Pediatric Neurology 67 (2017) 45–52

Contents lists available at ScienceDirect

Pediatric Neurology

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

Original Article

Variable White Matter Atrophy and Intellectual Development in a Family With X-linked Creatine Transporter Deficiency Despite Genotypic Homogeneity

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ABSTRACT

BACKGROUND: The X-linked creatine transporter deficiency (CRTD) caused by an *SLC6A8* mutation represents the second most common cause of X-linked intellectual disability. The clinical phenotype ranges from mild to severe intellectual disability, epilepsy, short stature, poor language skills, and autism spectrum disorders. The objective of this study was to investigate phenotypic variability in the context of genotype, cerebral creatine concentration, and volumetric analysis in a family with CRTD. **PATIENTS AND METHODS:** The clinical phenotype and manifestations of epilepsy were assessed in a Caucasian family with CRTD. DNA sequencing and creatine metabolism analysis confirmed the diagnosis. Cerebral magnetic resonance imaging (cMRI) with voxel-based morphometry and magnetic resonance spectroscopy was performed in all family members. **RESULTS:** An *SLC6A8* missense mutation (c.1169C>T; p.Pro390Leu, exon 8) was detected in four of five individuals. Both male siblings were hemizygous, the mother and the affected sister heterozygous for the mutation. Structural cMRI was normal, whereas voxel-based morphometry analysis showed reduced white matter volume below the first percentile of the reference population of 290 subjects in the more severely affected boy compared with family members and controls. Normalized creatine concentration differed significantly between the individuals ($P < 0.005$). **CONCLUSIONS:** There is a broad phenotypic variability in CRTD even in family members with the same mutation. Differences in mental development could be related to atrophy of the subcortical white matter.

Keywords: CRTD, *SLC6A8* gene mutation, intellectual disability, magnetic resonance spectroscopy, epilepsy, genotype–phenotype correlation, white matter atrophy

Pediatr Neurol 2017; 67: 45-52

Introduction

The X-linked creatine transporter deficiency (CRTD) caused by a mutation in the creatine transporter gene *SLC6A8* (MIM # 300036) represents the second most common cause of X-linked intellectual disability.[1,2] Intellectual disability associated with speech and behavioral disorders are clinical hallmarks of inherited defects of creatine (Cr) metabolism. To date three gene mutations have been described: two defects of creatine synthesis (arginine:glycine amidinotransferase and guanidinoacetate N-methyltransferase deficiencies) and one defect of creatine transport.[3] X-linked CRTD was first described in 2001 by Salomons et al.[1]

All defects of creatine metabolism are characterized by the depletion of brain creatine, significantly affecting brain development.[3] Creatine deficiency leads to deterioration in energy metabolism, which is also phenotypic for many neurodegenerative and age-related diseases.[4] Recent work suggests that creatine in the central nervous system may also act as a neuromodulator.[5]

Article History:
Received May 11, 2016; Accepted in final form October 8, 2016
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http://dx.doi.org/10.1016/j.pediatrneurol.2016.10.007

The clinical phenotype of CRTD ranges from mild to severe intellectual disability along with speech delay, seizures, short stature, poor language skills, and autism spectrum disorders. Female carriers may exhibit learning disabilities of varying degree and behavioral problems.[1] Accordingly, cerebral 1H-magnetic resonance spectroscopy (MRS) may be a helpful diagnostic tool, as CRTD is characterized by complete absence or dramatic diminution of the creatine peak in brain MRS.[6-8]

Although neuropsychological performance in children and adolescents with CRTD has been described in detail, data on structural correlates of neuropsychological deficits are lacking.[1,9] The question arises whether cognitive deficiencies are related to brain volumes. Especially subcortical white matter is known to play a crucial role in linking the different components of cortical processing networks necessary for cognitive functions.[10,11]

Here we describe five members of a family with X-linked CRTD presenting with variable phenotypes and cerebral creatine concentrations. This is the first analysis of brain structure and genotype–phenotype relations in CRTD.

Patients and Methods

Patient characteristics

Two Caucasian brothers were evaluated for developmental delay, short stature, and epilepsy. Family history revealed short stature in both nonconsanguineous young parents (mother: 158 cm; father: 164 cm) as well as mild learning disabilities in the mother. There was no family history of seizures or other neurological disorders. Consent to neuroradiological procedures was obtained except from the father living apart from the family.

Physical and neurological examinations were performed by an experienced pediatric neurologist. Height was measured with a Harpenden Stadiometer; standard deviation score values for height and body mass index were calculated by applying German reference data.[12]

The mother showed impaired intellectual functioning with reading comprehension difficulties. Nevertheless, she completed secondary school and qualified as childcare assistant. Clinical examination of Child 1 (female; age 18 years) was without abnormal findings except for short stature (height 158 cm; height SDS −1.28; Tanner stage 5).

In contrast, two boys and one girl showed a more complex phenotype. Child 2 (male; age 17 years) was first evaluated at age five years for global developmental delay, short stature (height 97.5 cm; height SDS −4.48), and delayed speech development. Pregnancy and delivery had been uneventful. Motor milestones were normal, but language and cognitive development had been markedly impaired since age two years. Hyperactive and impulsive behavior worsened over time without evidence of regression of cognitive and motor functions. Laboratory investigations for metabolic diseases, molecular genetic studies (karyotype, and molecular analysis of *FMR1, SCNA1A*, and Array-comparative genomic hybridization), and brain MRI did not identify an etiology of growth delay and intellectual disability. At age 6.1 years the boy presented with generalized epileptic seizures. Electroencephalography showed primary generalized irregular spike and waves and polyspikes. Afebrile generalized tonic-clonic seizures increased in frequency to two or more per day.

Child 3 (female; age 14 years) first presented at age four years with short stature (height 93.5 cm; height SDS −2.4), learning difficulties, and language delay. She developed a complex focal epilepsy at age seven years associated with electrographic spikes and irregular spike-wave complexes and a course refractory to pharmacologic treatment. Child 4 (male; age ten years) presented at age three years with global developmental delay, short stature (height 79 cm, height SDS −4.78), and retarded speech development. Like in his elder brother (Child 2), his motor milestones were normal, whereas language and cognitive development had been impaired from age two years. The severity of his hyperactive and impulsive behavior increased without regression in cognitive and motor functions. Laboratory tests for metabolic diseases, molecular genetic studies, and brain MRI were normal. At age seven years, he developed primary generalized epilepsy with generalized tonic-clonic seizures associated with irregular spike-waves and polyspikes. His generalized tonic-clonic seizures increased to two per day

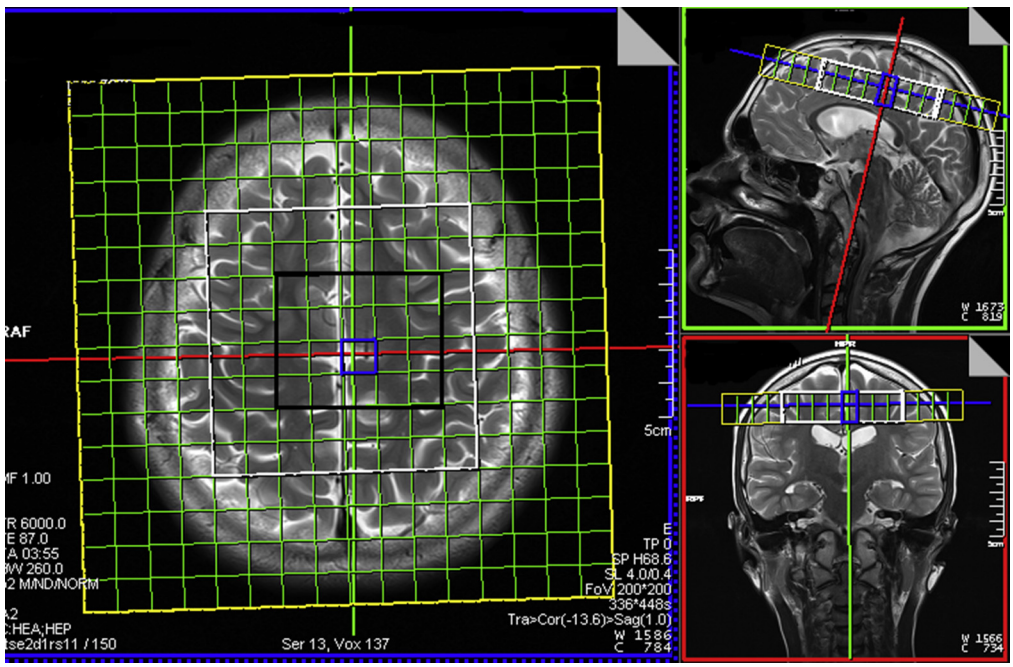

FIGURE 1.
Position of the chemical shift imaging-slice in the frontoparietal cortex and the bilateral semioval center of Child 3. The white box marks the PRESS–Box (point-resolved spectroscopy). Only the voxels inside the black rectangle fulfilled the quality criteria and were chosen for group comparison. In this patient, columns 7 and 10 of the chemical shift imaging-grid are predominantly white matter, whereas columns 8, 9, and 11 are assigned to gray matter. (The color version of this figure is available in the online edition.)