

Lithium in the multidisciplinary management of juvenile neuronal ceroid lipofuscinosis (Batten Disease): A novel approach to psychiatric symptoms

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Abstract

Juvenile Neuronal Ceroid Lipofuscinosis (JNCL), also known as CLN3 Disease or Batten's Disease, is a rare, progressive neurodegenerative disorder characterized by visual impairment, seizures, and cognitive decline. This case study presents the clinical course and management of an adolescent patient with JNCL from initial presentation through early adulthood. The patient's journey illustrates the complex, multifaceted nature of JNCL and the challenges in its management. Initially misdiagnosed with autism spectrum disorder, the patient experienced rapid visual deterioration, followed by seizures, cognitive regression, and psychiatric symptoms. The case highlights the importance of early, accurate diagnosis and the need for a multidisciplinary approach to care. A key feature of this case was the novel use of lithium in managing psychiatric symptoms, which showed promising results in mood stabilization and potential neuroprotective effects. The study also emphasizes the challenges of polypharmacy and the need for careful medication management to balance symptom control with side effect minimization. This case report provides valuable insights into the long-term management of JNCL, demonstrating the potential of personalized, adaptive treatment strategies in improving the quality of life for patients with this rare neurodegenerative disorder and appropriate support for their families. The findings underscore the need for further research into targeted therapies and optimized treatment protocols for JNCL, particularly in addressing its psychiatric manifestations.

Keywords: Juvenile neuronal ceroid lipofuscinosis; Batten disease; CLN3 disease; Neuropsychiatric disorders; Lithium therapy; Multidisciplinary care; Rare neurodegenerative disorders.

Introduction

Neuronal Ceroid Lipofuscinoses (NCLs) are a group of rare progressive neurodegenerative disorders categorized into various subtypes including infantile, late-infantile, juvenile, and adult-onset forms [1].

This case study focuses on the juvenile form caused by mutations in the CLN3 gene. JNCL is a challen-

ging condition with an onset usually between ages 4 and 9, characterized by initial visual impairment followed by progressive neurological and psychiatric manifestations [2]. Batten disease leads to lysosomal dysfunction from improper protein synthesis, causing accumulation of lipofuscin and leading to the death of pyramidal neurons and Purkinje cells through excitotoxicity and oxidative stress [1]. It is a rare autosomal recessive disease occurring at a rate of 0.2-0.7 per 100,000 live births worldwide, affecting about 12,500 people in Anglo-Saxon countries [1,3], with death commonly occurring by the third decade of life [4,5]. Given its rarity, diagnosis is often delayed, and symptomatic management, particularly of psychiatric symptoms, becomes crucial. There remains a pressing need for systematic assessment of psychiatric symptom treatment in NCL patients to advance management strategies for this complex disorder. This report details our experience treating an adolescent patient with Batten disease into early adulthood, highlighting key insights into personalized care strategies to improve the quality of care and life. Our experience underscores the critical importance of an individualized, multidisciplinary approach to care, with a specific focus on strategic pharmacotherapy including the potential efficacy of lithium in addressing psychiatric manifestations. This insight, coupled with our comprehensive management strategy, offers valuable guidance for clinicians striving to optimize care for individuals with Batten Disease. By adopting such a nuanced and patient-centered approach, there is significant potential for enhancing the well-being of both patients and their caregivers.

Case Presentation

GC, a now 20-year-old Caucasian female with Batten Disease, has been under our psychiatric care since August 2019. Initially presenting as a fifteen-year-old female with bizarre delusions, visual and auditory hallucinations, poor sleep, pressured speech, aggression, agitation, and self-injury; GC also struggled with seizures, visual impairment, bradycardia, and class one obesity. Misdiagnosed with Autism Spectrum Disorder (ASD) previously at nine years old and treated for seizures, her psychiatric symptoms had gone inadequately managed. After years of fragmented care by various providers, GC was genetically screened and diagnosed with JNCL in January 2018.

Initially, GC was prescribed Quetiapine 400 mg twice daily, Sertraline 50 mg, Trazodone 200 mg, and Zonisamide (for seizure management), which all provided limited relief. Sertraline dosage was escalated, and Hydroxyzine was introduced as needed for agitation. Her condition deteriorated, leading to hospitalization for uncontrolled seizures. Collaboration with her neurologist led to reintroducing Divalproex while maintaining a lower dosage of Quetiapine, with improved mood and seizure control. Despite initial therapeutic gains, GC experienced significant complications, including substantial weight gain and persistent seizures. Additional concerns about polypharmacy arose, necessitating a medication regimen adjustment. Quetiapine and Divalproex were tapered and discontinued, and Lamotrigine was introduced as an alternative treatment. This change was motivated by Lamotrigine's weight-neutral profile and its dual efficacy in seizure control and mood regulation. Following this adjustment, a modest improvement in seizure control was observed.

The COVID-19 pandemic then disrupted her care, support, and quality of life. The closure of schools

and cessation of multidisciplinary services (behavioral support services, crisis utilization services, and educational supportive staff) exacerbated her mental health struggles. GC was home with just her mother who became her sole caregiver as other providers could only perform their duties virtually. GC became increasingly isolated, leading to depression and disengagement from activities like bead-making. GC had two violent episodes requiring psychiatric emergency interventions. Attempts with Clonidine, but especially Risperidone and Haloperidol were unsuccessful due to side effects including extra-pyramidal symptoms (EPS). Our team intensified our care by facilitating weekly hour-long video visits.

Lithium was proposed as a novel treatment approach for the patient's complex symptom profile. This decision was driven by the need for a psychotropic medication with mood-regulatory properties to address persistent agitation and aggressive behaviors. The selection of lithium was based on its established mood-stabilizing effects and potential neuroprotective properties, including anti-apoptotic and anti-anoxic effects, inhibition of autophagy-induced cell death, and stimulation of neuroplasticity [6-9]. Lithium was titrated to a daily total of 900 mg, along with the transition to liquid medication formulations, which led to improved medication compliance and decreased behaviors of agitation, impulsivity, and self-harm.

GC's health further improved significantly with the introduction of a gastric tube, which enhanced her medication adherence. Following the easing of COVID-19 restrictions and the resumption of in-person services, we enhanced support for GC and her family, providing specialized bedding for seizure protection, and tailored physical, occupational, vision therapy, and palliative care. Collaboration with school officials led to a customized Individualized Education Program (IEP), boosting GC's school engagement and social participation. These adjustments resulted in weight loss, fewer behavioral crises, increased socialization, and renewed interest in activities like bead-making.

Empowering GC's mother to advocate for support led to the initiation of brief morning respite care services, markedly improving GC's school attendance from once a week to daily. Altogether these interventions reduced caregiver burnout and behavioral outbursts significantly. Current efforts focus on enhancing parental support through in-home nursing, peer support, and behavioral analysis with parental involvement to enhance caregiver-patient interactions and decrease residual behavioral outbursts expressed almost exclusively in the home, particularly during medication administration via gastric tube. These measures underscore the vital role of multidisciplinary care, advocacy for caregiver/ family support, and personalized pharmacological strategies in addressing the complex needs of adolescents with Batten Disease, demonstrating how comprehensive, tailored interventions can lead to substantial improvements in both patient and caregiver well-being.

Discussion

GC's case highlights several key aspects of managing JNCL. Firstly, the importance of early screening and diagnosis.

Importance of early diagnosis

The diagnostic process for JNCL typically involves genetic testing and detailed neuroimaging to identify specific mutations and characteristic brain changes. Diagnosis typically involves a comprehensive evaluation of family history for neuronal ceroid lipofuscinoses, coupled with a battery of diagnostic tests. These include genetic testing for prenatal detection, DNA analysis, and tissue sampling. Additional diagnostic methods such as neuroimaging, electroencephalograms, and electroretinograms may be employed based on the presenting symptoms.

JNCL is a slowly progressive disorder, with an average survival of 15 years from symptom onset [5,10]. While there is no specific treatment to halt, reverse, or prevent JNCL symptoms, symptom management remains a critical aspect of patient care. In 2017, enzyme replacement therapy with cerliponase alfa was approved for CLN2 disease, demonstrating the potential for targeted therapies. However, no specific treatments are currently available for CLN3 disease, the most common form of JNCL.

Despite the absence of disease-modifying treatments, associated symptoms such as seizures, anxiety, depression, and spasticity can be managed with pharmacotherapy. A holistic approach to care is essential, addressing all psychiatric symptoms and ensuring appropriate referrals for non-psychiatric manifestations. Any atypical psychiatric presentation should prompt specialty referral and comprehensive medical evaluation. In our case study, the identification of CLN3 gene mutations confirmed the diagnosis, underscoring the importance of thorough genetic screening in pediatric cases presenting with neuropsychiatric symptoms and visual impairment. Following diagnosis, regular specialty care follow-ups are crucial to prevent profound systemic decline. Early intervention and consistent monitoring can significantly impact the quality of life for patients with JNCL. However, there remains a pressing need for systematic assessment of psychiatric symptom treatment in NCL patients to advance management strategies for this complex disorder. While early diagnosis does not currently alter the disease course, it enables timely symptomatic treatment, appropriate family counseling, and enrollment in clinical trials when available. This approach can significantly improve patient outcomes and quality of life.

Visual impairment in JNCL

JNCL is characterized by a distinct pattern of symptom onset and progression, with visual impairment typically serving as the initial hallmark manifestation. Vision loss in JNCL is notably rapid, often progressing to complete blindness within approximately one year of onset [10]. This pattern was observed in our case study, where the patient's mother reported noticing visual issues shortly before GC entered kindergarten, followed by swift deterioration of vision. JNCL, like other forms of NCLs, generally manifests during childhood. Affected individuals frequently exhibit normal development until symptom onset [2]. While vision loss is commonly the first recognized sign, JNCL presents with a constellation of symptoms including seizures, regression of intellectual and motor skills, behavioral changes, anxiety, learning disabilities, and psychiatric symptoms [2,10,11]. The chronological sequence of symptom onset can vary among patients; however, vision loss remains the most frequently reported initial symptom by families [10]. This pattern of visual deterioration, particularly when occurring in the context of previously normal

development, should prompt healthcare providers to consider JNCL in their differential diagnosis. The clinical presentation of JNCL typically involves a combination of these symptoms, with vision loss following a rapidly progressive course [2,10,11]. Early recognition of this symptom pattern is crucial for timely diagnosis and management of JNCL. Given the progressive nature of this neurodegenerative disorder, prompt identification can significantly impact treatment strategies and potentially improve long-term outcomes. Healthcare providers should be vigilant for this constellation of symptoms, particularly when encountering pediatric patients with rapid vision loss accompanied by neurological or behavioral changes.

Neurological impairment in JNCL

The progression of neurological symptoms in JNCL is characterized by a gradual decline in multiple domains. Patients experience progressive loss of motor skills and speech, accompanied by a dementia-like syndrome that encompasses deterioration of cognitive function and adaptive skills. Concurrently, there is often an emergence or exacerbation of behavioral and mood disturbances.

Seizures, while a known feature of JNCL, typically manifest differently compared to other forms of NCL. In JNCL, seizure onset may be delayed, often occurring several years after the initial disease presentation. This contrasts with the infantile and late-infantile forms of NCL, where seizures tend to appear early in the disease course and are typically more frequent, severe, and challenging to manage. In our case study, the patient's seizure history aligns with the typical JNCL pattern. According to family reports, seizure activity began at age eleven, necessitating the initiation of anti-epileptic medication. The patient continues to receive neurological care, with current seizure frequency averaging approximately once per month. This clinical picture underscores the importance of long-term neurological monitoring and management in JNCL patients, even when seizures are not an early or prominent feature of the disease.

Complexity of psychiatric symptoms

The psychiatric manifestations of JNCL present a significant diagnostic challenge due to their resemblance to more common pediatric conditions. This similarity often leads to misdiagnosis and consequently, delayed appropriate care. Pediatric neurodegenerative disorders, including JNCL, frequently present with a complex array of neuropsychiatric symptoms. These can include neurocognitive decline (dementia), irritability, aggression, self-injurious behaviors, mood disorders, sensory alterations, and psychosis [2,4,10].

In our case study, the patient's initial symptoms were misinterpreted as ASD. This misdiagnosis is not uncommon in JNCL cases, primarily due to the overlap in neuropsychiatric manifestations, which can also co-occur in ASD. This scenario underscores the difficulty in differentiating JNCL from more prevalent developmental disorders without conducting specific genetic and neurological investigations.

The early onset of symptoms such as hallucinations, sensory alterations, mood disturbances, and aggression in JNCL necessitates a comprehensive differential diagnosis. Clinicians must consider rare neurodegenerative diseases alongside more common psychiatric conditions when evaluating pediatric

patients with complex neuropsychiatric presentations [7]. This approach is crucial for ensuring timely and accurate diagnosis, which is fundamental to appropriate management and care planning. This complexity in psychiatric symptomatology highlights the need for a multidisciplinary approach in the assessment and management of suspected JNCL cases. Collaboration between pediatricians, neurologists, psychiatrists, palliative care, and genetic specialists is essential to navigate the intricate landscape of symptoms and arrive at an accurate diagnosis.

Pharmacological management and challenges

The pharmacological management of NCLs presents significant challenges, primarily due to the absence of Food and Drug Administration (FDA) - approved treatments or well-studied behavioral interventions specifically targeting the neuropsychiatric features of these progressive neurological disorders. Management of these complex symptoms necessitates a multifaceted approach, integrating a collaborative multidisciplinary team, family-specific goals, and carefully tailored behavioral and psychopharmacological interventions, all while remaining cognizant of potential medical comorbidities.

The disease progression in NCLs typically begins with visual impairment, followed by the emergence of cognitive and neuropsychiatric symptoms, including mood disturbances, anxiety, and obsessive or perseverative thoughts and behaviors [4]. Agitation and aggression are common manifestations. As patients reach their teenage years, frank dementia becomes evident, with cognitive impairments significantly limiting the ability to acquire new skills or engage effectively in treatment protocols. Further neurological deterioration encompasses sleep disturbances, motor impairments, seizures, and extrapyramidal symptoms.

Pharmacotherapy for psychiatric symptoms in NCLs is complicated by the rarity of the disease, which precludes large controlled trials. Consequently, treatment approaches often rely on off-label use of medications approved for other conditions. Risperidone, an atypical antipsychotic FDA-approved for treating irritability in autistic children, has shown promise in managing behavioral symptoms in pediatric NCLs, particularly those with comorbid choreoathetosis [4]. In one case study, a patient started on risperidone showed improvement in hyperactivity, attention, and aggressive behavior [12]. A Finnish pilot study explored the efficacy of various psychotropic medications, including citalopram, risperidone, olanzapine, and quetiapine, in fourteen patients with JNCL [13]. Haloperidol has also been noted to address psychiatric symptoms in juvenile subtypes of NCLs conditions [1]. Alternatively, Lamotrigine has shown effectiveness in treatment, while other anticonvulsants such as carbamazepine, phenytoin, and vigabatrin have been observed to exacerbate psychiatric symptoms [1,14]. Other medications utilized in managing psychiatric symptoms in pediatric NCLs include alpha-agonists, gabapentin, trazodone, and mirtazapine [4].

The use of antipsychotics, while potentially beneficial for managing erratic, aggressive, or high-risk behaviors, must be approached with caution. Many JNCL patients present with comorbid conditions such as movement abnormalities (parkinsonism), seizures, irritability, sleep disturbances, and feeding-related issues (e.g., dysphagia, feeding tube dependence) [4]. The risk of psychotropic medications interacting with or exacerbating these comorbidities must be carefully evaluated. Potential adverse effects include

worsening of movement disorders, induction of extrapyramidal symptoms, lowering of seizure threshold, exacerbation of metabolic syndrome, and iatrogenic neurocognitive effects. Furthermore, polypharmacy is a significant concern in this population, necessitating coordinated use of agents to target multiple symptoms, when possible, coupled with frequent reevaluation of the need for continued psychotropic medication throughout the disease progression (i.e., progression from psychosis and agitation initially to apathy later) in the context of additional patient support systems in place [4].

Our case study introduces a novel approach to the management of JNCL: the use of lithium. This decision was predicated on lithium's established mood-regulatory properties and emerging evidence of its neuroprotective effects in neurodegenerative conditions. The progressive nature of JNCL complicated management, as evidenced by GC's poor response to conventional psychotropics and anti-seizure medications. Medication noncompliance further compromised GC's health, necessitating a switch to liquid formulations and ultimately gastric tube administration. The introduction of lithium marked a significant therapeutic shift, demonstrating effectiveness as an adjunct to sertraline in managing mood, agitation, aggression, and impulsivity.

This experience underscores the potential of lithium in managing mood and behavioral symptoms in JNCL, a finding that contributes to the limited existing literature on this topic. The efficacy of lithium in this context highlights the need for systematic assessments to improve treatment approaches for NCL patients and necessitates a reevaluation of neuropsychiatric strategies in neurodegenerative diseases. Our experience with divalproex and lamotrigine further demonstrated the benefits of multi-targeted medication approaches. The promising results observed with lithium suggest the need for further research into its broader applications in neurodegenerative conditions and its potential role in NCLs.

Multidisciplinary care

The neurobehavioral treatment of individuals with JNCL necessitates a comprehensive approach that integrates core features of both palliative and neuropsychiatric care. This strategy focuses on patient and family goals, prioritizing comfort enhancement and symptom burden reduction while striving to improve the quality of life for the entire family unit [4]. The case of GC vividly illustrates the indispensable role of a multidisciplinary approach that seamlessly integrates psychiatric care with neurological and educational strategies.

Notably, the COVID-19 pandemic's impact on GC's treatment underscored the critical importance of flexibility in care delivery. The rapid adoption of telemedicine and virtual support mechanisms became pivotal in maintaining continuity of care during these challenging times. This adaptation not only ensured ongoing treatment but also demonstrated the resilience and adaptability of multidisciplinary care models in the face of unprecedented challenges.

Support systems

The progressive and dynamic nature of Batten disease symptoms can have a devastating impact on

both patients and their families, leading to an enormous caregiver burden [4]. It is particularly noteworthy that females with Batten Disease typically experience a more severe disease course, characterized by a shorter disease duration, earlier loss of independence, and worsened quality of life [10]. These gender-specific differences underscore the need for tailored support strategies.

In GC's case, the reinforcement of support systems through customized educational plans, targeted caregiver support, and specialized medical services significantly contributed to her improved stability and quality of life. Specific interventions, such as adjustments made through the IEP and the integration of home-based palliative care services, effectively addressed both educational and health needs. These measures highlight the critical nature of comprehensive care frameworks in managing complex neurodegenerative diseases like JNCL.

Recent clinical insights from pediatric specialists treating children with CLN3 disease and other NCLs further emphasize the multifaceted approach required for optimal care. This approach encompasses several key elements:

1. Early family psychoeducation about the disease trajectory
2. Tailored parent management training
3. Targeted occupational therapy
4. Comprehensive family support, including grief counseling and family therapy
5. Integration of palliative care, aligned with patient and family goals for enhanced quality of life and safety [4].

When clinically indicated, individualized psychopharmacological management is implemented judiciously as part of this holistic care strategy. This comprehensive approach not only addresses the medical aspects of JNCL but also recognizes the broader impact of the disease on family dynamics and quality of life. The implementation of such a multifaceted support system is crucial in mitigating the challenges faced by individuals with JNCL and their families. By addressing both the medical and psychosocial aspects of the disease, this approach aims to provide a more holistic and effective management strategy, ultimately improving outcomes and quality of life for all those affected by this rare and complex disorder.

Conclusion

In summary, this case study enhances our understanding of Juvenile Neuronal Ceroid Lipofuscinosis (JNCL), also known as CLN3 Disease or Batten Disease, particularly in the management of its complex neuropsychiatric symptoms. Our experience underscores the critical importance of an individualized, multidisciplinary approach to care, with a specific focus on the potential efficacy of lithium in addressing psychiatric manifestations. The management of JNCL remains a formidable challenge, ne-

cessitating a delicate balance between symptom control and the minimization of side effects. Our findings emphasize the need for a thorough, case-specific treatment strategy that carefully considers the reduction of polypharmacy while addressing both quality of life and potential adverse effects, such as metabolic syndrome, EPS, and seizures. The novel use of lithium in our case highlights the potential for innovative approaches in improving outcomes for JNCL patients. This insight, coupled with our comprehensive management strategy, offers valuable guidance for clinicians striving to optimize care for individuals with Batten Disease. By adopting such a nuanced and patient-centered approach, there is significant potential for enhancing the well-being of both patients and their caregivers. Looking ahead, future research should focus on developing targeted therapies and further optimizing existing treatment strategies. This includes more extensive studies on the use of lithium and other potential mood stabilizers in JNCL, as well as investigations into novel interventions that could address the multifaceted symptoms of this rare and devastating disorder. By continuing to refine our understanding and treatment approaches, we can work towards substantially improving the quality of life for individuals affected by JNCL and similar neurodegenerative conditions.

Abbreviations: JNCL: Juvenile Neuronal Ceroid Lipofuscinosis; NCLs: Neuronal Ceroid Lipofuscinoses; ASD: Autism Spectrum Disorder; EPS: Extra-Pyramidal Symptoms; IEP: Individualized Education Program; FDA: Food And Drug Administration.

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