Early Infantile Krabbe Disease Due To a Novel Compound Heterozygous Mutation in a Tunisian Family

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Abstract

Background
Krabbe disease is a rare lysosomal storage illness caused by a mutation in the Galc gene. It characterized by severe neurological and metabolic disorders. The early infantile form is the most common. Regardless of the non-specific signs, diagnosis could be challenging. Over time, novel gene variants are uncovered.

Case Report
We report three cases of Krabbe disease in its early infantile form with atypical signs. The first sibling is a 7-month-old girl who suffered from a regression in psychomotor development and West syndrome. The second and third siblings were two boys who suffered from irritable, propotosis and psychomotor regression at the age of 5 months. One of whom had a non-epileptic tonic spasm. Three cases died at the ages of 8, 18, and 20 months, respectively. The genetic screening had shown a compound heterozygous for two novel mutations (frameshift and missense) that had not been reported previously.

Conclusion
We identified novel missense and frameshift mutations in a Tunisian family. The two new mutations may enhance the spectrum of GALC mutations and explain some clinical characteristics.

Keywords: GALC gene; Infantile form; Novel mutation; Proptosis; West syndrome

Introduction
Krabbe disease (KD) is an inherited autosomal recessive neurodegenerative disorder that is caused by a mutation in the galactocerebrosidegalactosidase (GALC) gene, which encodes the GALC enzyme. Early infantile KD (EIKD), occurring before the age of 6 months, is the most common form (85-90%) [1]. Despite the huge number of GALC gene mutations currently identified, novel mutations are constantly being discovered. Here, we report three siblings with unusual clinical findings of EIKD in a Tunisian family with a novel heterozygous compound mutation, suggesting that this rare illness is continually being updated.

Case Report
The three cases were born at term to non-consanguineous Tunisian parents following a normal pregnancy. The first sibling (IV11) is a 7-month-old girl (Figure 1) with normal developmental milestones. At the age of 2 months, their parents noticed a loss of smiling and eye tracking. At 3 months old, she developed spasms in clusters. Electroencephalography (EEG) performed at the age of 7 months showed hypsarrhythmia. West syndrome (WS) was diagnosed, and Vigabatrin was initiated. One month later, the EEG detected poor organization of the cerebral electro genesis, and the presence of diffuse spikes without sleep-wake differentiation. So, hydrocortisone was administered.

A neurological examination at this age revealed severe hypotonia and brisk tendon reflexes in all four limbs. Fundoscopy examination found optical atrophy. Brain MRI (Figure 2, Panel A) showed diffuse hyperintensities on the T2-weighted image (T2WI) in the periventricular white matter with involvement of the internal capsule’s posterior limb, brainstem and dentate nucleus. The lumbar puncture (LP) revealed a high level of protein in the cerebrospinal fluid at 1.5 g/l. The electromyography (EMG) showed a demyelinating neuropathy. The auditory evoked potential (AEP) identified a sensorineural hearing loss. The visual evoked potential (VEP) was normal. The follow-up was characterized by tonic seizures with ocular retraction and increasing spasticity of the four limbs. She died at the age of 8 months of general state alteration.

The second and third siblings (IV12, IV13) developed the same clinical features with normal psychomotor development until the age of 5 months, when her parents complained about irritability, crying, feeding difficulties with weight loss, and episodes of hyperpnea. The mother noticed a loss of previously acquired visual tracking and poor head control, with hypertonia exaggerated during crying. Physical examination at the age of 8 months revealed failure to thrive, decreased alertness, incessant crying at the slightest touch, and brisk tendon reflexes with clonus in both feet. The Denver test was estimated at 2 months. Ophthalmological examination of sibling IV12 showed bilateral proptosis with normal funduscopy examination. His brain MRI showed periventricular hyper intensity on T2WI with a tigroid pattern and optic nerve hypertrophy (Figure 2, Panel B). The LP revealed a high level of protein (2.2 g/l) and a lactate level of 3.07 mmol/l. The ENMG identified a demyelinating neuropathy. The AEP showed
an absence of brainstem waves. Two months later, the progression was toward the development of axial hypertonia, decreased crying, bilateral nystagmus, tonic spasms, and a lack of deep tendon reflex in the lower limbs. Repeated EEG during sleep (5 and 13 months old) remained normal. The two children died at the ages of 18 and 20 months, respectively, of respiratory distress.

In the IV12 sibling, GALC enzyme activity in peripheral blood leukocytes was collapsed (0 uKat/kg), for normal values ranging from 1.9 to 6.5 uKat/kg. Mutation screening of the GALC gene was carried out on both parents and sibling IV12 by sequencing exons 5 and 8 of the gene. The mother was heterozygous for p.Ala263 Thr-266dup (c.788_799dup) mutation, and the father for the p.Leu149Phe (c.447G>T) mutation. Correspondingly, sibling IV12 had a novel heterozygous compound mutation. A prenatal diagnosis was established during the 5th pregnancy (12 weeks of amenorrhea), and the couple was able to conceive a healthy daughter (IV14), who carries only the maternal heterozygous mutation p.Ala263_Thr266dup (c.788_799dup).

Discussion

Here, we report three cases of EIKD in a Tunisian family with unusual clinical features and novel variants. Tunisia was classified as having a low risk of KD [2]. To the best of our knowledge, there have been only two reported cases of EIKD in the Tunisian population. The first was observed by Kraoua and the second by Fiumara who reported three cases (3, 4, and 5 months, respectively), belonging to the same family, with an estimated GALC enzyme level of 1.9-2.5% of normal [3,4]. EIKD has a broad clinical spectrum with non-specific symptoms [5]. In our cases, proptosis and WS were the most interesting clinical findings. While the most common seizure types during EIKD were febrile seizures, myoclonic seizures, and generalized tonic-clonic seizures, WS has rarely been recorded [5-7]. It has been reported in one French and one Chinese study. The common features of KD patients with WS are the female gender, the age of onset (3 months), and drug resistance [6,7]. Kliemann highlighted that the EEG features of WS in KD were different from those commonly observed in infantile spasms. The amplitudes were frequently between 50 and 200 microvolts, with no spikes or sharp waves noted [8]. The EEG of our patient showed a typical pattern of hypsarrhythmia.

Visual abnormalities were dominated by discordant eye movements (48%), aberrant pupillary response (56%), strabismus (14%), nystagmus (11%), and blindness (3%) [5]. Meanwhile, sibling IV12 had bilateral proptosis. This may be explained by the optic nerve enlargement shown in his brain MRI. This is attributed to globoid cell accumulation and neuroinflammation caused by perivascular monoocyte and macrophage infiltrates in the optic nerve [9,10]. While this finding is consistent with previous reports of MRI findings in EIKD, proptosis has not previously been reported.

According to the ClinVar database, 992 variations of the GALC gene in Homo sapiens have been identified to date (https://www.ncbi.nlm.nih.gov/clinvar/). Only 176 variants are pathogenic. In our study, the mother had a frameshift mutation with a duplication of 12 nucleotides from position 788 to position 799 (c.788_799dup), which may alter the structure and function of the enzyme. For the father, the guanine (G) nucleotide was replaced by thymine (T) in the 447th position of the GACL gene (c.447G>T), and the Phenylalanine (F) replaced the Leucine (L). The alignment of GALC protein amino acid sequences indicates that guanine (G) is totally conserved across all investigated species (Figure 3, Panel A). We are based on the PolyPhen database (http://genetics.bwh.harvard.edu/pph2/), SIFT software (https://sift.bii.a-star.edu.sg/), and Mutation Taster (https://www.genecascade.org/MutationTaster2021/) to evaluate the pathogenicity of the father’s variation. PolyPhen database indicates that the missense mutation (p.Leu149Phe) is expected to be deleterious (Figure 3, Panel B) and to have a negative impact on protein structure (Figure 3, Panel C). The SIFT score was equivalent to 0, 0.00-0.05 which indicates that the substitution is expected to be damaging.

Conclusion

We reported these cases with novel compound heterozygous mutation and significant clinical findings to emphasize the importance of considering EIKD when dealing with non-specific clinical features and to expand GALC pathogenic mutation database.
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Author’s Contribution

Dr. Imen Ketata is responsible for case acquisition, manuscript drafting, and literature searches.

Dr. Emna Ellouz is responsible for case acquisition, literature searches, and revising the current manuscript.

Declarations of interest

The authors declare that they have no conflict of interest.

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The appropriate family’s consent was obtained.

References


