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Case report

Non-progressive leukoencephalopathy with bilateral anterior temporal cysts: a case report and review of the literature

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Abstract

A newly described disease is characterized by anterior bilateral temporal lobe cysts associated with multilobar leukoencephalopathy and a non-progressive clinical course. We report a patient with bilateral anterior temporal lobe cystic changes associated with a non-progressive neurological disorder, microcephaly, spasticity, mental retardation, and sensorineural deafness. From the literature, 12 other patients have shown a similar phenotype. The common neuroradiological findings in these patients have been bilateral anterior temporal lobe cystic changes and non-progressive leukoencephalopathy. By contrast, variability in the clinical phenotype has been observed, ranging from severe neuromotor handicap with mental retardation and microcephaly to spasticity in the lower limbs associated with normal cognitive function. The pathological basis of the defect remains to be defined.

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1. Introduction

Subcortical white matter cysts represent a cardinal neuroradiological marker of leukoencephalopathy with subcortical temporal cysts and megalencephaly [1], which is clinically characterized by normal or nearly normal early development and subsequent slow deterioration with progressive macrocephaly. White matter vacuolization is also observed in the Vanishing white matter disease, whose clinical course may be more progressive with acute psychomotor deterioration [2]. In such conditions, swelling of the white matter with diffuse demyelination is well demonstrated using magnetic resonance imaging (MRI) [1,2]. Subcortical temporal cysts have also been reported in a patient with subacute sclerosing panencephalitis, a progressive disorder related to early measles infection [3].

Moreover, a new nosographic entity has been described in which anterior bilateral anterior temporal lobe cystic

changes are associated with multilobar leukodystrophy and a non-progressive clinical course [4].

The aim of this report is to increase awareness of such new entity describing a patient with bilateral anterior temporal cystic changes, non-progressive leukoencephalopathy, spasticity, microcephaly, and sensorineural deafness. A literature review of similar cases is presented.

2. Case report

A 3-year-old girl was born to healthy and non-consanguineous parents at 35 weeks of gestation. Her birth weight was 2.2 kg (25–50th centile), length 45 cm (25–50th centile), and head circumference (HC) 31 cm (25–50th centile). Her APGAR indices were 7 and 8 (at 1 and 10 min). An older brother was reported to have had delayed psychomotor development during his first year of life. The patient exhibited neuromotor retardation during the first months of her life. At 10 months of age, a neurological examination showed axial hypotonia, lower limb spasticity

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with clonus and Babinski reflex. Dystonic movements were also present. The child was unable to sit, had poor interest in her surroundings and pronounced no words. Around the age of 15 months she started to sit and crawl. The patient first arrived under our care at the age of 19 months. She weighed 10.5 kg (25th centile), length 82 cm (50th centile) and head circumference of 44 cm (<3rd centile). A physical examination showed strabismus, mild axial hypotonia, brisk tendon reflexes at the lower limbs with clonus and a Babinski reflex. Upper limb functions were less impaired. The child was unable to walk and did not pronounce any words. Hematological tests were normal. Blood screening for metabolic diseases, including those for concentrations of very long-chain fatty acids, organic acids, lactate and pyruvate, gave results in the normal ranges. Her leukocyte lysosomal hydrolase activities were normal, as was her urine organic acid profile. Serum and urinary amino acid chromatography proved normal. Cerebrospinal fluid lactate and pyruvate concentrations were normal and no oligoclonal bands were detected. An ultrastructural skin examination proved normal. She had a normal 46, XY karyotype. There was no evidence of congenital infections such as toxoplasmosis, cytomegalovirus (CMV), or herpes. Electrophysiological studies included brainstem auditory evoked potentials, which detected a severe bilateral sensorineural deafness, but somatosensory evoked potentials in her limbs proved normal. Nerve conduction velocities, visual evoked potentials and electroencephalography were also normal. A brain MRI scan (1.5 T) showed patched areas of signal alteration in the white matter of both cerebral hemispheres, mainly involving the parieto-occipital areas, with small and scattered hyperintense foci in the U fibers. Subcortical white matter cystic changes were observed at the tips of both temporal lobes, associated with enlargement of the temporal horn of both lateral ventricles. Infratentorial structures were within the normal limits. There were no signs of white matter swelling or hemorrhage. After gadolinium administration, her brain MRI features were unchanged (Figs. 1 and 2). A computer tomography scan ruled out abnormal intracranial calcifications. At the age of 33 months, her brain MRI and electrophysiological investigations were repeated and found to be unchanged. Magnetic resonance spectroscopic imaging (MRSI) examination was also performed using a 1.5 T scanner (Philips Gyroscan NT system). Before the MRSI acquisition, a set of multi-slice spin-echo images was obtained in transverse plan parallel to the antero-posterior commissure line (TR = 2151 ms; TE = 20.90 ms; slice thickness 5 mm). These MR images were used to select an intracranial volume of interest for spectroscopy centered on the corpus callosum and measuring 90 mm antero-posterior \times 20 mm cranio-caudal \times 90 mm left-right. This included the gray matter (GM) and white matter (WM) of both hemispheres. Two-dimensional spectroscopic images were obtained using a PRESS sequence for volume selection (TR = 2000 ms; TE = 272 ms; 250 \times 250 mm

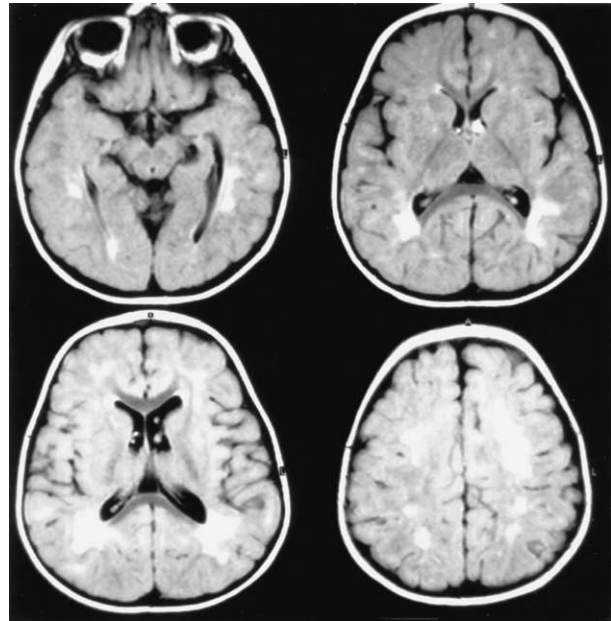


Fig. 1. Serial FLAIR axial images show patchy areas of high signals intensity in the white matter of both cerebral hemispheres, mainly located in the parieto-occipital regions with only minimal involvement of the U fibers.

field of view; 32 \times 32 phase encoding steps; one signal average per step), and raw data were then post-processed as previously described [5]. Proton MRSI results showed a diffuse decrease in the ratio of *N*-acetylaspartate to creatine (NAA/Cr) and increases in the ratio of choline to creatine

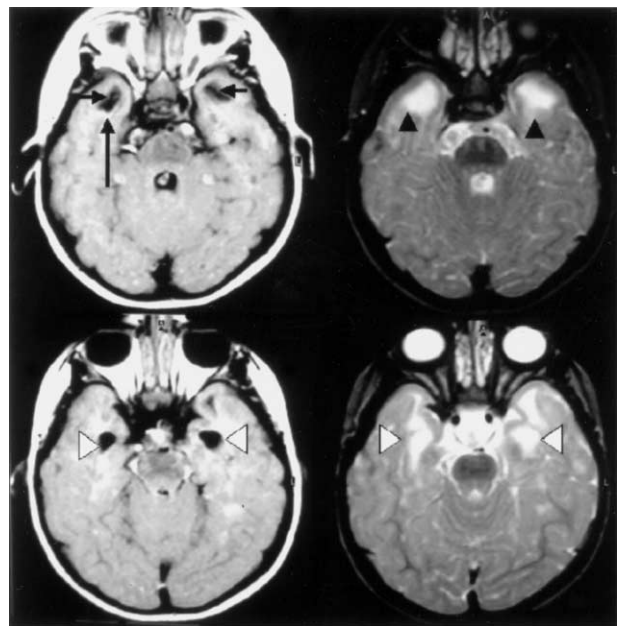


Fig. 2. Serial FLAIR (left row), and T2-weighted (right row) axial images show cystic degeneration (short arrows) within areas of altered myelination in the subcortical white matter of both anterior temporal lobes (black arrowheads). Note that these changes are associated with a thin marginal rim of high signal (long arrow), as well as enlargement of both lateral ventricles (white arrowheads); these signs are consistent with marginal reactive gliosis and parenchymal loss, respectively.

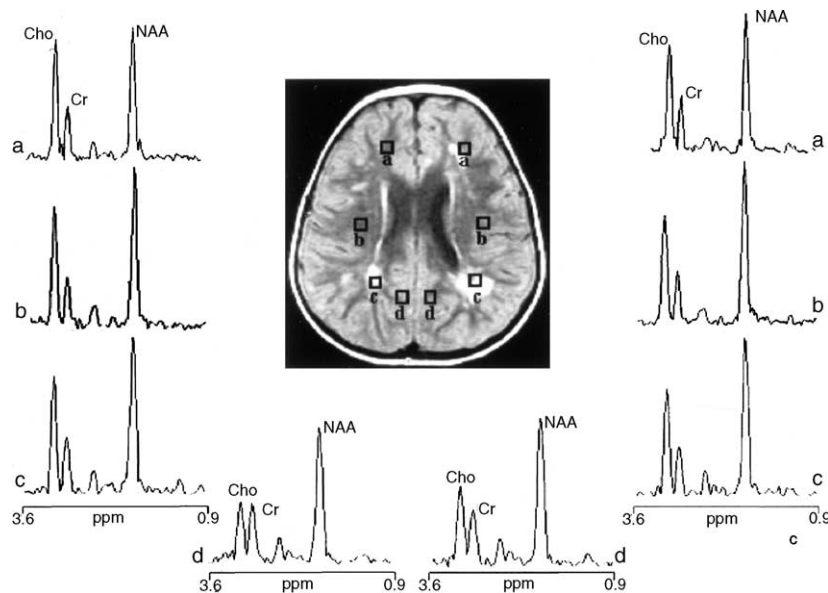


Fig. 3. Conventional FLAIR image and proton MR spectra corresponding to brain voxels located in the frontal WM (a), periventricular WM (b), posterior WM (c) and GM (d) of both hemispheres. Mild decreases in the NAA/Cr ratio and more substantial increases in the Cho/Cr ratios can be seen in symmetrical voxels of the WM of both hemispheres. No abnormalities can be seen in GM voxels.

(Cho/Cr) resonance intensity values in the cerebral WM (Fig. 3). No changes in metabolite ratios were seen in the inter-hemispheric GM.

During a follow-up period of 18 months, the psychomotor development of the child progressed slowly. She walked at 24 months of age, improved her ability to interact with her surroundings, but her intellectual abilities remained poor with severely impaired language functions.

3. Discussion

We report here a child with a non-progressive leukoencephalopathy, microcephaly and sensorineural deafness associated with bilateral anterior temporal lobe cystic changes. The clinical and neuroradiological pictures of this patient can be easily differentiated from those of the most known progressive disorders presenting with white matter cysts: leukoencephalopathy with subcortical temporal cysts and megalencephaly [1], and the vanishing white matter disease [2].

The peculiar clinical and neuroradiological picture presented by this patient is similar to that observed by Olivier et al. [4] in three patients from Turkey, including two siblings, who presented with neuromotor retardation since their first months of life, with spasticity and, in one case, with microcephaly. In all these three patients, MRI scans showed temporal lobe cysts and multifocal lobar white matter changes. The authors considered this disorder to be a possible new entity. Following this report, nine further individuals were described with similar clinical and neuroradiological features [6–10]. Some nosological problems arose with the two siblings reported by Wassmer et al. [8];

in these patients, temporal lobe cysts, leukoencephalopathy, microcephaly, learning difficulties and spasticity were associated with kyphosis, neck stiffness, and dyspraxia. Because limited movements of neck and shoulders, brisk reflexes, and dyspraxia were variably present in their mother, in a cousin and in the mother's father, the authors considered this disorder to be a new entity with a possible dominant model of inheritance. However, a brain MRI scan performed on the patients' mother failed to demonstrate temporal cysts or white matter lesions. For this reason we decided to include these patients in the same group. Sener [10] reported a 5-year-old boy with a non-progressive severe neuromotor retardation characterized by speech delay, dysarthria, and spasticity. His HC was in the normal range. Brain MRI scans showed patchy white matter lesions and cystic degeneration of the temporal lobe tips. The author considered the patient to be affected by a new type of leukoencephalopathy. However, because this clinical and neuroradiological picture overlaps that observed in Olivier's [4] patients, we have included this patient in the same group.

When globally considered, the lesions of all these 13 patients shown by MRI exhibit a common and defined profile represented by non-progressive leukoencephalopathy and bilateral anterior temporal cystic degeneration. The leukodystrophic process is characteristically patchy and not diffuse as observed in leukoencephalopathy with subcortical temporal cysts and megalencephaly [1]. Neither white matter swelling nor calcifications/hemorrhage lesions are present.

Proton MRSI data are available for only one patient described by Battini et al. [9], who found a normal Cho/Cr ratio in the WM and a decrease of this ratio in the GM. Our results here are to some extent different because we

Table 1
Clinical findings of patients with non-progressive leukoencephalopathy and anterior temporal cysts

Clinical features	Olivier et al. (1998)			Deonna et al. (1999)			Gomes et al. (2001)		Wassmer et al. (2001)		Battini et al. (2002)	Sener (2003)	Present case
	Case 1	Case 2	Case 3	Case 1	Case 2	Case 3	Case 1	Case 2	Case 1	Case 2	Case 1	Case 1	Case 1
Early development delay	+	+	+	+	+	+	+	+	+	+	+	+	+
Mental retardation	S	S	S	–	*ND	–	S	S	M	M	S	S	M
Spasticity	+	+	+	+	+	–	+	+	+	+	+	+	+
Extrapyramidal signs	–	–	+	+	NR	NR	–	–	–	–	+	+	–
Speech delay	+	+	+	–	–	–	+	+	+	+	+	+	+
Epilepsy	+	–	+	–	+	–	–	–	–	–	–	–	–
HC at birth	N	N	N	NR	NR	NR	MIC	N	NR	NR	N	N	N
HC in the clinical course	N	N	MIC	NR	NR	NR	MIC	MIC	MIC	MIC	NR	N	MIC
Sensorineural deafness	–	–	–	–	–	–	+	+	–	–	+	+	+

S, severe; *ND, present but not defined if severe or moderate; M, moderate; N, normal; MIC, microcephaly; NR, not reported.

observed a mild decrease in the NAA/Cr ratio and a more pronounced increase in the Cho/Cr ratio in the WM, whereas no metabolic changes were found in the GM (Fig. 3). The decrease in the NAA/Cr ratio suggests axonal damage. The large increase in the Cho/Cr resonance intensity ratio suggests an intense cellular membrane breakdown, possibly due to dysmyelination. Differences in the brain region studied or, more importantly, in the brain metabolism at a given disease stage, may explain this discrepancy in the reports.

From a clinical point of view, some variability is observed in the published reports. Indeed, although an early delay in neuromotor development has been noted, a variable severity in the clinical picture is evident, ranging from patients with severe mental retardation, severe spasticity, dystonia and inability to walk, to patients with mild spasticity and normal cognitive functions (Table 1). These observations led Deonna et al. [6] to assert that these individuals may not represent a distinct entity. Although the clinical course is characteristically non-progressive, it is worth noting that, with the exception of Gomes's patient 1 [7], who showed congenital microcephaly, seven patients had a normal head circumference at birth (data were not available for 5) and three of these developed microcephaly during the first year of life (Table 1).

From a pathogenetic point of view, although an autosomal recessive model of inheritance has been suggested [4], the basic defect of this condition remains to be defined. However, patient 1 of Gomes et al. [7] had laboratory evidence of congenital cytomegalovirus (CMV) infection. Although a possible CMV infection has been ruled out in some of these patients [4,7,9], direct relationship between CMV infection and temporal lobe cysts remains to be established. Barkovich et al. [11] found temporal lobe cysts in four of 11 patients with congenital CMV infection; however, all of these patients had associated brain anomalies,

including dysplastic hippocampi, diffuse cortical dysplasia, focal calcifications and hemorrhage. None of these lesions has ever been reported in patients with non-progressive leukoencephalopathy and bilateral temporal lobe cysts. Of course, it is possible that this peculiar clinical/neuroradiological picture may recognize different pathogenetic mechanisms. In fact, both genetic and infectious causes cannot be ruled out at this stage. Of course, on the basis of the clinical heterogeneity of the reported patients and the possible different pathogenetic mechanisms involved in that disorder, it is likely that the condition might be, in the future, regarded as a syndrome.

In conclusion, we have reported a further patient affected by non-progressive leukoencephalopathy with bilateral anterior temporal lobes cysts. The review of the literature seem to corroborate the hypothesis of a distinct dysmyelinating nosographic entity [7]. However, further investigations are necessary to define pathogenetic mechanisms underlying this disorder and rule out possible relationship with infectious diseases.

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