Eur J Pediatr (2008) 167:1141–1147
DOI 10.1007/s00431-007-0647-0

ORIGINAL PAPER

Disrupted cerebellar development in preterm infants is associated with impaired neurodevelopmental outcome

Agnes Messerschmidt · Renate Fuiko · Daniela Prayer · Peter C. Brugger · Eugen Boltshauser · Gerlinde Zoder · Walter Sterniste · Michael Weber · Robert Birnbacher

Received: 27 September 2007 / Accepted: 27 November 2007 / Published online: 3 January 2008

Abstract The unfavorable impact of prematurity on the developing cerebellum was recently recognized, but the outcome after impaired cerebellar development as a prematurity-related complication is hitherto not adequately documented. Therefore we compared 31 preterm patients with disrupted cerebellar development to a control group of 31 gender and gestational age matched premature infants with normal cerebellar development. Supratentorial brain injuries during the neonatal period were comparable between the groups. At a minimum age of 24 months motor and mental development was assessed by standardized tests. Disrupted cerebellar development was associated with significantly poorer scores both in the subtests for neuromotor ($p<0.001$) and mental development ($p<0.001$), respectively. Mixed CP was diagnosed in 48% of affected patients, whereas none of the patients of the control group had mixed CP. Microcephaly and epilepsy were significantly related to disrupted cerebellar development. Preterm patients with disrupted cerebellar development exhibit poorer outcome results in all investigated variables. The role of the cerebellum in neurodevelopment after prematurity seems to be underestimated so far.

Keywords Cerebellum · Disrupted development · Prematurity · Brain injury · Neurodevelopmental outcome

A. Messerschmidt · R. Fuiko · R. Birnbacher
Division of General Pediatrics and Neonatology,
Department of Pediatrics and Adolescent Medicine,
Medical University of Vienna,
Vienna, Austria

D. Prayer
Department of Neuroradiology, University Clinics of Radiodiagnostics, Medical University of Vienna,
Vienna, Austria

P. C. Brugger
Department of Anatomy and Cell Biology,
Medical University of Vienna,
Vienna, Austria

E. Boltshauser
Department of Neurology, University Children's Hospital,
Zurich, Switzerland

G. Zoder
Kinderklinik der Stadt Wien, Glanzing im Wilhelminenspital,
Vienna, Austria

W. Sterniste
Pediatric Department of the Danube-Hospital/SMZO,
Vienna, Austria

M. Weber
Department of Radiology,
University Clinics of Radiodiagnostics,
Medical University of Vienna,
Vienna, Austria

A. Messerschmidt (✉)
Department of Neonatology and Pediatric Intensive Care,
University Children's Hospital,
Medical University of Vienna,
Vienna, Austria
e-mail: agnes.messerschmidt@meduniwien.ac.at

Introduction

Brain injury and its implications on the neurodevelopment are a major problem in the treatment of premature infants. Survivors of preterm birth are at high risk for neurodevelopmental delay, cognitive dysfunction, and behavioral and emotional disturbances [22, 24, 27, 44]. Hitherto, supratentorial brain lesions such as intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) are considered to be the main underlying pathomorphological damage, whereas the impact of injury to the developing cerebellum is relatively underestimated [26].

Several recent papers outline both cerebellar injury [8, 17, 25], and cerebellar growth failure [1, 4, 21, 26, 31] as possible prematurity-related complications. Nevertheless, our understanding of the relationship between premature birth, brain injury, and cerebellar development remains limited. Preliminary analysis revealed supratentorial white matter injury [35, 37] to be the determining risk factor for impaired cerebellar development after preterm birth. We choose the term "disruption of cerebellar development" to emphasize the combination of acquired damage after preterm birth and subsequent developmental failure [26].

As the role of the cerebellum was recently acknowledged to extend to motor learning, adjusting motor operations, and also cognitive functions [7, 12, 23, 29], a prematurity-related impairment of cerebellar development may be of major concern in terms of cognitive and neuromotor long-term outcome of preterm patients [1, 22].

So far, little is known about the clinical impact of disruption of cerebellar development on the neurodevelopmental outcome of preterm patients. Cerebral palsy, mental retardation, and microcephaly [8, 17, 19] were mentioned in association with infratentorial brain injury, but these studies were limited by small numbers of patients and interfering supratentorial brain injuries. A recent paper by Limperopoulos et al. reported a high prevalence of long-term pervasive neurodevelopmental disabilities in preterm infants with cerebellar hemorrhagic injury [22]. However, Shah et al. found only a weak correlation of cerebellar volumes with cognitive and motor development at 2 years of age [35]. The neurodevelopmental outcome of preterm infants with disrupted cerebellar development was never investigated systematically in comparison to preterm infants with normal cerebellar development.

Therefore, the purpose of our study was to state more precisely the impact of disrupted cerebellar development on the neurodevelopmental outcome of preterm patients by comparing gender and gestational age-matched pairs of former preterm infants with disrupted cerebellar development in one group and with normal cerebellar development in the other group.

We hypothesized that disrupted cerebellar development would be associated with impairment of neurodevelopmental outcome in preterm infants independent from supratentorial brain injury.

Patients and methods

In our retrospective analysis we included 62 preterm born infants. Patients born between 1988 and 2004 were treated in three different level III neonatal intensive care units (NICU) in Vienna.

Group 1 consisted of 31 preterm patients in whom–after a normal initial cerebellar ultrasound within the first 2 days of life–a severe reduction of cerebellar volume was diagnosed during the first 12 weeks of life (Fig. 1). A morphological classification of the disruption of cerebellar development was the subject of our recent report [26].

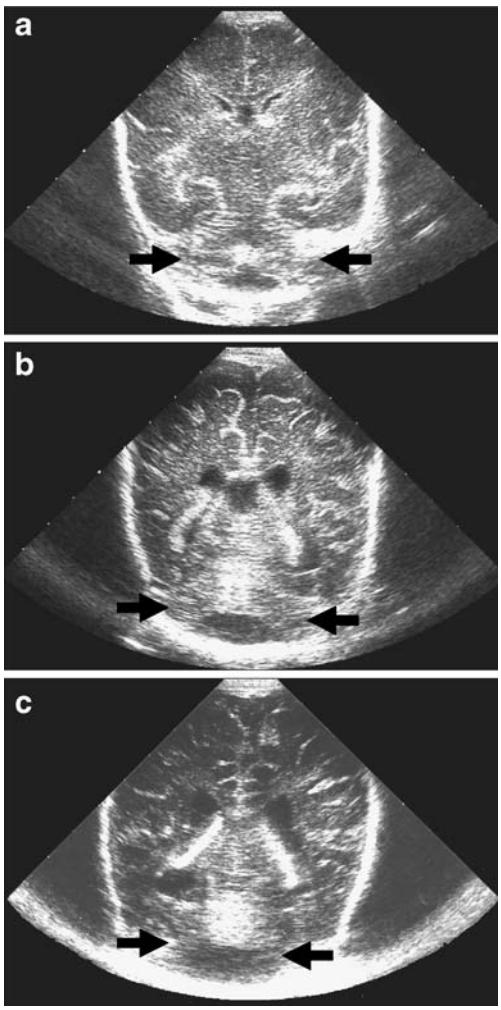

Fig. 1 Preterm infant born at 27+5 gestational weeks. Coronar ultrasound scan shows a normal cerebellum at day 6 (**a**), cerebellar reduction at day 65 (**b**), and severe cerebellar reduction with nearly empty posterior fossa at day 99 of life (**c**)

The age at birth varied between 24 and 31 gestational weeks (mean 27.0 wks±1.6 wks), and the birthweight ranged from 633 g to 1490 g (mean 969 g±212 g).

Our control group (group 2) consisted of patients enrolled in our follow-up program for premature born infants. Inclusion criteria for group 2 were occurrence of prematurity-related supratentorial brain injury (IVH or PVL) and a normal cerebellar ultrasound scan. Thirty-one gender and gestational age matched preterm infants were selected. Differences between the groups concerning birth weight, grading of supratentorial brain injuries, occurrence of posthemorrhagic hydrocephalus, and need for neurosurgical intervention (external ventricular drainage and/or ventriculo-peritoneal shunt insertion) were analyzed.

Ultrasound scans

Routine cranial ultrasound scans were obtained through the anterior fontanelle bedside with an Acuson device (Mountainview 128 XP) using a 7.5 MHZ sector transducer. Scans were made initially on days 1, 3, 5, and 7 of life, and at least once per week thereafter. Supratentorial hemorrhagic lesions included low grade intraventricular hemorrhage (grades I and II IVH) and high grade IVH (grade III IVH with ventriculomegaly and grade III IVH with periventricular hemorrhagic infarction) according to Volpe and Papile [30, 43] and de Vries [14]. Both hemispheres were evaluated by ultrasound, and the higher degree was taken for analysis. Diagnosis of PVL implicated only cystic lesions in two planes (c-PVL grades II, III, IV) [14]. All ultrasound scans performed from birth up to the third month of adjusted age as part of the routine follow-up program were used for analysis.

Neurodevelopmental follow-up

Outcome data concerning major morbidity and neurodevelopmental outcome were available in all patients of groups 1 and 2. All patients were evaluated at least twice a year in a neurodevelopmental follow-up program for premature infants, and in our analysis we refer to the results obtained between 24 and 36 months of age. Occurrence of microcephaly and epilepsy was assessed. Microcephaly was defined as a head circumference below the third centile in children. Epilepsy was diagnosed in children with recurrent clinical seizures and pathologic EEG recordings. A detailed clinical neurologic examination was performed by pediatricians specialized in pediatric neurology. Motor and mental developmental milestones were documented with a standardized questionnaire. Cerebral palsy (CP) was defined as a nonprogressive disorder of movement and posture due to a nonprogressive defect or lesion of the immature brain [2]. Both groups were evaluated for the occurrence of CP at a minimum age of 24 months. The following subtypes of CP were distinguished: spastic CP, ataxic CP, dyskinetic CP, and mixed CP (spastic–ataxic CP, spastic–dyskinetic CP, dyskinetic–ataxic CP) [10]. All investigation results were evaluated and classified by one experienced neuropediatrician (R.B.).

All patients underwent psychological testing, except those children not testable due to significant developmental and/or neurosensory delay who were assigned with verbal description. The Developmental Indices of the Bayley Scales were used as testing method [6]. All test results were evaluated and classified by one experienced psychologist (R.F.). Neuromotor and mental development were graded between score 0 and 3 according to the results of the neurodevelopmental tests and the neurological examination.

Neuromotor development was graded as normal (score 0) if no impairment was detected, or patients were classified in the normal range ±1 SD (Psychomotor Developmental Index 85–114). Score 1 defined mild to moderate motor disability with ambulatory status at least at the age of 3 years, equivocal to range ≤3 SD below the standard (Psychomotor Developmental Index 55–84). Severe motor disability (score 2) classified patients with absent ambulatory status at the age of 3 years and motor developmental scales >3 SD below the standard (Psychomotor Developmental Index <54). Score 3 of neuromotor development was assigned to patients without any targeted motor activity during the neurologic examination and without anticipation of any further motor development.

Mental development was graded in the normal range ±1 SD (Mental Developmental Index 85–114) (score 0), mild to moderate mental delay ranged ≤3 SD below the standard (Mental Developmental Index 55–84) (score 1), and severe mental delay for patients >3 SD below the standard (Mental Developmental Index <54) (score 2). Score 3 of mental development included only severely impaired patients whose expressive communication was limited to undifferentiated sounds without using words and who showed no constructive play behavior.

Statistical analysis

Statistical analysis was performed by using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). For the comparison of matched groups with respect to continuous variables (e.g. age, birth weight), paired *t* tests were used. To compare the percentage of dichotomous variables (e.g. PVL yes/no) exact versions of McNemar tests were used. To estimate the difference of IVH a Wilcoxon test was conducted. Additionally, the correlation between developmental scores

and IVH was calculated with Spearman rank correlation. Logistic regression was used to assess risk factors for epilepsy. A p value less than 0.05 was considered to indicate a significant result.

Results

In our study we compared 31 gender and gestational age matched pairs of former preterm infants. Birthweight did not differ significantly between the groups (group 1 mean 969 g±212 g, group 2 mean 937 g±208 g, p=0.352). No difference concerning severity of IVH (p=0.884) was found. In groups 1 and 2 low grade IVH was diagnosed in 17/20 patients and high grade IVH was diagnosed in 14/11 patients, respectively (Table 1). We found a trend towards a higher frequency of posthemorrhagic hydrocephalus in group 1 (22/14, p=0.077), and neurosurgical interventions were needed significantly more often in group 1 (20/9, p=0.019). Frequency of PVL (4/2, p=0.625) was similar between the two groups (Table 1).

The frequency of microcephaly was significantly higher among the patients of group 1 (27/9, p<0.001). Epilepsy was found significantly more often in group 1 (n=17) than in group 2 (n=4, p=0.002). In a correlation analysis for possible risk factors for the occurrence of epilepsy including gestational age, gender, IVH, PVL, posthemorrhagic hydrocephalus, and neurosurgical interventions no factor was found to be statistically significant.

The overall frequency of CP was significantly different between the groups. In group 1, 100% of the patients were diagnosed with CP, whereas in group 2, 39% of the patients developed CP. In particular, the distribution of CP subtypes showed significant differences between the groups. Spastic CP was distributed equally between the groups (16/12, p=0.629). No cases of "pure" ataxic or dyskinetic CP were found. Mixed (spastic–ataxic, spastic–dyskinetic) CP was diagnosed in 15 patients of group 1 and no patient of group 2 (p<0.001).

Table 1 Characteristics of cerebral pathologies (*ns* not significant)

	Group 1	Group 2	Significance
PVL grades II/III/IV	4	2	ns
IVH grade I	2	0	ns
IVH grade II	15	20	
IVH grade III	7	6	ns
IVH with parenchymal involvement	7	5	
Posthemorrhagic hydrocephalus	22	14	ns; p=0.077
External ventricular drainage	17	9	ns; p=0.077
Ventriculo–peritoneal shunt insertion	13	8	ns; p=0.332
Neurosurgical interventions (external ventricular drainage and ventriculo-peritoneal shunt insertion)	20	9	p=0.019

Table 2 Neuromotor and mental developmental outcome

		Group 1	Group 2
Neuromotor development	Score 0	0	12
	Score 1	2	8
	Score 2	17	9
	Score 3	12	2
Mental development	Score 0	0	13
	Score 1	2	8
	Score 2	17	8
	Score 3	12	2

Score 0: normal neuromotor or mental development
Score 1: minor to moderate motor disability or mental retardation
Score 2: severe motor disability or mental retardation
Score 3: neuromotor: no ambulatory status, no vectored motor activity; mental: unable to formulate any meaningful word, no personal autonomy

The scores for both neuromotor and mental development revealed significant differences between the groups. Patients of group 1 had significantly inferior scores both in the subtests for neuromotor development (p<0.001) and in the subtests for mental development (p<0.001) (Table 2). No correlation between motor and mental scores and the staging of IVH was found in group 1 (correlation r=0.19; p=0.31). In group 2 both motor (r=0.466; p=0.008) and mental (r=0.376; p=0.037) development were significantly correlated with the staging of IVH.

Discussion

Despite improvements in survival for preterm infants, motor, cognitive, and behavioral deficits are still major problems in the long-term outcome of these patients. Recent studies report constant rates of significant neurodevelopmental impairment [41], reaching up to 49% in the third year of life [44]. Among extremely preterm children at school age, the rates of severe, moderate, and mild disability were 22%, 24%, and 34%, respectively [24].

The most important predictors for cerebral alterations and following neurodevelopmental impairment are the degree of immaturity at birth and the concomitant cerebral injuries [16]. The correlation between neonatal ultrasound scans and neurodevelopmental outcome has been reported extensively [13, 36, 39, 42].

We excluded these confounding factors with influence on neurodevelopment outcome by choosing gender and gestational age matched pairs for our analysis. The supratentorial brain injuries detected by neonatal ultrasound scans were comparable between the groups (Table 1). Under provision of this comparable prematurity-related

initial situation, patients with additional cerebellar disrupted development had worse results in all variables investigated. The higher frequency of neurosurgical interventions we found in our affected patients confirm previous data [17] that complications after supratentorial hemorrhagic brain injuries are significantly related to the onset of cerebellar disrupted development.

The microcephalic appearance of our patients with disrupted cerebellar development reflects the absence of the normal increase in brain volumen after brain injury and is considered a predictor of neurodevelopmental impairment and mental retardation [3, 11]. As white matter loss is mostly responsible for impaired brain growth we suppose this could also be the reason for microcephaly in our patients. The frequency of cystic PVL was comparable between the groups; nevertheless, noncystic white matter lesions could be missed by the ultrasound scan.

The frequency of epilepsy was significantly higher in group 1, a fact which was only referred to in one more paper [25]. The hemosiderin deposition we found in our preliminary analysis [26] would be the only reasonable cause for the occurrence of epilepsy. The destructive processes after hemosiderin deposition are known pathophysiologic mechanisms of epileptogenesis in supratentorial brain structures [18], and surgical removal of hemosiderin-stained brain was found to improve seizure outcome [5]. On the other hand, no similar data are available for infratentorial brain structures. Therefore we may only suppose that comparable mechanisms on the cerebellar surface contribute to the high frequency of epilepsy in patients with disrupted cerebellar development. However, the higher frequency of epilepsy in group 1 could also be related to the higher frequency of neurosurgical interventions in this group.

Spastic CP as the characteristic long-term motor feature after supratentorial brain injury in preterm born infants [43] occurred in a similar frequency in both groups (51% vs 39%). The high percentage of patients with mixed CP in group 1 quite met our expectations as cerebellar dysfunction is known to be associated with ataxic movements [15, 28]. Preterm patients with cerebellar affections were reported to present with a mixture of motor abnormalities, including parts of spasticity, dystonia, and ataxia, resulting in a considerable motor handicap [8, 9, 17]. Recent work suggests that the cerebellum helps to generate appropriate patterns of limb movements, to regulate dynamically upright posture and balance, and to adjust the feedforward control of locomotor output through error–feedback learning [28]. However, in those patients presenting with spastic CP, either early cerebellar injuries are compensated regarding motor signs or, to some extent, the severity of motor and mental disability makes a detailed investigation impossible to detect subtle signs of cerebellar dysfunction.

The greater motor handicap in group 1 patients is also reflected by the poorer scores in the subtests for neuromotor development (Table 2). As no correlation with IVH could be detected, factors apart from supratentorial brain injury seem to be of particular interest for motor development in these patients. With growing evidence, cerebellar involvement in the learning of movement sequences is studied. Cerebellar functions in the area of establishment of motor set and movement initiation as well as spatial and temporal regulation of motor control [7, 12, 23, 29] may be a relevant factor for the serious impairment of neuromotor development in our patients.

In addition to significant motor problems, cognitive impairment and academic failure occur commonly in preterm survivors [22, 40]. Peterson et al. could pro- and retrospectively demonstrate a correlation between altered regional supratentorial brain volumes and later cognitive outcome in preterms [31]. Accordingly, in group 2 a significant correlation between mental scores and the extent of supratentorial brain injury could be found–a correlation that was again missing in our patients with disrupted cerebellar development. Preterm patients with disrupted cerebellar development exhibited significantly poorer mental scores in comparison to preterm patients with normal cerebellar development (Table 2).

Our vision of the cerebellum has been gradually transformed through recent years from only “coordinator of movements” to “a multitask neuronal machine” [33]. The major implications in nonmotor functions are documented in children surgically treated for benign cerebellar tumors [20, 32, 34, 38], data which support the recently attributed role of the cerebellum as a modulator of higher mental and social functions.

In preterm infants with increased risk of neurodevelopmental delay, cognitive dysfunction, and behavioral disturbances, the role of the cerebellum for these adverse outcomes has been unclear. Mental retardation in former preterm born infants with cerebellar affections was also reported by other authors [17, 19], and Allin and colleagues even demonstrated a significant correlation between cerebellar volume and various cognitive variables [1]. Recently, significant deficits in cognition, communication, and social-behavioral function were reported in preterm infants with isolated cerebellar hemorrhagic injury without supratentorial brain injury [22]. To summarize our results, cerebellar disrupted development was accompanied by a substantial cognitive impairment, by far more than we would expect from the degree of prematurity and supratentorial brain injury.

Conclusion

Disrupted cerebellar development in preterm patients was associated with a severe impairment both in motor and mental development after 24–36 months. Furthermore,

mixed cerebral palsy, microcephaly, and epilepsy were found in those patients. As prematurity-related cerebellar complications occur more often than hitherto expected, cerebellar development in preterm infants will require more attention in the future, especially considering this major negative impact on neurodevelopmental outcome.

References

1. Allin M, Matsumoto H, Santhouse AM, Nosarti C, AlAsady MH, Stewart AL, Rifkin L, Murray RM (2001) Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. Brain 124:60–66
2. Amiel-Tison C, Stewart A (1989) Follow up studies during the first five years of life: a pervasive assessment of neurological function. Arch Dis Childhood 64:496–502
3. Amiel-Tison C, Gosselin J, Infante-Rivard C (2002) Head growth and cranial assessment at neurological examination in infancy. Dev Med Child Neurol 44:643–648
4. Argyropoulou MI, Xydis V, Drougia A, Argyropoulou PI, Tzoufi M, Bassounas A, Andronikou S, Efremidis SC (2003) MRI measurements of the pons and cerebellum in children born preterm; association with the severity of periventricular and perinatal risk factors. Neuroradiology 45:730–734
5. Baumann CR, Schuknecht B, Lo Russo G, Cossu M, Citterio A, Andermann F, Siegel AM (2006) Seizure outcome after resection of cavernous malformations is better when surrounding hemosiderin-stained brain also is removed. Epilepsia 47:563–566
6. Bayley N (1993) The Bayley Scales of Infant Development. New York Psychological Corporation, New York, NY
7. Bloedel JR (2004) Task-dependent role of the cerebellum in motor learning. Prog Brain Res 143:319–329
8. Bodensteiner JB, Johnsen SD (2004) Cerebellar injury in the extremely premature infant: newly recognized but relatively common outcome. J Child Neurol 19:139–142
9. Bodensteiner JB, Johnsen SD (2006) Magnetic resonance imaging (MRI) findings in children surviving extremely premature delivery and extremely low birthweight with cerebral palsy. J Child Neurol 21:743–747
10. Cans C (2000) Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol 42:816–824
11. Cox J, Jackson AP, Bond J, Woods CG (2006) What primary microcephaly can tell us about brain growth. Trends Mol Med 12:358–366
12. Devor A (2002) The great gate: control of sensory information flow to the cerebellum. Cerebellum 1:27–34
13. De Vries LS, Van Haastert IL, Rademaker KJ, Koopman C, Groenendaal F (2004) Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr 144:815–820
14. De Vries LS, Eken P, Dubowitz LM (1992) The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res 49:1–6
15. Ilg W, Golla H, Thier P, Giese MA (2007) Specific influences of cerebellar dysfunctions on gait. Brain 130:786–798
16. Inder TE, Warfield SK, Wang H, Huppi PS, Volpe JJ (2005) Abnormal cerebral structure is present at term in premature infants. Pediatrics 115:286–294
17. Johnsen SD, Bodensteiner JB, Lotze TE (2005) Frequency and nature of cerebellar injury in the extremely premature survivor with cerebral palsy. J Child Neurol 20:60–64
18. Kraemer DL, Awad IA (1994) Vascular malformations and epilepsy: clinical considerations and basic mechanisms. Epilepsia 35:30–43
19. Krägeloh-Mann I, Toft P, Lunding J, Andresen J, Pryds O, Lou HC (1999) Brain lesions in preterms: origin, consequences and compensation. Acta Paediatr 88:897–908
20. Levisohn L, Cronin-Golomb A, Schmahmann JD (2000) Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. Brain 123:1041–1050
21. Limperopoulos C, Soul JS, Gauvreau K, Huppi PS, Warfield SK, Bassan H, Robertson RL, Volpe JJ, du Plessis AJ (2005) Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics 115:688–695
22. Limperopoulos C, Bassan H, Gauvreau K, Robertson RL Jr, Sullivan NR, Benson CB, Avery L, Stewart J, Soul JS, Ringer SA, Volpe JJ, duPlessis AJ (2007) Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics 120:584–593
23. Manto M, Bastian AJ (2007) Cerebellum and the deciphering of motor coding. Cerebellum 6:3–6
24. Marlow N, Wolke D, Bracewell MA, Samara M; EPICure Study Group (2005) Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med 352: 9–19
25. Mercuri E, He J, Curati WL, Dubowitz LMS, Cowan FM, Bydder GM (1997) Cerebellar infarction and atrophy in infants and children with a history of premature birth. Pediatr Radiol 27: 139–143
26. Messerschmidt A, Brugger PC, Boltshauser E, Zoder G, Sterniste W, Birnbacher R, Prayer D (2005) Disruption of cerebellar development: a potential complication of extreme prematurity. AJNR 26:1659–1667
27. Mikkola K, Ritari N, Tommiska V, Salokorpi T, Lehtonen L, Tammela O, Pääkkönen L, Olsen P, Korkman M, Fellman V (2005) Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996–1997. Pediatrics 116:1391–1400
28. Morton SM, Bastian AJ (2007) Mechanisms of cerebellar gait ataxia. Cerebellum 6:79–86
29. Nixon PD, Passingham RE (2001) Predicting sensory events. The role of the cerebellum in motor learning. Exp Brain Res 138:251–257
30. Papile LA, Burstein J, Burstein R, Koffler H (1978) Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 92:529–534
31. Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, Gore JC, Duncan CC, Makuch R, Ment LR (2003) Regional brain volumes and their later neurodevelopmental correlates in term and preterm infants. Pediatrics 111:939–948
32. Riva D, Giorgi C (2000) The cerebellum contributes to higher functions during development: evidence from a series of children surgically treated for posterior fossa tumours. Brain 123:1051–1061
33. Saab CY, Willis WD (2003) The cerebellum: organization, functions and its role in nociception. Brain Res Rev 42:85–95
34. Scott RB, Stoodley CJ, Anslow P, Paul C, Stein JF, Sugden EM, Mitchell CD (2001) Lateralized cognitive deficits in children following cerebellar lesions. Dev Med Child Neurol 43:685–691
35. Shah DK, Anderson PJ, Carlin JB, Pavlovic M, Howard K, Thompson DK, Warfield SK, Inder TE (2006) Reduction in cerebellar volumes in preterm infants: relationship to white matter injury and neurodevelopment at two years of age. Pediatr Res 60:97–102

36. Sherlock RL, Anderson PJ, Doyle LW; Victorian Infant Collaborative Study Group (2005) Neurodevelopmental sequelae of intraventricular haemorrhage at 8 years of age in a regional cohort of ELBW/very preterm infants. Early Hum Dev 81:909–916
37. Srinivasan L, Allsop J, Counsell SJ, Boardman JP, Edwards AD, Rutherford M (2006) Smaller cerebellar volumes in very preterm infants at term-equivalent age are associated with the presence of supratentorial lesions. AJNR 27:573–579
38. Steinlin M, Imfeld S, Zulauf P, Boltshauser E, Lövblad KO, Ridolfi Lüthy A, Perrig W, Kaufmann F (2003) Neuropsychological long-term sequelae after posterior fossa tumour resection during childhood. Brain 126:1998–2008
39. Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH, Lewis SW, Kingsley DP, Moseley IF, Foster O, Murray RM (1999) Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet 353:1653–1657
40. Taylor HG, Klein N, Hack M (2000) School-age consequences of birth weight less than 750 g: a review and update. Dev Neuropsychol 17:289–321
41. Tommiska V, Heinonen K, Lehtonen L, Renlund M, Saarela T, Tammela O, Virtanen M, Fellman V (2007) No improvement in outcome of nationwide extremely low birth weight infant populations between 1996–1997 and 1999–2000. Pediatrics 119:29–36
42. van de Bor M, den Ouden L (2004) School performance in adolescents with and without periventricular-intraventricular hemorrhage in the neonatal period. Semin Perinatol 28:295–303
43. Volpe JJ (2001) Neurology of the newborn, 4th edn. WB Saunders, Philadelphia, PA
44. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR; EPICure Study Group (2000) Neurologic and developmental disability after extremely preterm birth. N Engl J Med 343: 378–384