Article published online: 2023-06-17

Language Delay in Patients with CLN2 Disease: Could It Support Earlier Diagnosis?

Miriam Nickel[1] Paul Gissen[2] Rebecca Greenaway[3] Simona Cappelletti[4] Christiane Hamborg[5] Benedetta Ragni[4] Tanja Ribitzki[5] Angela Schulz[1] Ilaria Tondo[4] Nicola Specchio[4]

[1] Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2] National Institute for Health Research Great Ormond Street Hospital Biomedical Research Centre, University College London, London, United Kingdom
[3] Neurodisability Service, Great Ormond Street Hospital, London, United Kingdom
[4] Rare and Complex Epilepsy Unit, Bambino Gesù Children's Hospital, IRCCS, Full Member of European Reference Network: EpiCARE, Rome, Italy
[5] Hirtenweg School, Hamburg, Germany

Address for correspondence Miriam Nickel, MD, Department of Pediatrics, University Medical Center Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Germany (e-mail: m.nickel@uke.de).

Neuropediatrics

Abstract

Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) is a rare pediatric disorder associated with rapid neurodegeneration, and premature death in adolescence. An effective enzyme replacement therapy (cerliponase alfa) has been approved that can reduce this predictable neurological decline. The nonspecific early symptoms of CLN2 disease frequently delay diagnosis and appropriate management. Seizures are generally recognized as the first presenting symptom of CLN2 disease, but emerging data show that language delay may precede this. An improved understanding of language deficits in the earliest stage of CLN2 disease may support the early identification of patients. In this article, CLN2 disease experts examine how language development is affected by CLN2 disease in their clinical practices. The authors' experiences highlighted the timings of first words and first use of sentences, and language stagnation as key features of language deficits in CLN2 disease, and how deficits in language may be an earlier sign of the disease than seizures. Potential challenges in identifying early language deficits include assessing patients with other complex needs, and recognizing that a child's language abilities are not within normal parameters given the variability of language development in young children. CLN2 disease should be considered in children presenting with language delay and/or seizures to facilitate earlier diagnosis and access to treatment that can significantly reduce morbidity.

Keywords
- CLN2 disease
- neuronal ceroid lipofuscinosis
- language development
- enzyme replacement therapy
- cerliponase alfa

received
January 13, 2023
accepted after revision
April 26, 2023

DOI https://doi.org/10.1055/s-0043-1770143.
ISSN 0174-304X.

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

Introduction

Neuronal ceroid lipofuscinosis type 2 (CLN2 disease; OMIM # 204500) is a rare pediatric neurodegenerative disorder caused by mutations in *TPP1*, resulting in tripeptidyl peptidase 1 (TPP1) enzyme deficiency, build-up of lysosomal storage materials, and progressive neuronal loss.[1–4]

Seizures are generally recognized as the first presenting symptom of CLN2 disease, occurring between the ages of 2 and 4 years, but emerging data show that language delay may precede this, being evident from as early as 18 months of age.[2,4–6] Early language delay has been shown to be an initial sign of late-infantile classical CLN2 disease in up to 83% of affected children (dementia in childhood (DEM-CHILD) cohort), frequently preceding the onset of more overt symptoms.[2] By the age of 5 years, patients will lose almost half of the verbal abilities they had at diagnosis.[2]

Motor dysfunction may also be an early manifestation, commonly presenting as ataxia or clumsiness.[2] Functional decline is universally rapid and predictable for those with the classical late-infantile phenotype, leading to dementia, loss of the abilities to walk and talk, and blindness. CLN2 disease is usually fatal by mid-adolescence.[1,5–8]

Diagnostic delays of up to 20 months are common in CLN2 disease because of its scarcity, nonspecific presentation, and a diagnostic test that is not always part of standard laboratory screens.[8,9]

In 2017, both the U.S. Food and Drug Administration and the European Medicines Agency granted approval of cerliponase alfa, a recombinant intraventricular TPP1 enzyme replacement therapy (ERT), as a treatment for CLN2 disease. By helping replace deficient TPP1, the build-up of lysosomal storage materials is minimized, slowing further neuronal damage and decline in both motor and language function.[10,11] The availability of treatment that can potentially prolong the quality and quantity of life demands an immediate increase in the awareness of CLN2 disease among health care professionals (HCPs).

The identification of language delay in children presenting with a first seizure is a red flag that could help diagnose CLN2 disease in its earliest stages. Literature reports on language delay in CLN2 disease are limited despite the increasing recognition of this trait as an early hallmark. By collating current knowledge of the language features of CLN2 disease, we aim to provide a call to action for HCPs to consider CLN2 disease during differential diagnosis for all children with a language delay and/or first seizures, to support early identification and prompt intervention.

Methods

A group of experts on CLN2 disease met to discuss the types of language deficits commonly seen in clinical practice. This manuscript communicates their experiences, and uses patient cases to illustrate features of language delay in children with CLN2 disease. Retrospective, anonymized data from patient records are included (ethics committee approval was not required), and all data are from patients who received a diagnosis of CLN2 disease according to published expert diagnostic recommendations.[9] Ages at first words, first use of two-/three-word phrases, and first use of full sentences were analyzed, and age at first seizure and language scores at initiation of ERT were assessed using the CLN2 disease clinical rating scale.[12] The authors confirm that informed consent was taken from all the participants.

Results

Based on our experiences of caring for patients with CLN2 disease (see cases in ►**Table 1** and ►**Supplementary Fig. S1**), language abilities vary during the early stages of CLN2 disease prior to treatment initiation. Verbal ability ranges from broadly age appropriate to mild but detectable deficits or no speech at all.

The cases illustrate that timing of first words is broadly age appropriate (9–12 months), but progression to short phrases and longer combinations is limited.[13] Speaking in two- to three-word phrases, which is expected to occur at 18 to 24 months in the general population,[13] was not achieved in six patients and occurred after the expected age in seven patients. Of these seven patients, two (cases 15 and 16) had first seizures after the children would have been expected to be speaking in two- to three-word phrases, indicating that a language abnormality was present prior to seizures. The ability to form sentences, expected at 36 to 48 months in the general population,[13] is severely affected, with 87% (20/23) of our cases not achieving this milestone. Only three patients had a language domain score of 3 (normal function) at initiation of ERT, and eight patients had a score of 0 or 1, further emphasizing the extent of language regression, and the need for practitioners to specifically enquire about language development in children presenting with a first seizure.

In our experience, stagnation of language is common, with affected children often having difficulty in acquiring new vocabulary. As they get older, children with CLN2 disease may speak more slowly and with reduced clarity compared with their peers. It has been observed in some centers that receptive skills can be maintained for longer than expressive skills, but this is not a universal finding, and the current data are limited.[14]

It is likely that, as with children in the general population, the ability to recognize images outweighs the ability to verbally describe the image (when their cognitive resources and visual functions allow). Nonverbal communication, such as eye contact and body language, tends to be preserved for longer than structured language abilities. In addition to the disease process itself, there are other factors that may affect a child's capacity to speak, understand, and communicate. Side effects of antiseizure medication, therapeutic rehabilitation programs, frustrations, and family coping strategies may each have a significant impact on communication abilities.

Discussion

While the cases in this manuscript illustrate the language delays seen in patients with CLN2 disease, identifying

Table 1 Case studies

Case	Age at first words (mo)	Age at first use of two-/three-word phrases (mo)	Age at first use of full sentences (mo)	Age at first seizure (mo)	Language score at initiation of ERT (score and age)[a]
1	9	24	Not achieved	38	Score 3 at 46 mo
2	8	24	Not achieved	48	Score 2 at 48 mo
3	8–9	Not recorded prior to ERT initiation	Not achieved	38	Score 2 at 44 mo
4	7	24	36	59	Score 2 at 60 mo
5	6	36	Not achieved	38	Score 2 at 42 mo
6	10–12	36	Not achieved	41	Score 2 at 57 mo
7	6	Not measured prior to ERT initiation	Not achieved	–	Score 1 at 100 mo
8	14	Not achieved	Not achieved	36	Score 2 at 56 mo
9	Not achieved	Not achieved	Not achieved	36	Score 0 (nonverbal) at 58 mo
10	12	36	Not achieved	44	Score 1 at 70 mo
11	12	24	54	44	Score 2 at 48 mo
12	15	Not achieved	Not achieved	32	Score 1 at 52 mo
13	Not clearly reported	Not achieved	Not achieved	36	Score 1 at 54 mo
14	12	30	Not achieved	35	Score 2 at 54 mo
15	Not clearly reported	42	Not achieved	36	Score 2 at 47 mo
16	14	42	Not achieved	36	Score 2 at 43 mo
17	18	36	Not achieved	45	Score 1 at 53 mo
18	9	24	Not achieved	35	Score 3 at 39 mo
19	14	Not achieved	Not achieved	43	Score 3 at 51 mo
20	8	18	42	38	Score 1 at 51 mo
21	12	24	Not achieved	35	Score 1 at 45 mo
22	11	23	Not achieved	31	Score 2 at 52 mo
23	12	Not achieved	Not achieved	42	Score 2 at 48 mo
Median (range)	11.5 (6–18)	24 (18–42)	42 (36–54)	38 (31–59)	–

Abbreviation: ERT, enzyme replacement therapy.

Note: The table details the language development of patients cared for by the authors. Cases 1 to 7 were from Bambino Gesù Children's Hospital, Rome, Italy; cases 8 to 16 were from Great Ormond Street Hospital, London, United Kingdom; and cases 17 to 23 were from University Medical Center Hamburg-Eppendorf, Hamburg, Germany. All data included were collected prior to or at the initiation of enzyme replacement therapy (ERT).

[a]Cases were assessed using the CLN2 disease clinical rating scale. This scale is based on the Hamburg and Weill Cornell scales and examines motor, language, and visual functions, and seizures. Each category is scored from 0 to 3 (3 in the language category equates to normal function), with a score from 0 to 12 for the full scale.[12]

children with language delay who may have CLN2 disease remains a challenge for several reasons.

Seizures continue to be the most frequently reported presenting symptom,[2] perhaps because they may necessitate more immediate medical intervention than language delay. Mild delay in language development may be assumed to be within normal parameters. Specifically querying developmental milestones in language (beyond the timing of the first words) at seizure presentation might detect language delay before more severe regression.

There is also increasing evidence that autism spectrum disorder (ASD) may be associated with inborn errors of metabolism (IEM) such as the neuronal ceroid lipofuscinosis family of disorders that includes CLN2 disease.[15] ASD is rarely seen in isolation in IEM disorders, and as such, the presence of other symptoms with ASD should alert clinicians to the potential for patients to have such a disorder.[15] Further, a retrospective analysis of 59 children with ASD reported that 44% also had epilepsy, and a second study found that 75% of children with ASD had language impairments before starting kindergarten.[16,17] With ASD estimated to occur in 1% of the population, and this overlap with epilepsy and language impairment, ASD assessments and clinics may provide a further opportunity to identify patients with CLN2 disease. To avoid diagnostic delays, we recommend that if any symptoms of CLN2 disease (such as

language delay or seizures) are identified during ASD assessment, genetic testing for CLN2 disease be performed.

Assessing the language abilities of patients with CLN2 disease presents multiple complex challenges. It inevitably takes time to connect and successfully interact with children who have a short attention span, communication difficulties, and, as a result, significant levels of frustration. To optimize engagement, the child should be in a comfortable, familiar environment with few distractions.

Early language delays are frequently initially identified by parents, and childcare and educational providers, as well as HCPs. Depending on the health care system, children with suspected language delays may be assessed by speech and language therapists, neurologists, psychologists, and other HCPs using a range of informal tools, and standardized developmental and language assessments. Parent-reported outcomes and home videos can also be a useful part of the overall assessment as they provide real-life information about children's abilities. There is no universally accepted rating method for early language delay, and the choice is influenced by regional differences and professional preferences.

Although a language disorder would not formally be diagnosed before the age of 3 years, if a child has not progressed to use word combinations and has a vocabulary of less than 50 words at the age of 2 years, they should be considered for referral for support and for speech and language intervention and monitoring.[13]

Red Flags for Raising Suspicion of CLN2 Disease

Based on our experience and the cases in this article, it is our recommendation that CLN2 disease be considered in children presenting with any of these "red flag" features:

- Normal first word development, but slowing or stagnation with difficulty acquiring new words or progressing to word combinations.
- Plateau or loss of words and other developmental abilities when not accompanied by social communication regression.
- Seizures of unknown origin.
- Increasing clumsiness or ataxia.

Information on other features that could raise suspicion of CLN2 disease may have already been obtained during the diagnostic workup through magnetic resonance imaging (MRI) and electroencephalography (EEG), and could include subtle cerebellar or cerebral atrophy, or white matter hyperintensities on MRI, or background abnormalities or a photoparoxysmal response on EEG.[8,18–20] When clinical suspicion of CLN2 disease is raised, the next steps in the diagnostic process would incorporate analyses of TPP1 enzyme activity and *TPP1* genotype as outlined in the 2016 expert recommendations for early detection and laboratory diagnosis of CLN2 disease.[9]

Our recommendations to support the early identification of language delay and testing for CLN2 disease are summarized in ►**Table 2**.

Conclusion

A greater understanding of the types of language deficits that occur in CLN2 disease could support early identification of the disease, enabling provision of appropriate care and support. We consider these deficits to include limited progression to full sentences, a lack of vocabulary explosion, and language stagnation.

While emerging data show that language delay frequently precedes seizures in CLN2 disease,[2] identifying early language deficits continues to be a challenge, primarily because of the considerable variability in which children typically develop their language abilities during infancy when CLN2 disease first presents. A language delay may have been noticed by parents or other childcare, educational, and health care providers, and the child may be awaiting or receiving assessments and support. But if the potential for a diagnosis of CLN2 disease is not realized, diagnostic delays may continue until more well-known symptoms, such as seizures, become apparent. During this time, the affected child may lose a significant proportion of their verbal and motor capabilities that could have been maintained with appropriate treatment.

Table 2 Summary of recommendations to support the early identification of language delay

Recommendations
Investigate language milestones beyond timing of first words as achievement of this milestone may be age appropriate
If any symptoms of CLN2 disease (such as language delay or seizures) are identified during ASD assessment, carry out enzyme activity/genetic testing for CLN2 disease
During language assessments, ensure that children are in a comfortable, familiar environment with few distractions
Consider parent-reported outcomes as part of the overall assessment as they provide real-life information about children's abilities
If a child has not progressed to use word combinations and has a vocabulary of less than 50 words at the age of 2 years, consider for referral for support and for speech and language intervention and monitoring
Keep in mind the "red flag" features of CLN2 disease, including slowing or stagnation of language skills, other developmental impairments, seizures of unknown origin, and clumsiness or ataxia

Abbreviation: ASD, autism spectrum disorder; CLN2, neuronal ceroid lipofuscinosis type 2.

With the increasing recognition that language delay is a hallmark of early CLN2 disease and that an approved treatment, if started early, can significantly slow disease progression,[10] it is our opinion that clinicians should routinely assess language milestones in children with any of the "red flag" features outlined in this article.

This would improve patient outcomes through reduced diagnostic delay, earlier treatment with ERT, and prompt involvement and support from the multidisciplinary team.

Funding
This manuscript was developed after discussions at a meeting of experts organized and supported by BioMarin Europe Ltd.

Conflicts of Interest
Writing support was funded by BioMarin Europe Ltd. MN, PG, RG, CH, BR, TR, AS, IT, and NS received personal fees from BioMarin Europe Ltd for their attendance and contributions at the expert meeting. MN has received grants to their institution from BioMarin, REGENXBIO Inc., Orphion Therapeutics, and Polaryx; consulting fees from REGENXBIO Inc.; honoraria from BioMarin; meeting and/or travel support from BioMarin; and payments to their institution from BioMarin and REGENXBIO Inc. PG has received consulting fees, contracted research fees, honoraria, and travel expenses from BioMarin Europe Ltd. SC has a leadership role in the cognitive neurology and developmental epilepsy neuropsychology study group of the Italian League Against Epilepsy. BR has received travel expenses from BioMarin. AS has received grants to their institution from BioMarin, REGENXBIO Inc., Orphion Therapeutics, and Polaryx; consulting fees from REGENXBIO Inc.; honoraria from BioMarin; meeting and/or travel support from BioMarin; and payments to their institution from BioMarin and REGENXBIO Inc. IT has received travel expenses from BioMarin. NS has received travel expenses from BioMarin.
BioMarin Europe Ltd played no role in case study collection, writing of the report, or the decision to submit the manuscript.

Acknowledgments
Writing support was provided by Suzanne Brunt and Emma Conran, Porterhouse Medical, Reading, United Kingdom, and funded by BioMarin Europe Ltd.

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