Yonsei Medical Journal
Vol. 44, No. 2, pp. 331 - 335, 2003

A Case of Late Infantile Neuronal Ceroid Lipofuscinosis

Chang-Woo Lee[1], Hoil Bang[1], Yeon-Gyun Oh[1], Hyang-Suk Yun[1], Jong-Duck Kim[1], and Chang-Jun Coe[2]

[1]Department of Pediatrics, Wonkwang University College of Medicine, Iksan, Korea;
[2]Department of Pediatrics, Yonsei University College of Medicine, Institute for Handicapped Children, Seoul, Korea.

Neuronal ceroid lipofuscinosis, which is also known as Batten-Bielschowsky disease, is a group of neuro degenerative disorders, associated with various progressive symptoms including seizures, dementia, visual loss and cerebral atrophy.

We experienced a case of late infantile neuronal ceroid lipofuscinosis in a 6-year-old boy who had progressive myoclonic seizures, ataxia, rapid psychomotor deterioration and visual loss. Photic stimulation at 2 to 5 Hz elicited a discrete spike and wave discharges in the occipital region on an electroencephalogram. Magnetic resonance imaging of the brain showed generalized cerebral and cerebellar atrophy. An electron microscopic examination of the skin revealed characteristic curvilinear inclusion bodies. An optic fundoscopy revealed a devastated retina and severe optic atrophy. We report this case with the brief review of related literature.

Key Words: Late infantile neuronal ceroid lipofuscinosis, progressive myoclonic seizure

INTRODUCTION

Neuronal ceroid lipofuscinosis (NCL) is a group of inherited, progressive neurodegenerative disorders, which are believed to be the most common of the neurogenetic storage diseases with a prevalence of approximately 1 in 12,500 of the population.[1] Worldwide epidemiological data does not exist, but NCLs are more commonly reported in northern countries.

The clinical features consist of various combinations of progressive symptoms including seizures, dementia, blindness, and psychomotor detoriorations.[2] The onset of late infantile neuronal ceroid lipofuscinoses (LINCL) occurs between 2 and 4 years of age and is characterized by a rapid deterioration of the degenerative changes. Electrophysiological studies reveal characteristic features, and biopsies of the skin, mucosa or conjunctiva typically contain curvilinear inclusion bodies. There is no treatment available and the patients progress to a vegetative state and finally death.[3] These disorders are classified into the infantile (INCL), late infantile (LINCL), juvenile (JNCL), and adult-onset NCL, as well as a heterogenous group of atypical subtypes. LINCL is considered to be the second common form of NCL.

Jansky first described this form in 1908. However, it was not until 1913, that the first clear description of this form of NCL was differenciated by Bielschowsky.[4] This disease was first reported in Korea by Shin and Coe[5] in 1990 and by Whang et al.[6] in 1994 but since then, there has been no additional reports. Reports on Asian populations are rare. A Medline search found only three Chinese patients with LINCL[7] and nine Korean patients with NCL, which included three cases of LINCL, whereas a nationwide survey in Japan revealed 36 cases of NCL, which included 15 cases of LINCL.[8]

This report, describes 6-year-old Korean boy who presented psychomotor deteriorations, ataxia, and intractable progressive myoclonic seizures. Magnetic resonance imaging (MRI) of the brain showed generalized cerebral and cerebellar atrophy. An electron microscopic examination of the skin revealed characteristic curvilinear inclusion bodies. A characteristic photoparoxysmal response

Received October 18, 2002
Accepted December 23, 2002

This paper was supported by Wonkwang University in 2002.

Reprint address: requests to Dr. Chang-Jun Coe, Department of Pediatrics, Yonsei University College of Medicine, Institute for Handicapped Children, 134 Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea. Tel: 82-2-361-5515, Fax: 82-2-393-9118, E-mail: pedneu@yumc.yonsei.ac.kr

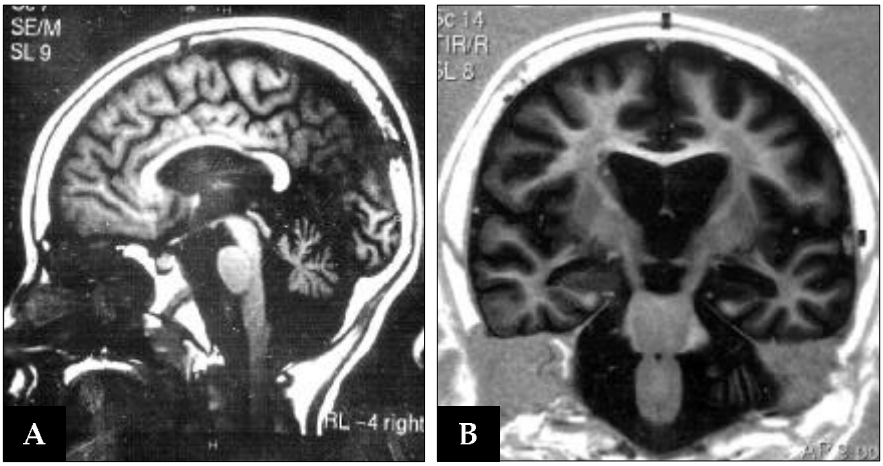

Fig. 1. Neuronal ceroid lipofuscinosis, a late infantile form, in a 6-year-old child. (A) Sagittal mage shows moderate cerebellar and brain stem atrophy. (B) Coronal image demonstrate a secondary hydrocephalus, white matter changes and cortical and cerebellar atrophy.

on an electoencephalogram (EEG) provided the important clue for a correct diagnosis of LINCL.

CASE REPORT

A 6-year-old boy presented with psychomotor and visual deterioration, which began at the age of 3. He was born as a full term baby, and had no complicated perinatal and birth history. His developmental status was delayed, he rolled at 7 months, sat up without support at 10 month, speech began at 12 months, and he walked at 14 months of age, The boy began to have seizures at the age of 3. He had variable convulsions including myoclonic seizures, atypical absence seizures and generalized tonic-clonic convulsions. Frequent brief staring began to occur, which was accompanied by irregular, asynchronous, and asymmetrical myoclonic jerks. Soon after, he developed another type of seizure consisting of left arm jerking followed by generalized tonic clonic activity.

At the age of 3, he could walk up and down the stairs with assistance, run about, and kick a ball. At 4 years of age he developed progressive ataxia and regression of speech. Within one year he became increasingly ataxic, incontinent and he lost his walking ability as well as vocalization.

At presentation, he had psychomotor deterioration, marked ataxia, spastic quadriplegia and difficulty in swallowing with significant drooling. The common blood count, liver and renal function tests, urine organic acid analysis, and serum

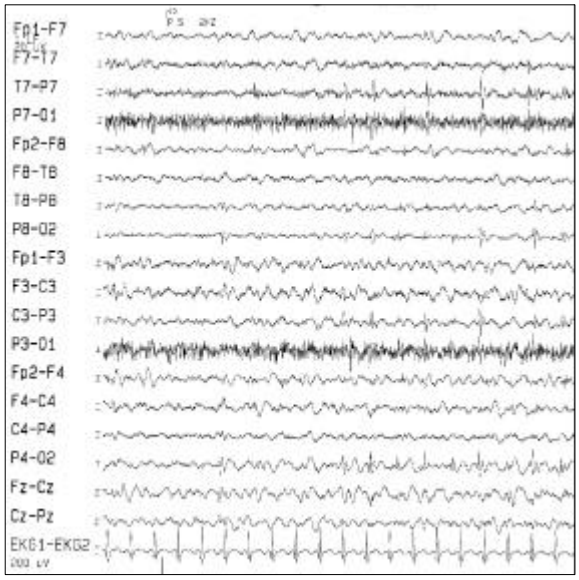

Fig. 2. Photic stimulation at 2 Hz elicited discrete spike and wave discharges at the occipital region, which were synchronous with the stimuli.

amino acid chromatography were all normal. The serum lactate, ammonia levels, alpha-fetoprotein, lysosomal enzymes and long chain fatty acid analysis were also normal.

Magnetic resonance imaging (MRI) of the brain revealed cerebral and cerebellar atrophy with a secondary hydrocephalus caused by parenchymal degeneration of brain (Fig. 1). His EEG revealed a photic-induced burst of a very high amplitude polyphasic spike and wave activity at 2 to 4 Hz in the occipital region (Fig. 2). These features diminished at the stimulation frequency of 10 to 16 Hz. An ophthalmological examination revealed

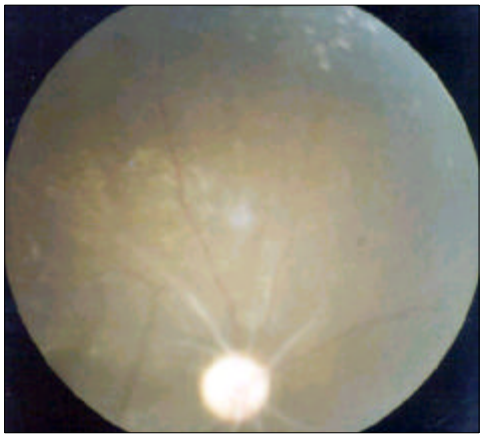

Fig. 3. The fundus shows a degeneration of the macula, pale optic disc and a marked attenuation of the vessels.

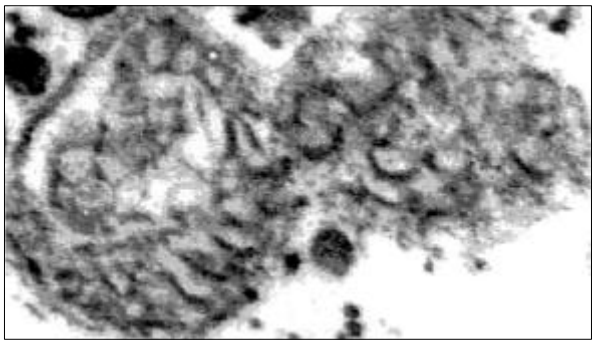

Fig. 4. Curvilinear bodies with a looser, slightly curved laminar with a tubular appearance. More distinct curvilinear bodies with randomly rounded profiles within a lysosome of the skin (×50,000).

bilateral optic atrophy, attenuation of the vessels, and degeneration of the macula (Fig. 3). The flash visual-evoked potential (VEP) was normal in amplitude but delayed in latency. No autofluorescent lymphocytes were detected by fluorescence microscopy. The electron microscopic examination revealed curvilinear inclusion bodies from the biopsy specimen of the skin (Fig. 4). The clinicopathological findings were typical of LINCL.

On his recent follow-up, his physical status was a semi-vegetative state with tube feeding, and mute with marked psychomotor deterioration. The frequency of seizure was reduced probably due to anticonvulsants, valproate, phenobarbital and diazepam.

DISCUSSION

The various NCLs are differentiated by the age of onset, the ultrastructural morphology, and genetic analysis. NCLs were first reported at the end of the nineteenth century. The main features are mental deterioration, progressive loss of vision and familial occurrence. JNCL was described by Spielmeyer[9] in 1905 and the adult form first reported by Kufs in 1925.[10] LINCL, which is characterized by progressive and severe neurological deterioration, seizure, mental regression with a later loss of vision, was first described by Jasnky in 1908 and was differentiated as a second form of NCL by Bielschowsky in 1913.[4] The infantile form (INCL) was first reported from Finland in 1973 by Santavuori.[11]

The pathogenetic mechanisms explaining how the enzymatic defects and lysosomal accumulation result in the organic dysfunction in NCL which leads to severe neuronal loss in the cerebral and cerebellar cortexes and retina, is unclear. The etiologic basis of LINCL is unknown, but recent evidence suggests that the LINCL variant is related to a defect in the transportation and degradation of the specific mitochondrial subunit C adenosine triphosphate synthase via defective methylase III. This allows a non-disunion of S-methylated methionine from this important subcellular protein and excessive accumulation in the lysosomes.[12] They are believed to be inherited by autosomal recessive genes, but there is no cross linking of families with this type and other form of NCL. The chromosome location has been mapped to 11p15.[13] These disorders are known to be relatively common in those of Scandinavia and European descent, while there are few reports in Asian populations. This disparity in prevalence is possibly due to difficulties in diagnosis. The rare occurrence of NCL often leads to a delayed diagnosis, which may be attributed to a lack of awareness of the disorders by ophthalmologists and pediatricians. Their relative frequencies in the clinical and pathologic series of Wisniewski are as follows: INCL, 11.3%; LINCL 36.3%; JNCL, 51.1%; and adult NCL, 1.3%.[14]

LINCL is characterized by normal mental and motor development for the first 24 months of life, although in many instances, slight clumsiness, a

slowing in the acquisition of speech can be recalled retrospectively. The age of onset usually ranges from 2.5 to 5 years. Deterioration in mental capacity is the leading presenting symptom. The seizures are myoclonic, akinetic, or tonic clonic, usually refractory to anticonvulsant therapy, which is followed by myoclonus and ataxia. Early acute and progressive myoclonic seizures are more typical than the other clinical characteristics of this type of NCL. The loss of motor, mental, and visual function is relentlessly progressive, and within a few months, the child progresses a chronic vegetative state. Death occurs usually approximately 10 years after diagnosis.

An ophthalmology consultation can be very helpful in evaluating children suspected of having NCL because there may be abnormal findings on the fundoscopic examination and ERG. Visual failure appears later, with optic atrophy being detectable within 2 years. These findings are commonly misdiagnosed in a routine assessment. The macular light reflex is defective and the optic disc is pale. The ophthalmoscopic findings are abnormal before the visual symptoms occur. Those early signs are an attenuation of vessels, early optic atrophy, and a degeneration of the macula. The ERG is abnormal and is lost early in the course of the disease due to storage material in the retina.

The earliest EEG finding is a disorganized background activity. Photic stimulation below 4 flashes per second typically elicits a high amplitude, polyspikes and wave discharges in the occipital area on the EEG.[15]

The VEP are also abnormal, which are characterized by gross enlargement of the early components. Occasionally, the VEP at the early stage may appear normal, but become abnormal at the later stages. Marked spasticity, as well as Parkinsonian features, can develop in the terminal stage. This condition progresses slowly, and death usually occur in late childhood.

Neuroimaging studies are characterized by progressive cerebral atrophy in all types of NCL. The major findings are variable cerebral and cerebellar atrophy associated with high signal intensity in the basal ganglia on the T2-weighted images. LINCL is conventionally described as a gray-matter disease, but hyperintense signals on the T2-weighted MRI scans involving the periventricular white matter, which mimic leukodystrophy, have also been reported.[16] Atrophy of the brain progresses more rapidly in the infantile form and earlier in the late infantile form than in the juvenile form. In LINCL, the atrophy is most obvious in the infratentorial region, as there is severe cerebellar involvement, and cerebellar involvement is an early finding in other cases. However, the cerebellar and cerebral atrophy progress simultaneously in the other forms.

Microscopic examination of the affected brain shows generalized neuronal swelling, and marked neuronal distention that manifests in the early stages of the disease. This pathological sequence is much more rapid in LINCL than in the other types of NCLs. The intraneuronal material stains with PAS and Sudan black. It is insoluble in lipid solvents and autofluorescent. The material is principally the hydrophobic mitochondrial ATP synthetase subunit C, a normal component of the inner mitochondrial membrane. On an ultrastructural examination, the storage material most commonly observed consists of curved stacks of lamellae with alternating dark and pale lines, which are characteristic curvilinear bodies in late infantile NCL.[17] In a few cases, the storage material appears as a 'fingerprint' configuration, which is more typical of JNCL. Some cases show only granular osmophilic inclusion material. These materials can be found in not only the neurons and astrocytes, but also in the extraneuronal tissues such as muscles, fibroblasts, skin, conjunctiva, lymphocytes, rectal mucosa, or secretory cells in such organs as thyroid, pancreas, and eccrine sweat glands.[18] In atypical cases these pathological findings may not be obtained by a biopsy.

There is no effective treatment available for LINCL, and the underlying metabolic error. Bone marrow transplantation has been attempted in animal models in a few cases with disappointing results. The seizures are difficult to control but in a few cases, it may respond in part to a combination of valproate, phenobarbital and clonazepam. The provision of new antiepileptic agents may help to control the intractable seizures.

The lack of awareness of this disorder may be the main cause of misdiagnosing this disorder in

Korea. The findings of abnormal EEG discharges to slow photic stimulation, a giant VEP and diminution of the ERG is diagnostic milestone of this disorder. In particular, the photoparoxysmal response in the low frequency flash provides an important diagnostic clue to atypical case of LINCL where the results of extraneuronal biopsies are normal and the MRI findings are similar to that of leukodystrophy. This report is the third case report of classic LINCL in Korea. Increased suspicion of this rare disorder would prevent a diagnostic delay as well as a misdiagnosis. NCL should be suspected in previously normal children who regress progressively with intractable myoclonic epilepsy and visual failure.

REFERENCES

1. Rider JA, Rider DL. Batten disease: past, present, and future. Am J Med Genet Suppl 1988;5:21-6.
2. Santavuori P. Neuronal ceroid lipofuscinosis in childhood. Brain Dev 1988;10:80-3.
3. Mole SE, Gardiner RM, Globel HH. The genetic and molecular basis of the neuronal ceroid lipofuscinoses. Eur J Paediatr Neurol 1998;2:2-6.
4. Bielschowsky M. Uber spat-infantile familiare amaurotische idiotie mit kleinhirn symptomen. Dtsch Z Nervenheilk 1913;50:7-29.
5. Shin SC, Coe CJ. 3 Cases of neuronal ceroid lipofuscinosis. Korean Med Assoc 1990;33:1149-53.
6. Hwang KT. Kim JW. Kim YH. A Case of late infantile neuronal ceroid-lipofuscinosis. Journal of the Korean Pediatric Society 1994;37:1745-50.
7. Yun Y, Jiong Q, Ming L. Late infantile type neuronal ceroid lipofuscinoses in Chinese. Chin J Neurol 1999;32: 7-9.
8. Oishi K, Ida H, Kurasawa K, Eto Y. Clinical and molecular analysis of Japanese patients with neuronal ceroid lipofuscinosis. Mol Genet Metab 1999;66:344-8.
9. Spielmeyer W. Weitere Mitteilung ueber eine besondere Form von familiaerer amaurotischer Idiotie. Neurol Zbl 1905;24:1131-2.
10. Kufs M. Uber eine Spatform der amaurotischen Idiotie und ihre heredofamiliaren Grundlagen. Z Ges Neurol Psychiat 1925;95:169-88.
11. Katz ML, Gerhardt KO. Methylated lysine in storage body protein in sheep with hereditary ceroid lipofuscinosis. Biochim Biophys Acta 1992;1138:97-101.
12. Santavuori P. Infantile type of so-called neuronal ceroid lipofuscinosis. Part I. A clinical study of 15 patients. J Neurol Sci 1973;18:257-67.
13. Sleat DE, Donelly RJ, Lackland H. Association of mutations in a lysosomal protein with classical late infantile neuronal ceroid lipofuscinosis. Science 1997; 277:1802-5.
14. Wisniewski KE. Variability in the clinical and pathological findings in the neuronal ceroid lipofuscinoses: review of data and observations. Am J Med Genet 1992; 42:525-32.
15. Pampiglione G, Harden A. So-called neuronal ceroid lipofuscinosis: neurophysiological studies in 60 children. J Neurol Neurosurg Psychiatr 1977;40:323-30.
16. Petersen B, Handwerker M, Huppertz HI. Neuroradiological findings in classical late infantile neuronal ceroid-lipofuscinosis. Pediatr Neurol 1996;15:344-7.
17. Carpenter S. The ultrastructural characteristics of the abnormal cytosomes in Batten-Kufs disease. Brain 1977; 100:137-56.
18. Farrell DF, Sumi SM. Skin punch biopsy in the diagnosis of juvenile neuronal ceroid-lipofuscinosis. Arch Neurol 1977;34:39-44.