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Neuropathology Education

A 14-year-old girl with lissencephaly and craniofacial dysmorphism

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CLINICAL COURSE

The patient was born at 38 weeks gestation with body weight of 2700 g from non-consanguineous parents. She was the third child with two healthy brothers. At 2 months of age, she had afebrile seizures. She was admitted to hospital because of an epileptic state. Her chromosomal pattern was 46XX by G-band analysis. A deletion in the Miller-Dieker syndrome (MDS) region was confirmed by fluorescence in situ hybridization (FISH) for chromosomal testing. Brain CT/MRI revealed lissencephaly and dysgenesis of corpus callosum: the absence of rostrum and splenium (Fig. 1). Radiologically, no abnormalities were found in the body except the brain. At the age of 4 years, she was hospitalized at a nursing center. Profound mental and motor retardation, seizures and hypertonia were found. She suffered from repeated episodes of bronchitis/pneumonia, depletion of carnitine, and chronic insufficiency of digestion. Gastrostomy was performed at 6 years of age owing to feeding problems. She died of pneumonia at 14 years of age.

NEUROPATHOLOGICAL FINDINGS

Autopsy was limited to the brain. On gross examination, the girl showed low height and low weight (124 cm, 21 kg) with minor facial dysmorphisms (square face, hypertelorism, small nose) and muscle atrophy of both extremities.

The brain was small, weighing 840 g at autopsy, less than the expected weight of 1315 g, and short in the longitudinal direction. External examination of the brain identified lissencephaly with diminished sulci and pachygyria over the entire convexity (Fig. 2a). Coronal sections were notable for smooth cortical surface, few primary sulci, markedly thickened cortex, ill-defined cortico-medullary junction, reduced white matter and partial defects of the corpus callosum (Fig. 2b).

Microscopic examinations of the cerebral cortices demonstrated that thickening and disorganization had replaced the normal 6-layered ribbon (Fig. 3a). In some regions such as the temporal cortex, the characteristic four-layered pattern with a myelinated third layer was observed (Fig. 3b). Staining with the antibody to neurofilament demonstrated dysmorphic pyramidal neurons in layer 2 (Fig. 3c). In the white matter of the cerebrum, some neurons were heterotopically scattered and the perivascular space was dilatated. The pia membrane was partly disrupted in the corpus callosum (Fig. 3d). As for the brain stem, leptomeningeal neuro-glio-mesenchymal heterotopias of the pons (Fig. 3e) and ectopic olivary heterotopias of the medulla (Fig. 3f) were observed. The pyramidal tract was also dysplastic. The cerebellum showed only partial dysplastic change, although folia formation was preserved. No calcifications were observed.

DIAGNOSIS

Miller-Dieker syndrome (lissencephaly, Type I).

DISCUSSION

Lissencephaly has been divided into two categories: type I or classic type, also named agyria-pachygyria, and type II or cobblestone lissencephaly.[1] Sporadic, autosomal dominant, autosomal recessive and X-linked inheritances of type I lissencephaly have been defined and to date linked with five genes: *LIS1*, *DCX*, *RELN*, *ARX* and *TUBA1A*.[2] Mutations in *DCX* result in type I lissencephaly in males and subcortical laminar heterotopia (SCLH) in females. Type II lissencephaly includes a variety syndromes, such as Walker-Warburg syndrome and Fukuyama congenital

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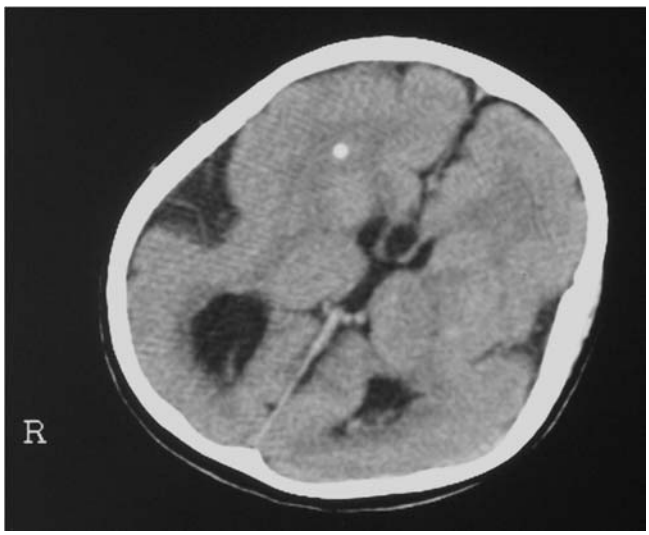

Fig. 1 Brain CT scan at 10 years of age. The CT scan demonstrates lissencephaly with smooth thickened cortex and a few shallow sulcal structures.

muscular dystrophy. All of the type II lissencephalies have congenital muscular dystrophy as a prominent component, whereas this is not a feature of any type I lissencephaly. The cerebellum is usually normal in type I lissencephaly, although mild focal abnormality of the cerebellum may be present, as in the present case. In contrast, severe cerebellar cortical dysplasia is a typical finding in type II lissencephaly. Olivary heterotopia is regularly associated with type I, while the inferior olivary complex is usually normal in type II.

The present case was considered as a typical case of MDS by clinico-radiologic findings, FISH analysis and neuropathological findings.

MDS was originally described by Miller[3] in 1963 and later by Dieker *et al*.[4] Clinicopathologically, MDS is characterized by lissencephaly type I and peculiar craniofacial features, including bitemporal hollowing, hypertelorism, frontal bossing, a short-upturned nose, microcephaly and high forehead. Larger deletions encompassing the *LIS1* gene, located at 17p13.3, and neighboring genes are responsible for MDS.[5] DNA probe corresponding to the D17S379 locus is often used to detect deletions of the MDS critical region in FISH analysis. Almost all MDS patients have been found to carry visible or submicroscopic deletions of DNA at the D17S379 locus on 17p13.3.[6] The incidence of MDS is difficult to estimate owing to the paucity of reports, but there are data from the Netherlands where 22 cases of lissencephaly type 1 were identified in 11.7 million births, giving an incidence of approximately 1:500 000.[7] The prognosis of MDS patients is poor, and death usually occurs within the first year. The present autopsy case with survival longer than 10 years is very rare.

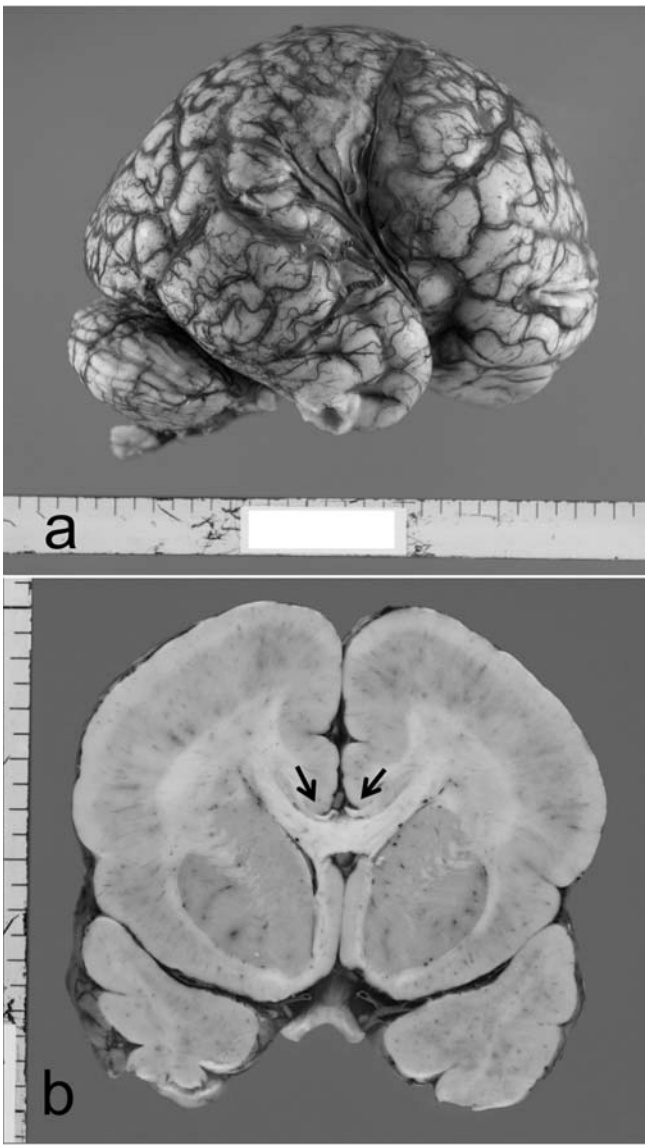

Fig. 2 Macroscopic findings of autopsied brain after fixation. (a) Lateral view of the brain demonstrates pachygyria of the entire cerebral cortex. (b) In coronal section of the cerebrum at the optic chiasm, thickened agyric cortex of the frontal lobe, pachygyria of the temporal lobe, diminished white matter and partial disruption of the corpus callosum (arrows) are shown.

Four-layered cortex is a characteristic finding of the cortical plate in MDS. The four-layered cortex has been characterized by a molecular layer (layer I) containing Cajal-Rezius cells, a relatively thick pyramidal cell layer (layer II), a cell-sparse layer that is myelinated in patients older than 2 years (layer III) and a thick layer of disorganized neurons (layer IV).[8] However, it has been noted that cortical regions may have normal six-layered cortex or a disorganized and thickened cortex that does not strictly coincide with the classic four-layered cortex frequently found in MDS.[9] Forman[8] showed that the

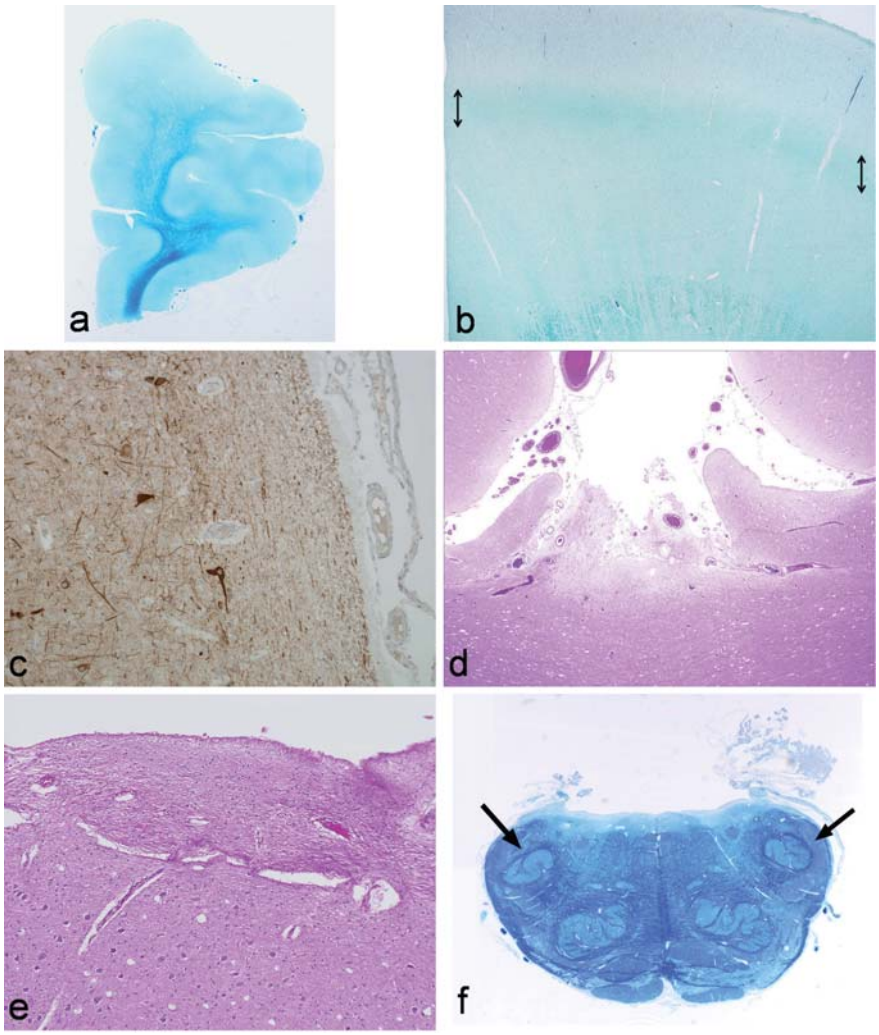

Fig. 3 Histological findings of the brain. (a) Coronal sections of the left frontal lobe show thickened cortex and ill-defined corticomedullary junction. The junction is relatively clear in the lower part. (b) The characteristic four layers with myelinated layer III (arrows) are seen in the temporal cortex. (c) Neurofilament staining shows dysplastic neurons in layer II in the occipital cortex. (d) Corpus callosum demonstrates partial defect of pia membrane. (e) Glioneuronal heterotopia is seen in the subarachnoid tissues of the pontine base. (f) Large heterotopic, convoluted, olivary nuclei (arrows) are present in the lateral medullary tegmentum. (a), (b), (f): KB stain; (d), (e): HE stain.

boundary between the grey and white matter was blurred by vertical clusters of axons that were myelinated in older patients. Thus, in older cases, four-layered cortex might be unclear in some areas of the cerebral cortical plate compared with that in the typical fetal cases of MDS.

In MDS, the corpus callosum and the cingulate gyrus are often unidentified. Agenesis of the corpus callosum seems to be more frequent in MDS than in other type 1 lissencephalies, possibly as a result of the loss of contiguous genes, especially *YWHAE*.[10] The present case was consistent with callosal defect, rather than agenesis of the corpus callosum. At the area of corpus callosum, midline septum and anterior commissure, anatomical anomalies such as heterotopic cingulum, dorsal fornix and Probst bundles have been known.[11] The Probst bundles should be considered in the differential diagnosis of the present case since Probst bundles are usually observed in cases of complete or partial agenesis of the corpus callosum.

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