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Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections in an 8-Year-Old Boy

Heriyanto[1], Dewi Sutriani Mahalini[2], IGN Made Suwarba[3]

[1-3] Child Health Department, Medical School Udayana University/Sanglah Hospital Denpasar

Abstract: ***Background: Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a rare neuropsychiatric disorder in children. Obsessive-compulsive symptoms, tics and other neuropsychiatric disorders may occur after a group A beta-hemolytic streptococcal infection. Treatment is still unclear and debate still continues. The objective of this case report is to describe the clinical presentation and the management of PANDAS at Sanglah General Hospital. Case Presentation Summary: An 8-year-old boy complained of involuntary movement of his head and eyes since 5 days before admission. There was history of sore throat and fever for 3-4 days one month before admission. Physical examination showed symptom of nystagmus with tic on the face. Laboratory test revealed ASO 400 IU/ml, ECG and MRI were normal. Blood culture and throat swab were performed and showed no bacterial growth. We treated with ampicillin 100 mg/kg/day orally, haloperidol 0.5 mg BID orally, and intravenous methylprednisolone 2 mg/kg/day divided every eight hours. The involuntary movement decreased after treated for 7 days and has achieved full recovery after 1 month. Learning Point/Discussion: PANDAS is a combination of acute symptoms of tic or obsessive-compulsive disorder (OCD) which follows group A beta-hemolytic streptococcal infection, mostly affects male children at the onset of 4-9 years old. We report an 8-year-old male with involuntary movement and history of throat infection 1 month prior. ASO 400 IU/ml was confirmed as a diagnostic marker of the streptococcal infection. Pharmacological therapy for PANDAS involve eradication of streptococcal infection by using antibiotic (i.e penicillin) up to 5 years duration. Our case achieved full recovery after 1 month of therapy. Multidiscipline investigation including pediatric neurology, radiology, microbiology, and antibiotic therapy will support a more better outcome without any disabilities.***

Keywords: ASO, PANDAS, streptococcal infection.

1. Introduction

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) was initially published on 1998. This disease occurs in children with obsessive-compulsive symptoms and/or tic that appears abruptly and is associated with a new infection by streptococcus. Determining the diagnosis of PANDAS is still controversial, due to the lack of direct evidence of its pathogenesis. It is believed that autoimmune process is the underlying cause of PANDAS.[1],[2]

Epidemiologically, PANDAS affects younger-aged children with a peak onset of 4-9 years old, mostly in male. Approximately 48% of patients show obsessive-compulsive disorders (OCD). As many as 52% show tic and 80% show a combination of OCD and tic.[1] From the first 50 reported cases of PANDAS, all showed an episode of OCD and/or tic with an abrupt onset, following a streptococcal infection which appeared a remission-relapse onset associated with an infection (being not exclusive to streptococcal infections). The principal of this disease is similar to sydenham chorea, which can also become relaps, and triggered by infection of hormonal. Children with PANDAS may also show unstable emotions (66%), deteriorated school performances (60%), changes in personality (54%), anxiety (46%), nightmares (18%), bedtime rituals (50%), disturbed handwriting (46%), opposing behaviour (32%), and motoric hyperactivitiy (50%).[1],[2] The neurological symptoms due to PANDAS may eventually disappear, but may remain as OCD for its patients.[3],[4]

2. Case

An 8-year-old patient complained his head and eyes are moving on their own unnoticeable since 5 days before admission to the hospital. The movements appeared more frequently, but he was still conscious. The movements in his head and eyes become uncontrollable so that he was taken to Mataram Hospital and was treated there for 4 days (cefotaxim, dexamethasone and mannitol were given at that time). The symptoms worsen, so he was referred to Sanglah Hospital for further treatment. One month before, he had a history of sore throat and fever for 3-4 days, but it resolved without treatment. Both his parents and his older sibling did not experience similar symptoms.

He was born spontaneously at Mataram Hospital, with a gestational age of 38 weeks, and birth weight 3300 grams. His mother was 35 years old and this was her second pregnancy. History of infection, seizure, and shortness of breath during pregnancy were denied. She visited an obstetrician regularly and ultrasound showed normal result. There was no illness during pregnancy and infections during pregnancy were denied.

On physical examination, he appeared alert. Blood pressure was 110/60 mmHg, respiratory rate was 22 per minute, pulse rate was 86 beats per minute, and axillary temperature was 36.5 C. Head size was within normal limit, there was tic on his face, nystagmus appeared on both eyes, conjunctiva palpebra weren't anemic, and both sclera weren't icteric.

Ear, nose, throat examinations were normal, no bluish lips. Involuntary movements of the neck were noticed, symmetrical chest and no retractions. Breathing sounds were vesicular, no rales and wheezing. Heart sounds were normal. Abdomen was not distended, liver and spleen were both unpalpable, extremities were warm, capillary refill time <2 seconds. Clinical findings led to a working diagnosis of observation involuntary movements due to PANDAS.

Laboratory tests showed hemoglobin (Hb) 13.64 g/dL, hematocrit 43.70%, leukocyte 9.36 l/mm3, neutrophil 43.6%, lymphocyte 45.80%, platelet 410.2 x 103/µL, C-reactive protein (CRP) 0.01 mg/dL, normal serum electrolyte and blood sugar, ASO 400 IU/mL and normal renal function. Magnetic resonance imaging (MRI) and electrocardiography (ECG) were normal, so he was diagnosed as PANDAS. Blood culture and throat swab was performed, and he received intravenous ampicillin 100 mg/kg/day orally, haloperidol 0.4 mg OD orally, and intravenous methylprednisolone 2 mg/kg/day every eight hours. On the sixth day of treatment he still showed involuntary movement so the haloperidol dosage was increased to 0.5 mg every 12 hours. The movements decline the next day. Blood culture and throat swab showed no bacterial growth. On the eighth day, methylprednisolone was switched to oral prednisone 2 mg/kg/day. On the fourteenth day, involuntary movements reduced significantly. Anti-streptolysin O (ASO) test was decreased to 200 IU/ml. He was discharged from hospital with oral ampicillin and haloperidol. On April 21st, 2017, ASO test was negative and his movement was normal.

3. Discussion

Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is an autoimmune disease in which the antibody that is supposed to fight streptococcal infection also invades a part of the brain called the basal ganglia. An abnormal immune response is followed by formation of antibodies that interfere with normal neuronal activity, eventually causing disruption of the blood-brain barrier due to the inflammation process and enters the central nervous system, affecting its normal function. Naturally, the basal ganglia cell surface is similar to the surface of streptococcal antigen. When the antibody of a child that is infected by streptococcal bacteria enters the blood-brain barrier, it can mistakenly recognize a basal ganglia cell as a streptococcal antigen, thus inactivates and then destroys the cell. This causes uncontrolled movements of the extremities, body and facial muscles, unstable emotion, attention disorders, and the patient tends to be impulsive. Clinical symptoms of PANDAS are a combination of acute symptoms of tic or obsessive-compulsive disorder (OCD) following group A beta-hemolytic streptococcal infection.[1]

Clinical diagnosis of PANDAS relies highly on one's ability in gathering proper history taking and physical examination. Using the clinical descriptions of 50 cases, a research program from the National Institute of Mental Health (NIMH) developed a diagnostic model for PANDAS. Based on Diagnostic and Statistical Manual of Mental Disorders (DSM-V), diagnosis of PANDAS involves 5 criteria: 1. OCD or tic disorders, 2. onset involves children aged 3 years until puberty, 3. abrupt onset and relatively severe, within days to weeks, 4. related with streptococcal infections (confirmed by antibody titer and throat swab), 5. physical examinations show neurological abnormality, usually motoric hyperactivities (choreiform movements, tic). The criteria reflects an underlying hypothesis that autoimmunity mediates the neuropsychiatric symptoms, and so the group was designated by the acronym PANDAS, which stands for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.[1],[4] In this case, the patient is 8 years old with symptoms of tic, which occurred soon after beta-hemolytic streptococcal infection was confirmed.

Tonsillopharyngitis caused by group A streptococcus (GAS) leads to the production of serum antibodies, such as anti-streptolysin O (ASO) and antideoxyribonyclease B (anti-DNase). Anti-streptolysin O is the antibody produced against streptolysin O; an immunogenic, oxygen-labile hemolytic toxin produced by most strains of group A and many other strains of group C and G streptococci. The appearance of ASO in a patient's serum or an increase in the ASO titer is usually indicative for a recent streptococcal infection. The absolute value of ASO is of diagnostic importance. Serologic diagnosis of GAS show 58% from normal ASO titer in 4-8 weeks after infection. Although ASO titer has provided a useful guideline to physicians, it has been shown to vary with age. The normal ASO level in healthy children based on age is 170 IU/ml on 5-6 years old, 160 IU/ml on 7-8 years old, 190 IU/ml on 9-10 years old, 200 IU/ml on 11-14 years old, and 210 IU/ml on 15 years old, higher levels are uncommon in children without recent streptococcal infection.[5],[6] In certain individuals, infection and antibody production lead to end organ damage, as antibodies cross-react with renal tissue (acute post streptococcal glomerulonephritis infection), heart tissue (rheumatic fever), and the brain (Sydenham chorea).[3] In this case, patient was found with ASO titer of 400 IU/ml, and the symptoms decreased in accordance to the decrease of ASO titer.

Therapy for PANDAS includes pharmacological and non-pharmacological (cognitive-behavioral therapy). Pharmacological therapy for PANDAS based on systematic reviews involve eradication of streptococcal infection by using antibiotics (penicillin, aminoglycosides) to tonsillectomy.[7] The duration for prophylactic antibiotics was reviewed and recommended by the American Academy of Pediatrics (AAP) and World Health Organization (WHO). American Academy of Pediatrics reported a prophylactic antibiotic use for up to 5 years after the last episode of disease until the age of 21 years old, depending on which takes the longer time. The downside of long-term prophylactic antibiotics include the potential of an evolving resistant strain to antibiotics, increased risk for allergy, shift of normal flora that may cause the patient to become more prone to infections such as Clostridium difficile. Clinicians must consider the risk and benefit to determine the most appropriate treatment for the patient.[4] In this case, at the time of diagnosis, patient was treated with intravenous ampicillin for 14 days and continued with oral ampicillin.

Tics are proposed to be the result of dysfunctional cortico-striatalthalamo-cortical circuits, prominently those subserving motor function. Tics appear to be sensitive to environmental stimuli such as temperature changes, stress, illness, and fatigue that can exacerbate tics. Some cases of tic disorders have been proposed to result from an infection-triggered autoimmune process similar to that of Sydenham chorea. Pediatric autoimmune neuropsychiatric disorders associated with streptococcus describe cases of childhood-onset OCD and/or tics that resemble Syndenham chorea characterized by acute onset following a streptococcal infection, accompanying neurological signs, and an episodic course.[9] Children with tic or OCD must receive the appropriate therapy according to the symptoms (alpha-agonist tic suppresants, classic or atypical antipsychosis, or anti-obsessive therapy such as serotonin-reuptake inhibitor). There is a number of conventional antipsychosis that effectively reduces tic in researches conducted on adults.[8],[9] In this case, patient was given haloperidol to reduce the tic. In order to understand the effectiveness of haloperidol in reducing tic symptoms in PANDAS, a journal review was conducted entitled "Systematic Review: Pharmacological Treatment of TIC Disorders-Efficacy of Antipsycotic and Alpha-2 Adrenergic Agonist Agent" by Weisman et al in 2014. This journal concluded that antipsychotic drugs and alpha-2 agonists can improve the symptoms of tic significantly. Alpha-2 agonists are better at improving tic in children with ADHD compared to children without ADHD.[10]

Symptoms of PANDAS are hypothesized to result from immune dysfunction at multiple levels: local (targeted) dysfunction related to cross-reactive antibodies that recognize specific central nervous system (CNS) antigens; regional dysfunction related to inflammation within neuronal tissues in the basal ganglia and possibly vasculature of the basal ganglia; and systemic abnormalities of cytokines or chemokines, with resultant disruption of the blood–brain barrier (BBB) and CNS functions. Corticosteroid use in this condition is still controversial. Some studies report significant improvement in patients receiving steroid, other show deteriorations. Steroid can no longer be used long term due to its side effects. If clinical improvement after steroid administration occurs, then the diagnosis of immune system-based disease can be confirmed, which in this case immune-based therapy can be very beneficial.[11] In this case, patient received corticosteroid therapy for 14 days and did show improvements. To understand the effectiveness of corticosteroid in the treatment of PANDAS, a journal search was conducted and showed: "Pediatric Acute-Onset Neuropsychiatric Syndrome Response to Oral Corticosteroid Bursts: An Observational study of Patients in an Academic Community-Based PANS Clinic" by Brown et al in 2017. This journal concluded that corticosteroid can shorten the duration of PANDAS symptoms. Early corticosteroid administration results in better therapy response, similar to corticosteroid use in most inflammation-based diseases (asthma, jouvenile arthritis, etc). Researchers found that a longer duration of corticosteroid therapy results in stronger response. This result is consistent with the research conducted in chorea sydenham, which stated that administrating a higher dose of corticosteroid for a longer period of time may cause a better improvement in symptoms and shorter duration of disease.[11]

In this case, it cannot be confirmed if the neuropsychiatric symptoms end in a complete remission or not. Latest studies that follow patients with OCD during childhood reveals that 41-56% of OCD symptoms remain until young adulthood.[12] This research does not differentiate OCD due to PANDAS with OCD due to other causes. To understand the long-term outcome of patients with PANDAS, a journal search was conducted and showed "Longitudinal outcomes of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS)" by Jill Leon in the European Child and Adolescent Psychiatry on 2017. This journal concluded that in a period of 4.8 years after the initial of diagnosis of PANDAS, as many as 88% subjects no longer experience significant OCD symptoms. This cohort study shows that PANDAS has a better prognosis than previous reported studies in children with OCD.[13]

4. Summary

An 8-year-old boy was hospitalized with history of his head and eyes are moving on their own unnoticeable since 5 days before admission. Physical examination revealed nystagmus with tic on face. Laboratory investigation showed increase in ASO titer, but normal complete blood count, MRI and ECG a normal limit. We diagnosed the patient as PANDAS. After diagnosed, the patient was given antibiotic (ampicillin), methylprednisolone and haloperidol. The patient was discharge after 14 days of treatment with a better condition and continue antibiotic in out-patient clinic. PANDAS occurs after infection by group A beta-hemolytic streptococcus. With multidiscipline investigation, including pediatric neurology, radiology, microbiology and prompt treatment with antibiotic and anti-inflammatory drugs, the outcome will be better without any disabilities.

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