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Seizures and movement disorders in patients with CLN2 disease treated with cerliponase alfa in the real-world setting

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Background

- CLN2 disease is a rare neurodegenerative disorder caused by deficient TPP1 enzyme activity.[1]
  - CLN2 disease typically presents with language delay and/or onset of seizures between 2 and 4 years of age; onset of symptoms is followed by rapid, progressive decline in motor and language function, worsening epilepsy, and vision loss.[1-3]
- Cerliponase alfa (recombinant hTPP1) is currently the only disease-modifying therapy approved for the treatment of CLN2 disease.
  - Over a period of more than 5 years of treatment, biweekly intracerebroventrical (ICV) administration of cerliponase alfa was shown to slow decline in motor and language function compared with natural history controls.[4,5]
  - Seizures are a predominant feature of CLN2 disease and present a significant burden throughout disease progression. In clinical trials, a reduction in the frequency of tonic-clonic seizures in treated patients was observed over time, suggesting that treatment may also have some benefit with respect to seizures.[5]
- In this retrospective, observational analysis, we evaluated the incidence and severity of seizures and movement disorders in patients with CLN2 disease treated with cerliponase alfa in a real-world setting.

Methods

- Patients included in this analysis were enrolled in the DEM-CHILD database (international NCL patient registry; NCT04613089); had a confirmed diagnosis of CLN2 disease by genetic and enzyme testing; initiated treatment with cerliponase alfa outside the clinical trial setting; and had at least 6 months of follow-up after treatment initiation.
  - Patients were followed from date of first cerliponase alfa infusion (index) to the earliest of death, disenrollment, or data cut off (31 Dec 2022).
- Seizure types, frequency, and complications were assessed based on information collected on the CLN2 Disease Seizure Inventory. Data on dystonia and myoclonus were derived from the CLN2 Disease Movement Disorder Inventory.
  - Numbers and proportion of patients experiencing seizures (primary generalized, atonic, myoclonic) and changes in seizure medications were assessed at 6-month intervals.
  - Time to onset or worsening of movement disorders was assessed using Kaplan-Meier methods.

Results

- A total 24 patients were included in the analysis (58% female), with a mean (SD) follow-up time of 43.8 (19.0) months. Mean age at diagnosis was 53.1 (25.6) months and mean age at ERT initiation was 61.4 (27.3) months **(Table 1)**.
- At baseline, 20 patients (83%) had history of seizures, 18 (75%) had ataxia, 2 (8.3%) had myoclonus, and 4 (16.7%) had dystonia.
- At baseline, 6 patients (25%) had a score of 6 on the motor-language domains of the Hamburg LINCL scale; 8 patients (33.3%) had a motor-language score of 3 or lower.

Table 1. Baseline demographics and characteristics

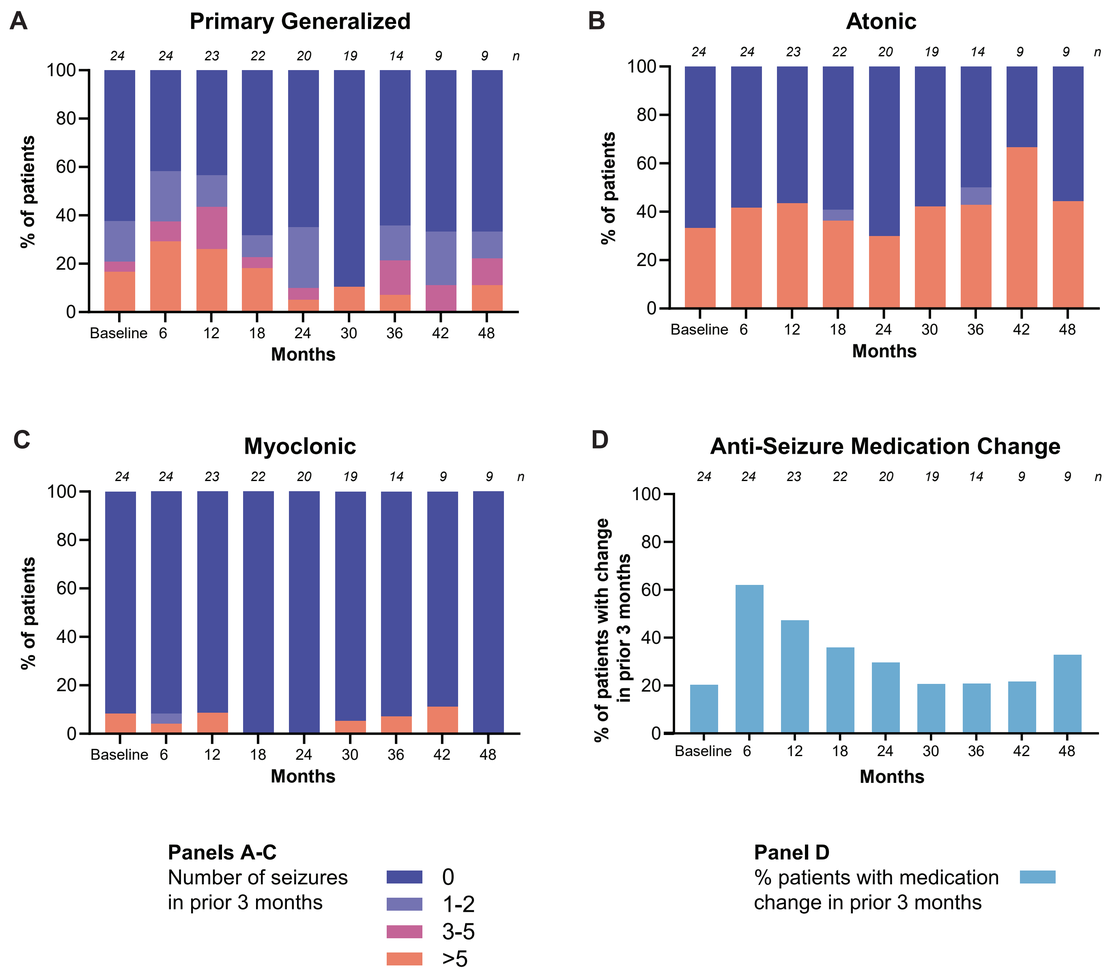
	N=24
Sex, n (%)	
Female	14 (58.3)
Male	10 (41.7)
Age at diagnosis (months), mean (SD)	53.1 (25.6)
Age at genetic analysis (months), mean (SD)	55.3 (26.6)
Age at ERT initiation (months), mean (SD)	61.4 (27.3)
Phenotype, n (%)	
Atypical	4 (16.7)
Presymptomatic	1 (4.2)
Typical	19 (79.2)
Affected sibling, n (%)	
Yes	8 (33.3)
No	16 (66.7)
Type of kindergarten/school[a], n (%)	
None	3 (12.5)
Regular kindergarten	4 (16.7)
Special kindergarten / integration group	9 (37.5)
Regular school	2 (8.3)
Special school / integration class	3 (12.5)
Not reported	5 (20.8)
Neurological symptoms at baseline[a], n (%)	
Seizures	20 (83.3)
Ataxia	18 (75.0)
Dystonia	5 (20.8)
Myoclonus	3 (12.5)
Hamburg LINCL motor-language domain score at baseline, n (%)	
6	6 (25.0)
5	2 (8.3)
4	7 (29.2)
3	3 (12.5)
2	5 (20.8)
1	1 (4.2)

[a] Multiple selection was allowed in the case report form for this variable, so aggregate percentage may exceed 100%
ERT, enzyme replacement therapy; SD, standard deviation

Seizures

- The proportion of patients experiencing primary generalized seizures in the prior 3 months increased from 37.5% at baseline to 56.5% at month 12, then declined to a low of 10.5% over the following 18 months, before increasing again to ~35% over the remainder of follow up **(Figure 1A)**.
  - The proportion of patients experiencing >5 primary generalized seizures over the prior 3 months increased from 16.7% at baseline to 29% at month 6, before declining to 5.0% at month 24, and ranged from 7.1% to 11.1% over the remainder of follow up.
  - No clear correlation was observed between LINCL motor-language score at baseline and frequency of seizures over follow up (data not shown).
- Occurrence of atonic seizures remained relatively stable over follow-up (~30-50%; **Figure 1B**).
  - Among those who experienced atonic seizures, almost all experienced seizures with a frequency of more than 5 seizures in the prior 3 months.
- Relatively few patients experienced myoclonic seizures over the follow-up period (5-10%); those who did generally reported experiencing more than 5 seizures in the prior 3 months **(Figure 1C)**.
- The proportion of patients experiencing a change in anti-seizure medication use (increase in dose or addition of new medication) in the prior 3 months showed an initial increase, from 20.8% at baseline to 62.5% in month 6, before declining thereafter **(Figure 1D)**.

Figure 1. Occurence of seizures over follow up

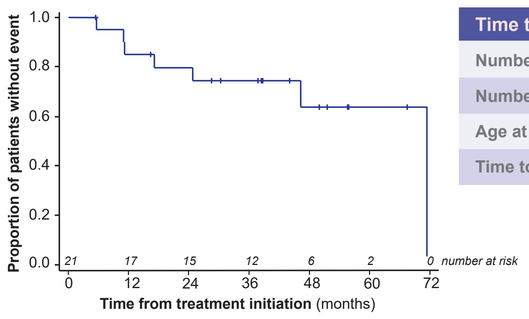


Movement disorders

- Out of 21 patients without myoclonus at baseline, one-third (n=7) experienced onset of myoclonus within 6 years after initiation of cerliponase alfa **(Figure 2A)**.
  - 64% (95% CI: 33.5–83.1) of patients remained event-free up until month 70; mean age at onset of myoclonus was 87.6 months.
- Out of 19 patients without dystonia at baseline, most patients (78.9%) had the first onset of dystonia within 3 years after initiation of ERT **(Figure 2B)**.
  - Median time to first onset of dystonia was 19.4 months; mean age at onset of dystonia was 79.6 months.

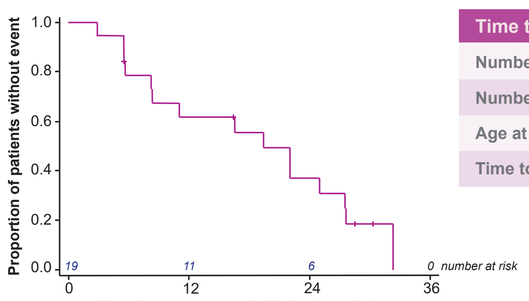
Figure 2. Time to onset of myoclonus and dystonia

A. Myoclonus



Time to first onset of myoclonus	N=21
Number of subjects without event (censored), n (%)	14 (66.7)
Number of subjects with an event, n (%)	7 (33.3)
Age at onset (months), mean (SD)	87.6 (41.8)
Time to onset (months), median (95% CI)	71.4 (24.8–71.4)

B. Dystonia



Time to first onset of dystonia	N=19
Number of subjects without event (censored), n (%)	4 (21.1)
Number of subjects with an event, n (%)	15 (78.9)
Age at onset (months), mean (SD)	79.6 (26.2)
Time to onset (months), median (95% CI)	19.4 (8.2–27.5)

Conclusions

- This analysis provides a comprehensive description of the time course of seizures and movement disorders in a cohort of CLN2 disease patients receiving treatment with cerliponase alfa in the real-world setting.
- Incidence and frequency of primary generalized seizures showed an initial increase after initiation of ERT, but declined thereafter. This finding supports observations from clinical trials in suggesting that cerliponase alfa may have benefit in mitigating the progressive worsening of seizures seen in untreated CLN2 patients.
- The majority of patients in this analysis experienced onset of dystonia within 3 years of initiation of ERT, indicating an ongoing burden despite treatment. In contrast, only one-third experienced onset of myoclonus during follow up and among those who did experience onset of myoclonus, the mean age at onset was 87.6 months, suggesting that treatment with cerliponase alfa may delay onset compared to natural history.[6]

References

1. Sleat et al. *Am J Hum Genet* 1999; 64: 1511-23. **2**. Schulz et al. *Biochim Biophys Acta* 2013; 1832: 1801-6. **3**. Nickel et al. *Lancet Child Adolesc Health* 2018; 2: 582-90. **4**. Schulz et al. *N Engl J Med* 2018; 378: 1898-1907. **5**. Schulz et al. *Lancet Neurol* 2024; 23: 60-70. **6**. Worgall et al. *Neurology* 2007; 69: 521-535.

Disclosures

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