Neuronal Ceroid Lipofuscinosis Type 6 (CLN6) Clinical Findings and Molecular Diagnosis: Costa Rica's Experience

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Abstract

Background: Commonly known as Batten disease, the neuronal ceroid lipofuscinoses (NCLs) are a genetically heterogeneous group of rare pediatric lysosomal storage disorders characterized by the intracellular accumulation of autofluorescent material (known as lipofuscin), progressive neurodegeneration, and neurological symptoms. In 2002, a disease-causing NCL mutation in the *CLN6* gene was identified (c.214G>T) in the Costa Rican population, but the frequency of this mutation among local Batten disease patients remains incompletely characterized, as do clinical and demographic attributes for this rare patient population.

Objective: To describe the main sociodemographic and clinical characteristics of patients with a clinical diagnosis for Batten Disease treated at the National Children's Hospital in Costa Rica and to genetically characterize their causative mutations.

Methods: *CLN6* gene sequences were determined from DNA extracted from patient buccal swabs. Participants' sociodemographic and clinical characteristics were also obtained from their medical records.

Results: Nine patients with a clinical diagnosis of Batten disease were identified. Genetic sequencing determined the presence of the previously-described Costa Rican homozygous mutation in 8 of 9 cases. One patient did not have mutations in the *CLN6* gene. In all cases where the Costa Rican *CLN6* mutation was present, it was accompanied by a substitution in intron 2. Patients were born in 4 of the 7 Costa Rican provinces, with an average onset of symptoms close to 4 years of age. No parental consanguinity was present in pedigrees. Initial clinical manifestations varied between patients but generally included: gait disturbances, language problems, visual impairment, seizures and psychomotor regression. Cortical and cerebellar atrophy was a constant finding when neuroimaging was performed. Seizure medication was a common element of treatment regimens.

Conclusions: This investigation supports that the previously characterized c.214G>T mutation is the most common causative NCL mutation in the Costa Rican population. This mutation is geographically widespread among Costa Rican NCL patients and yields a clinical presentation similar to that observed for *CLN6* NCL patients in other geographies.

Background

Neuronal ceroid lipofuscinoses (NCLs) constitute a group of genetic neurodegenerative diseases associated with motor and cognitive regression; progressive cortical, thalamic, and cerebellar atrophy; retinopathy; epilepsy; and a shortened lifespan¹. While these signs and symptoms are common to most forms of NCL, age of onset and sequence of symptom presentation varies with different genetic subforms. While the mechanism by which these mutations generate a common phenotype is not entirely clear, defects in the endolysosomal system are a shared cellular etiology². Autofluorescent ceroid lipopigment accumulates in lysosomes in various neuronal and extraneuronal cell populations in all forms of the disease^{1,3-6}. Causative mutations have been mapped to at least 13 different genes, which encode a diverse set of lysosomal enzymes, cytosolic chaperones, and transmembrane proteins with roles in secretory and endolysosomal trafficking⁷.

Despite the fact that NCLs are classified as rare diseases, they are collectively considered the most prevalent pediatric neurodegenerative disorders and more than 1500 new cases are diagnosed worldwide per year⁸. The term Batten disease refers to the entire spectrum of NCLs, which have historically been classified according to the age when symptoms initiated (i.e. infantile, late-infantile, juvenile, and adult). However, more recent classification schemes have instead focused on genetic and biochemical aspects of the disease along with clinical presentation, with sub-type naming commonly dictated by the causative ceroid lipofuscinosis neuronal (CLN) gene mutation⁹. With the exception of the autosomal dominant *CLN4* disease (caused by mutations in the cytosolic chaperone DNAJC5), NCLs are inherited in an autosomal recessive manner where patients have homozygous or compound heterozygous mutations³.

Approximately 500 mutations in the 13 NCL genes have been reported¹⁰, including more than 70 in the *CLN6* gene which are responsible for variant late infantile or adult-onset forms (i.e. Kufs Disease Type A) of the disease¹¹⁻¹³. The *CLN6* gene is located on 15q23 and encodes a 311 amino acid transmembrane endoplasmic reticulum protein that functions in the ER to Golgi transfer of lysosomal enzymes¹⁴. Downstream cellular pathologies ranging from synaptic alterations, glial activation, and autophagy have also hinted at additional cellular roles or, perhaps, specialized roles in neurons and glia^{2,13,15-19}.

The initial clinical manifestations of *CLN6* disease generally begin between the ages of 2 and 4 years²⁰ and are characterized by motor regression, visual loss, the presence of rapid and involuntary muscle movements, and multiple seizures types^{21,22}. In advanced stages, patients commonly develop ataxia, further cognitive and motor deterioration, and finally spastic quadriparesis^{23,24}. Imaging-based studies commonly find cortical and/or subcortical grey matter atrophy^{22,24-26} and, like most other NCLs, there are no approved disease-modifying treatments. Clinical treatment is focused on symptom management and includes the management of seizures, sleep alterations, extrapyramidal symptoms, behavioral disturbances, anxiety and psychosis²¹. Slight variations in the clinical course of *CLN6* disease have been linked to the causative mutations and the country of origin²⁷.

Mutations in the *CLN6* gene are observed mainly in patients of Portuguese, Indian, Pakistani or Czech descent, but have also been documented in countries such as Costa Rica, Sudan, Turkey and Japan^{23,28-30}. By the end of the 1990s, studies aimed at identifying and analyzing the most common genetic variant in late infantile NCL began in the Costa Rican population³¹⁻³³. From these studies, the causative alteration known as the Costa Rican *CLN6* gene mutation was defined³⁴. This genetic modification, described in 2002, corresponds to a nonsense change in exon 3 (c.214G > T; p.E72X) introducing a stop codon at amino acid position 72; which results in a premature termination and generates an incomplete and non-functional protein product that is degraded at the level of the endoplasmic reticulum^{13,29}. Other possible disease-related mutations in the *CLN6* gene (specifically in exons 4 [c.368G > A] and 7 [c.722T > C]) have

also been reported ¹⁰. Currently in Costa Rica, a NCL diagnosis is made by a clinical evaluation of the symptoms and signs recalled during medical history and present during physical examination by a pediatric neurologist.

Here, we aimed to determine the frequency of the c.214G > T *CLN6* gene mutation and any other mutations among Costa Rican NCL patients and to describe the main sociodemographic and clinical characteristics in patients diagnosed with NCL in the National Children's Hospital (HNN), the only pediatric hospital in Costa Rica, and part of the social security system (CCSS).

Methods

After obtaining approval from the Institution's Scientific Ethics Committee (CEC-CENTRAL-CCSS) and authorization from the Director of Costa Rica's National Children's Hospital (HNN), the parents of all patients with a clinical diagnosis of Batten disease currently treated at the HNN Neurology Department were contacted, the study was explained and the investigators invited the parents so their child could participate. Subsequently, an appointment was scheduled in the HNN and, after explaining the study and obtaining informed consent (informed assent was not possible), the investigator collected a buccal swab for each participant. The samples were disassociated from any personal identification and transported in compliance with international regulations to the appointed laboratory. The genetic analysis of the samples was performed by Sanford Research (Sioux Falls, SD; USA) in two independent laboratories where DNA was extracted and next generation sequencing (NGS) for the *CLN6* gene was performed for each study subject. Once the genetic results were obtained, the study participant's parents received the genetic testing results with an explanation as part of their usual clinical visit.

The main sociodemographic and clinical characteristics from the study subjects were examined with a descriptive analysis based on existing medical records. These included: age, sex, place of birth and residence, age of initial symptom onset, age of clinical diagnosis, relevant medical history, main clinical manifestations and pertinent evaluations previously performed (ophthalmological evaluation, visual evoked potentials, electroretinogram, electroencephalogram, imaging tests including computerized axial tomography or brain magnetic resonance imaging) at diagnosis, in addition to the result of the most recent neurological examination and current treatment.

All study procedures were carried out in accordance with the Declaration of Helsinki, Good Clinical Practice Standards and local Costa Rican regulations.

Results

Nine patients with a previous clinical diagnosis of NCL were identified. The average age of the subjects when the DNA sample was obtained was 9.9 ± 2.7 years (mean $\pm$ SD). The initial symptoms appeared at 3.9 ± 0.6 years on average (range 3–5 years) and the typical age at the time of the clinical diagnosis was approximately 7 years (range 3–10 years). Females outnumbered males in a 2:1 ratio. Most patients (77.8%, n = 7) did not report a significant medical history before the onset of symptoms related to the disease.

The Costa Rican mutation (homozygous nonsense variant in exon 3 c.214G > T in the *CLN6* gene) was reported in approximately 90% (n = 8) of study participants. In all cases where the Costa Rican *CLN6* mutation was present, it was accompanied by a substitution in intron 2 (c.198 + 104T > C, Table 1) as previously described ^{11,29}.

Table 1
Patient's main sociodemographic characteristics, medical history and genetic mutation.

	A	B	C	D	E	F	G	H	I
Age	11	13	13	7	12	6	8	8	11
Sex	Male	Female	Female	Male	Female	Female	Female	Female	Male
Age of onset	4	ND	5	4	3	4	4	4	3
Age of diagnosis	ND	ND	ND	ND	10	6	8	8	3
Relevant medical history	Severe myopia	Severe TBI w/ neurological sequelae	None	None	None	None	None	None	None
Genetic	NI	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Mutation	E3: NI	E3: c.214 G > T	E3: c.214 G > T	E3: c.214 G > T	E3: c.214 G > T	E3: c.214 G > T	E3: c.214 G > T	E3: c.214 G > T	E3: c.214 G > T
	I2: NI	I2: c.198 + 104 T > C	I2: c.198 + 104 T > C	I2: c.198 + 104 T > C	I2: c.198 + 104 T > C	I2: c.198 + 104 T > C	I2: c.198 + 104 T > C	I2: c.198 + 104 T > C	I2: c.198 + 104 T > C
	E3: NI	E3: p.E72X	E3: p.E72X	E3: p.E72X	E3: p.E72X	E3: p.E72X	E3: p.E72X	E3: p.E72X	E3: p.E72X
ND: no data, TBI: traumatic brain injury, NI: Not Identified									

Most of the patients were born in and currently live in areas distant from San José, Costa Rica's capital city. There was a fraternal relationship identified between two patients who live in the province of Limón. Nevertheless, there was no evidence suggesting the presence of specific geographic areas with a higher frequency of cases (Fig. 1). Likewise, no consanguineous relationships were reported between the parents of study participants.

Gait disorders, vision loss and speech disturbances were the most frequent initial manifestations registered in medical records. At the time of clinical diagnosis, 77.7% (n = 7) of the cases presented abnormalities in the ophthalmological assessment with 87.5% (n = 7) of study subjects presenting with altered visual potentials when such data were collected. The majority of study participants showed abnormalities in the EEG and neuroimaging tests, in which cortical, subcortical, and cerebellar atrophies were common (Table 2).

Table 2
Clinical Manifestations and Evaluations at Diagnosis

Clinical Manifestations and Evaluations at Diagnosis									
Patient codification									
	A	B	C	D	E	F	G	H	I
	Behavioral and walking disturbances	Personality and behavior. disturbances	Behavioral, walking, motor skills, and the ability to walk.	Alterations of motor skills and the ability to walk.	Alterations of motor skills and the ability to walk.	Alterations of motor skills and the ability to walk.	Alterations of walking ability (recurrent falls)	Visual and walking alterations.	Visual and walking alterations.
Main clinical manifestations	(ataxic)	Seizures (generalized clonic)	and sleep alterations	Cognitive decline			Myoclonic seizures	Attentional difficulties	Myoclonic seizures
		Extrapyramidal symptoms		Discrete dyspraxia			seizures	Cognitive decline	Attentional difficulties
	Normal	Bull's eye	Severe	Bull's eye	ON Atrophy	Normal	Bilateral ONs	Retinal	Bilateral ONs
		maculopathy	macular	maculopathy			atrophy	atrophy	Optic atrophy
		retinal vessels	and retinal				ONs total pallor	with light	Retinal pallor
Ophthalmological evaluation (OE)		atrophy, retinal pigment epithelium	pigment epithelium alteration				Generalized vascular thinning	discoloration	retinal pigment epithelium alteration
		and retinal							Generalized vascular thinning
		alteration							vascular thinning
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Patient codification									
			β activity	epileptiform	generalized		in the		
			in anterior	discharges	rapid		posterior		
			regions		rhythmic		quadrant		
					discharges				
	CT: cortical,	CT: cortical	CT: cortical	MRI: Generalized	MRI: severe	MRI: difuse	ND	MRI: Diffuse	M
Medical	subcortical	atrophy and	atrophy and	cerebral	cortical	cerebral		cerebral	c
Images	and	diffuse	diffuse	and cerebellar	atrophy	atrophy		and cerebellar	a
	cerebellar	subcortical	subcortical	atrophy		and severe		atrophy	a
	atrophy	atrophy	atrophy			cerebellar			c
						atrophy			a
ERG: Electroretinogram, EEG: Electroencephalogram ND: no data, ON: optic nerve, CT: computerized tomography, MRI: magnetic resonance imaging.									

The review of subject’s medical records allowed for a qualitative comparison between the initial clinical manifestations and the findings from the most recent neurological examination, showing a substantial deterioration in physical and functional capabilities over the observation period (Table 3). Valproic acid, carbamazepine and clonazepam were the medications mostly prescribed for the treatment of seizures.

Table 3
Most recent neurological examination findings and current treatment

Patient codification								
	A	B	C	D	E	F	G	H
Neurological examination:	Spastic tetraparesis,	Spastic tetraparesis,	Increased muscle tone in	General hypotonia,	Trunk ataxia,	Tone and muscle	Spastic quadriparesis,	Lack of visual
Motor,	Somnolence,	Somnolence,	lower limbs,	Complete	Axial	strength	Nistagmus,	response,
Consciousness level,	Complete	Lack of	Somnolence,	lack of	hypotonia,	preserved,	Focal	Right clonus,
Visual alterations,	lack	visual	Blindness,	visual	Limb hypertonia,	Alert,	Myoclonus,	Able to stand
Epilepsy,	of visual	response	Dyspraxia,	response,	Lack of	Normal	Bedridden.	in upright
Functional level	response,	to light	Wheelchair	Unstable in	visual	eye contact,		position
	bedridden.	stimuli,	bound	sitting	response	Inability		using both
		pupil		position		to walk		upper limbs
		deformity.						
Other Clinical Findings				Dysphagia (nasogastric tube)	Dysphagia			
Treatment	Valproic acid,	Valproic acid,	Valproic acid,	Valproic acid,	Valproic acid,	Valproic acid,	Valproic acid,	Carbamazepine,
	Carbamazepine	Carbamazepine	Clonazepam	Clonazepam	Clonazepam,	Clobazam	Carbamazepine	Clonazepam
		Topiramate		Levetiracetam	Haloperidol,			L-carnitine,
					Melatonin			Thiamine
								Biotin,
								CoQ10

Discussion

Worldwide, it has been reported that the initial clinical manifestations in CLN6 disease occur between 2 and 4 years of age²⁰, however in this investigation, the cases analyzed trended towards the older end of this range with regards to symptom onset (3.9 ± 0.6), with a range between 3 and 5 years of age. This may be due to the small number of cases studied, or possibly to certain variations in the clinical course of the disease linked to this causative mutation as has previously been reported for Costa Rican patients²⁷. The age of diagnosis in this study was an average of seven years. This could be due in part to the challenges associated with diagnosis of a complex rare disease in a locality with limited utilization of genetic testing. In this patient cohort, females outnumbered males 2:1. This level of sex disparity has not been reported in clinical literature and is likely due to the small sample size. Differences in severity between the sexes have been documented for some forms of NCL, with more aggressive forms commonly reported in female patients, however this was not recapitulated in our study^{35,36}.

The genetic alterations identified in the study population, pointedly the Costa Rican mutation and the substitution polymorphism in intron 2, have been previously reported^{11,29}. This substitution polymorphism has also been described in Argentinian populations^{10,11}. In the Costa Rican Batten disease population, the homozygous mutation and the presence of the polymorphism suggests that the polymorphism and the damaging mutation are inherited as a haplotype. Thus, unlike many other NCL mutations, the Costa Rican c.214G > T mutation has been associated with the founder effect^{27,37}. It is important to mention, that despite not having carried out multi-generation genealogical studies, the presence of the specific haplotype in all study samples, the absence of consanguinity registered in medical records and the varied geographical locations where study subjects were born and live, supports this local founder effect for this allele. It has been suggested that this founder effect was introduced in the initial pool of genes from the time of the Spanish and Portuguese colonization. This hypothesis has been mentioned in other medical conditions described in our country such as Wilson's Disease^{38,39}.

The main signs and symptoms observed in study participants generally agree with what has been reported worldwide for CLN6 patients, where visual loss, the presence of rapid and involuntary muscle movements, seizures, ataxia, and mental and motor deterioration are the most frequent findings described^{23,24}. Specifically, the published literature establishes that motor regression constitutes one of the first clinical manifestations²², an aspect confirmed in our study subjects, where gait disturbances were near constant findings in the initial stages of the disease.

Where neuroimaging studies were available, cortical and / or subcortical atrophy were common findings, as has been consistently reported in NCLs^{22,24-26}. Regarding imaging modalities, magnetic resonance imaging (MRI) had limited availability in Costa Rica over the study period; many patient records thus only had computed tomography (CT) scans. Likewise, ERG equipment was not operational for the duration of the study period and ERG data is available for only three patients in the study. In the majority of the analyzed cases, deterioration was reported in both the ophthalmological evaluation and in the visual evoked potentials (defective macular light reflection, optic disc pallor, attenuation of retinal vessels, pigmentary retinal changes, macular degeneration and optic atrophy); all of these findings are congruent with what has been described previously in medical literature⁴⁰. These changes can occur even before the onset of vision loss, which was documented in the present investigation. In this study, similar to what has been reported worldwide, substantial disease progression was observed when comparing the initial clinical manifestations reported in medical records with the findings of the most recent neurological examination^{41,42}.

Current therapeutic options in this disease include symptom management for: seizures, sleep problems, extrapyramidal symptoms, behavior problems, anxiety and psychosis. Seizures in NCLs are often refractory to treatment and require the prescription of multiple antiseizure medications such as sodium valproate, lamotrigine, topiramate, levetiracetam, carbamazepine, and benzodiazepine derivatives^{43,44}. There were no major differences regarding the main antiseizure medications prescribed when compared to other countries, and possible variations would be due mainly to the availability of the medication in the country and in the social security health care system (CCSS).

Regarding the study participant in whom the c.214G > T Costa Rican mutation was not identified, it is possible that mutations in other NCL genes could be responsible for their symptoms, as has been documented in other Costa Rican patients^{27,29}. It is worth noting that this was the only patient that presented with a normal ophthalmic evaluation and normal visual evoked potential at diagnosis, demonstrative of some disparity in their disease presentation. Additionally, while vast majority of Costa Rican patients with NCL are treated in the HNN, the possibility (although low) of patients in other regional or private healthcare centers cannot be disregarded.

Conclusion

Collectively, this investigation confirms the presence of the c.214G > T Costa Rican mutation in most Costa Rican patients with clinical symptoms of NCL and sustains that the clinical characteristics of these patients are similar to those described in other regions globally.

Abbreviations

CLN6: Neuronal Ceroid Lipofuscinosis Type 6

CCSS: Costa Rica Social Security System

NCLs: *neuronal ceroid lipofuscinoses*

HNN: Costa Rica's National Children's Hospital

DNA: Deoxyribonucleic acid

ER: Endoplasmic reticulum

NGS: next generation sequencing

SD: South Dakota

USA: United States of America

EEG: electroencephalogram

ERG: electroretinogram

ND: no data

ON: Optic Nerve

CT: Computerized tomography

VEP: Visually Evoked Potentials

APRONEP: Costa Rica's Association for Children with Progressive Neurological Diseases

Declarations

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Ethics approval and consent to participate:

After obtaining approval from the Institution's Scientific Ethics Committee (CEC-CENTRAL-CCSS) and authorization from the Director of Costa Rica's National Children's Hospital (HNN), the parents of all patients with a clinical diagnosis of Batten disease currently treated at the HNN Neurology Department were contacted, the study was explained, and the investigators invited the parents so their child could participate. All parents agreed and signed an informed consent form so the patient could participate.

Consent for publication:

Not applicable

Availability of data and materials:

The datasets generated and/or analysed during the current study are not publicly available due to internal policies of the CCSS that prohibited the publication of any patient's information in any website outside of its network, but are available from the corresponding author on reasonable request

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

ASC, RBP and AEM contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. AUC, AGM, LHC and SBL were the head doctors of the patients in the study, they contribute with the data collection and review the written manuscript. JW did the genetic sequencing of the patient and help with the writing of the article. ABM contributed with the extensive bibliographic search and support the writing of the manuscript. JB participated in the review, writing and as a consultant for clinical insight of the disease. ASR was part of the data collection team and writing, contributed to the data analysis and the design of the figures and graphics.

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Figures

Figure 1

Geographic distribution of cases. Blue pin indicates a patient with Batten disease without the CLN6 Costa Rican mutation.