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Hashimoto encephalopathy and peripheral neuropathy in an italian adolescent

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Abstract
Hashimoto encephalopathy (HE) has been described as a syndrome of encephalopathy associated with an elevated concentration of circulating serum anti-thyroid antibodies, and usually responsive to steroid therapy. We report a novel case of HE in a 14-year-old girl with central and peripheral nervous system involvement. The girl, prior to admission, had experienced a two-day history of high-grade pyrexia, intense global headaches and sleeplessness. Over the first few days after admission she had an ileus with a distended urinary bladder associated to hallucinations, progressive cognitive impairment and mood changes. A MRI of the brain and spinal cord revealed multiple foci of signal abnormality in the basal ganglia, thalami and hippocampal regions bilaterally, in the deep and periventricular white matter and in the spinal cord medulla at the C4-C6 levels. The motor conduction velocity test showed reduced amplitude in the upper and lower limbs. The anti-thyroglobulin (TG) antibodies were raised at 2121 IU/ml (normal range 0 - 40) and the anti-thyroperoxidase (TPO) was high at 886 IU/ml (normal range 0 - 50). Progressive neurological and psychiatric remission was noted after administration of intravenous methylprednisolone. A follow up MR study of the brain and spine performed 4 weeks later revealed almost complete resolution.

Introduction

In recent years, neurological and psychiatric symptoms associated with Hashimoto thyroiditis have been increasingly recognized in both adult and paediatric patients [1-5]. This neurologic complication has been termed "Hashimoto encephalopathy" (HE) and it has been described as a syndrome of encephalopathy associated with an elevated concentration of circulating serum anti-thyroid antibodies, and usually responsive to steroid therapy [1-6]. HE can begin abruptly, in the form of seizures or agitation, with or without other neurologic complaints, or it can develop gradually, in a relapsing-remitting manner, including, among others, cognitive deterioration and psychiatric illness [1, 2].

The presence of Hashimoto thyroiditis is not always necessary to make a diagnosis of HE as some affected individuals may have elevated thyroid autoantibodies and neurological and psychiatric involvement in the absence of thyroiditis. [1-7]. Positive findings on neuroimaging may help in the early detection of this condition, which remains rare in the paediatric age.

Adequate information is not available about the frequency of HE in children [6] despite its first description as a distinct clinical condition in adults in 1966 [7]. The estimated prevalence in adults is 2.1 in 100, 000 [1, 2, 6]. HE however remains rare in children, nevertheless can lead to serious consequences if not treated early.

We report a novel case of HE in a 14-year-old girl with central and peripheral nervous system involvement.

Case Report

This 14-year-old girl presented to the paediatric emergency room with a 2-day history of high-grade pyrexia, intense global headaches and sleeplessness.

She had been born at term after an uneventful pregnancy to healthy, non-consanguineous Italian parents. Her birth weight, length, head circumference and developmental milestones had been normal. There had been one past hospital admission with chronic cough of 3 years' duration with accompanying history of regular throat clearing and panic attacks. She had been discharged after thorough investigations with a diagnosis of psychogenic cough within the spectrum of somatoform respiratory disorders.

On present admission, the child was haemodynamically stable, GCS 15/15 found to be co-operative, alert and fairly orientated to time and place, but was witnessed to have transient episodes of auditory and visual hallucinations, delusions and loose association thoughts. The general examination was unrevealing; however on neurological assessment she was found to have neck stiffness with positive Lasegue's test. The deep tendon reflexes were reduced, there was a distal sensory deficiency.

A full ophthalmologic review was normal. An urgent computed tomography scan (CT) of the head was normal. The electroencephalogram (EEG) recording revealed diffuse slowing of the background activity. Routine blood tests including white cell count, erythrocyte sedimentation rate and C-reactive protein were within normal range; urine analysis was also normal. Thyroid function tests were carried out. The TSH, fT3 and fT4 were normal. The antithyroglobulin (TG) was raised at 2121 IU/ml (normal range 0-40); antithyroperoxidase (TPO) was high at 886 IU/ml (normal range 0-50). The neuronal voltage-gated calcium channel and potassium channel antibodies and other currently recognized paraneoplastic autoantibodies (e.g. anti-NDMA) were negative. Positive cerebrospinal (CSF) analysis findings included a white cell count of 40 cells/ml and proteins109 mg/dl and presence of oligoclonal bands. The initial head magnetic resonance imaging (MRI) was normal. Over the next few days, note was made of progressive lower abdominal distension with a distended urinary bladder (1, 500 cc of urine were drained after catheter insertion into the urethra) and muscular weakness in the lower limbs was noted upon clinical examination; her gait was unsteady. Abdominal radiograph showed mild dilatation of some colic loops [Figure 1].

Repeat MRI of the brain and spinal cord performed 7 days later revealed multiple foci of signal abnormality in the basal ganglia, thalami and hippocampal regions bilaterally with further signal change involving the deep and periventricular white matter [Figure 2] and in the spinal cord medulla at the C4-C6 levels. MR angiography was normal.

The motor conduction velocity test showed reduced amplitude in the upper and lower limbs indicating peripheral nervous system involvement likely a polyneuropathy. The patient was treated with intravenous methylprednisolone 1 g (20 mg/Kg) coupled with intravenous immunoglobulin 18 g/day (360 mg/Kg) for three days. Progressive neurological remission was noted with reversion of her psychotic status and dramatic improvement in behaviour.

A follow up MRI study of the brain and spine performed 4 weeks later revealed almost complete resolution [Figure 3].

Discussion

HE in the paediatric population can lead to serious neurological sequaele if unrecognized, such as cognitive decline, disturbed behaviour [1-5] and recurrent seizures [2-4].

HE is a rare syndrome of debatable pathogenesis. The role of anti-thyroid antibodies in the pathogenesis of HE remains uncertain [8, 9]. It is still unknown whether the presence of anti-thyroid antibodies is just an autoimmune epiphenomenon or if it is the real etiopathogenic factor [8, 9]. Possible pathogenic mechanisms may include: (a) autoimmune reaction to antigens shared by the thyroid gland and CNS: for example the possible role of an antigen common to the brain and thyroid; (b) autoimmune vasculitis with or without immune complex deposits [8]; and (c) toxic effects of thyroid-stimulating hormone in the central nervous system [10]. The neurotoxic hypothesis of thyroid-stimulating hormone increased concentration or the oedema-induced cerebral dysfunction acting as contributory factor are not likely pathogenic mechanisms especially since encephalopathy may also affect euthyroid subjects [11].

In the present case the motor conduction velocity test showed reduced amplitude in the upper and lower limbs indicating peripheral nervous system involvement. These findings are suggestive of a vasculitic process likely with involvement of vasa nervorum leading to polyneuropathy. An additional involvement of vasa nervorum could be hypothesised in the gut and bladder leading to the ileus and bladder retention even though the spinal involvement could be an additional cause to that. Interestingly, idiopathic forms of autoimmune autonomic neuropathies leading to gut motility disorders (specifically to intestinal dismotility) and chronic intestinal pseudo-obstruction have been recorded [12].

Clinical onset in HE may be acute or insidious with variable neurological symptoms [1-5]. In the acute setting, one often encounters a vasculitic-type episode with repetitive stroke-like events, such as hemiparesis, aphasia and ataxia and some cognitive impairment. The insidious type is usually progressive with cognitive decline, altered consciousness [9], hallucinations, psychotic episodes, attention deficit hyperactive disorder (ADHD), depression [13] and behavioural changes. An overlap of symptoms between the two types can occur. For example, myoclonus, tremors and seizures may occur in both types [10].

CSF protein levels are elevated in most cases [11]; IgG intrathecal synthesis may be elevated in some cases leading to detection of CSF oligoclonal bands as in the present case. EEG can show a generalized slowing in almost patients [14] as did in the present case.

The most important diagnostic clue is represented however by elevated levels of anti-thyroid peroxidase (mildly elevated in our case) and anti-thyroglobulin antibodies.

The MRI studies are negative in almost 50% of cases, but mild cerebral atrophy, infarction, focal mesiotemporal, basal ganglia and white matter abnormalities have been detected [3, 11]. Cerebral isotope studies or brain scans manifest abnormalities consisting of global, focal, or symmetric multifocal areas of decreased perfusion [3, 11]. Cranial involvement is more common than spinal, in fact to our knowledge there have been only three cases of isolated spinal cord involvement described in the literature- and none in the paediatric population [15, 16]. Notably, the initial brain imaging in the present girl yielded negative results but a progressive, albeit reverting, white matter and central brain involvement was noted over the following weeks.

Administration of corticosteroids is the treatment of first choice and usually results in complete healing; also plasmapheresis or intravenous immunoglobulin lower autoantibody titres acutely and are associated with resolution of clinical symptoms [1-6].

Peripheral nervous involvement in HE as in our case has not been previously reported in the literature.

HE is a rare condition in childhood but should always be taken in consideration in children with seizures, hallucinations, confusion and behavioural changes. It is often a curable disease if promptly recognized and treated. It is likely that anti-thyroid antibodies are not pathogenic, but antibodies titres can be a marker of treatment response. If anti thyroid autoantibodies are found, steroid treatment should be immediately administered.

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