Proton MRS shows cerebral lipid accumulation in Chanarin-Dorfman Syndrome

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Target audience: Researchers and clinicians interested in metabolic defects with cerebral involvement or brain metabolism in general.

Introduction

Chanarin-Dorfman Syndrome (CDS, OMIM 275630) is a rare autosomal recessive disorder of neutral lipid metabolism[1], caused by a wide variety of mutations in the gene CGI-58 (comparative gene identification-58) also annotate as ABHD5 (α/β-hydrolase domain-5)[2]. Since the description by Dorfman et al. in 1974[1], only a limited number of patients (<100) has been reported. All CDS patients suffer from congenital ichthyosis, but they show heterogeneous clinical features including myopathy, hepatomegaly, growth retardation, intestinal disease, and cataract [3]. In a minority of patients intellectual disability and neurosensory hearing loss have been described, but no distinct brain involvement has been reported for CDS.

The **aim of this study** was to confirm cerebral involvement in CDS after a coincidental finding of cerebral lipid accumulation in an undiagnosed patient with congenital ichthyosis suspected of having Sjögren-Larsson syndrome (SLS). SLS patients show impaired fatty aldehyde dehydrogenase activity and they have a characteristic "lipid" peak in proton MR spectra of white matter[4].

Methods

Subjects: The first patient was a girl, born premature with typical pruritic ichtyosis on the extremities, trunk and neck and (mild) developmental delay raising a suspicion of SLS. To further establish this diagnosis, FALDH activity was assessed in lymphocytes, and an MRI & MRS examination was performed at an age of 20 months (see below). After normal FALDH activity excluded SLS, CDS was suspected and this diagnosis was confirmed when a ABHD5 mutation was found. Follow-up at the age of three years showed normal motor and cognitive development without any neurological signs. The second patient was a boy already known to have CDS, previously confirmed by genetic analysis of the ABHD5 gene. At the age of seven his development was unremarkable, a previous hepatomegaly was not observed anymore and neurological examination was completely normal. To investigate cerebral involvement in CDS, he also underwent an MRI & MRS examination.

MR measurements: MRS measurements were performed at 3 Tesla (Magnetom Tim Trio, Siemens, Erlangen, Germany) using a 12-channel phased array head coil. Point-resolved spectroscopy (PRESS) was used for single voxel selection. Metabolite spectra were obtained with WET water suppression for short echo and long echo time (TE/Averages=30ms/64 and TE/Acq=136ms/128, respectively). In addition, spectra without water suppression were acquired for referencing (TE/Averages=30ms/4 and TE/Acq=136ms/4, respectively). The short-echo time spectra were obtained using a repetition time (TR) of 5000 ms for patient 1 and a TR of 3000 ms for patient 2. A TR of 2000 ms was used for the acquisition of the long-echo time spectra. For both patients spectra were obtained from voxels of 5.4-6.4 ml white and 4.9-8.7 ml gray matter and for patient 1 also from 5.2 ml of the putamen. Spectra acquired with short echo time were analyzed with the LCModel software[5] using the unsuppressed water signal for quantification of the normal brain metabolites and to determine relative signal intensities of the signal at 1.3 ppm.

Results and Discussion

For both patients MRI images were normal, but the MR spectra showed a remarkable signal at 1.3 ppm (indicated by an asterisk in fig.1), which probably originates from methylene protons of lipids. Although in SLS this "lipid"signal occurs only in white matter with its highest intensity at the occipital trigones, in CDS the "lipid"signal occurs all over the brain. Relative signal intensities in white matter, gray matter, and in basal ganglia were 16,15 and 10, respectively, for patient 1 and 18, 14 and not determined for patient 2. Besides the presence of the high signal at 1.3 ppm the patterns of the rest of the brain spectra were normal at all locations.

CGI-58 acts as co-factor in lipolysis (Fig. 2), and a deficiency in CGI-58 results in accumulation of cytoplasmic triacylglycerol in lipid droplets in multiple cell types[6]. Therefore, it is hypothesized that the MRS lipid peak represents cerebral accumulation of triacylglycerol indicating cerebral involvement in CDS, which has not been described before. Generally lipid accumulation in the brain in metabolic disorders leads to neurological impairment, but the two patients described do not show any obvious neurological signs so far. Therefore, a clear lipid signal in brain MRS in these two patients suggests cerebral involvement in CDS, but further research in a larger group patients is required to draw firm conclusions.

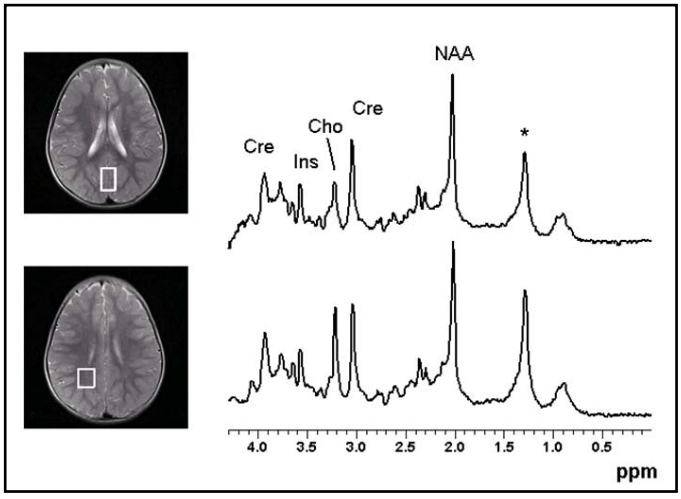

Figure 1. ^{1}H MR spectra obtained from gray and white matter of patient 1.
Both MR spectra (3T, TE=30ms) show a high lipid signal indicated by an asterisk at 1.3 ppm in addition to the normal brain metabolites. NAA, N-acetyl aspartate; Cre, creatine; Cho, choline; Ins, myo-inositol.

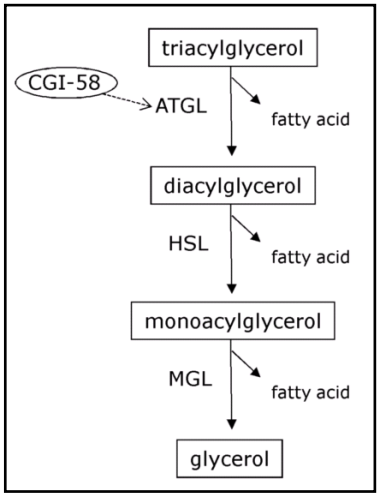

Figure 2. CGI-58 acts as co-factor in lipolysis.
ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase; MGL, monoglyceride lipase.

References: [1] Dorfman ML et al., *Arch Dermatol,* 1974;110(2):261-266, **[2]** Lefevre C et al., *Am J Hum Genet* 2001;69(5):1002-1012, **[3]** Peña-Penabad C et al., *Br J Dermatol* 2001;144(2):430-432, **[4]** Willemsen MA et al., *Am J Neuroradiol* 2004;25(4):649-657, **[5]** Provencher SW, *Magn Reson Med*, 1993;30(6):672-679, **[6]** Williams ML et al., *J Inherit Metab Dis* 1988;11(2):131-143.