Ketata I, et al., J Clin Stud Med Case Rep 2023, 10:185
DOI: 10.24966/CSMC-8801/1000185

HSOA Journal of Clinical Studies and Medical Case Reports

Case Report

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 irritability, proptosis 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

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Citation: Ketata I, Ellouz E (2023) Early Infantile Krabbe Disease Due To a Novel Compound Heterozygous Mutation in a Tunisian Family. J Clin Stud Med Case Rep 10:185.

Received: July 27, 2023; **Accepted:** August 9, 2023; **Published:** August 16, 2023

Introduction

Krabbe disease (KD) is an inherited autosomal recessive neurodegenerative disorder that is caused by a mutation in the galactocerebrosidase (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 hyper intensities 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 electroneuromyography (ENMG) 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 revulsion 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 (8 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_Thr266dup (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).

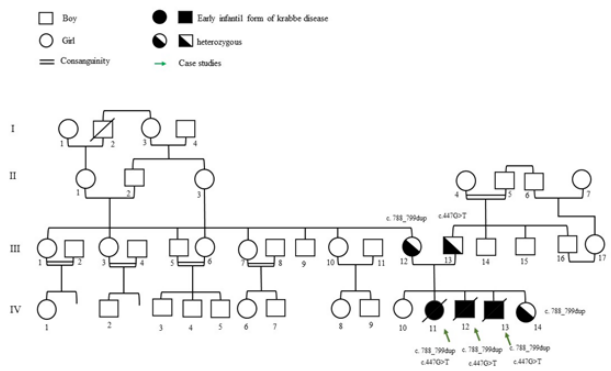

Figure 1: Pedigree of the affected family. The arrows represent the cases studied. The family tree showed that the three siblings (IV11, 12, and 13) had heterozygous mutations, and the father (III13), the mother (III12), and the youngest (IV14) carried out one mutation.

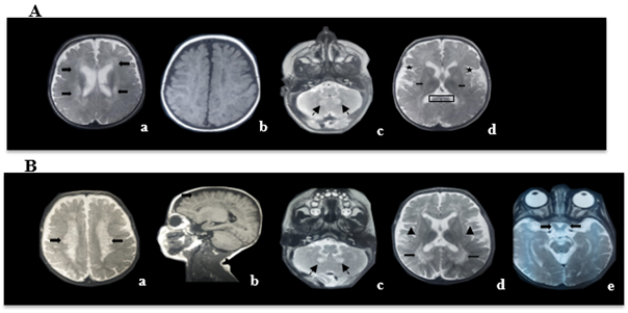

Figure 2: Panel A: Brain MRI of the sister (IV11). Axial T2-weighted image (Panel A,a; A,c; A,d) that shows T2 hypersignal in the bilateral periventricular area (A,a), in the posterior arms of the internal capsule (A,d, arrow), a thin corpus callosum (A,d, rectangle), damage to the dentate nuclei (A,c, dot arrow), and global cortico-subcortical atrophy (A,c, stars). Axial T1-weighted image (Panel A,b) shows cortico-subcortical atrophy. **Panel B:** Brain MRI of the brother (IV12). Sagittal T1-weighted image (panel B,b) that shows cortico-subcortical atrophy. Axial T2-weighted images (Panel B,a; B,c; B,d; B,e) show a tigroid pattern of the periventricular hyper signal (B,a, large arrow), which appears in T1 hypo signal with atrophy of the sylvian valleys (B, b, arrowhead) and cerebral cortico-subcortical atrophy (B,b), involvement of the dentate nuclei (B, d, dot arrow), and hypertrophy of the optic nerves (B,e, arrow).

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 monocyte 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 indicated 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, 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.

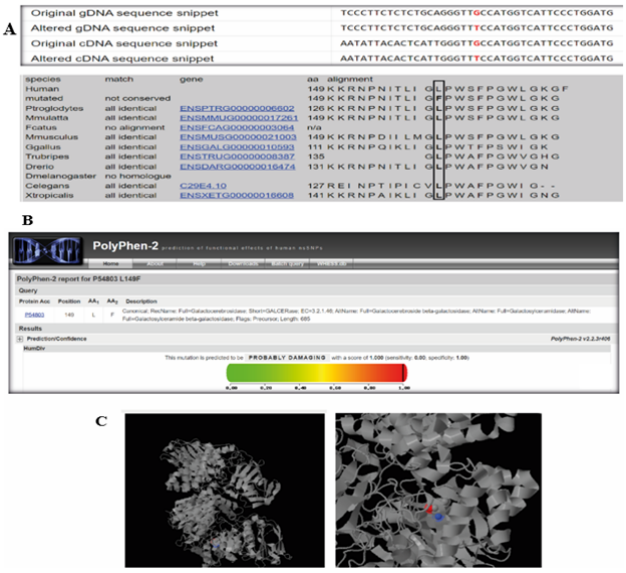

Figure 3: Panel A: Evaluation by Mutation Taster that shows substitution of guanine (G) by thymine (T) and conserved guanine amino acid at position 149 in other investigated species. **Panel B:** Evaluation of the pathogenicity by PolyPhen database shows a score of 1,000 with, as a result, a probably damaging variant. **Panel C:** Evaluation of the pathogenicity by SIFT software shows the negative impact of this mutation on 3D structure modeling.

Acknowledgement

We would like to express our sincere gratitude to Multi-site medical biology laboratory at Lyon University Hospital. Center for Biology and Pathology East, Biochemistry, and Molecular Biology.

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.

There has been no significant financial support for this work.

The appropriate family's consent was obtained.

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