CASE REPORT

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A Novel *CLN1* Variant in a Turkish Patient with Infantile Neuronal Ceroid Lipofuscinoses

Tuğçe Aras Çöl[1], Seda Güneş[2], Elif İşler Soylu[1], Kağan Çalışgan[1], Hanım Babazade Aghakishili[1], Tanyel Zübarioğlu[1], Mehmet Şerif Cansever[1], Serdar Ceylaner[3], Ayşe Çiğdem Aktuğlu Zeybek[1]

[1]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Metabolism and Nutrition, İstanbul, Türkiye
[2]Harran University Faculty of Medicine, Department of Metabolism and Nutrition, Şanlıurfa, Türkiye
[3]Intergen Genetics and Rare Diseases Diagnosis Research and Application Center, Ankara, Türkiye

Abstract

The neuronal ceroid lipofuscinoses (NCLs) are a group of progressive neurodegenerative disorders characterised by abnormal accumulation of ceroid and lipofuscin in lysosomes and the cytoplasm. The progressive accumulation of ceroid and lipofuscin in the central nervous system leads to psychomotor retardation, vision loss, and epilepsy. NCLs are the most common neurodegenerative diseases of childhood, and a diagnosis of NCLs should be considered in individuals presenting with characteristic clinical symptoms and magnetic resonance imaging findings. A definitive diagnosis should be confirmed by an enzyme activity assay, skin biopsy or variant analysis. We present a case of infantile NCL with a novel variant.

Keywords: *CLN1*, Infantile neuronal ceroid lipofuscinoses, Novel variant

INTRODUCTION

The neuronal ceroid lipofuscinoses (NCLs) are a group of inherited, progressive neurodegenerative disorders that primarily affect children. They are among the most common neurodegenerative diseases of childhood. The age at which symptoms first appear can range from birth to adulthood. The main clinical symptoms are vision loss, dementia, loss of motor skills, epilepsy and, eventually, premature death.[1] NCLs are characterised by total brain atrophy and the abnormal accumulation of autofluorescent pigment in neuronal tissues.[2]

NCLs are classified both clinically and genetically. They are categorised by the age at which the disease manifests (congenital, infantile, late-infantile, juvenile, or adult) and by the defective gene. To date, fourteen different NCL forms have been described based on genetic analysis.[3] However, NCLs are a genetically heterogeneous group, and variants in the same gene can lead to different clinical courses.[4] A definitive diagnosis should be confirmed by both an enzyme activity assay and variant analysis. Here, we present a case of infantile NCL with a novel variant.

CASE REPORT

A two-year-old girl born to parents who were first-degree cousins presented to our clinic with restlessness. The prenatal, natal, and postnatal periods were uneventful, and she developed age-appropriate physical skills by one year of age. The patient had approximately 10–15 meaningful words at 12 months of age; however, her speech development did not progress further and subsequently regressed. She gradually lost previously acquired words and developed an articulation impairment. After the age of one year, her parents noticed a significant deterioration in her speech and other cognitive functions. The patient achieved independent walking at 13 months of age; however, her gait became ataxic after one year of age and progressively

Address for Correspondence: Tuğçe Aras Çöl, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Metabolism and Nutrition, İstanbul, Türkiye
E-mail: tugce.col@iuc.edu.tr **ORCID ID:** orcid.org/0009-0001-5781-1168

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deteriorated, such that by 18 months she had completely lost her ability to walk. She developed myoclonic jerks, both spontaneous and stimulus-sensitive. There was no history of prolonged epileptic seizures or status epilepticus.

On physical examination, she was conscious and had significant hypotonia in her trunk and severe hypertonia in her limbs. Her deep tendon reflexes were increased. No visual tracking response was observed during the examination. Fundoscopic examination could not be performed at the time of evaluation; therefore, retinal findings could not be assessed. Examinations of the cardiac and respiratory systems were normal. There was no evidence of organomegaly. Inborn errors of metabolism, such as congenital defects of glycosylation, leukodystrophies, mitochondrial cytopathies, and NCL, were considered in the differential diagnosis. The complete blood count and biochemical parameters were within normal limits. Metabolic screening tests, such as Tandem MS and urinary organic acid analysis, revealed no pathological findings; however, nonspecific changes were observed in quantitative blood amino acid levels. Magnetic resonance imaging (MRI) of the brain revealed diffuse cerebral atrophy and corpus callosum agenesis. A skin biopsy revealed the presence of loose, membrane-bound granular osmiophilic deposits in sweat gland epithelial cells, blood vessel smooth muscle cells, endothelial cells, and fibroblasts. Examination by electron microscopy revealed buffy coat lymphocytes, which, together with the storage inclusions seen in the skin biopsy, were typical of the classic form of infantile NCL.

CLN1 gene sequencing was performed using the MiSeq next-generation sequencing platform (Illumina, San Diego, California, USA) according the manufacturer's instructions. The sequences were then aligned to the hg19 genome using the MiSeq Reporter software (Illumina Inc.). The data were visualised using IGV 2.3 (Broad Institute). A homozygous p.P238Cfs*56 (c.712_713delCC) variant was identified. This frameshift variant is predicted to result in a premature stop codon, leading to a truncated and likely non-functional protein. According to the American College of Medical Genetics and Genomics/Association for Molecular Pathology guidelines, the variant was classified as likely pathogenic. The frameshift nature supports the PVS1 criterion, and its absence from population databases and an in-house cohort of approximately 300 Turkish exome datasets supports PM2. In addition, *in silico* prediction tools provided supporting evidence, although conflicting results were also noted.The variant was further evaluated using standard bioinformatics pipelines in an in-house exome sequencing database comprising approximately 300 individuals of Turkish origin and was not detected in this cohort. Enzyme analysis was requested; however, the results were not available at the time of writing. Segregation analysis in the family was requested; however, the results were not available at the time of writing.

DISCUSSION

Here, we present a Turkish patient with infantile NCL carrying a novel *CLN1* variant. To date, fourteen different NCLs have been described, although some individuals with NCL were described as having a classical disease presentation despite no mutation being detected in the *NCL* gene.[1] *CLN1*, *CLN2*, *CLN10*, and *CLN13* are caused by defects in *lysosomal enzymes*, while *CLN3*, *CLN6*, *CLN7*, and *CLN8* are caused by defects in transmembrane proteins. *CLN12* and *CLN14*, on the other hand, are caused by mutations in the ATPase and potassium channel genes, respectively.[1,5,6] A newly described *CLN4* gene plays an important role in putative synaptic functions.[7]

Infantile NCL is caused by defects in palmitoyl-protein thioesterase-1 (PPT-1). PPT-1 cleaves long-chain fatty acid moieties from cysteine residues on a multitude of protein targets.[8]

NCLs present with similar clinical manifestations, including cognitive decline, motor impairment, myoclonus, seizures, deteriorating visual acuity, and other visual impairments. Although there are no specific laboratory tests available for NCL, MRI findings such as diffuse atrophy, cerebral atrophy, cerebellar atrophy and thalamic T2-weighted hypointensity, as well as diffuse T2-weighted hyperintensity in the periventricular area and centrum semiovale, can aid the differential diagnosis of NCL.[1,2]

In our patient, agenesis of the corpus callosum was also observed on MRI. This finding is not commonly reported in classical infantile *CLN1*-related NCL and may represent either an additional feature or a coincidental anomaly.

In infantile NCL, a previously healthy, normally developing child begins to lose developmental milestones. Additional symptoms include myoclonus, visual impairment and refractory seizures. Infantile NCL is a rapidly progressive lysosomal storage disorder, with patients experiencing fulminant brain atrophy and progressive microcephaly.[8] Electron microscopy of affected tissues demonstrates the accumulation of granular osmiophilic dense bodies. Our patient exhibits the same clinical features as those reported in the literature.[2] Although the identified variant is compatible with the clinical and pathological findings, the absence of enzyme activity analysis, segregation data, and fundoscopic examination is an important limitation. Biochemical and functional validation would further strengthen the diagnostic accuracy and interpretation of the variant.

To date, 64 pathogenic variants have been identified in the *CLN1* gene. The novel variant detected in our patient expands the mutational spectrum of *CLN1*-related disease. NCLs may present in congenital, infantile, late-infantile, juvenile, or adult

forms. However, this variant did not produce any additional or atypical phenotypic features. The patient exhibited findings fully consistent with the classical infantile form, indicating that the newly identified genotype does not appear to alter the expected clinical presentation. Further cases and functional studies will be necessary to confirm its pathogenicity and to determine whether this variant has any subtle effects on disease progression.

CONCLUSION

We present the case of a Turkish patient with classic infantile NCL who carries a novel *CLN1* variant. While this variant expands the known *CLN1* mutational spectrum, it does not appear to alter the expected clinical phenotype. The patient's symptoms were fully consistent with the classical infantile form. Further cases and functional studies are required to confirm the pathogenicity of this variant.

Ethics

Informed Consent: Informed consent was obtained from the parents of all patients included in this paper.

Footnotes

Authorship Contributions

Concept: T.A.Ç., S.G., Design: T.A.Ç., S.G., E.İ.Ş., A.Ç.A.Z., Data Collection or Processing: T.A.Ç., S.G., E.İ.Ş., K.Ç., T.Z., M.Ş.C., S.C., A.Ç.A.Z., Analysis or Interpretation: T.A.Ç., S.G., K.Ç., H.B.A., T.Z., M.Ş.C., S.C., A.Ç.A.Z., Literature Search: T.A.Ç., S.G., H.B.A., T.Z., S.C., A.Ç.A.Z., Writing: T.A.Ç., S.G.

Conflict of Interest: The author(s) have no conflicts of interest to declare.

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