CLN6 Variant of Late Infantile Neuronal Ceroid Lipofuscinosis Caused by a Homozygous Mutation: Case Report in Colombia

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Daniel Eduardo Manrique Hernandez[1], Diana Sanchez-Peñarete[2], Sandra Milena Castellar-Leones[3] and Lisseth Cabarcas-Castro[4]

Abstract

Introduction: Neuronal ceroid lipofuscinosis (NCLs) is an autosomal recessive neurodegenerative disorders group. We report the first case in Colombia involving a new genetically confirmed variant of a homozygous CLN6 mutation. **Case report**: 12-year-old male, history of blood parents and average growth until 5 years of age. At this age began focal crises, progressive regression of neurodevelopment, severe cognitive deficit, and swallowing disorder that led to gastrostomy. Clinical exome + CNVs + mitochondrial DNA genetic study identified variant NM_017882.3 (CLN6): c. 22C>T, p. (Gln8*) in homozygous, deleterious. Late-onset infantile neuronal ceroid lipofuscinosis was diagnosed. **Discussion**: Mutations in the CLN6 gene are associated with late-onset infantile lipofuscinosis of autosomal recessive inheritance. This variant has not been previously described in the medical literature nor is it listed in the population databases, which indicates that it is extremely rare. The treatment focuses on the control of seizures, sleep disturbances, extrapyramidal symptoms, behavioral disorders, anxiety, and psychosis. **Conclusion:** To date, this variant of the CLN6 gene has not been reported in the world. There are currently no etiological or disease-specific therapeutic approaches. The use of exome/whole genome sequencing can be very useful for etiological diagnosis and differential diagnosis. An early diagnosis opens the door to future care and treatment.

Keywords

CLN6, Neuronal ceroid lipofuscinoses, Lysosomal storage diseases, Batten disease, Variant late infantile.

Introduction

Neuronal ceroid lipofuscinosis (NCLs), collectively referred to as Batten's disease represents a group of autosomal recessive neurodegenerative disorders characterized by seizures, progressive cognitive deficit, motor impairment, and vision loss [1]. Its prevalence is estimated at 1:1,000,000 to 1:14,000, depending on the geographical region [2]. NCLs are characterized by the accumulation of autofluorescent lipopigments in body tissues due to mutations of the gene associated with neuronal ceroid lipofuscinosis. Eight different types of disease have been described due to the mutation of 14 genes, (CLN1-CLN14) [1–2]. The CLN6 gene is located at 15q23 and encodes a 311 amino acid transmembrane endoplasmic reticulum protein involved in the transfer of lysosomal enzymes from the endoplasmic reticulum to the Golgi apparatus [3].

Currently, about 130 patients have been described with mutations in the CLN6 gene, in which 3 clinical variants are described: Late-onset infantile or juvenile-onset, Kufs type A variant, and Kufs type B [4]. The subtype of early infantile-onset or early juvenile-onset present with visual impairment, motor impairment, epilepsy, movement disorders, myoclonus, cerebellar dysarthria, and ataxia [5]. We report the first case in Colombia involving a new genetically confirmed variant of a homozygous CLN6 mutation.

[1] Universidad de la Sabana, Resident of Physical Medicine and Rehabilitation, Bogotá, Colombia.
[2] Instituto Roosevelt, Medical Geneticist, Bogotá, Colombia.
[3] Universidad Nacional de Colombia, Instituto Roosevelt, Physical Medicine and Rehabilitation Physician, Bogotá, Colombia.
[4] Instituto Roosevelt, Pediatric Neurology, Bogotá, Colombia.

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Corresponding Author:
Daniel Eduardo Manrique Hernandez, email: danielmanriqueh@gmail.com

Case Report

12-year-old male, from the town of Mompox, department of Bolivar, Colombia, with a history of blood relatives, parents being cousins in first grade with triple consanguinity [Figure 1] without perinatal risk factors, neurodevelopment, and normal growth until the age of 5. At this age they began focal crises with electroencephalogram that reported epileptogenic discharges of occipital origin; simple brain resonance with findings compatible with loss of cortical parenchyma volume, supratentorial ventriculomegaly, thinning of the corpus callosum, and cerebellar atrophy. Concomitant with the onset of seizures, there was a progressive regression of neurodevelopment with ataxia, dysmetria, loss of gait at 8 years old, language loss at 9 years old, loss of cephalic support at 10 years old, severe cognitive deficit, loss of sphincter control, weight loss and swallowing disorder that led to gastrostomy. Cerebellar ataxia was initially suspected and NPC1 and NPC2 genes were sequenced and reported negative. Therefore, the genetic evaluation was extended with the performance of a clinical exome. In a meeting on neuromuscular diseases held at the Roosevelt Institute in Bogota, Colombia in May 2022, we found a patient with severe malnutrition, spastic quadriplegia, generalized hyperreflexia, Babinsky sign, without cephalic support, without communicative intention.

We reviewed a report of clinical exome + CNVs + mitochondrial DNA that identified variant NM_017882.3 (CLN6): c. 22C>T, p. (Gln8*) in homozygosity, deleterious. The diagnosis of Late-onset infantile neuronal ceroid lipofuscinosis (Neuronal Ceroid Lipofuscinosis Type 6) was made. Treatment was focused on symptomatic management (epilepsy and pain), nutrition, prevention of complications, and palliative care. Rehabilitative management focused on maintaining joint mobility, stretching, training caregivers in safe position changes, skin care, neurological wheelchair positioning, management of respiratory secretions, and emotional support to the family. Genetic counseling was provided to parents.

Discussion

Mutations in the CLN6 gene are associated with autosomal recessive type 6 lipofuscinosis [6]. CLN6 variants were described for the first time in 1997 to be associated with Batten's disease (Sharp et al., 1997). More than 70 pathogenic variants have been identified, as described in the NCL mutation database (https://www.ucl.ac.uk/ncl-disease/mutation-and-patient-database/mutation-and-patient-datasheets-human-ncl-genes/cln6).

In almost all cases of NCL caused by biallelic CLN6 variants, visual loss is the main symptom; however, there are some reports of patients without visual impairment. The first case was reported by Cannellie et al. in 2009, who described three families without visual impairment, another case report was described by Sun et al. in 2018. Additionally, two unrelated patients without visual impairment were reported by Chin et al. in 2019 (Cannelli et al., 2009; Sun et al., 2018; Chin et al., 2019).

The variant in exon 4 of CLN6 was previously reported in a homozygous state in a Turkish blood family (Karaca et al., 2015). Three patients were recently reported from two unrelated families with biallelic variants in the CLN6 gene, with different clinical characteristics, where two were homozygous for a known CLN6 pathogenic variant (exon 4) while the other case was a heterozygous compound for the well-known novel de novo variant CLN6 (exon 7) [7].

Lipofuscinosis type 6 is characterized by regression of motor, language, and cognitive abilities, progressive associated with epilepsy, ataxia, and loss of vision, among others [6]. These findings correlate with the case of the patient presented. The variant NM_017882.3 (CLN6): c. 22C>T, p. (Gln8*), has not been previously described in the medical literature, which indicates that it is extremely rare. It is a null variant that generates a premature stop codon in exon 8 residue 1. Considering the type of mutation and its location, it is expected to result in a severely truncated and therefore non-functional protein. All the in-silico predictors consulted support a deleterious effect of the variant. According to the most recent recommendations of ACMG [8], and Mutation Taster [9] It is a severe stop variant in homozygous, the variant detected in the CLN6 gene is deleterious.

There are no currently approved disease-modifying treatments. Clinical treatment focuses on symptom control and includes control of seizures, sleep disturbances, extrapyramidal symptoms, behavioral disorders, anxiety, pain, and psychosis [10].

Conclusion

To date, this variant of the CLN6 gene has not been reported in the world. There are currently no etiological or disease-specific therapeutic approaches, which can only be treated symptomatically. NCLs generally do not represent an initial suspicion in practice, not only because of low disease awareness and non-specific clinical presentation but also because of limited access to diagnostic approaches in some regions. The use of complete exome/genome sequencing or some panel of genes to investigate unexplained seizures, leukoencephalopathies, or hereditary metabolic disorders can be very useful for diagnosis and differential diagnosis. An early diagnosis opens the door to future care and treatment.

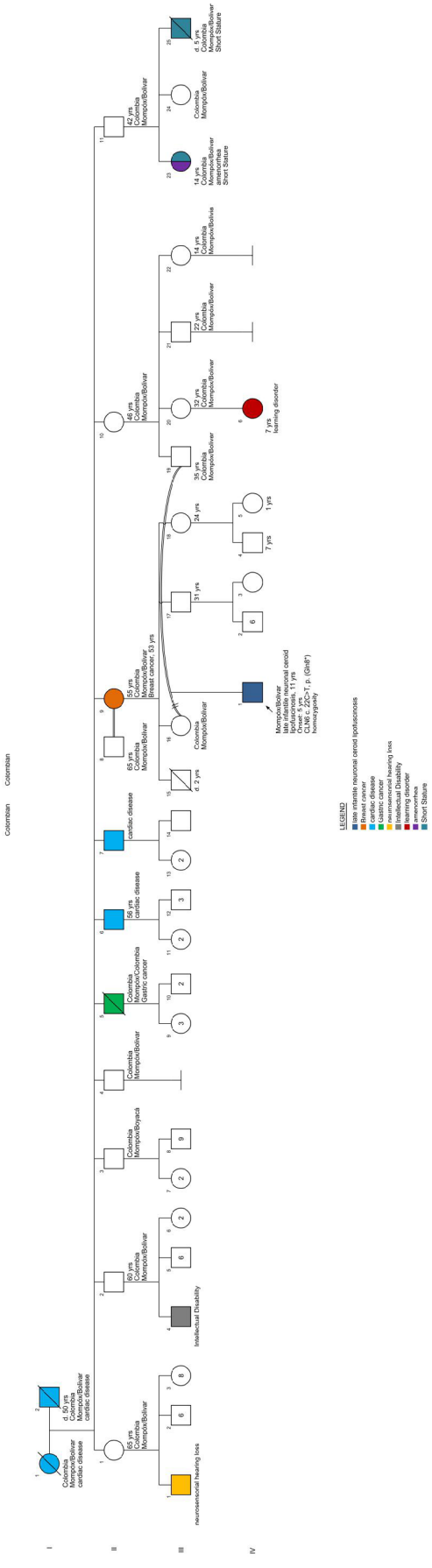

Figure 1. Fourth-Generation pedigree. Showing triple consanguinity.
Source: Authors' elaboration.

Declaration of Conflicting Interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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