Miller-Dieker Syndrome in an Extremely Low Birth Weight Infant

Miller-Dieker syndrome (MDS) is characterized by severe lissencephaly and facial dysmorphism including the prominent forehead, bitemporal hollowing, a short nose with upturned nares, a protuberant upper lip, and a small jaw. MDS can be caused by deletions or mutations of the LIS1 gene on 17p13.3. Our patient was born at 28+3 weeks gestation and weight 950 g at birth. He was suffered from respiratory distress syndrome and feeding intolerance. And he showed colpocephaly with agenesis of corpus callosum on the first brain ultrasonography. So, brain magnetic resonance imaging was performed 2 months of age and revealed agyria, colpocephaly, agenesis of corpus callosum and band heterotopias. At initial physical examination revealed no specific abnormal findings. However, hypotonia and abnormal facial morphology including prominent forehead, a short nose with upturned nares and protuberant upper lip were developed gradually as he got older. Chromosomal microarray was performed and confirmed microdeletion on 17p13.3. In conclusion, MDS should be considered when the baby shows colpocephaly, agenesis of corpus callosum, hypotonia, feeding problem and abnormal facial features even though the baby is preterm infant.

Key Words: Miller-Dieker syndrome, Preterm infants, Infant, Very low birth weight

Introduction

Miller–Dieker syndrome (MDS) is characterized by severe lissencephaly and facial dysmorphism including the prominent forehead, bitemporal hollowing, a short nose with upturned nares, a protuberant upper lip, and a small jaw.1 MDS can be caused by deletions or mutations of the LIS1 gene on 17p13.3.2 Perinatal diagnosis of lissencephaly and MDS is unusual, because evaluation of the cerebral cortex is not routinely included in fetal ultrasound. Especially, sonographic diagnosis is difficult before 28–30 weeks of gestation when gyri can be recognized first.3

We experienced an extremely low birth weight infant showing respiratory distress syndrome, hypotonia, feeding problems and colpocephaly with agenesis of corpus callosum. We thought his problems were due to his prematurity. It is not easy to consider MDS when the patient was preterm infant with colpocephaly. However, it is important to diagnosis MDS early so that we expect their disease progression and outcome exactly.

To the best of our knowledge, our patient is the first report of MDS in preterm infants and extremely low birth weight infants. Therefore, the authors herein describe a male baby delayed diagnosis of MDS due to his premature birth.

Case

A 29 year old, primigravid woman was referred to our hospital at 28 weeks’s gestation
because of polyhydroamnios and fetal ventriculomegaly. Preterm premature rupture of the membrane and preterm labor occurred 3 days later and a 950 gram male baby was delivered at 28+3 weeks gestation by cesarean section. The patient was first baby of non-consanguineous parents. There was no family history of congenital anomaly. Apgar scores were 4 at 1 minute and 7 at 5 minutes. The body length was 35 cm (10-25 percentile), and the head circumference was 25 cm (10-25 percentile). After transferred to neonatal intensive care unit, the baby showed respiratory distress. He was intubated and mechanically ventilated. A chest radiograph showed diffuse haziness on the both lung field. He was diagnosed to respiratory distress syndrome and surfactant was administrated. But not long after surfactant administration, his lung was deteriorated and developed to severe bronchopulmonary dysplasia gradually.

In addition to respiratory problem, he showed feeding problem as well. He could not pass meconium within 48 hours after birth and showed small amount of meconium after saline enema performed on the 3rd day of life. Breast milk feeding was started by gastric gavage tube on the 4th day of life. But feeding was stopped often because of frequent abdominal distension and bilious gastric residuals. Gastrografin enema was performed on the 3 weeks of life but could not pass the splenic flexure well. His symptoms remained after these procedures. Therefore, the baby underwent open laparotomy for ileostomy at 5 weeks of age. Incidental appendectomy and pathologic evaluation were performed to rule out hirschsprung’s disease. There were ganglion cells in the resected small bowel and appendix. We could diagnose neonatal pseudobstruction finally.

Our patient showed colpocephaly with agenesis of corpus callosum at 3 days of age and persisted until 2 months of age (Fig. 1). So, brain magnetic resonance imaging (MRI) was performed to evaluate at 2 months of age. Brain MRI revealed agyria, colpocephaly, agenesis of corpus callosum and band heterotopias (Fig. 2).

At initial physical examination of the patient revealed no

![Fig. 1. The initial brain ultrasonography showed colpocephaly and agenesis of corpus callosum at 3 days of age.](image)

![Fig. 2. A brain magnetic resonance imaging showed agyria, colpocephaly, agenesis of corpus callosum and band heterotopia at 2 months of age.](image)
specific abnormal findings. However, hypotonia and abnormal facial morphology including prominent forehead, a short nose with upturned nares and protuberant upper lip were developed gradually as he got older (Fig. 3).

So chromosomal test and metabolic study were done. The patient’s karyotype was normal 46,XY and screening for metabolic disease was unremarkable. Laboratory studies including TORCH (toxoplasma, rubella virus, cytomegalovirus, and the 2 herpes simplex viruses) panel were all normal. Chromosomal microarray (Cytoscan TM 750K array; Affymetrix®, Santa Clara, CA, USA) was performed and confirmed microdeletion on 17p13.3. The baby was diagnosed to MDS finally.

We tried to wean mechanical ventilation several times but failed. After steroid administration, he was extubated successfully at 2 months of age. Tube feeding was needed because of weak suck. He was discharged with supplemental oxygen and nasogastric tube at 3 months of age. He was re-admitted for stoma closure at 4 months of age (postconceptual age of 44 weeks) and discharged uneventfully. At 6 months of age, he manifested generalized clonic seizures, which responded to levitracetam and oxacarbazepine. One week later after first seizure, he developed infantile spasm, which improved on vigabatrin. After that, he was required several admissions due to frequent seizures. Currently at the age of 9 months, he has severe neurodevelopmental delay with significant seizure burden.

![Image](https://example.com/image.jpg)

**Fig. 3.** The patient showed prominent forehead, a short nose with upturned nares and a protuberant upper lip.

![Image](https://example.com/image2.jpg)

**Fig. 4.** The serial brain ultrasonography showed agyria at (A) 4 weeks, (B) 5 weeks, (C) 6 weeks, and (D) 8 weeks of age respectively.
Perinatology

Discussion

MDS was first described by Miller in 1963 as reporting girl siblings having intrauterine growth retardation, faciocranial anomaly and severe neurodevelopmental impairments. Perinatal diagnosis of lissencephaly and MDS is unusual, because evaluation of the cerebral cortex is not routinely included in fetal ultrasound. Especially, sonographic diagnosis is difficult before 28–30 weeks of gestation when gyri can be recognized first.

The prenatal diagnosis of MDS was verified by fetal chromosomal analysis by fluorescence in situ hybridization, on chorioic villus sampling or amniocentesis. In fact, several cases of perinatal diagnosis were reported by Greenberg et al. and so on.7-11

The case report of MDS in preterm infants is very rare even though it is well known that MDS is associated with intrauterine growth retardation. Our patient was not only preterm infant but also extremely low birth weight infant. Our patient was born at 282-3 weeks of gestation when cerebral agyria cannot be recognized generally. For that reason, we could not find agyria at his first a few examination. However, we overlooked agyria findings after that time. In fact, we could know that his brain ultrasonography has showed agyria persistently throughout 3 months of hospitalization when we reviewed his findings again (Fig. 4). And also, we misunderstood his problem including abnormal facial morphology, generalized hypotonia and feeding problem was due to his prematurity.

We believe that delayed diagnosis of MDS did not affect his disease progress. However, we could have expected disease progression and outcome more and served more accurate information to his parents if we could consider MDS earlier.

MDS can be caused by deletions or mutations of the LIS1 gene (PAFAH1B1; OMIM 61545) on 17p13.3. The loss of LIS1 gene can be caused by a de novo deletion in approximately 80% of the MDS patients and be caused by inheritance in the remaining 20% of cases.12 However, the karyotype analysis of the proband’s parents was not performed due to their refusal. So we cannot know whether this case is caused by a de novo deletion or parental balanced translocation. If his parents will plan next pregnancy, we have to offer that they needs karyotype analysis.

In conclusion, MDS should be considered when the baby shows colpocephaly, agenesis of corpus callosum, hypotonia, feeding problem and abnormal facial features even though the baby is preterm infant.

Acknowledgements

This work was supported by a clinical research grant from Pusan National University Hospital 2016.

References