

A girl presenting with intractable seizure and decreased visual acuity

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Abstract. Neuronal ceroid lipofuscinoses are the most common neurodegenerative childhood-onset disorders characterized by autosomal recessive inheritance, epileptic seizures, progressive psychomotor deterioration, visual failure, and premature death. At least eleven subtypes of childhood-onset neuronal ceroid lipofuscinoses have been identified. The most common types are the infantile and classic juvenile forms. In this article, we present a 5-year-old girl with late infantile neuronal ceroid lipofuscinosis who presented with seizures and decreased visual acuity. She was healthy and her developmental milestones were normal until 3 years of age. At the age of 3-year-old, her intractable seizures started and decreased visual acuity was recognized. Based on the clinical findings and enzymatic test results, she was diagnosed as late-infantile ceroid lipofuscinosis.

Key words: Neuronal ceroid lipofuscinosis, seizure, visual failure

1. Introduction

Neuronal ceroid lipofuscinosis (NCL) is a group of inherited, progressive, neurodegenerative disorders, which are accepted to be the most common (1 in 12,500 births) neurodegenerative storage disorders of childhood (1-3). According to age of onset, and clinical and pathological findings, the disorders are classified into the infantile, late infantile, juvenile, and adult-onset NCL, as well as a heterogeneous group of atypical subtypes. Late infantile neuronal ceroid lipofuscinosis (LINCL) is considered to be the second common form of NCLs. Classic LINCL presents at the ages of 2 to 4 years. It is characterized by progressive myoclonic epilepsy, ataxia, mental deterioration, and visual failure. The symptomatology usually evolves over a period of months. Parents or

healthcare providers notice a previously normal child begin to develop vision problems or seizures. Over time, affected children develop worsening seizures, progressive loss of sight and motor skills, mental impairment, and dementia. The disease is often fatal by the late teens or twenties (2-5).

In this article, we present a 5-year-old girl with LINCL diagnosed at 3 years of age after experiencing seizures and decreased visual acuity.

2. Case report

At 3 years of age, a previously healthy girl was admitted to a local hospital with generalized tonic-clonic seizure and decreased visual acuity. Her birth history was normal and her developmental milestones were normal until 3 years of age. Her uncle had a history of epilepsy and was still on treatment. She had abnormal magnetic resonance imaging and abnormal electroencephalogram (EEG). EEG showed spikes in the temporal lobe. She was started on valproic acid (15 mg/kg/day) and was gradually increased to 30 mg/kg/day. Her parents continued to report breakthrough seizure activity while she was taking valproic acid. At 4 years of age, she was still experiencing breakthrough myoclonic

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seizures. Another EEG was abnormal, with the presence of brief runs of 2 to 3 Hz generalized spike and wave activity lasting about 2 to 4 seconds.

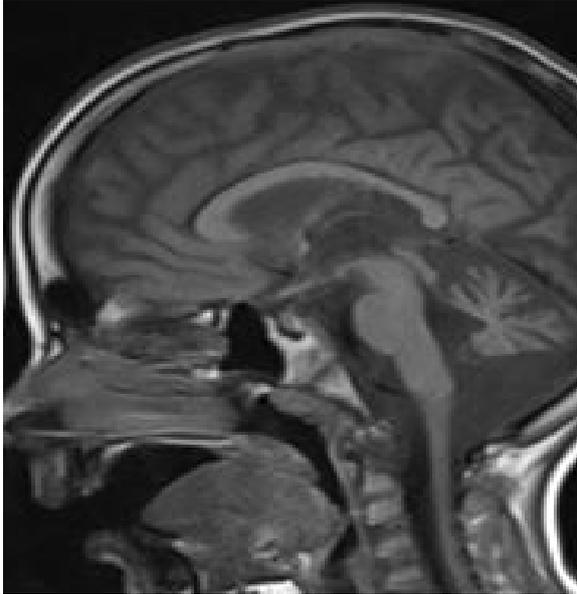


Fig. 1. T1-weighted sagittal MRI demonstrates diffuse cerebral and cerebellar atrophy and atrophy of corpus callosum.

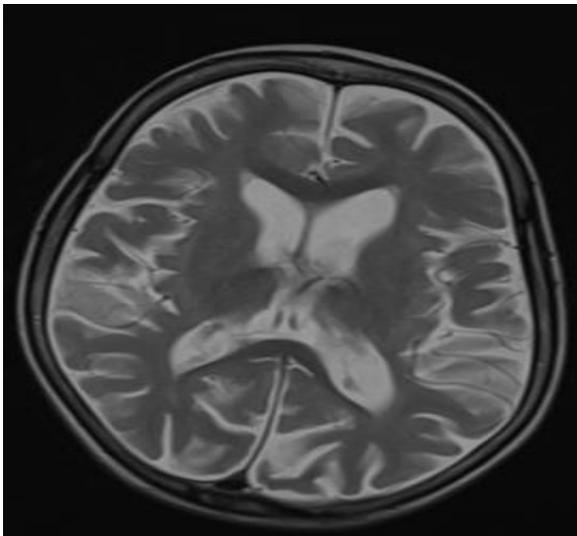


Fig. 2. T2-weighted axial MRI shows hyperintense periventricular white matter, although the basal ganglia and thalamus is normal. Thalamus appears slightly hypointense compared to putamen.

In addition, brief runs of 2 to 3 Hz generalized spike and wave activity during photic stimulation were noted. Clonazepam was added to her medication regime after this EEG, which was gradually increased to 0.3 mg/kg/day.

At 5 years of age, her initial neurological examination showed dysarthria and nystagmus. Her Parents reported that the myoclonic seizure activity stopped since adding Clonazepam,

additionally her parents reported a slight improvement in the generalized tonic clonic seizure activity since adding valproic acid. On laboratory analysis, a complete blood count, liver and renal function tests, urinary organic acid analysis, and serum aminoacid chromatography were normal. Serum lactate and ammonia levels were also normal. No tripeptidyl-peptidase 1 activity on blood, which indicates late-infantile ceroid lipofuscinosis, was noted. Biopsy and mutation analysis was not performed because of her parents' refusal. Magnetic resonance imaging (MRI) showed diffuse cerebral, cerebellar atrophy and atrophy of corpus callosum (Figures 1,2 and 3). EEG showed spikes in the temporal lobe. Ophthalmological examination showed bilateral macular degeneration (Figures 4 and 5).

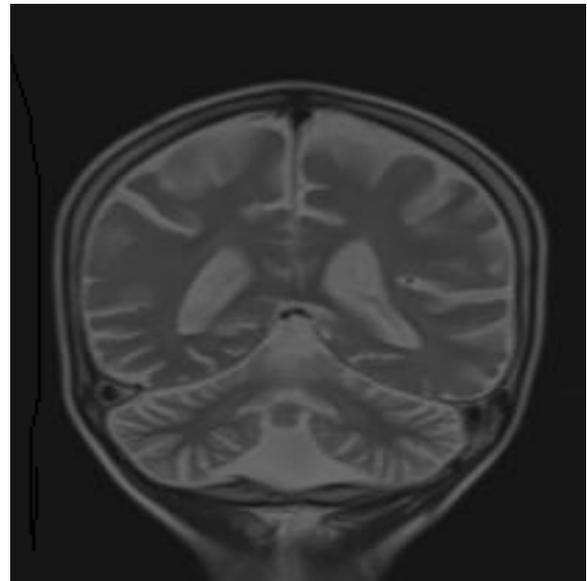


Fig. 3. T2-weighted coronal MRI shows diffuse cerebral and cerebellar atrophy, white matter thinning and prominence of the extra-axial fluid spaces and ventricles.

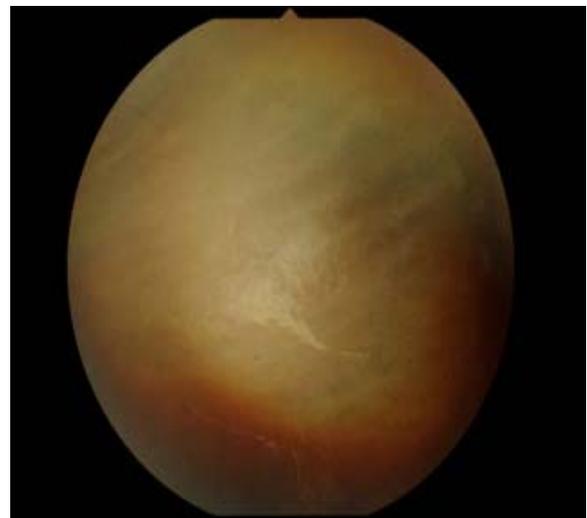


Fig. 4. Pigment accumulation in the peripheral retina.

Table 1. Defined neuronal ceroid lipofuscinosis (NCL) types and their mutations in children

Disease	Gene involved	Chromosome location	Gene product
Congenital NCL	Not known	Not known	Not known
Infantile NCL	<i>CLN1</i>	1p32	Lysosomal palmitoyl protein thioesterase
Classic late-infantile NCL	<i>CLN2</i>	11p15	Lysosomal pepstatin-insensitive peptidase
Finnish variant late-infantile NCL	<i>CLN5</i>	13q31-32	Lysosomal transmembrane CLN5 protein
Variant late-infantile/early juvenile NCL	<i>CLN6</i>	15q21-23	Not known
Variant late-infantile NCL, Turkish	<i>CLN7</i>	Not known	Not known
Variant late-infantile NCL with GRODs	<i>CLN1</i>	1p32	Lysosomal palmitoyl protein thioesterase
Classic juvenile NCL	<i>CLN3</i>	16p12	Lysosomal transmembrane CLN3 protein
Northern epilepsy/EPMR	<i>CLN8</i>	8p23	Membrane protein
Variant juvenile NCL with GRODs	<i>CLN1</i>	1p32	Lysosomal palmitoyl protein thioesterase
Variant juvenile NCL	<i>CLN2</i>	11p15	Lysosomal pepstatin-insensitive peptidase

GRODs: Granular osmophilic deposits, EPMR: Progressive epilepsy with mental retardation



Fig. 5. Granularity of the retinal pigment epithelium in the central macula.

Based on the clinical findings and enzymatic test results, she was diagnosed as late-infantile ceroid lipofuscinosis. On the 4th month of follow up, she was still on clonazepam and valproic acid therapy and her myoclonic seizures continued.

4. Discussion

NCLs are a group of autosomal recessive inherited disorders of childhood that share a number of features (5). They are characterized by progressive blindness, neurodegeneration, and the accumulation of auto fluorescent lipopigment material in neurons and other cell types. NCLs were firstly reported at the end of 19th century. LINCL was first described by Jansky in 1908 and was differentiated as a second form of NCL by Bielschowsky in 1913 (3). The disease is caused by mutations in the gene encoding tripeptidyl-peptidase 1. The age of onset ranges from 2 to 11

years. Deterioration in mental capacity is the leading presenting symptom. The seizures are myoclonic, akinetic or tonic clonic and usually refractory to anticonvulsant therapy as in our patient. The loss of motor, mental and visual function is progressive and within a few months, the child progresses a chronic vegetative state. Death usually occurs nearly 10 years after diagnosis (27). Neuroimaging studies are characterized by progressive cerebral atrophy in all types of NCL (3, 4). Our patient had diffuse cerebral, cerebellar and corpus callosum atrophy on.

NCL is associated with defects in eight different genes (*CLN1-CLN8*) (8). Several recurrent mutations account for 80% of all cases of the disease (Table 1). In addition, more than 100 rare *CLN* gene mutations causing NCL were reported. A mutation in *CLN7*, which has not yet been identified, causes a Turkish variant of late infantile NCL, with onset at ages 1-6 years (9).

There is no specific treatment known that can cure or reverse the symptoms of NCLs. Seizures can be managed with anticonvulsant therapy (3-9).

Symptoms of NCLs are linked to the buildup of substances called lipofuscins in the body's tissues. The lipofuscins are made up of fats and proteins. The lipopigments (lipofuscins) build up in cells of the brain, eye, skin, muscle, and other tissues. Inside the cells, the pigments form deposits with distinctive shapes. These deposits can be seen under an electron microscope. The presence of these on a sample of skin or blood is used to diagnose Batten's disease (10).

In conclusion, we suggest that NCL should be suspected in previously normal child who develops intractable myoclonic epilepsy and

visual failure. Increased suspicion of this rare disorder would prevent diagnostic delay as well as a misdiagnosis.

References

1. Haltia M. The neuronal ceroid-lipofuscinoses: from past to present. *Biochim Biophys Acta* 2006; 1762: 850-856.
2. Levin SW, Baker EH, Gropman A, et al. Subdural fluid collections in patients with infantile neuronal ceroid lipofuscinosis. *Arch Neurol* 2009; 66: 1567-1571.
3. Lee CW, Bang H, Oh YG, et al. A case of late infantile neuronal ceroid lipofuscinosis. *Yonsei Med J* 2003; 44: 331-335.
4. Topçu M, Tan H, Yalnizoğlu D, et al. Evaluation of 36 patients from Turkey with neuronal ceroid lipofuscinosis: clinical, neurophysiological, neuroradiological and histopathologic studies. *Turk J Pediatr* 2004; 46: 1-10.
5. Mitchison HM, Mole SE. Neurodegenerative disease: the neuronal ceroid lipofuscinoses (Batten disease). *Curr Opin Neurol* 2001; 14: 795-803.
6. Kuizon S, DiMaiuta K, Walus M, et al. A critical tryptophan and Ca²⁺ in activation and catalysis of TPP1, the enzyme deficient in classic late-infantile neuronal ceroid lipofuscinosis. *PLoS One* 2010; 5: e11929.
7. Santavuori P. Neuronal ceroid-lipofuscinoses in childhood. *Brain Dev* 1988; 10: 80-83.
8. Mole SE, Zhong NA, Sarpong A, et al. New mutations in the neuronal ceroid lipofuscinosis genes. *Eur J Paediatr Neurol* 2001; 5: 7-10.
9. Ranta S, Topcu M, Tegelberg S, et al. Variant late infantile neuronal ceroid lipofuscinosis in a subset of Turkish patients is allelic to northern epilepsy. *Hum Mutat* 2004; 23: 300-305.
10. Batten Disease Fact Sheet. National Institute of Neurological Disorders and stroke website. <http://www.ninds.nih.gov/disorders/batten/batten.htm>. Accessed on September 12, 2008.