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Research Article

Management of CLN1 Disease: International Clinical Consensus

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ABSTRACT

Background: CLN1 disease (neuronal ceroid lipofuscinosis type 1) is a rare, genetic, neurodegenerative lysosomal storage disorder caused by palmitoyl-protein thioesterase 1 (PPT1) enzyme deficiency. Clinical features include developmental delay, psychomotor regression, seizures, ataxia, movement disorders, visual impairment, and early death. In general, the later the age at symptom onset, the more protracted

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the disease course. We sought to evaluate current evidence and to develop expert practice consensus to support clinicians who have not previously encountered patients with this rare disease.
Methods: We searched the literature for guidelines and evidence to support clinical practice recommendations. We surveyed CLN1 disease experts and caregivers regarding their experiences and recommendations, and a meeting of experts was conducted to ascertain points of consensus and clinical practice differences.
Results: We found a limited evidence base for treatment and no clinical management guidelines specific to CLN1 disease. Fifteen CLN1 disease experts and 39 caregivers responded to the surveys, and 14 experts met to develop consensus-based recommendations. The resulting management recommendations are uniquely informed by family perspectives, due to the inclusion of caregiver and advocate perspectives. A family-centered approach is supported, and individualized, multidisciplinary care is emphasized in the recommendations. Ascertainment of the specific CLN1 disease phenotype (infantile-, late infantile-, juvenile-, or adult-onset) is of key importance in informing the anticipated clinical course, prognosis, and care needs. Goals and strategies should be periodically reevaluated and adapted to patients' current needs, with a primary aim of optimizing patient and family quality of life.

Introduction

CLN1 disease, or neuronal ceroid lipofuscinosis type 1 (OMIM 256730), is a rare, autosomal recessive, neurodegenerative lysosomal storage disorder caused by homozygous or compound heterozygous pathogenic variants in *CLN1* encoding the palmitoyl protein thioesterase 1 (PPT1) enzyme, resulting in deficient PPT1 production.[1] CLN1 is one of 13 or more distinct neuronal ceroid lipofuscinosis (NCL) disorders with unique genetic etiologies.[2] In the classic form of CLN1 disease, symptoms begin during infancy; additional phenotypes have been observed with late infantile, juvenile, and adult onset.[2] Estimated incidence ranges from 0.03 per 100,000 live births in the United Kingdom to 5 per 100,000 live births in Finland.[3-7] Prevalence estimates range from 0.03 per 1 million inhabitants in Italy to 5.4 per 1 million inhabitants in Finland.[5,7]

The pathophysiology of CLN1 disease remains poorly understood, but likely involves multiple cellular pathways, as *PPT1* is expressed in neurons and other cell types, within lysosomes, as well as in extralysosomal compartments.[1,8] PPT1 plays a critical role in the catabolism of lipid-modified proteins by removing fatty acids from cysteine residues.[9] Dysfunction in the PPT1 enzyme results in intracellular accumulation of autofluorescent lysosomal storage material, which has several associated downstream findings, including impaired autophagy and neuronal death in the brain and spinal cord.[10-15]

The main clinical features are developmental delay, psychomotor regression, seizures, ataxia, movement disorders, acquired microcephaly, visual impairment, and premature death.[16] The complex constellation of symptoms can be diagnostically challenging, and the disease course can have devastating impacts on affected individuals and families.

Disease-modifying therapies are not presently available for CLN1 disease, although clinical trials are being planned.[17] Current management strategies focus on symptom relief and palliative care. Owing to disease rarity, many clinicians lack experience treating individuals with *any* NCL disorder. A care guidance document has the potential to aid clinicians in decision-making,[18] providing family support, and optimizing patient quality of life. Yet, there are no clinical management guidelines or consensus statements specific to CLN1 disease.

Families affected by CLN1 disease led an international initiative to develop a clinical care consensus statement based on the guidance of clinicians, researchers, and patient advocates who have direct experience with the care of patients with CLN1 disease. Most recommendations are based on clinical experience, as there have been few clinical trials of management interventions in CLN1 disease.[19-21] Family perspectives were included in the process to ensure that their most salient needs were addressed.

Methods

A nonprofit rare disease patient advocacy group, Taylor's Tale, created a partnership between families and clinicians modeled, in part, on a consensus-building process on management strategies for CLN2 disease.[22]

Literature review

A comprehensive literature review relevant to CLN1 disease management was conducted by searching Pubmed, Embase, and Scopus. No broad management guidelines specific to CLN1 disease were found. Eleven publications regarding management of specific symptoms associated with CLN1 disease, or neurological conditions in general, were reviewed and incorporated into consensus development.

CLN1 disease expert survey

A 180-question online survey of CLN1 disease experts was adapted, with permission, from a survey used for the CLN2 disease management consensus process.[22] Experts were identified based on clinical experience, publications, and referrals. Participants were selected to provide diversity of geography, discipline, and experience. Survey topics included experience level, testing approaches, occurrence of core symptoms and co-morbid conditions, and management goals and strategies.

CLN1 disease caregiver survey

A 68-question online survey of caregivers was developed, in English and German languages, to define unmet needs and provide family perspectives. This survey was submitted for review to the Western Institutional Review Board, which deemed it exempt under 45 CFR § 46.104(d)(2). Primary caregivers of individuals with CLN1 disease, living or deceased, were invited to complete the survey through collaboration with several international Batten disease advocacy organizations. Survey topics included age at onset and diagnosis, symptom burden, challenges and rewards of care, management strategies, unmet needs, support systems, and school accommodations.

Advisory board meeting

An advisory board meeting was held on May 18 to 20, 2019. Meeting presentations included survey results, case studies, caregiver perspectives, and management strategies. Roundtable discussions were held to identify areas of consensus and clinical practice differences. Simultaneous translation was available to participants upon request.

Results

Expert survey and advisory board meeting

Fifteen experts from seven countries on four continents completed the survey. Respondents included 10 pediatric neurologists, a neuropsychologist, a metabolic specialist, a developmental physical therapist, a hospice nurse, and a social worker. Of these, 14 participated in the advisory board meeting. Almost all clinicians were from institutions with well-established referral centers for NCL disorders. Collectively, clinicians had experience caring for and/or evaluating over 75 patients with CLN1 disease.

Caregiver survey

Forty-four surveys were completed by respondents from six countries. Five surveys were excluded because the respondents were not primary caregivers. Select results are presented throughout this publication as *Caregiver Survey Insights*.

Consensus

Multiple phenotypes require tailored clinical management

CLN1 disease was initially described as infantile-type NCL in 1973.[23,24] At that time, NCLs were classified into four types (infantile [Haltia-Santavuori], late infantile [Jansky-Bielschowsky], juvenile [Spielmeyer-Sjögren], and adult [Kufs] NCL) and were differentiated based on age at symptom onset and histochemical findings. Infantile NCL was defined by onset between age eight and 18 months and presence of autofluorescent granular osmiophilic deposits on ultrastructural examination.[25] It is now understood that CLN1 disease is caused by pathogenic variants in *CLN1* and has multiple phenotypes. The terms *infantile*, *late infantile*, *juvenile*, and *adult* are used for phenotype classification based on age at onset.[1,25] A juvenile-onset form (variant juvenile NCL with granular osmiophilic deposits) was recognized in 1973 and further characterized in the early 1990s.[26,27] Late infantile CLN1 disease was described in 1998, and an adult-onset form was reported in 2001.[28-30]

The different CLN1 disease phenotypes vary by age at onset, order of symptom onset, rate of disease progression, and life expectancy (Table 1 and Fig 1). Thus the ages presented in Table 1 and throughout the text are meant to serve as a general guide rather than an absolute definition, as there are no universally accepted age boundaries and the literature varies. In general, the later the age at symptom onset, the more protracted the disease course.[31]

For children who fall on an age boundary, it can be challenging to predict which phenotypic category is most appropriate.

There are at least 71 different disease-causing pathogenic variants in *CLN1* reported to date, with strong genotype-phenotype correlations for certain mutations.[31,34] The reference sequence for PPT1 protein variant locations (P50897) can be found at www.uniprot.org.[35] In Finland, the classic infantile-onset form occurs almost exclusively due to a founder effect in a single pathogenic variant p.(Arg122Trp). Common in Germany and Italy, the pathogenic variant p.(Leu222Pro) is associated with late infantile onset; the p.(Asp43_Gly145del) variant is shared between infantile and late-infantile forms in both countries. In Scotland, two pathogenic variants contribute to a founder effect in juvenile-onset disease: p.(Thr75Pro) and p.(Leu10Ter).[27,36,37] A highly truncated enzyme is more likely to be found in patients with the severe infantile form.[38,39] By extension, absent enzyme activity is typically associated with a more severe CLN1 disease phenotype, although even this association is not absolute,[40] making it challenging to predict phenotype based on enzyme level. Enzyme levels for adult-onset forms of CLN1 disease can be found within the same range as late infantile- and juvenile-onset forms.[30] Siblings are likely to present with similar phenotypes.[29,30,38,41-43]

Data are limited regarding the rate of neurological decline and anticipated lifespan for each CLN1 disease phenotype. One of the most comprehensive studies of the longitudinal course of CLN1 disease occurred in a trial of cysteamine and *N*-acetylcysteine.[19] Nine children with severe PPT1 mutations were followed longitudinally over a range of eight to 75 months. Severe neurological impairment or vegetative state, represented by isoelectric electroencephalography (EEG), occurred at a mean age of 59 (S.D. 13) months. In general, individuals with the infantile phenotype have the most aggressive course, with age at death in the first or second decade (published reports range from three to 12 years). Those with the late infantile phenotype develop a severe impairment phase by age six to 12 years and may survive into the second or third decade. Those with the juvenile phenotype reach a severe state in the third decade and typically live into the third or fourth decade. In a recent survey, the median age of death was 9.5, 16.6, and 27 years for infantile, late infantile and juvenile forms, respectively.[37] The degree to which lifespan is impacted in the adult-onset phenotype is unknown.

The diversity of disease phenotypes has implications for clinical management. Age at symptom onset influences functional impact and perhaps quality of life, based on the developmental status of the individual. For example, those with juvenile onset may experience greater loss in independent function than those with infantile onset, who may never develop certain independent skills. Furthermore, caregiver needs, such as assistance with lifting and diapering, differ with an adolescent compared with an infant. An understanding of the clinical phenotype may help caregivers and clinicians prepare for the disease course ahead.

TABLE 1.
Clinical Spectrum of CLN1 Disease Phenotypes[31-33]

Phenotype	Typical Ages at Symptom Onset	Rate of Progression	Clinical Features
Infantile	6-18 months	Rapid	Cognitive and motor decline, hypotonia, ataxia, myoclonus, seizures, hand stereotypies, vision loss, acquired microcephaly
Late infantile	>18 months-4 years	Rapid	Developmental delay, early cognitive decline, later vision loss, ataxia, myoclonus, seizures
Juvenile	>4 years-early adolescence	Slow	Cognitive decline, seizures, motor decline, ataxia, spasticity, later vision loss
Adult	Late adolescence and older	Protracted	Cognitive decline, depression, ataxia, parkinsonism, vision loss

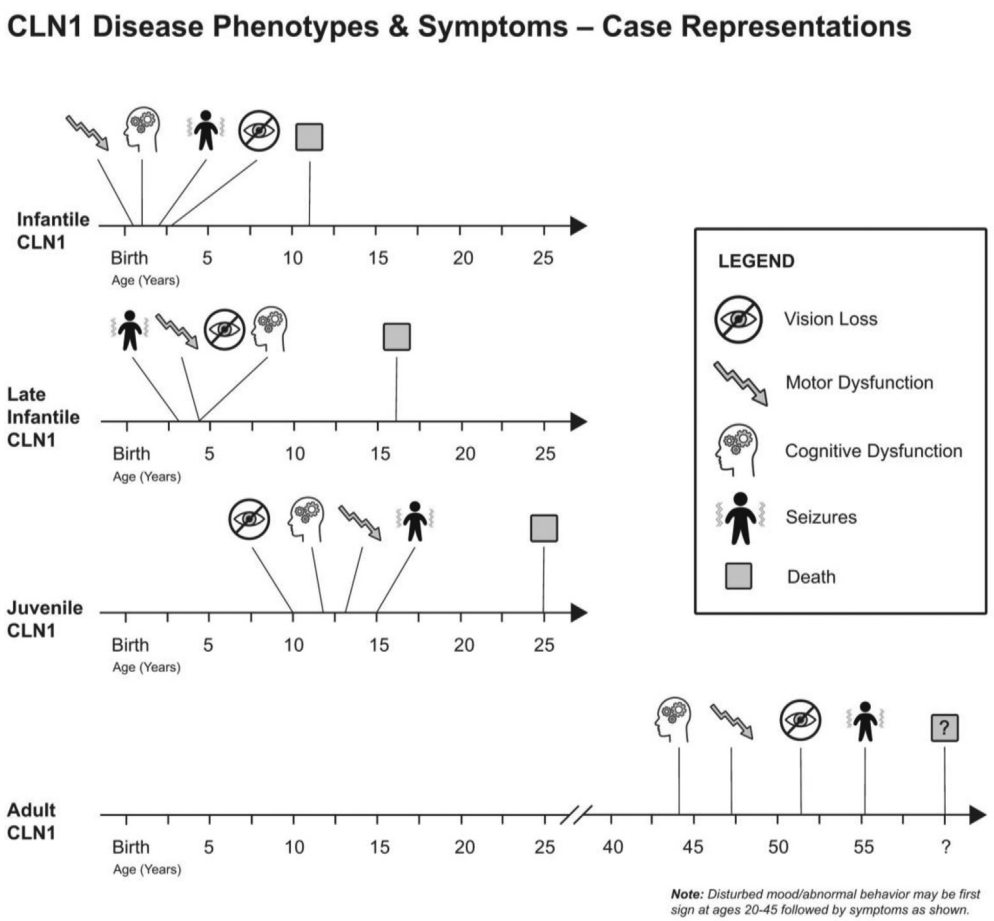

FIGURE 1. Examples of CLN1 disease phenotypes and symptom progressions. The ages at symptom onset depicted here are derived from clinical experience and published data and are intended to represent *sample* cases. The specific occurrence, order, and age at symptom onset are variable. Figure adapted from Miriam Nickel, MD.

Optimal management relies on early diagnosis

Early diagnosis is critical for providing optimal symptom management, minimizing complications, and connecting families to appropriate psychosocial support and genetic counseling.[44,45] Because CLN1 disease is rare and its presentation is nonspecific, it is not uncommon for diagnosis to take two years or more.

CLN1 disease should be considered in (1) young children older than age six months with developmental plateauing or regression, slowed head growth, and/or newly occurring drug-resistant epilepsy, especially with myoclonic seizures, and (2) school-aged children with some combination of visual loss, dementia, or epilepsy. Although incredibly rare, a CLN1 disease diagnosis could be considered in adults with recent onset of progressive visual, cognitive, motor, and/or behavioral abnormalities.[32,33] The differential diagnosis should include other neuronal lysosomal storage and neurodegenerative disorders with a similar age of onset.[33] Testing siblings of patients with confirmed CLN1 disease may also be discussed with families.

Caregiver Survey Insights

The distribution of caregiver-reported CLN1 disease phenotypes was: 51% infantile, 21% late infantile, 23% juvenile, 0% adult, and 5% unspecified.

Diagnostic algorithms for CLN1 disease vary. The approach to a child with a suspected neurometabolic or neurodegenerative condition often includes neuroimaging, EEG if seizures have occurred, and ophthalmologic assessment. Neuroimaging in the infantile-onset form is primarily characterized by rapid progressive volume loss, predominantly of the hemispheres, followed by the cerebellum, and then the brainstem.[46] In one series, incidental chronic subdural hematomas were evident in four of nine participants.[47] Photoparoxysmal response to low-frequency intermittent photic stimulation has been described in CLN2 and CLN6 disease,[48-50] although it is not clear if this is a specific feature in CLN1 disease.[48] Loss of sleep spindles is also observed, particularly in early-onset forms.[51] Retinopathy is a hallmark of the NCLs. Electroretinography may hold an important diagnostic clue, with early b-wave loss and electronegative configuration being a classic finding, followed by early extinction.[52]

Genotyping of *CLN1* may be the first-line diagnostic at certain centers. Additional strategies, including gene panels (epilepsy, lysosomal storage diseases) and whole-exome sequencing, are increasingly used first line and are often sufficient for establishing diagnosis, as the majority of known pathogenic variants are sequence variants. The exact frequency of large deletions and duplications is not well known.[16,53] When results demonstrate pathogenic variants that have not previously been reported, or genetic testing is not available, PPT1 enzymatic testing for diagnostic confirmation and/or clarification should be pursued.[54] When genetic testing is not available or is inconclusive, electron microscopy of skin, rectal, or conjunctival tissue may be useful for narrowing to

Caregiver Survey Insights

The first symptoms that most frequently prompted seeking medical attention were motor delay or decline (36%), vision decline (22%), learning delay or decline (14%), and seizures (14%). Additional symptoms included language delay or decline, behavior, and sleep disturbances.

an NCL condition if autofluorescent ceroid lipofuscin is detected. Regardless of the approach, testing for CLN2 disease should be considered (either genotyping or tripeptidyl peptidase 1 enzymatic testing), as CLN2 disease may present similarly, and enzyme replacement therapy is currently available in many countries.[55]

General goals and principles of management

Primary management goals are to minimize symptoms and maximize quality of life for the patient and family. Decision-making should be a clinical team-family partnership, with respect and support for a broad range of beliefs and choices. Caregiver empowerment is critical; there is often a high burden of home care and substantial uncertainty surrounding prognosis.[56] Symptom management includes a broad range of strategies: pharmacologic and nonpharmacologic therapies, nutrition, psychosocial and school support, palliative care, and hospice support. Care should be customized to meet a variety of needs, as illustrated in Fig 2.

Management goals and interventions may evolve as the disease progresses. Care plans should be reassessed regularly based on disease stage and changing needs. Table 2 summarizes approaches to common therapeutic needs. Decision-making should be guided by the composite of benefits, risks, and impact on family and patient stress. Medication overuse should be avoided, and care plans should not be overly burdensome. Modifications to accommodate functional impairment should be applied across all settings: home, school, social environments, public spaces, and clinical settings.

Ongoing management requires a coordinated care team

Owing to varied disease manifestations, ongoing management often involves a multidisciplinary clinical team. Regular communication and coordination of care among providers is critical. When needed, consultation with specialists experienced in NCLs may aid in clarification of diagnosis, addressing specific care challenges, or providing information about research.

Seizure management

Patients with CLN1 disease may experience multiple seizure types, including focal seizures (with or without impaired awareness, with or without evolution to bilateral convulsive activity) and/or primary generalized seizures (most often myoclonic, and also myoclonic-atonic, tonic-clonic, atonic, tonic, or absence). Generalized tonic-clonic seizures are less common in the infantile phenotype than in the juvenile phenotype.[57] Seizure semiology typically changes over time, and myoclonic seizures become prominent.[33] Seizure frequency often depends on the stage of the disease, with numerous daily seizures earlier in the disease course and few to none later, when the EEG shows diffuse suppression, due to cortical degeneration.[58] Seizures present relatively early in the infantile phenotype, typically between ages 14 to 36 months, following slowed head growth, hypotonia and developmental plateauing or regression, and often preceding visual loss.[57,58] In later-onset phenotypes, epilepsy typically begins several years after the initial symptom of visual impairment, following developmental regression and behavior changes.[58,59]

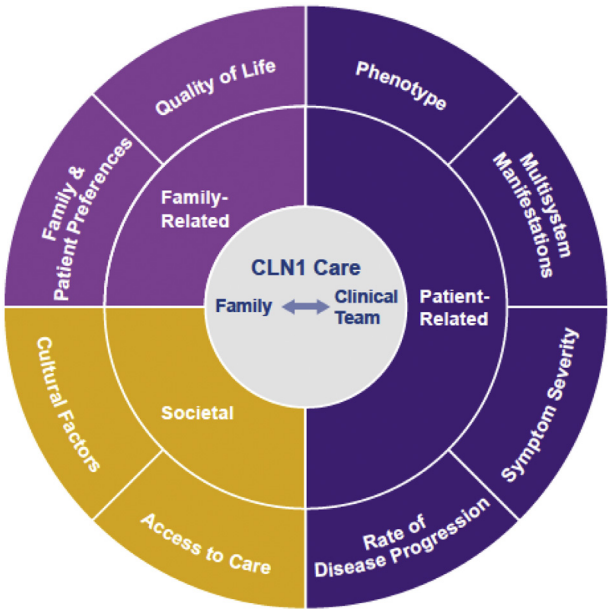

FIGURE 2. Factors impacting shared decision-making and customization of care for patients with CLN1 disease. The color version of this figure is available in the online edition.

ASMs are generally started at the time of seizure onset, which may precede or follow the clinical diagnosis of CLN1 disease. The goal of seizure management is to attain sufficient seizure control to maximize patient safety and quality of life while minimizing side effects, particularly sedation and irritability. Achieving seizure freedom may not be a realistic expectation, as epilepsy is drug-resistant in nearly all cases.[58] Therefore, priority should be given to minimizing the most problematic seizures, such as prolonged or clusters of convulsive seizures requiring rescue medication, more severe seizure types resulting in increased risk of aspiration, and seizures having a prolonged postictal phase. Myoclonus and brief seizures lasting less than one minute that are not clustering or causing other problems are often tolerated without changing ASMs. Patient comorbidities and potential drug-drug or drug-symptom interactions should be carefully weighed when making treatment decisions.

Accurate identification of seizures is key, as it is not uncommon for caregivers to mistake irritability with prominent arching and dystonia for seizure; video can help clarify, although distinction of epileptic from nonepileptic myoclonus even by video-EEG is challenging. Fortunately, the major overlap in treatments for epileptic and nonepileptic myoclonus lessens the impact of this difficulty. The impact of seizures should be judged within the context of the patient's functional status (e.g., drop seizures may be more problematic for patients who are ambulatory or sit independently).

General approaches to seizure management apply, including initial ASM selection, ongoing reassessment, and use of rescue medications.[58,60] The need for ASM typically lessens as the disease progresses, and it may be possible to shift patients on polytherapy to monotherapy.[58] Regularly scheduled EEGs are usually not required for routine monitoring, although they may be beneficial in the evaluation of new events with uncertain etiology.

TABLE 2.
Summary of Management Strategies for CLN1 Disease

Domain	Recommendations
Epilepsy	• Apply general principles of epilepsy management - Accurately identify seizures - Introduce optimal ASM based on seizure type - Explore non-drug epilepsy therapies (e.g., ketogenic diet) as appropriate • Complete seizure freedom is often not attainable - Balance reduction in seizure frequency and severity against potential side effects of ASMs - Myoclonic or other brief seizures that have limited impact on QOL may not require medication adjustment • Regularly assess ongoing benefit of specific ASMs and wean if ineffective • Seizures may become less problematic over time
Movement disorders	• Focus treatment on movement disorders that result in functional impairment • Evaluate potential sources of movement disorders (drug side effect versus intrinsic disease symptom)
Physical, occupational, and complementary therapies	• Initiate occupational, physical, and speech therapy early in disease course • Provide adaptive devices and feeding therapy to maintain function and independence, as disease progresses • Focus on range of motion and positioning needs toward end of life
Nutritional needs, gastrointestinal	• Assess for nutritional needs and swallowing dysfunction or aspiration risk as motor decline ensues • Provide nutritional supports, modified diets, and/or alternate routes of feeding as needed
Respiratory/infection management	• Maintain typical childhood vaccination schedule • Screen periodically for aspiration risk
Sleep disturbance	• Maintain positive sleep hygiene practices • Match pharmacologic strategies to the nature of the sleep disturbance
Vision	• In later-onset phenotypes, obtain optimal refraction correction, aids, and vision or mobility therapies to accommodate visual impairment
Mood and behavioral symptoms	• Consider whether concomitant medications are worsening mood and behavioral symptoms • Consider input from a behavioral/developmental disabilities specialist to identify triggers and potential modifications to environment, routine, or interactions
Neurocognitive assessment and educational strategies	• Assess developmental/cognitive function as appropriate for age/phenotype and needs of the child • Classroom placement and instructional approach should match the child's needs and educational goals • Flexibility is needed as child's school support requirements may change as disease progresses
Family support	• Provide patient group peer support opportunities • Educate about ancillary needs of families throughout disease course including sibling needs • Reassess continually
Palliative care and end-of-life considerations	• The earlier the disease onset, the sooner palliative care integration may be appropriate

Abbreviations:
ASM = Antiseizure medication
QOL = Quality of life

Rescue medications allow home management of seizures that are prolonged or cluster. Recommended first- and second-line therapies for myoclonic and convulsive seizures in CLN1 disease, based on clinical experience, are listed in Table 3. Drug availability may vary by country.

In general, broad-spectrum ASMs should be prioritized over sodium channel blockers, which may exacerbate myoclonus.[62] However, if effective and tolerated, sodium channel blockers should not be discontinued in patients already taking them. Furthermore, carbamazepine, oxcarbazepine, or phenytoin may be considered for treatment of refractory focal seizures without prominent myoclonus. Patients should be closely observed for side effects, such as myoclonus, irritability, crying, sleep disorders, or regression.

Interest in cannabidiol (CBD) among caregivers is common, stemming from development of pharmaceutical-grade CBD for Lennox-Gastaut syndrome and Dravet syndrome, anecdotal evidence, and growing general availability. Quality control concerns arise in the setting of self-treatment using unregulated products. Clinicians should maintain open dialogue with caregivers regarding use without a prescription in case adverse events or drug-drug interactions occur due to CBD or contaminants.

Caregiver Survey Insights

The majority of caregivers (72%) think the interventions they use help improve their child's quality of life. The interventions used by the greatest number of families include antiseizure medications (ASMs), physical therapy, massage, home/school modifications, and dietary changes. A total of 19 different interventions were reported.

Nonpharmaceutical options may be effective for intractable seizures. Three experts had experience overseeing use of the ketogenic diet in CLN1 disease and reported positive results with some, but not all, patients. There are no published reports on the efficacy or safety of the vagus nerve stimulator in CLN1-related epilepsy. In other drug-resistant childhood epilepsies, vagus nerve stimulation may provide modest seizure reduction and the option to disrupt seizures without the use of rescue medication.[63] However, there are several challenges related to device use, including size, exacerbation of dysphagia and drooling, and need for placement under general anesthesia. This intervention should be considered only in highly intractable cases of CLN1 disease having few remaining alternatives for seizure control.

Management of movement disorders

Many different movement disorders can occur in patients with CLN1 disease, including myoclonus, ataxia, dystonia, chorea,

Caregiver Survey Insights

Seizures and motor delay/decline are the symptoms that worry caregivers the most (24% and 26% of responses).

Caregiver Survey Insights

Caregivers expect some amount of sedation to achieve better seizure control, but most prioritize maintaining alertness and the ability to interact over controlling seizures.

Caregiver Survey Insights

Ketogenic diet had been tried in two patients. Respondents said there was "significant seizure control" and "increased alertness," but "maintaining stable ketosis was difficult to manage."

parkinsonism, tremor, dyskinesia, and stereotypies. Presentation varies slightly by phenotype, with myoclonus characteristic of infantile and late infantile forms, parkinsonism more common in juvenile and adult forms, and ataxia occurring in all forms.[19] Chorea has been described in infantile-onset disease, but it is an infrequent occurrence.[64]

The goals of treatment are to maintain function and quality of life, prevent pain and rhabdomyolysis, and maintain range of motion and posture. Medications should be selected based on the type of movement disorder and the effect of side effects in relation to quality of life. Recommended medications are listed in Table 4. Ataxia is not responsive to currently available medications. Caregivers should be directed to develop adaptive strategies to accommodate ataxia, using physical and occupational therapy, adaptive equipment and technology, and visual rehabilitation.

Neurocognitive assessment and educational strategies

Patients with CLN1 disease experience progressive cognitive decline, ultimately resulting in significant regression of cognitive and language skills.[40,43,65] Individuals with infantile and late infantile phenotypes may first exhibit delays in early developmental milestones, whereas those with juvenile onset typically experience problems with attention and concentration, processing speed, memory, reading, and writing.[19,29,40,42,43,66,67]

Individuals with CLN1 disease should undergo assessments of cognition or development (as appropriate for age and developmental level) and adaptive function upon diagnosis to establish understanding of baseline function. These evaluations help to create reasonable expectations based on individuals' current capabilities and inform educational and support services. Children with a rapidly progressing infantile-onset phenotype may not require extensive testing, and the assessment should consider anticipation and management of emerging symptoms over a relatively short timeline. Repeat testing for individuals with the juvenile or adult phenotype is recommended when new cognitive concerns arise or existing cognitive symptoms or adaptive skills worsen.[68]

Selection of tests can be guided by work in other rare diseases that result in pediatric-onset dementia.[69] It is important to monitor changes in both age-corrected test scores, which are benchmarked against performance by typically developing children, and "raw scores," which describe an individual child's change over time in relation to their own past performance on the same test. Children with greater disease burden may need indirect assessment via observational tools and parent/caregiver proxy report measures.[70,71] Finally, evaluations should be selected with consideration for the extent of vision loss.

Educational approaches should consider a pediatric dementia model in which children may not acquire skills at the expected rate for their age, may reach an early plateau in their maximum attainment of skills, and will ultimately lose skills. Thus, benchmarks for success may focus on maintenance of existing skills to the degree possible, and/or support to remain engaged in the school environment despite regression. School-based goals may include one or more of the following: academic skills development, optimizing quality of life, social and community engagement, response to developmental delays or regression, management of challenging behaviors, supportive care, and offering daytime respite hours to parents and caregivers.

Existing resources from other complex neurological conditions may be leveraged to develop educational plans for patients with CLN1 disease, including guides produced by the Niemann-Pick Disease Group, Rettsyndrome.org, the MPS Society, and Genetic Education Materials for School Success.[72-75] A published approach to educational and social supports for patients with CLN3 disease may be applicable to individuals with the juvenile CLN1 disease phenotype.[76]

TABLE 3.
Recommended Antiseizure Medications for Use in CLN1 Disease, Per Clinical Experience

Myoclonic Seizures		Convulsive Seizures	
First Line	Second Line	First Line	Second Line
Benzodiazepines (including clobazam) Levetiracetam Valproic acid*	Brivaracetam Phenobarbital Topiramate† Zonisamide Pregabalin	Lamotrigine‡ Levetiracetam Valproic acid	Benzodiazepines (including clobazam) Brivaracetam Cannabidiol§ Perampanel Phenobarbital Rufinamide
Not recommended: Sodium channel blockers,‖ vigabatrin			Sodium channel blockers‖ (carbamazepine, oxcarbazepine phenytoin) Topiramate† Zonisamide

* In some countries, including the United Kingdom, female patients of childbearing potential taking valproic acid are required to undergo pregnancy monitoring and be placed on birth control due to potential teratogenicity.

† Use with caution; may adversely affect language and speech.

‡ Lamotrigine may increase myoclonic seizures but is not contraindicated.

§ For patients on clobazam cotherapy, the dose of clobazam should be reduced and the patient carefully monitored for excessive sedation, as cannabidiol increases blood levels of both clobazam and its active metabolite, norclobazam.[61]

‖ Sodium channel blockers should be avoided if myoclonic seizures are prominent, as they can exacerbate myoclonus.

Caregiver Survey Insights

"Motor delay or decline" and "vision decline" were ranked as the symptoms with the greatest unmet need for therapeutic intervention (one-third of respondents).

Ophthalmologic considerations

Vision loss is a hallmark symptom of NCL disorders. In infantile-onset disease, severe visual impairment occurs as early as age one to two years due to optic atrophy and retinal degeneration. On ophthalmic examination, atrophic optic discs, retinal hypopigmentation, narrow vessels, and severely reduced electroretinogram responses are reported.[77] Ocular motility disturbances are thought to be secondary to diminished vision. Reduced vision can be the presenting symptom in the later-onset phenotypes, along with degenerative findings on the retina or pale optic nerve heads.[30,43,78,79] Progression to extinguished electroretinogram response occurred in most by 60 months (range 37 to 71 months) in one study of nine children with infantile-onset CLN1 disease.[19] Those with later-onset phenotypes may benefit from refraction correction (i.e., glasses), adaptive strategies for visual impairments (e.g., braille reading), or orientation and mobility interventions. Unfortunately, no specific interventions are currently available to treat visual pathway degeneration.

Caregiver Survey Insights

Two-thirds of respondents completely or somewhat agree with the statement, "I feel my child is welcomed at his/her school, and that the school has partnered with me to accommodate his/her needs."

Physical, occupational, and speech therapy

Conventional approaches, such as physical, occupational, and speech/language therapy, should comprise the core of treatment of motor and language dysfunction, starting as soon as possible post-symptom onset.[80] Physical therapy is often the initial therapy recommended for the infantile phenotype due to rapid progressive motor loss and gross motor delay, whereas occupational and/or speech therapies may be established earlier for the juvenile or adult phenotypes due to the need for adaptive strategies to cope with vision loss and loss of language and comprehension. Adjunct therapies may include vision, aquatic, vibration, and music therapies along with acupuncture, massage, and hippotherapy.[22] Care plans should account for ways that impairments in some areas lead to deficits in others (e.g., fine motor skills and communication, communication and behavior).

Therapy may take place across multiple settings, including the outpatient clinic, home, and school. Caregivers should learn

TABLE 4.
Recommended Medications for Treatment of Movement Disorders in CLN1 Disease, Per Clinical Experience

Myoclonus	Valproate
	Benzodiazepines (clonazepam > lorazepam)
	Piracetam*
	Levetiracetam
	Zonisamide
	Primidone
	Pregabalin
	Phenobarbital
Dystonia	Trihexyphenidyl†
	Baclofen (oral)
	Benzodiazepines
	Levodopa with decarboxylase inhibitor (e.g., carbidopa)
	Limited use:
	Clonidine
	Baclofen pump
	Tizanidine
	Tetrabenazine
	Pallidotomy‡
	Deep brain stimulation‡
Chorea	Benzodiazepines
	Dopamine receptor antagonists (e.g., haloperidol, risperidone)
	Dopamine-depleting medications (VMAT2 inhibitors) (e.g., tetrabenazine)
Parkinsonism	Levodopa with decarboxylase inhibitor (e.g., carbidopa)
	Dopamine agonists (e.g., pramipexole, ropinirole)
Tremor	Propranolol
	Primidone
	Benzodiazepines
Other motor-related considerations (e.g., spasticity)	Baclofen (oral)
	Benzodiazepines
	Botulinum toxin (intramuscular)
	Tizanidine
	Limited use:
	Selective dorsal rhizotomy
	Phenobarbital
	Baclofen pump

* Not available in the United States.
† Use with caution in patients with dementia.
‡ Only if life threatening.

appropriate exercises for home administration. Goals of therapy evolve as functional status declines. Strength, function, and mobility should be maintained as long as possible, specifically large muscle group activity such as walking or crawling, while progressively adapting activities of daily living to compensate for increasing disability, including feeding, dressing, bathing, and school performance. Eventually, as patients lose voluntary control of muscle movement, therapy should focus on maintaining range of motion, spasticity management, positioning, and pain management. Over time, sessions may shift to periodic or consultative, while positioning and range of motion exercises are implemented by caregivers at home. Availability and health care coverage of these services vary greatly by country.

Adaptive and assistive devices can play an important role in maintaining quality of life. Those with the juvenile- and adult-onset forms may require assistance when ambulating, progressing from use of a cane, to posterior or anterior walker, to gait trainer, to wheelchair. When possible, medical, school, and home evaluations are recommended to identify appropriate treatment, equipment, safety supports, and adaptations for each setting.

When appropriate, speech and language therapy should be introduced early on to optimize learning of an effective communication system before cognitive decline and to monitor for swallowing and feeding needs.

Nutritional, gastrointestinal, secretion, respiratory, and anesthesia management

Motility disorders, including gastroesophageal reflux, constipation, and dysphagia, are common secondary complications of CLN1 disease. The goals of gastrointestinal symptom management are to maintain nutritional status, minimize reflux and constipation, and maximize patient comfort.[22]

Dysphagia increases the risk of aspiration, pneumonitis, and secondary lung infection.[22] Caregivers should be taught to recognize signs of dysphagia, such as coughing and choking during meals. Periodic observation of feeding by a speech-language specialist is recommended, along with swallowing therapy to maintain oral feeding as long as feasible. Diets typically require modification based on swallowing ability and are optimized for nutrient content and gut motility. Coordination of care with a nutritionist can help ensure that nutritional needs are met. Some experts recommend use of nutritional supplements, multivitamins, and vitamin D/calcium due to high fracture risk, as well as carnitine in patients taking valproic acid. Families may use additional supplements; clinicians should regularly enquire about supplement use to monitor for potential drug interactions or adverse effects.

Eventually, other feeding routes (typically, nasogastric or gastrostomy/jejunostomy tube) should be considered, as most patients with CLN1 disease become unable to meet nutritional requirements through oral feeding, experience aspiration pneumonia, or demonstrate signs of dysphagia.[81] Evaluation for pharmacologic management of secretions may also be warranted.[82-84] Decision-making around feeding should be incorporated into ongoing palliative care discussions.

Caregiver Survey Insights

Physical therapy and occupational therapy were ranked as the most effective ways to manage CLN1 disease symptoms, after antiseizure medications.

Caregiver Survey Insights

Families reported using a wide variety of adaptive devices, including bath chairs, wheelchairs, standers, feeding chairs, adaptive toilet chairs, lift/pulley systems, and exercise equipment.

Excess secretions leading to increased aspiration risk can be managed using positioning and suctioning techniques and/or pharmacologic intervention. Appropriate agents include glycopyrronium bromide, scopolamine patch, inhaled terbutaline, hyoscyamine/hyoscine butylbromide, and botulinum toxin injected into salivary glands.

In advanced disease stages, respiratory compromise may develop due to a combination of weakness, poor cough or airway clearance, central or obstructive apnea, or recurrent aspiration pneumonitis or pneumonia. Adherence to the typical recommended vaccination schedule is suggested, including seasonal influenza vaccination, given the higher-than-average risk for complications from respiratory and other illnesses.[85,86] Specific supports are determined based on the cause(s) of respiratory compromise and may include pulmonary hygiene (e.g., chest physical therapy) and bronchodilators. Decisions to initiate monitoring or breathing support should include discussion regarding end-of-life care with families.

Children with CLN1 disease may also be at increased risk for episodes of hypothermia and/or sinus bradycardia during anesthesia and should be monitored for complications accordingly.[87]

Management of sleep disturbance

Nearly all patients with CLN1 disease suffer from sleep disturbance, including difficulty falling asleep, reduced sleep duration, and/or night wakings.[60] Sleep dysfunction in the NCLs can be associated with seizures, pharmacotherapy, movement disorders, and circadian rhythm disruption due to vision loss and neurodegeneration.[88-93]

Sleep disruption can impair seizure control and affect mood, cognition, and behavior, with profound impacts on the entire family.[60,94,95] Sleep onset disorders may respond to melatonin, whereas sleep maintenance dysfunction may not.[60,96,97] If snoring is present, an overnight polysomnogram should be considered to evaluate for sleep-disordered breathing. Restless legs syndrome can occur, responsive to iron supplementation for low ferritin levels.[98,99] In the absence of any known cause, off-label use of medications like clonidine, gabapentin, pregabalin, or benzodiazepines may be considered.[100] One clinician reported success with levomepromazine and nitrazepam for children with the infantile phenotype. However, there is high variability in the types of sleep disturbances experienced by patients and lack of consistent success with any single approach to strongly recommend a specific strategy. Families may benefit from working with a sleep specialist to

Caregiver Survey Insights

Caregivers reported using different supplements, including multivitamins, melatonin, levocarnitine, *N*-acetylcysteine, microalgae, apigenin, coQ10, curcumin, CBD oil, tetrahydrocannabinol, vitamin C, vitamin B complex, and fiber.

Caregiver Survey Insights

91% of caregiver respondents reported sleep disturbance among patients. The symptoms most frequently reported were trouble staying asleep/night waking and trouble falling asleep.

implement behavioral strategies for sleep management, including positive sleep hygiene practices.

Management of pain and distress

Assessment of pain in CLN1 disease can be challenging due to lost verbal communication, yet appropriate treatment is essential to optimal quality of life. CLN1 disease is associated with multiple symptoms that may be misinterpreted as pain and distress, particularly myoclonus, spasticity, opisthotonos, crying, screaming, hypersalivation, tachycardia, tachypnea, and sweating. Suspected pain has many possible etiologies, such as dystonia, gastrointestinal discomfort, injury, fracture, and reduced mobility. A systematic review of possible causes of pain (Table 5) can help caregivers differentiate clinical pain from other physical manifestations and allow the root cause to be addressed.

For clinical assessment of pain, most experts rely on appearance and family accounts, with some using vital signs and pain scales. Many of the pain assessments used in the general pediatric population are not well-suited for individuals with visual and communication impairments combined with motor and cognitive dysfunction. Scales that may be useful before loss of communication in older patients include the Batten observational pain scale, Pediatric Pain Profile, and Non-Communicating Children's Pain Checklist (NCCPC-R).[101-104] Postoperative pain may be assessed using the NCCPC-PV (postoperative version) or the revised Faces, Leg, Activity, Cry, Consolability scale.[105,106] None of these scales have been validated for use specifically with patients with CLN1 disease, and results should be evaluated with caution.

Pain and/or distress should be managed as appropriate for children and in accordance with the presumed pain/distress source.

Management of mood and behavioral symptoms

A broad range of mood, behavioral, and cognitive symptoms can occur across the various CLN1 disease phenotypes (Table 6). Assessment of psychiatric symptoms often depends on caregiver report; patients who are developmentally and verbally capable of contributing to assessment should be evaluated directly. Use of standardized child behavior questionnaires, may help ensure a comprehensive review of all potentially concerning symptoms. Regardless of direct patient involvement, evaluation of anxious or sad mood should always include soliciting caregiver report of crying, reduced or lost appetite, stomachaches, headaches, sleep disorders, clingy behavior, restlessness, aggression, and agitation. Although not specific to anxiety or sadness, these symptoms are common behavioral correlates of these internalizing symptoms. Possible medical causes of emotional or behavioral distress should be considered, such as aggression or irritability related to antiepileptic drug use.

Management of mood and behavior varies based on the symptom or clinical syndrome. Pharmacologic strategies should be targeted to the primary symptom when possible. Avoid neuroleptic drugs, if possible, due to risk of extrapyramidal side effects, especially in patients with parkinsonism. However, neuroleptic medications may be the best choice in some patients with severe aggression and may be effective for chorea. Caregivers should evaluate potential environmental triggers for emotional and behavioral distress and use nonpharmacologic interventions to the extent possible. For clinical support of children with challenging behaviors, a functional behavioral assessment (FBA) may be used to determine the function of patients' undesirable behaviors, identify factors that may (intentionally or inadvertently) result in maintenance of the behavior, and apply this information to the design of positive behavioral interventions. FBAs are administered by FBA specialists in any environment where challenging behaviors occur, for example, school or home.[109-111]

Other considerations

Some families will need to manage a transition of care from pediatric to adult service providers. The transition to adult care should be planned well in advance. Ideally, a meeting is convened with the lead pediatric and adult care clinicians and the family to facilitate transition. Organizations such as the Child Neurology Foundation and the International League Against Epilepsy have transition tools that may be applicable.[112,113]

Palliative care and end-of-life considerations

Palliative care and hospice follow a family-centered care approach that considers impacts on the whole family. At an increasing number of centers, palliative care teams are integrated from the time of diagnosis and are considered partners in the management of complex symptoms. It should be emphasized to parents that palliative care does not equate to focusing on end-of-life care or limiting the scope of treatment. Rather, palliative care is an approach to optimizing patient comfort throughout the lifespan.

TABLE 5.
Potential Somatic Sources of Pain in CLN1 Disease

Pain	Cause	Hints
Muscle Joints Bones	Spasticity, contractures, scoliosis, joint dislocation, uncomfortable position, fracture	Alleviation or worsening when moved, abnormal positions or movements, new-onset lack of movement
Abdominal Urinary Genital	Reflux, gastritis, upper gastrointestinal bleeding, constipation, concrements, cystitis, urine retention, testicular torsion, ovarian cysts	Nightly wakening, problems before/after feeds, weight loss, hematemesis, anemia, stool/urine consistency/frequency, hard stools
Head ENT Dental	Dental problems, infections	Malodorous breath, swelling, bleeding
Skin	Lack of movement, repetitive involuntary movements	Pressure areas, blisters, wounds
Interventions	Suctioning, tube feeding, wound care	Timing and association with specific activities

TABLE 6.
Cognitive and Behavioral Symptoms of CLN1 Disease by Phenotype[29,42,43,65,66,107,108]

Phenotype (Age at Initial Symptom Onset)	Initial Cognitive and Behavioral Symptoms	Later Cognitive and Behavioral Symptoms
Infantile (6-18 months)	Developmental delay Regression in milestones Irritability Stereotypic hand movements	Loss of motor and language milestones Loss of social interaction
Late infantile (>18months-4 years)	Developmental delay Regression in milestones Irritability Aggression Oppositional behaviors	Loss of motor, speech, and language milestones Irritability Anxiety, social interaction difficulties Stereotypic hand movements Echolalia Psychosis*
Juvenile (>4 years to early adolescence)	Poor concentration Learning difficulties Hyperactivity	Loss of motor, speech, and language skills Dementia Hallucinations Psychosis*
Adult (late adolescence and older)	Disorientation Decreased verbal fluency Poor attention and memory Dysthymia, apathy	Dementia Loss of motor skills and language

* Symptoms related to psychosis may include auditory and visual hallucinations, delusions, rapid mood swings, sudden episodes of fear, sudden fits of crying, and hyperactivity.[29,43,65,108]

The goals for end-of-life care are to maximize quality of life for the patient and family and to minimize pain and discomfort. Families should be empowered to make their wishes known, including the preferred location for death, and decision-making should be collaborative. Hospice services may include nursing visits, 24-hour availability, home health aides, social work, child life, spiritual support, palliative care, and medication and equipment support. Do-not-resuscitate orders and decisions to escalate care depend on the family wishes and the patient's current state and should be reassessed periodically. Such decisions are typically made earlier in the disease course for infantile CLN1 disease compared with later-onset phenotypes, due to more rapid progression.

Common causes of death in CLN1 disease include pneumonia, infection, and general decline. Families should be encouraged to develop a strong social network and participate in support groups for bereavement support. Memory-making and legacy-building can be helpful tools to cope with impending loss.

Family support

Support is essential to meeting the primary goal of CLN1 disease management: optimizing patient and family quality of life. Families report that coping with CLN1 disease can be emotionally traumatic through the entire course of illness and beyond. Clinicians may consider a trauma-informed care approach to reduce the potential trauma of medical visits, address general distress, and provide anticipatory guidance in a supportive manner.[114] Disease prognosis, to the degree that it is well understood, should be discussed with families upon diagnosis and in an ongoing fashion, as new information emerges.

Community/psychosocial support should be tailored to family needs, culture, rituals, and belief systems. Sibling needs are particularly important to address, as their needs may be overlooked due to the pressing needs of the patient with CLN1 disease. Important sources of support include other families affected by NCL disorders (including sibling-to-sibling connections), support groups specific to Batten disease or rare diseases in general, social workers, families' prediagnosis communities, and the entire clinical care team.

Future perspectives

Looking ahead, there is a growing pipeline of candidate disease-modifying treatments for CLN1 disease, including small molecules, enzyme replacement therapy, and gene replacement therapies. These emerging approaches have been recently reviewed comprehensively.[17,115,116]

Conclusions

CLN1 disease is an ultrarare illness with a limited evidence base surrounding management that can leave clinicians and caregivers with uncertainty in clinical decision-making. Because of its broad constellation of symptoms and multiple phenotypes, CLN1 disease often requires individualized, multidisciplinary care. Goals and strategies should be re-evaluated over time and adapted to patients' current needs, with a primary aim of optimizing patient and family quality of life.

The success of this partnership between families and clinicians in creating a clinical management consensus demonstrates the viability of this approach. This can be a model for other rare disease

Caregiver Survey Insights

"Cater to the heart, cater to the senses. Everything in their short life should make them as happy and comfortable as possible. When vision goes, play more music and let them listen to their favorite movies. Ask yourself, 'Will I regret not doing this' and do it."

Caregiver Survey Insights

Some caregivers reported that pediatric palliative care options are not readily available in many locations and hospice providers are largely inexperienced with pediatric cases. Additional support is needed to make families more comfortable when things get difficult.

Caregiver Survey Insights

"The first few months are devastating. Then, if you're lucky you have a great support system, get put in contact with the BDSRA. It never gets easier; each day is our new normal."

Families reported that the biggest difference is made by having help from family/friends (18%), respite/other caregivers (16%), connecting via social media (14%), and outside support groups (11%), among other support strategies.

advocacy groups to spearhead family-clinician collaborations to share clinical experience and recommendations. Participants demonstrated a high level of engagement, and novel insights to advance the clinical care of CLN1 disease were obtained. Integration of the family perspective into this project was unique and valuable. Such opportunities for ongoing collaboration are transformational to the community, with the benefits of bringing people together and synergistic effects that have a ripple effect beyond the meeting.

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