Parkinsonism and Related Disorders 19 (2013) 709–716

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Review

Movement disorders and the osmotic demyelination syndrome

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ARTICLE INFO

Article history:
Received 9 February 2013
Received in revised form
11 April 2013
Accepted 13 April 2013

Keywords:
Parkinsonism
Osmotic demyelination
Central pontine myelinolysis
Extrapontine myelinolysis
Movement disorders

ABSTRACT

With the advent of MRI, osmotic demyelination syndromes (ODS) are increasingly recognised to affect varied sites in the brain in addition to the classical central pontine lesion. Striatal involvement is seen in a large proportion of cases and results in a wide variety of movement disorders. Movement disorders and cognitive problems resulting from ODS affecting the basal ganglia may occur early in the course of the illness, or may present as delayed manifestations after the patient survives the acute phase. Such delayed symptoms may evolve over time, and may even progress despite treatment. Improved survival of patients in the last few decades due to better intensive care has led to an increase in the incidence of such delayed manifestations of ODS. While the outcome of ODS is not as dismal as hitherto believed – with the acute akinetic-rigid syndrome associated with striatal myelinolysis often responding to dopaminergic therapy – the delayed symptoms often prove refractory to medical therapy. This article presents a review of the epidemiology, pathophysiology, clinical features, imaging, and therapy of movement disorders associated with involvement of the basal ganglia in ODS. A comprehensive review of 54 previously published cases of movement disorders due to ODS, and a video recording depicting the spectrum of delayed movement disorders seen after recovery from ODS are also presented.

Since Adams and Victor's original description of "pontine myelinolysis" in alcoholic patients in 1959 [1], the disease subsequently named "osmotic demyelination syndrome" (ODS) in recognition of the importance of osmotic shifts in its pathogenesis has seen significant changes in diagnosis, course, and outcomes over the past few decades [2,3]. Increasingly common ante-mortem diagnosis after the advent of magnetic resonance imaging (MRI) has led to a revision of long-held concepts about the clinical course and prognosis of this disease. The recognition of osmotic demyelination in locations other than the central pons provided a pathophysiologic basis for the frequent association of movement disorders with ODS. These may be present in the acute phase or manifest as delayed sequelae, after recovery from the initial quadriparesis. With increasing survival from acute ODS due to better intensive care, it is likely that more delayed movement disorders will be seen as sequelae [4]. This review describes the epidemiology, clinical features and prognosis of movement disorders due to ODS in the modern era.

1. Epidemiology and pathophysiology

Hitherto thought to be uncommon, ODS is increasingly reported today, and has accounted for 0.4–0.56% of admissions to neurology services at tertiary-care referral centres and 0.06% of all admissions to the medical service of a general hospital [4–6]. Clinically recognised ODS may be on the rise possibly due to the inability of some patients to tolerate rapid increase in sodium levels [2]. Magnetic resonance imaging (MRI) has enabled ante-mortem diagnosis of ODS, and has expanded its clinical spectrum with detection of many mild, atypical or asymptomatic cases [7–11]. Recent data suggest that ODS is under-diagnosed: 0.3–1.1% of consecutive unselected autopsies showed evidence of unsuspected CPM and the proportion was as high as 9.8–29% in liver transplant recipients and 9.5% in asymptomatic patients with chronic liver disease [12–17]. Autopsy findings and retrospective clinical correlation, as well as studies in living patients using MRI suggest that many, if not most, cases of ODS are clinically asymptomatic, possibly due to the small size of the lesion [2,12,13,18,19]. Thus the true incidence of ODS is unknown: it has been suggested that this rate may be most accurately estimated by autopsy series [13]. The fact that ODS, despite the striking pathological abnormalities seen, was not recognised before the 1950s suggests that it is an iatrogenic disease: the consequence of the widespread use of intravenous fluid therapy at that time following the introduction of plastic tubing [16,20].

Recent evidence suggests that the distinctive clinical, pathological, and radiological features of ODS may not be as characteristic as once believed, and that the clinical syndrome of ODS may be expanding to include a wider variety of patients [16]. Central pontine myelinolysis (CPM) and extrapontine myelinolysis (EPM) are but two

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http://dx.doi.org/10.1016/j.parkreldis.2013.04.005

aspects of the same disease. Initially considered a distinct entity from CPM, EPM is now well-recognised as the manifestations of ODS occurring in the brain in locations other than the pons. CPM and EPM have the same pathology, associations and time course but show differing clinical features [20]. Although the classic description of ODS includes the central pontine myelinolytic lesion affecting the transverse pontocerebellar fibres and the long rostrocaudal tracts [21], histological examination failed to show a pontine lesion – hitherto the sine qua non of ODS – in 21% of cases of ODS. Extrapontine sites were involved in 53% of patients in the same autopsy series [22]. These involve predominantly subcortical grey matter nuclei, rather than white matter tracts, and include the cerebellum, putamina, caudate nuclei, thalami, lateral geniculate bodies, and fronto-temporal cortex or subcortical white matter. Other locations include the cerebellar peduncles, fornix, hippocampi and external capsules [2,5,7,21,23–25]. Initial reports found the cerebellum to be most frequently involved (33–55%), followed by the thalami and striatum (34% each) which characteristically spares the globus pallidus although rare cases of presumed myelinolysis restricted to the pallidum have been reported [2,7,22,23,26,27]. Recent papers have highlighted the high incidence of striatal lesions in ODS (76–100%) which may be more common than pontine involvement [5,6]. This topographical localisation is responsible for the clinical syndrome in the individual patient, and is useful to make a diagnosis. A variety of movement disorders result from striatal involvement in ODS [2,5,22–24] (Table 1).

Early reports stressed the rarity of EPM: in many series, as few as 10% of patients with CPM had concomitant EPM [15,17,20,23,28]. However, in other published series, the proportion of EPM in ODS detected on imaging or at autopsy varies from 22 to 80% [2,5,7,12,19,22]. In specific situations, for example liver transplant recipients, EPM probably occurs in a higher proportion of patients than is currently recognised, but is not adequately investigated. It may be responsible for many cases of "acute encephalopathy" following liver transplantation, which are not adequately investigated and no definite cause is found [7]. Similarly, presentation of EPM as a diffuse encephalopathy may lead to confusion with persistent hyponatraemic encephalopathy, and thus to its underdiagnosis. Progression of CPM to involve extrapontine locations on subsequent MRI or autopsy has also been demonstrated [29]. The high incidence of EPM in recent studies has been attributed to better quality MRI, use of diffusion-weighted imaging, or to the fact that MRI done later in the course of the illness would detect more lesions [5].

ODS occurs in the setting of significant medical illness: hyponatraemia was associated with 21.5% of all ODS cases reported between 1986 and 2002 with 39% were associated with alcohol use [2,18]. Myelin destruction follows osmotic stress resulting from a failure to compensate for rising plasma tonicity: oligodendrocytes are most susceptible to physical damage and triggering of apoptosis following shrinkage [7,20,22]. The end result is circumscribed spheroidal areas of demyelination, loss of oligodendrogliocytes, and astrocytic and microglial hyperplasia without inflammation or destruction of neuronal bodies or axons [2,7,9,10,17,19,23,29]. The predilection for certain areas such as the central pons may be due to the inflexible "grid-like" arrangement of oligodendrocytes in these regions, rendering them prone to osmotic damage during electrolyte correction [5,30]. ODS is also more common in sites where grey and white matter interdigitate, and may be due to the chemical effect of endothelial myelinotoxic factors entering the more vascular grey matter from blood (particularly after correction of dyselectrolytaemia as the blood–brain barrier is often disrupted at this time) [11,18,26,28,31] or the mechanical effects of vasogenic oedema or rapid local shifts in osmolarity as ions diffuse across the blood–brain barrier [7,17,24,28,29]. Detailed discussions of factors predisposing to ODS and pathogenesis are available [2,6,7].

2. Movement disorders due to ODS

Clinical or radiologic evidence of neurologic damage due to ODS begins 0.5–7 days after osmotic shifts occur, but may be delayed by as long as 16 days [19,23,31,32]. Symptoms may be mild and a high degree of suspicion is necessary to make the diagnosis [11]. Patients generally – but not in all cases – exhibit a biphasic course in which the first set of symptoms are due to a nonlocalising encephalopathy due to hyponatraemia, and a period of relative improvement (the "lucent interval") lasting one to seven days separates this from the subsequent development of ODS [5,6,19,22,29,33]. The disease has been characterised as a prominent neuro-behavioural disorder due to white matter disease in the pons and elsewhere in the brain [2]. CPM is classically associated with severe tetraparesis, bulbar palsy, coma or locked-in state, and less commonly dysarthria, dysphagia, ophthalmoplegia, or facial paresis [7,8,10–12,17,23,26,34]. The varied topographic localisation of lesions in EPM leads to many different clinical symptoms: altered consciousness, confusion, emotional lability, ataxia, tremor, myoclonus, akinetic mutism, catatonia, dysautonomia, quadriparesis and others with later progression to dystonia, choreoathetosis or parkinsonism which is often poorly responsive to levodopa (Table 2) [2,15,16,19,20,35–39].

Early reports stressed the rarity of extrapyramidal symptoms in ODS, often thought to be masked by corticospinal or brainstem dysfunction, but noted delayed development of tremor, rigidity, bradykinesia, dystonia, choreoathetosis and released reflexes which manifested 10–150 days after ODS begins [20,23,39,40]. Such delayed clinical features are due to ineffective neuronal reorganisation or repair, and may be progressive and refractory to treatment [19,20,35,36,38,39]. These delayed movement disorders may be analogous to delayed dystonia seen with static encephalopathy, and are likely due to neuronal reorganisation with new synaptic connections, delayed death of affected neurons, denervation supersensitivity, trans-synaptic degeneration of neural structures or ongoing myelinolysis [39]. Patients may evolve through a variety of clinical features: from the initial spastic tetraparesis to an akinetic-rigid state to choreoathetosis or dystonia (Video) [7,20,39,41].

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.parkreldis.2013.04.005.

However, extrapyramidal syndromes are now well recognised as common early manifestations of ODS: 44–50% of patients with ODS had parkinsonism at onset, and a further 16% developed delayed symptoms – either parkinsonism, choreoathetosis or dystonia [5,6]. Hypokinesia, cogwheel rigidity and tremor were present with varying combinations and severity. Tremor has been reported in 33% of all cases of ODS [11], and an anecdotal report of cortico-basal syndrome is available. The latter patient presented with asymmetric cogwheel rigidity and bradykinesia with ideomotor apraxia and pyramidal signs, but with only CPM on MRI. The authors were unable to explain the presence of cortical signs or continued progression with a single pontine lesion [38]. Generalised dystonia due to striatal myelinolysis has been reported in patients with hypoadrenalism due to sellar tumours [42]. Akinesia, catatonia, encephalopathy with altered consciousness, opsoclonus, emotional lability, and gait disorders have also been attributed to striatal involvement in other reports [2,15,16,19,20,37–39]. Due to the combination of hypo- and hyper-kinetic movement disorders seen in EPM it has been postulated that striatal lesions result in variable disruption of both direct and indirect striato-pallidal pathways. Both types of movement disorders can be seen due to alterations in the rate or pattern of activity in thalamic, pallidal, subthalamic or cortical neurons [20].

EPM is a rare cause of secondary parkinsonism, which is thought to result from a relative dopamine deficiency due to reduction of