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Delayed myelination in a rhizomelic chondrodysplasia punctata case: MR spectroscopy findings

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Abstract

Rhizomelic chondrodysplasia punctata is a member of genetic peroxisomal disorders. Delayed myelination, which is probably related to the inadequacy of plasmalogens biosynthesis, is an important feature of this disorder. Direct assessment of neuropathologic aspects of RCDP syndrome such as neuronal degeneration and delayed myelination is possible with MR spectroscopy.

In this report, MR spectroscopy findings (decreased Cho/Cr and increased Ins-Gly/Cr ratios and increased levels of mobile lipids) of a rhizomelic chondrodysplasia punctata case supporting delayed myelination are presented. This is the second report of MR spectroscopy examination of the specific brain metabolic changes associated with rhizomelic chondrodysplasia punctata.

Keywords: Rhizomelic chondrodysplasia punctata; MR spectroscopy

1. Introduction

Rhizomelic chondrodysplasia punctata (RCDP) is a genetic peroxisomal disorder characterized by a deficiency in the biosynthesis of plasmalogens [1]. Acyl-CoA hydroxyacetonephosphate acyltransferase (DHAP-AT), alkyldihydroxyacetone phosphate synthase (alkyl-DHAP synthase), 3-ketoacyl-CoA thiolase and phytanol-CoA hydroxylase are among the peroxisomal enzymes involved in plasmalogen synthesis, and these enzymes have reduced or absent activity in liver, and/or fibroblasts of patients with RCDP [1,2].

RCDP patients clinically present as having a symmetrical shortening of the proximal limbs, contractures of joints, typical dysmorphic facial appearance, cataracts, impaired hearing, and psychomotor retardation [3,4]. Calcified stippling of the epiphyses, shortening of both femora and humeri with epi-metaphyseal widening and coronal clefts in most of the vertebral bodies are the common radiographical anomalies.

White matter abnormalities such as increased signal intensity in the periventricular white matter and centrum semiovale of patients with RCDP are seen on MR imaging studies [5,6]. Delayed myelination, especially in the occipital region was also reported [7]. The number of neurons was found to be reduced in the brains of the RCDP patients at autopsy [4].

To the best of our knowledge, MR spectroscopy findings of RCDP were reported only in one case [4], and this is the second case.

2. Case Report

A 8-month old boy with unresponsiveness to sounds and unability to make eye contact was admitted to the pediatrics clinic. His weight was 5600 g (<3p); length, 58 cm (<3p); and head circumference, 39 cm (<3p, microcephaly). Family history revealed first degree kinship between parents, and death of an 11 months old male child with the same complaints. Physical examination revealed typical facial dysmorphism consisting of a broad nasal bridge, generalized flexion contractures that were more severe in lower extremities, abduction deficiency of hip, hypertelorism, epicantus, bilateral cataracts, impaired hearing, hypospadias,

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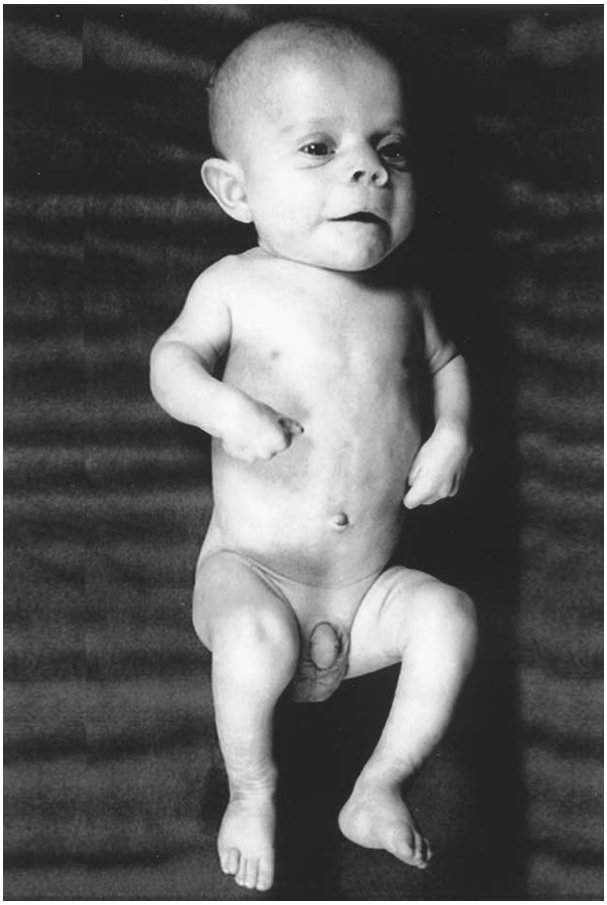

Fig. 1. Photograph of the patient demonstrates typical facial dysmorphism, and generalized flexion contractures.

and high arched palate (Fig. 1). Plain radiography showed symmetrically shortening and metaphyseal widening in humeri and femurs, punctate calcific stippling of joints localized in the knee, contractures of elbow and knee joints, bilateral acetabular dysplasia (Fig. 2). With these clinical and radiologic findings patient was diagnosed as having RCDP.

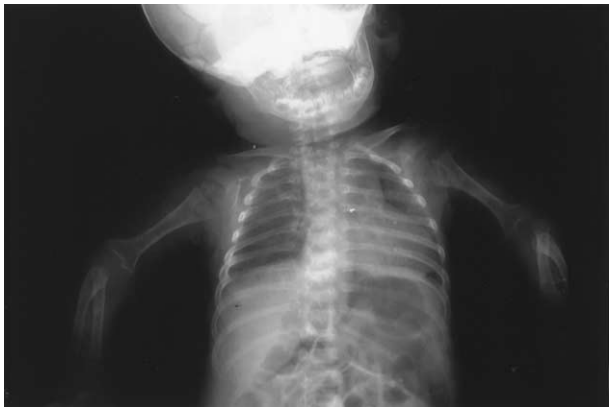

Fig. 2. Plain radiography shows symmetrically shortening and metaphyseal widening of humeri.

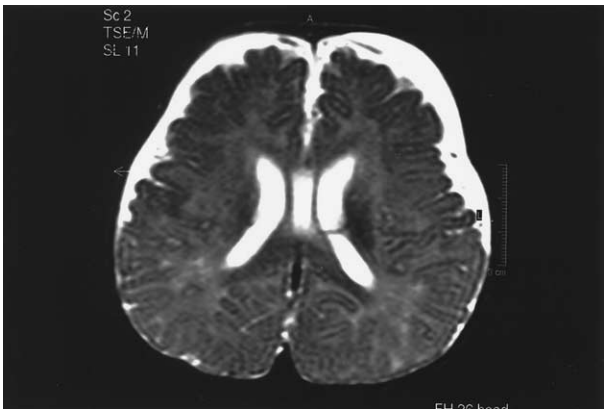

Fig. 3. Axial T2-weighted image (TR: 4530, TE: 110 ms) shows bilateral areas of high intensity in the parieto-occipital regions.

MR imaging and spectroscopy of the brain were performed on a 1.5-T system (Philips, Gyroscan Intera, Netherlands). The patient was sedated. Axial and sagittal T1 weighted images (TR: 560, TE: 15 msec), and axial and coronal T2 weighted images (TR: 4530, TE: 100 msec) were obtained. Also, fluid-attenuated inversion recovery (FLAIR) (TR: 7000, TE: 110, T1:2000) image in the axial plane was obtained. T2-weighted images revealed high signal intensity, symmetrically located in subcortical white matter of the parieto-occipital regions (Fig. 3).

Single voxel proton MR spectroscopy was performed by using the point-resolved spectroscopy sequence (PRESS) (TE: 135 and 31 msec). Proton spectra were acquired, in an 8 cm^3 region of interest placed in the parieto-occipal region (Fig. 4). Localized shimming and optimization of the Gaussian pulse amplitude for maximum water suppression was adjusted prior to acquisition of the spectra. Total study time averaged 25 min. The parieto-occipal voxel location was fixed dependently of the MR imaging information. The spectra were referenced to creatine (2.98 ppm). The signal from choline (Cho), creatine and phosphocreatine (Cr), and N-acetylaspartate (NAA) were integrated. Peak area metabolite ratios (NAA/Cr, Cho/Cr, NAA/Cho, Ins-Gly/Cr) were calculated.

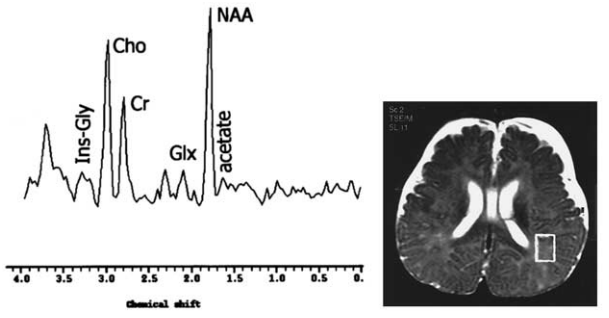

Fig. 4. Proton MR spectrum (TE: 135 msec) obtained from parieto-occipital subcortical white matter.

3. Discussion

Peroxisomes have an important role in humans in ether phospholipid biosynthesis that their deficiency leads to a group of genetic diseases called peroxisomal disorders [8]. RCDP is a genetically heterogeneous, autosomal recessive disorder of peroxisomal metabolism [2,9] in which patients have mutations of the PEX7 gene that is located on chromosomal 6q22-24. This gene is important for the synthesis of specific peroxisomal membrane proteins [10]. The biosynthesis of ether phospholipids starts with the acylation dihydroxyacetonephosphate (DHAP) the enzyme DHAP-AT. The ether linkage is then introduced by the enzyme alkyl-DHAP synthase that catalyzes the exchange of the acyl-chain acyl-DHAP for long chain fatty alcohol. These enzymes are located in peroxisomes [9].

Deficient de novo plasmalogen synthesis in fibroblasts of RCDP patients as a result of low DHAP-AT activity is found, while the very-long chain fatty acid profile, phytanic acid concentration, alkyl-DHAP synthase activity, and peroxisomal 3-ketoacyl-CoA thiolase protein are normal [2,6]. DHAP-AT and alkyl-DHAP synthase initiate the synthesis of plasmalogens, which are major constituents of myelin phospholipids [6]. It was reported that abnormal formation of myelin is probably related to the inadequacy of plasmalogens biosynthesis, which is likely to be due to deficient DHAP-AT activity [6].

NAA is accepted as a neuronal marker, and as such, its concentration will decrease with many insults to the brain. Choline is a constituent of the phospholipid metabolism of cell membranes and reflects membrane turnover. Phosphocreatinine content provides information regarding cell energy metabolism and is associated with the degree of cell viability [11]. By age 5 months, NAA is the largest metabolite peak in the spectrum and the Cho/Cr is reversed compared with ratios in the neonate [12]. A plot of the metabolite ratios versus age showed that NAA/Cr and NAA/Cho ratios increased rapidly in the neonatal period ($\leq$ 1 month), continued to rise during infancy. NAA/Cr ratio in infants and children, and the NAA/Cho ratio in neonates were sensitive indicators of the severity of injury for all causes of brain injury [12]. NAA/Cho ratio is regarded as a significant indicator in the assessment of neuronal activities, because it represents a relative ratio of neuronal density to cellular density. In practice, alterations in the NAA/Cho ratio have been reported to result in findings suggestive of neuronal damage that are consistent with pathologic findings of neuronal disorders [13]. In the autopsy of these cases, the number of neurons was found to be reduced in the brains [4]. NAA/Cr and NAA/Cho ratios were in the normal limits, which indicate that there is no neuronal loss, in our case. When compared to age-matched normal subjects, Cho/Cr ratio in our case was prominently decreased (Table 1). The decrease in choline level supports delayed myelination due to lack of plasmalogens needed for myelin synthesis (Fig. 5).

Table 1
Comparison of metabolite ratios from MR spectroscopy (TE: 31 msec) findings of parieto-occipital subcortical white matter of our case with normal values

Metabolite ratios	Our case	Control value*
NAA/Cr	1.75	1.93 ± 0.39
Cho/Cr	1.08	1.76 ± 0.23
Ins-Gly/Cr	1.67	1.10**

* From reference 17.
**From reference 16.

High levels of Ins-Gly are encountered during neonatal period; nevertheless, it is also reported in patients with peroxisomal disorders together with increases in glutamate (Glx) and lactate which in turn reflect demyelination and glial proliferation in these patients [14–16]. Increased levels of brain lipids detected in patients with RCDP presumably are a result of the deficient DHAP-AT. The ratio of the Ins-Gly/Cr and level of mobile lipids are prominently increased in our case (TE: 31 ms). Lactate was not detected in spectra. Viola et al. [4] reported an increase in mobile lipids in the white matter of their case that could directly reflect the accumulation of long chain acyl CoAs. Very long chain fatty acids were reported to be normal, and also no ketone bodies other than acetate had been detected in their patient. In our case, the acetate was detected in the spectra. We, also, could not find a satisfactory explanation for this increase.

Eventually mental retardation develops in patients with RCDP. It was reported that prenatal diagnosis may reveal a severe DHAP-AT deficiency in the amniotic fluid cells [2]. For that reason, genetic counseling should be offered to the parents especially if they had a previous child with this syndrome as in our case.

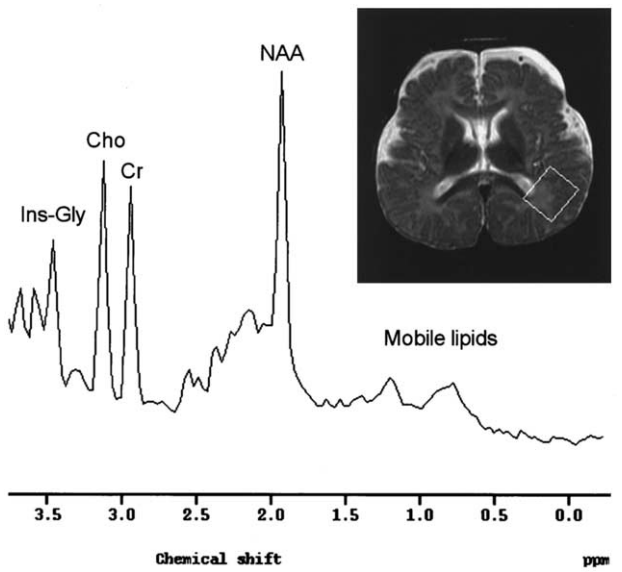

Fig. 5. The spectrum (TE: 31 msec) demonstrates an increase in the Ins-Gly/Cr and mobile lipids, and decrease in Cho/Cr ratios.

MR spectroscopy provides a convenient and safe tool for the direct assessment of neuropathologic aspects of RCDP syndrome such as neuronal degeneration and delayed myelination.

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