Miller-Dieker syndrome

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Abstract

Miller-Dieker syndrome (MDS) is a rare genetic disorder characterized by lissencephaly, congenital craniofacial anomalies, cardiac malformations, growth retardation, and intellectual disability with seizures. The objective of the present study is to aid in the early diagnosis of the syndrome, correlating the clinical data of the patient with those described in the literature. The authors report a child with lissencephaly, neuropsychomotor development delay and MDS compatible phenotype. Infant, 2 months old, hypoactive, significant axial hypotonia and recurrent seizures from the 3rd day of life. At the morphological examination, presence of epicanthus, flat nasal base, small and anteverted nostrils, palpebral fissures with lower slope, bitemporal narrowing and prominent forehead. Computed tomography and MRI of the skull evidencing lissencephaly and agiria. The diagnosis of the studied patient was considered by the presence of typical facial dysmorphisms of the syndrome and severe delay of neuropsychomotor development. The phenotype and brain disorders found in both imaging and clinical presentation should be considered since it is often not possible or feasible to perform better genetic tests.

Keywords: Lissencephaly, Genetic Diseases, Inborn, Syndrome, Seizures.
INTRODUCTION

The Miller-Dieker Syndrome (MDS) is a rare genetic disorder characterized by classical lissencephaly, congenital craniofacial anomalies, cardiac malformations, growth retardation, and delayed neuropsychomotor development\(^1,2,3\). There are seizures that are difficult to control and electroencephalogram (EEG) abnormalities\(^1\). Caused by deletion or mutation in the LIS1 (lissencephaly 1) gene on chromosome 17p13.3, MDS has an autosomal dominant inheritance pattern\(^1\).

The most common craniofacial anomalies found in MDS include microcephaly, prominent forehead, bitemporal narrowing, wrinkled skin over the glabella, protruding upper lip, micrognathia, lower inclined eyelid fissures, and anteverted and small nares\(^1,2,4\).

There are three types of lissencephaly, and the classic lissencephaly is the one in which there is a neuronal migratory abnormality resulting in a smooth and thick cerebral cortex due to deficiency of sulci and gyrus development\(^2,5,6,7,8\). In these cases, the head circumference at birth is usually within normal range. The LIS1 gene, located at 17p3, is required for neuronal precursors to properly promote migration. MDS is associated with deletions in this region of the 17p3, usually with complete absence of the LIS1 gene, being the most common cause of classical lissencephaly\(^2,5\).

Children with MDS also develop severe intellectual deficits, inadequate growth, seizures and hypotonia or spasticity\(^1,2\). There is lower life expectancy\(^4\). Death usually occurs before 2 years of age, often within the first 3 months of life\(^4\).

CASE REPORT

J.M.D, male, 2 months old, born to non-inbred parents, has 4 healthy siblings. Born at term, vaginal delivery, Apgar 8/9, being classified as appropriate for gestational age. Mother attended 6 prenatal consultations, syphilis in the 3rd trimester of pregnancy was treated, upon admission to the maternity ward, with 3 doses of Benzathine Penicillin, and her husband received the same treatment. The mother's VDRL before treatment was 1:32. The newborn's VDRL at birth was 1:32. His long bones radiograph was normal. We did not do a lumbar puncture due to the unavailability of this examination in our unit at the time. We treated the newborn for neurophilis and administered crystalline penicillin for 10 days.

Still in the maternity ward, J.M.D presented an episode of isolated cyanosis in the left upper limb after the first hours of postpartum, and his echocardiography had no abnormalities. Such event spontaneously resolved within hours. Two days later, J.M.D evolved with episodes of fever, initially focal seizures that later generalized. Laboratory tests found hyperkalemia of 6.8 mmol/L and sodium within normal limits. The patient was kept under observation for clinical surveillance and control of the hydroelectrolytic disorder, but maintained 6.7 mmol/L hyperkalemia, refractory to Calcium Gluconate administration (1 ml/kg/day).

Non-contrast-enhanced computed tomography (CT) of the brain, which found lissencephaly and agyria, magnetic resonance imaging (MRI) of the cranium showed a disorder of cortical development characterized by lissencephaly appearance in the frontoparietal and pachygyria regions of the temporal lobes, as well as commissural dysgenesis and dysmorphic aspect of the nuclei and the brainstem, with pons hypoplasia (Figure 1).

On physical examination, J.M.D was hypoactive, with significant axial hypotonia and no palmar and plantar reflexes. Morphological examination showed epicanthus, flat nasal base, small, anteverted nostrils, lower sloping eyelids, bitemporal narrowing, and prominent forehead. The patient was then referred to the pediatric neurology department for diagnostic investigation of genetic and metabolic disorder.

We order a screening for innate metabolism error (EIM), which yielded a slight change concerning reducing substances, keto acids and ketone bodies. Analysis of amino acids in urine had changes in group 5 (more pronounced alanine and presence of tyrosine) and group 6. Analysis of amino acids in the plasma showed a slight change without apparent significance. The urinary tract ultrasonography was within normal parameters.

J.M.D evolved with persistent episodes of focal-type seizures, all lasting approximately 10 seconds. He was started on Phenobarbital without improvements in his condition. We adjusted his anticonvulsant dose, but the child had episodes of seizures, improving only after replacement of Phenobarbital with the combination of Clobazam and Levetiracetam.

DISCUSSION

The patient under study has a characteristic MDS phenotype. This diagnosis was considered due to the presence of facial dysmorphia typical of the syndrome, and delayed neuropsychomotor development (DNPM).

MDS is mainly associated with lissencephaly, where the cerebral cortex is thick and has no gyrus\(^5,6,7,8\). In some areas of the brain, the gyrus is smaller but wider and shallower than normal, called pachygyria, and in other brain areas the absence of such gyrus, called agyria or complete lissencephaly may occur\(^5,6,7\). Neurons migrate to the final position in the brain during nervous system development, which occurs between 12 and 16 weeks of gestation\(^2,3\) by the process. Neurons are created in the ventricular zone and extend along the radial glia to reach the cortical zone\(^2\). It is the disruption of radial and tangential migration that causes reduction or absence of turns, resulting in lissencephaly\(^3\).

The LIS1 gene is closely related to microtubules and is responsible for their regulation. Microtubules are part of the cytoskeleton and play important roles in cellular processes such as mitosis and cytokinesis. Migrating neurons first extend a major process along the radial glial framework, and then the centrosome and nucleus are pulled toward the main process.
The network of microtubules and molecular motors, dynein, is central to this centrosome and nucleus migration. The LIS1 protein interacts with dynein and regulates this microtubule-based molecular motor. In lissencephaly, there is brain cell migration failure. The form of lissencephaly found in MDS was designated as classic or lissencephaly type 1. The patient under study had lissencephaly with confirmed agyria on CT and MRI reports, which is in agreement with the literature.

Seizures occur in more than 90% of children with lissencephaly, usually beginning before six months of age. Approximately 80% have infantile spasms, although EEG does not always show the typical pattern of hipsarrhythmia. J.M.D has not been submitted to an EEG so far, but has had difficult-to-control seizures, and his signs and symptoms match the diagnosis of MDS.

Due to the associated brain abnormalities, babies with MDS have reduced developmental capacity and severe and profound DNPMD. Most newborns develop significant hypotonia, as was the case of our patient.

Patients with the syndrome can be diagnosed based on clinical presentation and suggestive radiological changes. However, the diagnosis is difficult because signs and symptoms may vary among patients. This may be related to the actual size or exact location of chromosome 17 exclusion. Confirmation is performed by cytogenetic testing and FISH. J.M.D has not yet been submitted to genetic testing, being considered as a spectrum of MDS through its phenotypic characteristics and image demonstrating lissencephaly. There were also serum changes in potassium as well as screening for IMT. Such disorders were nonspecific and do not point to the neurological condition presented by the patient under study. The authors consider these results as confounding factors for the diagnosis, which became clear after MRI.

**CONCLUSION**

MDS has a poor prognosis. Because it is a pathology that leads to difficult-to-control epilepsy, one should be aware of the possibility of cortical malformation and, therefore, refer all cases of epilepsy in young infants. The phenotypic characteristics of the syndrome and brain disorders found in both imaging studies and in the presence of neuropsychomotor delay should be considered for diagnosis, since it is often neither possible nor accessible to perform more refined genetic tests.
REFERENCES