

Autoimmune neuropsychiatric disorders associated with infection

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There have been many observations of the relationship between infectious disease and behaviour changes such as the development of tics documented in medical literature over a long period of time. Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a controversial diagnosis because it relies on linking a causal association between a common childhood illness with less common psychiatric symptoms. This case report describes a possible case of PANDAS in a young person, the course of treatment and its outcome.

In 1894 Sir William Osler noticed a difference in behaviour in patients with Sydenham's chorea¹ (following rheumatic fever due to streptococcal infection) and Dr Laurence Selling reported three cases of tics associated with sinusitis in the 1920s.² Later studies of children with Sydenham's chorea revealed that obsessive compulsive symptoms were present in the majority and these presented before the onset of chorea, giving strength to the theory that these symptoms were part of the illness rather than a consequence of physical disability.^{3,4}

The first cases of paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) were described by Swedo *et al.* in 1998.⁵ Five clinical criteria were established: presence

of obsessive compulsive disorder (OCD) or tic disorder; pre-pubertal onset; acute symptom onset and episodic (relapsing-remitting) course; presence of associated neurological abnormalities (particularly choreiform movements), and temporal association with group A streptococcal (GAS) infection.^{5,6} The diagnosis of PANDAS has been a cause for debate with some evidence supporting it⁵⁻⁷ while others question it.^{8,9}

Here, we present the case of our patient who initially presented to services when he was 11 years old and document and discuss his presentation and treatment over the following seven years.

Case presentation

Initial presentation

An 11-year-old boy presented with sudden-onset severe OCD symptoms during the summer between primary and secondary school. Within six weeks of the first onset of symptoms he was unable to walk due to his many time-consuming complex rituals, having to turn taps on and off 20 times and praying while getting undressed. He also developed motor tics and inappropriate sexual behaviour such as licking his mother's arm suggestively and shouting out sexual remarks. His family had recently moved into temporary accommodation, which he had not reportedly shown any anxiety over. He was due to start secondary school, which he attempted but was unable to attend properly due to the severity of his OCD symptoms. It was also noted that as well as these social stressors, two days after his OCD symptoms started, he

developed a severe impetigo infection. The situation at home reached crisis point and he stopped eating and was admitted to a paediatric medical unit where all investigations, including routine blood tests, MRI brain, EEG and antistreptolysin O titre, were all within normal limits. During admission he made a slight improvement and was discharged following a child and adolescent mental health services (CAMHS) review during which he was started on a low dose of sertraline. The following month he was admitted urgently to a CAMHS inpatient unit due to a relapse. He made a gradual improvement except for a sudden deterioration after a couple of months but this resolved quickly. During the admission he was treated with sertraline, low dose risperidone, cognitive behaviour therapy (CBT) and family therapy.

Course of illness

Over the next few years his OCD symptoms persisted but were noticed to follow a relapsing-remitting course. He continued to have outpatient CBT and took sertraline as well as risperidone. Risperidone was changed to aripiprazole as he started gaining weight excessively. It was identified that each time he was unwell with an upper respiratory tract infection his OCD symptoms worsened and on one occasion he had a positive antistreptolysin O titre. He and his mother felt that each time he received antibiotics there was a marked improvement in his OCD symptoms and functioning.

During his course of illness he moved to a different geographical

area and his motor tics were thought to be related to Tourette's syndrome. He was also diagnosed with high functioning autistic spectrum disorder (ASD). By the age of 15 years he had become prone to depressive episodes, was self-harming and his body mass index (BMI) was almost 30.

His mother was keen to find a link between his OCD and upper respiratory tract infections causing his symptoms to worsen and antibiotics improving them and the family sought several opinions around the country. He was eventually given a diagnosis of PANDAS by a private specialist child psychiatrist in London, although his local CAMHS treatment team at the time did not feel that antibiotics would be beneficial and did not agree with the diagnosis of PANDAS, feeling it was not a proven illness.

As well as the PANDAS diagnosis and ASD the patient was observed to be losing weight rapidly as well as developing body image issues and other anorectic symptoms. Following a throat infection it was felt that his dietary restriction worsened and at the age of 17 years he was admitted again to a CAMHS unit in order to stabilise his weight and was diagnosed with anorexia nervosa. His BMI was just under 17. Although he stabilised his weight during this four-month admission, after he was discharged his weight plummeted and his BMI was 13 and his relationship with his treating team became very difficult as he was so worried about having to increase his calorie intake.

Recent treatment

Following his transfer from CAMHS to an adult eating disorders service the patient started attending regularly for appointments. During this time a full case review was undertaken: it appeared that his psychiatric and behavioural symptoms improved

while on antibiotics for other reasons. It was agreed that he could start a trial of co-amoxiclav. He reported an improvement in his OCD symptoms and started making slow progress in terms of weight gain.

Just over a year on he continues to take antibiotics but at a lower dose than he initially started on. His BMI is continuing to slowly improve, his OCD is minimal and he has been able to return to education. There have been significant advances in building up his social life having spent his teenage years debilitated by OCD and not being able to attend school properly. As well as this improvement in his OCD and anorexia nervosa, he has had far fewer depressive episodes, and has not self-harmed. His motor tics have also improved to a stage where they are more or less non-existent. At this stage he was treated with fluoxetine, co-amoxiclav and various over the counter vitamins and probiotics that he felt were helpful.

He has still noticed that when he has an upper respiratory tract infection his OCD becomes worse and he will often increase the dose of his antibiotics for a few days. He is aware that he will not be able to stay on the antibiotics in the long term and has already been attempting to reduce the frequency at which he takes them.

Background history

As a young child the patient suffered from a reflex anoxic seizure and several febrile convulsions including a severe one at the age of four years. He reached normal milestones apart from slight speech delay, which resolved spontaneously and he was speaking in full sentences by the age of two and a half years. Although clumsy as a child he had no neurological deficit and was academically able and popular with other children at school albeit

slightly shy. There were no problems with separation anxiety and he was able to go away on school trips without concern.

His parents' relationship ended within the first couple of years of his life and he had fairly infrequent contact with his father until his later teenage years. He has a very close relationship with his mother and three younger half siblings.

Family history

The patient's mother has suffered from OCD and anxiety, his maternal aunt has bipolar affective disorder and a maternal cousin has severe ASD.

Discussion

PANDAS is a controversial diagnosis because it relies on linking a causal association between a common childhood illness with less common psychiatric symptoms.¹⁰ The aetiology of PANDAS is unknown but it is thought to be similar to Sydenham's chorea in that it is a post-infective complication of infection with group A streptococcus. The proposed hypothesis is that infection with GAS in a susceptible host leads to the production of antibodies that affect the basal ganglia, especially the caudate nucleus and putamen. The psychiatric symptoms, including obsessions, compulsions and tics, that arise are thought to be the result of an interaction of these antibodies with the neurons of the basal ganglia.¹¹

The PANDAS diagnostic criteria state that there should be proof of an infection with a positive throat culture and/or elevated anti-group A beta haemolytic streptococcus (GABHS) antibody titres.⁵ Making a diagnosis of PANDAS can therefore be difficult as upper respiratory tract infections are common in childhood and most will resolve without treatment or with a short

course of antibiotics with no long-term sequelae. PANDAS could be a diagnosis that is not thought of acutely and GABHS are not routinely investigated or screened for in the community making unnecessary treatment with antibiotics more likely if a GABHS infection is presumed rather than confirmed.¹²

The PANDAS diagnostic criteria also state that infection and the symptoms should be temporally related.⁵ The temporal relationship between GABHS and symptom exacerbation can vary over the course of the illness and in cases of rheumatic fever there can be a delay of up to six to nine months between evidence of infection and the appearance of symptoms of Sydenham's chorea.⁵ There can also be occasions when symptoms are not associated with GABHS, as is the case with rheumatic fever and Sydenham's chorea due to streptococcal infections being undetectable, or there may be another cause other than GABHS.³ There have been only a small number of longitudinal studies that prospectively identified PANDAS cases to examine the temporal relationship between GABHS and the onset of OCD and tic symptoms.^{14,15} Both these studies have shown little support for the PANDAS hypothesis.⁶

There have been several case reports linking PANDAS and other infectious illness with certain eating disorders.^{10,17,18} Our case adds to these as well as to the idea that there may be other manifestations of PANDAS as well as OCD symptoms, although our patient had a longer period of illness overall than other reported cases. Our patient followed a relapsing and remitting course of illness in a similar way to other cases, however, and had a good response to treatment with antibiotics. Our case adds to a school of thought that some eating

disorders may be autoimmune-mediated in some way.

As well as difficulties with diagnosis, treating PANDAS can be difficult. There is little evidence for any treatments that have been put forward.

Antibiotics have been suggested as a treatment for PANDAS but some studies have not found any conclusive evidence.¹⁹ Other studies have been too small to prove that they are an effective treatment, however, penicillin and azithromycin prophylaxis did decrease both streptococcal infections and neuropsychiatric symptom exacerbations in children with PANDAS.²⁰

Other treatments that have been used for children with PANDAS are plasmapheresis, which involves removing offending antibodies and treatment with intravenous immunoglobulin and should result in an improvement in symptoms if the hypothesised aetiology is correct. Several studies have found these to be beneficial.^{21–3} The evidence for these therapies is not conclusive, however, and larger trials would provide more information.

There is mixed evidence for tonsillectomy as a treatment for PANDAS. However, there have been a few cases where this has been performed and shown good results.^{24,25} Other evidence has found this not to be the case, therefore tonsillectomy is not currently indicated in PANDAS.²⁶

Our case shows that our patient's OCD and eating disorder symptoms responded well to antibiotics. An alternative interpretation is that the patient's symptoms improved with age and the antibiotics had a placebo effect, magnified by the family's belief in the PANDAS diagnosis.

More research is required to prove the causal effect of GABHS in PANDAS and to find an appropriate treatment.

Declaration of interests

No conflicts of interest were declared.

Dr Lawrence is ST4 General Adult Psychiatry and Dr Baggott is Consultant Psychiatrist and Lead Consultant FYPC, both at Leicestershire Partnership NHS Trust.

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POEMs

Patient Orientated Evidence that Matters



EEG inaccurate in diagnosing ADHD

Clinical question

Can electroencephalograms (EEG) replace clinical assessment in diagnosing children with attention deficit hyperactivity disorder (ADHD)?

Bottom line

High-quality data are lacking, but it appears that electroencephalograms (EEGs) are not reliable enough to replace clinical assessment for diagnosing attention-deficit/hyperactivity disorder (ADHD) in children, and should not be used to confirm an ADHD diagnosis nor to support further testing after clinical evaluation. (LOE = 5)

Reference

Gloss D, Varma JK, Pringsheim T, Nuwer MR. Practice advisory: The utility of EEG theta/beta power ratio in ADHD diagnosis: Report of the Guideline Development,

Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2016;87(22):2375–2379.

Study design: Practice guideline
Funding source: Foundation
Setting: Various (guideline)

Synopsis

This committee of the American Academy of Neurology summarize the DSM-5 criteria for diagnosing ADHD. The various tools that we use (eg, the Connors or Vanderbilt scales) are slightly more than 90% sensitive and 90% specific. Other than a comprehensive physical and neurologic examination, no additional laboratory or diagnostic tests are routinely recommended for diagnosing ADHD. However, it has been postulated that specific findings on EEGs might replace clinical assessment. To assesses the

clinical utility of EEG, this panel systematically searched multiple databases. The panel found a single study that showed that the combination of EEG and clinical assessment was 88% accurate, but reported no diagnostic accuracy for either test alone. The authors found 32 studies that compared EEG with clinical assessment, only 2 of which were high quality. In these studies, the overall accuracy of EEG was approximately 90% with a greater than 5% false-positive rate, which was judged to be unacceptably high by the panel.

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