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The First Neural Ceroid Lipofuscinosis Type 2 Case in Ecuador: A Case Report

Viteri Rodríguez Juan Alberto[1], Montero Proaño María Fernanda[2], Medina Parra Karen Alejandra[3], Olivo Torres Rosita[4]

[1]Carrera de Medicina, Grupo de Investigación Biomédica, Universidad Regional Autónoma de los Andes, Uniandes. Ambato. EMAIL: Ua.juanviteri@uniandes.edu.ec
ORCID ID: https://orcid.org/0000-0002-2463-7036

[2]Carrera de Medicina, Grupo de Investigación Biomédica, Universidad Regional Autónoma de los Andes, Uniandes. Ambato. EMAIL: ma.mariafmp79@uniandes.edu.ec
ORCID: https://orcid.org/0000-0002-2159-7067

[3]Carrera de medicina. Grupo de Investigación Biomédica. Universidad regional Autónoma de los Andes, Uniandes. Ambato. EMAIL: ma.karenamp92@uniades.edu.ec
ORCID ID: https://orcid.org/0000-0003-1113-1121

[4]Carrera de medicina. Universidad Regional Autónoma de los Andes. EMAIL: ua.rositaolivo@uniandes.edu.ec
ORCID ID: https://orcid.org/0000-0002-6474-141X

**Corresponding author's E-mail: Ua.juanviteri@uniandes.edu.ec*

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Abstract

Neuronal ceroid lipofuscinosis type 2 is a neurodegenerative disease of autosomal recessive inheritance that produces an accumulation of ceroid lipofuscin in the brain and retina. The late infantile phenotype is characterized by rapid psychomotor deterioration and seizures. It has a prevalence of 0.1 to 7 per 100,000 live newborns worldwide. In this case, a male patient presented from 2 years 9 months of age, neurodevelopmental delay with regression, ataxic gait and language impairment; initially diagnosed as inborn error of metabolism; After different studies, the definitive diagnosis of type 2 Neural Ceroid Lipofuscinosis was established. Objectives. Report the only confirmed case in Ecuador demonstrating the importance of early diagnosis to prioritize timely treatment that will improve the quality of life of the patient. The study of the first case of Neural Ceroid Lipofuscinosis in Ecuador is reported, through the collection of qualitative-quantitative data of the clinical picture, evolution of the disease, complementary studies including biochemical and genetic analysis for diagnosis. The patient presented an initial picture of seizures without apparent pathology, with psychomotor problems, ataxic gait and language impairment. The enzymatic study and the clinic led to a possible diagnosis of Neuronal Ceroid Lipofuscinosis type 2, finally confirmed by the molecular analysis of the TPP1 gene. Cerliponase alfa is the only drug accepted to slow the progress of the disease, which was approved in 2017 in the United States, in Ecuador it is a drug that does not have access or coverage in the Ministry of Public Health. LCN2 is a rare disease, however, the most common within the lipofuscinosis. Therefore, a knowledge of them is necessary for an early diagnosis and thus improve life expectancy.

Keywords: *LNC 2, Seizures, Psychomotor Retardation*

1. Introduction

Neuronal Ceroid Lipofuscinosis type 2 (CLN2), is transmitted in an autosomal recessive manner with mutations of two pathogenic variants in the transin of the TPP1 gene (11p15) encoding lysosomal serine

tripeptidyl pepditadase-1 (TPP1 / CLN2) causing the enzyme deficiency of TPP1 that leads to the accumulation of ceroid lipofuscin resulting in a progressive and severe neurodegenerative disease (Nickel et al., 2018; Lewis et al., 2020; Gissen et al., 2021).

The classic phenotype is marked by epileptic seizures and delayed language development that rapidly progresses to dementia. Clinical manifestations occur between two and four years of age; psychomotor impairment (loss of the ability to walk and talk), progressive tonic-clonic and myoclonic epiletic seizures, retinopathy that evolves to vision loss, cerebellar atrophy and finally ends in the death of the patient between 6 years of age and early adolescence (Nickel et al., 2018; Nunes et al., 2020; Gardner et al., 2019; Vasquez-Baiocchi & Burneo, 2020).

Differential diagnosis includes inborn errors of metabolism and inflammatory brain diseases; definitive diagnosis is confirmed by the finding of low activity of the enzyme tripeptidyl peptidase I (TPP1) in dried blood drop (DBS), cultured leukocytes or fibroblasts, and by identifying a pathogenic mutation in each of the alleles of the TPP1 gene. CLN2 has a prevalence of 0.1 to 7 per 100,000 live births worldwide, in Finland the prevalence is 1 in 12,500 people (Dozières-Puyravel et al., 2020; Gardner et al., 2019; Gissen et al., 2021). In Europe and Latin America there have been pediatric patients diagnosed with myoclonic seizures in which malformations, infections and neoplasms have been ruled out, this leads to the investigation of the different types of progressive myoclonic epilepsies (PME) within which are the (LCN) of the subtype of (CN2) (Johnson et al., 2020; Beltrán et al., 2018). The incidence in Germany estimated at 1.28 cases per 100,000 live births, so in Ecuador it is estimated that there are 4 6 cases (. Effective management of LCN2 disease requires timely diagnosis; Irreversible neurodegeneration occurs before a diagnosis is reached at 5 years of age (Johnson et al., 2020; Gardner et al., 2019; Pesaola et al., 2019).

The first and only treatment approved for the management of patients with LCN2 is Cerliponase alfa, which slows the progression of long-term functional decline, both motor function (HR 0.04; CI95% 0.00 to 0.29; p=0.002) and language (HR 0.15; CI95% 0.04 to 0.52; P = 0.003), for administration is infused with cerebrospinal fluid with a reservoir and a catheter that is implanted in the intracerebroventricular route and administered 200ml every 15 days. The cost per infusion is $32,368.00 and annually has a cost of $776,832.00 (Dozières-Puyravel et al., 2020; Pisetsky, 2018; Report Of Unfavorable Interventions, 2018). The objective of this article is to report the only confirmed case in Ecuador demonstrating the importance of early diagnosis to prioritize timely treatment that improves the patient's quality of life.

2. Methods

The study of the first confirmed case of Neural Ceroid Lipofuscinosis in Ecuador is reported, through the collection of quali-quantitative data of the clinical picture, evolution of the disease, complementary studies including biochemical and genetic analysis for diagnosis. In addition, a literature review of the disease to understand the evolution of the disease according to the literature.

Documents were collected with verified information, medical history, analyzes performed, in addition to informed consent.

Case Report

Male patient 4 years 9 months old, mestizo, born in the city of Ambato. No family history with neurodegenerative pathology, non-consanguineous parents, prenatal history without alterations, perinatal without complications, presented a neurodevelopmental delay with regression from 2 years 9 months of age, recurrent seizures characterized by ocular supraversion, generalized hypotonia, hemifacial clones, relaxation of sphincters; diagnosed with epilepsy at 3 years of age, starting clinical treatment with improvement one year later. In addition, he presented ataxic gait, behavioral alteration, absence of language development, axial hypotonia. Left orchidopexy at 3 years 3 months of age.

The patient was initially treated in the city of Ambato, after a seizure he was transferred to the pediatric hospital, after the assessment of the neuropediatrician of said hospital he was referred to the specialty hospital to the genetics service, in Quito.

To identify the etiology of the seizures, electroencephalogram and magnetic resonance imaging were requested. MRI concludes two diagnostic options: 1) image suggestive of variant Dandy Walker syndrome, 2) Arachnoid cyst of left temporal fossa. The electroencephalogram report determines a global organizational and slow disorder of brain electrical activity, multifocal interictal epileptiform disorder, active in the registry, global slow disorder with predominance in the bilateral frontal region, no subclinical seizures, with normal auditory brainstem evoked potentials (PEATC) and visual evoked potentials of the brainstem (PEVTC) with myelitic involvement in both pathways. Therefore, treatment with valproic acid is started at 3 milliliters every 12 hours. At the same time, specific studies were carried out such as: broad metabolic screening, molecular study of spinocerebellar ataxia type 2, Gaucher disease study.

In the enzymatic examination for ceroid lipofuscinosis type 1 and 2; Palmitoyl Thioesterase (CLN1) was found to be normal and triepdidyl peptidase (CLN2) low with 0.6 nmol/h/ml (4.0-23), was obtained as a result suggestive of Neuronal Ceroid Lipofuscinosis (CLN2). To confirm the diagnosis, a molecular genetic analysis of the TPP1 gene was performed by Next Generation Sequencing (NGS) – TPP1, with dried blood drop (DBS) sample, the results indicated the c.229G>C variant (p.Gly77arg) in exon 3 of the TPP1 gene in homozygous state, associated with Neuronal Ceroid Lipofuscinosis (LCN2).

With the definitive diagnosis of the patient, a treatment plan focused on: epilepsy and ataxia with valproic acid 5ml and levetiracetam 4.5ml every 12 hours orally; to manage Ostium Secundum type atrial septal defect: furosemide 14 mg and spironolactone 12 mg orally each day. This treatment decreased seizures by improving the patient's quality of life, but NCL 2 could not be controlled. Subsequently, the procedures to access treatment for LCN2 with cerliponase alfa begin, due to its high cost and the fact that the drug is not available in Ecuador.

3. Results And Discussion

LCN 2 is the most frequent cause of neurological deterioration in children and the most common lysosomal disorder, however, it is one of the most under-diagnosed mutations due to the clinical manifestations associated with other pathologies (speech delay, seizures and ataxia) can be found in several neurological disorders and rapid neurodegenerative progression.

Patients diagnosed with lipofuscinosis through a clinical picture, presents as a rapid or more slowly progressive disorder, with visual alterations, epilepsy, dementia and motor disorders, with onset at different ages initially in childhood being 20% of cases is not clearly framed in this description.

In this case the patient currently 7 years old, with no family history of neurodegenerative pathology, presented epileptic seizures and ataxia at 2 years 9 months of age; and it was not until 3 years that he received his first diagnosis of epilepsy, going through several diagnoses while the picture evolved with regression in neuropsychomotor development, slow and incomprehensible speech at times, as well as fine shaking throughout the body and instability.

At 4 years 9 months he received the definitive diagnosis and later the procedures to acquire the medication. The favorable prognosis of LCN2 is directly related to early diagnosis and timely treatment, so knowledge of the pathology is essential to provide adequate management. Given clinical suspicion, it is necessary to perform an analysis of enzymatic activities of PTT1 and TPP1 in leukocytes, fibroblasts or DBS; the gold standard for the diagnosis of NCL2 is the reduction of TPP1. In the present case, after the analysis of the two enzymes only TPP1 was reduced confirming the mutation in the exons with genetic tests (Rojas Reynoso Amalia GAG, 2001).

This therapy had not been used before in Ecuador, so the treatment protocol was implemented at the Day Hospital with the help of a multidisciplinary team that included: pediatrics, neurosurgery, pediatric neurosurgery, genetics, pediatric cardiology.

The lack of evidence supporting treatment when the disease is already advanced suggests that it is not effective, in the present case, there is a significant gap of 3 years between the onset of symptoms (3 years) and diagnosis (6 years). This can be assessed using the LCN2 Clinical Rating Scale, where motor and language domains are assessed (0 to 6, where 0 represents no function and 3 represents normal function in each of the two domains).

4. Conclusion

LCN2 is a rare disease, however, the most common within lipofuscinosis. So it is necessary to know them for an early diagnosis and thus improve life expectancy. LCN2 belongs to a more common group of neurodegenerative lysosomal storage in childhood, the clinical suspicion of this pathology is based on clinical and low enzyme activity. The first case of Neural Ceroid Lipofuscinosis has been reported in Ecuador, from a patient 4 years 9 months of age. Currently the patient is being treated with cerliponase alfa, however life expectancy is 6 to 7 years. Cerliponase alfa (brineura) is administered once a day orally, prevents neurological deterioration, seizures, psychomotor and speech regression. The drug has an annual cost of $776,832.00. the parents have resorted to the treatment for the patient being free and provided in hospitals such as Carlos Andrade Marín and the Ministry of Public Health in view of the fact that a trial process has been carried out so that the patient has priority attention and his disease is treated in time.

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