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; generated to hiccousness; progressive cognitive impairment; mood and mictural 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 upper cord medullate 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-thyroid peroxidase (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 become evident that HE is 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.

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-consanguinous 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 been having transient episodes of auditory and visual hallucinations, delusions and loose association though with no change in consciousness (Figure 1). An elevated serum concentration of circulating serum anti-thyroid antibodies, and usually responsive to steroid therapy [1-6], had been noted in our case. The level had been 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 unremarkable. Brain MRI performed was normal. The TSH, T3 and T4 were normal. The anti-thyroglobulin (TG) was raised at 2121 IU/mL (normal range 0-40); antithyroidperoxidase (TPO) was high at 886 IU/mL (normal range 0-50). The neonatal voltage gated calcium and potassium channel antibodies and other currently recognized paraneoplastic autoantibodies (e.g. anti-NMDA) 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, the child developed a 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 (360 mg/Kg) over three days. Progressive neurological remission was noted with reversion of her psychiatric 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 sequelae if unrecognized, such as cognitive decline, disturbed behaviour [1-5] and recurrent seizures [2-4]. HE is a rare syndrome of debilitating pathologies. 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 reaction 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 dysfuction 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, idopathic forms of autoimmune autonomic neuropathies leading to gut motility disorders (specifically to intestinal dismotility) and chronic intestinal pseudo-obstruction have been recorded [12].

The 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, psychiatric 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 or multifocal areas of decreased perfusion [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 case yielded negative results but a progressive, albeit reverting, white matter and central brain involvement detected was detected [3, 11]. Cerebral isotope studies or brain scans manifest abnormalities consisting of global, focal, or symmetric multifocal areas of decreased perfusion [3, 11].

Administration of corticosteroids is the treatment of first choice and usually results in complete healing; also plasmapheresis or intravenous immunoglobulin lower antibody 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 symptoms of Hashimoto encephalopathy. The presence of HE should be suspected in a child with multi-organ involvement, usually associated with clinical features of polyneuropathy, and the anti-thyroperoxidase (mildly elevated in our case) and anti-thyroglobulin antibodies.

References

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Hashimoto encephalopathy and peripheral neuropathy in an Italian adolescent
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Hyphenated Adjectives and Proper Nouns

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