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Isolated lissencephaly  
sequence or Miller-Dieker  
syndrome?

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This female infant was born to a 28-year-old G2/P2 by vaginal delivery at 36 5/7 weeks of gestation. Pregnancy, although poorly followed, was uneventful. Parents are not consanguineous; a 3-year-old brother is in good health.

At 2 1/2 months of age, the patient was referred to our NICU from a smaller hospital because of suspected seizures. On clinical examination, growth parameters including head circumference were normal. Apart from marked hypotonia, subtle craniofacial anomalies were evident. These included a prominent forehead, a short nose with slightly upturned nares and a low nasal bridge (Fig. 1, 2). Neither striking bitemporal hollowing nor prominent skin folds were noticed. There was no evidence of cardiovascular, urogenital or limb anomalies.

Initial laboratory investigations ruled out acute infections and electrolyte disturbances. Distribution of amino and organic acids was normal. TORCH testing revealed positive ELISA for CMV IgG and IgM and a positive CMV-EA in the mother's urine. Cerebral ultrasound showed lissencephaly and periventricular heterotopia, confirmed by MRI later on. EEG was highly pathologic with a typical hypsarrhythmic pattern. Ophthalmologic investigations showed no signs of chorioretinitis.

Axial T1-weighted MRI image (Fig. 3) showed areas of marked gyral malformation, manifested by a smooth cerebral surface and an abnormally thick cortex. The outer cortical layer of neurons was separated from a thick layer of arrested neurons by normal white matter. An anterior to posterior gradient was apparent with the lissencephaly more severe posteriorly than anteriorly. The shallow, vertical sylvian fissures, possibly a result of failed opercularization, result in a figure-of-eight-shape of the brain. There were no midline calcifications in the region of the septum pellucidum or the genu of the corpus callosum. The coronal T2-weighted image (Fig. 3) showed similar agyria-pachygyria pathology.

FISH-analysis of the patient's chromosomes revealed a submicroscopic deletion in the MDS-ILS (Miller-Dieker Syndrome - Isolated Lissencephaly Sequence) region on chromosome 17p13.3. Parental studies were normal, indicating a de novo event, and thus a very low recurrence risk. The patient, now 10 months old, presents with profound motor delay with marked hypotonia and recurrent seizures that are difficult to control.



Fig. 1

*Patient at the age of 2½ months.*



**Fig. 2**

*Patient at the age of 2½ months.*

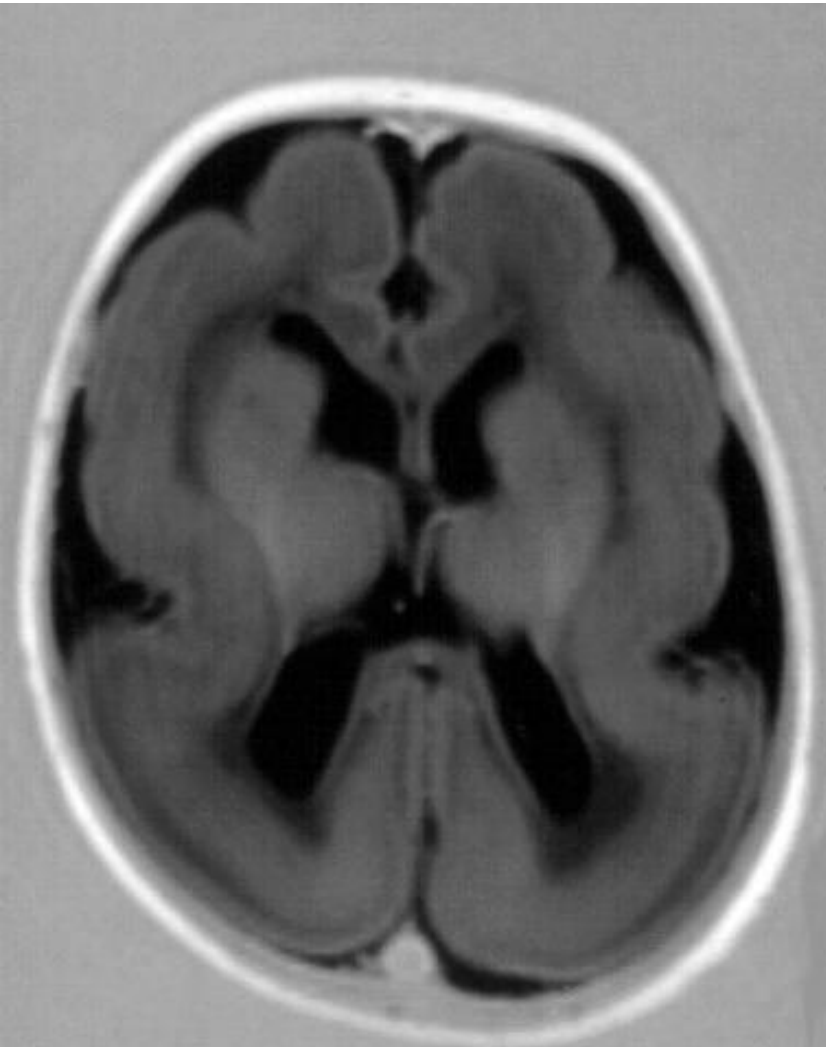
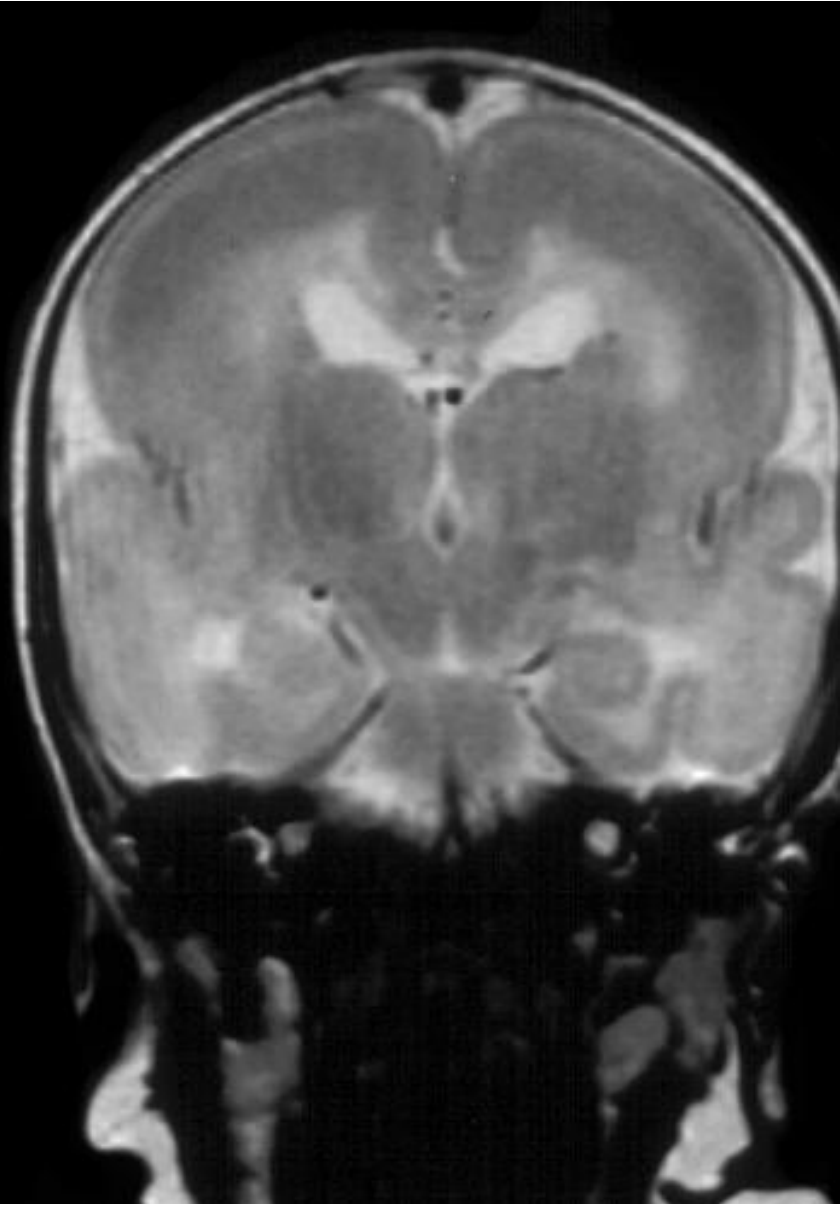


Fig. 3

*T1-weighted MRI: lissencephaly.*



**Fig. 4**

*T2-weighted MRI: agyria and pachygyria patterns.*



Microdeletions in the MDS-ILS region on chromosome 17p13.3 cause two similar conditions, Miller- Dieker Syndrome (MDS) and Isolated Lissencephaly Sequence (ILS).

Miller-Dieker Syndrome (MDS) is a rare disorder, which consists of classical or type I lissencephaly, a characteristic facial appearance and often other anomalies. The syndrome was first described by Miller (1) and Dieker et al. (2), and the eponym was first used by Jones (3). Children with the same brain anomaly who lack the striking facial changes are classified as having isolated lissencephaly sequence (ILS).

In both disorders, the cortical malformation results from arrest or incomplete migration of neurons at about 13-14 weeks during the second prenatal phase of CNS development. According to the clinical grading system for lissencephaly (4), severity of CNS malformations in MDS range from grades 1 to 3. The brain malformations in ILS are more variable than in MDS (grades 1-4). In both conditions an anterior to posterior gradient (lissencephaly more severe posteriorly) is commonly seen.

The defining facial abnormalities in MDS consist of a prominent forehead, bitemporal hollowing, a short nose with upturned nares, a low nasal bridge with prominent skin folds leading down and outward to the cheeks, a flat midface, a thick upper lip with downturn-

ned vermilion borders and a small jaw (5). The facial features of ILS are subtle but consist, too, of a prominent forehead, bitemporal narrowing and a small jaw.

In both conditions pregnancy is often complicated by diminished fetal movements and polyhydramnios, presumably secondary to poor fetal swallowing. The latter is postulated to be due to hypokinesia (5), which in turn is causing the development of a small jaw. The bitemporal narrowing seems to be caused by the enlargement of the Sylvian fissure and failed opercularization (5).

Other anomalies that are relatively common in MDS and ILS include transverse palmar creases, clinodactyly and urogenital anomalies such as cryptorchidism and small penis. Severe hydronephrosis or unilateral renal agenesis is much less common in both disorders. Congenital heart defects occur in approximately 65% of MDS patients (PDA and VSD being the most frequent), but are almost never seen in ILS. Growth parameters are usually normal in both conditions.

Our patient with lissencephaly but only subtle facial features and no other associated malformations would thus be classified as isolated lissencephaly sequence or classical lissencephaly.

The long-term prognosis is very poor. All affected children are profoundly mentally retarded and suffer

from intractable epilepsy including infantile spasms that most commonly begin at 3 to 4 months of age.

## REFERENCES

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CONTACT

Swiss Society of Neonatology

[www.neonet.ch](http://www.neonet.ch)

[webmaster@neonet.ch](mailto:webmaster@neonet.ch)