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FRONTIER

Brainstem tegmental lesions in neonates with hypoxic-ischemic encephalopathy: Magnetic resonance diagnosis and clinical outcome

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Abstract

Lesions of the brainstem have been reported in the clinical scenarios of hypoxic-ischemic encephalopathy (HIE), although the prevalence of these lesions is probably underestimated. Neuropathologic studies have demonstrated brainstem involvement in severely asphyxiated infants as an indicator of poor outcome. Among survivors to HIE, the most frequent clinical complaints that may be predicted by brainstem lesions include feeding problems, speech, language and communication problems and visual impairments. Clinical series, including vascular and metabolic etiologies, have found selective involvement of the brainstem with the demonstration of symmetric bilateral columnar lesions of the tegmentum. The role of brainstem lesions in HIE is currently a matter of debate, especially when tegmental lesions are present in the absence of supratentorial lesions. Differential diagnosis of tegmental lesions in neonates and infants include congenital metabolic syndromes and drug-related processes. Brainstem injury with the presence of supratentorial lesions is a predictor of poor outcome and high rates of mortality and morbidity. Further investigation will be conducted to identify specific sites of the brainstem that are vulnerable to hypoxic-ischemic and toxic-metabolic insults.

Key words: Magnetic resonance; Asphyxia; Hypoxic-ischemic encephalopathy; Tegmentum; Neonates; Brainstem

Core tip: Brainstem tegmental lesions in neonates with hypoxico-ischemic encephalopathy: Magnetic resonance diagnosis and clinical outcome.

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HYPOXIC-ISCHEMIC ENCEPHALOPATHY IN NEONATES

Neonatal hypoxic-ischemic encephalopathy (HIE) is a pathological pattern secondary to perinatal events that reduce blood flow in the brain of neonates[1]. Most cases of encephalopathy in neonates born at term are related to HIE that occurs *in utero* or during the delivery from different intrapartum conditions[2]. Despite strategies of therapeutic hypothermia such as the whole body cooling have been adopted as a standard treatment for HIE and data from the TOBY (Total Body Hypothermia for Neonatal Encephalopathy) trial have demonstrated its efficacy in improving neurologic outcomes at 18 mo and at 6-7 years of age[3,4], HIE is still an important cause of early mortality or morbidity and adverse neurodevelopmental outcome in children[1].

In pre-term or very low birthweight neonates, periventricular leukomalacia is observed in at least 50% of the cases[2]. In infants born at 32 gestation weeks and above, neonatal and perinatal strokes are expected in about 1 in 4000 live births[5] and encephalopathy is expected in up to 2 per 1000 term live births[6].

Brain magnetic resonance (MR) is able to discriminate normal from pathological patterns in the neonatal brain[7]. Three typical MR imaging patterns have been recognized in neonates with HIE: (1) "watershed", involving the cerebral cortex and subcortical white matter especially in the posterior lobes, following a mild to moderate hypotension or a partial hypoxia with prolonged duration; (2) "basal ganglia-thalamus", following an acute short-duration severe hypoxic or profound hypotensive event; and (3) "total brain injury", involving supra- and infra-tentorial areas following a prolonged and severe hypoxic or hypotensive event[8]. While peripheral and basal ganglia-thalamus patterns involve supra-tentorial structures exclusively, the total brain injury shows diffuse supra-tentorial involvement that may be associated with damage of the dorsal brainstem and/or the entire cerebral cortex[8,9].

Involvement of the brainstem in HIE and MR diagnosis

Lesions of the brainstem have been reported at MR imaging in the clinical scenarios of HIE[10-15], although the prevalence of these lesions is probably underestimated due to the small size of the brainstem, to the need of dedicated MR protocols under sedation in neonates and, probably, to the "satisfaction of search" effect when diffuse supra-tentorial lesions are present in the condition of total brain injury[16,17].

Neuropathologic studies have demonstrated brainstem involvement in severely asphyxiated infants as an indicator of poor outcome[18-20]. Leech *et al*[20] reported brainstem injury in 93% of asphyxiated infants, especially after prolonged insults. Several gray matter nuclei were involved including the substantia nigra, inferior colliculi, inferior olives, the nuclei of cranial nerves Ⅲ, Ⅳ and Ⅵ, the superior olive, the vestibular nuclei, and the nuclei of the solitary tract, gracile tracts, cuneate tracts and reticular formation[20]. A neuropathologic study in autoptic cases of patients with various developmental disorders including HIE and congenital metabolic errors highlighted the involvement of the central tegmental tract (CTT)[21]. CTT is located between the medio-central tegmentum of the pons and dorsomedial part of the medulla oblongata and has been reported to be included in the dentato-rubro-olivary system, also called Guillain–Mollaret triangle, whose lesions are associated with the inferior olivary nucleus hypertrophic degeneration[22].

The physiopathological mechanisms underlying HIE-related brainstem alterations are currently unknown and debated. From a topographical point of view, selective vulnerability of the tegmentum, territorial vascularization, haemodynamic compensatory mechanisms under hypoxia, metabolic and biochemical mechanisms have been advocated. In fact: (1) the tegmentum of the brainstem represents the watershed area of the vertebro-basilar vascularization between the terminal territories of the paramedian and circumferential branches[15,23] (Figure 1); (2) the dorsal brainstem has higher metabolic demands than the ventral one and could be selectively damaged under hypoxic-ischemic conditions[24]; and (3) experimental studies in mammals have shown that blood flow of the brainstem increases after acute hypoxia[25], as opposed to a blood flow reduction in the cerebrum, suggesting a relative protection of the brainstem fetal circulation. In summary, neuropathologic studies in humans and experimental studies lead to consider the brainstem a less vulnerable site to HIE, with the tegmentum being considered at risk only in the context of severe total brain injury[26].

More recent clinical series[14,15,27-29] have reported on neonates with less severe birth asphyxia than previous neuropathology reports and found selective involvement of the brainstem with the demonstration of symmetric columnar bilateral lesions of the brainstem tegmentum, even in the absence of supratentorial lesions in some cases. In neonates with isolated injury of the brainstem tegmentum, MR imaging shows faint hyperintense signal on T2 weighted images that is associated with the clinical pattern of the so-called "dorsal brainstem syndrome". Bilateral and symmetric lesions of the tegmentum are found that involve the dorsal para-central portions on axial planes and the medulla oblongata and caudal pons cranio-caudally, with sparing of the rostral pons and midbrain (Figure 2). As it has been speculated, these brainstem sites are supplied by branches of the vertebro-basilar artery with less flow compensation from the anterior circulation, as compared with the midbrain; also fetal risk factors may

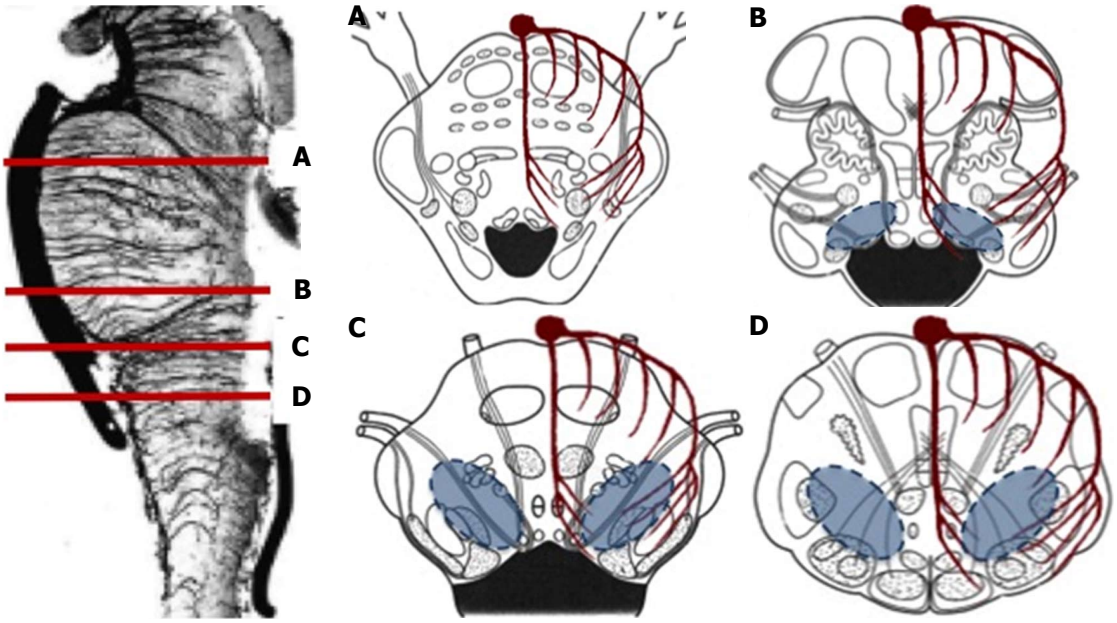

Figure 1 Schematic diagram of the brainstem vasculature. A: Rostral pons; B: Caudal pons; C: Rostral medulla oblongata; D: Caudal medulla oblongata. Basilar artery, the terminal paramedian, short circumferential and long circumferential arteries are depicted. Blue shaded areas represent the tegmental watershed areas that are most frequently affected in neonates and infants with dorsal brainstem syndrome and a history of hypoxic-ischemic encephalopathy.

exist and confer vulnerability to the brainstem, even after not prolonged periods of hypoxia/hypotension[24], such as polyhydramnios or oligoidramnios[15,29]. Moreover, unknown genetic susceptibility could be taken into consideration.

Differential diagnosis for this MR pattern includes the columnar-shaped bilateral and symmetric T2 hyperintense signal of the central tegmental tracts that have been reported in various developmental disorders[21,30-32], metabolic diseases including non-ketotic hyperglycinemia[33], mitochondrial diseases[34], perinatal asphyxia[27], during vigabatrin treatment, and even in control children younger than 25 mo of age[35], with a prevalence of about 5% in children ranging between 1 and 6 years of age[36]. A physiological maturation process that may be influenced by different genetic, metabolic or toxic factors has been proposed to explain its presence in both control and diseased children[35]. These lesions usually show net margins on T2 weighted images, involve the dorsal para-central portions on axial planes and the pons and midbrain in a preferential manner (Figure 3).

In summary, the discrepancy between neuropathology reports, experimental studies in animals and clinical observations has generated a debate on the role of brainstem lesions in HIE. In fact, the severity of hypoxic-ischemic injury is an important issue to consider when interpreting results from autopsy studies and comparing them to clinical studies that are conducted on neonates who survived to HIE; also, the pathologic conditions and related events that lead to HIE in neonates are complex and very difficult to replicate in the experimental design of animal studies. Nevertheless, neonates with HIE and isolated brainstem lesions (in the absence of detectable supratentorial injury) suggest that a "brainstem watershed pattern" of brain HIE-related injury might exist, although rare in prevalence[15].

Clinico-radiological correlation and outcome

Tegmental lesions of the brainstem involve several structures that are crucial for vital functions: The tegmentum of the medulla oblongata includes the XII nerve nucleus, dorsal nucleus of the X cranial nerve, nucleus ambiguus, gracile nucleus of Goll, cuneate nucleus of Burdach, spinal nucleus of the trigeminal nerve, reticular formation, solitary tract and the pre-Botzinger complex, crucial for the stereotyped sequence of feeding and respiration[37]; the tegmentum of the pons includes the VII and VI cranial nerve nucleus, spinal nucleus, main sensory nucleus and mesencephalic nucleus of the V cranial nerve and reticular formation; the tegmentum of the midbrain includes the central nucleus of the inferior colliculus, the III and IV cranial nerve nucleus, the mesencephalic nucleus of the V cranial nerve, locus coeruleus, and reticular formation.

In the clinical scenario of total asphyxia the involvement of the brainstem in neonates has been associated with oculomotor disturbances, bilateral facial nerve palsy, ventilatory disturbances, and impaired sucking and swallowing[8,15]. These patients also show hypotonia, spastic tetraplegia, seizures, and psychomotor delay in different combinations and carry a high risk of postnatal mortality[15]. Association studies do not demonstrate causality, especially in the case of respiratory and swallowing alterations that are finely modulated by the functional and structural connectivity between the brainstem, suprabulbar cortex and basal ganglia. Nevertheless, the central pattern generators of these functions are located in the brainstem[37] and their damage needs to be considered in neonates and infants with HIE.

A preferential involvement of the brainstem with

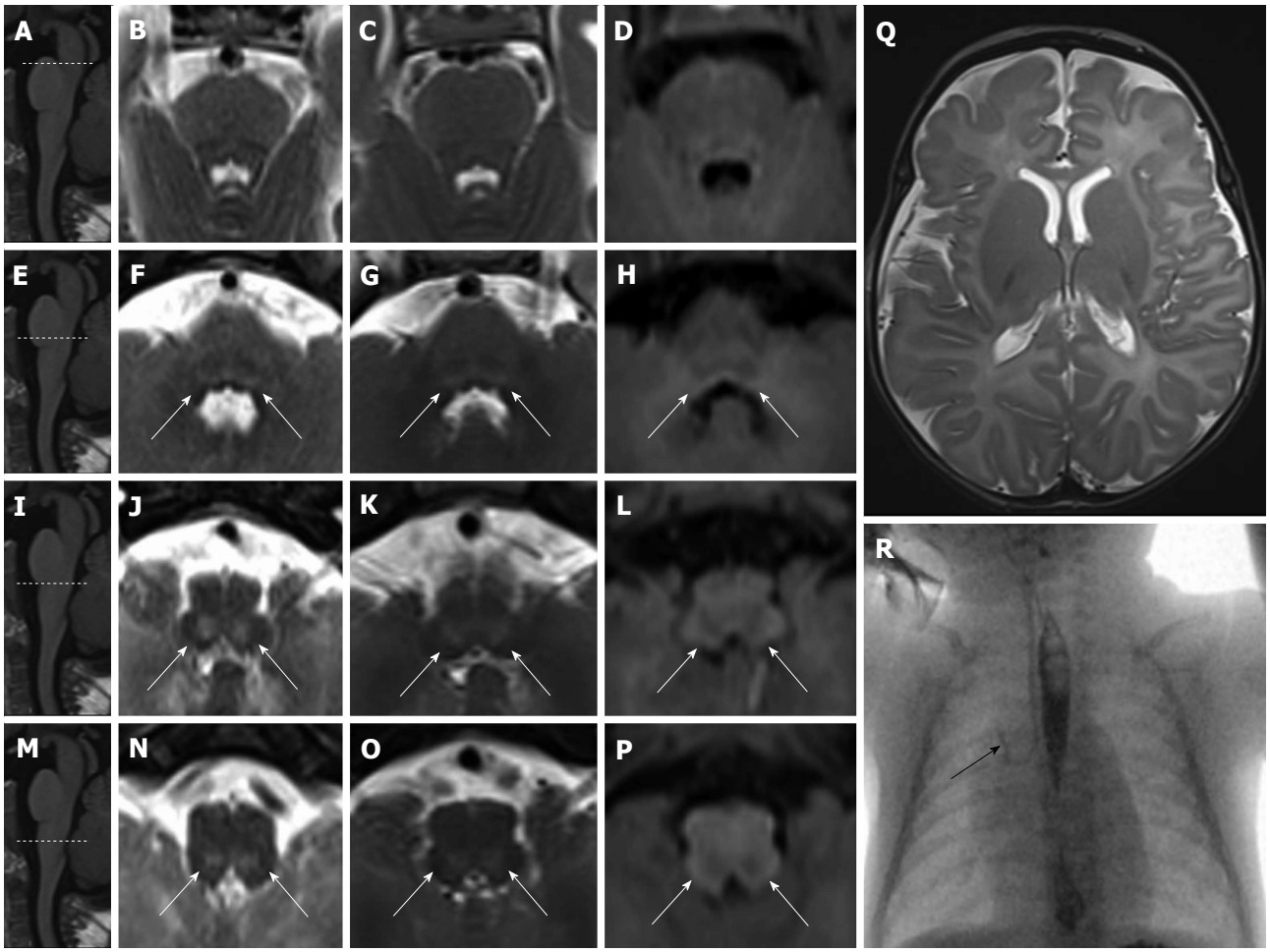

Figure 2 Brainstem tegmental lesions and oral motor dysfunction. An infant with perinatal asphyxia due to knotting of umbilical cord around the neck is shown. Apgar score at five minutes after birth. Eighteen days after birth (panels B, F, J and N), MR images show faint T2 hyperintense (white arrows in F, J, and N) bilateral and symmetric tegmental lesions of the caudal pons and medulla oblongata. Forty days after birth (panels C, D, G, H, K, L, O and P), MR images confirm T2 hyperintense (white arrows in G, K, and O) and T1 hypointense (white arrows in H, L, and P) bilateral and symmetric tegmental lesions of the caudal pons and medulla oblongata. No signal alterations are detected at the level of the cranial pons (B-D) and at supratentorial level (Q). At 1 mo, an upper GI tract X-ray showed iodinated contrast (Iopamidol, IOPAMIRO 300) inhalation (black arrow in panel R points to the right bronchus). Gastrostomy was performed. At the age of 2 years, psychomotor delay and dysphagia are present. Sagittal views of the brainstem (panels A, E, I and M) are used for reference of axial images. MR: Magnetic resonance.

specific involvement of the facial and abducens nuclei has been known as Möbius syndrome. A spectrum of symptoms caused by lesions located rostral and caudal to these nuclei may be associated with other oculomotor nerve nuclei and with dysphagia-gastroesophageal reflux complex[15,29]. Heterogeneity of clinical presentation, outcome[38] and genetic loci involved in Möbius syndrome[39,40] led to propose a syndromic spectrum that may also include the rarely reported cases of neonates with a history of HIE or perinatal sentinel events of HIE[41], who present tegmental lesions without supratentorial involvement at MR imaging[15,29]. A recent systematic review conducted on the literature published between 1980 and 2011 has shown that there is currently limited evidence on the relationship of early sucking and swallowing problems in neonatal brain injury with patterns of neonatal brain injury[42]. Early sucking and swallowing problems were reported to be present in 35% to 48% of infants with different types of neonatal brain injury. However, data from the few available relevant studies were shown to be heterogeneous in terms of the research design, levels of evidence (levels Ⅱ, Ⅲ and Ⅳ), infant populations described, and assessment measures used[42].

When lesions in the brainstem are diagnosed with basal ganglia-thalamus and/or cortex lesions, the outcome is often dismal and brainstem injury is the most powerful predictor of death[43,44] in children with HIE, with up to 50% of children dying in the neonatal period or during infancy[45]. Among survivors to HIE, the most frequent clinical complaints that may be predicted by brainstem lesions include feeding problems, speech, language and communication problems and visual impairments. Prediction of these symptoms is crucial to appropriately plan the short and long term care of an infant who has suffered with HIE and counsel the parents for a better neurocognitive development and outcome[44].

Feeding problems can range from some difficulties with swallowing solids or liquids to being unable to

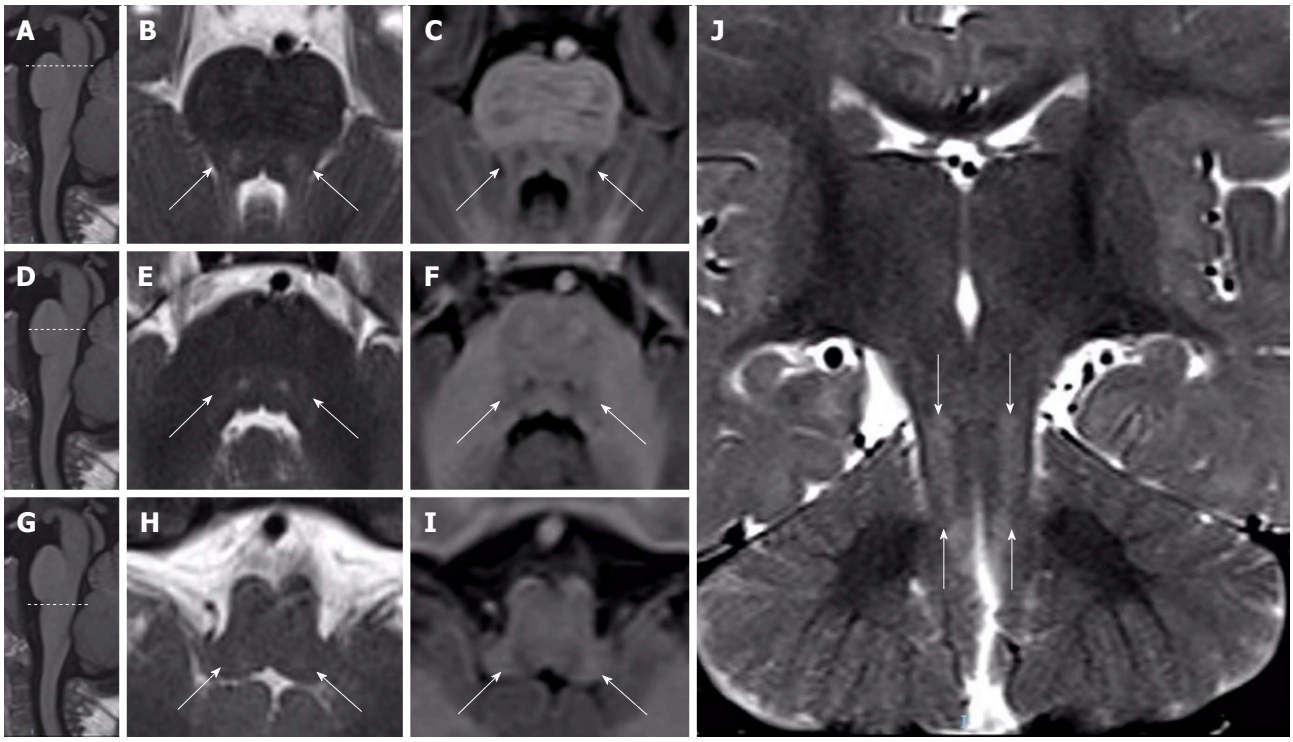

Figure 3 Brainstem tegmental lesions of the central tegmental tracts. A 1-year-old infant shows generalized hypotonia, macrocephaly and psycho-motor developmental delay, without a history of hypoxic-ischemic encephalopathy or adverse perinatal events. A genetic syndrome is suspected and is currently not known. MR images show isolated T2 hyperintense (white arrows in B, E, and H) and T1 hypointense (white arrows in C, F, and I) bilateral and symmetric tegmental lesions of the pons and caudal midbrain. Faint T2 hyperintense signal is observed at the rostral medulla oblongata. Columnar shape of alterations is demonstrated in coronal T2 weighted images (J). No signal alterations are detected at the supratentorial level (J). Sagittal views of the brainstem (A, D, and G) are used for reference of axial images. MR: Magnetic resonance.

feed orally with the need for long-term gavage feeding. When gavage feeding is necessary, almost all neonates show involvement of the brainstem[15,45]. Logistic regression analyses have shown that only the severity of basal ganglia-thalamus and mesencephalic injury are independently associated with feeding impairment and that only the severity of basal ganglia-thalamus injury and pontine involvement are independently associated with gastrostomy insertion[45].

These data show that assessment of the brainstem on neonatal MRI may provide important prognostic information about the severity of feeding impairments in survivors to neonatal HIE.

Despite their impact on children quality of life and prevention of malnutrition and other complications, gavage feeding and gastrostomy are procedures that are not easily accepted by parents. Thus, early identification of infants likely to need these procedures, allows early implementation of strategies in the care of children and their families[45].

Future perspectives

The current knowledge on the so-called "dorsal brainstem syndrome" is limited, mainly due to the relative low frequency of isolated brainstem involvement in neonates with HIE, which remains an exceptional event. However, timing of scans, high quality neonatal MRI and radiologist awareness are necessary pre-requisites to identify brainstem lesions. Also the wide range of differential diagnoses for T2 hyperintense tegmental lesions requires careful analysis of images and often second opinion for a correct interpretation. Prospective multicenter studies should be designed to conduct analyses on larger and homogeneous populations of neonates and infants. Such studies will help to identify vulnerable children carrying susceptibility genes, to find mechanisms of early vulnerability of the brainstem to hypoxic-ischemic damage and to predict motor and/or neurocognitive outcomes.

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