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### ► To cite this version:

Bastien Estublier, Aline Cano, Célia Hoebeke, Samia Pichard, Didier Scavarda, et al.. Cerliponase alfa changes the natural history of children with neuronal ceroid lipofuscinosis type 2: The first French cohort. *European Journal of Paediatric Neurology*, 2021, 30, pp.17-21. 10.1016/j.ejpn.2020.12.002 . hal-03578032

**HAL Id: hal-03578032**

**<https://hal.science/hal-03578032v1>**

Submitted on 29 Nov 2024

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## Cerliponase alfa changes the natural history of children with Neuronal Ceroid Lipofuscinosis type 2 : the first French cohort

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**Abstract:**

Introduction: Neuronal Ceroid Lipofuscinosis type 2 (CLN2) is a neurodegenerative lysosomal disease which leads to early dementia and death without treatment. The recently available therapy consists of intracerebroventricular enzyme substitution: cerliponase alfa. In this report, we describe the evolution of the first French children treated with cerliponase alfa.

Method: CLN2 Clinical Rating Scale Motor-Language (CLN2 ML) assesses the motor and language evolution of CLN2 patients. We retrospectively studied patients' medical records: clinical symptoms, MRI conclusions, gene mutation, side effects of infusions, patient's age and CLN2 ML scores at diagnosis, at the beginning of enzyme replacement therapy (ERT) and at the last evaluation. Seven patients were included.

Results: Average age at diagnosis was 50 months (+/- 10) with CLN2 ML score equal to 3.6 [1.5 – 5]. Average age at the beginning of ERT was 56 months (+/- 13) with CLN2 ML score equal to 3.1 [1 – 5]. At the last available evaluation, average age was 82 months (+/- 20) with CLN2 ML score equal to 2.8 [0 – 5]. Thus, in 26 months, the mean CLN2 ML score only decreased by 0.3 points. However, patients with a CLN2 ML score greater than three at the onset of ERT experienced a stabilisation or improvement of clinical signs, whereas patients with a CLN2 ML score less than three at baseline continue to deteriorate.

Conclusion: For patients starting ERT at an early stage of the disease, cerliponase alfa changes the natural history of the disease with a halt in disease progression or even a slight improvement in clinical symptoms.

**Keywords:**

Neuronal Ceroid Lipofuscinosis type 2, lysosomal storage disorders, tripeptidyl peptidase I, enzyme replacement therapy, cerliponase alfa

**Highlights:**

- Neuronal Ceroid Lipofuscinosis type 2 (CLN2) is a neurodegenerative disease
- Speech delay, myoclonic epilepsy and gait disturbance must lead to a rapid diagnosis
- Cerliponase alfa is an intracerebroventricular enzyme replacement therapy (ERT)
- Early initiation of ERT can stop evolution of the disease
- ERT in patients with advanced stage of the disease does not prevent the worsening of the symptoms

**Abbreviations:**

- CLN: Neuronal Ceroid Lipofuscinosis
- CLN2: Neuronal Ceroid Lipofuscinosis type 2
- CLN2 ML: CLN2 Clinical Rating Scale Motor-Language
- ERT: enzyme-replacement therapy
- MRI: Magnetic Resonance Imaging
- PCR: Polymerase Chain Reaction
- TPP1: Tripeptidyl Peptidase-1

**Introduction:**

Neuronal Ceroid Lipofuscinosis (CLN) is a group of neurodegenerative diseases resulting from a lysosomal storage disorder. The late infantile form, Neuronal Ceroid Lipofuscinosis type 2 (CLN2), is the most frequent form of CLN in France. CLN2 is an autosomal recessive disease with mutations in a gene encoding a lysosomal enzyme: tripeptidyl peptidase-1 (TPP1) (1). The lack of TPP1 causes an accumulation of autofluorescent material in the lysosome leading to degeneration and neuronal death in the central nervous system and retina (2).

The onset and evolution of symptoms is homogenous in patients with classic late-infantile CLN2. The child's development is at first normal and then, around 18 months a language delay may be noted. A progressive neurodegenerative disease appears between 2 and 4 years of age, with myoclonic epilepsy, ataxia, movement disorders, dementia, spasticity and ophthalmologic deficiency with macula atrophy. The brain MRI is normal in the early stages of the disease, then cerebral and cerebellar atrophy appears. Without treatment, cognitive and motor skills decline rapidly around the age of 4 to 6 years, with loss of the ability to walk, speak and react to visual stimuli. Deterioration culminates in early death with a median death age of about ten years (3) (4) (5) (6).

The classical diagnosis method is the study of TPP1 activity followed by the research of the specific gene mutation (7). More recently, clinicians can use a CLN disorder gene panel or epilepsy gene panel (8) and the diagnosis is confirmed by studying TPP1 activity.

Enzyme-replacement therapy (ERT) has recently become available using cerliponase alfa, a recombinant proenzyme form of human TPP1. Intraventricular infusions of TPP1 in young CLN2 animals resulted in reduction in brain inflammation, slower progression of neurologic symptoms and prolonged life span (9) (10). This therapy consists of TPP1 administration by intraventricular infusions (11) at a dose of 300mg through an Ommaya ventricular reservoir which is inserted by a neurosurgeon. The reservoir is placed under the scalp and a catheter is inserted into the lateral ventricle. Each infusion of cerliponase alfa lasts around four hours and must be repeated every 15 days. This therapy has been reported to modify the natural course of the CLN2 disease in children by slowing the decline in motor and language functions and increasing lifetime (12).

In this study, the progress of the first French children treated with cerliponase alfa has been evaluated.

### ***Patients and methods:***

There are different scales for assessing children with CLN2 disease. The Hamburg motor and language scale (13) measures loss of motor function, loss of language, frequency of tonic-clonic generalised seizures and visual function. The Weill Cornell late infantile neuronal ceroid lipofuscinosis scale (14) includes the same grading regarding motor and language functions, but assesses two other domains: movement disorders and feeding autnomia.

The CLN2 Clinical Rating Scale Motor-Language (CLN2 ML) (Table 1) has been adapted from the common domain of the Hamburg and the Weill Cornell scales for motor and language assessment (15). Each domain is scored on a scale of 0 (no function) to 3 (normal function) points, resulting in a 0 to 6 point scale.

We collected data from the first French patients treated with cerliponase alfa in three university hospital (Hôpital La Timone, Marseille; Hôpital Necker, Paris; Hôpital R. Debré, Paris).

We retrospectively studied the patient's medical records: family backgrounds, clinical symptoms, age at onset of epilepsy, MRI conclusions, gene mutation. We also compiled age and CLN2 ML score at diagnosis, at the beginning of ERT and the most recent CLN2 ML score evaluation available. Side effects of infusions were considered. In three patients, when the CLN2 ML score was not assessed by physicians, we retrospectively evaluated the CLN2 ML score based on clinical description of motor and language skills.

The first French patients treated with cerliponase alfa were 4 boys and 4 girls. The parents of 5 children were consanguineous. In our statistical analysis, we do not include the patient 8 who has been treated since she was one year old, before any symptoms appeared. All patients had a similar development with language delay, initial normal motor acquisition followed by regression of development, ataxia with falls and behavioural or sleeping troubles. The diagnosis of CLN2 was genetically confirmed: all patients had a pathogenic variant in TPP1 gene (16). (Table 2).

Non-opposition agreements for this study were sought for each patient and were recorded in the patient's medical file. Our study was approved by ethics committee of Aix-Marseille University.

## Results

Epilepsy appeared at 40.5 (+/- 4) months and was often the first symptom of disease. First seizures were generalized tonic-clonic seizures, febrile seizures, atonic or myoclonic seizures associated with falls. In all our patients, epilepsy progressed towards a myoclonic, drug-resistant epilepsy. MRI was either normal at the onset of the disease or showed non-specific cortical or cerebellar atrophy.

The mean age at diagnosis was 50 (+/- 10) months with a mean CLN2 ML score of 3.6 [1.5 – 5] (Table 3).

The mean age at the beginning of ERT with cerliponase alfa was 56 (+/- 13) months, with a mean CLN2 ML score of 3.1 [1 – 5].

The last evaluation took place around the age of 82 (+/- 20) months, that is 26 months after the start of ERT. The mean CLN2 ML score at this last assessment was 2.8 [0 – 5]. The decrease of 0.3 point between onset of ERT and last evaluation is clearly less than the diminution of the CLN2 ML score in the natural cohort during the same period (around 2.5 points).

Figure 1 shows the evolution of each patient reported with the curve of the natural course of CLN2 extracted from Nickel, Schulz et al. Lancet, 2018 (5). Each line represents the evolution of a patient, and is composed of three points corresponding to the CLN2 ML scores according to age at the time of diagnosis, at the beginning of the ERT and at the last available assessment.

Our patients had approximately the same CLN2 ML scores in function of age as those of patients from the natural history cohort (without ERT). Thereafter, treatment by cerliponase alfa significantly changed the evolution of motor and language functions. We observed a major difference between the evolution of two groups within our cohort. On the one hand, patients placed late on ERT and having a CLN2 ML score below 3 at the onset of ERT continued to deteriorate. On the other hand, early-treated patients with a CLN2 ML score greater than 3 at the onset of ERT appeared to have a better outcome with cessation of disease progression: the patient 4 had a stabilisation of symptoms, the patients 2 and 3 experienced a little recovery of language skills.

In addition, it was found that almost all patients with ERT had better control of epilepsy, allowing for a reduction in antiepileptic medication. At the last assessment, patients 1, 2, 3 and 4 had only two antiepileptic medications that provided good epilepsy control. One patient (patient 4) had begun epilepsy after the very beginning of ERT.

Fever and convulsions after the infusion were common side effects. For patient 3, these symptoms have ended after the introduction of premedication with oral steroids. Four patients underwent reservoir removal due to catheter dysfunction related to device infection or suspected infection. These four patients received intravenous antibiotics treatment during reservoir removal and replacement. They did not have serious infection or clinical meningitis. Bacteria were identified in three patients. Patient 4 was suspected of reservoir infection with a positive PCR for *Candida Albicans* and *Enterococcus Faecalis*. However, further analyses did not show a cellular reaction in the cerebrospinal fluid, positive culture or clinical infection indicating a probable contamination. In all these cases, treatment with cerliponase alfa was slightly delayed.

## Discussion:

To our knowledge, this is the first cohort describing patients with treatment by cerliponase alfa outside of trials. An observational cohort (5) from two independent and international datasets has shown the natural progression of CLN2 disease without treatment. This large cohort includes 140 patients with genetically confirmed CLN2 disease, periodically evaluated in specialised centers. The median age at first symptom was 35 months and the median age at first seizure was 37 months. We can observe a rapid decline in motor and language functions between 36 and 72 months with a median age at death of 10 years (Figure 1).

With the exception of patient 7, we note that the evolution of our patients prior to treatment is similar to that of other patients in the historical cohorts describing the natural course of CLN2 disease. Secondly cerliponase alfa enables a change in the developmental trajectory for patients whose condition had deteriorated little before the onset of ERT. However, the patient 7 has an atypical form of CLN2 with juvenile onset and despite a rapid set up of ERT before major deterioration, patient 7's condition continued to worsen. This leads us to question the benefits of cerliponase alfa in atypical form of CLN2.

Patients with a CLN2 ML score greater than or equal to three at baseline appear to have a better outcome than patients with a score less than three. This threshold corresponds to the criteria for legal authorization to market the therapy in France since May 2017, and corresponds to the inclusion criteria for clinical trials (12). Patient 3 is the patient with a CLN2 ML score greater than three in our cohort with the longest treatment period (25 months) and did not show any clinical deterioration but rather an improvement in language skills. In contrast, patients 5 and 6 continued to deteriorate at the same rate as patients without treatment. They were very severely affected at the onset of ERT with low CLN2 ML scores and probably should not have been treated.

This ERT is a heavy treatment with intraventricular infusions every two weeks. It must be administered in reference centers with a qualified and trained medical team in order to reduce side effects and device dysfunctions. In our cohort, four patients underwent device removal, including two patients with an authenticated infection. Some patients may experience fever and convulsions after the infusion, which improves with premedication with antihistamines or corticoids. This suggests an immune mechanism. In phase 1 / 2 of the study (17), the production of anti-cerliponase alfa antibodies was 25% in cerebrospinal fluid and 79% in serum. In this study, there was no relation between antibody production, allergic symptoms and the efficacy of the ERT. Nevertheless, immune mechanism is probably responsible for some side effects which encourages to generalize premedication.

In our cohort, CLN 2 disease was diagnosed around the age of 50 months (compared to 54 months in the historical cohort (5)). Around 50 months is a critical period during which cognitive decline is rapid but patients are still eligible to treatment if they have a CLN2 ML score greater than three. However, since an ERT is now available for CLN2, the diagnosis should be made as soon as possible. As a treatable disease, CLN2 needs to be better known by neuro-paediatricians, epileptologists and paediatricians in order to make the diagnosis faster. Myoclonic epilepsy, speech delay and gait disturbance are the most common symptoms. Detection of a photoparoxysmal response to intermittent photic stimulation at a low frequency on electroencephalography is a simple sign, which although not constant could be an early marker that could facilitate diagnosis (18). Siblings of a patient with CLN2 should receive good medical follow-up. The older sister of patient 8 in our cohort, had CLN2 disease, which is why patient 8 have benefited from an ERT before the onset of any symptoms. A longer medical follow-up of patient 8 is necessary to ensure the effectiveness of presymptomatic treatment.



The care of patients with CLN2 disease remains complex (19) and requires a multidisciplinary team including specialist paediatricians, general practitioners, nurses, physiotherapists, social workers, dieticians and psychologists working in collaboration with the patient and his/her family (20). The team aims to ensure the quality of life of the children with maintenance of ambulation, communication, school participation, comfort, family support and end-of-life care (21). With regards to seizures, experts state (19) that freedom from seizure is not a realistic goal, but that it is important to minimise the impact of seizures and polytherapy. In our cohort, treated patients with good evolution have better epilepsy control with reduction in antiepileptic drugs, continue to walk and improve their language skills which we assume is part of a better quality of child's life.

In conclusion, the patients of our cohort with early start of ERT experienced a halt in disease progression. Two of them showed a little recovery in language skills. Based on historical data, cerliponase alfa changes the natural history of CLN2 disease. These results are encouraging given the inevitable motor and cognitive decline of CLN2 patients without treatment. A longer medical follow-up is necessary for this cohort. The optimal duration of the ERT is still an unknown, especially as it is a complicated and expensive treatment. Others emerging therapies are in development (22) (23). It is important for physicians to keep in mind the uncertainty of the long term functional, visual and behavioural prognosis after a treatment with cerliponase alfa. This uncertainty must be the source of ethical questionings, the main objective of which remains the quality of the child's life.

**Declaration of interests:** AC, SP,DS, ID, SA, BC reports grants personal fees from BioMarin independent of the submitted work. All other authors report no competing interests.

**Funding source:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Tables:**

<b>Score</b>	<b>Motor</b>	<b>Language</b>
3	Grossly normal gait. No prominent ataxia, no pathologic falls.	Apparently normal language. Intelligible and grossly age-appropriate. No decline noted yet.
2	Independent gait, as defined by ability to walk without support for 10 steps. Will have obvious instability and may have intermittent falls	Language has become recognisably abnormal: some intelligible words may form short sentences to convey concepts, requests, or needs. This score signifies a decline from a previous level of ability
1	Requires external assistance to walk or can crawl only	Hardly understandable. Few intelligible words
0	Can no longer walk or crawl	No intelligible words or vocalisations

***Table 1: CLN2 Clinical Rating Scale Motor-Language***

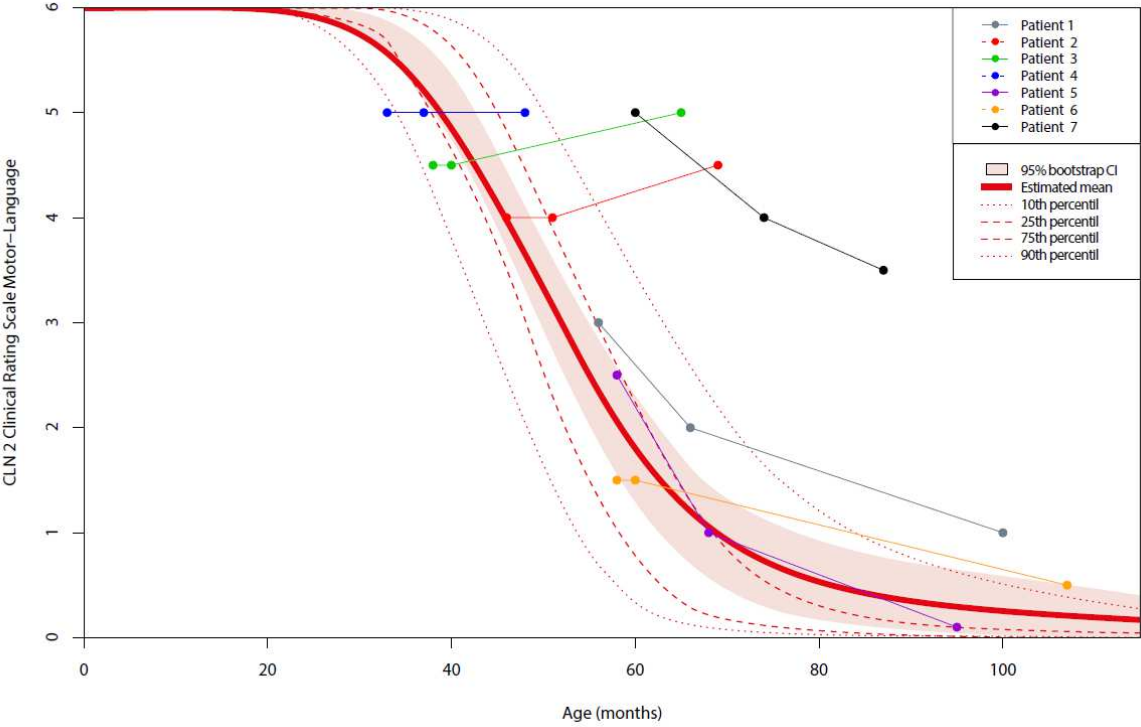
*(Excel file)*

***Table 2: Detailed characteristics of the patients***

<b>Average age (months) / CLN2 ML Score</b>	<b>Age (months)</b>	<b>CLN2 ML score</b>
At diagnosis	50 (+/-10)	3.6 [1.5 – 5]
At the beginning of ERT	56 (+/-13)	3.1 [1 – 5]
At last evaluation	82 (+/- 20)	2.8 [0 – 5]

***Table 3: Average age and average CLN2 ML score at the different stages of the disease (diagnosis, the beginning of the ERT and at the last evaluation available)***

**Figures:**



**Figure 1:** Superposition of clinical evolution of patients in our cohort with the curve of natural course of CLN2 disease (extracted from Nickel, Schulz et al. Lancet, 2018 (5)).

Each line is comprised of three points :

- the first point is the CLN2 ML score depending on age at diagnosis
- the second point is the CLN2 ML score depending on age at the beginning of ERT
- the third point is the CLN2 ML score depending on age at last evaluation available

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