Neonatal-Onset Brainstem Reticular Reflex Myoclonus Following a Prenatal Brain Insult: Generalized Myoclonic Jerk and a Brainstem Lesion

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Brainstem reticular reflex myoclonus (BRRM) is characterized by sudden, generalized, shock-like movements that can be elicited by sensory stimulation. We present a boy, born after 35 weeks gestation, who was diagnosed with neonatal-onset BRRM. Within 1 hr of birth, the patient showed spasticity and generalized clonic movements of all limbs elicited with tactile stimulation anywhere on the body. Surface electromyography showed co-contraction of agonistic and antagonistic muscles, revealing that his generalized clonic movements were tremulous myoclonus in nature. Brain magnetic resonance imaging (MRI) at 21 hrs after birth disclosed high-intensity lesions in the Rolandic area, thalamus, basal ganglia, and brainstem, including the dorsal pons and medulla, the center of BRRM, in T1-weighted images. Follow-up MRI at 1 month revealed dramatic improvement in the pontine lesion. The patient showed gradual remission of the characteristic movements, which disappeared at 1 year of age, but the patient died unexpectedly at 1 year and 3 months. In conclusion, neonatal BRRM arises as a result of severe brainstem injury, and the associated lesions may only be seen temporarily on MRI taken soon after birth.

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Post-hypoxic myoclonus (Lance and Adams 1963; Obeso et al. 1983; Sugama and Kusano 1995; Hallett 2000) is caused by hypoxic-ischemic brain injuries. There are two types of post-hypoxic myoclonus, acute and chronic. The acute type has not been studied intensively but probably originates in the brainstem (Hallett 2000). One such condition is brainstem reticular reflex myoclonus (BRRM), characterized by sudden generalized shock-like movements that can be elicited by sensory stimulation (Brown et al. 1991; Rothwell 1996). Most patients who develop post-hypoxic myoclonus are between the ages of 15 and 60 years (Frucht 2002), whereas such movement disorders are very rarely reported in childhood. Obeso et al. (1983) and Sugama and Kusano (1995) reported children with action myoclonus that appeared beginning a few years after perinatal asphyxia.

We report a neonatal case of BRRM attributable to a prenatal insult, and discuss the relationship between the clinical course and temporal changes seen on magnetic resonance imaging (MRI), focusing on the pons and medulla.

**Case Report**

The boy was the first child of non-consanguineous healthy parents with an unremarkable family history. No noticeable events were observed until 35 weeks gestation, when caesarian section under general anesthesia was performed because of accelerated delivery, with a fetal foot presentation. A dose of suxamethonium chloride, double the normal dose, was given to relax the mother’s muscles. As the boy did not breathe spontaneously after birth, he was resuscitated with immediate endotracheal intubation. His Apgar scores at 1 and 5 min were both 2 (heart rate, >100). At 43 min after birth, spontaneous breathing and right hand “seizure” were noted. He was judged to need intensive care, and vigorous investigation to reveal his pathophysiology.

He needed respirator care for about 1 month. After successful withdrawal from respirator care, he required supplemental oxygen for an additional month. The neurological examination revealed some abnormalities. He had little spontaneous movement. Muscle tonus was increased severely, and the clasp-knife phenomenon was prominent. Deep tendon reflexes were exaggerated. He had little facial expression and was not seen to smile or cry. Loss of rooting and sucking reflexes was observed, and difficulty in swallowing was detected. Tapping the tip of the nose did not produce the typical startle reaction observed in the main type of hyperekplexia. From the day of admission, generalized clonic movements that could be elicited by tactile stimulation were observed frequently, especially during periods of wakefulness. These phenomena were easily

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Fig. 1. MRI at birth (A-C, T1WI).

A: Bilateral Rolandic area shows high intensity (arrow).

B: Diffuse hyperintensity is observed in the lentiform nuclei and thalami (circle).

Low intensity is noted in the posterior limb of the internal capsule, which is normally the brightest structure in the brain at this age.

C: The midbrain shows abnormal intensities (arrow).
evoked even by subtle tactile stimulation.

Brain computed tomography (CT) at 15 hrs of age revealed a high density in the thalamus bilaterally (data not shown). MRI at 21 hrs of age disclosed a high-intensity lesion in the Rolandic area, thalamus, basal ganglia, and brainstem, and especially in the midbrain, pons, and medulla in T1-weighted images (Fig. 1A-C, 3A and 4A). T2-weighted images showed hypointensity in the dorsal pons and medulla (Fig. 3D and 4D).

An electroencephalogram (EEG) recorded on day 2 showed abnormal activity consistent with a suppression/burst pattern, which was not improved by intravenous vitamin B6. This abnormal EEG pattern gradually improved to show organized background activity with several spikes in the central areas bilaterally. His seizure-like movement was considered to be non-epileptic, based on the observation that the ictal EEG had not shown any epileptic changes; in addition, this movement was easily stopped by grasping the extremities. Surface electromyography (EMG) revealed that the rhythmical clonic movement was tremulous myoclonus in nature, because both agonistic and antagonistic muscles contracted synchronously (Fig. 2).

Investigation at 3 months of age included a complete cell blood count, urinalysis, urinary gas chromatography, and analyses of glucose in the cerebral spinal fluid (CSF), blood gas, serum amino acids, lactate and pyruvate in blood and the CSF, plasma very long chain fatty acids, serum anti-glutamic acid decarboxylase antibody (GAD Ab), and neopterin and biopterin in the serum, urine, and CSF. No specific condition was indicated. No intrauterine infection was implied, and he had a normal karyotype (46, XY). No mutation was detected in the GAD67 gene, encoding glutamic acid decarboxylase, which is responsible for gamma-amino-butyric acid (GABA) synthesis, or in the GLRA1 gene, encoding the glycine receptor alpha 1 subunit, which is implicated in

Fig. 2. EMG recorded during characteristic clonic movements reveal synchronous contraction of the systemic muscles.
Simultaneous contraction of agonistic and antagonistic muscles indicate that this movements are myoclonus.
Timescale: 1 s/div., vertical scale: 100 μV.
Fig. 3. MRI focusing on the pons. A-C: T1-weighted images, evaluated at 21 hrs, 1 month and 6 months of age, respectively, D-F: T2-weighted images, evaluated at 21 hrs, 1 month and 6 months of age, respectively.
A-C: In T1-weighted images, MRI at 21 hrs of age shows a high-intensity lesion in the dorsal pons (A), but this signal abnormality improved by 1 month (B). MRI at 6 months shows no obvious abnormal signal region (C) but reveals atrophic changes.
D-F: The T2-weighted images at both 21 hrs and 1 month of age show hypointensity in the dorsal pons. MRI at 6 months showed a small, high-intensity area in the dorsal pons (D, E), suggesting necrosis or gliosis, as a result of brain insult (F).

Fig. 4. MRI focusing on the medulla. A-C: T1-weighted images, evaluated at 21 hrs, 1 month and 6 months of age, respectively, D-F: T2-weighted images, evaluated at 21 hrs, 1 month and 6 months of age, respectively.
A-C: In T1-weighted images, MRI at 21 hrs of age shows a high-intensity lesion in the medulla (A), but this abnormal signal improved by 1 month of age (B). MRI at 6 months shows no obvious abnormal signal (C), but atrophic change is evident.
D-F: In T2-weighted images at both 21 hrs and 1 month of age, there is hypointensity in the medulla (D, E). MRI at 6 months shows no obvious signal change, but atrophy is evident (F).
the major type of hereditary hyperekplexia (Bakker et al. 2006) characterized by an exaggerated normal startle response. The CSF levels of homovanillic acid (HVA), 5-hydroxy-indoleacetic acid (5-HIAA), and GABA were 54.0 ng/ml, 29.2 ng/ml, and 17.0 pmol/ml, respectively, which were very low compared with the respective normal values (mean ± s.d.) for near-age subjects: 173 ± 28.5 ng/ml, 95.2 ± 18.2 ng/ml, and 98 ± 40 pmol/ml (Langlais et al. 1985; Goldsmith et al. 1987). Repeated examinations of the auditory brain stem response (ABR) and short-latency somatosensory evoked potential (SSEP) were not reproducible.

T1-weighted images evaluated at 1 month showed improvement in the abnormal intensity in the brainstem and medulla (Fig. 3B, 4B), compared with that at 21 hrs of age. The T2-weighted images at 1 month showed hypointensity in the pons and medulla, as the first MRI did. At 6 months of age, the images revealed a new lesion, a small high-intensity region in the dorsal pons, where the first MRI had shown an abnormal high-intensity area in T1-weighted images (Fig. 3F). This lesion could have been the result of prenatal brain damage. T1-weighted images at 6 months showed no abnormal intensity (Fig. 3C) but the atrophic change had become clearer.

For treatment, diazepam seemed to be more effective at decreasing the spasticity than any other medication used, including dantrolene sodium, phenobarbital, and valproic acid. However, it resulted in little improvement, and we judged its efficacy to be limited. The exaggerated clonic movements improved gradually over time and disappeared at 1 year of age, although his lower extremities had residual spasticity and little spontaneous movement. He had severe psychomotor developmental delay, without head control, social smiling, or vocalization. He was unexpectedly found dead in his home in the morning at 1 year and 3 months of age. No autopsy was performed.

**DISCUSSION**

This baby showed spasticity and irritability and presented with generalized clonic movement that could be elicited by a light touch anywhere on his body within 1 hr of birth. Generally, babies suffering from perinatal injury are initially flaccid, and they become irritable and hypertonic after 12 to 48 hrs (Brown et al. 1974). There are few reports on a newborn with spasticity at birth (Eicke et al. 1992), in which spasticity at birth implies the existence of antenatal brain insult. Therefore, the spasticity appearing at birth is evidence that the insult to the fetus must have occurred before delivery. Although the cause of the presumed prenatal hypoxic insult was not apparent in our case, hypoxic brain insult could occur as a result of a subtle event, such as fetal bradycardia, which could be hard to detect in some cases (Okumura et al. 2000). In our case, an insult in the Rolandic area was involved bilaterally, which would not affect a baby up to 34 weeks of gestational age, even on suffering a hypoxic insult (Barkovich 2000). Therefore, although there were no recognizable antenatal events, the lesions that were clearly detected on MRI at 21 hrs of age are likely the result of a brain insult that occurred during the week before birth. Perhaps the baby was flaccid during the first 43 min as a consequence of the maternal general anesthesia and transfer of muscular relaxant via the placenta.

Electromyography showing exaggerated, synchronized rhythmic myoclonic contraction of all extremities, which was easily elicited by sensory stimulation, was more compatible with BRRM (Brown et al. 1991; Rothwell 1996; Hallett 2002) than with other types of myoclonus, including that of cortical or spinal origin, although additional electrophysiological data were not available. The possibility of hyperekplexia was ruled out by examining GLRA1 gene mutation. Surprisingly, the only the initial MRI taken at 21 hrs of age showed remarkable lesional changes in the pons and medulla, which are the center of the BRRM. There are no reports of neonatal BRRM due to a prenatal brain insult. The patient’s BRRM was prominent soon after birth, became less notable over time, and disappeared at 1 year of age. Temporal changes in the MRI images of our patient were grossly consistent with those of previous reports on perinatal asphyxia without
BRRM. In one report, the lesion showed high-intensity changes in T1-weighted images in the acute phase, which appeared as early as 3 days, and this abnormal signal diminished within a few months, whereas the T2-weighted images revealed necrotic or gliotic lesions as high-intensity regions several months after the brain insult (Barkovich 2000). Low levels of CSF neurotransmitters, not only GABA but also HVA and 5-HIAA, were observed in our patient. As GABAergic neurons are very vulnerable to hypoxic-ischemic insult (Romijn et al. 1992) and as it has been reported that hypoxia could cause a decrease in CSF neurotransmitters, including HVA and 5-HIAA (Gordon et al. 1990), it is reasonable to postulate that a prenatal hypoxic insult in our patient caused the observed global neurotransmitter decrease. GABA is an important inhibitory neurotransmitter in the brainstem, and a patient with no brainstem lesion on MRI and with a low CSF GABA concentration was reported to have shown an exaggerated startle response for which brainstem dysfunction could be responsible (Dubowitz et al. 1992). In our case, however, we cannot be certain that the low CSF GABA concentration was related to the primary cause of BRRM.

Unfortunately, diffusion-weighted images, which are known to be sensitive for cell injury, were not evaluated in our study. Nevertheless, we believe that this is the first study to examine the relationship between the clinical course of neonatal BRRM and temporal imaging changes.

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References


