a case report

Autoimmunologiczny pediatriczny zespół zaburzeń neuropsychiatrycznych w przebiegu nawracających ostrych bakteryjnych zapaleń gardła – opis przypadku

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Abstract

Pharyngitis and tonsillitis, regardless of their aetiology, are one of the most frequent reasons for visiting a family doctor or a paediatrician. Nearly 85% of pharyngitis cases are viral. It is estimated that bacterial throat infection occurs in 15% of school-age children and in 4–10% of adult patients. *Streptococcus pyogenes* is the most common cause of bacterial pharyngitis. PANDAS stands for paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. The term is used to describe a subgroup of children and adolescents who develop acute obsessive-compulsive disorder or tics as a result of group A streptococcal infection, such as tonsillitis. The aim of the paper is to describe a case of a 4-year-old boy who presented to the Laryngology Clinic due to recurrent tonsillitis, time-correlated with obsessive-compulsive disorder.

Keywords: paediatric autoimmune neuropsychiatric syndrome, PANDAS, bacterial pharyngitis, obsessive-compulsive disorder

Streszczenie

Zapalenia gardła i migdałków podniebiennych, niezależnie od etiologii, są jednymi z częstszych przyczyn wizyt u lekarza rodzinnego czy pediatri. Blisko 85% przypadków zapalenia gardła ma podłoże wirusowe. Szacuje się, że bakteryjne zakażenie gardła występuje u 15% dzieci w wieku szkolnym i u 4–10% dorosłych pacjentów. Najczęstszą przyczyną bakteryjnego zapalenia gardła jest paciorkowiec ropotwórczy, czyli *Streptococcus pyogenes*. Pojęcie PANDAS – skrót od *paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections* (autoimmunologiczny pediatriczny zespół zaburzeń neuropsychiatrycznych związanych z infekcją streptokokową) – jest stosowane w odniesieniu do podgrupy dzieci i nastolatków, u których w następstwie infekcji paciorkowcem z grupy A, np. w przebiegu anginy, doszło do nagłego pojawienia się ostrych zaburzeń obsesyjno-kompulsyjnych lub tików. Celem pracy jest opis przypadku 4-letniego chłopca, który został skierowany do Kliniki Otolaryngologii z powodu nawracających angin, skorelowanych czasowo z zaburzeniami zachowania o typie zespołu obsesyjno-kompulsyjnego.

Słowa kluczowe: autoimmunologiczny pediatriczny zespół zaburzeń neuropsychiatrycznych PANDAS, bakteryjne zapalenie gardła, zaburzenia obsesyjno-kompulsyjne

INTRODUCTION

Pharyngitis and tonsillitis, regardless of their aetiology, are one of the most frequent reasons for visiting a family doctor or a paediatrician. It is estimated that they account for 6–8% of medical consultations of children and adults in the United States⁽¹⁾.

Almost 85% of pharyngitis cases are viral. It is estimated that bacterial throat infections occur in 15% of school-age children and in 4–10% of adult patients.

In everyday practice, pharyngitis is diagnosed on the basis of clinical symptoms.

The McIsaac and Centor score (Tab. 1) is commonly used to assess the likelihood of bacterial aetiology of pharyngitis. Pyogenic streptococcus, i.e. *Streptococcus pyogenes*, is the most common cause of bacterial pharyngitis. In less than one percent of patients, other bacteria such as *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Neisseria gonorrhoeae* and anaerobic bacteria are a causative agent^(3,4).

Streptococcus pyogenes infections spread via droplets, and these bacteria can occur epidemically in large numbers of people. The infectious period ends 24 hours after the initiation of effective antibiotic therapy. In most cases, the M protein is responsible for virulence, and anti-M protein antibodies protect against reinfection with the same type of streptococcus. Up to 20% of carriers are young patients aged 5–15 years^(5,6). Chronic adenoid tissue inflammation plays an important role in the pathogenesis of many systemic diseases such as rheumatic disease, glomerulonephritis, endocarditis and other autoimmune diseases. It has been shown that children with chronic tonsillitis have a statistically higher prevalence of circulating immune complexes. This proves the pathogenic role of tonsils as an immunologically active spot of inflammation and indicates the risk of developing autoimmune diseases⁽⁷⁾. Improper treatment of tonsillitis may be one of the reasons for the occurrence of these types of complications. Where indicated, the only appropriate therapeutic option for pathologically changed tonsils is their surgical removal⁽⁸⁾.

Criteria	Points
Fever (>38°C)	1
Absence of cough	1
Swollen, tender anterior cervical nodes	1
Tonsillar swelling or exudate	1
Age 3 to <15 years	1
Age 15 to <45 years	0
Age ≥45 years	–1
Clinical Scoring System and Likelihood of Positive Throat Culture for Group A Streptococcal Pharyngitis	
A score of 0 or a negative score is associated with 2–2.5% risk.	
A score of 1 is associated with a risk of 5–10%.	
A score of 2 is associated with a risk of 11–17%.	
A score of 3 is associated with a risk of 28–35%.	
A score of 4 or more is associated with risk of 51–53%.	

Tab. 1. The McIsaac and Centor score⁽²⁾

When qualifying for tonsillectomy, according to Paradise, the standard should be to determine the frequency of acute bacterial infections of the tonsils. For children, it should be 7 or more episodes in the last year, 5 or more episodes in the last 2 years, or 3 or more episodes in the last 3 years. Other indications for tonsillectomy are of general nature and include rheumatic disease, nephritis (especially chronic glomerulonephritis) and other diseases where there is a causal and temporal relationship with tonsillar disease^(9,10). Disturbances in the child's behaviour may be one of complications of group A streptococcal infection, most likely as a result of the damaging effect of autoantibodies on the basal ganglia.

CASE REPORT

A 4-year-old patient was reported to the Laryngology Outpatient Clinic due to recurrent tonsillitis. After collecting medical history, laryngological examination and analysis of the existing documentation, he was qualified for tonsillectomy in the Laryngology Clinic of the Polish Mother's Memorial Hospital – Research Institute (PMMH RI).

Six months earlier, he was hospitalised in the Department of Neurology of the PMMH RI due to behavioural disturbances in the form of involuntary repetition of vulgarisms, compulsions to lick and bite various objects, and sleep disorders lasting for 2 weeks. In addition, the history included purulent angina experienced about a month earlier, treated on an outpatient basis by a primary care physician. Initially, the patient received clarithromycin at a dose of 15 mg/kg body weight (b.w.)/day, followed by amoxicillin at a dose of 75 mg/kg b.w./day.

The neurological examination revealed that the boy was conscious and in full verbal-logical contact. There were no meningeal symptoms, there was isocoria with an adequate response to light, no oculomotor disorders and no bulbar symptoms. The facial expressions were symmetrical, the remaining cranial nerves were available for examination without any discernible abnormalities, muscle strength full, tone normal, and reflexes symmetrical. The boy had agile gait, including toe, heel and line gait, with no signs of ataxia. There were no root canal symptoms, efficient sphincter function, Romberg's and Unterberger's tests were negative. Contrast-enhanced computed tomography of the head showed no organic changes.

In the lumbar puncture, cerebrospinal fluid was obtained without signs of neuroinfection. Electroencephalography – without focal and paroxysmal activity, and ultrasound of cranial vessels – without rheological disorders.

Laboratory tests showed a slight deficiency of vitamin 25(OH) D (26.5 ng/mL), as well as a positive anti-Borrelia IgM titre in the ELISA test (22 AU/mL), which was not confirmed by the Western Blot test. No antibodies to Epstein-Barr virus or *Mycoplasma* were observed, and the panel of antiphospholipid antibodies, antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) was non-pathogenic.

In view of persistent symptoms of obsessive-compulsive disorder (OCD) related to past tonsillitis, acute neuropsychiatric syndrome PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) was diagnosed. The treatment included 5 pulses from human normal immunoglobulin (IVIG) at a dose of 2 g/kg b.w. with a good therapeutic effect. The patient, in a stable general and neurological condition, was discharged home. Four months later, the same boy returned to the Department of Neurology due to recurrence of OCD-like symptoms after another instance of tonsillitis. The patient received 3 infusions of human normal immunoglobulin (IVIG) at a dose of 2 g/kg b.w., again achieving good therapeutic outcomes.

Then the boy was referred for an urgent ENT (ear, nose, and throat) consultation. About a month later he was admitted to the Laryngology Clinic of the PMMH RI for surgery. Under general anaesthesia, the adenoid and tonsils were removed. Surgery and postoperative period were uneventful. The child was discharged home in good general and local condition. After the surgery, the symptoms of the obsessive-compulsive syndrome resolved, however the boy remains under constant psychiatric care due to the persistent sleep disturbances.

DISCUSSION

PANDAS stands for paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections. This term is used to describe a subgroup of children and adolescents who develop acute OCD and/or tics as a result of group A streptococcal infection, such as tonsillitis. Typically, the disease is accompanied by additional symptoms such as increased levels of anxiety and/or separation anxiety, increased motor disturbances (including tics and dysgraphia), behavioural regression, sudden decline in school performance, and mood disturbances (irritation, aggression and/or acute defiant behaviour), urination disorders, including bedwetting, and sleep disturbance⁽¹¹⁾.

In 1894, Sir William Osler was the first to mention bizarre and peculiar behaviour in children with chorea minor (Sydenham's chorea). This was probably the first description of a relationship between OCD and Sydenham's chorea, a complication of streptococcal infection⁽¹²⁾. In 1965, Langlois and Force reported a coexistence of tics and Sydenham's chorea due to infections, which were then successfully treated with antibiotics and neuroleptics, in a six-year-old boy⁽¹³⁾. In 1978, Kondo and Kabasawa described a case of an 11-year-old boy in whom tic disease began suddenly about 10 days after febrile illness associated with elevated levels of anti-streptolysin O antibodies (ASO) and a good response to corticosteroid treatment⁽¹⁴⁾. Allen et al. described a subgroup of children who developed OCD after an infectious disease without meeting the criteria for Sydenham's chorea. They summarised the most important features of the described cases in the acronym

PITAND (paediatric, infection-triggered autoimmune neuropsychiatric disorders)⁽¹⁵⁾. In 1998, Swedo et al. renamed the PITAND subgroup to PANDAS, and for the first time proposed a set of diagnostic criteria⁽¹⁶⁾.

In 2015, in the "Journal of Child and Adolescent Psychopharmacology," the PANDAS research consortium in consultation with the National Institute of Mental Health (NIMH) issued a statement on reaching a consensus on the diagnosis of PANDAS.

The currently accepted PANDAS criteria include:

1. the presence of OCD and/or tics, especially numerous, complex or atypical;
2. age criterion (symptoms of disorders occur for the first time between the age of 3 years and adolescence);
3. acute onset and episodic course (periods of intensification of symptoms–remission);
4. relationship with group A streptococcal infection;
5. relationship with neurological abnormalities, including unexpected movements^(17,18).

Several studies have assessed the relationship between infection and sudden onset of neuropsychiatric symptoms. Two large cohort studies conducted in Taiwan⁽¹⁹⁾ and Denmark⁽²⁰⁾ showed an increased odds ratio of OCD, tics and psychiatric disorders following streptococcal angina or other respiratory infections. In a cohort study of 1,067,743 Danish children up to the age of 18 years, the incidence rate for any of these disorders was higher in those with positive rapid streptococcal test than in those who had never had it. The mechanism underlying PANDAS development, like rheumatic fever, is that antibodies against bacteria are directed against the host's tissues. In the case of PANDAS, these are the tissues of the brain. Streptococci contain amino sugar, N-acetyl-beta-D-glucosamine (NABG), against which the body produces antibodies. These antibodies also bind to similar sugar groups on the surface of neurons, altering the function of dopamine receptors and intracellular CaMK II (calcium/calmodulin-dependent protein kinase type II). This leads to changes in neurotransmission and intracellular signal transmission, which disrupts the work of nerve cells. Therefore, it is rather a change of cell function rather than destruction. In PANDAS, the proper functioning of the caudate nucleus is disrupted. Excessive activity of neurons in this area is associated with the symptoms of OCD^(21,22). Neuroimaging MRI (magnetic resonance imaging) studies show an association between post-streptococcal neuropsychiatric disorders and pathology in the basal ganglia. Volumetric measurements conducted by Giedd et al. in 2000 showed that the mean sizes of the caudate nucleus, putamen and globus pallidus were significantly greater in people with streptococcal infection as compared with healthy individuals⁽²³⁾.

The treatment of PANDAS includes antibiotic therapy if a streptococcal infection is confirmed, as well as symptomatic treatment (selective serotonin reuptake inhibitors, SSRIs). In OCD, clonidine or neuroleptics are administered to control tics, and in severe cases, plasmapheresis

and IVIG are required. Human immunoglobulin is administered at a dose of 1 g/kg b.w. for 2 consecutive days, in turn, plasmapheresis is performed serially at intervals of 1 day or more. Human immunoglobulin contains IgG of all subclasses, owing to the presence of the so-called free Fc regions which can bind to cells possessing the appropriate receptors. The effectiveness of the above methods is associated with the immunomodulatory effect. The severity of OCD symptoms decreases by 45–58% one month after treatment with immunoglobulins and plasma exchange, respectively. Additionally, the role of non-steroidal anti-inflammatory drugs and systemic steroids is emphasised. Behavioural therapy is used as supportive therapy^(16,24,25).

The role of surgical intervention in the treatment of PANDAS is widely discussed in the literature. Tonsillectomy or adenoidectomy has long been considered an alternative to pharmacotherapy. Despite the fact that many patients with PANDAS meet the generally recognised criteria for surgery, there is still considerable disagreement about the effectiveness of this treatment in providing remission or improving symptoms due to insufficient scientific evidence. The role of tonsillectomy in PANDAS was mainly demonstrated in case reports showing a reduction in the incidence of tics and OCD after surgery^(2,26,27).

CONCLUSION

Rapid and correct diagnosis, effective antibiotic therapy in accordance with the standards of care (remember that in the treatment of streptococcal infections, penicillin remains the treatment of choice), and in the case of carriership and recurrent episodes, appropriate diagnosis and treatment are essential in streptococcal infection of the upper respiratory tract. Currently, the widespread use of antibiotic therapy has significantly reduced the risk of both local and systemic post-tonsillitis complications, however, special attention should be paid to the fact that in predisposed persons, past and recurrent streptococcal infections may cause autoimmune diseases such as rheumatic fever, Sydenham's chorea or PANDAS. Case reports and case series reported significant improvement or resolution of PANDAS neuropsychic symptoms after removal of the palatine tonsils^(2,28). Similarly, in the case of the described patient, the symptoms of obsessive compulsive syndrome resolved after adenotonsillectomy, but he remains under psychiatric care due to sleep disorders. This is evidence of improvement in PANDAS symptoms, but not complete recovery.

In our opinion, in the case of neurological disorders where there is a suspicion that the cause is autoimmune central nervous system reactions in the course of group A streptococcal infection, treatment should include surgical removal of the infection focus as an adjunct to immune and psychiatric therapy. Based on our experience of surgical treatment with tonsillectomy in this group of patients, a significant reduction in symptoms and an improvement in the quality of life was achieved.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

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