CASE REPORT

Neuropsychiatric symptoms following sore throat in a young boy

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SUMMARY

A previously healthy 6-year-old boy was referred to us by his primary provider, with a history of sudden onset behavioural abnormalities including irritability, sleep disturbance and anxiety. Physical examination revealed no significant findings; further analyses were not suggestive of meningitis, encephalitis, metabolic abnormalities, toxicity or any other obvious cause. On rechecking the patient's history, an episode of throat pain 1 week prior to the symptom onset was noted. Therefore, the possibility of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) was considered. The antistreptolysin O titre was high (1078 IU/mL), and it increased to 1194 IU/mL 4 weeks later, leading to a diagnosis of PANDAS. He was started on ampicillin and administered one dose of intravenous immunoglobulin. His abnormal behaviours subsided and he returned to a normal state within 48 hours of treatment. This report aims to provide insights into the symptomology and diagnosis of PANDAS in children.

may be due to challenges faced by clinicians in the identification and diagnosis of PANDAS. Mabrouk and Eapen reported five cases of neuropsychiatric symptoms that had been triggered by streptococcal infections in an Arab population.⁵ Out of these five, only one fulfilled all of the criteria for a diagnosis of PANDAS and was consequently diagnosed as such. The rest were determined to be either probable or possible PANDAS cases. Another case, this time in India, was reported by Srivastava *et al.*⁶ This case featured prominent tics in an individual who presented to a psychiatric clinic after experiencing symptoms for 4 years, during which time the patient experienced multiple remissions and symptomatic exacerbations. He was seen by multiple physicians but none diagnosed his condition correctly. This is a clear example of delayed diagnosis and treatment of PANDAS due to a lack of awareness. Here, we describe a case of PANDAS in a 6-year-old boy, cured with one dose of intravenous immunoglobulin treatment.

CASE PRESENTATION

A 6-year-old Indian boy residing in Bahrain was referred to us by his general practitioner (GP) after experiencing 4 days of irritability in the form of increased proneness to anger, which got worse with time, sleep disturbances, severe eating restrictions, parental separation anxiety, emotional lability, personality changes, loss of speech and intermittent eye blinking. The onset of these symptoms was abrupt. Over the following 2 days, he began to cry excessively and shout without an obvious cause, developed anxiety about separation from his parents and reported irrational fears of darkness and strangers who might harm him. His mother further reported that he refused to eat on the day prior to his admission and was force fed. His sleep was also disturbed, with one episode of night time bed wetting. Additionally, he injured two of his teeth as a result of his agitated behaviour. The patient was seen by his GP, who referred him to our paediatric clinic with suspected encephalitis. His past medical and family history were unremarkable. No history suggestive of any kind of child abuse or trauma was noted. He had a history of good performance at school and his social history revealed a happy family with good income, with his mother working as a neonatal intensive care unit nurse and his father working as a clerk. The child has one sister who is in good health.

Roughly 1 week prior to the onset of his symptoms, the patient's mother recalled that the child

BACKGROUND

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, or PANDAS as it is commonly referred to, is a diagnosis used for a subset of children and adolescents who have obsessive-compulsive disorder (OCD) and/or a tic disorder, and in whom symptoms worsen following streptococcal infections such as strep throat or Scarlet fever. The exact prevalence of PANDAS is not known, as most studies of PANDAS include targeted populations.¹ However, it has been shown that the prevalence of PANDAS is higher in males than in females.² A child with a diagnosed tic disorder or OCD or both, who is of prepubertal age, and who presents with the abrupt onset of neuropsychiatric symptoms that are precipitated or exacerbated by a streptococcal infection, is typically diagnosed with PANDAS.³ Treatment of PANDAS is based on disease severity and trajectory and includes psychoactive drugs, antibiotics and immunotherapeutics including steroids, intravenous immunoglobulins and/or therapeutic plasmapheresis. Furthermore, new-onset, acute flare, relapsing-remitting, chronic-static and chronic progressive forms of PANDAS are all often treated with intravenous immunoglobulin therapies.⁴

To the best of our knowledge, only one PANDAS case series has been reported in the Middle East. The lack of data regarding PANDAS in this region

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was suffering from a sore throat and had a mild fever. A physical examination revealed normal neurological function apart from tics in the form of intermittent eye blinking. His cranial nerve examination was normal, and there were no signs suggestive of cerebellar involvement. With the help of his mother, he was able to walk with a normal gait. A skin examination revealed no neurocutaneous markers. His throat examination was normal, as was the rest of his systemic examination.

INVESTIGATIONS

The initial investigations revealed white cell counts $10.04 \times 10^9/L$, neutrophils $6.59 \times 10^9/L$ and lymphocytes $2.56 \times 10^9/L$. His renal and liver function tests showed urea 2.7 mmol/L , creatinine $28 \text{ } \mu\text{mol/L}$, alkaline phosphatase 242 IU/L , gamma glutamyl transferase 10 IU/L , alanine transferase 11.7 IU/L , aspartate transferase 21.7 IU/L and bilirubin $5.7 \text{ } \mu\text{mol/L}$. Erythrocyte sedimentation rate was 46 mm/hour , and his C reactive protein level was 0.21 mg/L . His thyroid profile was normal, with a thyroid stimulating hormone level of $0.694 \text{ } \mu\text{IU/mL}$, free triiodothyronine 3 level of 3.8 pmol/L and free thyroxine 4 level of 19.01 pmol/L . His vitamin B_{12} level was also within normal limits (618.9 pg/mL).

A lumbar puncture was performed to rule out meningoen- cephalitis. His cerebrospinal fluid examination showed nil white blood cells, nil red blood cells, protein 19.2 mg/dL , glucose 3.63 mmol/L and chloride 123.2 mmol/L with negative cultures, and a negative PCR assay for herpes simplex virus. A metabolic screen with tandem mass spectrometry was also normal. Serum ammonia and lactate levels were $16.6 \text{ } \mu\text{mol/L}$ and 0.95 mmol/L , respectively. An organic urine screen and urine toxicology were also negative. MRI brain revealed normal neuroanatomy. Finally, an antistreptolysin O titre test revealed levels elevated to roughly five times above the normal upper limit (1078 IU/L). While anti-DNAse antibody testing, which is commonly used for the detection of streptococcal (strep), was not available, a rapid strep PCR was performed, which came out negative. Throat cultures did not reveal any growth of the group A streptococcal organism. However, a repeat antistreptolysin O titre test 4 weeks later revealed further increases to 1194 IU/mL .

DIFFERENTIAL DIAGNOSIS

Approaching a case like the one described here, where a child experiences the sudden onset of abnormal behaviours, can be quite challenging as there are multiple possible aetiologies that might underlie these symptoms. Common causes include infections, metabolic disorders, toxin ingestion, endocrine abnormalities, child abuse and primary psychiatric disorders. The case investigated here was evaluated for all of these possibilities, each of which was ruled out with the exception of recent streptococcal infection. Our patient was also seen by the psychiatric team in the hospital, and they were not able to attribute these sudden onset of symptoms to any specific psychiatric disorder. A diagnosis of PANDAS is based on the presence of all five of the following diagnostic criteria, first proposed by Swedo *et al* in 1998³:

1. The presence of OCD and/or a tic disorder.
2. Paediatric onset, between 3 years of age and the beginning of puberty.
3. An abrupt onset of symptoms with an episodic course of severity.
4. An association with a recent streptococcal infection (ie, a positive throat culture and/or rising antistreptococcal antibody titres).

5. An association with neurological abnormalities; motor hyperactivity and/or adventitious movements, including choreiform movements, are particularly common.

In the case presented here, a young boy presented with an irrational fear of being harmed by strangers and intermittent eye blink tics, but no history suggestive of compulsive behaviours such as word repetition or ordering of objects. The age of the patient described here aligns perfectly with that described in the criteria above, as does the abrupt onset of his symptoms. His symptoms were also strongly associated with the timing of a streptococcal infection, indicated by rising antistreptococcal antibody titres ($1084\text{--}1194 \text{ IU/mL}$). These symptoms are strongly suggestive of the neuropsychiatric disorders associated with PANDAS. As this was the patient's first episode; however, we cannot comment on any exacerbation of his symptoms.

TREATMENT

In view of the severity of the patient's restlessness and hyperactivity symptoms, he was started on 0.25 mg of risperidone a day (orally), which was later increased to 0.5 mg a day; this treatment resulted in a very mild improvement in his symptoms. Later, when the patient was diagnosed with PANDAS, he was given a dose of immunoglobulin (1 gm/kg intravenously, 12 hours infusion). He was then also started on ampicillin (550 mg intravenously, 8 hours daily for 7 days).

OUTCOME AND FOLLOW-UP

The patient described here responded dramatically and positively after immunoglobulin infusion. Within 48 h of therapy, his behaviour and activity levels became normal. His appetite and speech and all other symptoms resolved. He was discharged after a 9-day-long admission and was prescribed prophylactic penicillin V (250 mg orally, twice daily) for at-home administration. An antistreptolysin O titre test was repeated on follow-up 4 weeks after his treatment, which showed an increase in titre to 1194 IU/mL .

DISCUSSION

An association between paediatric autoimmune neuropsychiatric disorders and streptococcal infection, resulting in PANDAS, has been suspected since the 1980s, though first clinically described in 1998 by Swedo *et al*.³ These authors were the first to publish diagnostic criteria for PANDAS. A PANDAS workshop conducted in 2010 concluded that PANDAS is more common in boys than in girls (2:1), with an onset of symptoms usually occurring before 8 years of age. The workshop further determined that all cases of PANDAS also featured obsessive-compulsive symptoms and that 90% of patients with PANDAS also had comorbid neuropsychiatric symptoms.⁷ In agreement with these findings, the case described here features a 6-year-old boy with neuropsychiatric symptoms and who was diagnosed with PANDAS. This PANDAS workshop also reported that all cases featured a sudden and dramatic onset of symptoms, and caregivers could determine the precise onset time of the cases. The abnormal behaviour in the case presented here was both acute in onset and progressed to extremes within 1–2 days. We did not encounter any flare up of symptoms during follow-up in our case. The episodic flare ups was mentioned in the first criterion for the diagnosis of PANDAS. However, later cases were labelled as PANDAS without episodic flare up. Murphy *et al*¹ reported that only 65% of the cases labelled as PANDAS had episodic flare ups. In

our case the child was continued on prophylactic antibiotics on follow-up to prevent further episodes of group A streptococcal infection leading to PANDAS.

The proposed pathophysiology of PANDAS is molecular mimicry between antibodies or immune cells cross-reacting between group A beta haemolytic streptococci and basal ganglia cells. This leads to autoimmune damage to the basal ganglia, which causes the neuropsychiatric disturbances associated with PANDAS.⁸ The proposed antineuronal antibodies associated with PANDAS are antipyruvate kinase antibody, anti-dopamine receptor antibody, and antilysoanglioside GM1 antibody.⁹

Treatment of PANDAS typically follows a three-pronged approach. First, treatment of symptoms with psychoactive medications and/or behavioural interventions is indicated, especially when symptoms cause the child severe distress.¹⁰ Antipsychotic medications, such as risperidone, can also be used to treat more severe behavioural symptoms.

Second, the use of antibiotics to treat an underlying infection and thus eliminating the source of inflammation is indicated.¹¹ Studies have documented improvement in neuropsychiatric symptoms of acute onset PANDAS with early initiation of antibiotics against acute group A streptococcal infection.¹² Antibiotics used for treating group A streptococcal pharyngitis are penicillin or amoxicillin.¹¹

Third, the use of immunotherapy to treat PANDAS symptoms due to neuroinflammation or post-infectious autoimmunity is also often indicated. Immunotherapy is employed in accordance with the severity and progression of the disease.⁴ Non-steroidal anti-inflammatory drugs and short oral steroid courses are used for milder presentations of the disease. Intravenous immunoglobulin is the preferred treatment for acute onset moderate-to-severe disease. Therapeutic plasma exchange is the first-line therapy for extreme and life-threatening impairment, and it is administered either alone or in combination with intravenous immunoglobulins, high-dose intravenous corticosteroid and/or rituximab.⁴ Latimer *et al* observed that therapeutic plasma exchange is an effective treatment method used in cases whose symptoms include life-threatening suicidality or aggressive behaviour.¹³ We categorised the present case as moderate-severe grade, as there was no life-threatening symptoms such as suicidal behaviour, unstable vital signs or significant weight loss (>10%), and we treated our case with one dose of intravenous immunoglobulins.

Various studies support secondary antimicrobial prophylaxis, as was administered in the present case, for children with PANDAS. Snider *et al* reported 75% and 56% reductions in neuropsychiatric exacerbations after using penicillin V and azithromycin, respectively, for 1 year after PANDAS diagnosis.¹⁴ Penicillin also has some immunomodulatory and neuroprotective effects, which can provide protection against the exacerbation of symptoms in PANDAS cases.¹⁵ We prescribed 250 mg of oral penicillin V twice daily as prophylaxis in the present case.

Despite the contributions by our group and others to the understanding of PANDAS and its clinical presentation, the long-term outcomes of this condition are not well understood. For instance, Murphy *et al* reported that individual PANDAS subtypes and their associated risks of remission or progression to a more chronic course are not known.¹

The scarcity of PANDAS case reports from the Middle East prompted our reporting the present case. Specifically, in Bahrain, where the current case was reported, no prior reports have been made.

Patient's perspective

The boy's mother shared her experience with us. She is a healthcare professional working as a neonatal nurse. She used some medical terms in her interview. We spoke in English.

Interviewer dialogue is italicised.

Q1: *Ma'am, thank you for taking the time to speak with us. Can you describe your experience with the recent illness of your son?*

My child initially complained of throat pain. Roughly 1 week later, when my son returned from school in the afternoon, I noticed that he didn't remove his shoes at the door of the house, which he was in the practice of doing for the last 2–3 years. He instead sat on the sofa with his shoes on. Even after repeated requests, he didn't remove his shoes. The next day he became aggressive.

Q2: *What was going through your mind regarding his abnormal behaviour?*

We were extremely worried. My husband and I began to pray. We thought that someone had bullied or abused him. We thought that our child was suffering from a psychiatric illness and that it would take months and years for him to recover. I even planned to take a long leave from my job to take care of him.

Q3: *How did the paediatric team manage your child's condition?*

The next day they mentioned to us that he was diagnosed with PANDAS. His condition improved very quickly after they administered immunoglobulin. Within a few hours of the immunoglobulin infusion, his irritability subsided. The next day, when he woke up, he began to behave normally as if nothing had happened. He returned to his normal behaviour.

Thank you for sharing your story with us.

Learning points

- To increase the awareness of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) among general practitioners and paediatricians in order to avoid delayed diagnoses and management of such cases.
- Once diagnosed, PANDAS can be rapidly cured with appropriate antibiotics and immunoglobulin administration.
- A follow-up antistreptolysin O titre test is necessary for accurate prediction of streptococcal infection in some cases.

Contributors RHSJ was involved in patient care as he was the consultant in charge of the concerned patient; he drafted the summary, background and discussion. In addition, he reviewed and improved the paper. AAM was also involved in patient care; he drafted the sections on case presentation, investigations, differentials, follow up and outcome. He also interviewed the mother.

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