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Source / Izvornik: **Expert Review of Neurotherapeutics**, 2021, 21, 1275 - 1282

Journal article, Published version

Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

<https://doi.org/10.1080/14737175.2021.1885374>

Permanent link / Trajna poveznica: <https://um.nsk.hr/um:nbn:hr:184:506279>

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Download date / Datum preuzimanja: **2024-08-29**



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To cite this article: Maria Mazurkiewicz-Beldzińska, Mireia del Toro, Göknur Haliloğlu, Hidde H. Huidekoper, Ružica Kravljanac, Chris Mühlhausen, Brian Nauheimer Andersen, Igor Prpić, Pasquale Striano & Stéphane Auvin (2021) Managing CLN2 disease: a treatable neurodegenerative condition among other treatable early childhood epilepsies, Expert Review of Neurotherapeutics, 21:11, 1275-1282, DOI: [10.1080/14737175.2021.1885374](https://doi.org/10.1080/14737175.2021.1885374)

To link to this article: <https://doi.org/10.1080/14737175.2021.1885374>



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Published online: 04 Mar 2021.



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## Managing CLN2 disease: a treatable neurodegenerative condition among other treatable early childhood epilepsies

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### ABSTRACT

**Introduction:** Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) is a rare pediatric neurodegenerative condition, which is usually fatal by mid-adolescence. Seizures are one of the most common early symptoms of CLN2 disease, but patients often experience language deficits, movement disorders, and behavioral problems. Diagnosis of CLN2 disease is challenging (particularly when differentiating between early-onset developmental, metabolic, or epileptic syndromes), and diagnostic delays often overlap with rapid disease progression. An enzyme replacement therapy (cerliponase alfa) is now available, adding CLN2 disease to the list of potentially treatable disorders requiring a prompt diagnosis.

**Areas covered:** Although advances in enzymatic activity testing and genetic testing have facilitated diagnoses of CLN2 disease, our review highlights the presenting symptoms that are vital in directing clinicians to perform appropriate tests or seek expert opinion. We also describe common diagnostic challenges and some potential misdiagnoses that may occur during differential diagnosis.

**Expert opinion:** An awareness of CLN2 disease as a potentially treatable disorder and increased understanding of the key presenting symptoms can support selection of appropriate tests and prompt diagnosis. The available enzyme replacement therapy heralds an even greater imperative for early diagnosis, and for clinicians to direct patients to appropriate diagnostic pathways.

### ARTICLE HISTORY

Received 7 December 2020  
Accepted 1 February 2021

### KEYWORDS

CLN2 disease; diagnosis; epilepsy; language; late infantile; seizures

## 1. Introduction

Neuronal ceroid lipofuscinosis type 2 (CLN2 disease) is a rare, but severe, rapidly progressive, pediatric neurodegenerative disease associated with seizures, language deficits, and motor dysfunction. In later stages, it is characterized by a progressive decline of visual and cognitive functions, and it is usually fatal by early adolescence [1–6]. Because of the nonspecific nature of the presenting symptoms of CLN2 disease, there is often a diagnostic delay, which can result in delays to the provision of disease-specific treatment [7], including complex multidisciplinary care and the enzyme replacement therapy (ERT) cerliponase alfa [6,8,9]. In this article, we aim to emphasize the importance of early diagnosis for potentially treatable pediatric epilepsy syndromes such as CLN2 disease and highlight the key features that can raise clinical suspicion, as well as presenting diagnostic challenges.

The determination of the etiology of seizures and epilepsy is vital, as some etiologies have a treatment that may modify the disease course or be managed with a specific approach

[10]. Although some etiologies can be established by imaging, or associations with infectious diseases or immune disorders, the identification of a genetic or metabolic epilepsy may be more challenging [10].

Inherited metabolic diseases associated with epilepsy can be caused by a broad range of genetic defects [10]. Although metabolic epilepsies are rare, seizures are a common feature of metabolic disorders, alongside other neurological symptoms such as motor dysfunction and intellectual disabilities [11,12]. Given the potential severity of these disorders, the progressive nature of symptoms, and the availability of potential pharmacological or metabolic treatments, identification of the cause is imperative [11,12]. As metabolic epilepsies are rare [11–13], there may be limited awareness of specific individual epilepsies among clinicians who assess patients in early disease stages. To combat diagnostic delays, testing for potentially treatable metabolic diseases in patients with epilepsy can be considered a priority.

Such rare, but treatable, early childhood metabolic epilepsies include, among others, pyridoxine-dependent epilepsy (PDE),

**Article highlights**

- CLN2 disease is a rare pediatric disease associated with seizures, language deficits, and progressive neurological decline.
- CLN2 disease is usually fatal by mid-adolescence, although an enzyme replacement therapy that slows disease progression is now available.
- Early diagnosis is key to accessing treatment, but diagnosis is challenging because of similarities with other disorders and limited awareness of CLN2 disease because of its rarity.
- Seizures are one of the most common presenting symptoms, although patients may also present with language deficits, movement disorders and behavioral issues.
- The results of clinical tests, such as electroencephalography (EEG) and magnetic resonance imaging (MRI), may also provide clues that can raise suspicion of CLN2 disease.
- Although enzyme activity testing and genetic testing have advanced, a range of tests are now available, and selection must be guided by an understanding of the diseases that each test can diagnose.
- An awareness of key presenting symptoms is of vital importance in directing clinicians to seek expert advice or appropriate tests that can confirm a diagnosis and providing patients with opportunities to access treatment at an early disease stage.
- We ask that clinicians consider CLN2 disease as a treatable disorder for which diagnosis should be prioritized.

cerebral folate deficiency, cerebral creatine deficiency syndromes, and glucose transporter 1 (GLUT1) deficiency. These diseases exemplify the breadth of nonspecific symptoms that metabolic epilepsies can present with and how clinical tests can raise suspicion before confirmatory diagnostic tests (Table 1).

Alongside the supportive and palliative care provided for pediatric patients with rare progressive disorders, more and more of these diseases may increasingly be treated with causative dietary and pharmacological therapies. Although knowledge of the long-term outcomes of patients treated with the described therapies is limited, these therapies can have a positive impact on various symptoms, and, in some cases, are most effective if started in the early stages of disease. Early diagnosis for all severe progressive disorders is of high importance in order to ensure that genetic counseling can be provided, if appropriate, and that multidisciplinary teams can be established to provide symptomatic, supportive, and palliative care as the disease progresses. For those disorders with a specific pharmacological or dietary treatment, early identification of the cause is of additional importance to ensure that treatments can be provided at a disease stage at which they can have the greatest positive impact. As clinical assessments such as EEG and MRI may be carried out routinely in children with seizures, information on nonspecific features (such as cerebellar atrophy) may be readily available and used to guide the focus toward specific diagnostic tests. These tests may then be selected to include disorders with a pharmacological or dietary treatment and provide information associated with multiple diseases. Indeed, an algorithm to support test selection has been developed, focusing on identifying treatable metabolic disorders [12]. With genetic testing available for each of the disorders in Table 1, the key to early diagnosis is piecing together the timeline of nonspecific signs and symptoms in order to select appropriate genetic and

other diagnostic tests as early as possible [14]. An ERT for CLN2 disease is now available, and early diagnosis of this disease should be imperative, as for other metabolic epilepsies with specific pharmacological or dietary interventions as described above.

## 2. CLN2 disease

CLN2 disease is a lysosomal storage disorder in the neuronal ceroid lipofuscinosis (NCL) family caused by deficiency of the lysosomal enzyme tripeptidyl peptidase 1 (TPP1), resulting from mutations in the *TPP1* gene [2,28]. CLN2 disease is rare, affecting fewer than 1 in 100,000 live births in most studied populations [1,2,6,29–31]. CLN2 disease typically presents with seizures between the age of 2 and 4 years, with language delays increasingly reported as a preceding symptom [1,3–5,7,32]. In an observational cohort study, seizures and language deficits were one of the presenting symptoms in 70% of patients and 57% of patients, respectively [7]. Other symptoms reported at presentation included developmental delay, motor dysfunction, ataxia, behavioral abnormalities, and dementia [1,7,32,33].

### 2.1. Natural history of CLN2 disease and management of symptoms and progression

Beyond the potential variation in presenting symptoms, CLN2 disease is universally rapidly progressive, with motor, cognitive, and visual decline becoming apparent, and behavioral disturbances in some patients [1–5,7,33–36]. The period of rapid progression begins soon after symptom onset and lasts from approximately 3–6 years of age [7]; CLN2 disease is usually fatal by mid-adolescence [1–3,7]. Seizures frequently become more severe, more frequent, and resistant to AEDs as the disease evolves, and several commonly used AEDs (such as carbamazepine and phenytoin) may be associated with deterioration of motor functions in patients with CLN2 disease [3,5,6,33]. Visual decline can result in blindness by the age of 10 years [1,4,5], and as language deficits progress, speech is also lost [5,7]. Progressive motor dysfunction and movement disorders can incorporate myoclonus, dystonia, and spasticity, and patients usually become wheelchair-bound [5–7], and movement disorders, discomfort, and pain can also disrupt sleep [1]. In the later stage of CLN2 disease, patients commonly have respiratory infections and swallowing difficulties that require percutaneous endoscopic gastrostomy tubes [2,3,5–7,33].

CLN2 disease requires a well-planned multidisciplinary approach through its progression because of these multiple, complex symptoms. Historically, management of CLN2 disease has relied on multidisciplinary symptomatic and palliative care with input from a diverse range of experts, such as pediatric neurologists, epileptologists, and ophthalmologists [6]. The establishment of the multidisciplinary team at an early stage is crucial in maintaining quality of life and proactively planning the management of complications.

In 2017, the first ERT for an NCL was approved in the USA and European Union [8,9]. Cerliponase alfa (recombinant human TPP1) is approved for the treatment of CLN2 disease (and specifically for slowing the loss of ambulation in

**Table 1.** Symptoms and diagnostic features of childhood epilepsy syndromes with pharmacological or dietary treatments.

Disorder/group of disorders	Neurological symptoms	Diagnostic features	Treatment
PDE [14–17]	Seizures, dystonia, increased startle response, irritability, intellectual disability and developmental delay	<p>Electroencephalography (EEG)</p> <ul style="list-style-type: none"> <li>• Diffuse slowing</li> <li>• Generalized bursts of polyspike slow waves</li> <li>• Focal or generalized sharp waves</li> <li>• Hypsarrhythmia</li> <li>• Focal or multifocal discharges</li> </ul> <p>Magnetic resonance imaging (MRI)</p> <ul style="list-style-type: none"> <li>• Hemispheric hypoplasia or atrophy</li> <li>• Cerebellar or cortical dysplasia</li> <li>• Intracerebral hemorrhage</li> <li>• Periventricular hyperintensity</li> </ul> <p>Urinary, plasma and cerebrospinal fluid (CSF) metabolite, amino acid, and neurotransmitter level abnormalities</p>	<p>Acute intravenous pyridoxine, followed by long-term oral or enteral pyridoxine</p> <p>A lysine-restricted diet may be an addition to pyridoxine therapy to improve seizure control and psychomotor development</p> <p>Some patients may have seizures that respond to folinic acid</p>
Cerebral folate deficiency [14,18–22]	Seizures, psychomotor regression, and behavioral symptoms	<p>MRI</p> <ul style="list-style-type: none"> <li>• Demyelination defects and cerebellar atrophy</li> </ul> <p>Low levels of methyltetrahydrofolate in CSF</p>	Oral and/or intrathecal folinic acid, which is most effective if started in early childhood
Cerebral creatine deficiency syndromes [14,23]	Seizures, developmental delay movement disorders, language deficits, and behavioral symptoms	<p>MRI</p> <ul style="list-style-type: none"> <li>• Globus pallidus involvement (GAMT deficiency)</li> </ul> <p>Magnetic resonance spectroscopy</p> <ul style="list-style-type: none"> <li>• Absence of brain creatine peak</li> </ul>	<p>Dietary supplements for seizures and movement disorders in AGAT deficiency (oral creatine) and GAMT deficiency (oral creatine, arginine, and ornithine)</p> <p>Antiepileptic drugs (AEDs) for seizures in CT1 deficiency</p>
GLUT1 deficiency [14,24–27]	Seizures (absence before 4 years of age; myoclonic and other types; developmental delay; movement disorders; language deficits; cognitive deficits; and microcephaly)	Low levels of glucose in CSF and normal levels of lactate in CSF	Ketogenic diet for seizures, movement disorders, and cognitive deficits, which is most effective if initiated early in the disease

GLUT1, glucose transporter 1; PDE, pyridoxine-dependent epilepsy.

symptomatic children aged  $\geq 3$  years in the USA) following trials showing that intracerebroventricular infusions every other week reduce the rate of decline of motor and language function [37]. Trials of cerliponase alfa are ongoing in younger, potentially asymptomatic patients ( $< 3$  years old), and for extended periods to understand the long-term impact of this ERT [38].

With the advent of treatment for CLN2 disease, it is now imperative to ensure that patients are diagnosed as early as possible to allow treatment to be initiated. Further to cerliponase alfa, trials of gene therapies for CLN2 disease are ongoing [39], and with the potential for different treatment options, the impetus to diagnose patients promptly will become even greater. Prompt diagnosis is also key for ensuring support for family and caregivers and for provision of genetic counseling.

The healthcare professional (HCP) who first assesses CLN2 disease can vary depending on the healthcare system. Patients with seizures alone can present to a range of specialists from primary care or family physicians, to pediatric neurologists, general pediatricians, or neurologists, or accident and emergency clinicians. Speech and language therapists or psychologists can also be involved. In some cases, there may be a suspicion of genetic or metabolic epilepsy, and metabolic or genetic specialists can be involved at an early stage. Across this spectrum of HCPs, there is

a varying degree of awareness of NCLs and CLN2 disease, and this in turn can lead to delays in diagnosis and delays in accessing disease-specific treatment.

## 2.2. Diagnosis of CLN2 disease: possibilities and pitfalls

Diagnostic delays of over 2 years are not uncommon for patients with CLN2 disease, and these coincide with the period during which rapid disease progression begins [7]. Aside from limited awareness of CLN2 disease, several other factors may delay its diagnosis. Early symptoms such as seizures and language delays are also associated with many other diseases. As a result, non-specific language disorders and other epilepsy syndromes are common misdiagnoses (Table 2; this table is not to be considered a full list of potential misdiagnoses, and other metabolic disorders may share some overlap with CLN2 disease).

Language deficits may be subtle, and because language development within the general population in early childhood is highly variable, the significance of this early symptom may not be fully considered [5,6]. Also, motor dysfunction, ataxia, and coordination problems may be attributed to being a side effect of AEDs rather than diagnostic clues for CLN2 disease [6]. Treatment-responsive seizures or delay between early

**Table 2.** Common misdiagnoses associated with the nonspecific symptoms of CLN2 disease.

Symptoms \ Disorder(s)	Epilepsy	Language deficits	Motor impairment	Visual impairment	Developmental delay	Behavioral issues	Intellectual disabilities, cognitive deficits, or dementia	Brain abnormalities on MRI
Cerebral palsy [40]	✓	✓	✓	✓	✓	✓	✓	✓
Other NCLs [2,32,33]	✓	✓	✓	✓	✓	-	✓	✓
	Age of onset varies by subtype		Tremor, falls, hypotonia		Regression		Regression	Cerebral or cerebellar atrophy
Dravet syndrome [41–43]	✓	✓	Ataxia, hypotonia	✓	✓	✓	✓	-
	Occurs from infancy					Autism, attention deficit hyperactivity disorder, aggression, irritability		
GLUT1 deficiency [14,24]	✓	✓	✓	-	✓	-	✓	-
	Occurs from infancy		Hypotonia, spasticity, dystonia, ataxia, movement disorders					
Myoclonic astatic epilepsy (MAE or Doose syndrome) [44,45]	✓	-	-	-	-	-	✓	-
	Occurs from early childhood or infancy							
Chromosomal abnormalities [46–51]	✓	✓	✓	-	✓	✓	✓	-
Mitochondrial disorders [52,53]	✓	✓	✓	✓	✓	✓	✓	✓
Angelman syndrome [54,55]	✓	✓	✓	-	✓	✓	✓	-
Autism spectrum disorder [56,57]	✓	✓	-	-	-	✓	✓	-
Other inherited metabolic disorders with accumulated cellular material <sup>a</sup> [58–62]	✓	✓	✓	✓	✓	✓	✓	✓
					Regression		Regression	Periventricular abnormalities, hyperintensities, demyelination

<sup>a</sup>Including leukodystrophies, lipid storage disorders, mucopolysaccharidoses, and peroxisomal disorders. GLUT1, glucose transporter 1; MRI, magnetic resonance imaging; NCL, neuronal ceroid lipofuscinosis.

seizures and the development of pharmacoresistance are further challenges, as are ‘watch and wait’ approaches (which may delay diagnosis).

Several potential features that may be reported in early disease stages can be extremely useful in raising suspicion of CLN2 disease. EEGs, both while the patient is awake and asleep, are frequently carried out after a seizure. Some patients with CLN2 disease may have a characteristic photoparoxysmal response (PPR) during EEG with low-frequency (1–3 Hz) intermittent photic stimulation (IPS) [63–65]. Although not always reported during the first post-seizure EEG [32], the use of low-frequency IPS could raise suspicion of CLN2 disease. Currently, low-frequency IPS may not be routinely included in early assessments of patients with seizures, and an opportunity for early diagnosis or a heightening of clinical suspicion may be missed.

Early anatomic changes (such as cerebral or cerebellar atrophy; cortical thinning; or white matter changes) may be detectable on MRI [5,34,63,66–68]. As MRI is often performed in the early post-seizure period to detect structural

abnormalities, there exists the possibility of using these MRI data to raise suspicion of CLN2 disease. Although visual impairment is not a common feature of early CLN2 disease [7], a small number of patients may show retinal dysfunction on an electroretinogram (ERG) or abnormal visual evoked potentials (VEPs) [32].

The diagnostic algorithm for CLN2 disease incorporates genetic testing for *TPP1* mutations and enzyme activity testing of *TPP1* to confirm the diagnosis [69]. This algorithm provides several routes to confirmatory diagnosis, based on levels of suspicion for CLN2 disease, ranging from suspicion of genetic epilepsy to suspicion of an NCL, and then suspicion of CLN2 disease. Although pediatric neurologists and epileptologists may recognize that genetic epilepsy is present, because CLN2 disease and NCLs as a group are so rare [1,2,6,29–31,70] there is a risk that any molecular diagnostic tests conducted do not include *TPP1*. Although genetic screens and diagnostic panels are becoming increasingly available [71,72], the percentage of screens and assays that include CLN2 disease is not known, and these methods can be expensive and/or take longer to provide



results than more limited analyses [69]. An advantage of screens is that there does not need to be clinical suspicion of all the diseases that the screen can diagnose. In contrast, the disadvantage is that screens rely on an awareness of disease coverage, and not all rare and ultra-rare diseases will be included.

A deficiency of TPP1 activity in dried blood spots (DBS), fibroblasts, and leukocytes is considered diagnostic of CLN2 disease in combination with genetic testing. As with genetic testing, there is variation between these testing options, in terms of turnaround times for analysis, sample stability, and specificity [69]. A simple, inexpensive, yet reliable fluorometric method has been developed to assess TPP1 activity in DBS [73], and the use of this sample type may be an important consideration in regions where logistical difficulties affect sample storage and transport by providing a simple, quick screening option that can be followed by targeted confirmatory genetic tests.

### 2.3. Summary of key presenting symptoms and steps to reduce time to diagnosis

In order to diagnose CLN2 disease as early as possible, the following features of CLN2 disease should be noted, and if present, screening tests for CLN2 disease should be implemented:

- First unprovoked seizure between the age of 2 and 4 years in combination with any of:
  - A family history of CLN2 disease, unexplained neurological disease or death associated with neurological factors during childhood
  - Patient history or family reports of the patient experiencing:
    - Language deficits or delays
    - Clumsiness or a lack of coordination; tremors; frequent falls; a wide-based gait; spasticity; or hypotonia
    - Behavioral problems
    - Hyperactivity/attention deficit hyperactivity disorder
  - Regression, slowing, or loss of acquired developmental milestones
  - Myoclonus
  - PPR with low-frequency IPS
  - Cerebellar atrophy on MRI

The following steps on the diagnostic pathway should be undertaken accordingly:

- Collect a detailed medical history, incorporating family and caregiver reports of language, motor, cognitive, social, and behavioral abilities
- Carry out or reassess:
  - EEG (awake and asleep) and using low-frequency IPS, to identify PPR
  - ERG and VEPs, to identify abnormalities
  - MRI, to identify cerebellar atrophy and/or periventricular white matter changes
- Test for CLN2 disease and treat, or refer to a specialist

- Undertake diagnostic enzyme activity or genetic testing
  - It is important to understand differences in time frames and costs between the available testing options in different healthcare systems in order to select an appropriate screen for patients with a rapidly progressive disease
  - Fluorometric enzyme activity assays using DBS followed by genetic analysis of *TPP1* can provide a quick, inexpensive route to diagnosis
  - Be aware that not all targeted epilepsy gene panels include *TPP1*

If all diagnostic features have been collated and considered and a diagnosis has still not been achieved, request specialist advice, and reevaluate the patient, testing strategy and differential diagnosis.

### 3. Conclusion

A diagnosis of CLN2 disease must not be missed or delayed. CLN2 disease is a severe, rapidly progressive neurodegenerative disorder that is fatal in late childhood or early adolescence. Prompt diagnosis is key, not only for ensuring access to treatment at an early disease stage but also for putting in place long-term strategies to optimize quality of life as the disease progresses and for providing families with support.

The characteristic presenting symptom of unprovoked seizures between the ages of 2 and 4 years can be considered alongside a potentially broad range of other symptoms affecting language, motor function, coordination, and behavior. Thorough assessments of medical and family history can provide diagnostic clues, as can other clinical assessments. If diagnosis is uncertain, broad screening tests (such as DBS analyses) may provide simple, inexpensive options, although it is vital to ensure that any large-scale screens or confirmatory tests include *TPP1*. If resources need to be managed carefully, diagnostic tests could initially be focused on excluding treatable diseases. When the diagnostic process has come to a halt, it will be necessary to seek advice from a specialist or involve other clinicians in a panel discussion; these discussions may include other clinicians in the same hospital or be established at a national or international level with input from rare disease centers or European Reference Networks. Although challenging, ensuring that no diseases are forgotten during the differential diagnosis is a key step in timely diagnosis and starting patients on a pathway to optimal outcomes.

### 4. Expert opinion

The key presenting symptoms described above highlight what is already known about the presentation of CLN2 disease. While patients often present with seizures, other diagnostic clues, such as language deficits, motor dysfunction and behavioral issues, can be obtained through a detailed examination of medical histories, and discussions with family members and caregivers. In addition, clinical assessments, such as EEG and MRI, may be conducted in children who present with seizures, and the information needed to raise suspicion of CLN2 disease could be close

at hand during early disease stages. The main challenges of putting this information into practice are that the presenting symptoms are very similar to those of other, sometimes more common, disorders, and CLN2 disease is rare. To combat the first challenge, nonspecific presenting symptoms, clinicians can use broad diagnostic tools covering a wide range of disorders associated with the symptoms in question. With TPP1 included in both enzyme activity and genetic screens, clinicians need not choose to consider a diagnosis of CLN2 disease in isolation from other possible disorders; the key is ensuring that selected tests include disorders with a treatment so patients can benefit from a specific intervention in the early stages of disease.

The second challenge, diagnosing a rare disease, requires a heightened awareness among clinicians treating patients in early disease stages. Indeed, clinicians may see patients with CLN2 disease very rarely, if at all, and it is likely that, as they work through a differential diagnosis, other more common disorders are considered first. Raising awareness likely involves campaigns targeting clinicians with differing expertise in rare metabolic neurological syndromes, such as CLN2 disease. For clinicians with a more general expertise across a diverse range of diseases, such as emergency room specialists, the aim of campaigns could be to ensure that expert advice is sought to direct the patient to appropriate testing. For pediatric neurologists, campaigns could focus on clarifying the relevance of potential presenting symptoms and ensuring that the diagnostic tests selected cover CLN2 disease and other disorders for which early treatment may have the greatest positive impact. Managers of diagnostic departments could be contacted to confirm that their screening processes incorporate CLN2 disease.

An example of how panels may be used to identify patients with genetic epilepsies is a prospective, multicenter study of targeted resequencing using a 283-gene next-generation sequencing panel to analyze samples from 21 children with neurodevelopmental abnormalities (aged 24–60 months) after the first unprovoked seizure [74]. Four children were diagnosed with a genetic disorder, resulting in a diagnostic yield of 19%. One patient was diagnosed with CLN2 disease, as a homozygous splice acceptor variant (c.509–1G>C) was identified in *TPP1*, further supporting the efficacy of targeted resequencing in identifying genetic causes of childhood epilepsy. Such studies raise awareness of the ability of panels and screens to diagnose rare genetic disorders.

In the coming years, as trials of cerliponase alfa continue and long-term data are collected, we might expect that awareness of CLN2 disease will increase. Advances in diagnostic testing will continue, and with increasing disease coverage comes an increasing likelihood that CLN2 disease will be incorporated. Even so, CLN2 disease will remain a rare disease, and broad diagnostic screens could still be one of the most expensive testing options. Moving forward there will be an enduring need to make sure that clinicians consider CLN2 disease, and targeted campaigns have a role to play in this.

If the symptomatic clues can be spotted and appropriate testing tools are in place, early diagnosis is a realistic outcome for patients with CLN2 disease. As a treatment, cerliponase alfa, is now available, we ask that clinicians move from considering CLN2 disease as a very rare disorder requiring symptomatic and palliative management to one for which patients

now have a disease-modifying option that requires diagnosis to be prioritized.

## Abbreviations

AED	Antiepileptic drug
AGAT	L-Arginine:glycine amidinotransferase
CLN2	Neuronal ceroid lipofuscinosis type 2
CSF	Cerebrospinal fluid
CT1	Creatine transporter 1
DBS	Dried blood spot
EEG	Electroencephalography
ERG	Electroretinogram/electroretinography
ERT	Enzyme replacement therapy
GAMT	Guanidinoacetate methyltransferase
GLUT1	Glucose transporter 1
HCP	Healthcare professional
IPS	Intermittent photic stimulation
MAE	Myoclonic astatic epilepsy
MRI	Magnetic resonance imaging
NCL	Neuronal ceroid lipofuscinosis
PDE	Pyridoxine-dependent epilepsy
PPR	Photoparoxysmal response
TPP1	Tripeptidyl peptidase 1
VEP	Visual evoked potential

## Acknowledgments

This manuscript was developed after discussions at a meeting of experts organized and supported by BioMarin Europe Ltd. Writing support was provided by Emma Conran, Porterhouse Medical, Reading, UK, and funded by BioMarin Europe Ltd.

## Funding

P Striano developed this research within the framework of the DINOGMI Department of Excellence of MIUR 2018–2022 (Legge 232 del 2016).

## Declaration of interest

All authors received an honorarium from BioMarin Europe Ltd for their contributions to an expert meeting at which it was agreed that this manuscript should be developed. In addition, H Huidekoper reports institutional reimbursement from BioMarin Europe Ltd, outside of the submitted work. M Mazurkiewicz-Beldzińska reports personal fees from Biogen; personal fees from Roche; personal fees from BioMarin Europe Ltd; and personal fees from Novartis, outside of the submitted work. C Mühlhausen reports personal fees from PTC Therapeutics Germany GmbH, outside of the submitted work. I Prpić reports non-financial support from Dravet Syndrome Association Croatia; grants, personal fees and non-financial support from BioMarin Europe Ltd; non-financial support from Merck; non-financial support from Belupo d.d.; personal fees and non-financial support from Makpharm d.o.o.; personal fees and non-financial support from Pliva d.o.o.; non-financial support from Academy for Child Neurodevelopment; personal fees from Medis d.o.o.; non-financial support from the organizer of 'New Challenges in Paediatrics' Symposium, Croatia, March 2020; and personal fees and non-financial support from BioMarin Pharmaceutical Inc., outside of the submitted work. P Striano reports personal fees from Zogenix; personal fees from GW Pharmaceuticals; personal fees from Enecta BV; and personal fees from Proveca during the conduct of the study. S Auvin reports personal fees and non-financial support from BioMarin, outside of the submitted work. The authors have no other relevant affiliations or financial involvement with any organization or



entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

## Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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