Early-onset encephalopathy and cortical myoclonus in a boy with MECP2 gene mutation

V. Leuzzi, MD; M.L. Di Sabato, MD; M. Zollino, MD; M.L. Montanaro, MD; and S. Seri, MD

Abstract—The authors report the unusual clinical and neurophysiologic features of a sporadic case of a boy carrying an 806delG mutation on the MECP2 gene. A 28-month-old boy was examined for severe developmental delay, seizures, microcephaly, breathing dysfunction, and spontaneous and evoked myoclonic jerks of upper limbs. Neurophysiologic study proved the cortical origin of myoclonus; however, it was not associated with signs of cortical hyperexcitability. 3-Methoxy-4-hydroxy-phenylethylene glycol and valine concentrations were low in CSF.

Case report. A boy, now age 28 months, was born to healthy nonconsanguineous Italian parents after a normal pregnancy and cesarean section, performed for fetal malpresentation. Body weight was 3,070 g, length was 51 cm, head circumference was 33.4 cm, and Apgar score was 6 at 1 minute and 6 at 5 minutes. During the neonatal period, he was markedly hypotonic with weak suck and vomiting. Chaotic ocular movements and masticatory automatisms were observed. At that time, the child experienced brief episodes characterized by increase in axial tone and arching with cyanosis and apnea, which were diagnosed as tonic seizures. EEG showed severe background disorganization. By age 4 months, he had prolonged focal seizures with secondary generalization. Brain MRI was normal. Progressive psychomotor retardation, arrest of head growth, gastroesophageal reflux, severe intestinal dysfunction, and breathing abnormalities ensued in the following few months.

The child was first brought to our attention at age 10 months. On examination, he exhibited microcephaly (head circumference, 40.5 cm; <2 SD), severe developmental delay, axial hypotonia and limb rigidity, hyperreflexia, continuous irregular brief jerks of the upper limbs, lack of purposeful movements of hands, poor eye contact and face recognition, and pendular nystagmus. Brief jerks could also be elicited by acoustic and tactile stimuli and waned during sleep. Frequent and polymorphic ictal episodes were reported, including brief loss of contact, jerks mainly affecting the upper limbs, and generalized tonic-clonic seizures. These were unresponsive to conventional antiepileptic drugs.

Laboratory investigations detected increased blood ammonia (135 and 147 µg/dL in two subsequent examinations; normal, 15 to 56); reduced concentration of CSF 3-methoxy-4-hydroxy-phenylethylene glycol (MHPG; 39.3 nmol/L; normal, 47 to 81) with normal homovanillic (HVA), 5-hydrossindolacetic acid (5-HIAA), and pterins; and reduced valine in CSF (6.8 µmol/L; normal, 11.9 to 29.4) with normal plasma and CSF amino acids.

Genetic testing showed a 46XY karyotype. The direct sequencing of the three coding exons of the MECP2 gene detected a deletion of guanine at position 806 (806delG), leading to a frameshift and premature stop codon at position 288 within the transcriptional repression domain. Molecular analysis of the mother failed to demonstrate the mutation, suggesting a germline mosaicism or a mutation occurred de novo as a postzygotic event.

At age 15 months, the patient underwent long-term awake video-EEG monitoring to characterize the nature of the paroxysmal movements. A polygraphic video-EEG was recorded, with synchronous EMG signal acquisition. Delib Epoch, flexor, and extensor muscles of the forearm and abductor pollicis brevis muscles were recorded bilaterally. The EEG showed dominant rhythmic activity at 5 to 6 Hz in the centroparietal leads. There was abundant multifocal paroxysmal interictal epileptiform activity, mainly in the frontocentral and temporal leads. The patient showed arrhythmic multifocal myoclonus at rest, mainly localized on distal muscles, increasing in frequency after spontaneous movement, and unrelated to the interictal focal epileptiform transients (figure 1). Jerk-locked averaging of the EEG centered on the EMG onset showed a negative–positive negative wave with a dipolar distribution, with maximum negativity on F3/F4 and maximum positivity on P3/P4, which preceded the onset of the EMG signal by 24 ms (figure 2). Somatosensory evoked potentials (SEPs) and C reflex after stimulation of the median nerve were investigated. The latencies of N9 and P14 components of the SEPs were normal, whereas the cortical N18 component was absent bilaterally. C reflex was absent. Visual evoked potentials and electroretinogram were normal.

At age 20 months, he had protracted status epilepticus, recurrent urinary tract infections, and aspiration pneumonias associated with central hypoventilation episodes, requiring mechanical ventilation. Since age 24 months, he has been fed by gastrostomy.

Discussion. Rett syndrome is an X-linked neurologic disorder caused by mutation in the gene encoding methyl-CpG-binding protein 2 (MECP2), mapped on chromosome Xq28. After the identification of this gene, a few affected male patients have been described. Apart from patients with somatic mosaicism for the mutation or carrying an extra X chromosome, male patients with MECP2 mutations show phenotypes different from classic Rett syndrome. Movement disorders, including tremor, choreoathetosis, dystonia, ataxia, spasticity, and motor stereotypes, are a clinical hallmark of male patients with MECP2 mutations. We report a sporadic case of a boy carrying the 806delG mutation on MECP2. A boy with two affected female members in the family carrying the same mutation as our patient has been previously reported. He had a similar phenotype, but the parox-
ysmal motor manifestations were in the form of an intermittent tremor. The neurologic picture of our patient is dominated by severe hypotonia and a persistent spontaneous myoclonus of the upper limbs, facilitated by sensory stimuli and movement, for which neurophysiologic investigations proved a cortical origin. The topographic distribution of the activity and its mainly arrhythmic presentation resemble those of Rett female cases, the differential features being the loss of the N20 component of the SEP and the absence of C reflex. The neurophysiologic pattern recorded in female patients with Rett syndrome has been considered expression of an enhanced activity of sensorimotor columns, processing input-output volleys from and to the corresponding somatic area, associated with a reduced horizontal transmission along corticocortical connections. It has been regarded as the result of circuitry derangement arising from the reduction in dendritic branching development found in several cortex regions in female patients with Rett syndrome. This hypothesis is also congruent with the cortical alterations of auditory evoked potentials in these patients. Neuropathologic studies in male patients with MECP2 mutation are scarce and do not allow us to draw univocal conclusion to explain our findings. A possible hypothesis could be that the severity of the clinical picture and of the neurophysiologic changes seen in our patient would suggest a more marked impairment of synaptic connectivity and a severe involvement of somatosensory cortex, which would preclude the degree and extent of synchronous activation of the cortical structure required to produce a scalp-recorded evoked response. A similar mechanism has been invoked in patients with myoclonus and vascular lesions of the somatosensory cortex.

In our patient, we found a reduction of CSF MHPG with normal HVA, 5-HIAA, and pterins. Conflicting results have been reported in female patients with Rett syndrome, with CSF HVA and MHPG reported either as normal or reduced (with an increase of total biopterin). To our knowledge, no systematic study of CSF biogenic amines has been performed in male patients carrying MECP2 mutations. A mild increase of serum ammonia was also observed.

Figure 1. Arrhythmic multifocal myoclonus at rest (mainly localized on distal muscles), usually unrelated with the interictal focal epileptiform transients on EEG. EMG 1 = left deltoid; 2 = right deltoid; 3 = right wrist flexor; 4 = right wrist extensor; 5 = right abductor pollicis brevis (APB); and 6 = left APB.

Figure 2. Jerk-locked averages showed a negative-positive-negative EEG wave with a dipolar distribution, with maximum negativity on F3/F4 and maximum positivity on F3/P4, which preceded the onset of the rectified EMG signal by 24 and 23 ms in the two averages. L-FL = left wrist flexor; R-DELT = right deltoid; R-FL = right wrist flexor; R-EDB = right extensor digitorum brevis.
Hyperammonemia was an early reported metabolic trait in female patients with Rett syndrome but was not confirmed afterward.10 However rare this condition might be, MECP2 gene mutations in male patients affected by early-onset severe encephalopathy, myoclonus, and epilepsy should be investigated, even in the absence of a supportive family history.

References

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