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Preterm birth and disruptive cerebellar development: Assessment of perinatal risk factors

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ABSTRACT

Objective: Abnormal cerebellar development was recently recognized to be related to prematurity. Aim of the present study was to evaluate preterm birth and possible peri- and postnatal risk factors associated with this type of brain injury.

Patients and methods: We report on a series of 35 very low birth weight infants (birth weight 986±257 g S.D.) born between 24 and 32 weeks of gestation (27.0±1.8 weeks of gestation S.D.) sustaining disruption of cerebellar development after preterm birth. Perinatal medical records of study patients were compared to 41 preterm control infants (birth weight 900±358 g S.D., gestational age 26.3±2.1 weeks S.D.) with normal cerebellar development on MRI scan.

Results: A severely compromised postnatal condition with consecutive intubation and catecholamine support was found to be significant risk factor. Additional supratentorial hemorrhagic brain injury followed by posthemorrhagic hydrocephalus, neurosurgical interventions and hemosiderin deposits on the cerebellar surface were significantly related to disruptive cerebellar development. No other differences in perinatal factors were found between the groups.

Conclusion: Premature birth between 24 and 32 gestational weeks associated with poor postnatal conditions and complicated supratentorial hemorrhagic brain lesions represents a high-risk situation for disruption of cerebellar development.

1. Introduction

Increasing survival rates of extreme premature infants are associated with higher rates of prematurity-related brain injuries. Whereas different patterns of supratentorial brain pathologies have been well described earlier,[1,2] cerebellar injuries are receiving more attention recently in this group of patients.[3–10] Magnetic resonance imaging (MRI) studies of

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very low birth weight (VLBW) infants have shown reduced cerebellar volumes at term[3,9] and in later childhood[11] compared to term-born controls. In a group of 67 extremely premature survivors with cerebral palsy undergoing MRI, 45% were found to have cerebellar injury.[4] As most of the severe cerebellar lesions are associated with lesions in the supratentorial regions, functional interactions between the cerebrum and the cerebellum seem reasonable.[9] Duration of mechanical ventilation and presence of patent ductus arteriosus were stated to be associated with reduced cerebellar volume.[3,12] Neurodevelopmental outcome of preterm patients with cerebellar injury was complicated by severe motor impairment[4,10] and cognitive deficits.[13] The impact of preterm birth on the further development of the cerebellum and the neurodevelopment seems to be greater than hitherto expected.

We report a series of 35 VLBW infants, who had a normal cerebellar ultrasound immediately after birth, and developed severe cerebellar volume reduction during the first 12 weeks of life. A morphological classification was subject of our recent report.[14] As these cerebellar changes have been identified as an acquired sequelae and subsequent developmental failure, the term disruptive cerebellar development seems to be appropriate.

The purpose of the current study was to identify risk factors in the perinatal course associated with subsequent disruption of cerebellar development. Therefore, we compared the clinical history of our affected preterm patients to a control group of preterm infants with normal cerebellar development.

2. Patients and methods

In our retrospective analysis, we included 35 VLBW infants with a normal initial cerebellar ultrasound within the first week of life, who subsequently exhibited a disruptive cerebellar development. These 35 patients were born between 1987 and 2005 and cared in three different level III neonatal intensive care units (NICU) in Vienna, Austria.

All patients were investigated both by ultrasound and by MR imaging. All radiologic investigations were performed as part of the clinical routine. Twenty-one patients were diagnosed as having a decreased cerebellar volume in the neonatal period. In 10 patients, the initial diagnosis was made by routine ultrasound and then confirmed by MRI, while in the remaining 11 patients MR imaging led to the diagnosis. Review of all MRI scans obtained in children less than 5 years of age performed in the last 6 years in our institution revealed another 14 patients with comparable infratentorial pathologies, who were also found to be prematurely born. Careful evaluation of the clinical history of these patients showed normal cerebellar ultrasound scans in the first postnatal days and indicated prematurity-related complications as the reason for the MR investigations. In all 35 VLBW infants, metabolic disorders that can mimic cerebellar disruption were ruled out.

Cerebellar abnormalities were defined as a symmetric reduction of the cerebellar hemispheres mainly affecting the vertical dimensions, with a nearly normal transverse diameter (Fig. 1). The cerebellar vermis was smaller than usual with a variable loss of its shape (Fig. 1a and b). Distinctive additional features as an inclined tentorium, a small brainstem and a supratentorial white matter loss were seen in all affected patients (Fig. 1a and b).

Inclusion criteria for the control group were preterm birth prior to week 33 of gestation, and normal cerebellar development on a cerebral MRI examination performed at least 3 months after birth. All ultrasound and MR investigations of the control group were also done for clinical reasons.

Affected preterm patients and the control group of preterm infants were analyzed for the following perinatal risk factors: gestational age, birth weight, gender, APGAR values at 1, 5 and 10 min postpartum, early postnatal intubation (<3 h of life), duration and mode of mechanical ventilation, large patent ductus arteriosus, pre- and postnatal glucocorticoid administration, need for catecholamines, infections, and occurrence of seizures.

Routine cranial ultrasound scans were obtained at the bedside with an Acuson device (Mountainview 128 XP) using a 7.5-MHz sector transducer. In all patients, the initial scans were obtained in the first 2 days of life as part of our clinical routine, and the following scans in short intervals afterwards. MRI scans were performed on a 1.5-T machine with at least T1- and T2-weighted sequences in two section planes with a slice thickness ranging from 3 to 5 mm. All MR investigations in both groups were done for clinical indications. For our study, all MR images were reviewed by one experienced pediatric neuroradiologist blinded to clinical findings. MR evaluation was focused on the following findings: supratentorial lesions including low-grade intraventricular hemorrhage (grades I and II IVH), high-grade IVH (grade III IVH with ventriculomegaly and grade III IVH with periventricular hemorrhagic infarction) and cystic periventricular leukomalacia (PVL grades II, III and IV), and the presence of superficial hemosiderin infratentorially, respectively. Patients and controls were further assessed for posthemorrhagic hydrocephalus, neurosurgical interventions (external ventricular drainage and/or ventriculoperitoneal shunting), and ventriculitis.

Statistical analysis was performed by using SPSS 13.1. For the comparison of continuous variables between groups *t*-tests were used. To test the association between categorical variables, chi-square or Fisher's exact tests—when appropriate—were applied at first. In the second part, a stepwise logistic regression (forward/Wald method) and a blockwise logistic regression were performed using only variables which showed significant results at step 1. A *p*-value less than 5% was considered as significant.

3. Results

The study group consisted of 35 VLBW infants (mean birth weight 986±257 g S.D.) born between 24 and 32 weeks of gestation (mean 27.0±1.8 weeks of gestation S.D.; Table 1). The control group included 41 VLBW infants (mean birth weight 900±358 g S.D.) born between 23 and 32 weeks of gestation (mean 26.3±2.1 weeks of gestation S.D.). Distribution of gestational ages and birth weights was comparable between patients and controls. Male gender was more

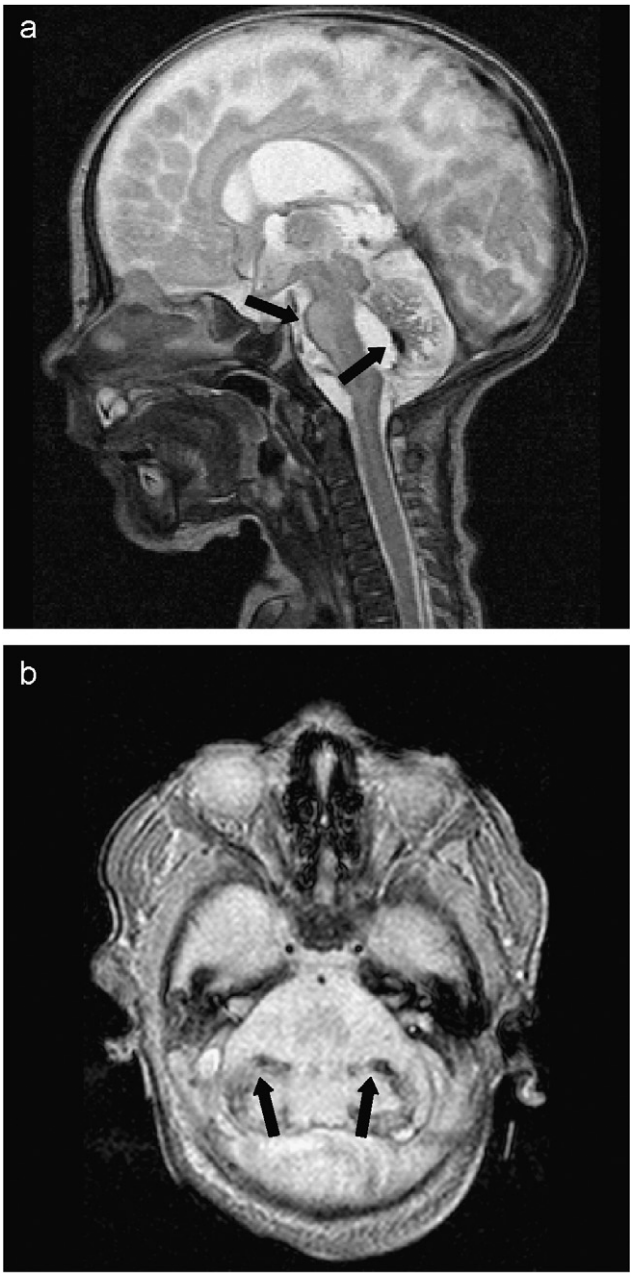

Fig. 1 – (a) Preterm born at gestational week 26+1; sagittal T2*-weighted MR image; small vermis, enlarged fourth ventricle, reduced dimensions of the brainstem, thin corpus callosum, and an inclined tentorium; hemosiderin deposition on the surface of the pons and in the fourth ventricle (black arrows). (b) Preterm born at gestational week 25+4; axial T2*-weighted image shows the reduction of cerebellar volume, hemosiderin deposition in both residual hemispheres (black arrows).

predominant in the study group (study group 24, control group 21).

Lack of antenatal corticosteroid therapy was found to be significantly related to group 1 ($p = 0.04$; Table 2). APGAR values at 1 min were significantly lower in study patients (APGAR mean 4) compared to the controls (AGPAR mean 6; $p = 0.007$). The frequency of early postnatal intubation was significantly higher in study patients ($p = 0.01$). Moreover, need for catecholamine support was significantly associated with the study group ($p = 0.005$).

No difference was found in the APGAR values at 5 min (AGPAR mean 7 vs. 8) and 10 min (AGPAR mean 8 vs. 9), respectively. Neither the sum of all days on ventilation nor the subdivision into ventilator days of conventional ventilation and high-frequency ventilation differed significantly. There was no significant difference in postnatal corticosteroid therapy, occurrence of patent ductus arteriosus, infections and seizures.

Preterm patients with disruptive cerebellar development suffered more often from IVH ($p = 0.008$; Table 3). A classification into low-grade and high-grade IVH did not show statistical significance. Cystic PVL was not found to be a risk factor, non-cystic PVL was not included in our analysis. The frequency of posthemorrhagic hydrocephalus ($p = 0.001$) and subsequent need for neurosurgical interventions ($p = 0.0007$) were significantly higher in study patients. For analysis of hemosiderin deposits on the cerebellar surface, in group 1 MR images of 20/35 patients and in group 2 MR images of 41/41 patients were available. Cerebellar hemosiderin deposition was found to be significantly associated with disruptive cerebellar development ($p < 0.0001$).

The logistic regression including all significant variables revealed a correlation of 0.950. Despite this high correlation, no isolated variable predicted disruptive cerebellar development, indicating multicollinearity of the predictors. Therefore, stepwise as well as blockwise logistic regressions were performed. Using stepwise logistic regression, hemosiderin deposits in the posterior fossa were the most important predictor of disruptive cerebellar development (OR 0.63). Additionally, hemosiderin deposits (OR 0.47) and posthemorrhagic hydrocephalus (OR 0.6) were important predictors. Blockwise logistic regression showed IVH (block 1) to be a significant factor, but including hemosiderin in the analysis (block 2) IVH loses its statistical power. The same is true for all other significant clinical factors (block 3).

Hemosiderin in the posterior fossa revealed a sensitivity of 0.70 (95% CI (0.48, 0.86)) and a specificity of 0.95 (95% CI (0.84, 0.99)). The positive predictive value of hemosiderin was 0.88 (95% CI (0.64, 0.97)), and the negative predictive value was 0.87 (95% CI (0.74, 0.94)), respectively.

4. Discussion

Advances in neonatology during the last 20 years led to a higher survival rate of extreme premature infants with high risk for cerebral injuries. Beside the known supratentorial lesions, cerebellar injuries in connection with prematurity are increasingly noticed.[3,4,10,13] Cerebellar volume reduction in VLBW infants has been attributed to hemorrhages,[6,7] infarcts,[5] atrophy[5,8] or interpreted as crossed diaschisis.[15] In a selected group of former preterm infants <1000 g birth weight with cerebral palsy as many as 45% had an additional cerebellar injury.[4]

The most important risk factor for disruption of cerebellar development is extreme prematurity per se. A decrease in

Table 1 – Group characteristics of patients and controls

	Patients ($n = 35$)	Controls ($n = 41$)	Significance
Gestational age, mean ± S.D. (range)	27.0 ± 1.8 weeks (24–32)	26.3 ± 2.1 weeks (23–32)	n.s., $p = 0.1$
Birth weight, mean ± S.D. (range)	986 ± 257 g (574–1740)	900 ± 358 g (470–2130)	n.s., $p = 0.24$
Sex, males:females	24:11 (69%:31%)	21:20 (51%:49%)	n.s., $p = 0.12$

n.s., not significant.

Table 2 – Clinical details of the perinatal course of patients and controls

	Patients ($n = 35$)	Patients available for analysis	%	Controls ($n = 41$)	Patients available for analysis	%	Significance
Antenatal corticosteroids	15	28	54	31	40	78	$p = 0.04$
APGAR 1 min, mean (range)	4 (1–8)	30		6 (1–10)	41		$p = 0.007$
APGAR 5 min, mean (range)	7 (2–9)	28		8 (2–10)	40		n.s., $p = 0.08$
APGAR 10 min, mean (range)	8 (4–10)	25		9 (3–10)	37		n.s., $p = 0.4$
Early postnatal intubation	34	35	97	32	41	78	$p = 0.01$
Postnatal corticosteroids	18	35	51	16	41	39	n.s., $p = 0.28$
Patent ductus arteriosus	14	35	40	13	41	32	n.s., $p = 0.5$
Catecholamine support	25	35	71	16	41	39	$p = 0.005$
Infections	35	35	100	39	41	95	n.s., $p = 0.19$
Neonatal seizures	22	35	63	24	41	59	n.s., $p = 0.7$
Conventional ventilation	34	35	97	35	41	85	n.s., $p = 0.08$
Conventional ventilation days, mean ± S.D. (range)	20 ± 14 (0–54)	35		19 ± 21 (0–104)	41		n.s., $p = 0.9$
High-frequency ventilation	21	35	60	18	41	44	n.s., $p = 0.16$
High-frequency ventilation days, mean ± S.D. (range)	6 ± 7 (0–24)	35		4 ± 7 (0–31)	41		n.s., $p = 0.2$
Ventilation days summary, mean ± S.D. (range)	26 ± 16 (5–72)	35		24 ± 23 (0–111)	41		n.s., $p = 0.7$

n.s., not significant.

Table 3 – Characteristics of cerebral and cerebellar pathologies

	Patients ($n = 35$)	Patients available for analysis	%	Controls ($n = 41$)	Patients available for analysis	%	Significance
IVH	34	35	97	31	41	75	$p = 0.008$
Low-grade IVH	18	35	51	19	41	46	n.s., $p = 0.66$
High-grade IVH	16	35	46	12	41	29	n.s., $p = 0.14$
PVL-grade II/III/IV	6	35	17	10	41	24	n.s., $p = 0.44$
Posthemorrhagic hydrocephalus	24	35	69	13	41	32	$p = 0.001$
Neurosurgical interventions	22	35	63	10	41	24	$p = 0.0007$
Ventriculitis	5	32	16	2	41	5	n.s., $p = 0.12$
Hemosiderin infratentorially	14	20	70	2	41	5	$p < 0.0001$

n.s., not significant.

cerebellar volume was recently reported in 169 preterm infants, and was found to be significantly related to gestational age and weight at birth.[3] All similar cases of severe cerebellar volume reduction were found exclusively in patients born between gestational weeks 24 and 32.[4,8,10,15]

The first weeks of extreme prematurity coincide with a highly vulnerable phase of cerebellar development. This period is characterized by high mitotic activity, extensive changes in the cortical layering pattern, and the onset of complex interrelationships between various classes of young

neurons and glial differentiation.[16] Moreover, during this phase, cerebellar growth far exceeds that of the cerebral hemispheres.[3] The selective vulnerability of the growing cerebellum during gestational weeks 24–32 with increased responsiveness to any kind of injury seems to be of particular importance for the disruption of subsequent neurodevelopmental processes.

As disruption of cerebellar development is not seen in all preterm infants, we aimed to detect specific risk factors for its appearance. Low APGAR values at 1 min and the need for early postnatal intubation indicate a poor postnatal condition in patients with later disruptive cerebellar development, which in part could be explained by the lower rates of antenatal steroid administration in study patients. Apart from the early postnatal intubation, no other ventilation parameter—neither necessity nor duration of conventional ventilation and high-frequency ventilation—differed significantly between study patients and controls (Table 2). These results differ from the findings of Argyropoulou et al.[12] and Limperopoulos et al.[3]

Despite the extensive destruction of the cerebellum we found in our study group, no obvious pattern of direct cerebellar injury could be detected. One may speculate that in the remnants of cerebellum left in our very severe cases, an earlier infarction or hemorrhage may no longer be visible. Contrariwise, in the patients with early diagnosis of disruptive cerebellar development, we could document a continuous decline of cerebellar volume over weeks without any typical injury pattern. No vascular injury pattern was seen on MR imaging neither supra- nor infratentorially, but the significant association between need for catecholamine therapy and disruptive cerebellar development indicates a potential etiologic role of hemodynamic instability. Vascular injury may be part of the pathophysiological mechanisms leading to cerebellar destruction, but not in typical infarction pattern.

Occurrence of additional supratentorial brain injury was the outstanding perinatal risk factor associated with subsequent disruption of cerebellar development. IVH—but not its severity—and related complications such as posthemorrhagic hydrocephalus and neurosurgical interventions were statistically significant associated with disruptive cerebellar development—similar to previous observations.[4,5,15] The association of early supratentorial brain damage and compromised cerebellar development may imply a causal relation. Recently, a correlation between associated brain injury and the severity of cerebellar volume decline in ex-preterm infants was described.[3,9] Disturbance of the highly integrated anatomic and functional interactions between cerebellum and the contralateral cerebral cortex was recognized to result in crossed cerebellar diaschisis in preterm infants[9,15] and also the reverse situation in cerebellocerebral diaschisis.[9]

As our patients had bilateral cerebral parenchymal lesions and 31 of 35 patients had symmetrical cerebellar alterations, the question of crossed trophic impairment between cerebrum and cerebellum cannot be addressed. We assume that functional disconnection may be one, but not the only mechanism, since we and others[8,12,13] found no correlation between severity of supratentorial brain injury and cerebellar volume reduction.

Superficial hemosiderin deposition on the cerebellar surface was the most important risk factor for disruption of cerebellar development. Though the number of available MR investigations is limited, these MRI studies showed occurrence of hemosiderin in 70% of affected patients and 5% of control patients ($p<0.0001$; Table 3). By logistic regression analysis, hemosiderin was even the main risk factor predicting disruptive cerebellar development with a high positive and negative predictive value. Therefore, the action of hemosiderin on the cerebellar surface needs to be further investigated.

The prompt conversion of blood breakdown products to hemosiderin on the surface of cerebellum and brainstem is contributed to ferritin-reactive microglia,[17,18] and the subsequent destructive processes include gliosis, neuronal loss and demyelination.[19] Cerebellar volume reduction after superficial siderosis is known from several MRI[19,20] and histopathological[21] studies. Siderosis is a chronic condition of repeated hemorrhages. However, in preterm infants, bleeding into the posterior fossa during cerebellar development was reported to lead even to olivopontocerebellar alterations.[22,23] Also neurotransmitter circuits are severely disturbed in preterm infants with bleeding into the posterior fossa leading to reduced function of specific cerebellar glutamate transporters EAAT4 and GLAST.[24] The subsequent glutamate overload causes excitotoxicity, followed by cell death through necrotic and apoptotic mechanisms.[24,25]

In view of these pathogenetic mechanisms specific for preterm infants, the hemosiderin deposits we detected on the cerebellar surface may be the pathway to cell death and olivopontocerebellar degeneration of particular importance.

The causative mechanism of hemosiderin deposition imparing cerebellar development is certainly speculative, and needs further clinical and experimental investigations.

5. Conclusion

Disruption of cerebellar development is a phenomenon only seen in preterm infants less than 32 weeks of gestation. The clinical course of our study patients was characterized by a severely compromised postnatal condition and hemodynamic instability. The cascade of hemorrhagic supratentorial brain injury causing posthemorrhagic hydrocephalus with subsequent need for neurosurgical drainage facilitates hemosiderin deposition on the cerebellar surface, which may be the crucial factor for cell death and permanent developmental arrest.

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