Prenatal Brainstem Disruptions: Small Lesions–Big Problems

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Introduction

Congenital posterior fossa anomalies include malformations and disruptions that result from inherited (genetic) and acquired (disruptive) causes, respectively. A malformation is defined as a morphological defect of an organ, part of an organ, or a larger region of the body resulting from an intrinsically abnormal developmental process. A disruption is defined as a morphological defect of an organ, part of an organ, or a larger region of the body resulting from an extrinsic breakdown of, or an interference with, an originally normal developmental process. In the literature, the adjectives “disruptive,” “destructive,” and “encephaloclastic” are often used as equivalent. An accurate diagnosis of congenital posterior fossa anomalies including the differentiation between malformations and disruptions is important to determine the inheritance pattern and risk of recurrence and to counsel the affected child and his/her family about the long-term neurologic and neurodevelopmental outcome.

Abstract

Prenatal disruptive injuries within one or both cerebellar hemispheres, which are mostly caused by hemorrhages, are well known. Primary disruptive lesions of the brainstem, however, are exceptional. Here we report on clinical and neuroimaging findings, as well as outcome of four male infants with prenatal brainstem disruptions that have been seen between 2005 and 2015. Two infants with extensive brainstem defects (from the midbrain to the medulla) had respiratory insufficiency and died at the age of 12 weeks and 22 months, respectively. Two patients had smaller, unilateral/asymmetrical lesions in the pontomesencephalic and medullary regions, respectively, and presented with permanent multiple cranial nerve deficits and long tract signs. Recognition of prenatal brainstem disruptions and distinction from malformations are essential for the management and the estimation of a recurrence risk.

Keywords

► brainstem
► disruption
► prenatal
► neuroimaging
► children

This article is dedicated to the memory of Dr. Andrea Poretti who died unexpectedly following submission of this manuscript.
Disruptions can be caused by different pathomechanisms including vascular events (ischemic or hemorrhagic), infections, teratogens, and mechanical forces. Disruptions are acquired lesions, but in rare cases, a genetic predisposition to disruptive lesions may be present, such as a microangiopathy due to COL4A1 mutations or congenital amegakaryocytic thrombocytopenia. Disruptions affecting the developing brain are rather common findings in pediatric neurology. The supratentorial brain (cerebrum) is particularly susceptible to hemorrhagic and/or ischemic injuries. The vast majority of hemiplegic cerebral palsies are caused by disruptive lesions affecting one cerebral hemisphere. Hydranencephaly, hemihydranencephaly, and schizencephaly are also caused by prenatal disruptive lesions involving one or both cerebral hemispheres. The spectrum of infratentorial disruptions is wide and includes some forms of cerebellar agenesis, unilateral cerebellar hypoplasia, some forms of global cerebellar hypoplasia, cerebellar clefts, forms of unilateral dysplasia with cysts, and vanishing cerebellum in Chiari II malformation. The vast majority of infratentorial disruptions primarily involve the cerebellum, whereas disruptions affecting primarily the brainstem are very rare. We are not aware of publications focusing on this topic. In this article, we report on clinical and neuroimaging findings and neurologic, as well as neurodevelopmental outcome in four children with a prenatal brainstem disruption and discuss possible pathomechanisms.

Patients and Methods

This retrospective study did not require approval by the Institutional Review Board.

Patients

The patients included in this study were collected by the first author in collaboration with other colleagues who contributed cases. The patients presented at our institutions between 2005 and 2015. Review of the clinical histories and clinical–neurologic follow-up examinations provided detailed information about clinical features.

Qualitative Neuroimaging Analysis

In a retrospective analysis, two pediatric neurologists with experience in neuroimaging of the pediatric posterior fossa (E. B. and A. P.) qualitatively analyzed all available neuroimaging datasets for morphological abnormalities of the brainstem, such as location and laterality of the tissue defect. In addition, the cerebellum and other brain structures have been also assessed for morphological and signal abnormalities. All magnetic resonance imaging (MRI) data have been acquired for clinical indication, and the local departmental imaging protocols have been used.

Results

Four male children with prenatal brainstem disruptions were included in this study. All patients presented within the first 2 months of life, and three had their first symptoms at birth. Two patients died at 12 weeks and 22 months of age, respectively. The relevant clinical information is summarized in Table 1. There was no family history of a coagulation disorder and no evidence for substance/teratogen abuse during pregnancy. The ages of the mothers were 38, 39, 32, and 34 years, respectively. Patients 2 and 4 had two older healthy siblings. The neuroimaging evaluation was mostly based on conventional MRI sequences. The neuroimaging findings are summarized in Table 1, and for each patient, a figure is provided, with focus on brainstem findings (Figs. 1–4). Susceptibility-weighted imaging (SWI), a gradient-echo technique that is highly sensitive to blood and blood products, was not available for the evaluation of all patients. The first patient presented in 2005, when SWI was not yet used for clinical applications. For patients 2 and 3, SWI sequences have not been acquired. For patients 2 to 4, MRI follow-up studies have been acquired at the age of 32 months, 12 months, and 8 weeks, respectively, and showed stable findings. Additional detailed information about the patients is provided in the following.

Patient 1 did not make any developmental progress. He never responded to light or faces. He had repeated myoclonic seizures. The EEG showed repeatedly multifocal poly-sharp waves, but there was no EEG correlate for myoclonic jerks. He had problems with temperature regulation and had several episodes of hyperthermia (body temperature above 38°C) without any evidence of infection. Brain MRI has not been repeated due to lack of therapeutic consequences. At the age of 22 months, he died suddenly for unknown reasons. Autopsy was not performed.

Patient 2 presented at the age of 2 months for developmental delay that was noted by his mother. Neurologic examination revealed a unilateral facial nerve palsy and a complex ocular motility disorder. Swallowing function was moderately impaired most likely because of enoral hypersensitivity. Later, he was diagnosed with left-sided spastic–ataxic cerebral palsy. Despite intense support including physical, occupational, and speech therapy, his cognitive and language development remained moderately delayed. A follow-up brain MRI at the age of 32 months revealed stable findings, with the brainstem asymmetry being more obvious (Fig. 2).

Patient 3 came to attention as a neonate because of marked stridor due to vocal cord paralysis and absent swallowing requiring nasogastric tube feeding and later a percutaneous endoscopic gastrostomy and tracheostomy due to ongoing aspirations. Neonatal neurologic examination showed multiple cranial nerve deficits causing hypotrophy of the left sternocleidomastoid muscle and left–sided atrophy of the tongue. On follow-up, he achieved several developmental milestones: he started to walk with assistance at approximately 24 months of age, and at 30 months of age, his verbal comprehension appeared to be age appropriate and he communicated with gestures. Brain MRI (Fig. 3) showed a marked asymmetry at the level of the medulla oblongata and a prominent arterial vessel whose significance remained unknown (causally related versus normal variant in the territory of the posterior inferior cerebellar artery).
Table 1 Clinical and neuroimaging findings in four children with brainstem disruption

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Pregnancy (age of the mothers)</td>
<td>Uneventful (38 y)</td>
<td>Uneventful (39 y)</td>
<td>Polyhydramnios (32 y)</td>
<td>Polyhydramnios (34 y)</td>
</tr>
<tr>
<td>Delivery</td>
<td>Spontaneous</td>
<td>C-section mat</td>
<td>C-section mat</td>
<td>C-section mat</td>
</tr>
<tr>
<td>Gestational age at birth</td>
<td>35 wk</td>
<td>Term</td>
<td>37 wk</td>
<td>Term</td>
</tr>
<tr>
<td>Age at first symptom(s)</td>
<td>At birth</td>
<td>6–8 wk</td>
<td>At birth</td>
<td>At birth</td>
</tr>
<tr>
<td>First symptom(s)</td>
<td>No respiration, floppy, seizures</td>
<td>Developmental delay</td>
<td>Stridor, impaired swallowing</td>
<td>No respiration, no swallowing, no mimic</td>
</tr>
<tr>
<td>First MRI (age)</td>
<td>9 d</td>
<td>5 mo</td>
<td>20 d</td>
<td>1 d</td>
</tr>
<tr>
<td>MRI findings brainstem</td>
<td>Large defect</td>
<td>Unilateral defect right pontomesencephalic</td>
<td>Asymmetrical defect medulla oblongata</td>
<td>Large defect</td>
</tr>
<tr>
<td>MRI findings supratentorial</td>
<td>Normal</td>
<td>Normal</td>
<td>Small hemorrhage left medial temporal</td>
<td>Normal</td>
</tr>
<tr>
<td>MRI follow-up</td>
<td>Not done</td>
<td>32 mo, findings stable</td>
<td>19 mo, findings stable</td>
<td>8 wk, findings stable</td>
</tr>
<tr>
<td>Clinical deficits</td>
<td>Absent</td>
<td>Mild difficulties</td>
<td>Severely impaired</td>
<td>Absent</td>
</tr>
<tr>
<td>Swallowing</td>
<td>No mimic no fixation, convergent squint</td>
<td>VII left palsy, complex strabismus</td>
<td>VII–XII left palsy</td>
<td>III, V, VII palsy</td>
</tr>
<tr>
<td>Cranial nerve deficits</td>
<td>Poor spontaneous</td>
<td>Left spastic hemiparesis</td>
<td>Right spastic hemiparesis</td>
<td>Poor spontaneous</td>
</tr>
<tr>
<td>Movements</td>
<td>Ventilated 4 wk, PEG</td>
<td>None</td>
<td>PEG, jejunal tube, tracheostomy</td>
<td>Ventilated (no respiratory drive)</td>
</tr>
<tr>
<td>Interventions</td>
<td>Died at the age of 22 mo</td>
<td>Mild motor, speech and cognitive delay</td>
<td>Motor and speech delay</td>
<td>Died at the age of 12 wk</td>
</tr>
</tbody>
</table>

Abbreviations: C-section mat, cesarean section for maternal indication; MRI, magnetic resonance imaging PEG, percutaneous endoscopic gastrostomy.

Fig. 1 Brain magnetic resonance (MR) images of patient 1 at the age of 9 days. (A) Midsagittal T1-weighted and (B,C) axial T2-weighted images show a large irregular defect extending from the lower midbrain to the medulla (arrow in A). At the level of the pons, a large dorsal defect is noted that also affects the middle cerebellar peduncles (arrows in B) and the cerebellum. At the level of the lower midbrain, the brainstem defect is asymmetric and affects the left more than the right side, as shown by absence of the left superior cerebellar peduncle (arrow in C).
arteriovenous malformation was noted. In addition, sequela of a small bleeding of unknown origin (no suggestions of a vascular malformation) was seen within the left medial temporal lobe (Fig. 3D). Follow-up brain MRI at 19 months of age showed stable findings, with the exception of a more prominent left-sided medullary atrophy. The sequela of the hemorrhagic lesion within the left medial temporal lobe was faintly visible (data not shown).

Patient 4 presented as a newborn with respiratory insufficiency and absent swallowing requiring neonatal inten-
neuroimaging in this patient is clearly different from brainstem disconnection. In brainstem disconnection, there is nearly complete absence of a brainstem segment, and only thin strands of tissue connect the upper and lower segment. Cerebellar hypoplasia is a consistent associated finding, not present in this boy.

**Discussion**

We report on four children with prenatal brainstem disruption and discuss (1) aspects that favor a disruptive lesion, (2) the possible timing of injury, (3) the potential pathomechanism, and (4) correlations between neuroimaging and clinical findings.

In all patients, the neuroimaging findings are characterized by a focal tissue defect within the brainstem. In two patients (patients 2 and 3), the brainstem tissue defect involves only one side of the brainstem and resembles unilateral cerebellar clefts, a form of prenatal cerebellar disruption.\(^1\) In patient 1, the lesion is large, irregular, and partially asymmetric, involving only the right superior cerebellar peduncle. In patient 4, multiple membranes are seen anterior and lateral to the brainstem and represent most likely residual changes following tissue destruction. In addition, the overall neuroimaging pattern observed in our patients is very different from those reported in defined brainstem malformations, in particular pontine tegmental cap dysplasia,\(^15,16\) horizontal gaze palsy, and progressive scoliosis due to pathogenic variants in the *ROBO3* gene,\(^17\) diencephalic–mesencephalic junction dysplasia,\(^18\) tubulino-pathies with brainstem involvement,\(^19\) and brainstem disconnection.\(^20,21\)

It is not possible to exactly date the destructive event, but we think that there is compelling support for a prenatal injury: patients 1, 3, and 4 were symptomatic immediately after birth, polyhydramnios in patients 3 and 4 is most likely caused by prenatal swallowing impairment secondary to dysfunction of the fetal brainstem, and neuroimaging studies showed abnormal findings on day 1 (patient 4), day 9 (patient 1), and day 20 (patient 3) of life.

Considering the focal and asymmetric/unilateral lesions in patients 2 and 3, we think that a vascular injury is the most likely pathomechanism of brainstem disruption in our patients. The neuroimaging pattern and the clinical presentation would be very unusual for a prenatal infection.\(^22–24\) The lack of positive history and facial dysmorphic features, as well as the asymmetry of neuroimaging findings do not favor a teratogenic effect.\(^25,26\) Boix et al reported on a male neonate who was born at term from a cocaine-addicted mother and presented with absence of spontaneous breathing requiring intubation, generalized hypotonia, facial diplegia, ophthalmoplegia, micrognathia, and temporomandibular ankyloses.\(^27\) The brain MRI of this newborn showed an abnormally concave configuration of the dorsal pons and upper medulla that resembled the neuroimaging findings of patient 1 in our series. The abnormal dorsal brainstem configuration in our patient 1, however, is asymmetric, whereas it is symmetric in the patient reported by Boix et al. Disruptions caused by microangiopathy due to *COL4A1* pathogenic variants are usually multifocal and often involve the cerebral and cerebellar hemispheres.\(^3,5\) We are not aware of reports on brainstem involvement in children with *COL4A1* pathogenic variants. It remains speculative whether the vascular injury is ischemic or hemorrhagic in nature. The lack of hemosiderin deposition within the brainstem does not exclude the possibility of a hemorrhage. In preterm infants with proven cerebellar hemorrhage, hemosiderin is usually no longer detected from 4 to 6 weeks after its occurrence.\(^10,11\) This is probably due to the high permeability of the blood–brain barrier to the hemosiderin-loaded macrophages. In analogy to the higher prevalence of prenatal hemorrhagic compared with ischemic cerebellar lesions, we favor hemorrhages as the most likely cause of brainstem disruptions.\(^11,28,29\)

The clinical findings of our patients are well explained by brainstem dysfunction due to the brainstem defects shown...
by neuroimaging. Small, rather well-circumscribed, unilateral/asymmetrical defects in patients 2 and 3 cause cranial nerve deficits and ipsilateral/contralateral long-tract signs. More extensive lesions in patients 1 and 4 result in more severe, global brainstem dysfunction including breathing insufficiency, swallowing impairment, and temperature regulation difficulties, causing death. Thus, relatively small lesions within the brainstem may cause severe problems to the affected children.

This study has several limitations including (1) its retrospective nature, (2) the small number of patients due to the very low prevalence of prenatal brainstem disruptions, (3) unavailability of SWI data in three patients to evaluate with high sensitivity for residual hemosiderin deposition, and (4) absence of postmortem neuropathological investigation in the two children who died (permission not granted by the parents). Nevertheless, we discussed several arguments that favor strongly a disruptive origin, most likely a prenatal hemorrhage, for the brainstem lesions in our patients.

In conclusion, prenatal disruptive lesions are not uncommon in the cerebellum, while seem to be exceptionally rare in the brainstem. Despite the relative small size of the brainstem lesions in our patients, the sequelae including cranial nerve deficits, long-tract involvement, and respiratory insufficiency causing death may be devastating. Recognition of prenatal brainstem disruptions and differentiation from malformations are essential for the management and the estimation of a recurrence risk.

Conflict of Interest
All authors do not report conflicts of interest.

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References