Osmotic demyelination syndrome in two haemodialysis patients

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ABSTRACT

Osmotic demyelination syndrome is a well-known clinicopathologic entity characterised by oedema and demyelination in the pons and extrapontine regions, the aetiology and pathogenesis of which remain unclear. Renal failure patients on haemodialysis are at increased risk due to both the renal failure and the osmotic changes haemodialysis induces.

We report two cases of patients with motor symptoms suggestive of an extra-pyramidal disorder. Both were diabetic with renal failure and were receiving haemodialysis regularly three times a week. Brain magnetic resonance in both patients revealed bilateral high signal intensity at the lentiform nucleus on the T2-weighted and fluid-attenuated inversion recovery images with decreased signal intensity on the T1-weighted images. There was no involvement of the pons. These findings were characteristic of osmotic demyelination syndrome. This is an unusual form of presentation of this syndrome; the lesions are exclusively in an extra-pontine location. One case was treated with steroids and had a favourable evolution with clinical improvement and complete resolution of the brain lesions. The other was treated symptomatically with levodopa-carbidopa and we have no follow-up data since the patient systematically refused both treatment and further neurological re-evaluation.

Although osmotic demyelination syndrome is rare in dialysis patients, this is a risk population for its development. Nephrologists should be aware of its existence and consider it in the differential diagnosis of any dialysis patient who newly appears with sudden/progressive neurological symptoms. In this paper we describe the clinical features of the patients, present the brain magnetic resonance findings of these cases and include a review of the relevant literature on this subject.

Key-Words:
Extra-pontine myelinolysis; haemodialysis; osmotic demyelination syndrome.

INTRODUCTION

Central and peripheral nervous system disorders are fairly common in end-stage renal disease patients on haemodialysis (HD)¹,². The introduction of dialysis has led to a marked reduction in the incidence of metabolic complications traditionally referred to as uraemic encephalopathy which arise from untreated or undertreated renal failure. Other disorders stem from long-term dialysis therapy, “dialysis-dependent encephalopathy” or from the renal replacement therapies themselves, such as dialysis disequilibrium syndrome and dialysis dementia²,³.

Osmotic demyelination syndrome (ODS) is a well-known demyelinating disorder known to involve both pontine and extra-pontine central nervous system structures⁴,⁵. It is usually related to rapid correction of serum sodium in hyponatraemic patients but it has been repeatedly described in association with end-stage renal disease⁶-⁸.
We report two cases of ODS in two patients receiving HD in which the neurological presentation was extra-pyramidal symptoms and in which the affected areas of the brain were the basal ganglia, without involvement of the pons. This is a rare presentation of this syndrome that has only been reported in sporadic cases.\textsuperscript{9-12}

Since dialysis patients are a risk population for the development of ODS, nephrologists should be aware of its existence and consider it in the differential diagnosis of any dialysis patient who newly appears with sudden/progressive neurological symptoms.

\section*{CASE 1}

A 57 year-old male patient was admitted to the emergency room (ER) at the end of November 2006 with progressive symptoms of muscle weakness and marked bradykinesia which had started one week previously. Past medical history was significant for hepatitis C with positive viral replication (diagnosed 3 years before), severe hypertension and diabetes type 2 (diagnosed 4 years before) with associated diabetic retinopathy and diabetic nephropathy (diagnosed by kidney biopsy) leading to end-stage renal disease. He had been on HD, 4 hours thrice a week, for about 7 months. For the previous 2 months he had been dialysed through a central venous catheter. He was well adapted to dialysis treatments and there had been no significant interdialytic events in the past months. Records from the HD centre for the previous 3 months revealed mean haemoglobin of 11.4g/dL, mean Kt/V and URR of 0.86 and 50\% respectively, showed no significant pre/post dialysis sodium imbalances, mean albumin of 31g/l and mean HgA1c of 5.5\%.

Neurological examination revealed an alert, cooperative and oriented patient with slightly depressed mood. He had fixed facial expression and dysarthria with hypophonia. Ocular movements were slow with globally diminished amplitude. Examination of the motor system showed symmetrically increased tone, with cog-wheel rigidity. There was diminished motor strength of the lower limbs (grade 3). Tendon reflexes of the lower limbs were abolished and no Babinski’s reflex was noted. There was marked bradykinesia, for example in rising from a chair, or performing other voluntary or alternate movements.

Patient also had impairment of vibration sense, position sense and pin-prick in the lower limbs, in stocking distribution. Coordination was normal.

Gait was characterised by short, unsteady steps, with slight forward flexion of the trunk and marked difficulty on turning. No involuntary movements were observed.

Initial diagnostic work-up at the ER was inconclusive. There was no significant biochemical abnormality and the cerebrospinal fluid was normal.

Electromyography showed bilateral sensitive-motor polyneuropathy. Head CT scan revealed bilateral and symmetrical diffuse hypo-densities at the lentiform nucleus, without involvement of the thalamus or the caudate nucleus. These lesions were suggestive of extra-pontine myelinolysis. Brain MRI revealed bilateral and symmetrical high intensity signal involving the lentiform nucleus and, to a lesser degree, the head of the caudate nucleus on the fluid attenuated inversion recovery (FLAIR) and T2-weighted images with decreased signal intensity on the T1-weighted images (Fig. 1). Diffusion study showed increased signal compatible with vasogenic oedema. There was no involvement of the pons. These images confirmed the diagnosis suggested by the previous head CT scan of extra-pontine myelinolysis.

The patient was discharged and no specific therapy was initiated. There was no clinical improvement and the patient was subsequently admitted to the neurology ward for further evaluation in January 2007. A brain MRI was similar to the one previously described. Immunology study of antinuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA) and complement and thyroid function tests, cerebrospinal fluid evaluation and study of the mitochondrial respiratory chain for exclusion of Leigh disease were all normal. The patient was started on amitriptilin 10mg b.i.d. and carbidopa-levodopa 125mg t.i.d. and discharged. There was no compliance with the medication and only slight improvement in the motor symptoms. He presently remains on haemodialysis and has refused all further proposals for neurological re-evaluation.
CASE 2

A 66 year-old female patient was admitted to the nephrology ward in February 2007 with progressive neurological symptoms of bradykinesia, gait disturbances, headache and nausea which had begun about one month before.

She had an extensive past medical history of hypertension and diabetes mellitus type 2, diagnosed for about 12 years, with poor metabolic control. Four years before she had suffered a lacunar stroke with resulting neurological sequelae of mild left facial paresis and dysarthria and, more recently, had developed end-stage renal disease due to diabetic nephropathy and had been on HD, 4 hours thrice a week, for about 20 months. She was dialysed through an arteriovenous fistula, was well adapted to HD treatment and there was no record of significant interdialytic events. Records from the HD centre for the previous 3 months revealed mean haemoglobin of 12.1g/dL, mean Kt/V and URR of 1.3 and 68% respectively, showed no significant pre/post dialysis sodium imbalances, mean albumin of 34g/l and mean HgA1c of 7.1%.

Neurological examination revealed an oriented and cooperative patient with depressed mood and hypomimia. Speech was slightly dysarthric and hypophonic. An examination of cranial nerves showed no abnormalities. Motor examination revealed bilateral increased tonus of all segments, with cogwheel rigidity. Motor power was relatively well preserved, but there was bradykinesia, with some slowness and fatigability of alternate movements bilaterally. Tendon reflexes were present and symmetrical, but no Babinski’s reflex was noted. Pinprick, vibration and proprioception were unimpaired, and coordination was normal. The gait was short and unsteady, with slight forward flexion of the trunk, reduced arm swinging and marked difficulty on turning. Postural reflexes were preserved, with patient able to protect herself from falling backward. No involuntary movements were observed.

Subsequent initial diagnostic work-up shed no light on the diagnosis. Erythrocyte sedimentation rate was high (92 mm/first hour) and, except for a slight post-dialysis serum hypoosmolality (pre/post dialysis serum osmolality was 307/267mOsm/kg), biochemistry was normal including pre/post dialysis serum sodium (135/136mEq/L) and normal muscle enzymes. Cerebrospinal fluid examination was normal including cytology, protein electrophoresis, search for oligoclonal bands and serology for toxoplasma, cytomegalovirus and herpes simplex virus 1. Immunological evaluation (ANA, ANCA, complement), tumour markers, serum protein electrophoresis, thyroid and
adrenal function tests, angiotensin-converting enzyme levels and electromyography were normal.

Finally, brain MRI (Fig. 2) revealed bilateral and symmetrical high intensity signal involving the lentiform nucleus and sub-cortical white matter on the FLAIR and T2-weighted images with decreased signal intensity on the T1-weighted images. Diffusion study was inconclusive. There was associated marked cortical atrophy. The images were diagnostic of ODS. The patient was empirically treated with amitriptylin 10mg i.d. and oral prednisolone 1mg/kg/day, 60mg i.d. and subsequently discharged.

An evaluation one month later showed some clinical improvement and corticosteroid reduction was started. Control MRI two months after (Fig. 3) revealed nearly complete resolution of the lesions at the lentiform nucleus. The patient presently remains on haemodialysis and no further neurological revaluations were made.

DISCUSSION

Central pontine myelinolysis (CPM) was first described in 1959 by Adams et al.13 and since then many cases have been reported. The widespread use of CT scan and MRI has made diagnosis easier and it was realised that simultaneous or exclusively extra-pontine involvement might also occur5,14. The definition of CPM broadened and the concept of extra-pontine myelinolysis (EPM) and the encompassing definition of ODS emerged5,8,10, with 10-50% of the patients with pontine myelinolysis also exhibiting extra-pontine lesions4,14,15. These are most frequently located in the midbrain, thalamus, basal nuclei, deep ventricular white matter and cerebellum7.

This syndrome is usually described in association with chronic alcoholism, liver transplantation, hepatic cirrhosis of different aetiologies, pulmonary infections and malignant tumors14. However, chronic hyponatraemia is commonly present in most of the cases and the rapid correction of the imbalance usually triggers the syndrome14.

The association with end-stage renal disease on dialysis was first made by Endo et al.6 in 1981. Later, Tarhan et al.8 described a series of 17 dialysis patients with ODS established on the basis of typical MRI findings. Lesions were located centrally in the pons, medulla oblongata and mesencephalon. In eleven patients (65%) there was involvement of the pons and in five of these the pons was the only site involved while extra-pontine sites only were involved in six patients (35%).
The clinical presentation depends on the affected brain structures. Classically, involvement of the corticospinal and corticobulbar tracts in the pons manifests with dysarthria, dysphagia and psychiatric changes, with consciousness disturbances, spastic quadripareisis and pseudobulbar palsy likely to follow later. Signs and symptoms due to extrapontine myelinolysis are rare (usually masked by the simultaneous involvement of the pons and the predominance of pyramidal symptoms).

In our cases, the selective involvement of the basal ganglia, without involvement of the pons, accounted for the absence of the classical symptoms of ODS and for a clinical presentation dominated by extra-pyramidal, Parkinson-like symptoms and signs. Some neurological findings were related to previous pathology; patient 1 had clinical signs and neurophysiological findings suggesting a sensory-motor polyneuropathy, probably secondary to diabetes and renal failure. Cases of ODS with similar presentations have been reported. Sajith et al. reported a case of a female patient who presented with ataxia and cog-wheel rigidity within two weeks of a rapid correction of severe hyponatraemia caused by Addison’s disease. Brain MRI of this patient showed similar involvement of basal ganglia. We were also able to find reports on three other cases of EPM, following rapid correction of hyponatraemia, with bilateral selective involvement of the basal ganglia documented on MRI, in which the clinical presentation was Parkinsonism. Our cases differ in that the underlying cause of the myelinolysis was probably the osmotic changes associated with HD treatment.

The diagnosis of ODS is established through neuroimaging. CT scan usually shows typical symmetrical hypo-dense areas in the affected locations but MRI is generally superior to CT scan, especially at an early stage, and used to confirm the diagnosis. The presence of symmetrical and hypo-intense lesions on the T1-weighted images that are hyper-intense on the T2-weighted and FLAIR images establishes the diagnosis. Such lesions may not become apparent until after one or two weeks, making early diagnosis difficult. In our cases the symptoms had been evolving for one week and one month in turn, so the brain lesions were already clearly established and visible on both CT scan and MRI.

The pathogenesis of ODS is poorly understood. During chronic hyponatraemia there is a gradual loss of intracellular organic osmotically active particles, which prevent cerebral oedema. As this is a slow process, the brain is then vulnerable to rapid osmotic shifts. An acute increase in serum osmolality leads to brain dehydration, resulting in damage.
to the myelin sheaths and vascular endothelial cells, eventually resulting in vasogenic oedema and leakage of myelin-toxic substances from the vessels, leading to demyelination\textsuperscript{14}. Hyponatraemia, however, does not have to onset in the development of this syndrome; hyponatraemia-free cases have been reported\textsuperscript{16}. In end-stage renal disease patients, it is felt that the rapid osmotic fluctuations resulting from rapid changes in plasma solute levels during and after dialysis may be the most likely explanation for the occurrence of the syndrome\textsuperscript{7,8}. This is compatible with research findings using MRI, documenting an approximately 3% increase in brain volume after HD, related to significant decrease of serum osmolality during the treatment\textsuperscript{17}. In the Tarhan series, only four cases had normal serum osmolality at the time of the episode. In our own cases, only in case 2 were we able to document the presence of significant serum osmolality changes pre- and post-dialysis. Since osmotic changes during dialysis are common, it is not clear why only some patients develop this syndrome. It is felt that the presence of some underlying chronic condition may be an important risk factor\textsuperscript{8}. Both our patients were diabetic and this may have been an important risk factor for the development of the syndrome. In fact, cases of ODS have been reported in association with diabetes, particularly in the context of poor metabolic control\textsuperscript{18}, and eight of the Tarhan\textsuperscript{8} series patients were diabetic.

As to other clinical factors in dialysis patients, in the Tarhan\textsuperscript{8} series, although 9 of the 17 patients had started HD in the previous 6 months, there were patients who had been on HD for several years (1 to 7 years). All patients had undergone an HD session 14 to 24 hours before the appearance of the symptoms.

There is no therapy of choice for ODM. There is some experimental data supporting the use of steroids in the prevention of CPM\textsuperscript{19} and some cases of successful treatment of ODS with steroids have been reported\textsuperscript{10,20}. Regrettably, in the largest series concerning dialysis patients, the authors make no comment on the therapeutic options pursued, focusing instead on clinical and radiological evolution\textsuperscript{8}. In our first case, there was initially an expectant attitude. Later, an anti-Parkinson agent was tried to improve the patient’s symptoms. This was unsuccessful due to patient non-compliance and further treatment options could not be pursued for the same reason. In the second case use of steroids led to clinical and radiological improvement. Since one of the mechanisms that may lead to demyelination could be the release of myelin-toxic compounds due to the endothelial damage induced by osmolar shifts, there is at least a pathogenic basis to the use of steroids\textsuperscript{10}.

Although ODS was initially considered to be irreversible, cases of successful outcomes are increasingly being reported\textsuperscript{14}. In the Tarhan \textit{et al.}\textsuperscript{8} series, in 6 out of 9 patients for which follow-up data was available there was complete clinical recovery and resolution of the MRI lesions and in two patients there was significant improvement with only one patient showing no improvement. The clinical improvement was within the first 5 weeks. The authors raise the possibility that the prognosis of ODS due to HD may be associated with better outcomes than in other clinical settings, because the brain lesions probably represent a combination of oedema and demyelination. A more favourable evolution would be due to the resolution of brain oedema.

\section*{CONCLUSIONS}

Osmotic demyelination syndrome is a differential diagnosis that needs to be considered in HD patients who develop progressive or sudden neurological signs and symptoms. The clinical presentation of ODS may be varied and this diagnosis needs to be considered when there are extra-pyramidal signs and symptoms such as those presented by our cases. Haemodialysis patients may be a group particularly vulnerable to the occurrence of ODS due to the osmotic shifts experienced in dialysis treatment. The presence of diabetes is likely to be an important risk factor for the development of the syndrome. Diagnosis is established through the use of brain MRI and its characteristic findings. Steroids may be helpful in inducing or speeding up clinical recovery. The prognosis of ODS in HD patients is reported to be better than in other clinical settings due to the important component of oedema present in the brain lesions.

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