Commentary — Cerebellar underdevelopment in the very preterm infant: Important and underestimated source of cognitive deficits

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Received 28 March 2021
Accepted 7 April 2021

Keywords: Cerebellum, cognitive deficits, hemorrhage, premature, underdevelopment

1. Introduction

Impairment of cognitive, behavioral, language and socialization functions occur subsequently in approximately 25–50% of preterm infants, especially those of < 28 weeks' gestational age [1]. The deficits are attributed principally to destructive and developmental disturbances of cerebral gray and white matter structures [2]. However, a considerable corpus of data in recent years indicates that disturbances of the developing cerebellum play a crucial role in mediating a substantial portion of this disability (see later). For over two centuries, the principal role of the cerebellum has been considered to involve motor functions. Indeed, only in the past 20–25 years has the role of the cerebellum in cognitive functions been recognized in adults, initially through the pioneering studies of Schmahmann and coworkers [3]. Recognition of such a role in survivors of extremely preterm birth began with the seminal observations of Limperopoulos and coworkers (see later) [4]. Moreover, underlying the disturbed cerebellar development in such preterm infants are a variety of factors, some of which are modifiable or preventable. The purposes of this commentary are to highlight the remarkable developmental events occurring in the cerebellum in the early preterm period, the factors known to disturb these events, the neurocognitive consequences of the developmental disturbance, and the potential means of preventing the cerebellar maldevelopment and its deleterious functional effects.

2. Cerebellar development

Overall growth of the cerebellum from 24–40 weeks' gestation is remarkable, with volumes increasing 4-5-fold [5–7]. The structure also shows...
exponential growth in foliation during this period, with the surface area of the cerebellar cortex increasing more than 30-fold from 24 weeks’ gestation to term [8]. The principal cellular events during this period (reviewed in detail elsewhere) [9] involve a highly proliferative layer of neuronal precursors on the surface of the cerebellum, the external granular layer (EGL), which reaches a peak at 25–30 weeks’ gestation. During this period, these neuronal precursors proliferate exuberantly, under the influence of Sonic hedgehog, secreted by underlying Purkinje cell processes. Subsequently, these neuronal precursors migrate inward, along fibers of specialized glia (Bergmann glia), through the Purkinje cell layer, to form the internal granule cell layer, crucial for formation of cerebellar circuitry. The importance of this proliferative phase is perhaps best understood by considering that the total number of internal granule cells accounts for more than 95% of all neurons in the adult cerebellum and that the number of granule cells in the mature cerebellum, about $10^{11}$, exceeds the total number of neurons in the entire cerebral cortex by 4-fold as well as the total number of all neurons in the human body in aggregate. Thus, occurring during the early premature period, especially from 24 to 32 weeks, is a remarkably important series of events essential for the structural and functional integrity of the cerebellum. As might be expected, these rapidly developing, complex events are vulnerable to a variety of factors, as discussed later.

2.1. Cerebellar hemorrhage

Although the principal focus of this commentary is impaired overall development of the cerebellum, brief discussion of the major form of cerebellar parenchymal injury, i.e., cerebellar hemorrhage (CBH) is important, especially because the initial studies of CBH in the very preterm were the first to identify the relation of cerebellar affection to later cognitive-language-socialization deficits. Thus, in 2007 Limperopoulos and colleagues studied 35 premature infants (mean gestational age, 26 weeks) with isolated CBH [4]. Of this group, as predicted on the basis of the long-known association of the cerebellum with motor functions, 66% exhibited various neuromotor abnormalities consistent with cerebellar dysfunction. However, additionally, other deficits broadened the scope of apparent cerebellar-related sequelae, i.e., impaired receptive (37%) and expressive (42%) language, cognitive deficits (40%), socialization-behavioral deficits (34%), and abnormal autism screening (37%). Comparable data have been observed subsequently, especially most recently by Garfinkle et al. ($n=36$) [10] and Boswinkel et al. ($n=218$) [11]. Notably, the incidence of CBH in very preterm infants is approximately 16% [10], and although important, it appears likely that impaired cerebellar development as described next, is more pervasive, especially in infants of <28 weeks’ gestational age.

2.2. Cerebellar underdevelopment

Impairment of growth of the cerebellum, in the absence of direct cerebellar parenchymal injury (e.g., CBH), is a prominent feature in preterm infants, especially those born very and extremely preterm. Identification of the abnormality is made most readily by quantitative measures with cranial ultrasonography (e.g., transcerebellar diameter) or more readily with MRI (e.g., transcerebellar diameter or regional and total volumes) [12]. The underdevelopment is associated with subsequent neurodevelopmental deficits, including cognitive-behavioral-language-socialization deficits (see later). Two broad mechanistic categories leading to the impaired development can be distinguished, i.e., direct effects and remote effects, as described next.

2.3. Cerebellar underdevelopment — direct effects

Direct effects on cerebellar development refer to those circumstances in which the effector acts directly on the cerebellum, most often at the level of the proliferating neuronal precursor cells of the EGL described earlier. The principal responsible effectors are blood products, glucocorticoid exposure, pain and opioid exposure, hypoxia-ischemia, systemic infection/inflammation, and preterm birth per se.

The likelihood that cerebellar underdevelopment can be related to blood products was shown initially by Messerschmidt et al. who described severe cerebellar growth failure in premature infants after severe IVH [13–15]. Hemosiderin deposition over the cerebellar hemispheres was shown by MRI. Hemosiderin is derived from blood by the following steps: hemolysis of red blood cells, formation of heme, conversion of heme to free iron (and biliverdin) by heme oxygenase, and formation of ferritin and then hemosiderin [16]. Free iron is toxic because it leads to the generation of reactive oxygen species, especially the hydroxyl radical by the Fenton reaction. The neuronal
premature infants, Because subarachnoid blood is a common finding in
ated with both mild and severe grades of IVH [18]. Because subarachnoid blood is a common finding in premature infants, even without overt IVH, this mech-
ism of iron facilitated free radical formation may be operative even in the absence of overt IVH [19].

Glucocorticoid exposure has been associated with impaired cerebellar growth in premature infants. Although antenatal glucocorticoid exposure is not associated with changes in cerebellar growth, post-
natal exposure to betamethasone and dexamethasone has been followed by cerebellar underdevelopment [20, 21]. In one careful study of 224 very preterm infants, compared to 40 full-term infants, cerebellar volumes were smaller at term-equivalent age and at 7 years of age, with the largest deficits in the preterm infants of the earliest gestational ages [21]. The cellular site of the effect is almost certainly the granule precursor cells of the EGL, which are enriched in glucocorticoid receptors, activation of which leads to apoptosis of these crucial neuronal precursors [22]. Of additional importance in this context are the find-
ings that (1) in premature infants, basal and peak serum cortisol responses in the first 2 weeks of life are highly variable, and (2) high serum cortisol levels documented in many infants likely represent continuing “stress” from respiratory and related disorders [23]. Taken together, the data suggest that the cere-
bellum of the very and extremely preterm infant may be exposed to high glucocorticoid levels from a variety of sources, exogenous and endogenous, and that these compounds may play a critical additive and/or central role in impaired proliferation of the EGL and thereby cerebellar underdevelopment.

Pain, stress and opioid exposure are associated with cerebellar underdevelopment in very and extremely preterm infants [24–26]. Studies have quantitated pain and stress in relation to the under-
development and have also identified morphine and fentanyl as negative effectors on cerebellar growth. That the site of the negative effects is the EGL is supported by experimental studies [27].

Hypoxia-ischemia and infection/inflammation have been associated with cerebellar underdevel-
velopment in preterm infants [24, 28]. Experimental studies suggest that the EGL is the principal cellular target [29, 30]. In one such study glucocorticoids accentuated the deleterious effects of hypoxia [30]. However, because hypoxia-ischemia and infec-
tion/inflammation are so important in pathogenesis of cerebral lesions, especially cerebral white matter injury, in the very preterm infant, the role of remote (trans-synaptic) effects is difficult to separate from a direct cerebellar effect (see later).

Finally, premature birth and early extrauterine life may be directly deleterious to cerebellar devel-
opment, in the absence of any appreciable cerebral injury and with varying degrees of control of other deleterious factors described earlier [21, 31–34]. Controlling for the variety of factors potentially dele-
terious to cerebellar growth is difficult. For example, in one experimental study in prematurely delivered baboons, ventilatory regimens seemed to play a role in cerebellar growth impairment [35]. Nevertheless, in one excellent experimental model (preterm piglets) preterm birth disrupted cerebellar development by impairing granule cell proliferation in the EGL [36]. The investigators concluded that preterm birth with precocious exposure to the ex-utero environment altered expression of key cerebellar developmental genes, affecting predominantly granule neuronal pre-
cursors in the EGL and Bergmann glia (along which the precursors migrate to populate the internal gran-
ule cell layer, as described earlier).

2.4. Cerebellar underdevelopment — remote
effects

A second major mechanism involved in the cere-
bellar underdevelopment of the very and extremely preterm infant involves remote trans-synaptic affects, principally involving neuronal connections between the cerebrum and cerebellum. The major circuit involved begins in neurons of the cerebral cortex, axons of which traverse the vulnerable cerebral white matter, eventually synapsing on pontine nuclei in the brain stem. Pontine axons (so-called “mossy fibers”) then proceed (via the contralateral middle cerebral peduncles) to synapse on neurons of the internal gran-
ule cell layer of the cerebellum, the axons of which (“climbing fibers”) proceed to the dendrites of Purk-
inje cells. The latter cells send their axons to the cerebellar roof nuclei, principally the dentate, the axons of which proceed to the thalamus and then, via thalamocortical fibers, to multiple regions of the cerebral cortex. The tight relationship between cere-
bral cortical electrical activity and cerebellar growth was shown in a recent report of preterm infants from
30–40 weeks’ gestational age [37]. Lesions within this circuitry from the cerebral cortex to the cerebellum will lead to a loss of synaptic input and its associated trophic effects. The result is impaired development. Thus, it is not unexpected that there is a strong relation of cerebellar underdevelopment with such cerebral pathologies as cerebral white matter injury, periventricular hemorrhagic infarction and posthemorrhagic hydrocephalus [6, 15, 28, 38–42]. In one study in which the severity of white matter injury was evaluated relative to cerebellar volume deficit, a direct correlation was observed [40]. Consistent with the cerebellar circuitry just described and the trans-synaptic effects, infants with unilateral periventricular hemorrhagic infarction have been shown to exhibit diminished volume in the contralateral cerebellar hemisphere [38].

2.5. Cerebellar underdevelopment —neurodevelopmental outcome

Delineation of neurodevelopmental outcome attributable to cerebellar underdevelopment per se is hindered in those cases associated with prominent supratentorial disease, e.g. cerebral white matter injury, periventricular hemorrhagic infarction. In such cases, major motor deficits (spastic diplegia, hemiplegia, etc.) related to the cerebral lesions are prominent.

Of great interest is the relatively large number of cases of cerebellar underdevelopment, without major cerebral lesions, in whom neurodevelopmental outcomes relate principally to the cerebellar abnormality per se. Not unexpectedly, neuromotor deficits are apparent [21, 43–45]. However, most strikingly, disturbances of language development, cognition, executive and visual-spatial functions, mathematical computation, and IQ have been documented [21, 44, 46, 47]. The deficits have been observed as late as 7 and 10 years of age. The disturbances in cerebellar growth with diminished volumes have also been noted at similar later ages. These disturbances of higher neurological functions are consistent with affection of specific cerebellar circuits, involving cerebellar outflow via the dentate nucleus (see earlier) to the prefrontal cortex (executive functions), posterior parietal cortex (spatial cognition) and superior temporal cortex (language and complex auditory and visual processing). Disturbances of vermis are likely involved in the socialization defects observed in these children. Many of the features observed in infants with cerebellar underdevelopment are similar to the so-called cerebellar cognitive affective syndrome described initially in adults (see earlier).

It is reasonable to speculate that less severe disturbances of cerebellar development in extremely and very preterm infants contribute importantly to the spectrum of cognitive-behavioral-language-socialization deficits often attributed entirely to cerebral lesions. Herein lies a very fertile area for future clinical research.

3. Conclusions

The principal emphases of this commentary are cerebellar underdevelopment in the very preterm infant and the role thereof in causation of the critical cognitive-behavioral-language-socialization deficits observed subsequently. Because studies of the principal cerebellar parenchymal destructive lesion, CBH, first identified cerebellar involvement in the mediation of such deficits, brief consideration of this entity is included.

The origin of cerebellar underdevelopment appears to occur principally between 24–32 weeks’ gestation, when cerebellar development is extraordinarily active. The most vulnerable site appears to be the EGL, located on the surface of the cerebellum. The two most likely pathogenic mechanisms operative involve either direct effects on the cerebellum, especially the EGL, or remote trans-synaptic effects emanating from the cerebrum. The most promising foci for intervention involve the direct effects. Modifiable factors relate to the use of glucocorticoids or morphine and related opioids, management of neonatal pain and stress, and prevention of hypoxic-ischemic and/or systemic infection/inflammatory events. Prevention of IVH, a complicated and elusive goal [48], would be of particular value. However, because premature birth per se, with reprogramming of cerebellar development, appears to be important, prevention of prematurity, perhaps the most elusive goal of all, would be critical. Nonetheless, many of the pathogenetic factors are modifiable, thereby providing optimism for prevention of this important underdevelopment.

References

[1] Neil JJ, Volpe JJ. Encephalopathy of prematurity: Clinical-neurological features, diagnosis, imaging, prognosis, therapy. In: Volpe JJ, Inder TE, du Plessis AJ, Darras BT,
Perlman J, Neil J, et al., editors. Volpe’s Neurology of the Newborn. Chapter 16, 6th ed. Philadelphia, PA: Elsevier; 2018; pp. 425-57.

[2] Volpe JJ. Dysmaturity of premature brain: Importance, cellular mechanisms and potential interventions. Pediatr Neurol. 2019;95:42-66.

[3] Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. J Neuropsychiatr Clin Neurosci. 2004;16:367-78.

[4] Limperopoulos C, Bassan H, Gauvreau K, Robertson RL, Sullivan N, Benson CB, et al. Does cerebellar injury in premature infants contribute to the high prevalence of long-term cognitive, learning, and behavioral disability in survivors? Pediatics. 2007;120:584-93.

[5] Chang CH, Chang FM, Yu CH, Ko HC, Chen HY. Assessment of fetal cerebellar volume using three-dimensional ultrasound. Ultrasound Med Biol. 2000;26:981-8.

[6] Limperopoulos C, Soul JS, Gauvreau K, Huppi PS, Warfield SK, Bassan H, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics. 2005;115:688-95.

[7] Clouchoux C, Guizard N, Evans AC, du Plessis AJ, Limperopoulos C. Normal fetal brain growth by quantitative in vivo magnetic resonance imaging. Am J Obstet Gynecol. 2012;206:173 e1-8.

[8] Lemire RJ, Loeser JD, Lecch RW, Alvord EC, Jr. Normal and abnormal development of the human nervous system. Hagerstown: Harper & Row; 1975.

[9] Volpe JJ. Cerebellum of the premature infant – rapidly developing, vulnerable, clinically important. J Child Neurol. 2009;24:1085-104.

[10] Garthinkle J, Guo T, Synnes A, Chau V, Branson HM, Ufkes S, et al. Location and size of preterm cerebellar hemorrhage and childhood development. Ann Neurol. 2020;88:1095-108.

[11] Boswinkel V, Steggerda SJ, Fumagalli M, Parodi A, Ramenghi LA, Groenendaal F, et al. The CHOPIn study: A multicenter study on cerebellar hemorrhage and outcome in preterm infants. Cerebellum. 2019;18:989-98.

[12] du Plessis AJ, Limperopoulos C, Volpe JJ. Cerebellar development. In: Volpe JJ, Inder TE, du Plessis A, Darras BT, deVries LS, Perlman J, et al., editors. Volpe’s Neurology of the Newborn. Chapter 4, 6th ed. Philadelphia: Elsevier; 2018. pp. 73-99.

[13] Messerschmidt A, Brugger PC, Boltsheuer E, Zoder G, Sterniste W, Birnbaecher R, et al. Disruption of cerebellar development: potential complication of extreme prematurity. AJNR Am J Neuroradiol. 2005;26:1659-67.

[14] Messerschmidt A, Fuiko K, Prayer D, Brugger PC, Boltsheuer E, Zoder G, et al. Disrupted cerebellar development in preterm infants is associated with impaired neurodevelopmental outcome. Eur J Pediatr. 2008;167:1141-7.

[15] Messerschmidt A, Prayer D, Brugger PC, Boltsheuer E, Zoder G, Sterniste W, et al. Preterm birth and disruptive cerebellar development: Assessment of perinatal risk factors. Eur J Paediatr Neurol. 2008;12:455-60.

[16] Thompson KJ, Shoham S, Connor JR. Iron and neurodegenerative disorders. Brain Res Bull. 2001;55:155-64.

[17] Jeong HJ, Shim SY, Cho HJ, Cho SJ, Son DW, Park EA. Cerebellar development in preterm infants at term-equivalent age Is impaired after low-grade intraventricular hemorrhage. J Pediatr. 2016;175:86-92 e2.

[18] Tam EW, Miller SP, Studholme C, Chau V, Glidden D, Poskitt KJ, et al. Differential effects of intraventricular hemorrhage and white matter injury on preterm cerebellar growth. J Pediatr. 2011;158:366-71.

[19] Inder TE, Perlman JM, Volpe JJ. Intracranial hemorrhage: Subdural, subarachnoid, intraventricular (term infant), miscellaneous. In: Volpe JJ, Inder TE, Darras BT, de Vries LS, du Plessis A, Neil JJ, et al., editors. Volpe’s Neurology of the Newborn. Chapter 22, 6th ed. Philadelphia: Elsevier; 2018. pp. 593-622.

[20] Tam EW, Chau V, Ferriero DM, Barkovich AJ, Poskitt KJ, Studholme C, et al. Preterm cerebellar growth impairment after postnatal exposure to glucocorticoids. Sci Transl Med. 2011;3:105ra.

[21] Matthews LG, Inder TE, Pascoe L, Kapur K, Lee KJ, Monson BB, et al. Longitudinal preterm cerebellar volume: Perinatal and neurodevelopmental outcome associations. Cerebellum. 2018;17:610-7.

[22] Noguchi KK, Wallis KC, Wozniak DF, Olney JW, Roth KA, Farber NB. Acute neonatal glucocorticoid exposure produces selective and rapid cerebellar neural progenitor cell apoptotic death. Cell Death Differ. 2008;15:1582-92.

[23] Ng PC. Is there a “normal” range of serum cortisol concentration for preterm infants? Pediatics. 2008;122:873-5.

[24] Ranger M, Zwicker JG, Chau CM, Park MT, Chakravartthy MM, Poskitt K, et al. Neonatal pain and infection relate to smaller cerebellum in very preterm children at school age. J Pediatr. 2015;167:292-8 e1.

[25] Zwicker JG, Miller SP, Grunau RE, Chau V, Brant R, Studholme C, et al. Smaller cerebellar growth and poorer neurodevelopmental outcomes in very preterm infants exposed to neonatal morphine. J Pediatr. 2016;172:81-7 e2.

[26] McPherson C, Haslam M, Pineda R, Rogers C, Neil JJ, Inder TE. Brain injury and development in preterm infants exposed to fentanyl. Ann Pharmacother. 2015;49:1291-7.

[27] Hauser KF, Houidi AA, Turbek CS, Elde RP, Maxson W, 3rd. Opioids intrinsically inhibit the genesis of mouse cerebellar granule neuron precursors in vitro: Differential impact of mu and delta receptor activation on proliferation and neurite elongation. J Eur Neurosci. 2000;12:1281-93.

[28] Brossard-Racine M, Poretti A, Murnick J, Bouyssi-Kobar M, McCarter R, du Plessis AJ, et al. Cerebellar microstructural organization is altered by complications of premature birth: A case-control study. J Pediatr. 2017;182:28:33.

[29] Rees S, Stringer M, Just Y, Hooper SB, Harding R. The vulnerability of the fetal sheep brain to hypoxemia at midgestation. Brain Res Dev Brain Res. 1997;103:103-18.

[30] Nguyen V, Sabeur K, Maltepe E, Ameri K, Bayraktar O, Rowitch DH. Sonic hedgehog agonist protects against complex neonatal cerebellar injury. Cerebellum. 2018;17:213-28.

[31] Pieterman K, White TJ, van den Bosch GE, Niessen WJ, Reiss IKM, Tibboel D, et al. Cerebellar growth impairment characterizes school-aged children born preterm without perinatal brain lesions. AJNR Am J Neuroradiol. 2018.

[32] Herzmann CS, Snyder AZ, Kenley JK, Rogers CE, Shimony JS, Smyser CD. Cerebellar functional connectivity in term- and very preterm-born infants. Cereb Cortex. 2019;29:1174-84.

[33] Brossard-Racine M, McCarter R, Murnick J, Tinkleman L, Vezina G, Limperopoulos C. Early extra-uterine exposure alters regional cerebellar growth in infants born preterm. Neuroimage Clin. 2019;21:101646.

[34] Wu Y, Stoodley C, Brossard-Racine M, Kapse K, Vezina G, Murnick J, et al. Altered local cerebellar and brainstem development in preterm infants. Neuroimage. 2020;213:116702.
[35] Rees SM, Loeliger MM, Munro KM, Shields A, Dalitz PA, Dieni S, et al. Cerebellar development in a baboon model of preterm delivery: Impact of specific ventilatory regimes. J Neuropathol Exp Neurol. 2009;68:605-15.

[36] Iskusnykh IY, Buddington RK, Chizhikov VV. Preterm birth disrupts cerebellar development by affecting granule cell proliferation program and Bergmann glia. Exp Neurol. 2018;306:209-21.

[37] De Wel O, Van Huffel S, Lavanga M, Jansen K, Dereymaeker A, Dudink J, et al. Relationship between early functional and structural brain developments and brain injury in preterm infants. Cerebellum. 2021;Epub Ahead of Print.

[38] Limperopoulos C, Soul JS, Haidar H, Huppi PS, Bassan H, Warfield SK, et al. Impaired trophic interactions between the cerebellum and the cerebrum among preterm infants. Pediatrics. 2005;116:844-50.

[39] Shah DK, Anderson PJ, Carlin JB, Pavlovic M, Howard K, Thompson DK, et al. Reduction in cerebellar volumes in preterm infants at term-equivalent age are associated with the presence of supratentorial lesions. AJNR Am J Neuroradiol. 2006;27:573-9.

[40] Kersbergen KJ, Makropoulos A, Aljabar P, Groenendaal F, de Vries LS, Counsell SJ, et al. Longitudinal regional brain development and clinical risk factors in extremely preterm infants. J Pediatr. 2016;178:93-100.

[42] Shany E, Inder TE, Goshen S, Lee I, Neil JJ, Smyser CD, et al. Diffusion tensor tractography of the cerebellar peduncles in prematurely born 7-year-old children. Cerebellum. 2017;16:314-25.

[43] Spittle AJ, Doyle LW, Anderson PJ, Inder TE, Lee KJ, Boyd RN, et al. Reduced cerebellar diameter in very preterm infants with abnormal general movements. Early Hum Dev. 2010;86:1-5.

[44] Anderson PJ, Treyvaud K, Neil JJ, Cheong JLY, Hunt RW, Thompson DK, et al. Associations of newborn brain magnetic resonance imaging with long-term neurodevelopmental impairments in very preterm children. J Pediatr. 2017;187:58-65.e1.

[46] Allin M, Matsumoto H, Santhouse AM, Nosarti C, AlAsady MH, Stewart AL, et al. Cognitive and motor function and the size of the cerebellum in adolescents born very preterm. Brain. 2001;124:60-6.

[47] Van Kooij BJ, Benders MJ, Anbeek P, Van Haastert IC, 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;54:260-6.

[48] Inder TE, Perlman JM, Volpe JJ. Preterm intraventricular hemorrhage posthemorrhagic hydrocephalus. In: Volpe JJ, Inder TE, Darras BT, de Vries LS, du Plessis A, Neil JJ, et al., editors. Volpe’s Neurology of the Newborn. Chapter 24, 6th ed. Philadelphia, PA: Elsevier; 2018, pp. 637-98.