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WEST VARIANT IN MILLER-DIEKER SYNDROME

Marino S[1], Falsaperla R[1], Marino SD[1], Smilari P[2], Greco F, [2] Vitaliti G, [1] Caccamo M[2], Barbagallo M[3] & *Pavone P[1,2]

[1]University-Hospital 'Policlinico-Vittorio Emanuele, University of Catania, Italy
[2]Department of Clinical and Experimental Medicine, Section of Pediatrics and Child Neuropsychiatry, A.U.O. Vittorio Emanuele–Policlinico of Catania, Italy.
[3]Department of Pediatric, Hospital Garibaldi, Catania, Italy

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Abstract

Introduction. Miller-Dieker syndrome (MDs) is a severe malformative condition characterized by a smooth surface known also as lissencephaly . The syndrome is linked to a contiguous gene deletion of short arm of chromosome 17 (17p13.3) causing cerebral dysregulation. Affected children present with facial dysmorphisms, severe intellectual disability and drug resistant seizures. Infantile spasms are the most frequently reported types of seizures with the EEG recording presenting with the typical aspect of hypsarrhythmia**.**

Case Report. Recently an infant with MDs was diagnosed soon after birth and followed up for 12 months with clinical and serial electroencephalographic (EEG) recording. During the course of the disorder, wide variability of the clinical and EEGraphic pattern were reported. At the age of 6 months the EEG showed a pattern of modified hypsarrhythmia without the classic clinical association with infantile spasms which recurred afterward.

Conclusion. We have hypothesized the EEG pattern reported in this infant as an anticipation phenomenon of subsequent onset of infantile spasms.

Introduction

Lissencephaly (LIS) is a malformation of cortical development manifested by a smooth cerebral surface (agyria/pachygyria). The development of the human cerebral cortex follows several steps mainly involving cell proliferation, cell migration and cortical organization. The disruption of any of these steps, including molecular genetic causes, results in abnormal formation of cerebral convolution or gyri[1]. The histopathologic features show incomplete neuronal migration with widened cortex only organized into layers, and large numbers of heterotopic neurons below the cortex[2]. LIS, together with subcortical band heterotopia (SBH), represent two of the most severe forms of cerebral malformation[3-5]. From the discovery of the first genetic cause of LIS involving the deletion 17p13.3 and of the most common causal genes LIS1 (PAFAH1B1) and DCK, more than 19 LIS-SBH associated genes have been reported[6-11]. Miller-Dieker syndrome (MDS) is a contiguous gene deletion of short arm of chromosome 17 (17p13.3) presenting with severe intellectual disability, drug resistant seizures and facial dysmorphisms. Body organs may be also affected including heart, genital and kidneys. The facial dysmorphisms are quite distinctive and includes microcephaly, high and prominent forehead, bi-temporal hollowing, short nose with upturned narix, edge lips downward and thin vermillian border of the upper lip and microretrognathia[4-6]. The steps of development are only poorly reached and severe intellectual disability is the most frequent clinical sign. Most of the affected children die precociously as a result of intractable seizures and aspiration pneumonia. The seizures in MDS are widely variable and may present in several different types but more commonly as "infantile spasms" (IS)[5]. Herewith we report on clinical features and electroencephalografic (EEG) recording in a child with MDS in the course of the first months of life. Clinical and elettroencephalografic patterns displayed a notable variability along the course of the disorder.

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The EEG pattern performed in this patient allowed us to releave a not reported relationship between EEG and clinical pattern. As usual, the Modified Hypsarrhythmia is associated with a clinic appearance of infantile spasms[12]. Differently, at the age of 6 months, we have documented at the video-EEG a pattern of Modified Hypsarrhythmia (MH) not associated to the typical infantile spasms (MHWIS) which appeared afterwards. We have hypothesized the EEG pattern MH seen in the infant as an example of anticipation phenomenon of subsequent onset of infantile spasms (IS).

Case report

A 12 month-old boy was referred to the Pediatric Clinic Policlinico-Vittorio Emanuele hospital, Catania (Italy), for drug resistant seizures with the diagnosis of Miller-Dieker syndrome. He is the second born of healthy, unrelated Italian parents. At the time of gestation the mother was aged 34 and the father 38 years. The sister aged 3 years is healthy. The mother felt normal fetal movements during the gestation. A diagnosis of brain malformation was recorded during the six month of gestation as the result of intrauterine ultrasound (US) which disclosed ventriculomegaly, absence of corpus callosum and intrauterine growth restriction. The mother denied having any infection diseases or having used drugs or alcohol during her pregnancy. The boy was born at 37 weeks of gestation by spontaneous vaginal hasty delivery. The birth weight was 1800 gr, length 45 cm and head circumference 32 cm. The APGAR scores were 5 and 8 at 1 and 5 minutes, respectively. Soon after birth, he was admitted to the Neonatal Intensive Care Unit (NICU) in another city hospital for treatment and clinical evaluation related to facial dysmorphisms, cerebral malformation, low weight and episodes of cyanosis and bradycardia. During this hospitalization, treatment for his respiratory distress and poor alimentation was started. In this period of time, lasted 26 days, he was submitted to several laboratory findings, genetic analysis and neurological investigations. Routine laboratory findings disclosed the presence of mild metabolic acidosis, immediately corrected. The EEG showed poorly organized background and the presence of spike, mainly in the temporo-central-occipital regions. At US, colpocephaly and absence of normal cortical gyration with simplified sulci and cerebral scissors were noticed. Brain MRI showed severe lissencephaly consisting of wide-spread agyria and restricted areas of pachygyria (fig 1-2) After the discharge from the hospital, the child showed episodes of tonic movements associated with sudden scream. General hypotonia was still present with difficulty to maintain the head held and episodes of partial tonic movements were reported. During this period the baby had a good growth improvement.

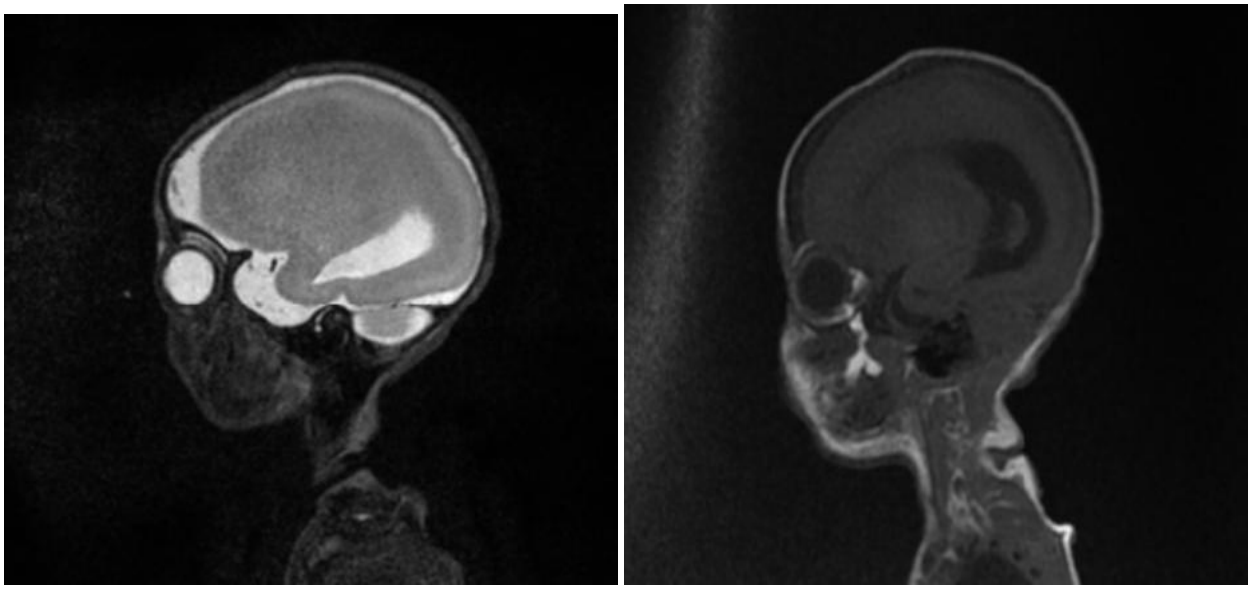

Fig 1(a-b) Brain MRI to 5 days of life: a)T2 sagittal sequence b) T1 sagittal sequence

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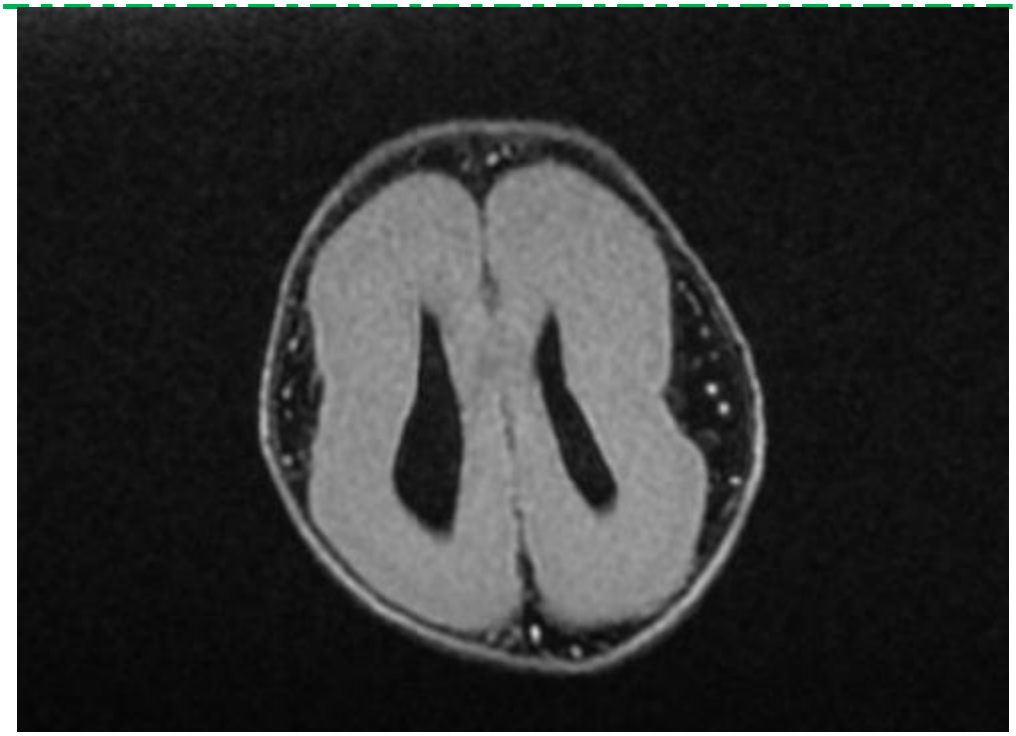

Fig 2 Brain MRI to 5 days of life: T2- axial FLAIR sequence

At the age of 6 months he was admitted for the first time to our observation, due to tonic seizures sometime associated to short phase of desaturation prevalently during the sleep. His weight is 6 kg (3° percentile); length 62 cm (>3° percentile) and head circumference 40 cm (<3° percentile). Mild facial dysmorphism is noticed and consists of high forehead, slight bi-temporal hollowing, epicanthus, small upturned nose, low set and abnormally shaped ears, slim lips with edge under-down, retrognathia. The neurological examination shows severe hypotonia with difficulty to keep the sitting position. The anterior fontanelle is open 0,5 x 0,5. Partial bilateral ptosis is noticed. The seizures are mainly localized at the face with blinking and clonic movements of the arms appearing prevalently before sleeping and the intercritical Video-EEG shows a pattern of modified hypsarrhythmia consisting of random high-voltage spikes and slow wave and a lack of synchronism with a cahotic appearance predominant in the occipital areas.

A few weeks later the types of seizures changed, presenting with brief and synchronous movements of the head, trunk, and limbs, or sometimes of the head, trunk, or limbs typical of infantile spasms. These critical movements last about a few seconds but sometimes occur in clusters. The critical Video-EEG showed a typical electrical suppression during an epileptic spasms. The background is variable and mainly consists of the combination of a hypervoltage slow wave with a bout of rapid low-amplitude activity or a diffuse attenuation of the trace (fig4). These episodes did not respond to hormonal treatment and Phenobarbital (PB) at high dosage.

As the seizures persisted with high frequency treatment with valproic acid (40 mg/kg/day), levetiracetam (54 mg/kg/day) and Vit B6 (5 mg/kg/day) was started. Ketogenic diet was unsuccessful. With the treatment in gradual add-on of midazolam a reduction of the frequency of seizures has been reached , but the seizures still persist. Routine laboratory analyses are normal including blood count, coagulation testing, blood lactate, pyruvate, glucose and ketones, CK, copper, Vit D, ceruloplasmin, plasma and urine amino acids, organic urinary acids, purine e pyrimidine, 7-dehydrocholesterol, total cholesterol. Renal and abdominal ultrasound are normal.

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Genetic analysis

Chromosomal microarray analysis C4X180K (AMADID 022060-Agilent Cytogenomies edition 3.0) showed a micro-duplication of the distal extremities of the long arm of chromosome 1 in the region 1q44 about 4,2 Mb and micro-deletion of the distal region of the short arm of chromosome 17 in the region p13.3p13.2 about 3.8 Mb including the critical region for the Miller-Dieker syndrome. The fluorescence in situ Hybridization (FISH) test confirmed the molecular anomaly and allowed us to associate the micro rearrangement to the chromosome 17 deriving from a "de novo umbalance translocation between the long arm of chromosome 1 and the short arm of chromosome 17 with breakpoint in 1q44 and 17p13.2, respectively.

Discussion

The child showed the typical clinical features of DMs. Diagnosis of cerebral malformation was made through US during the gestation, at 6 month of intrauterine life. The diagnostic suspicion was confirmed at birth on the presence of microcephaly, facial dysmorphisms and brain MRI which disclosed the typical aspect of lissencephaly. The subsequence result of molecular analysis with the microdeletion of one district region of the short arm of chromosome 17 in the region p13.3p13.2 confirmed the diagnosis of LIS1 and in particular of MDS. The clinical manifestation in children with MDS involving mainly the brain. Microcephaly may be present at birth, but it may manifest as the child grew older. Length is usually normal at the birth while the birth weight is low. Subsequently poor feeding and frequent episodes of vomiting are the main cause of poor weight growth. Distress respiratory and infections of the respiratory tract are frequently recorded. Abnormal neurological examination, intellectual disability and epileptic seizures are the main manifestations of the syndrome. Hypotonia and spasticity are frequently reported and intellectual disability is recorded with score between severe to profound[4-5].

In MDS different phenotypes of seizures, including partial complex and epileptic syndromes such as West Syndrome are recorded [6-8]. The patients complain intractable epileptic seizures and the onset of the crises are precocious and manifested in a range from a few days to 2 years[11]. In a study of de Wit[11] ,five patients had their onset of seizures in neonatal period, 17 had infantile spasms and 2 suffered by multifocal epilepsy. The prognosis of MDS is severe. According to the survey of Dewit et al.[11] in a long term (mean length follow-up of 14 years) performed in 24 patients affected by LIS type 1, only eleven were alive at the evaluation. All the patients showed severe intellectual disability, intractable epilepsy and need of special care and dependency.

According to "consensus statement of the West Delphi group"[13] , the term hypsarrhythmia is used to describe an EEG pattern that is characterized by random, high.voltage slow waves with variable amplitude (generally >200 MicronV), spikes and waves from many foci, and varying with time, a lack of synchronism, with a generally chaotic appearance. Variations of the EEG prototypic pattern defined "modified hypsarrhythmia" (MH) includes different pattern of hypsarrhythmia with increased interhemispheric synchronization, and asymmetrical, with a consistent focus of abnormal discharge, with episodes of attenuation, and hypsarrhythmia including primarily high-voltage slow activity with little sharp-wave or spike activity[12-13].

In the proband, at the age of 6 months, the Video-EEG showed a persistent occipital focus discharge suggestive of MH without a corresponding clinical feature of typical infantile spasms reporting with a sigle MHWIS. In our case the MH has preceded the onset of IS. Only after a short period of time, the correlation between MH and infantile spasms became clear.

We maintained that this is an example of a MH anticipating the onset of infantile spasm and may be considered such a new variant of "modyfying features of hypsarrhythmia".

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Conclusion

In the proband, the clinical course, clinical phenotypes and EEG recording have had a clear variability. Moreover it has been demonstrated that the Modified Hypsarrhythmia may precede the clinical appearance of infantile spasms and it may be considered as a "new variant" of the "modyfying features of hypsarrhythmia".

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Declaration of conflicting interest

The Authors denied any conflict of interest

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