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Classic and Atypical Late Infantile Neuronal Ceroid Lipofuscinosis in Latin America: Clinical and Genetic Aspects, and Treatment Outcome with Cerliponase Alfa

Norberto Guelbert [a], Oscar Mauricio Espitia Segura [b,*], Carolina Amoretti [c], Angélica Arteaga Arteaga [d], Nora Graciela Atanacio [e], Sabrina Bazan Natacha [f], Ellaine Doris Fernandes Carvalho [g,h], Maria Denise Fernandes Carvalho de Andrade [g,h,i,j,k], Inés María Denzler [l], Consuelo Durand [m], Erlane Ribeiro [n], Juan Carlos Giugni [o], Gabriel González [p], Dolores González Moron [q], Guillermo Guelbert [r], Zulma Janneth Hernández Rodriguez [s], Katiane Embiruçu Emilia [t], Marcelo Andrés Kauffman [q], Nury Isabel Mancilla [u], Laureano Marcon [v], Alessandra Marques Pereira [w], Carolina Fischinger Moura de Souza [x], Victor Adrián Muñoz [r], Ricardo Andrés Naranjo Flórez [b], André Luiz Pessoa [n], María Victoria Ruiz [p], Martha Luz Solano Villareal [y], Norma Spécola [z], Lina Marcela Tavera [aa], Javiera Tello [ab,ac], Mónica Troncoso Schifferli [ab,ac], Sonia Ugrina [ad], María Magdalena Vaccarezza [l], Diane Vergara [ab,ac], María Mercedes Villanueva [ae]

[a] *Clínica Universitaria Reina Fabiola, Córdoba, Argentina*
[b] *Fundación Hospital Pediátrico la Misericordia, Bogotá, Colombia*
[c] *Hospital Universitário Professor Edgar Santos, Salvador, Brazil*
[d] *Clínica León XIII, Medellín, Colombia*
[e] *Hospital de Niños Pedro de Elizalde (HNPE), Buenos Aires, Argentina*
[f] *Hospital Italiano Buenos Aires, Buenos Aires, Argentina*
[g] *Christus University Center (UNICHRISTUS), Fortaleza, Brazil*
[h] *General Hospital Dr. Cesar Cals, Fortaleza, Brazil*
[i] *Universidade Estadual do Ceará (UECE), Fortaleza, Brazil*
[j] *Hospital Universitário do Ceará, Fortaleza, Brazil*
[k] *Faculdadde Paulo Picanço, Fortaleza, Brazil*
[l] *Hospital Italiano de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina*
[m] *Laboratorio de Neuroquímica Dr. N.A. Chamoles, Ciudad Autónoma de Buenos Aires, Argentina*
[n] *Hospital Infantil Albert Sabin, Fortaleza, Brazil*
[o] *Hospital Dr. Guillermo Rawson, San Juan, Argentina*
[p] *Centro Hospitalario Pereira Rossell (CHPR), Montevideo, Uruguay*
[q] *Hospital JM Ramos Mejía, Buenos Aires, Argentina*
[r] *Hospital de Niños de la Santísima Trinidad, Córdoba, Argentina*
[s] *Hospital Central de la Policía Nacional, Bogotá, Colombia*
[t] *Hospital Universitario Professor Edgard Santos, Salvador, Brazil*
[u] *Universidad Nacional de Colombia, Bogotá, Colombia*
[v] *Instituto de Neurología y desarrollo (INEDEM), Buenos Aires, Argentina*
[w] *Hospital Moinhos de Vento, Porto Alegre, Brazil*
[x] *Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil*
[y] *Fundación Cardioinfantil, Bogotá, Colombia*
[z] *Hospital de Niños Sor Maria Ludovica, La Plata, Argentina*
[aa] *Fundación Conexión Neurológica, Armenia, Colombia*
[ab] *Hospital Clínico San Borja Arriarán, Santiago, Chile*
[ac] *Universidad de Chile, Santiago, Chile*
[ad] *Hospital Provincial Neuquén, Neuquén, Argentina*
[ae] *Hospital General de Niños Dr. Pedro Elizalde, Buenos Aires, Argentina*

* Corresponding author at: Institution: HOMI Fundación Hospital Pediátrico la Misericordia, Avenida Caracas 1-65, Bogota, Colombia.
E-mail address: omespitias@unal.edu.co (O.M. Espitia Segura).

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ABSTRACT

Introduction: Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), is a neurodegenerative autosomal recessive disease caused by *TPP1* gene variants, with a spectrum of classic and atypical phenotypes. The aim of treatment is to slow functional decline as early as possible in an attempt to improve quality of life and survival. This study describes the clinical characteristics as well as the response to treatment with cerliponase alfa.

Materials and methods: A retrospective study was conducted in five Latin-American countries, using clinical records from patients with CLN2. Clinical follow-up and treatment variables are described. A descriptive and bivariate statistical analysis was performed.

Results: A total of 36 patients were observed (range of follow-up of 61–110 weeks post-treatment). At presentation, patients with the classic phenotype ($n = 16$) exhibited regression in language (90%), while seizures were the predominant symptom (87%) in patients with the atypical phenotype ($n = 20$). Median age of symptom onset and time to first specialized consultation was 3 (classical) and 7 (atypical) years, while the median time interval between onset of symptoms and treatment initiation was 4 years (classical) and 7.5 (atypical). The most frequent variant was c.827 A > T in 17/72 alleles, followed by c.622C > T in 6/72 alleles. All patients were treated with cerliponase alfa, and either remained functionally stable or had a loss of 1 point on the CLN2 scale, or up to 2 points on the Wells Cornel and Hamburg scales, when compared to pretreatment values.

Discussion and conclusion: This study reports the largest number of patients with CLN2 currently on treatment with cerliponase alfa in the world. Data show a higher frequency of patients with atypical phenotypes and a high allelic proportion of intron variants in our region. There was evidence of long intervals until first specialized consultation, diagnosis, and enzyme replacement therapy. Follow-up after the initiation of cerliponase alfa showed slower progression or stabilization of the disease, associated with adequate clinical outcomes and stable functional scores. These improvements were consistent in both clinical phenotypes.

1. Introduction

Ceroid neuronal lipofuscinoses (CLN) are a set of neurodegenerative lysosomal storage diseases that, collectively, have an estimated incidence of 1–3/100.000 births per year and a prevalence of 2–4/1000000 [1]. To date, 14 NCL types have been described with specific characteristics in terms of age of onset and causative gene [2], and approximately 537 causal variants [3]. Ceroid neuronal lipofuscinosis type 2 (CLN2) is an autosomal recessive disease caused by variants of the *TPP1* gene (11p15.4). Approximately 131 variants have been described for the classic and atypical phenotypes [4]. The most frequent variants found across the world are c.509-1G > C and c.622C > T [p.Arg208X]. In Latin America, where allelic variations are high [5–7], different variants have been reported with varying frequency in patients with CLN2, the most frequent being c.827 A > T/p.Asp276Val [8,9]. The incidence and prevalence of the disease might vary by geographic region [10,11].

Patients are pre-symptomatic during the first two years of life, although some manifest milder sings [12,13]. The first symptom is usually early language delay [14], while polymorphic seizures are among the primary symptoms at the time of medical consultation (70% of cases) with an age of onset between 2 and 4 years [15,16], when ataxia usually manifests [17]. At the same time, there is cognitive decline as well as progressive motor deterioration, leading eventually — by approximately 6 years of age — to the loss of voluntary movements and of the ability to swallow and speak. Patients also experience visual loss as a result of retinal degeneration, as well as abnormal movements (myoclonus, spasticity, dystonia, and chorea). Death occurs between 8 and 15 years of age [15]. CLN2 presents as a well-described spectrum, with the atypical phenotype having a more variable presentation later on in life [18,19].

Arriving at a precise clinical suspicion is often not possible given the heterogeneity described above and the low level of awareness regarding this disease. This results in delayed specific testing [20], and hence the recommendation to use multigene testing in the diagnosis of unexplained seizures, even in the absence of a specific clinical suspicion [19]. Diagnosis is confirmed by the presence of two pathogenic homozygous or heterozygous *TPP1* variants, accompanied by deficient or absent TPP1 enzyme activity [33]. Early diagnosis is crucial for the immediate initiation of disease-modifying therapy. With the advent in recent years of new advances in genetics and genomic medicine, low-cost and faster techniques are now available for accurate and early diagnosis, particularly in cases of clinical suspicion of CLN2 or in families with evidence of affected individuals. This allows initiation of the therapy while the patient is still pre-symptomatic or has early symptoms of the disease [20].

Regular assessment of functional performance in patients with CLN2 using scales validated in the literature [21] including the Hamburg [22], Weill Cornell [23] and CLN2 clinical rating scales [24], as well as the SARA scale [25] (supplement 1), allows to evaluate motor and language parameters, determine disease progression, and assess the degree of disability, among other things [21]. These patients require comprehensive management with a multidisciplinary approach to ensure early diagnosis and treatment initiation with the aim of achieving a positive impact on quality of life [13].

Recombinant TPP1 (Cerliponase alfa, BioMarin Pharmaceutical Inc., Novato, CA) is, to date, the only FDA and EMA-approved medication for the treatment of patients diagnosed with CLN2, with documented efficacy at modifying the natural history of the disease [9,26–28]. Cerliponase alfa has been shown to slow the progression of the disease in terms of motor and language impairment, or both, when comparing the results on the CLN2 functional assessment scale between patients treated with cerliponase alfa versus historical cohorts [28].

This study describes the characteristics of the cohort with the largest number of CLN2 patients reported in the world, before the start of treatment and during follow-up, as well as the impact of cerliponase alfa on disease progression.

2. Materials and methods

2.1. Patients and methods

A retrospective study was carried out in institutions across Latin America, in 36 patients diagnosed with CLN2 who had at least 6 months of treatment. Patients with enzyme and genotype confirmation of the CLN2 classic phenotype (defined as onset at 2–3 years with rapid progression) and atypical phenotype (defined as onset at 5 years with slow progression) who were prescribed cerliponase alfa in accordance with product label and medical judgment were included. At least two follow-up visits after treatment initiation were reviewed.

The study was approved by the ethics committee of all the institutions where patients received treatment and was carried out in

accordance with the local regulations and the principles set forth in the Declaration of Helsinki [29].

2.2. Study design

An Excel (*version 16.35*) database was created with descriptive patient variables (age at enrollment, gender, carrier family members, consanguinity and perinatal history); disease onset variables (age at the time of consultation, initial symptoms, symptoms at the time of the first consultation, initial pharmacological management, initial tests and *TPP1* gene sequencing); follow-up variables (additional symptoms manifesting over the course of the disease, score on the Weill Cornell, Hamburg, SARA and CLN2 functional assessment scales); enzyme replacement-related variables (age at initiation, dose, interval, time on therapy, adherence percentage) and post-treatment variables (score on the CLN2 functional assessment, Weill Cornell, Hamburg, and SARA scales). Slower progression was defined as maintenance or loss of up to 1 point on the CLN2 functional assessment scale, or up to 2 points on the Weill Cornell and Hamburg scales at the end of follow-up. Patients were followed at least 6 months after treatment initiation or until the drug was discontinued due to any cause, such as family choice or medical judgment.

Anonymized data were collected by the treating physicians, while a third party was entrusted with data preservation, conservation, and verification. Researchers were trained in data collection. Cases in which missing or incomplete data were found were reviewed, when available, by the treating physicians.

2.3. Statistical analysis

The statistical analysis was carried out using the SPSS software package (*version 26*). A descriptive analysis was performed following the normality test (Shapiro-Wilk). Categorical variables were described as frequencies and percentages; quantitative variables were described as central trends and scatter. For the bivariate analysis, tables were built, and normal distribution quantitative variables were analyzed using Student's *t*-test; the Wilcoxon test was used for non-normal distribution. Qualitative variables were analyzed using Pearson's chi square or the exact Fisher test, as appropriate.

3. Results

A total of 36 patients with a diagnosis of CLN2 coming from 5 Latin American countries [Argentina (41.7%, $n = 15$), Colombia (27.8%, $n = 10$), Brazil (16.7%, $n = 6$), Chile (11.1%, $n = 4$) and Uruguay (2.8%, $n = 1$)] were included in the study. Median age at the time of enrollment was 13.5 (IQR 9.5) years, and 47.2% ($n = 17$) were males. A total of 20 (55.6%) had a *classic phenotype* and 16 (44.4%) had an *atypical phenotype*, with no differences in gender by phenotype ($p = 0.709$) (Table 1). In patients with the *classic phenotype,* the most frequent symptoms at the time of the first consultation were language regression (90%), seizures (80%), ataxia (60%), and developmental delay (60%), while in patients with the *atypical phenotype*, the most frequent symptoms were seizures and language delay (87% and 68%, respectively) at the time of the first consultation.

When the two groups were compared, a higher frequency of seizures ($p = 0.022$), language impairment ($p = 0.003$) and ophthalmological symptoms ($p = 0.001$) was found in the patients with the *classic phenotype*. Seizures presented as an earlier symptom in patients with the classic phenotype when compared to patients with the atypical phenotype ($p = 0.0156$). Moreover, there was a higher use of second line medications (lamotrigine [$p = 0.001$] and oxcarbazepine [$p < 0.001$]) in patients with the classic phenotype when compared to those with the atypical phenotype (Supplement 2). During the pretreatment visit, the prevalence of ataxia, movement disorders ($p = 0.022$), language impairment ($p < 0.001$) and developmental regression ($p = 0.035$) was found to be slightly higher in patients with the classic phenotype (Fig. 1).

Table 1
Sociodemographic variables for classic and atypical patients.*

Variable		Classic		Atypical	
		% (*n*)	Median (IQR)	% (*n*)	Median (IQR)
Carrier family members		35 (7)		37.5 (6)	
Carrier family type	Sibling				
	Parent	10 (2)		12.5 (2)	
Parental consanguinity		10 (2)			
Other history	Maculopathy	5 (1)		6.25 (1)	
	Febrile seizure			6.25 (1)	
	Head injury / subdural hematoma			6.25 (1)	
Tripeptidyl peptidase	Undetectable	50 (10)		–	43.8 (7)
	Below range	45 (9)		–	56.2 (9)
Age (months)			108 (79.5)		191.5 (63)
Age (years)			9 (7)		15.5 (4.75)
Age of onset of symptoms (years)			3 (2.5)		6 (2)
Age of onset of symptoms (months)			39.5 (34)		78 (21)
Age at the time of first consultation (years)			3 (4.5)		7 (2)
Age at the time of first consultation (months)			40 (57)		84 (25.25)
Age of language regression (months) ($n = 24$)			36 (90.5)		31 (61)
Age of neurodevelopmental regression (months) ($n = 20$)			48 (87)		96 (51)

* IQR: Interquartile Range.

Enzymatic activity of tripeptidyl peptidase was undetectable in 47.2% of patients; *TPP1* gene sequencing data are shown in Supplement 3.

In patients with the *classic phenotype*, the predominant symptom immediately before therapy initiation was language impairment (100%), followed by ataxia (90%) and movement disorders (85%) (Fig. 2), while in patients with the *atypical phenotype*, the predominant symptoms were language regression (87.5%), ataxia (87.5%) and language impairment (81.25%) (Fig. 2).

After the first consultation, brain magnetic resonance imaging (MRI), electroencephalography (EEG), paroxysmal response to light, visual evoked potentials, electroretinography (ERG), and optical coherence tomography (OCT) were performed (Supplement 2); concomitant treatments are stated in Supplement 4.

As part of their treatment, all patients (100%) received intracerebroventricular treatment with cerliponase alfa, at the recommended dose of 300 mg, with a median interval of 15 days, as indicated by the treating physicians. Median age at treatment initiation was 14 (IQR = 5) years for *atypical patients* with an interval between initial symptoms and treatment initiation of 7.4 years, and 6.12 years between diagnosis and treatment initiation. In the *classic patients,* median age at treatment initiation was 5 (IQR = 9) years, and the interval between initial symptoms and treatment initiation was 3.8 years, and 2.4 years between diagnosis and treatment initiation.

The average length of treatment was 22.86 ± 14.82 months, with an overall median rate of adherence to planned doses of 73%. Treatment was discontinued in 25% ($n = 5$) of the *classic patients* and 37.5% ($n = 6$) of the *atypical patients*, with a mean time between initiation and discontinuation of 15.9 ± 10.03 months; 5.5% ($n = 2$) of patients

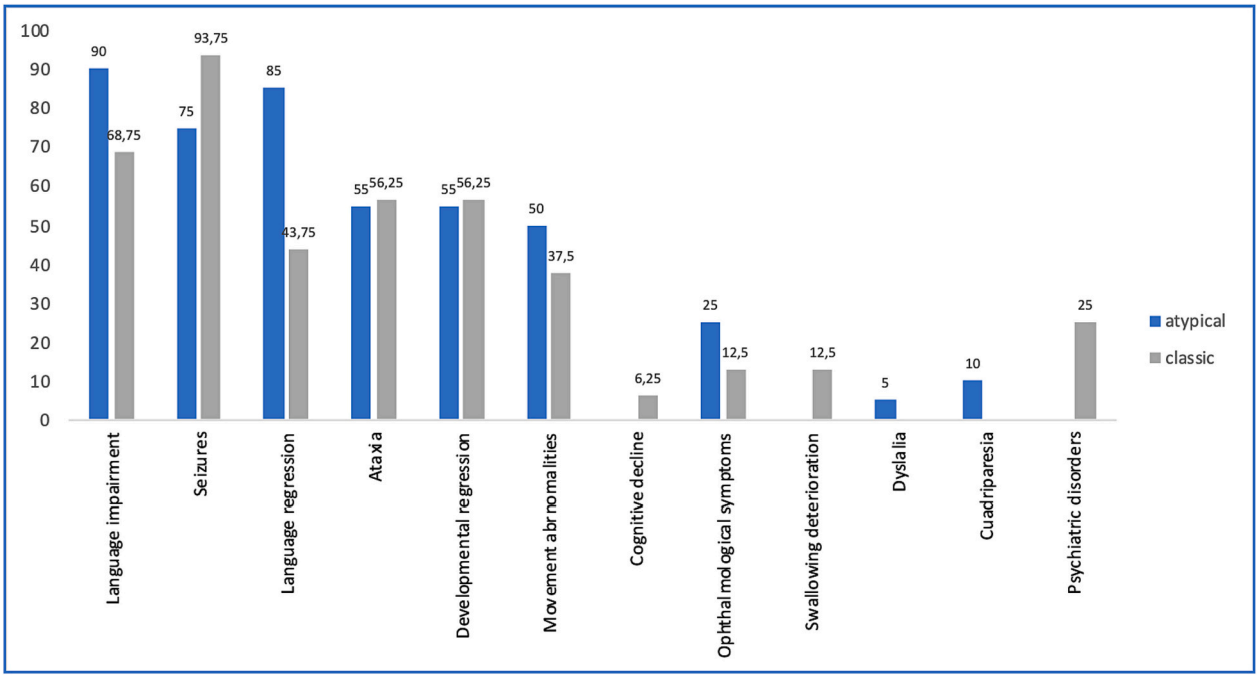

Fig. 1. Frequency of symptoms at the time of the first consultation in classic and typical patients.

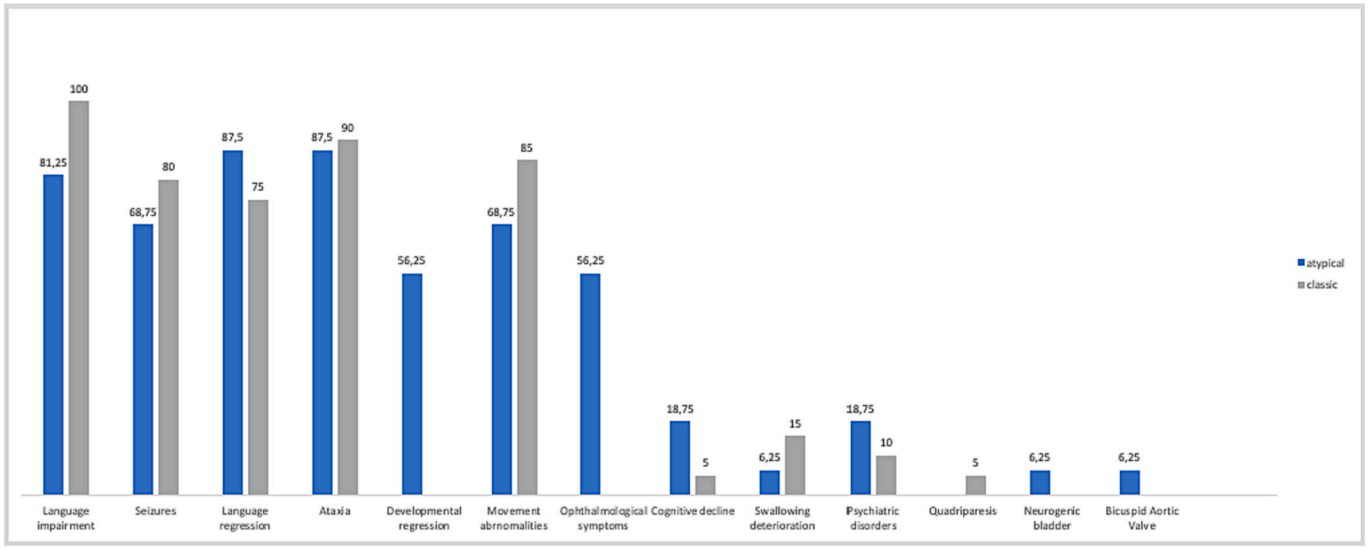

Fig. 2. Symptoms on follow-up of classic and atypical CLN2 patients.

discontinued treatment due to issues arising during the SARS-CoV2 pandemic; 2.8% ($n = 1$) due to family decision, 13.9% ($n = 5$) due to infection, and 8.3% ($n = 3$) due to lack of access to insurance.

At the time of the first follow-up visit (ranging between 11 and 60 weeks after treatment initiation), 55% ($n = 11$) of the patients with the *classic phenotype* showed improvement in abnormal movements, 35% ($n = 7$) a lower seizure frequency, 50% ($n = 10$) of patients were seizure-free, and central nervous system infections as an adverse therapy-related event occurred in 15% ($n = 3$) of patients. In the *atypical phenotype,* 25% ($n = 4$) of the patients showed improvement in abnormal movements, 31.25% ($n = 5$) a lower seizure frequency, 50% ($n = 8$) of patients were seizure-free, and central nervous system infections as an adverse therapy-related event occurred in 12.5% ($n = 2$) of patients.

At the time of the second follow-up visit (range of 61–110 weeks post-treatment), in the *classic phenotype,* 40% ($n = 8$) of the patients showed improvement in abnormal movements, 40% ($n = 8$) a lower seizure frequency, and 30% ($n = 6$) of patients were seizure-free, while in the *atypical phenotype,* 12.5% ($n = 2$) of the patients showed improvement in abnormal movements, 18.75% ($n = 3$) a lower seizure frequency, and 43.75% ($n = 7$) of patients were seizure-free. No assessments of movement disorder by a rating scale were made.

In the *classic phenotype,* 100% of the patients had slower progression, defined as maintenance or loss of up to 1 point on the CLN2 functional assessment scale, or up to 2 points on the Weill Cornell and Hamburg scales at the end of follow-up (pre-treatment and second follow-up), and 90% on the Hamburg scale. Slower progression of ataxia was evident in 80% ($n = 4$) of the patients (SARA scale), while in the *atypical phenotype*, 93.75% ($n = 15$) had slower progression on the CLN2 functional scale, 100% on the Weill Cornell scale, and 87.5% ($n = 14$) on the Hamburg scale. Slower progression of ataxia (SARA scale) was reported in 81.25%

(n = 3) of these patients (Supplement 5). A statistically significant decline on the SARA scale (which is used to assess ataxia in many diseases but not specifically for functional evaluation in terms of response to enzyme replacement therapy) [21] was observed (p 0.048) (pre-treatment and second follow-up). Of these patients with decline, 86% were older than 8 years when they started treatment, 43% had an atypical phenotype, and two patients had low adherence at 19 and 30%, respectively. In this group, one patient showed an increase of 18 points on the SARA scale during follow-up, likely due to treatment discontinuation driven by SARS-CoV2-related social and family difficulties, 11 months after therapy initiation. Of the patients with decline on the Hamburg scale, 71.42% were older than 6 years at the time of treatment initiation, with adherence >60% except for one patient with 19% adherence.

4. Discussion

This is the largest cohort of patients with CLN2 on treatment with cerliponase alfa, followed in a real-world setting, reported to date in the medical literature. The median age of symptom onset in Latin-American patients, in both the classic and atypical phenotypes, is consistent with what is described in the literature (2–4 years for the classic phenotype and a later onset [>4 years] in atypical patients) [7,18,28]. Symptoms at presentation and disease progression in our patients are consistent with the reports in the literature [7,18]. However, there is a median interval of 1 years for both phenotypes between the moment the patient reports the first symptom and access to CLN2 specialized consultation. This can be an indirect marker of healthcare hurdles faced by patients suffering from orphan diseases such as CLN2, and care inequalities in the region, probably resulting in delayed diagnosis and treatment.

As already alluded to, the long interval between initial symptoms, diagnosis and treatment highlights access barriers to diagnosis and treatment, as well as the fact that diagnosis is challenging given that the classical literature describes mostly classic phenotypes, thus requiring physicians to rely on a high index of suspicion and their own medical judgment. Delayed initiation of disease-modifying therapies was found, with a potentially negative effect on patient quality of life and survival, with deterioration between diagnosis and therapy initiation [9,27,28,30]. Although programs have been created in Latin America for patients with diseases like CLN2 that also aim to reduce access barriers [30–32], the data derived from this study suggest that there is a need to improve access to diagnosis and therapies if quality of life and outcomes in these patients are to be improved. Moreover, patients with the atypical phenotype are a clinical challenge because they can be overlooked and remain with no diagnostic suspicion for a long period of time. This underscores the importance of suspecting CLN2 in patients presenting with seizures, ataxia, language impairment or cognitive deterioration, as reported [7,9,18,19].

According to the study results, the proportion of patients with the atypical phenotype (44.4%) in Latin America is higher than reported in the international literature [11,18], which is consistent with case series reported in some Latin-American countries where genetic heterogeneity has been reported [5,7,9]. Among patients in the region, the most frequent variants were the ones that involve intron regions in 20/72 alleles, namely c.887-10 A > G (10/72 alleles) reported in Argentina, Chile, Colombia, Portugal, and Spain [7,9,33], likely causing an in-frame inclusion of intron 7 [32]. With this variant, clinical manifestations occur at a later age [33,34]; in this study it was found in heterozygosis in 8 atypical patients and 2 classic patients (one in homozygous state and another in association with c.622C > T). In the analysis of exon mutations, the most frequent variant was c.827 A > T in 17/72 alleles, followed by c.622C > T in 6/72 alleles. These two variants have been reported in the literature, with a frequency of 2% and 23%, respectively. The most frequent variant in our study was c.827 A > T, which has also been previously reported in Argentina and Chile [33]. A novel variant (c.496deIC) was found in the study population and is predicted to be potentially pathogenic based on the results of the *in-silico* Mutation Tester [35,36] and SIFT [37–39] software. Finally, it is worth noting that the changes found in frequencies of allele mutations associated with atypical phenotypes are likely a cause for the high frequency of this phenotype in Latin America.

Discontinuation due to issues related to access to the medication underscores the importance of ensuring that these patients are treated consistently and of avoiding the effects of access inequalities or healthcare barriers, as discontinuation might reduce treatment effectiveness and, consequently, patient functionality. In 5.5% of cases, discontinuation was attributed to the SARS-Cov2 pandemic which likely disrupted drug administration, as reported for rare diseases [40]; 13.9% of patients discontinued the medication due to infection, and all of them reinitiated later, with no other adverse events leading to discontinuation or drug-related events being reported.

After cerliponase use, there was an improvement in abnormal movements and seizure frequency, with 50% and 72% of patients being seizure-free at the time of the first and second follow-up visits, respectively, and a similar result in seizure frequency. The use of cerliponase showed some absolute change in the scales measured, but when significant changes were assessed (defined as a loss of up to 1 point on the CLN2 functional assessment scale, or up to 2 points on the Weill Cornell and Hamburg scales at the end of follow-up) a slower disease progression was found in 96.43% of the patients with the classic and atypical phenotypes, showing a positive effect of the treatment in less than two years of follow-up, and even in patients who received ERT after a longer disease course without treatment.

This study has potential limitations. The effect measured is based on a retrospective study, and some variables (specific to type of seizure and duration of the seizure) were not available.

For post-treatment weeks 61–110, a mild increase of >2 points in ataxia was found in 7 patients (median of change 8), using the SARA scale. In view of the above, in the setting of a real-world study, the decline on the Hamburg and increase in SARA scores might be at least partially explained by adherence. Consequently, regular treatment could be associated with improvement in clinical outcomes [21]; however, this remains to be studied specifically.

5. Conclusions

This study reports the largest number of CLN2 patients on treatment with cerliponase alfa followed in the real world setting during a period of 61–110 weeks post-treatment. The study shows a higher frequency of the atypical phenotype than previously reported, due in part to a higher frequency of allele intron mutations. This fact has been reported mainly in publications coming from Spain and Portugal. In the Americas, access barriers and inequalities in terms of care and access to genomic studies have imposed reporting limitations. The behavior of the disease in our region is consistent with what has been described in previous publications pertaining to the natural history of the disease. However, time intervals are longer for diagnosis, access to specialized healthcare and enzyme replacement therapy initiation, which could affect outcomes in quality of life and treatment response in patients with CLN2. A high suspicion index is of paramount importance, as phenotypes might be variable, and earlier diagnosis is associated with better outcomes. This study suggests that cerliponase alfa is effective and safe in the treatment of patients with CLN2, slowing the functional deterioration associated with the natural history of the disease in adherent patients. Clinical and functional improvements are related to the amelioration of epileptic seizures as well as functionality stabilization as assessed by means of functional scales, with a positive impact on the patients being consistent in both clinical phenotypes.

Therefore, it is important to work on early diagnosis, including medical education that can help disseminate information regarding the characteristics of the atypical phenotype in Latin America. This would lead to earlier initiation of enzyme replacement therapy, thus improving

quality of life and functional outcomes in patients with CLN2.

Ethics approval and consent to participate

The ethics committees of each of the institutions where the patients were diagnosed and followed gave their authorization.

Consent for publication

Since no individual data are reported, no consent for publication was required.

Availability of data and materials

The datasets used and/or analyzed as part of the study are available from the corresponding author on reasonable request.

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Authors' contributions

NG and OM.ES were resposible for data collection, analysis and interpretation. Data analysis and editorial coordination were provided by a third party. All the authors (GN, ES.OM, AC, AA.A, A.NG, B.NS, CE. DF, CA.MDF, D.IM, DC, RE, G.JC, GG, G.MD, GG, HR.ZJ, E.EK, K.MA, M. NI, ML, MP.A, FMS.C, M.VA, NF:RA, P.AL, R.MV, SV.ML, SN, T.LM, TJ, TS.M, V.MM, VD, SU, V.MM) determined the objectives of the study, collected data, contributed with adjusments to the paper, read and approved the final manuscript.

Editorial coordination

Integralis HGS (Doctors Daniel Rodríguez and María Stella Salazar).

CRediT authorship contribution statement

Norberto Guelbert: Conceptualization, Methodology, Writing – review & editing. **Oscar Mauricio Espitia Segura:** Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Carolina Amoretti:** Conceptualization, Methodology, Writing – review & editing. **Angélica Arteaga Arteaga:** Conceptualization, Methodology, Writing – review & editing. **Nora Graciela Atanacio:** Conceptualization, Methodology, Writing – review & editing. **Sabrina Bazan Natacha:** Conceptualization, Methodology, Writing – review & editing. **Ellaine Doris Fernandes Carvalho:** Conceptualizacion, Methology, Writing – review & editing. **Maria Denise Fernandes Carvalho de Andrade:** Conceptualization, Methodology, Writing – review & editing. **Inés María Denzler:** Conceptualizacion, Methodology, Writing – review & editing. **Consuelo Durand:** Conceptualization, Methodology, Writing – review & editing. **Erlane Ribeiro:** Conceptualization, Methodology, Writing – review & editing. **Juan Carlos Giugni:** Conceptualization, Methodology, Writing – review & editing. **Gabriel González:** Conceptualization, Methodology, Writing – review & editing. **Dolores González Moron:** Conceptualization, Methodology, Writing – review & editing. **Guillermo Guelbert:** Conceptualization, Methodology, Writing – review & editing. **Zulma Janneth Hernández Rodriguez:** Conceptualization, Methodology, Writing – review & editing. **Katiane Embiruçu Emilia:** Conceptualization, Methodology, Writing – review & editing. **Marcelo Andrés Kauffman:** Conceptualization, Methodology, Writing – review & editing. **Nury Isabel Mancilla:** Conceptualization, Methodology, Writing – review & editing. **Laureano Marcon:** Conceptualization, Methodology, Writing – review & editing. **Alessandra Marques Pereira:** Conceptualization, Methodology, Writing – review & editing. **Carolina Fischinger Moura de Souza:** Conceptualization, Methodology, Writing – review & editing. **Victor Adrián Muñoz:** Conceptualization, Methodology, Writing – review & editing. **Ricardo Andrés Naranjo Flórez:** Conceptualization, Methodology, Writing – review & editing. **André Luiz Pessoa:** Conceptualization, Methodology, Writing – review & editing. **María Victoria Ruiz:** Conceptualizacion, Methodology, Writing – review & editing. **Martha Luz Solano Villareal:** Conceptualization, Methodology, Writing – review & editing. **Norma Spécola:** Conceptualization, Methodology, Writing – review & editing. **Lina Marcela Tavera:** Conceptualization, Methodology, Writing – review & editing. **Javiera Tello:** Conceptualization, Methodology, Writing – review & editing. **Mónica Troncoso Schifferli:** Conceptualization, Methodology, Writing – review & editing. **Sonia Ugrina:** Conceptualization, Methodology, Writing – review & editing. **María Magdalena Vaccarezza:** Conceptualization, Methodology, Writing – review & editing. **Diane Vergara:** Conceptualization, Methodology, Writing – review & editing. **María Mercedes Villanueva:** Conceptualization, Methodology, Writing – review & editing.

Declaration of competing interest

Dr. Atanacio has been a lecturer for the Biomarin Laboratory. Dr. Denzler has been a speaker for BioMarin. Dr. Durand has maintained a financial relationship with BioMarin through service contracts as speaker. Dr. Erlane has received travel grants, speaker fees, and educational grants from Biomarin. Dr. Espitia Segura reports a relationship with BioMarin Pharmaceutical Inc., including speaker fees and travel reimbursement. Dr. N Guelbert has received speaker fees from Biomarin. Dr. Pessoa has been a speaker for Biomarin. Dr. Naranjo and Dr. Tavera report a relationship with BioMarin Pharmaceutical Inc. that includes speaker and conference fees, as well as travel reimbursement.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101060.

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