Turkish Medical Journal, 2025; 10(1),29-34.

Olgu Sunumu / Case Report
https://doi.org/10.70852/tmj.1556973

A RARE CASE OF NEURONAL CEROID LIPOFUSCINOSIS 5 IN A CHILD: FROM INITIAL ATTENTION DEFICIT HYPERACTIVITY DISORDER SYMPTOMS TO SEVERE NEURODEGENERATION

Nadir Görülen Nöronal Seroid Lipofuskinozis 5 Olgusu: Dikkat Eksikliği Hiperaktivite Bozukluğu Belirtilerinden Ağır Nörodejenerasyona

Merve OKUYUCU[1], Esra KAYGISIZ[2]

Afiliasyon / Affiliation:
[1]Department of Child and Adolescent Psychiatry, Ministry of Health Dogubayazit Dr. Yasar Eryilmaz State Hospital, Ağrı, Türkiye

[2]Department of Child and Adolescent Psychiatry, Private Consultant, Ankara, Türkiye

Sorumlu Yazar / Correspondence:
Esra KAYGISIZ, MD.
Department of Child and Adolescent Psychiatry, Private Consultant, Kızılay, Ankara, Türkiye.
E-mail: esra.yphn@gmail.com

Geliş / Received: 27.09.2024
Kabul / Accepted: 14.11.2024

Cite as:
Okuyucu, M., Kaygısız, E. (2025). A Rare Case of Neuronal Ceroid Lipofuscinosis 5 in a Child: From Initial Attention Deficit Hyperactivity Disorder Symptoms to Severe Neurodegeneration. Turkish Medical Journal, 10(1),29-34. https://doi.org/10.70852/tmj.1556973

ABSTRACT

Neuronal ceroid lipofuscinosis (NCL) is a group of rare, inherited neurodegenerative disorders characterized by the accumulation of lipopigments in neuronal cells. Among these, CLN5 lipofuscinosis is generally considered a juvenile-onset variant, presenting with a complex clinical Picture that includes psychiatric, cognitive, and motor impairments. The aim of this report is to describe a rare case of pediatric CLN5 lipofuscinosis initially presenting with psychiatric symptoms, contributing to early diagnostic challenges. We report the case of a boy aged 7;11 (years; months) who initially presented with symptoms of inattention, hyperactivity, and verbosity at the age of 5, which led to an early diagnosis of attention-deficit/hyperactivity disorder (ADHD). Psychiatric assessments and evaluations were conducted in accordance with DSM-5 guidelines to support the diagnosis and monitor the progression of symptoms. As the disease advanced, additional clinical evaluations, including genetic testing, were performed to confirm the diagnosis of CLN5 lipofuscinosis and assess the progression of motor, cognitive, and psychiatric symptoms. The patient, initially diagnosed with ADHD, experienced a rapid progression over approximately one year to severe neurodegenerative symptoms, including loss of ambulation, vision impairment due to retinal atrophy, and cognitive decline. Genetic testing confirmed CLN5 lipofuscinosis, with accompanying psychiatric symptoms such as anxiety. Early psychiatric symptoms in CLN5 lipofuscinosis may be underrecognized, delaying appropriate diagnosis and intervention. This case highlights the importance of a multidisciplinary approach in the evaluation of psychiatric and neurological symptoms in pediatric patients, especially in the context of rare neurodegenerative diseases.

Keywords: Attention-deficit/hyperactivity disorder, Cognitive decline, Neuronal ceroid lipofuscinosis, Pediatric neurodegenerative disorders, Psychiatric symptoms,Visual impairment

ÖZET

Nöronal seroid lipofüsinozis (NCL), nöronal hücrelerde lipopigment birikimi ile karakterize nadir, kalıtsal nörodejeneratif bozukluklar grubudur. Bunlar arasında, CLN5 lipofüsinozis genellikle psikiyatrik, bilişsel ve motor bozuklukları içeren karmaşık bir klinik tablo ile ortaya çıkan, juvenil başlangıçlı bir varyant olarak kabul edilir. Bu olgu sunumu başlangıçta psikiyatrik semptomlarla ortaya çıkan nadir bir pediatrik CLN5 lipofusinoz vakasını tanımlamayı ve erken tanı sürecindeki zorluklara dikkat çekmeyi amaçlamaktadır. Bu olgu sunumunda, 5 yaşında iken dikkat eksikliği, hiperaktivite ve aşırı konuşkanlık semptomları gösteren ve bu belirtiler doğrultusunda erken dönemde dikkat eksikliği/hiperaktivite bozukluğu (DEHB) tanısı alan 7 yaş 11 aylık bir erkek olgu sunulmaktadır. Tanı ve takip süreci için DSM-5 kılavuzuna uygun olarak psikiyatrik değerlendirmeler yapılmıştır. Hastalık ilerledikçe, CLN5 lipofusinozis tanısını doğrulamak ve motor, bilişsel ve psikiyatrik semptomların ilerleyişini değerlendirmek için genetik testler de dâhil olmak üzere ek klinik değerlendirmeler yapılmıştır. Başlangıçta DEHB tanısı konulan hasta, yaklaşık bir yıl içinde ambulasyon kaybı, retinal atrofiye bağlı görme bozukluğu ve bilişsel gerileme gibi şiddetli nörodejeneratif semptomlara doğru hızlı bir ilerleme yaşamıştır. Genetik testler, anksiyete gibi psikiyatrik semptomların eşlik ettiği CLN5 lipofusinozisi doğrulamıştır. CLN5 lipofusinozisindeki erken psikiyatrik semptomlar yeterince tanınmayabilir ve bu durum uygun tanı ve tedaviyi geciktirebilir. Bu olgu, özellikle nadir görülen nörodejeneratif hastalıklar kapsamında, pediatrik hastalarda psikiyatrik ve nörolojik semptomların değerlendirilmesinde multidisipliner bir yaklaşımın önemini vurgulamaktadır.

Anahtar Kelimeler: Bilişsel gerilik, Dikkat eksikliği ve hiperaktivite bozukluğu, Görme bozukluğu, Nöronal seroid lipofusinozis, Pediatrik nörodejeneratif hastalıklar, Psikiyatrik semptomlar

INTRODUCTION

Lipofuscinoses are a group of hereditary neurodegenerative lysosomal storage disorders (LSDs) characterized by the accumulation of lipopigments within cells (Staretz-Chacham et al., 2010). Epidemiological data indicate an incidence of 1-3 per 100,000 and a prevalence of approximately 2-4 per 1,000,000 (Simonati et al., 2017). These disorders primarily affect the brain and retina, with clinical presentations varying in disease onset, associated features, and progression. Common manifestations include progressive visual impairment, seizures, cognitive decline, pyramidal and extrapyramidal motor deficits, and premature death (Mole & Cotman, 2015; Staretz-Chacham et al., 2010). Based on the age of onset, NCL is classified into congenital, infantile, late-infantile, juvenile, and adult types, with over 10 genes identified as associated with the neuronal ceroid lipofuscinosis (NCL) phenotype (Mole & Cotman, 2015). Mutations in the CLN5 gene, which were first identified in Finland, result in CLN5 lipofuscinosis (Mole & Cotman, 2015; Simonati et al., 2017). CLN5 lipofuscinosis typically presents with initial signs between the ages of 4 and 7 years (Basak et al., 2021), including mild intellectual decline, clumsiness, unsteady gait, and speech delay (Rakheja & Bennett, 2018). As the disease progresses, symptoms may evolve to include motor delays, intellectual disability, ataxia, vision loss, and seizures. Psychiatric or behavioral symptoms, however, can also manifest as early signs of the disorder (Staretz-Chacham et al., 2010). Cognitive dysfunction is often recognized when the child begins school, with progressive deterioration ultimately leading to severe dementia (Rakheja & Bennett, 2018). Considering the clinical course of neurological and psychiatric symptoms, cognitive decline in CLN5 lipofuscinosis manifests as a two-phase process (Simonati & Williams, 2022). In the early stages, children's developmental trajectoriess low; they acquire new skills at a slower pace compared to their peers but often remain within a normal range for some time before concerns arise. Eventually, they reach a plateau and then begin to lose the cognitive abilities they had acquired in the first months or years of life, which typically triggers diagnostic investigations. Cases involving the psychiatric aspects of CLN5 have been documented in the literature (Bäckman et al., 2005; Simonati et al., 2017). While several NCL cases have been reported in Türkiye (Kose et al., 2021; Sürücü Kara et al., 2024), to our knowledge, only one case involving CLN5 has been previously published (Duz, 2021). However, none of these reports have specifically focused on the psychiatric aspects of the disease. In this report, we present the case of a 7-year, 11-month-old boy with a CLN5 mutation, who was initially diagnosed with attention-deficit/hyperactivity disorder (ADHD), highlighting the psychiatric manifestations of juvenile NCL.

CASE REPORT

This report describes a 7-year, 11-month-old boy who presented with psychiatric symptoms that began at an early age, leading to an early diagnosis of ADHD. The diagnosis, treatment, and follow-up are briefly discussed. This case was assessed and treated in the Child and Adolescent Psychiatry Department outpatient clinic of the Ministry of Health Doğubayazıt Dr. Yaşar Eryılmaz State Hospital in Türkiye. ADHD and other specified anxiety disorder were classified using Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) (APA, 2013). Verbal and written informed consent was obtained from the parent to publish this case. The presentation of the case report adheres to the CARE (Consensus-based Clinical Case Reporting Guideline) guidelines, which provide recommendations for authors of case reports to improve their completeness and transparency (Riley et al., 2017). At the beginning of the second semester of first grade, our patient presented to our clinic at the first time with complaints of inattention, clumsiness, and hyperactivity. At this visit, his chronological age was 6 years and 5 months. He frequently interrupted others, had difficulty waiting his turn, was excessively talkative, easily bored, restless, and impulsive. By the end of the first semester of first grade, he had not yet acquired reading or writing skills. At the time of this visit, there

was no known chronic illness. The first onset of psychiatric symptoms was noted about two years ago, at the age of 5, when the patient started kindergarten. He was described as hyperactive, inattentive, and restless. Approximately 2-3 months after starting kindergarten, he sustained a left femoral head fracture after jumping from a wall about 1 meter high. After a recovery period of approximately three months, he resumed walking. During this period, the patient exhibited behaviors consistent with hyperactivity, such as being highly energetic, unable to stay seated, and very talkative. By the time he entered first grade, although his hyperactivity had decreased somewhat in comparison to the previous year, he continued to be more energetic than his peers. During the first semester of first grade, he encountered significant difficulties with concentration and academic performance, particularly in reading and writing. Consequently, he was referred to a child and adolescent psychiatry department, where he was diagnosed with ADHD early in the school year and was prescribed immediate-release methylphenidate (IR-MPH) 10 mg/day. However, due to the onset of symptoms such as dullness and withdrawal, the family discontinued the medication after approximately 3-4 days. At the first visit of our patient was alert and fully oriented. He maintained appropriate eye contact and responded accurately to questions, indicating intact sensory perception and comprehension. His speech was coherent and notably verbose, with marked impulsivity and restlessness observed. His judgment was appropriate for his developmental age. Based on the DSM-5 criteria, a diagnosis of ADHD was established (APA, 2013). Subsequently, extended-release methylphenidate (ER-MPH) at a dose of 18 mg/day was prescribed, with a follow-up appointment recommended in one month; however, the patient did not return for this appointment. Approximately four months later, shortly after the end of the school year, the patient returned to our clinic for a second visit at the age of 6 years and 9 months. The family reported that they had initially administered ER-MPH 18 mg/day for approximately 10 days after the previous visit, but discontinued it because the patient exhibited dullness. His ability to concentrate in class deteriorated, and he had not learned to read or write by the end of first grade. As a result, his academic performance declined and he was required to repeat the first grade. Over the past 2-3 months, the patient had experienced fear of the dark, fear of being alone, separation anxiety from parents, sleep difficulties, restlessness, and significant anticipatory anxiety before bedtime. In addition, over the same period, the patient experienced more frequent falls, which became progressively worse. On mental status examination, the patient was alert and fully oriented. He maintained adequate eye contact and responded correctly to questions. His speech was coherent with normal rate and volume. His motor function was intact, as he was able to walk independently. A diagnosis of an Other Specified Anxiety Disorder was made based on the DSM-5 criteria (APA, 2013). Fluoxetine 2.5 mg/day was started to treat his anxiety symptoms. However, ADHD treatment was not resumed due to school vacation. He was referred to physical therapy and rehabilitation and to a pediatric neurologist for the falls. One year later, the patient returned for follow-up at the chronological age of 7 years and 11 months. Over the past year, he had experienced progressive vision loss due to retinal atrophy and a marked decline in motor function, resulting in the loss of independent ambulation. Approximately four months prior, he had developed urinary incontinence, necessitating the use of diapers. In the past month, he also lost bowel control and was unable to dress himself. He had been diagnosed with epilepsy, for which valproate 600 mg/day was prescribed. Genetic testing revealed a homozygous c.594_597 del (p.W198*) variant in the CLN5 (NM-006493) gene. During the physical examination, the patient made meaningless sounds, displayed an inappropriate affect, was unable to comprehend or respond to questions, and exhibited repetitive forward and backward rocking movements while seated. Additionally, he was unable to walk without assistance.

Table 1: Chronological Order of Symptoms and Clinical Course

Age	Mental Status Examination	Psychiatric Symptoms	Progressive Symptoms
5 years	-	Excessive hyperactivity, inattentiveness, restlessness	
5 years 3 months	-	Hyperactivity-related behaviors, excessive talkativeness	-
6 years	-	Difficulty concentrating, poor school performance	-
6 years 5 months	Alert and fully oriented, intact eye contact, sensory perception, and comprehension, coherent speech	Interrupting others, difficulty waiting for turn, talkative, easily bored, impulsiveness, clumsiness, hyperactivity	-
6 years 9 months	Alert and fully oriented, intact eye contact, sensory perception, and comprehension, coherent speech	Declining school performance, fears	Frequent falls, worsening with time
7 years 11 months	Unable to comprehend or respond to questions, uttered meaningless sounds, displayed inappropriate affect, exhibited repetitive forward and backward rocking movements while seated	Progressive deterioration in thinking, memory, and understanding, urinary incontinence, loss of bowel control (requiring diaper use)	Vision loss due to retinal atrophy, seizures, urinary incontinence, loss of bowel control, decline in motor function resulting in the loss of independent ambulation

The patient was 7-year, 11 month-old boy, the second of four children. His prenatal, perinatal, and early developmental history was unremarkable. He began speaking his first words around the age of 12 months and started walking at approximately the same age. He completed toilet training around 2.5 years of age. His mother, a 31-year-old homemaker with a high school education, and his father, a 35-year-old construction worker with limited literacy who did not complete primary school, are second cousins. A family history of mild mental retardation documented on the father's extended family (i.e. father's cousin).

DISCUSSION

This case presents a rare and challenging progression from ADHD to a severe neurodegenerative condition, ultimately diagnosed as CLN5 lipofuscinosis. The early presentation of psychiatric symptoms such as hyperactivity, inattention, and delayed literacy initially led to a diagnosis of ADHD. However, as the disease progressed, the patient developed neurological symptoms, including motor decline, visual impairment, and seizures, which are characteristic of CLN5 lipofuscinosis. This case highlights the importance of considering neurodegenerative disorders in the differential diagnosis when psychiatric symptoms present alongside progressive neurological decline. Psychiatric manifestations in LSDs can range from mild depression to severe conditions such as psychosis or early dementia, often accompanied by behavioral problems such as hyperactivity, aggression, and anxiety (Staretz-Chacham et al., 2010). In this context, the early psychiatric symptoms observed in our patient, including hyperactivity and inattention, align with previous findings in the literature (Bäckman et al., 2005; de Paiva et al., 2023), where these symptoms are often underrecognized as potential early indicators of neurodegenerative conditions like CLN5 lipofuscinosis. In a study conducted by Bäckman et al. (2005) involving 27 patients diagnosed with juvenile NCL, 74% of the participants were found to have some degree of psychiatric disturbance, including hyperactivity, aggression, and anxiety (Bäckman et al., 2005). Similarly, in a case series by Paiva et al. (2023) involving 17 patients with CLN5 mutations, early psychiatric symptoms, such as anxiety, inattention, and stereotypic behaviors, were commonly observed (de Paiva et al., 2023).

These findings are consistent with our case, where psychiatric symptoms were among the initial clinical manifestations, reinforcing the need for early recognition and intervention in patients presenting with similar symptoms. Furthermore, Simonati et al. (2017) analyzed 15 children with CLN5 mutations and found that cognitive and motor impairments were among the first symptoms to appear, with a mean age of onset of 5 years 9 months and 6 years 7 months, respectively (Simonati et al., 2017). In six patients, regression in language skills was observed as an initial symptom. At the same time, behavioral disorders such as hyperactivity, aggression, and motor stereotypes were reported in 11 patients, often emerging early in the disease course. These findings paralel the clinical course of our patient, who presented with hyperactivity and inattention before progressing to more severe neurological symptoms, emphasizing the importance of a comprehensive and multidisciplinary approach in the management of CLN5 lipofuscinosis. The development of anxiety and behavioral disturbances underscores the importance of monitoring and treating psychiatric symptoms as part of the overall management of CLN5 lipofuscinosis.

CONCLUSION

In conclusion, this case highlights the importance of considering neurodegenerative disorders such as CLN5 lipofuscinosis in the differential diagnosis of psychiatric symptoms, especially in the setting of progressive neurological decline. Early recognition and a multidisciplinary approach, including genetic testing, are crucial for appropriate diagnosis and management.

Limitations

Limitations of this case report include the reliance on family-provided information for the child's early psychiatric symptoms. One of the limitations is that self-report scales were not used in the case study. In addition, the lack of regular psychiatric follow-up of the child after initial diagnosis and treatment initiation limited the ability to objectively monitor the clinical course and treatment response, potentially preventing a comprehensive assessment of symptom progression and treatment outcomes.

Conflict of Interest: There is no conflict of interest between the authors.
Financial Support: The authors received no financial support for the research and/or authorship of this article.
Author Contributions: MO conducted the psychiatric evaluations and clinical interviews, drafted the initial manuscript. EK Contributed to the interpretation of psychiatric findings, participated in the literature review and the writing of the manuscript, and created the tables for the manuscript. MO and EK reviewed the manuscript and on the final drafts.

REFERENCES

American Psychiatric Association. (1980). Diagnostic and statistical manual of mental disorders. American psychiatric association, Washington, DC, 205-224.

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders: DSM-5. American psychiatric association.

Bäckman, M. L., Santavuori, P. R., Åberg, L. E., & Aronen, E. T. (2005). Psychiatric symptoms of children and adolescents with juvenile neuronal ceroid lipofuscinosis. Journal of Intellectual Disability Research, 49(1), 25-32.

Basak, I., Wicky, H. E., McDonald, K. O., Xu, J. B., Palmer, J. E., Best, H. L., ... & Hughes, S. M. (2021). A lysosomal enigma CLN5 and its significance in understanding neuronal ceroid lipofuscinosis. Cellular and Molecular Life Sciences, 78, 4735-4763.

de Paiva, A. R. B., Pessoa, A. L. S., Nóbrega, P. R., Moreno, C. A. M., Lynch, D. S., Taniguti, L. M., ... & Kok, F. (2023). Ceroid lipofuscinosis type 5: novel pathogenic variants and unexpected phenotypic findings. Journal of Neurology, Neurosurgery & Psychiatry, 94(5), 405-408.

Duz, M. B. (2021). A novel CLN5 mutation in Turkish patient with variant late-onset neuronal ceroid lipofuscinosis and recurrent fractures that causes severe morbidity. Neurocase, 27(6), 437-440.

Kose, M., Kose, E., Ünalp, A., Yılmaz, Ü., Edizer, S., Tekin, H. G., ... & Yildirim, E. S. (2021). Neuronal ceroid lipofuscinosis: genetic and phenotypic spectrum of 14 patients from Turkey. Neurological Sciences, 42, 1103-1111.

Mole, S. E., & Cotman, S. L. (2015). Genetics of the neuronal ceroid lipofuscinoses (Batten disease). Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease, 1852(10), 2237-2241.

Rakheja, D., & Bennett, M. J. (2018). Neuronal ceroid-lipofuscinoses. Translational Science of Rare Diseases, 3(2), 83-95.

Riley, D. S., Barber, M. S., Kienle, G. S., Aronson, J. K., von Schoen-Angerer, T., Tugwell, P., ... & Gagnier, J. J. (2017). CARE guidelines for case reports: explanation and elaboration document. Journal of clinical epidemiology, 89, 218-235.

Simonati, A., & Williams, R. E. (2022). Neuronal Ceroid Lipofuscinosis: The Multifaceted Approach to the Clinical Issues, an Overview. Frontiers in neurology, 13, 811686. https://doi.org/10.3389/fneur.2022.811686

Simonati, A., Williams, R. E., Nardocci, N., Laine, M., Battini, R., Schulz, A., Garavaglia, B., Moro, F., Pezzini, F., & Santorelli, F. M. (2017). Phenotype and natural history of variant late infantile ceroid-lipofuscinosis 5. Developmental medicine and child neurology, 59(8), 815–821. https://doi.org/10.1111/dmcn.13473

Staretz-Chacham, O., Choi, J. H., Wakabayashi, K., Lopez, G., & Sidransky, E. (2010). Psychiatric and behavioral manifestations of lysosomal storage disorders. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 153(7), 1253-1265.

Sürücü Kara, İ., Köse, E., Çavdarlı, B., & Eminoğlu, F. T. (2024). Neuronal ceroid lipofuscinosis type 11 diagnosed patient with bi-allelic variants in GRN gene: case report and review of literature. Journal of Pediatric Endocrinology and Metabolism, 37(3), 280-288.