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Case Report

An Unusual Presentation of Neuronal Ceroid Lipofuscinosis With CLN6 Mutation

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ABSTRACT

Background: Neuronal ceroid lipofuscinoses (NCL) is a rare progressive neurodegenerative disorder caused by more than 530 mutations of at least 13 different genes (CLN 1-14). NCL is a part of the lysosomal disease characterized by the presence of neuronal and extraneural autofluorescent lipopigment accumulations that leads to motor and mental deterioration, developmental regression, seizure, vision loss, and premature death. NCL is classified into four main groups based on the different clinical manifestations and age of presentation. In this study, we aimed to report an unusual presentation of NCL with CLN6 mutation without retina involvement.

Case Presentation: We reported a 10-year-old boy with mixed types of seizures, developmental delay, cognitive problems, unsteady gait, and speech disorders. Although after a thorough assessment, CLN6 mutation was diagnosed, he had all symptoms of this mutation, except the visual impairment.

Conclusion: According to recent NCL case reports from Asia, full familiarity with its presentation by pediatricians and neurologists is obligatory. Children with developmental regression or refractory seizures, who also have visual or other neurological symptoms such as ataxia and other cerebellar symptoms, even at older ages, should be evaluated for NCL. Attention to ophthalmological examinations and neurological signs and confirming the diagnosis by biopsy or genetic analysis is desirable to prevent missed diagnosis.

Keywords: Neuronal ceroid-lipofuscinoses, Phenotype, Mutation, Vision disorders

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Highlights

• Neuronal ceroid lipofuscinoses (NCL) is a rare genetic disorder characterized by the accumulation of autofluorescent lysosomal lipopigments.

• Decreased vision due to retinal pigmentation or blindness are common symptoms of more types of NCL, especially in NCL6.

• This report is an unusual presentation of NCL with CLN6 mutation without retina involvement.

Introduction

Neuronal ceroid lipofuscinoses (NCL) is a progressive neurodegenerative disorder. The incidence is estimated at 1:14000 to 1:100000. The first childhood onset NCL case was described by Batten in 1903 and by Vogt in 1905 [1]; however, the first case was diagnosed by Stengel in 1826 [2].

NCL is a rare genetic disorder characterized by the accumulation of autofluorescent lysosomal lipopigments, comprised of lipids and proteins, referred to as lipofuscin, due to various enzymatic defects [3]. NCL is classified as a lysosomal storage disease, caused by more than 530 mutations in the CLN gene [3, 4]. This gene encodes transmembrane lysozyme proteins and is expressed in numerous cells, especially in brain cells [4]. Symptoms begin at different ages, depending on the type of gene mutation. NCL affects the central nervous system initially (brain and cerebellum), and leads to progressive neuronal apoptosis and degeneration of the brain. Almost all NCL patients undergo normal development at first, but gradually the patient develops evolutionary developmental regression, a decline in motor skills, mental deterioration, behavioral disturbances (anxious or depressed mood, aggression, hallucinations, and psychosis), dementia, recurrent seizures, movement problems (ataxia, parkinsonism), dysarthria, muscle twitches (myoclonus), and spasticity [4, 5]. Microcephaly may be evident on examination due to cerebral atrophy. Retina also would be involved after central nervous system involvement. Decreased vision due to retinal pigmentation or blindness is a common symptom of more types of NCL [6].

As the disease progresses and worsens, the child loses the ability to feed, speak, and walk. Some affected patients develop frequent respiratory infections [5]. The majority of cases develop symptoms during early childhood, but some types can be presented as late as 60 years or older. Based on the onset time and the presentation of the disease, NCL is classified into four main groups including infantile (Haltia-Santavuori disease), late infantile (Jansky-Bielschowsky disease), juvenile (Batten-Spielmeyer-Vogt disease), and adult types (Kufs Parry disease). The disease is also divided into six subgroups, which include the congenital, infantile, late infantile, and variant of late infantile, juvenile, and adult types [3]. Based on the genetic mutations, NCL is divided into 13 different types: CLN 1 through CLN 14. The CLN gene encodes a trans-membrane protein whose function is still unknown. Each NCL type is given the designation "CLN," (ceroid lipofuscinosis neuronal), and a number assigned for its subtype. CLN9 has not yet been established as a separate mutation and overlaps with a mutation in CLN5 [3].

In some case reports, patients have been reported to have several types of combined mutations [7]. The course and severity of the disease and the age of onset are diverse in different types of disease. It is worth noting that type of gene mutation does not necessarily predict disease phenotype, and vice versa. The age of onset of NCL is not correlated with the degree of the mutated gene dysfunction [4]. Some findings may help diagnose the type of disease. CLN3 is associated with vacuolated lymphocytes in blood smears which are pathognomonic for this type [8]. CLN4 (Kufs Parry disease) is inherited in an autosomal dominant manner contrary to all other types that are inherited in an autosomal recessive manner. It is characterized by adult-onset presentation; however, sometimes late-onset might be a result of recessive mutations [3]. Kufs disease presents with dementia after 30 years old and vision is usually intact in this type [9]. All patients with NCLs, except those with a rare congenital form (CLN10) seem to have normal psychomotor development before the onset of the primary symptoms [10]. Two NCL cases were reported in 2019, with common presentations of Batten disease, including seizures, developmental regression, ataxia, dysarthria, dysphagia, dystonia, and impaired cognitive function, but without visual impairment. Therefore, NCL should be suspected in patients presenting with Batten disease even without visual impairment [1].

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The diagnosis of NCL is confirmed by biopsy, enzyme assay, and genetic analysis (hole exome sequence). Ophthalmoscopy, visual evoked potential (VEP), and electroretinogram (ERG) are among the essential tests for the evaluation of ocular involvement in these patients [11]. NCL has a differential diagnosis with lysosomal disease, inborn errors of metabolism such as defects of glycosylation, leukodystrophy, mitochondrial cytopathies, Niemann-Pick C, Alzheimer, type 1 Gaucher, and Parkinson's disease [4, 12]. Several characteristics have been found to differentiate NCL from other types of lysosomal storage diseases. Like lysosomal storage diseases, proteins are located in the lysosomes, and lipofuscin-like ceroid lipopigments aggregate in the lysosomes. Under the microscope, different accumulated materials including granular osmiophilic deposits (GRODs), curvilinear profiles (CLP), fingerprint profiles (FPP), as well as rectilinear complex (RLC) or so-called condensed forms might be detected [13].

Despite the different forms of inclusion bodies in each type of NCL, it is not possible to differentiate the type of disease based on them, and these shapes are not specific to a particular type of disease [14, 15]. Unfortunately, a definite cure for NCL is not yet known and premature death eventually will occur. Life expectancy depends on the type of NCL [12]. Recently, Flupirtine has been suggested for the deceleration of disease progression, but the data are not enough to support its efficacy [12, 15]. Enzyme replacement therapy, stem cell therapy, and gene therapy by replacing the faulty gene with a correctly functioning copy are some of the newly proposed treatments for this disease that are under investigation [16, 17]. Seizures are resistant to most anti-epileptic drugs and refractory epilepsy is common. Hence, in this study, we aimed to report an unusual presentation of NCL with CLN6 mutation and no retinal involvement.

Case Presentation

A 10-year-old boy, the first child of sanguineous parents, was born through Cesarean delivery. Until he reached four years of age, there was no developmental delay or sign or symptom of any disease, except for microcephaly. He started experiencing general tonic colonic seizures at the age of four. After a while, he developed neurological symptoms, including cognitive problems, which were later accompanied by unsteady gait, speech disorders including loss of fluency, and dysarthria. After a few months, the patient could not walk independently due to muscle twitching and myoclonic seizure. He gradually developed mixed-type seizures. Seizure frequency increased and they were poorly controlled with antiepileptic drugs. Microcephaly, no response to the environment, and no eye contact were reported on the head and neck examination. He did not have fix gaze on any objects. Pupils were normal in size and were reacting to light. There were no neurocutaneous markers in the skin exam. The cranial nerve exam was normal except for a weak gag reflex. He had spasticity of upper and lower extremities on motor examination with some deformity. The patient had hyperreflexia of the upper and lower extremity as well. Eye consultation was requested for the patient, and no abnormalities were seen in the ophthalmoscopy. Cardiac and respiratory systems examination were normal. There was no organomegaly on the abdominal examination. Genetic analysis was compatible with CLN6 mutation and was explained in the genetic analysis section below. Other laboratory data revealed no abnormality. In the electroencephalogram (EEG), generalized sharp and slow wave discharges were detected. Cerebral and cerebellum atrophy and hyperintensity in cortical and subcortical gray matter were present in brain magnetic resonance imaging (MRI) as shown in Figure 1. The patient was hospitalized several times for aspiration pneumonia and resistant seizures, and finally, at the age of 10 years, he was intubated due to refractory seizures and status epilepticus, and was admitted to the ICU and underwent a midazolam drip. He eventually died of severe pulmonary infection and respiratory failure after several days of hospitalization.

Genetic analysis

Whole exome sequencing was used to examine the protein-coding region of the CLN6 (NM-017882, OMIM 601780) gene. The result showed c.266 A>G variants, which caused P.Y89c in exon 3. Sanger sequencing showed homozygote mutation for CLN6. DNA was extracted from blood cells, and direct DNA sequencing was performed for exon 3 of the CLN6 gene and almost 20 bases of flanking non-coding sequence. The variant was confirmed in homozygous mutation in the patient. We also performed a genetic analysis for parents. Maternal and paternal genetic analysis was performed for exon-3 of the CLN6 gene (NM-017882) and both had heterozygote mutation on chromosome 15.

Discussion

NCL categorization has been built on the age of onset along with clinical manifestations, ultrastructural morphology of the storage material, and, more recently, genetic mutations. Patients were categorized into one of the six basic CLN mutation subtypes including congenital (CLN10), infantile (CLN1), late infantile (CLN2), variant late infantile

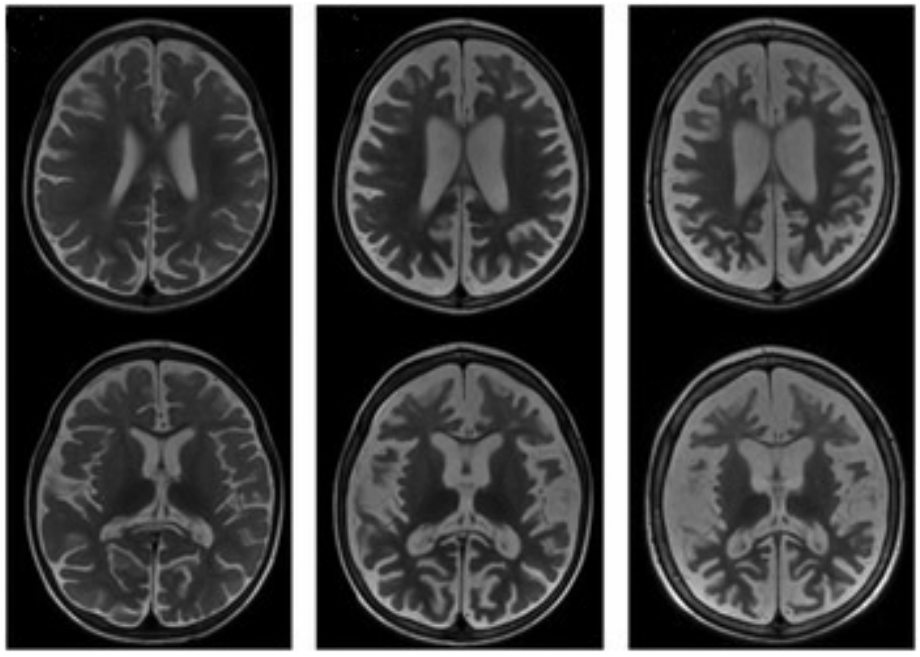

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Figure 1. Axial T2-Weighted

Brain and cerebellar atrophy, hyperintense cortical, subcortical, and periventricular area. The gray matter is atrophic in combination with a hyperintense white matter.

(CLN5, CLN6, CLN7, and CLN8), juvenile (CLN3), and adult (CLN4 or Kufs disease) NCL [11]. According to a previous study, CLN6 presented its first symptoms during the late infantile period; however, CLN6 mutation is the most important cause of type A (autosomal recessive) of Kufs disease [9]. Kufs disease is an uncommon form of NCL that differs from most other types of NCL since there is no retinal involvement and intact vision, and it is considered a late-onset type of disease. Kufs disease locus was designated as CLN4 in the 1990s but was never explicitly mapped and has remained enigmatic and unsolved [7, 17].

Regarding genetic issues, CLN6 with over 60 known mutations, located on 15q21-q23, was at first identified in Costa Rican and Venezuelan patients. Up to now, missense and nonsense mutations, small deletions or insertions, and splice-site mutations have been reported [18]. Despite the presence of previous studies on CLN6 mutation, we aimed to mention a new case with all common manifestations except visual impairment.

Guilian Sun et al. reviewed all CLN6 missense mutations in NCLs and found that the missense mutations distributed mostly in luminal (45.2%), followed by transmembrane (32.2%), and then cytoplasmic domains (22.6%). Mutations occurred more often in the TM3-TM4 loop. CLN6 gene encodes 311 amino acid transmembrane protein in the reticulum and acts as reticulum to Golgi enzyme transfer. This mutation affects the lysosomal degradation of Arylsulfatase A and interacts with Collapsin response mediator protein-2 (CRMP-2) [14]. The age of onset with CLN6 mutations shows a bimodal mode in infantile and adult versions of the disease, with patients tending to be older than another gene. The signs and symptoms associated with CLN6 mutations can also vary according to the different loci [19]. Early symptoms of CLN6 mutation are included motor regression, visual loss, myoclonus, and seizure. As the disease progresses, symptoms such as ataxia, cognitive impairment, motor deterioration, and finally spastic quadriparesia may appear as mentioned in the present case except for retinal involvement [20]. MRI commonly shows cortical/subcortical grey matter atrophy. Premature death in CLN6 type usually occurs between 5 and 12 years of age [21].

Mutation of CLN6 is responsible for the variant of late infantile ceroid lipofuscinosis and is also the most important cause of the recessive type of Kufs Parry disease [9]. In a study by Samuel F. Berkovic, 20 patients with CLN 6 mutation in conjunction with Kufs disease were reported. The average age of onset was 28 years old (range 12-51) on a background of normal growth with no specific antecedent factors [9]. An NCL case diagnosed during the prenatal period has been reported by Guererrio in Pakistan based on electron microscopy and confirmed by genetic analysis [22].

The age of onset of type 6 symptoms is about 18 months up to 8 years; however, later onset cases have been reported. In the majority of CLN6 patients, convulsions are the earliest presentation, starting before age of 5 which corresponds to our patient [21]. Early vision loss and ophthalmologic findings such as optic disc pallor, optic atrophy, and pigmentary changes in retina and macula degeneration are seen in most cases of NCL6 [12, 21]. However, this case revealed none of these symptoms in the ophthalmologic consult. In the previous reports, visual loss appears between ages 3 and 8 years and rapidly progresses to blindness. Although, rare cases of adult-onset CLN6 disease without loss of vision, referred to as the recessive type of Kufs disease have been reported [16]. Language articulation disorders and uncoordinated movements were the initial signs in our case. Unfortunately, such characters went unrecognized during earlier clinical visits and were not addressed until the repeated seizure episodes [9]. Progression is rapid in this type and death occurs at 10-12 years of age as happened in the presented case [21]. As mentioned above, the age CLN 6 mutations presentation may differ from infantile age to adulthood, which can be associated with ophthalmologic involvement. Here, we submitted a rare case of NCL disease who presented the first symptoms at the age of 4 without retina involvement.

Conclusion

According to recent NCL case reports from Asia, full familiarity with NCL presentation by pediatricians and neurologists is obligatory. Children with developmental regression or refractory seizures, who also have visual or other neurological symptoms such as ataxia and other cerebellar symptoms, even at older ages, should be evaluated for NCL. Attention to ophthalmological examinations, and neurological signs confirming the diagnosis by biopsy or genetic analysis, is desirable to prevent missed diagnosis.

Limitations

The patient was referred to our center in the final phase and intubated subsequently and died. Although previously the clinician requested an outpatient retiogram and VEP, they were not performed due to a lack of parental follow-up, it was impossible to check them at this stage of the disease.

Ethical Considerations

Compliance with ethical guidelines

Written informed consent was obtained from the patient's parents, and the study was approved by the Ethics Committee of Guilan University of Medical Sciences (Code: IR.GUMS.REC.1399.621). All study procedures were done in compliance with the ethical guidelines of the 2013 version of the Declaration of Helsinki.

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Authors contributions

Conceptualization and Supervision: Shahin Koohmanaee, Seyyedeh Azadeh Hoseini Nouri, Setila Dalili; Methodology: Seyyedeh Azadeh Hoseini Nouri, Vahid Aminzadeh, Manijeh Tabrizi, Reza Bayat, Setila Dalili, Ehsan Kazem Nejad Leili; Investigation, writing-original and writing-final draft, review, and editing: all authors.

Conflict of interest

All authors declared no conflict of interest.

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