Case Report

Progressive cavitating leukoencephalopathy: Case report of a rare childhood onset neurodegenerative disease

Minal V Kekatpure, G A Karthik[1], Venkatraman Bhat[1]

From Department of Neurology, Division of Pediatric Neurology, and [1]Department of Radiology, Narayana Hrudayalaya Multispecialty Hospital, Mazumdar Shaw Medical Center, Bengaluru, Karnataka, India

Correspondence to: Dr. Minal V Kekatpure, Department of Neurology, Narayana Hrudayalaya Multispecialty Hospital, Mazumdar Shaw Medical Center, Narayana Health City, 258/A, Bommasandra, Hosur Road, Anekal Taluk, Bengaluru - 560 099, Karnataka, India. E-mail: minal.kekatpure.dr@nhhospitals.org

Received – 30 June 2014 Initial Review – 21 July 2014 Published Online – 05 August 2014

Abstract

The leukoencephalopathies with cystic changes form a distinct subtype of childhood onset neurodegenerative disorders. This group has heterogeneous etiological differentials that primarily include mitochondrial disorders, some leukodystrophies and central nervous system infections. We report this case of a 17-month old girl who presented with seizures, episodic encephalopathy, elevated blood lactate level and lactate peak on magnetic resonance spectroscopy, a typical imaging picture noted on cranial magnetic resonance imaging and absence of deletions or duplications of mitochondrial deoxyribonucleic acid. Progressive cavitating leukoencephalopathy (PCL) is a recently described entity with only a few cases reported so far. We report the first case of PCL from India. Accurate diagnosis can be made, not only, by the presence of typical clinicoradiological findings of PCL, but also by the awareness of, and, ruling out of, the various other differential diagnoses that are discussed in detail below.

Key words: *Episodic encephalopathy, Elevated lactate, Progressive cavitating leukoencephalopathy*

The childhood onset leukoencephalopathies have a heterogeneous etiology. Leukoencephalopathies with cystic changes are a distinct subgroup; that have been characterized in the recent years by their typical radiological and clinical findings [1,2]. Naidu et al. described a series of 19 patients from 16 families with episodic acute clinical deterioration associated with focally enhancing white matter (WM) lesions on the cranial magnetic resonance imaging (MRI) that progressed to multifocal cystic degeneration without any identifiable cause. Early lesions predominantly affected corpus callosum (CC), centrum semiovale (CSO), deep cerebral WM with or without the involvement of the cerebellum and the spinal cord. Later after repeated episodes, areas of tissue loss coalesce with older lesions to form larger cystic regions in brain and spinal cord. Gray matter is usually spared until the later stages. Eventually spasticity, seizures, dementia, vegetative state and death ensues. This clinical course may vary from rapid deterioration to prolonged periods of symptom stability. Familial occurrence and consanguinity in some families suggested an autosomal recessive inheritance. This entity was described as progressive cavitating leukoencephalopathy (PCL) in view of its unique clinical and radiological features with no apparent identifiable etiology [3].

CASE REPORT

A 17-month-old female child born of third degree consanguineous parentage was brought for evaluation of intermittent episodes of acute encephalopathy. The child had been well until 8 months of age, when she suddenly became ill with extreme irritability, inconsolable cry alternating with drowsiness and lethargy. She was hospitalized and managed as acute encephalitis. Hematological, biochemical and septic work up, as well

as cerebrospinal fluid (CSF) study were unremarkable at this time; except for significant lactic acidosis (blood lactate was 10.5 mmol/L; normal range up to 2 mmol/L). Subsequently, after this episode, her development plateaued. At 15 months, symptoms recurred in the form of a shrill cry, recurrent arching of the body, punctuated by spells of lethargy and drowsiness, which resolved spontaneously over 2 days. After this episode, the child was noted to have poorer visual responses. At 17 months, child was able to stand with support but unable to walk, sat unsupported and had a vocabulary of two single words (amma, appa). Examination revealed a normal head circumference (HC - 47.1 cm), no dysmorphic features, bilateral corticospinal signs, and bilateral optic atrophy on fundus examination.

Laboratory investigations, including creatinine phosphokinase, and CSF study were unremarkable except for an elevated blood lactate (7.5 mmol/L). Neurophysiologic studies, including electroencephalogram, nerve conduction study and needle electromyography were normal. Tandem mass spectrometry, specifically to rule out glycine leukoencephalopathy, was within normal limits. Study of the mitochondrial genome did not show deletions or duplications.

Contrast-enhanced cranial MRI showed WM T2 hyperintensities with fluid-attenuated inversion recovery hypointensities in bilateral periventricular areas, adjacent bilateral CSO and CC (Fig. 1a and b). Lesions were T1 hypointense in T1W images (Fig. 2a). CC lesions showed restricted diffusion, and low apparent diffusion coefficient values probably due to active demyelination in these regions (Fig. 3a and b). There was no significant diffusion restriction in periventricular lesions and CSO. Subcortical U fibers were entirely spared. Basal ganglia, thalami, brainstem, cerebellum and upper cervical cord were unaffected. Gadolinium-enhanced images showed patchy enhancement in the lesion of left CSO and intense areas of focal homogeneous enhancement in callosal lesions (Fig. 2b). Magnetic resonance spectroscopy (MRS) showed elevated lactate, low N-acetylaspartate and choline levels in cystic areas of WM lesions (Fig. 4).

The age of onset, parental consanguinity, episodes of acute unexplained encephalopathy, progressive neurological deficits (in this case slowing of development and visual impairment), typical MRI and

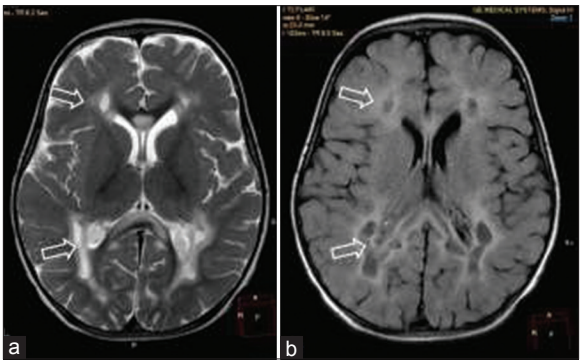

Figure 1: (a and b) Magnetic resonance imaging findings showing features suggestive of progressive cavitating leukoencephalopathy. (a) Axial T2 and (b) fluid-attenuated inversion recovery (FLAIR) images showing bilateral T2 hyperintense lesions in periventricular areas, adjacent bilateral centrum semiovale and corpus callosum (open arrows). FLAIR image differentiates cystic component from edema

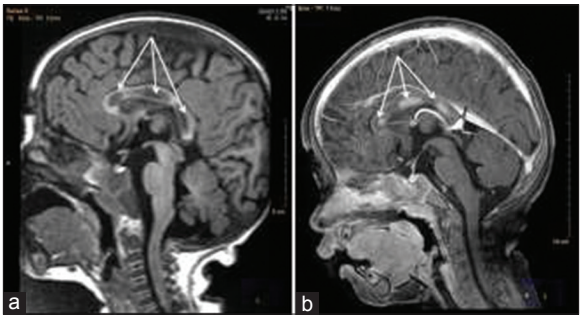

Figure 2: (a and b) Magnetic resonance imaging findings showing features suggestive of progressive cavitating leukoencephalopathy. Sagittal T1 (a) and gadolinium enhanced (b) images demonstrating hypointense corpus callosal lesions (arrows) showing homogeneous & solid enhancement on intravenous gadolinium

MRS picture, normal CSF and metabolic studies and significant lactic acidosis with a normal mitochondrial genomic study lead to diagnosis of PCL in this case.

DISCUSSION

Neurological deterioration with cystic leukodystrophic changes should preempt differentials of megalencephalic leukoencephalopathy with subcortical cysts (MLC), Alexander's disease, acute disseminated encephalomyelitis (ADEM), autosomal dominant acute necrotizing encephalopathy (ADANE), hemophagocytic

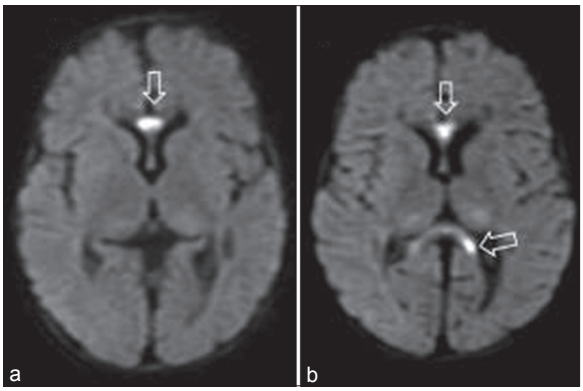

Figure 3: (a and b) Magnetic resonance imaging findings showing features suggestive of progressive cavitating leukoencephalopathy. Corpus callosal lesions showed restricted diffusion and low apparent diffusion coefficient values probably due to active demyelination in these regions (open arrows). Also noted was that, there was no significant diffusion restriction of lesions in the periventricular area or in the centrum semiovale and there was sparing of subcortical U fibers. The basal ganglia, thalami, brainstem, cerebellum and upper cervical cord were uninvolved

lymphohistiocytosis (HLH), progressive vacuolating glycine leukoencephalopathy (PVGL), progressive cystic leukoencephalopathy and mitochondrial cytopathies specifically Leigh's syndrome.

In this case, the typical constellation of findings described above was suggestive of the original definition of PCL by Naidu et al. [3] than of a progressive cystic leukoencephalopathy [4]. Our case demonstrated some variation from classical features of PCL. Whereas, cystic changes in CC are a typical feature of PCL, our patient demonstrated solidly enhancing T1 hypointense lesions in CC. In view of diffusion restriction and intense enhancement, these lesions were probably active, and, were likely to show cystic evolution over time.

ADEM is characterized by elevated CSF protein, involvement of both gray and WM lesions, with contrast enhancement of the active lesions [5]. Cystic changes on MRI are unusual in ADEM. ADANE can mimic acute encephalopathic phase of PCL, however, neuroimaging shows predominant thalamic and brainstem involvement with elevated CSF protein; all of which were absent in our case [6]. Normal

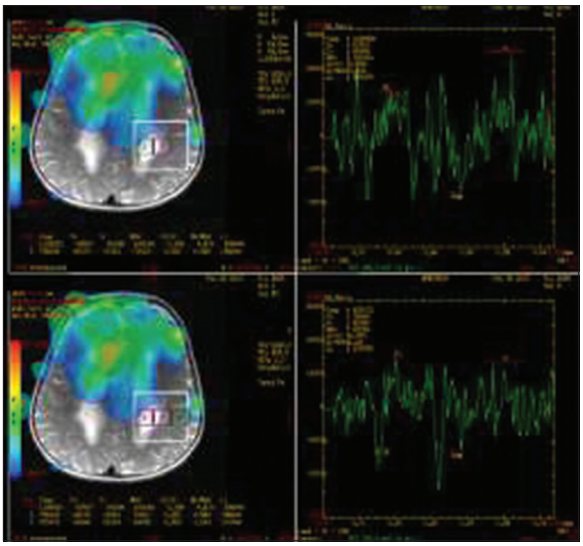

Figure 4: Magnetic resonance spectroscopy (MRS) findings showing features suggestive of progressive cavitating leukoencephalopathy. MRS showed elevated lactate, low N-acetyl aspartate and choline levels in cystic areas of the white matter (WM) lesions. Necrotic regions showed lactate levels of 30600 (More than 1.75 that of normal brain regions). Necrotic regions showed Ch/Cr of 0.789, Ch/N-acetylaspartate (NAA) of 0.674 as against Ch/Cr of 0.955, Ch/NAA of 1.244 in the adjacent normal brain. Transition zone had nearly similar Ch/Cr as the adjacent normal brain, whereas Ch/NAA was low in transition zone. Peripheral normal WM showed normal peaks of lactate and minimally reduced levels of choline and NAA

glycine levels on TMS and absence of other typical features ruled out PVGL [7]. Lack of macrocephaly excludes leukodystrophies like MLC and Alexander's disease [8]. HLH has multisystem involvement, hematological abnormalities and meningeal involvement, none of which was seen in this case [9].

In our patient, episodic, acute deterioration without any evidence of preceding brain infections or obvious metabolic stress, normal HC and CSF study rules out all of the above mentioned conditions, with the exception of Leigh's disease, especially COX deficiency and SURF1 mutation [10]. However the study of the mitochondrial genome for common deletions and duplications was unremarkable in this case. Moreover, despite the detection of elevated lactate in Naidu's original series, consistent abnormalities in the metabolic profile, muscle respiratory chain enzymes,

and identifiable mitochondrial deoxyribonucleic acid mutations or deletions were not found [3]; similar to the case we describe here.

A typical case of PCL is characterized by episodic, acute onset of irritability or neurological deficits occurring between 2 months and 3.5 years of age, followed by steady or intermittent clinical deterioration. Clinical course varies from rapid deterioration to prolonged periods of stability, not predictable by clinical picture or by imaging profile. During periods of remission, the patients can recover some skills, although not to the previous levels. Progressive spasticity, dementia, vegetative state, or death ensues between 11 months and 14 years of age [3]. Treatment remains symptomatic and supportive.

CONCLUSION

To conclude, episodic encephalopathy in a child with leukodystrophy and cystic changes, callosal involvement, with focal contrast enhancement on MRI and lactic acidosis or lactate peak on MRS should lead to consideration of possible PCL, after ruling out above mentioned differentials.

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Funding: None; Conflict of Interest: None Stated

How to cite this article: Kekatpure MV, Karthik GA, Bhat V. Progressive cavitating leukoencephalopathy: Case report of a rare childhood onset neurodegenerative disease. Indian J Child Health. 2014;1(2):61-4.