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Review

Preterm birth and cerebellar neuropathology

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SUMMARY

Improved survival rates in premature infants and more sensitive neuroimaging techniques have expanded the scope of recognized neurodevelopmental disabilities in this vulnerable population and have implicated a role for cerebellar pathology in their origin. Although supratentorial pathologies are well studied, cerebellar pathology has been under-recognized in premature infants. The purpose of this review is to provide a concise description of established acquired cerebellar pathologies in premature infants including cerebellar atrophy/hypoplasia, hemorrhage, and infarction. The cerebellum develops over an extended period during which time cerebellar injury tends to occur with the potential to derail the cerebellum from its expected growth trajectory and perturb the establishment of cerebellar neural circuitry. The occurrence of cerebellar injury in this vulnerable period may have life-long implications that extend beyond the immediate damage sustained by the cerebellum, all of which needs to be considered as we research the causes and effects of neurodevelopmental disabilities in these patients.

1. Introduction

Improvements in survival rates of premature infants and neuroimaging techniques have spawned a reconsideration of the neurodevelopmental sequelae and neuropathology in this patient population [1,2]. To date, most of the research that addresses this problem has centered on the cerebrum, with particular emphases on white matter injury and supratentorial hemorrhages and how these processes contribute to cerebral palsy. However, the sequelae of preterm birth are diverse and encompass not only the typical motor system perturbations of cerebral palsy, but also impairments in cognitive, behavioral, language, psychological and social domains. Furthermore, cerebellar injury has been associated with neurodevelopmental sequelae, which raised awareness of the role of the cerebellum in the range of disabilities experienced by surviving premature infants and illustrated how previously under-recognized neuropathologies may contribute to neurodevelopmental disability beyond the clinicopathologic scope of cerebral palsy [3–5].

Cerebellar injury in the preterm infant ranges widely in severity on a spectrum from minute focal, unilateral lesions to lesions that involve both hemispheres and the vermis, up to lesions that destroy the entire cerebellum [6–12]. Extreme prematurity is perhaps the most consistently documented risk factor for cerebellar injury, which is believed to occur in about 19% of extremely preterm infants weighing <750 g [7]. The incidence is highest in the most premature infants [13] and studies have identified a number of associated maternal and perinatal risk factors [4,7,9,10,12]. Typically cerebellar injury is clinically silent [11]; however, some infants may exhibit motor findings [14]. Frequently there is a prominent hemorrhagic component and often, but not always, cerebellar injury is accompanied by supratentorial injury such as intraventricular hemorrhage, periventricular hemorrhagic infarction, periventricular leukomalacia (PVL), or posthemorrhagic hydrocephalus [3,6,7,10,12].

Cerebellar hemorrhages are likely more common and probably better studied than infarctions, which are also a well-recognized complication of premature birth [6,15]. Practically speaking, hemorrhages and infarctions are probably not as distinct as the literature (and this article) may make them appear, since varying degrees of each pathologic process may be present in a particular case and it is unclear what makes hemorrhage predominate in one lesion and infarction in another. Both hemorrhages and infarcts tend to occur in the inferior cerebellum, in the territory supplied by the posterior

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inferior cerebellar artery (PICA), suggesting that this vessel may be at risk for prematurity-related perturbations in blood flow. Cerebellar atrophy or hypoplasia is likely the most prevalent cerebellar pathology in premature infants [13]. Strictly speaking, hypoplasia refers to a structure exhibiting incomplete development or underdevelopment, often due to a developmental arrest, whereas atrophy is due to degeneration of previously existing cells in a formed structure that results in decreased organ or tissue size. Often the terms hypoplasia and atrophy are used imprecisely or synonymously and, since they may be difficult to distinguish, they will be considered together in this review. It is possible that both atrophy and hypoplasia are occurring simultaneously or at different stages of injury in the cerebella of these patients. The pathogenesis of atrophy/hypoplasia is unclear and likely due to both direct and remote effects of various injures, which will be discussed.

This review focuses on acquired cerebellar pathology of premature infants with an emphasis on depicting the neuropathology of atrophy/hypoplasia, hemorrhage, and infarction. The neuropathologic findings frame a discussion of potential pathologic mechanisms underlying these cerebellar lesions. We begin with a brief account of cerebellar development and neural connectivity to set the stage for a discussion of how the neuropathologic processes under consideration may disrupt the developmental trajectory of the cerebellum.

2. Cerebellar development, neural circuitry, and vulnerability

Cerebellar development is complex and readers are referred elsewhere for a detailed overview [16,17]; however, it is important to discuss some of the essentials here [16,17] so that the impact of these injuries on the cerebellum and, ultimately, on survivors of premature birth can be appreciated. The cerebellum develops over a long period beginning in the fourth week of gestation and extending to about 20 postnatal months. The essential neural foundation of the cerebellum is established early, and is followed by a much longer period of elaboration and fine tuning of neural networks within the cerebellum and its critical relay nuclei (i.e. the inferior olivary nuclei, basis pontis, and deep cerebellar nuclei), which extends well into the postnatal period. The pace of cerebellar growth is unparalleled in development as imaging studies show a 3.5-fold increase in volume from 28 to 40 weeks of gestation [13] and a 30-fold increase in surface area, which is largely driven by the expansion of the external granule cell layer on the cerebellar cortical surface that is mediated by Sonic Hedgehog (Shh) elaborated by Purkinje cells [18,19].

The cerebellar relay nuclei are intricately interconnected with the cerebellum and are actively developing during this critical period of external granule cell proliferation and migration when the patterns of cortical neural connectivity are being established. Axons from neurons in the inferior olivary nucleus extend into the cerebellum at 20 weeks of gestation and ascend the dendrites of Purkinje cells at 34 weeks in a process that continues postnatally [20,21]. The basis pontis expands rapidly from 13 to 28 gestational weeks as neuronal differentiation occurs and axons extend into the cerebellar cortex [22]. The dentate is the largest deep cerebellar nucleus and it is heavily interconnected with the cerebellar hemispheres, thus being closely associated with higher neurologic functions [23]. The complex infolding required for the dentate nucleus to adopt its mature serpentine configuration starts at 24 weeks and continues until about 35 weeks of gestation [24]. Neurons in the dentate nucleus also have a slower phase of maturation that extends into the postnatal period, during which time dendritic complexity is enhanced [24].

This lengthy developmental period likely enables the cerebellar cortex and relay-nuclei to become larger and more intricately interconnected, thereby enhancing processing capacity; however, there could be a price to pay for these benefits. The long developmental period seemingly places the cerebellum at risk by rendering it vulnerable to a wide variety of potential injuries. In fact, this period of robust cerebellar growth, cellular migration and differentiation also seems to be when cerebellar injury is prone to occur. For example, the mean gestational age of premature infants in an autopsy study of cerebellar hemorrhage was 25 weeks [12], at which time the cerebellum has only achieved 20–25% of its expected term volume and the thickness of the external granule cell layer is at its peak [25,26]. Therefore, an injury occurring in this timeframe not only causes immediate damage to the cerebellum, but could also derail the cerebellum from its expected growth trajectory, and disrupt neural connectivity patterns among the cerebellum, its relay-nuclei, and other neuroanatomic sites. This is important to consider in interpreting neuropathological findings and neurodevelopmental studies.

3. Cerebellar atrophy/hypoplasia

Atrophy/hypoplasia may be the most prevalent cerebellar pathology of prematurity based on neuroimaging studies conducted at term equivalent age or months to years after injury [8,9,13,27–32]. Different patterns of cerebellar involvement have been described in imaging studies, but typically there is bilateral, often symmetric involvement of the cerebellar hemispheres (Fig. 1A–C) associated with reduced pontine size (Fig. 1D) and supratentorial injury [8,26,33]. Imaging studies show that unilateral or bilateral cerebellar atrophy develops subsequent to infarcts or hemorrhages, occurring in 37% of subjects about two months after hemorrhage [7,11].

Atrophy/hypoplasia likely arise due to the net effects of diverse, interrelated pathogenetic mechanisms on cerebellar development. These mechanisms have been considered as either direct factors, which directly injure developing cerebellar tissue, or as remote factors, which can perturb cerebellar development from a distance, potentially via disrupted trans-synaptic interconnections [26]. Direct and remote effects are not readily separable and likely coexist [26]. Direct factors include infarcts and hemorrhages, and a number of others have been described. The presence of subarachnoid blood may lead to excitotoxic cell death and hemosiderin may generate toxic free radicals [8,9,34]. Hypoxic–ischemic conditions directly injure the cerebellum and have been associated with small cerebellar volumes in survivors [9,29]. Experimentally, direct hypoxic–ischemic injury reduced proliferation and enhanced apoptosis in external granule cells while decreasing Purkinje cell numbers – changes that would be expected to impair the formation of the internal granule cell layer and cerebellar cortical connections [35,36]. Furthermore, imaging studies have correlated cerebellar hypoplasia with PVL, which is well known to be associated with hypoxia–ischemia and infection–inflammation [7,28–30,37,38]. Postnatal glucocorticoids, another direct factor, were associated with impaired cerebellar but not cerebral growth in a serial neuroimaging study of premature infants [39]. The proliferative effect of Shh on external granule cell precursors is antagonized by glucocorticoids, and compounds that activate the Shh-pathway have been experimentally shown to reverse the effects of glucocorticoids, suggesting that these precursor cells may represent a druggable target [40]. Other direct factors have been implicated [26] and yet others will likely be identified.

It has been known that cerebellar injury is associated with brainstem hypoplasia or atrophy [41,42], which may be due to neuronal loss and gliosis following trans-synaptic degeneration [12]. More recently, volumetric neuroimaging studies of premature infants have revealed an association between supratentorial