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Case Report

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A Forensic Autopsy Case of Lissencephaly for Evaluating the Possibility of Child Abuse

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A 9-year-old Korean boy with lissencephaly was found dead at home. He had previously been diagnosed with lissencephaly that presented with infantile spasm on the basis of magnetic resonance imaging and electroencephalogram results. Antemortem chromosomal banding revealed a normal karyotype. A legal autopsy was requested to eliminate the possibility of neglect or abuse by his parents. The autopsy findings revealed type I lissencephaly with the associated microcephaly. No external wounds or decubitus ulcers were noted. Postmortem fluorescence in situ hybridization for the LIS1 locus and nucleotide sequence analysis of the whole coding regions of the LIS1 gene did not reveal any deletions. The antemortem and postmortem findings revealed that lissencephaly syndrome was associated with isolated lissencephaly sequence. External causes of death were excluded by the full autopsy and toxicology test results. Because patients with mental retardation are frequently victimized and suffer neglect or abuse, thorough external and internal examinations should be conducted at the time of autopsy.

Key Words : Lissencephaly, Child neglect, Child abuse, Forensic pathology, Autopsy

Introduction

Lissencephaly ('smooth brain') is a severe cerebral malformation which can be classified as type I, II, or III.[1)] In type I lissencephaly, neuronal migration is impeded during brain development, resulting in agyria/pachygyria of the cerebral cortex, whereas in types II and III, more severe malformations, such as polymicrogyria or hypoplastic brain stem, can occur.[1,

[2] According to Orphanet, the European portal for rare diseases and orphan drugs, the incidence of type I lissencephaly is about 1 in 100,000 births.[3] Type I lissencephaly often occurs in genetic syndromes such as Miller-Dieker syndrome (MDS) and Norman-Roberts syndrome (NRS) and can also occur by itself in a condition called isolated lissencephaly sequence (ILS).[1] Although all lissencephaly syndromes are rare, MDS is relatively common among type I lissencephaly and is known for its cytogenetic abnormality on chromosome 17, especially the 17p13.3 deletion, which is frequently shared by ILS.[4] The cytogenetic abnormalities found in MDS and ILS are visible or submicroscopic deletions detectable through chromosome banding or chromosomal fluorescence in situ hybridization (FISH) for the LIS1 gene (also known as PAFAH1β1) locus at 17p13.3, whereas in NRS, chromosomal analyses are frequently normal.[2, 5, 6] MDS is characterized by facial deformities such as a prominent forehead, a flat midface, bitemporal

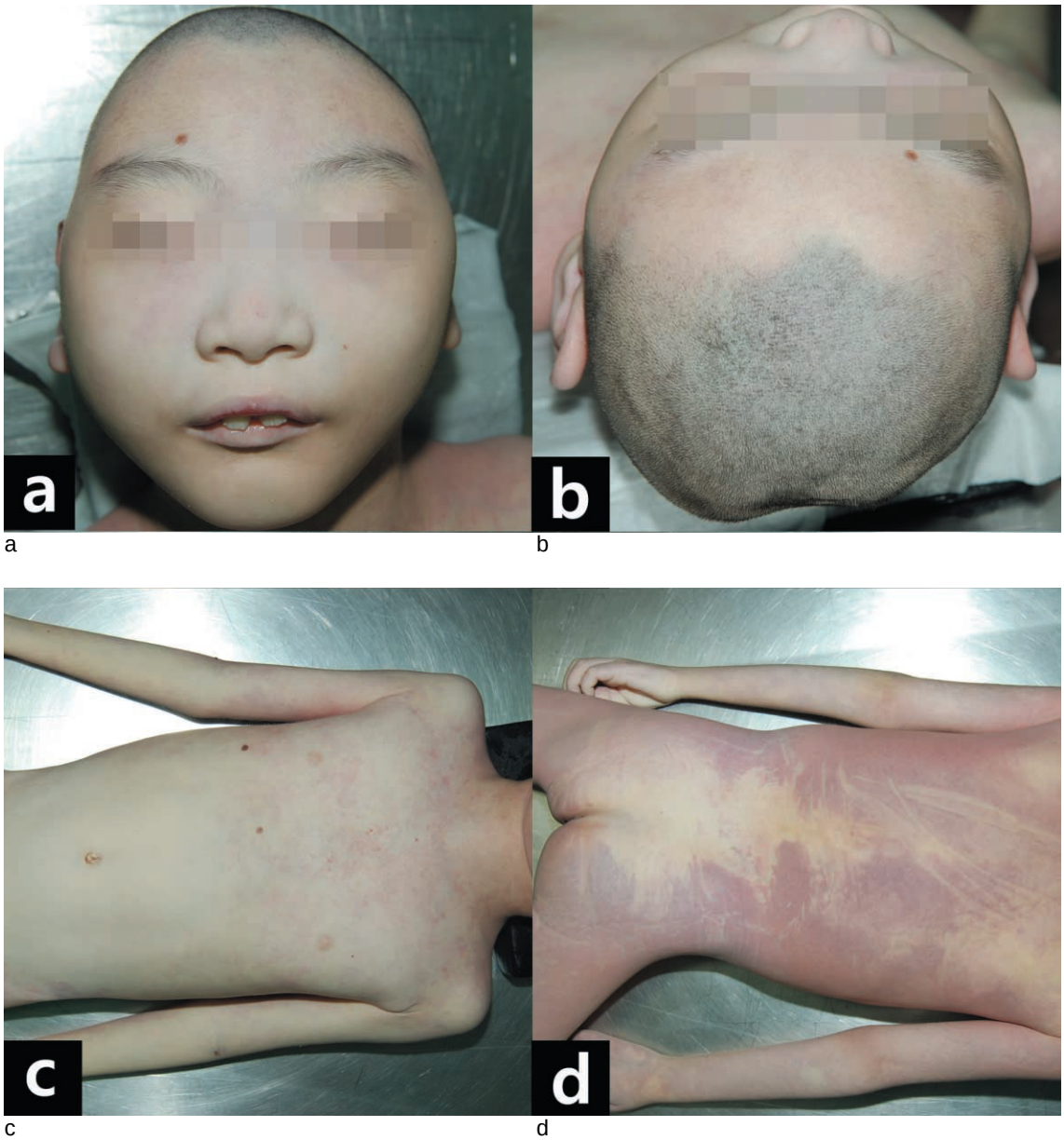

Fig. 1. External examination reveals microcephaly and growth retardation. No external wounds or decubitus ulcers were found.

narrowing, a small nose with upturned nares, and a protuberant upper lip with a thin vermillion border and a small jaw, quite different from the physical characteristics of NRS and ILS.[6] NRS is characterized by typical craniofacial features consisting of a sloping forehead, a prominent occiput, widely set eyes, bitemporal grooving, posteriorly angulated ears, micrognathia and a prominent nasal bridge.[7, 8] In patients with ILS, facial phenotypes are normal except for features associated with lissencephaly itself.[1] Patients frequently show severe hypotonia, feeding problems, frequent pneumonia, and seizure at early ages.[9] Because many deleterious phenotypes which are frequently existing in lissencephaly syndrome, including psychomotor retardation, seizures that are often intractable, severe developmental retardation, and chronic feeding problems, the lifespans of patients are usually shortened.[6, 10] The authors report a very rare forensic autopsy case of type I lissencephaly without any definite craniofacial phenotype except for

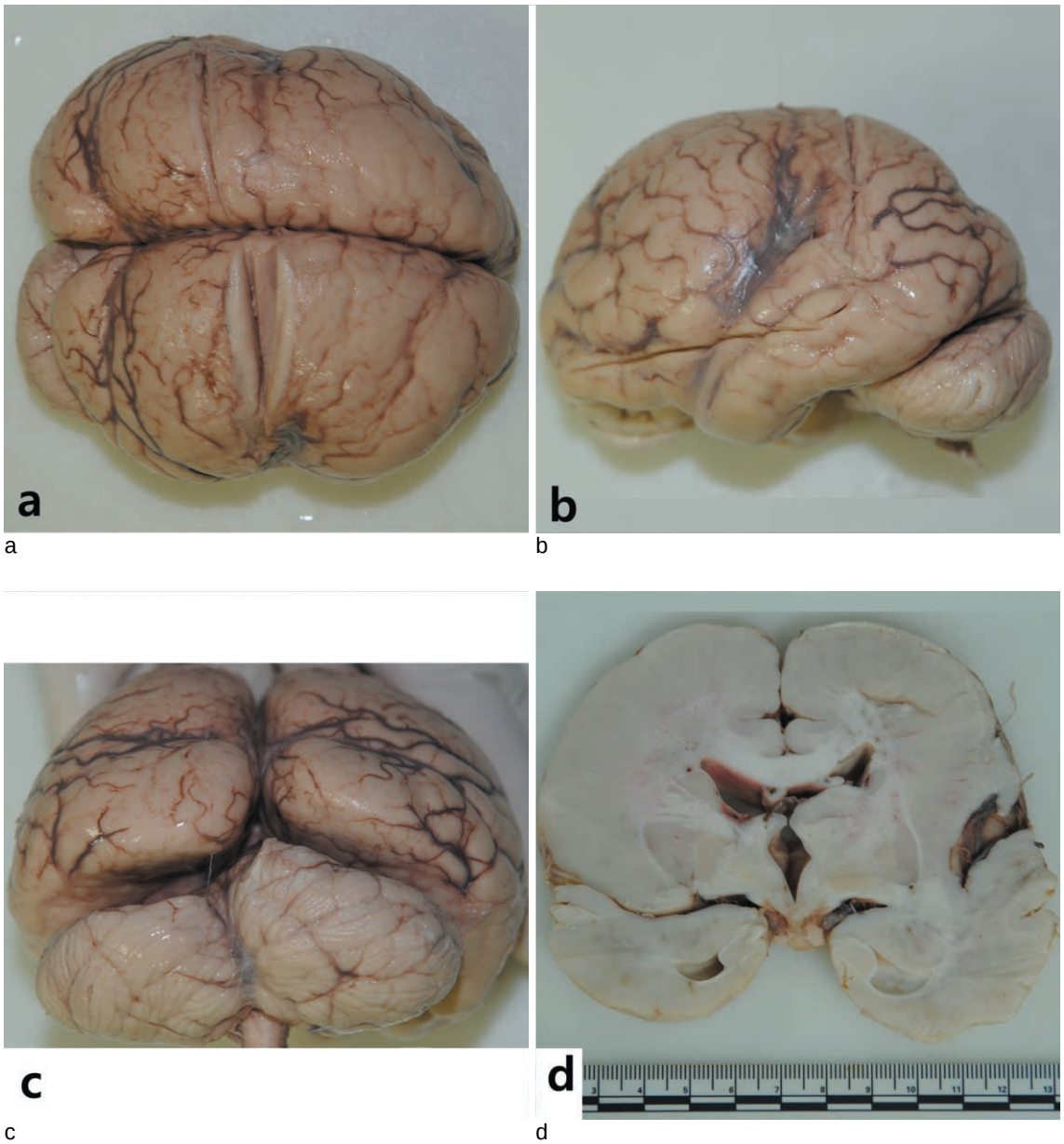

Fig. 2. Gross findings of the brain show a smooth surface and cortical thickening. Cerebellum and hippocampus are intact.

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microcephaly.

Case Description

A nine-year-old Korean boy who had been previously diagnosed with lissencephaly was found dead at home. He was classified as grade I physical disability by Korean government. Suspecting the possibility of abuse or neglect, the prosecutor's office requested a legal autopsy. On a past history review, antenatal sonogram revealed microcephaly with a head circumference lower than normal at birth. There was no history of inborn error of metabolism, poor feeding, or lethargy, and no familial history of congenital anomaly or genetic diseases. At the age of three months, the deceased visited a pediatric clinic due to seizures consisting of eyeball deviation with intermittent mild tonic posturing followed by several clusters of myotonic spasms. The body weight (7.8 ㎏) and head circumference (36 ㎝) were below the third percentile. Although the deceased had a high arched palate, there were no other external findings compatible with MDS. On electroencephalogram (EEG) at three months, right frontocentral and temporal or left fronto-temporal spike discharges with modified hypsarrhythmia features were observed. However, EEG at 14 months showed prominent high amplitude 8~9 ㎐ alpha activities on the diffuse bilateral background, compatible with lissencephaly. The deceased underwent no further neurologic evaluation after the age of 17 months. At the time of autopsy, body weight (16 ㎏) and height (110 ㎝) indicated severe growth retardation. On inspection, the deceased had a microcephalic appearance (Fig. 1).

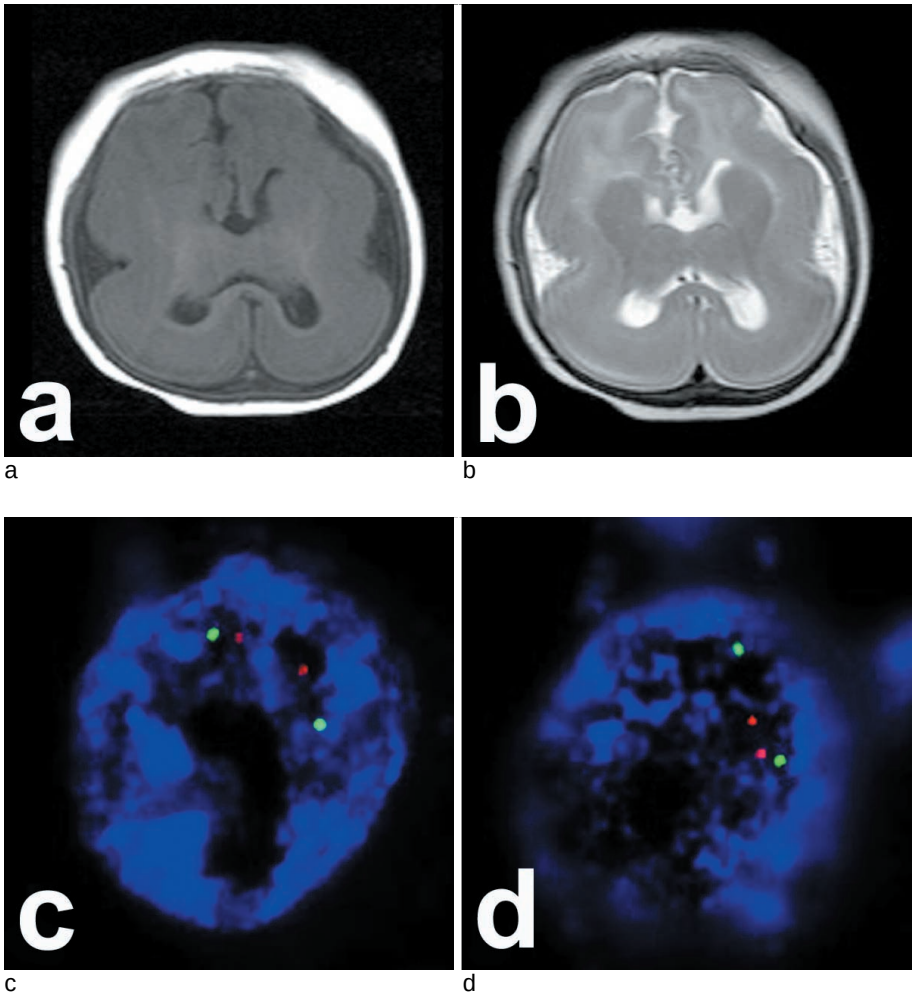

Fig. 3. On magnetic resonance imaging (MRI), T1(a)- and T2(b)-weighted images (performed at four months of age) show a decreased number of gyri with a figure eight configuration, compatible with lissencephaly. Fluorescence in situ hybridization (FISH) with a probe for the LIS1 locus fails to detect a deletion (c and d).

No external wounds or decubitus ulcers were noted. The hygiene and nutritional status was grossly good. The internal examination revealed widespread agyria resulting in a smooth brain surface and an accompanying thickening of the cortex (Fig. 2). There was no cranial synostosis. The corpus callosum and basal ganglia were grossly well identified. Cerebellar hypoplasia was not found. The brain stem and spinal cord were normal. Microscopic findings of the cerebral hemispheres displayed a decreased number of layers in the cerebral cortex, having from superficial to deep, a molecular layer, a cellular layer with pyramidal neurons, a less cellular layer with neurons, and a broad band of disorganized neurons. Solid organs such as the heart, the lungs, the liver, the kidneys, and the spleen were normal in number and shape. Postmortem toxicology detected no toxins or drugs from the blood or gastric contents of the deceased.

Magnetic resonance imaging (MRI) at four months of age revealed a decreased number of gyri, compatible with lissencephaly (Figs. 3a and 3b). The antemortem routine karyotype was 46, XY, and postmortem fluorescence in situ hybridization (FISH) analysis failed to detect a deletion in the LIS1 gene (Figs. 4a and 4b). Nucleotide sequencing of whole coding sequences in exons 2 to 11 of the LIS1 gene showed no mutations compared with the reference sequence from NCBI Genbank (NM_000430.3). Primer sequences are listed in Table 1.

Discussion

1. Diagnosis of the congenital anomaly and the cause of death

The present case showed lissencephaly in the brain without any craniofacial anomaly except for microcephalic feature. According to Dobyns et al., lissencephaly without craniofacial anomalies should be categorized as group IV lissencephaly, which is compatible with ILS.[6] Although patients with severe neurodevelopmental disorders frequently die from aspiration or associated pulmonary complications, the deceased did not show any sign of aspiration or pulmonary complications. External causes of death were excluded by full autopsy and toxicology examinations. There was no remarkable finding except for lissencephaly and its associated signs. Therefore, the cause of death was determined to be 'an internal cause of death associated with lissencephaly.'

2. Excluding the possibility of child neglect or abuse

It is apparent that individuals with intellectual disabilities may be easily victimized due to neglect or abuse. Children with any kind of disability are reported to be physically or sexually abused about twice as often as are children without disabilities[11] If parents also have mental retardation, the risk of child neglect and abuse is even higher.[12] Because the

Table 1. Primers Sequences for Amplification of Full Coding Region of LIS1 Gene

Region	Upstream	Downstream
Exon 2	TTTCCCAAAGGAGGGACATA	GAAGAGACCTCCCAAAGCTG
Exon 3	GGAGTCATTTGAATTTTTCTTTCA	TGACAAAATTGTGCGTAACTG
Exon 4	GAGGATCATAGTTAAGCCATTTTT	ATGCAGAAGAATGTTATTTTCAGA
Exon 5	TGTACGTAACTACATGTTCTTTTTCAA	GCCTCCCGTTAAGTCTGCTT
Exon 6	AACCAATTTTCTGTTCACTTGAC	AAAGCACTATCCTCTACCCCTTA
Exon 7	TGCTCTTGGTGGTATATTACTTCA	GATGCCTTTTCAACTAAACTTACTTAC
Exon 8	GATGATTGTCATTCACAGTGTAAGTT	ACCACATGCTCATGCTCTCG
Exon 9	CCTAACTTCTTGTGTGGGAAACTT	CAAAAGAAATGGTAAGATTATGCAA
Exon 10	AAACATTTTGCCTTTTACTGAGTC	GGCACTCCAAAATCTAATGTTCA
Exon 11	TTGTTGTCCAGGCTTACGTG	GGGCCGAAGGAGACACAA

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deceased in this case had a severe neurodevelopmental anomaly, the investigators in the police department and the prosecutor's office felt the necessity to eliminate the possibility of child neglect or abuse. Despite detailed external and internal examinations in the autopsy, no external wounds were found. Moreover, the nutritional and hygiene statuses of the deceased were excellent, and there were no decubitus sites. Additional investigation through questioning of the neighbors and close relatives by the police also indicated that the parents had done their best to care for the deceased. Therefore, the possibility of neglect or abuse was considered very low.

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