Cover Page

Universiteit Leiden

The handle http://hdl.handle.net/1887/28766 holds various files of this Leiden University dissertation

Author: Steggerda, Sylke Jeanne
Title: The neonatal cerebellum
Issue Date: 2014-09-24

Chapter 1

General introduction and outline of the thesis

Introduction

In The Netherlands approximately 4000 infants are admitted to a neonatal intensive care unit (NICU) each year. The majority of these infants are very preterm, born at a gestational age less than 32 weeks. This group of approximately 2500 infants represents 1.4% of all live births and has increased gradually over the past decade (1). The remainder are late preterm and full-term infants with perinatal complications such as asphyxia, respiratory disorders, congenital malformation and perinatal infection.

Brain injury is an important complication in newborn infants requiring intensive care treatment. In preterm infants it may lead to significant cognitive, behavioral, attentional and socialization deficits, and neuromotor disorders (2). Until recently, supratentorial brain injury and especially supratentorial white matter injury, was considered the main cause of impaired neurologic outcome in these infants. However, as a result of improvements in cranial ultrasound (CUS) techniques and the more widespread use of magnetic resonance imaging (MRI) in the last decade, cerebellar injury is now considered an additional important complication of preterm birth and is also increasingly recognized in the full-term infant (3-10). Neonatal cerebellar injury is associated with a broad spectrum of neurodevelopmental disabilities including motor, cognitive, behavioral, language and social deficits (9,11-13).

In this chapter, we will provide background information on the development of the cerebellum, which is extremely rapid in the 3rd trimester of pregnancy, and the pathogenesis of impaired cerebellar development in preterm infants. Cerebellar hemorrhage, being the most frequently occurring form of cerebellar injury in preterm infants, and cerebellar injury in full-term infants will be discussed in more detail. We will describe the advantages and limitations of neuroimaging techniques that can be used for the detection of cerebellar injury in the newborn. Finally, we will discuss the consequences of cerebellar injury for long-term neurodevelopmental outcome.

Cerebellar development

Cerebellar development starts early in fetal life, at 4 weeks of gestation, and continues until about 20 months of age. Growth is extremely rapid in the fetal period between 24-40 weeks of gestation, and by far exceeds supratentorial hemispheric growth. During this period there is a 3-5-fold increase in cerebellar volume and an exponential growth in foliation. As a consequence the cerebellar surface area increases more than 30-fold between 24 and 40 weeks of gestation (2, 5,14-19) (Figure 1).

There are two main proliferative zones in the developing cerebellum (2,5,17,20). The first is the dorsally placed ventricular zone, which is the origin of the Purkinje cells and interneurons of the dentate nuclei. The second proliferative zone is the dorsolateral placed rhombic lip that is the origin of the granular precursor cells that migrate over the subpial cerebellar surface to form the external granular layer. Between 20 and 40 weeks of gestation, the external granular layer is site of vigorous proliferation (5, 19). It expands over the cerebellar surface and is very important for the acceleration in cerebellar growth and foliation. Proliferation occurs in the outer zone, which is in contact with the cerebrospinal fluid and subarachnoid space. The inner zone contains cells that migrate inwards to form the internal granular layer. After 40 weeks of gestation cerebellar growth decelerates and the external granular layer gradually disappears over the first year of life.

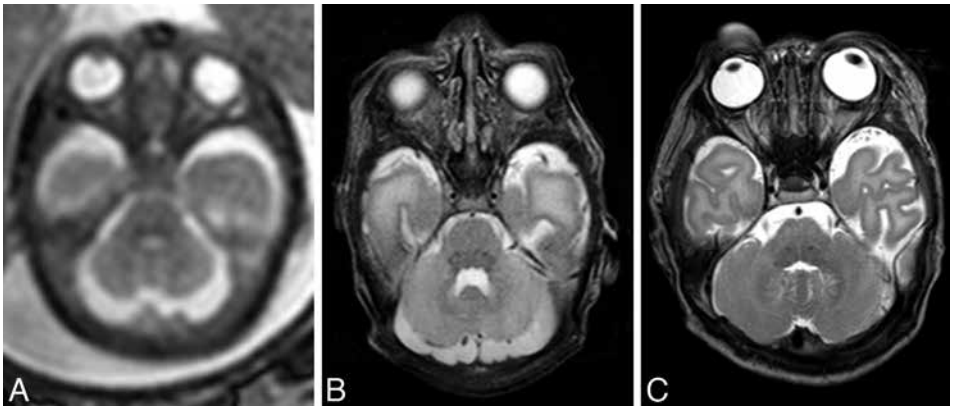

Figure 1. T2-weighted transverse MR images showing fetal cerebellar development at **(A)** 24 weeks gestation and postnatal cerebellar development at **(B)** 31 weeks gestation in a preterm infant and at **(C)** 40 weeks gestation in a full-term baby.

Impaired cerebellar development in preterm infants

Because of its rapid growth and development during late gestation, the cerebellum is very vulnerable in the preterm infant (5). Both the germinal matrix of the external granular layer and the subependymal germinal matrix of the fourth ventricle are fragile structures and susceptible to injury. This may subsequently impair further cerebellar development.

Two forms of impaired cerebellar development can be distinguished in preterm infants (5,19). First, impaired development due to direct, destructive cerebellar injury in the neonatal period. This can be diagnosed before or around term equivalent age (TEA) by CUS and MRI. Second, impaired cerebellar growth and development in the absence of direct cerebellar injury, usually diagnosed after the neonatal period on volumetric MRI studies.

Impaired cerebellar development with direct cerebellar injury

Destructive cerebellar injury diagnosed in the neonatal period is usually hemorrhagic or ischemic in nature. Cerebellar hemorrhage (CBH), one of the topics of this thesis, is the best-studied form of direct cerebellar injury. It may cause destruction and atrophy, usually within 2 months after the insult (Figure 2A). Cerebellar infarction can also occur and may result in the development of cerebellar atrophy (21,22). Profound cerebellar parenchymal loss has been reported in surviving preterm infants with cerebral palsy. This may be due to focal infarction (23,24). However, since these cerebellar lesions are often bilateral and symmetrical, and occur in combination with supratentorial white matter injury, they may also be the result of a more generalized hypoxic-ischemic insult (5).

Impaired cerebellar development in the absence of direct cerebellar injury

Quantitative MRI studies have shown that infants born prematurely have smaller cerebellar volumes at TEA, even in the absence of direct MRI demonstrable cerebellar injury (19,25-28). This may be explained by several factors that complicate the preterm period and can affect brain growth, such as glucocorticoid exposure, hypoxia-ischemia, inflammation and undernutrition (5,15,29-31). Impaired cerebellar development has also been described as a consequence of smaller hemosiderin deposits on the cerebellar surface in the absence of a large CBH. These blood products in the cerebrospinal fluid are toxic to the granular precursor cells of the external granular layer and may disrupt further development (7,32) (Figure 2B).

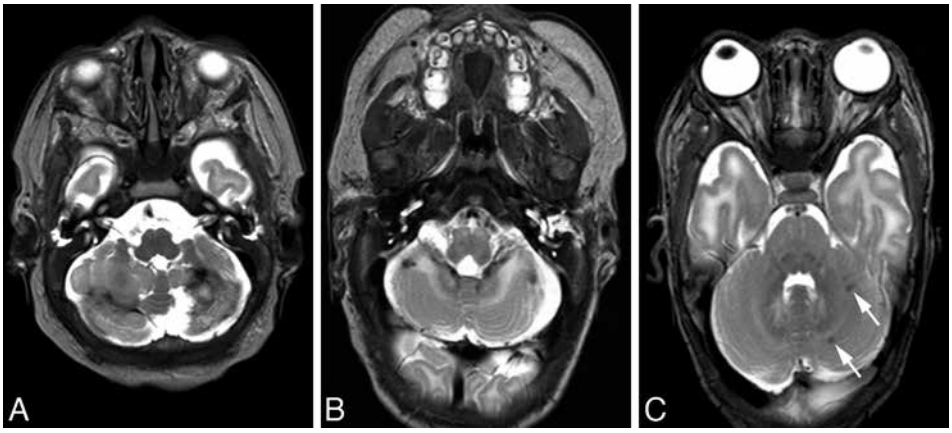

Figure 2. T2-weighted MR images obtained at term equivalent age.
(A) in a preterm infant born at 26 weeks gestational age with ultrasound detected bilateral cerebellar hemorrhage, showing destructive lesions in both cerebellar hemispheres and vermis. **(B)** in a preterm infant born at 27 weeks gestational age, showing small hemosiderin deposits around the fourth ventricle and at the surface of the cerebellar hemispheres, which have become slightly atrophic and asymmetric. **(C)** in a preterm infant born at 27 weeks gestation, showing punctate hemorrhages in the left cerebellar hemisphere (arrows).

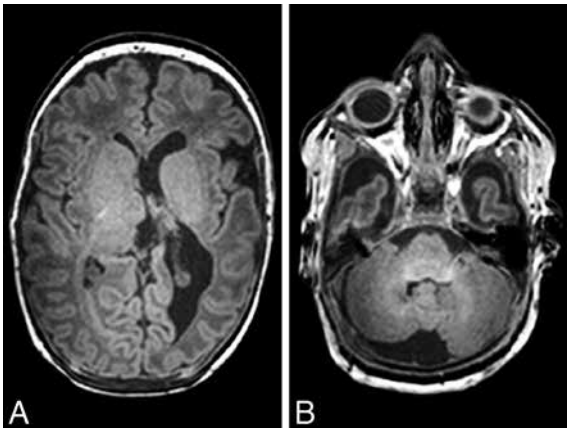

Figure 3. Female infant who was diagnosed with a left-sided fetal intraventricular hemorrhage and ventriculomegaly at 24 weeks gestational age. T1-weighted MR images obtained postnatally at term equivalent age, showing **(A)** dilatation of left ventricle with periventricular white matter loss and underdevelopment of left thalamus and posterior limb of internal capsule, and **(B)** a decreased volume of the contralateral cerebellar hemisphere.

Impaired cerebellar development without direct cerebellar injury can occur as a consequence of remote trans-synaptic effects. Primary supratentorial brain injury, in an area that is functionally connected to the cerebellum can influence the development of the contralateral cerebellar hemisphere. Volumetric MRI studies performed in preterm infants demonstrated a relation between supratentorial white matter injury and supratentorial hemorrhage, and cerebellar underdevelopment (25-27,33). Unilateral cerebral brain injury was associated with a decreased volume of the contralateral cerebellar hemisphere and bilateral parenchymal injury resulted in a reduction of total cerebellar volume. This phenomenon is called crossed cerebrocerebellar diaschisis (33) (Figure 3). Vice-versa, cerebellocerebral diaschizis may also occur as a consequence of a loss of feedback from a primary affected cerebellar hemisphere to the contralateral cerebral cortex and by this route affect subsequent supratentorial cortical brain development (33,34).

Cerebellar hemorrhage

CBH in the preterm infant originates in the vulnerable germinal matrix of the external granular layer and/or the subependymal germinal matrix of the fourth ventricle. In these structures, fragile capillary networks are present that can easily rupture. This risk is enhanced by the pressure passive circulation in sick and prematurely born infants (6,35). Two main patterns of CBH are described in the literature. The first includes large focal CBH, which is mostly unilateral and hemispheric, but can also occur bilaterally or affect the vermis (Figure 2A). These larger hemorrhages can be diagnosed with CUS, especially with the use of additional acoustic windows (4,8,36). Large and destructive CBH especially occurs in extremely preterm or low birth weight infants (gestational age <28 weeks and/or birth weight <750 grams) in whom the incidence may be as high as 19% (4). Presenting signs can be motor agitation and unexplained ventriculomegaly on CUS, but clear clinical symptoms are often lacking (37). CBH often occurs in combination with supratentorial germinal matrix/intraventricular hemorrhage (GM/IVH). This is related to the fact that the mechanisms causing CBH resemble those of GM/IVH and both can occur simultaneously. The pathogenesis of large CBH is multifactorial, as in GM/IVH, and includes perinatal circulatory events compromising cerebral circulation such as fetal distress, patent ductus arteriosus, and hypotension, and factors that affect cerebro-

vascular autoregulation, such as low pH and hypercarbia (4,5,38). Large destructive CBH is associated with high neonatal mortality and significant risk for impaired neurodevelopmental outcome (11,39,40).

The second pattern of CBH includes smaller or punctate hemorrhagic lesions that are difficult to detect on CUS but are frequently seen on MRI and can occur as a single focal hemorrhage or as multiple bilateral hemorrhages (Figure 2C). The etiology and outcome of these smaller hemorrhagic lesions may be different from large CBH. Up to now, little is known about perinatal and postnatal factors that may be associated with small CBH, and information on neurodevelopmental outcome is limited (41).

Cerebellar injury in term infants

The more widespread use of advanced neuroimaging techniques has led to an increased detection of cerebellar injury in high-risk full-term infants. In these infants CBH can occur as a consequence of traumatic delivery and has been associated with asphyxia, perinatal infection, supratentorial hemorrhage and extra-corporeal membrane oxygenation (3,9,42) (Figure 4). Cerebellar involvement can occur in infants with hypoxic-ischemic encephalopathy (HIE). The Purkinje cells and the granule cells of the internal and external granular layers are vulnerable to hypoxic-ischemic injury (35). Especially the cerebellar vermis can be involved in term HIE and a disturbance of growth has been described (43-45). It is not clear whether this is the result of direct cerebellar injury or the consequence of remote trans-synaptic effects related to supratentorial brain damage. However, cerebellar abnormalities have also been reported on early neonatal MR scans and in combined MRI/autopsy studies in infants with severe HIE (46-48).

Central nervous system infections can affect the cerebellum. In both term and preterm infants cerebellar abscesses have been described. The cerebellum can also be affected by viral infections, such as herpes and enterovirus meningoencephalitis (49,50) and by congenital cytomegalovirus infection, which can induce cerebellar hypoplasia (51,52). Disrupted cerebellar development can also be detected at birth as a consequence of an intra-uterine hypoxic or hemorrhagic event. Several inborn errors of metabolism can affect the development of the cerebellum during early and late pregnancy and lead to structural abnormalities and hypoplasia or

induce progressive cerebellar atrophy (53) (Figure 5). Finally, congenital cerebellar malformations can be a component of several syndromic and chromosomal disorders (54).

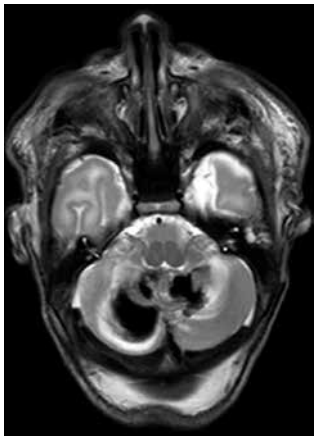

Figure 4. Female infant born asphyxiated at 40 weeks gestational age after vaginal breech delivery.
T2-weighted MRI shows bilateral extensive cerebellar hemorrhages and extra-axial posterior fossa hemorrhage.

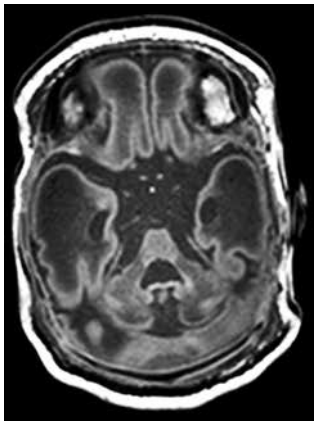

Figure 5. Male infant from consanguineous parents born at 38 weeks gestational age with refractory neonatal seizures, persistent lactate acidosis and a suspected metabolic disorder.
T1-weighted MRI shows severely hypoplastic cerebellum (vermis and hemispheres) and abnormal gyration and signal intensity of the temporal lobes.

Imaging the cerebellum

Cranial ultrasound

CUS is the preferred technique for brain imaging in high-risk neonates. Its major advantages are that it is safe, inexpensive, and can be performed early and repeatedly at the bedside, with little disturbance to the infant. Although the advantages of CUS are numerous, there are also limitations. Quality of CUS imaging depends on the skills and experience of the operator. It is routinely performed through the anterior fontanel (AF). With optimal settings, this provides an excellent view of most supratentorial structures, but evaluation of the peripheral and superficial structures located at the convexity of the cerebral hemispheres may remain difficult. Furthermore, visualization of infratentorial structures is suboptimal because of the distance from the transducer to the posterior fossa. In addition, the echogenic tentorium and vermis may impede the detection of lesions (55). The use of the mastoid fontanelle (MF), located at the junction of the parietal, temporal and occipital bones improves visualization of the posterior fossa. The transducer is positioned closer to its structures and they are approached at a different angle, avoiding the echogenic tentorium. Previous studies have stressed the advantages of CUS using the MF approach for the detection of posterior fossa lesions in neonates (4,56-59). Despite the clinical relevance of cerebellar injury, MF views are in most centers not part of routine CUS examination in high-risk neonates.

Magnetic resonance imaging

MRI has several advantages over CUS imaging. It provides detailed images of the whole brain and detects abnormalities in areas that are difficult to visualize with CUS, such as the posterior fossa. MRI demonstrates maturational processes in the brain in more detail and allows more precise depiction of the site, extent and origin of lesions. Modern MRI techniques, including diffusion-weighted and susceptibility-weighted imaging are of additional value in the detection of acute hypoxic-ischemic lesions and sensitive for small hemosiderin deposits. However, compared with CUS, MRI is more expensive and burdensome in critically ill neonates. It requires sedation and transportation to the MR unit and is therefore less suitable for early and serial imaging (60).

Outcome of cerebellar injury

The cerebellum does not only play an important role in motor function, but also in several non-motor functions. Clinical correlates of cerebellar disorders in children and adults involve cognitive deficits concerning visual-spatial abilities, language, learning and memory, attentional deficits, and disorders in mood, affect and behavior (5,61-65). These deficits may be caused by an interruption in the functional interactions between the cerebellum and the cerebral cortex. Follow-up studies in very preterm infants show a relation between cerebellar volumes and cognitive function (66,67). Extensive cerebellar lesions are associated with a significant risk for impaired neurodevelopmental outcome (11,13,24). A detailed study by Limperopoulos et al. describes neurological abnormalities in 66% of a group of 35 preterm infants with isolated CBH as compared to 5% in a control group (11). Infants with isolated cerebellar injury had a high incidence of neuromotor disabilities (48%), cognitive disabilities (40%), expressive (42%) and receptive (37%) language disorders, internalizing behavioral problems (34%) and abnormal autism screening (37%). These deficits could not be explained by associated cerebral injury and were worse in infants with bilateral involvement of the cerebellum. Involvement of the vermis was associated with a higher risk of social behavioral deficits and abnormal autism screening.

The outcome of smaller CBH that causes less or no destruction of the cerebellar parenchyma may be more optimistic. However, up to now information on neurodevelopmental outcome is limited. One study assessed the outcome of preterm infants with small MRI-diagnosed CBH. Although outcome was more favorable than in infants with large CBH, infants with small CBH were still at increased risk of neurological abnormalities. The number of cases with follow-up in this study was small (41).

Aims and outline of this thesis

The general aim of this thesis was to study and describe the incidence and characteristics of cerebellar injury and to investigate the role of different neuroimaging techniques (CUS and MRI) for the detection of posterior fossa abnormalities in both preterm and high-risk full-term infants.
The work described in this thesis is divided in three parts:

Part I Neonatal neuroimaging

In experienced hands, CUS is an excellent tool to detect the most frequently occurring brain abnormalities in preterm and full-term infants. However, there are also limitations and MRI is additionally needed in most infants with suspected parenchymal brain injury and/or neurologic symptoms.
Chapters 2 and 3 describe the standard CUS procedure and supplementary imaging techniques, including the use of different transducer types and scan frequencies, and the use of additional acoustic windows to optimize the performance of CUS.

Part II Cerebellar injury in the preterm neonate

Cerebellar injury is a frequent complication of preterm birth with important prognostic consequences. This part focuses on the detection, risk factors and prognostic implications of cerebellar injury in preterm infants.
Chapter 4 describes the characteristics of cerebellar injury in a prospective cohort of very preterm infants and compares the diagnostic performance of serial CUS with AF and additional MF views for the detection of cerebellar injury, with the results of MRI.
Chapter 5 Small CBH are a frequent MR finding in preterm infants. In this chapter we report the association between perinatal risk factors and the occurrence of these small hemorrhages, and examine the association with supratentorial brain injury and neurodevelopmental outcome at 2 years of age.
Chapter 6 Gradient echo T2*-weighted MR sequences are more sensitive for the detection of (small) hemorrhages in the brain than T2-weighted echo sequences. This chapter describes the clinical value of gradient echo MRI for brain imaging in very preterm infants.

Part III Cerebellar injury in the term neonate

Similar to preterm infants, cerebellar injury in full-term infants is associated with a broad spectrum of neurodevelopmental disabilities. Early detection is therefore important.

Chapter 7 describes the technique of MF sonography in full-term infants and the combined ultrasound and MR features of posterior fossa abnormalities that may be encountered in various neonatal disorders and conditions.

Chapter 8 describes the incidence and characteristics of posterior fossa abnormalities in a retrospective cohort of high-risk full-term infants and compares the diagnostic performance of serial CUS with AF and additional MF views for the detection of posterior fossa abnormalities, with the results of MRI.

In **Chapter 9** we discuss the main findings of this thesis and suggest directions for future research. A summary of the work described in this thesis is provided in **Chapter 10. Chapter 11** provides a Dutch summary.

References

1. Stichting Perinatale Registratie Nederland. Perinatale Zorg in Nederland 2012. Utrecht, Stichting Perinatale Registratie Nederland, 2013.
2. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol 2009; 8:110-124.
3. Miall LS, Cornette LG, Tanner SF, Arthur RJ, Levene MI. Posterior fossa abnormalities seen on magnetic resonance brain imaging in a cohort of newborn infants. J Perinatol 2003; 23:396-403.
4. Limperopoulos C, Benson CB, Bassan H, et al. Cerebellar hemorrhage in the preterm infant: ultrasonographic findings and risk factors. Pediatrics 2005; 116:717-724.
5. Volpe JJ. Cerebellum of the premature infant: rapidly developing, vulnerable, clinically important. J Child Neurol 2009; 24:1085-1104.
6. Fumagalli M, Bassi L, Sirgiovanni I, Mosca F, Sannia A, Ramenghi LA. From germinal matrix to cerebellar haemorrhage. J Matern Fetal Neonatal Med 2013; 23:
7. Messerschmidt A, Brugger PC, Boltshauser E, et al. Disruption of cerebellar development: potential complication of extreme prematurity. AJNR Am J Neuroradiol 2005; 26:1659-1667.
8. Merrill JD, Piecuch RE, Fell SC, Barkovich AJ, Goldstein RB. A new pattern of cerebellar hemorrhages in preterm infants. Pediatrics 1998; 102:E62.
9. Limperopoulos C, Robertson RL, Sullivan NR, Bassan H, du Plessis AJ. Cerebellar injury in term infants: clinical characteristics, magnetic resonance imaging findings, and outcome. Pediatr Neurol 2009; 41:1-8.
10. Bodensteiner JB, Johnsen SD. Cerebellar injury in the extremely premature infant: newly recognized but relatively common outcome. J Child Neurol 2005; 20:139-142.
11. Limperopoulos C, Bassan H, Gauvreau K, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatrics 2007; 120:584-593.
12. Williamson WD, Percy AK, Fishman MA, et al. Cerebellar hemorrhage in the term neonate: developmental and neurologic outcome. Pediatr Neurol 1985; 1:356-360.
13. Messerschmidt A, Fuiko R, Prayer D, et al. Disrupted cerebellar development in preterm infants is associated with impaired neurodevelopmental outcome. Eur J Pediatr 2008; 167:1141-1147.
14. Chang CH, Chang FM, Yu CH, Ko HC, Chen HY. Assessment of fetal cerebellar volume using three-dimensional ultrasound. Ultrasound Med Biol 2000; 26:981-988.
15. Dobbing J, Sands J. Quantitative growth and development of human brain. Arch Dis Child 1973; 48:757-767.
16. Dobbing J. The later growth of the brain and its vulnerability. Pediatrics 1974; 53:2-6.
17. Rakic P, Sidman RL. Histogenesis of cortical layers in human cerebellum, particularly the lamina dissecans. J Comp Neurol 1970; 139:473-500.
18. Triulzi F, Parazzini C, Righini A. MRI of fetal and neonatal cerebellar development. Semin Fetal Neonatal Med 2005; 10:411-420.
19. Limperopoulos C, du Plessis AJ. Disorders of cerebellar growth and development. Curr Opin Pediatr 2006; 18:621-627.
20. Sidman RL, Rakic P. Neuronal migration, with special reference to developing human brain: a review. Brain Res 1973; 62:1-35.

21. Mercuri E, He J, Curati WL, Dubowitz LM, Cowan FM, Bydder GM. Cerebellar infarction and atrophy in infants and children with a history of premature birth. Pediatr Radiol 1997; 27:139-143.
22. Johnsen SD, Tarby TJ, Lewis KS, Bird R, Prenger E. Cerebellar infarction: an unrecognized complication of very low birthweight. J Child Neurol 2002; 17:320-324.
23. Bodensteiner JB, Johnsen SD. Magnetic resonance imaging (MRI) findings in children surviving extremely premature delivery and extremely low birthweight with cerebral palsy. J Child Neurol 2006; 21:743-747.
24. Johnsen SD, Bodensteiner JB, Lotze TE. Frequency and nature of cerebellar injury in the extremely premature survivor with cerebral palsy. J Child Neurol 2005; 20:60-64.
25. Shah DK, Anderson PJ, Carlin JB, et al. Reduction in cerebellar volumes in preterm infants: relationship to white matter injury and neurodevelopment at two years of age. Pediatr Res 2006; 60:97-102.
26. Srinivasan L, Allsop J, Counsell SJ, Boardman JP, Edwards AD, Rutherford M. Smaller cerebellar volumes in very preterm infants at term-equivalent age are associated with the presence of supratentorial lesions. AJNR Am J Neuroradiol 2006; 27:573-579.
27. Limperopoulos C, Soul JS, Gauvreau K, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics 2005; 115:688-695.
28. Tam EW. Potential mechanisms of cerebellar hypoplasia in prematurity. Neuroradiology 2013; 55 Suppl 2:41-46.
29. Tam EW, Chau V, Ferriero DM, et al. Preterm cerebellar growth impairment after postnatal exposure to glucocorticoids. Sci Transl Med 2011; 3:105ra105.
30. Chase HP, Lindsley WF, Jr., O'Brien D. Undernutrition and cerebellar development. Nature 1969; 221:554-555.
31. Parikh NA, Lasky RE, Kennedy KA, et al. Postnatal dexamethasone therapy and cerebral tissue volumes in extremely low birth weight infants. Pediatrics 2007; 119:265-272.
32. Tam EW, Miller SP, Studholme C, et al. Differential effects of intraventricular hemorrhage and white matter injury on preterm cerebellar growth. J Pediatr 2011; 158:366-371.
33. Limperopoulos C, Soul JS, Haidar H, et al. Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. Pediatrics 2005; 116:844-850.
34. Bolduc ME, du Plessis AJ, Evans A, et al. Cerebellar malformations alter regional cerebral development. Dev Med Child Neurol 2011; 53:1128-1134.
35. Volpe. Neurology of the newborn (ed 5.). Philadelphia: Saunders, 2008.
36. Muller H, Beedgen B, Schenk JP, Troger J, Linderkamp O. Intracerebellar hemorrhage in premature infants: sonographic detection and outcome. J Perinat Med 2007; 35:67-70.
37. Ecury-Goossen GM, Dudink J, Lequin M, Feijen-Roon M, Horsch S, Govaert P. The clinical presentation of preterm cerebellar haemorrhage. Eur J Pediatr 2010; 169:1249-1253.
38. Sehgal A, El-Naggar W, Glanc P, Asztalos E. Risk factors and ultrasonographic profile of posterior fossa haemorrhages in preterm infants. J Paediatr Child Health 2009; 45:215-218.
39. Zayek MM, Benjamin JT, Maertens P, Trimm RF, Lal CV, Eyal FG. Cerebellar hemorrhage: a major morbidity in extremely preterm infants. J Perinatol 2012; 32:699-704.
40. McCarthy LK, Donoghue V, Murphy JF. Ultrasonically detectable cerebellar haemorrhage in preterm infants. Arch Dis Child Fetal Neonatal Ed 2011; 96:F281-F285.
41. Tam EW, Rosenbluth G, Rogers EE, et al. Cerebellar hemorrhage on magnetic resonance imaging in preterm newborns associated with abnormal neurologic outcome. J Pediatr 2011; 158:245-250.

42. Bulas DI, Taylor GA, Fitz CR, Revenis ME, Glass P, Ingram JD. Posterior fossa intracranial hemorrhage in infants treated with extracorporeal membrane oxygenation: sonographic findings. AJR Am J Roentgenol 1991; 156:571-575.
43. Sargent MA, Poskitt KJ, Roland EH, Hill A, Hendson G. Cerebellar vermian atrophy after neonatal hypoxic-ischemic encephalopathy. AJNR Am J Neuroradiol 2004; 25:1008-1015.
44. Connolly DJ, Widjaja E, Griffiths PD. Involvement of the anterior lobe of the cerebellar vermis in perinatal profound hypoxia. AJNR Am J Neuroradiol 2007; 28:16-19.
45. Le Strange E, Saeed N, Cowan FM, Edwards AD, Rutherford MA. MR imaging quantification of cerebellar growth following hypoxic-ischemic injury to the neonatal brain. AJNR Am J Neuroradiol 2004; 25:463-468.
46. Jouvet P, Cowan FM, Cox P, et al. Reproducibility and accuracy of MR imaging of the brain after severe birth asphyxia. AJNR Am J Neuroradiol 1999; 20:1343-1348.
47. Alderliesten T, Nikkels PG, Benders MJ, de Vries LS, Groenendaal F. Antemortem cranial MRI compared with postmortem histopathologic examination of the brain in term infants with neonatal encephalopathy following perinatal asphyxia. Arch Dis Child Fetal Neonatal Ed 2013; 98:F304-F309.
48. Martinez-Biarge M, Diez-Sebastian J, Kapellou O, et al. Predicting motor outcome and death in term hypoxic-ischemic encephalopathy. Neurology 2011; 76:2055-2061.
49. Vossough A, Zimmerman RA, Bilaniuk LT, Schwartz EM. Imaging findings of neonatal herpes simplex virus type 2 encephalitis. Neuroradiology 2008; 50:355-366.
50. Komatsu H, Shimizu Y, Takeuchi Y, Ishiko H, Takada H. Outbreak of severe neurologic involvement associated with Enterovirus 71 infection. Pediatr Neurol 1999; 20:17-23.
51. Barkovich AJ, Lindan CE. Congenital cytomegalovirus infection of the brain: imaging analysis and embryologic considerations. AJNR Am J Neuroradiol 1994; 15:703-715.
52. de Vries LS, Gunardi H, Barth PG, Bok LA, Verboon-Maciolek MA, Groenendaal F. The spectrum of cranial ultrasound and magnetic resonance imaging abnormalities in congenital cytomegalovirus infection. Neuropediatrics 2004; 35:113-119.
53. Steinlin M, Blaser S, Boltshauser E. Cerebellar involvement in metabolic disorders: a pattern-recognition approach. Neuroradiology 1998; 40:347-354.
54. Patel S, Barkovich AJ. Analysis and classification of cerebellar malformations. AJNR Am J Neuroradiol 2002; 23:1074-1087.
55. van Wezel-Meijler G. Neonatal Cranial Ultrasonography: Guidelines for the Procedure and Atlas of Normal Ultrasound Anatomy. Second edition. Springer Berlin Heidelberg; 2012.
56. Enriquez G, Correa F, Aso C, et al. Mastoid fontanelle approach for sonographic imaging of the neonatal brain. Pediatr Radiol 2006; 36:532-540.
57. Buckley KM, Taylor GA, Estroff JA, Barnewolt CE, Share JC, Paltiel HJ. Use of the mastoid fontanelle for improved sonographic visualization of the neonatal midbrain and posterior fossa. AJR Am J Roentgenol 1997; 168:1021-1025.
58. Di Salvo DN. A new view of the neonatal brain: clinical utility of supplemental neurologic US imaging windows. Radiographics 2001; 21:943-955.
59. Luna JA, Goldstein RB. Sonographic visualization of neonatal posterior fossa abnormalities through the posterolateral fontanelle. AJR Am J Roentgenol 2000; 174:561-567.
60. van Wezel-Meijler G, Leijser LM, de Bruine FT, Steggerda SJ, Grond van der GJ, Walther FJ. Magnetic resonance imaging of the brain in newborn infants: practical aspects. Early Hum Dev 2009; 85:85-92.

61. O'Halloran CJ, Kinsella GJ, Storey E. The cerebellum and neuropsychological functioning: a critical review. J Clin Exp Neuropsychol 2012; 34:35-56.
62. Gordon N. The cerebellum and cognition. Eur J Paediatr Neurol 2007; 11:232-234.
63. Baillieux H, De Smet HJ, Paquier PF, De Deyn PP, Marien P. Cerebellar neurocognition: insights into the bottom of the brain. Clin Neurol Neurosurg 2008; 110:763-773.
64. Steinlin M. Cerebellar disorders in childhood: cognitive problems. Cerebellum 2008; 7:607-610.
65. Tavano A, Grasso R, Gagliardi C, et al. Disorders of cognitive and affective development in cerebellar malformations. Brain 2007; 130:2646-2660.
66. Allin M, Matsumoto H, Santhouse AM, et al. Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. Brain 2001; 124:60-66.
67. van Kooij BJ, Benders MJ, Anbeek P, van H, I, de Vries LS, Groenendaal F. Cerebellar volume and proton magnetic resonance spectroscopy at term, and neurodevelopment at 2 years of age in preterm infants. Dev Med Child Neurol 2012; 54:260-266.