CASE REPORT

PANDAS versus Hashimoto`s encephalopathy: a diagnostic dilemma in a Saudi girl

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ABSTRACT

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a rare recently recognised clinical syndrome with common presentations that include tics, Tourette's-like syndrome or obsessive-compulsive disorder. It is associated with various behavioural and psychiatric manifestations in children, such as separation anxiety disorder, body dysmorphic disorder, and attention deficit hyperactivity disorder. Steroid responsive encephalopathy with autoimmune thyroiditis (SREAT) is a rare disorder in children associated also with various movement disorders and neuropsychiatric manifestations. The present report describes a previously healthy 10-year-old girl who presented with motor tics, visual hallucination, separation anxiety, and emotional liability. Her workup showed an evidence of Hashimoto's thyroiditis on laboratory results, in addition to the elevation of antistreptolysin O titre (ASO). Based on this, a diagnosis of SREAT was made, and she was given courses of methylprednisolone with inadequate response. Then, the possibility of PANDAS was considered, and she responded to multiple courses of antibiotics with abate of symptoms after a course of intravenous immunoglobulin combined with monthly benzathine penicillin injections. To the best of our knowledge, this is the first reported case of PANDAS associated with autoimmune thyroiditis causing such diagnostic dilemma.

KEYWORDS

Paediatric neuropsychiatric disorder associated with streptococcal infection; PANDAS; Autoimmune disorder; Hashimoto`s encephalopathy; Streptococcal infection.

INTRODUCTION

Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) is a rare recently recognized clinical syndrome with common presentations that include tics, Tourette's-like syndrome or obsessive-compulsive disorder, or chorea in the context of an immediately precedent streptococcal infection. The term PANDAS was coined by Swedo et al. [1] to describe cases of childhood obsessive-compulsive disorders (OCD) and tic disorders that were triggered by group A beta-hemolytic streptococcal (GABHS) infection. In some cases, such infections lead to other behavioural

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and psychiatric manifestations in children. The current diagnostic criteria in Table 1 mandates the presence of temporal association between GABHS infection and onset or exacerbation of symptoms, i.e., positive throat culture accompanied by increased antistreptococcal titres (two-folds rise in a month following infection), or increased titres and recent history of scarlet fever or pharyngitis. It is an autoimmune disorder that develops on the base of molecular mimicry [2]. Therapy for PANDAS includes immunosuppressive agents in acute stage [3]. Long lasting cure was reported in some to be associated with long course antibiotic therapy ranging between 2 weeks to 3 months, monthly injection with benzathine penicillin and adenotonsillectomy. Neurological symptoms have been treated with compounds, such as haloperidol, respirdone, clonidine, and serotonin reuptake inhibitors [4].

Steroid responsive encephalopathy with autoimmune thyroiditis (SREAT) is a rare, but probably underdiagnosed, steroid-responsive persistent progressive or relapsing encephalopathy characterised by neurologic or neuropsychologic manifestations that is associated with elevated blood concentration of antithyroid peroxidase antibody. It is diagnosed in individuals of all the age groups, including children [5]. Affected individuals are usually euthyroid or mildly hypothyroid. The spectrum of clinical manifestations is wide [5] (Table 2). In 50%, the onset is abrupt or subacute with clinical presentation of mainly seizures followed by an encephalopathy with confusion, and hallucination, and in contrary to adult vasculitic presentation, in children focal neurologic signs are rare, such as ataxia or quadriplegia. Some may progress to coma over few days. In 30%, the course is more insidious and progressive than in adults, with cognitive decline and depression lasting several months to a few years. Attention deficit hyperactivity disorder (ADHD) is a rare presentation of SREAT in childhood, refractory to medications, and only responds to steroids [6–9].

This report aimed to discuss the diagnostic dilemma of PANDAS vs Hashimoto's emncephalopathy in a previously healthy 10-year-old girl who presented with combined picture of both movement disorder (tics) and neuropsychatric manifestations (visual hallucination, separation anxiety, and emotional liability), and was found to have hypothyroidism with elevated antipyroxidase antibody, and elevated antistreptolysin O (ASO) titre.

CASE REPORT

A 10-year-old female child was brought by her parents with a 14-month's history of repeated episodes of abnormal behaviour and neuropsycatric manifestations alternating with periods of normal personality and mood. These symptoms were abrupt in onset, and the first one was preceded by 2 days duration of fever and pharyngitis treated with antibiotic for 1 week. Each episode occurred once every 12 days and lasted for 3–7 days. The episodes usually start with non-specific bifrontal headache, fatigability and muscle aches, and left knee arthalgia. Mild motor tics involving eyes (frequent blinks), eye brow, mouth with abnormal gaze-like look and intermittent choriform piano-like finger movements, were noted some times with these

Table 1. Current diagnostic criteria for PANDAS.

(1) Presence of clinically diagnosed obsessive compulsive (OCD) and/or tics disorder (meeting DSM-IV criteria).
(2) Pediatric onset (3 years of age—puberty).
(3) Episodic waxing and waning course of symptom severity with abrupt onset and dramatic exacerbations in relation to GABHS infection.
(4) Documentation of a temporal association of less than 6 weeks between (GABHS) infection and onset of symptoms.
(5) Association with neurological abnormalities, such as adventitious movements, motoric hyperactivity, or piano-playing choreiform movements that present during symptom exacerbations.

episodes. Further detailed history revealed obsessions for contamination, compulsions behaviour; washing, cleaning, checking, repeating, ordering, and arranging. Excessive sleepiness, mood disturbance with irritability, separation anxiety, emotional liability, social withdrawal, loss of interest in her usual activities, fidgetiness, aggressive behaviour, abnormal slow and non-fluent speech, periodic excessive eating, poor concentration and attention, with intermittent confusion and deterioration in hand writing resulting in poor school performance. It was noted that such symptomology peaked sometimes with pharyngitis, but not necessarily with each febrile illness. She had difficulty in completing any work at home, like helping her mother in her chores, as well as being unable to complete her homework.

During all this period, her family did not seek medical advice, and the child stopped going to school for about 4 months prior to presentation to our hospital. There was no recent stressor in the child's life either at home or school. Her birth and developmental history were normal. She was good in her studies and there was no past history of school refusal or failures. Family history was insignificant for any neurological or psychiatric disorders. An extensive work-up screening for possible infectious, toxic, metabolic, paraneoplastic, and vasculitis disorders revealed negative results. Erythrocyte sedimentation rate was normal, and throat swab showed no growth. ASO titre was elevated initially (579 IU/ml), and reduced during remission (Figure 1). At the same time, she had abnormal thyroid function test, high thyroid stimulating hormone [TSH, 15.64 mU/l (NR = 0.25–5)] with normal free thyroxin [FT4, 12.06 pmol/L (NR = 10.3–25.8)], and she was clinically euthyroid. Antithyroglobulin antibody titre was high range (800–1,000 IU/ml, NR = 0–60), and anti-microsomal (anti-perioxdase antibody titre was also high (347–880 IU/ml, NR = 0–100).

Table 2. Clinical, radiological, and laboratory features of Hashimoto`s encephalopathy.

Clinical features	Heterogeneous.
	Cognitive impairment.
	Fluctuating encephalopathy, hallucinations.
	Seizures.
	Movement disorders: myoclonus, tremor, motor tics, and choreic movements.
	Central nystagmus, ataxia, and gait disturbance.
	Neuropsychiatric features: behavioral , agitation, apathy, subtle personality changes, psychosis –like manifestations, and suicidal ideation.
Neuroimaging studies	MRI: T2-weighted image high signal intensity in subcortical white matter suggesting demyelination or inflammation; may be normal.
	SPECT: reversible hypoperfusion in frontal or frontotemoporal (rare).
	PET: reversible diffuse hypometabolic areas (rare).
Laboratory features	High anti-thyroid antibodies (anti-thyroid peroxidase, anti-thyroglobulin antibodies).
	Neck ultrasound: CLT/goiter (sometimes).
	Thyroid scintigraphy – increased uptake consistent with thyroiditis.
	Thyroid hormone level- euthyroid, hypothyroid, hyperthyroid (rare).
	CSF analysis: high protein (mild-moderate), OCB, MBP (rare), anti-thyroid peroxidase antibody.
	EEG: general or focal slowing of background, may be normal.

CLT, chronic lymphocytic thyroiditis; CSF, cerebrospinal fluid; EEG, electroencephalogram; MBP, myelin basic protein; MRI, magnetic resonance imaging; OCB, oligoclonal bands; PET, positron emission tomogram; SPECT, single photon emission tomogram.

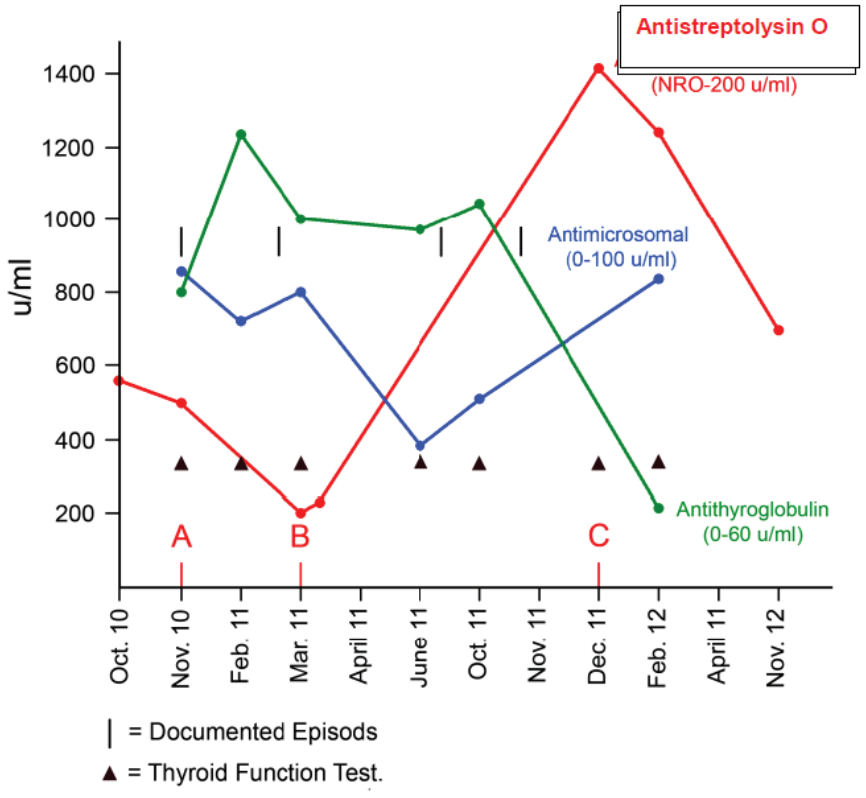

Figure 1. The titres of antistreptolysin O, and anti- thyroid [anti-microsomal (anti-perioxidase) and antithyroglobulin] antibodies over a 24-months period. Treatment with corticosteroids was started at diagnosis (A) and 4 months later on (B). IVIG therapy was started at (C).

During the second episode, ASO titre was only 200 IU/ml while anti-perioxdase antibody titre was high. Based on this, Hashimoto`s encephalopathy was suspected, and she was started on L. thyroxin 50 ug once daily. Further work-up included cerebrospinal fluid (CSF) analysis for oligoclonal bands which was negative. Protein and glucose were normal, and CSF anti-perioxdase antibody assay was not available. Echocardiogram, multiple electroencephalograms (EEGs, awake and sleep), and brain MRI were normal. She was given pulse methylpredinsolone therapy, followed by oral prednisolone for 6 weeks, and showed remission for 2 months. Then, episodes recurred with tapering of steroids, and she was given another two more courses with long maintenance of prednisolone, but there was no further response and episodes became more prolonged for up to 15 days. She remained clinically euothyroid but with mild decrease in FT4 [9.44 pmol/L (NR=10.3–25.8)], and mildly elevated TSH [6.11 mU/L (NR = 0.25–5)] with persistent elevation of anti-thyroglobulin antibody, and anti-perioxdase antibodies titres (800–1,218 IU/ml, NR = 0–60), (347–840 IU/ml, NR = 0–100), respectively. Fluoxetine (SSRI) 10 mg once daily was started, and no treatment was given for her tics as it was not bothering her.

Reviewing the ASO titre during the repeated episodes, it showed a range of 579–1,410 IU/ml. A probable diagnosis of PANDAS was adopted for the child, and she was given multiple courses of antibiotics (augmentin and cephalexin), with partial response. Finally, she was given intravenous immunoglobulin (IVIG, 1 g/Kg/ dose for two consecutive days), and started on benzathine penicillin (1.2 million units intramuscular injection monthly for 6 months). Surprisingly, she showed impressive response with no more episodes, and disappearance of previous symptoms for 12 months with drop in ASO titre level to 1,220 IU/ml, and then to 753 IU/ml. At the same time, anti-perioxdase antibody

titre remained elevated at 820 IU/ml (NR = 0–100) and anti-thyroglobulin level was 200 IU/ml (NR = 0–60). She was planned for a second course of IVIG with recurrence of symptoms and possible tonsillectomy.

DISCUSSION

Possible causes of complex neuropsychiatric manifestations, including temporal lobe epilepsy, vitamins deficiencies, autoimmune encephalitis, and vasculitis were excluded in this patient. During her initial evaluation, she was diagnosed as a case of autoimmune thyroiditis because of elevation of both anti-thyroid antibodies, and TSH. She was started on L. thyroxin. Despite that, her symptoms had gradually worsened; she had become forgetful, and developed decreased school performance with more obvious tic disorder, and personality changes, for which SREAT was suspected [6]. The clinical features of SREAT are heterogeneous (Table 2), and a high degree of suspicion is necessary for its diagnosis. It is always associated with elevated levels of anti-thyroid antibodies especially anti-thyroid peroxidase antibody, and only sometimes associated with chronic lymphocytic thyroiditis and goitre [8]. There was no goitre, but thyroid auto-antibodies were elevated and thyroid scintigraphy was consistent with thyroiditis. Thyroid status varies greatly between SREAT patients who may be either euthyroid, hypothyroid and, rarely, hyperthyroid [10].

Children with PANDAS may manifest an acute onset of OCD, tics or Tourette-like syndrome [11,12]. Other psychiatric comorbidities of PANDAS include emotional liability, oppositional behaviours [13], body dysmorphic disorder, attention deficit hyperactivity disorder [14] and separation anxiety [15].

PANDAS was considered as an important differential diagnosis for SERAT, but temporal association with streptococcus infection, i.e., throat infection or febrile illness was not documented in this patient in all episodes in the period prior to the presentation [1].

A sensitive marker for SREAT, CSF anti-perioxdase antibody test was not available. A normal EEG and brain MRI did not rule it out. Hashimoto's encephalopathy (HE) was considered initially, and although it is a steroid sensitive encephalopathy [5,6], the patient did not show impressive clinical response to high dose corticosteroid therapy but rather worsening of the duration of the episodes. Dilemma in diagnosis appeared at this stage. Is this a SREAT or PANDAS? In SREAT, antithyroid antibodies help in diagnosis, but serial measurement does not help in monitoring the response i.e. high levels can be seen during complete clinical remission. Other forms of immunomodulation, such as azathioprine, methotrexate, cyclophosphamide and hydroxychloroquine sulphate as well as plasmapheresis and IVIG, have been used in some cases with clinical benefit [16,17].

A probable diagnosis of PANDAS was suspected based on later follow-up of her clinical course and serial measurement of ASO titre that confirmed the temporal association of symptoms with streptococcus infection even in the absence of positive throat culture. Measurement of both ASO and anti-DNAse-B titres are more accurate than either alone [13]; anti- DNAse-B was not feasible for our case. Impressive response was noted in clinical and serial titres after IVIG therapy combined with benzathine penicillin monthly [18].

In PANDAS, multiple courses of antibiotics (penicillin, cephalosporin and azithromycin, benzathine penicillin), immunomodulatory treatment with plasma exchange and IVIG were found to be effective in lessening the neuropsychiatric symptom severity and in controlling the disease [18,19].

We believe that her clinical picture was consistent with PANDAS, and the presence of autoimmune thyroiditis masked the picture. The question was raised whether this is a coincidental finding or there is a possible relationship between these two autoimmune disorders. Autoimmune thyroid diseases are often part of a general tendency to develop other autoimmune disorders such as pernicious anaemia and systemic lupus erythematosus, but what about PANDAS? Is it a part of such autoimmune spectrum during childhood period? Both diseases share a common pathogenesis related to production of

autoantibodies. Is it possible that anti-neural antibodies in PANDAS that attack the basal ganglia cross react with specific antigen or receptor on thyroid gland and attack the thyroid gland as well? Even in the absence of antithyroid antibodies, the inflammatory cytokines which are usually present in chronic infections and inflammatory states interfere with T4 to T3 conversion and thus can cause clinical symptoms of hypothyroidism. This postulated theory cannot be supported as measurement of serum antineural (anti-basal ganglia) antibody and CSF antipyroxidase antibody were not measured in this patient, in addition there was no complete normalization of thyroid function test or thyroid antibodies post PANDAS treatment.

There is a high prevalence of GABHS throat infections among paediatric populations, but only a small percentage of individuals develop post-streptococcal autoimmune illnesses. A theory of an autoimmune-mediated mechanism involving molecular mimicry was pursed by researchers [2,20] similar to that of rheumatic fever and Sydenham chorea, where basal ganglia are targeted by the resultant IG antibodies against GABHS M protein, which is responsible for the movement and behaviour disorders [1]. These serum anti-BG can be detected by immunofluorescence (IM), ELISA, and western blot. An important fact is that circulating antibody is not able to pass through an intact blood-brain barrier (BBB). In PANDAS, it is unknown whether BBB might be disrupted or whether inflammatory cells pass into the brain where the cross-reacting antibodies are produced. Impairment and disability result from neuronal damage secondary to antigen-antibody complexes in brain and activation of cytokines.

In SERAT, a proposed mechanism for neuropsychiatric manifestation is an immune-mediated phenomenon, either secondary to autoimmune cerebral vasculitis (commonly in adults) or an antineuronal antibody-mediated cerebral inflammatory reaction, or toxic effect of thyroid releasing hormone on the central nervous system. Another possibility is that the presence of elevated antithyroid antibodies plus the presumed toxic effect of thyroid releasing hormone have altered the BBB and made this patient more vulnerable to develop PANDAS.It was found that certain genetic, developmental and immunologic factors predispose the child to develop PANDAS. Genetics can place an individual at increased risk, but environmental triggers are also necessary. Monoclonal antibody D8/17 is a genetic marker with increased expression in PANDAS. Measurement of this antibody was not feasible for our patient. Further case reports of such combinations may help in delineating the basis of such relationship. We suggest screening for the presence of serum antineural (anti-BG) antibody, and the genetic marker monoclonal antibody D8/17, as well as screening for autoimmune thyroiditis in patients presenting with PANDAS. To the best of our knowledge, this is the first reported case of PANDAS with Hashimoto`s thyroiditis, with major psychiatric manifestations, producing a diagnostic dilemma in a child, and showing an impressive response to IVIG and poor response to steroids. In conclusion, streptococcal infections may present with movement disorders and varied psychiatric manifestations in the paediatric age group and one needs to be more vigilant in cases that have an abrupt onset and unusual presentation. A high index of suspicion is important to diagnose such cases and provide them with a timely treatment.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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ETHICAL APPROVAL

Signed informed consent for participation and publication of medical details was obtained from the parents of this child. Confidentiality of patient's data was ensured at all stages. The author declares that ethics approval was not required for this case report.

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