Idiopathic central pontine myelinolysis in childhood

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Central pontine myelinolysis (CPM) is rare in childhood with only a few cases reported in world literature. We report a 7-year-old male who presented with acute ataxia, swallowing difficulties, dysarthria, and radiological features consistent with the disorder. He improved remarkably with oral prednisolone therapy and was almost back to normal by 2 weeks. A review of the literature is also included.

Case report

A 7-year-old male presented with a 9-day history of sudden onset ataxia and worsening ‘clumsiness’. Four days before presentation he developed dribbling of saliva and slurred speech. His mother gave a clear history of him choking on his food on at least one occasion. In addition, he had been polydipsic, consuming up to 1.8 litres (104 mL/kg) of water daily.

He had received antibiotics from his general practitioner for a mild coryzal illness the week preceding onset of these symptoms. There was no history of a recent varicella infection or trauma.

The patient had been healthy previously but had always been small for his age and was receiving help at school for mild learning disability. He was on the special educational needs register. Three years earlier, he had been investigated for polydipsia and psychogenic polydipsia was diagnosed, supported by an early morning urine osmolarity of more than 600 mosm/L.

On examination, the child weighed 17.2 kg (<3rd centile), height was 109 cm (<3rd centile), with a head circumference of 48.9 cm (>3rd centile). He was conscious and alert, but drooled saliva continuously and his speech was slurred. He had no cutaneous signs of neurological disease. His pupils were of equal size, central, and reactive. He had marked truncal and limb ataxia (accentuated with running), tremulous hand and finger movements with dysmetria. His writing had deteriorated and he could not copy circular shapes satisfactorily. His tone was increased generally. He had generalized brisk reflexes with ankle clonus but downgoing plantar responses. His joint position sense was difficult to assess with confidence. His gait was stiff, awkward, and wide-based.

Plasma urea, electrolytes, liver enzymes, and albumin were normal, as was the full blood count. Acanthocytes were absent in his blood film. A CT of his brain was reported as
normal as was the EEG. Further neurophysiological investigations, including a blink reflex, showed bilateral gross conduction abnormalities at the brain-stem level involving nuclei and crossed interneurons (Fig. 1).

MRI of the brain using a 1.5 tesla scanner showed bilateral symmetrical high-signal abnormalities in the pons centrally extending into the midbrain. The pons was bulky (Figs. 2 and 3). Gadolinium was not given. CSF obtained for lactate, protein, sugar, culture, viral studies, immunoglobulins, and oligoclonal bands revealed no abnormalities. Cytokines and other inflammatory markers were not measured.

A diagnosis of central pontine myelinolysis (CPM) based on the patient’s clinical features, neurophysiological, and MRI findings was made and he was started on oral prednisolone 4 mg/kg/day for 2 weeks with a 4-week tail. He made a steady recovery with improvement in his gait, speech, manual dexterity, and normalization of his tone and tendon reflexes. At review 2 weeks later, his parents reported that he had made substantial recovery with nearly complete resolution of his symptoms. An MRI of his brain 9 weeks later showed that the pontine lesions were significantly smaller.

**Discussion**

CPM was described initially in 1959 relating specifically to adults with alcoholism and malnourishment (Adams et al. 1959). The symptoms and signs, which range from asymptomatic to coma and death, include reflex changes, pathological corticospinal reflexes, quadriparesis or quadriplegia, extrapyramidal signs, tremor, dysarthria, dysphagia, incontinence, and mutism (McCormick et al. 1967). The patient in this case report presented with ataxia, dysarthria, and dysphagia. Ataxia is an unusual symptom in CPM but has been reported (Defebvre et al. 1995).

The first comprehensive review of this disorder in children was in 1969 (Cadman and Rorke 1969). In their series, chronic illness was a significant feature in all 15 children reported and CPM was uniformly fatal. Most (nine of 12) were poorly nourished and nearly all (11 of 14) had evidence of electrolyte imbalance or dehydration requiring correction.

The unifying pathological feature of all demyelinating disorders is myelin destruction with relative axonal preservation (Allen and Kirk 1992). Many pathological mechanisms are possible including a T-cell mediated inflammatory process. When T-cells enter the CNS, they are activated by specific antigens. Myelin basic protein is assumed to be the key target antigen, however, immune responses to different CNS components have been detected: proteolipid protein, myelin oligodendroglia glycoprotein, and myelin associated glycoprotein and alpha-B-crystalline. The topographical distribution of demyelination seems to be determined by the antigen specificity of the T-cell response. Thus in CPM, demyelination may be related to a T-cell response towards a specific target antigen in the pons.

Another mechanism of demyelination is an antibody-mediated response against specific antigens expressed on the surface of myelin sheaths and oligodendrocytes. Myelin associated glycoprotein appears currently to be the most important antigen.

Tumour necrosis factor-alpha (TNF-a) is the third possible mechanism. The demyelinating effects of TNF-a depend on the presence of microglia cells and macrophages and are mediated through the apoptosis of oligodendrocytes.

A fourth mechanism is that oligodendrocytes can be destroyed directly by activated cytotoxic T-lymphocytes (CD4+ T-cells). Some data suggest that the target antigens for cytotoxic T-cell reactions are stress proteins expressed locally in the CNS. These stress proteins are expressed as part of an endogenous protective programme for oligodendrocytes. However, they can also be recognized by cytotoxic T-cells resulting in progressive destruction.

Demyelination may also be induced by direct oligodendrocyte injury. Virus infection of oligodendrocytes in experiments with animals leads to demyelination.

Just as the pathology varies, demyelination can be due to various causes. Although CPM is widely held to be associated with rapid correction of hyponatraemia and is thus iatrogenic (Laureen and Karp 1997), it has also been reported in patients with severe burns who are hyperosmolar (McKee et al. 1988), following liver transplantation (Murdoch et al. 1995), in hyperemesis gravidarum (Olinlo et al. 1997), and folate deficiency (Ramaekers et al. 1997). Furthermore, it has been described in patients with normal sodium levels (Mast et al. 1995), following slow correction of hyponatraemia (Pradhan et al. 1995) and following correction of hypoglycaemia (Rajbhandari et al. 1998).

This patient developed symptoms and signs following a chronic history of polydipsia with an acute exacerbation at the time of the illness. Random urine osmolality was 385 mosm/L. It is possible that hyponatraemia may have contributed to his symptoms. However, despite repeated checks of his plasma sodium on days 0, 1, and 19 of his illness, we did not document hyponatraemia. Furthermore, we did not restrict oral fluids during admission nor treat him with intravenous fluids.
Polydipsia has been known to cause fluctuations in osmolality (Vieweg and Karp 1994). The brain is capable of both an immediate and delayed response to changes in serum osmolality (Brown 2000). Movement of electrolytes out of brain cells occurs in the first 48 hours. If the serum abnormality persists other organic osmolytes move into the extracellular space to help make the brain more isoosmolar with respect to serum. Low concentrations of organic osmolytes, creatinine, and amino acids ‘shrink’ the brain. Oligodendroglial cells appear to be especially vulnerable to the physical stress that occurs with ‘shrinkage’.

Infective agents have been linked to demyelinating diseases. Herpes simplex virus is associated with demyelination and acute disseminated perivenous encephalomyelitis is reportedly of viral aetiology (Allen and Kirk 1992). Localized brain-stem involvement is rare in encephalitis but may occur both with primary and postinfectious diseases. Varicella virus, mumps, and Epstein–Barr virus have been implicated. Listeria monocytogenes rhomboencephalitis and Borrelia burgdorferi focal encephalitis are rare, but treatable, examples (Frith et al. 1987, Bingham et al. 1995). This patient had a mild coryzal illness before the onset of CPM but no infective cause was found in his urine, blood, or CSF.

Other encephalopathies have been compared to CPM. Although clinical features are similar in subacute necrotizing encephalomyelopathy (Leigh disease) the histology is different and anatomical involvement is wider (Faris and Fleckenstein 1970).

Our patient’s brain MRI findings were consistent with the diagnosis of CPM. Acute disseminated encephalomyelitis (ADEM) was the differential diagnosis. However, brain MRI showed no other typical areas of abnormal white-matter signal and there was no evidence of intrathecal immunoglobulin G synthesis. Cytokines, antibodies, and other inflammatory markers were not measured. It remains possible that the pathology in this case was a focal pontine inflammatory demyelination analogous to ADEM.

MRI has been shown to be a sensitive investigation in children for detecting the focal pontine demyelination characteristic of CPM (Tabarki et al. 1997). The typical findings of CPM, as illustrated in this patient, can be seen on MRI after approximately 1 week of the clinical symptoms appearing. As there was sparing of the raphe area, the MRI findings were not entirely typical. MRI has made it possible to diagnose CPM more frequently and in less severely affected patients and histological diagnosis is no longer necessary. This may be the reason that sparing of the raphe area has not been reported previously.

Previous reports have shown that there is no connection between the extent of the lesion on MRI and either the clinical severity at presentation (Korogi et al. 1993) or the clinical course subsequently (Menger et al. 1993). Reports on the relation between clinical resolution and MRI resolution differ. MRI changes can improve (Ho et al. 1993) or may parallel clinical recovery (Ragland et al. 1989). However, clinical recovery may predate MRI recovery by several months.

**Figure 2:** Coronal $T_2$-weighted image demonstrating areas of high signal in basis pontis extending into midbrain.

**Figure 3:** Axial $T_1$-weighted image through basis pontis showing bilateral symmetrical hypointense areas centrally in pons characteristically sparing ventral lateral tracks.
(Martin and Young 1995, Maddison et al. 1996). Also, residual changes have been shown on MRI scanning after full resolution of the clinical symptoms (Yuh et al. 1995), and it has been suggested that these changes may be due to fibrillary gliosis (Thompson et al. 1998).

Steroids have been used in the management of CPM by some (Nakano et al. 1995), but have been found unhelpful by others (Laureno and Karp 1997). Theoretically, immune modulation may be helpful in CPM, as activated glial, inflammatory, and T-cells are probably involved, and the myelinotoxic processes are likely to be similar to immune-mediated demyelination (Brown 2000). In some of the case reports above it is not clear if steroids were given specifically for the management of the condition. It was clearly useful in our patient and we are not aware of any randomized controlled study looking at the role of steroids in CPM.

In summary, we have reported a 7-year-old male who presented with acute clinical and neurophysiological features of CPM. MRI showed changes consistent with this diagnosis and he was treated with oral prednisolone. We identified neither electrolyte imbalance, chronic debilitating disease, nor any infective agent, which may have played a role in causing his illness. He responded very well to oral steroid therapy with nearly complete recovery at 2-weeks post illness onset.

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References