COMMENTARY

Selective Vulnerability and the Cerebellum in Neonates

In this issue of the *AJNR*, Drs. Connolly, Widjaja, and Griffiths report involvement of the anterior portion of the cerebellar vermis after profound perinatal hypoxia.[1] This is not a new observation; it has been previously reported in this journal.[2] What is clear is that many of us are seeing this type of injury more frequently. What is not clear is what causes it.

When we talk about diffuse cerebral anoxia, the term "selective (or regional) vulnerability" is commonly used to imply that certain brain regions are affected more than others. This process results in a peculiar lesion distribution depending on the type of injury. In general, diffuse anoxia injures the "older parts" of the brain first and foremost. That is why the hippocampi and the cerebellum are commonly involved.[3] Overall, the third most commonly affected region is the neocortex. These patterns of injuries are commonly seen in adults and in older children, but they are less common in neonates. Thus, selective vulnerability depends on the patient's age (or "brain maturity") and the severity and duration of the hypoxic event.

During a mild-to-moderate reduction in perfusion, the brain's autoregulatory mechanisms preserve blood flow to the brain stem, cerebellum, and basal ganglia. This results in cerebral watershed–region injuries. If perfusion is markedly reduced, all of the brain is affected, but the areas with higher metabolism such as the cerebellar cortex, hippocampi, deep gray nuclei, and peri-Rolandic cortices suffer the most. Eventually, the remainder of the cortex and white matter will be affected too. These 2 patterns of injury are seen mostly in adults, older children, and mature babies.

It has been traditionally thought that in premature babies the periventricular white matter is a watershed zone between ventriculofugal and ventriculopetal arteries (some investigators refute this concept). The arteries in these "terminal" zones have limited vasodilatory ability during hypoxia, further exacerbating damage. Oligodendrocyte activity (during myelination) increases the metabolism of white matter, rendering it more susceptible to ischemia and resulting in the so-called "periventricular leukomalacia." Brain stem injury may also occur in premature babies, reflecting increased metabolic activity, particularly of cranial nerve nuclei. Germinal matrix hemorrhages are due to reperfusion of the arterial system supplying the periventricular regions and to rupture of the walls of blood vessels previously damaged by ischemia. Injury to the cerebellar germinal matrix may result in peripheral cerebellar bleeds. All of these injuries are seen with mild-to-moderate anoxia. Profound anoxia in preterm babies produces injuries in the dorsal brain stem, ventrolateral thalami, and anterior cerebellar vermis.[4]

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None of the above explains involvement of the anterior vermis in term babies as reported in this issue of the *AJNR*. Cerebellar cortical (Purkinje) cells are particularly prone to ischemic damage due to their lack of ability to generate energy during anoxia, a factor that increases the damage produced by the initial hypoxia. Not only are Purkinje cells affected, but cells in the granular layer also die. Experiments on animals indicate that during artificial ventilation, oxidative metabolism in the brain stem and cerebellum becomes abnormal even if it is not preceded by hypoxia.[5] Blood oxygen level–dependent MR imaging shows decreased fetal cerebellar signal intensity in animals after maternal hypoxia.[6] All of these mechanisms support diffuse cerebellar injury, but not a focal one in the vermis. In the many babies with diffuse anoxia whom I have seen, diffusion-weighted images have shown no acute lesion in the vermis. So, why does this lesion occur?

Limperopoulos et al reported unilateral cerebellar atrophy following contralateral cerebral injuries and vice versa in preterm babies.[7] They thought that these findings were due to trophic transynaptic effects. The cerebral cortex relates to the cerebellum (particularly its white matter) via corticothalamocerebellar pathways. Efferent pathways (cerebellothalamic) run from the deep gray matter nuclei of the cerebellum to the thalami via the superior peduncles. If thalamic nuclei are damaged, retrograde degeneration of their related pathways may occur. The data presented by Connolly and co-authors indicate that in 2 patients without thalamic lesions the vermis was spared whereas 18 patients with vermian lesions had thalamic involvement.[1] It would be interesting to measure the volume of the superior peduncles in these patients. Because the cerebellothalamic tracts begin in the deep gray nuclei (dentate and fastigial), it is unclear why these structures are preserved while the efferent white matter is damaged with anoxia. The key to this observation may lie in apoptosis. In adults, anoxia kills cells predominantly by necrosis, whereas in children immature cells may also die by apoptosis.[8] In children, dentate nuclei of adult configuration are not seen until nearly term.[9] The Purkinje cells in the cerebellar cortex are still more immature than the neurons in the dentate nuclei.[10] It is conceivable that this relative lack of maturity somehow protects the cerebellar gray matter (no articles report injuries to the cortex or deep nuclei of the cerebellum in preterm or term babies). In this environment, the white matter is thus relatively more mature than the gray matter. Transynaptic degeneration via the cerebellothalamic tracts may result in damage to the relatively more mature white matter that is not appreciable immediately but becomes evident later because of programmed cell death. In the article by Sargent et al, of the 12 children with vermian lesions, only one had questionable acute abnormalities in the same region on neonatal imaging studies.[2]

Although the sequelae of cerebral anoxia are devastating at any age, they are particularly cruel in children because of their longer projected lifespan. We need to be able to recognize the imaging signs of this type of injury to help plan for the care of these children. It is clear from the recent literature that involvement of the anterior cerebellar vermis is a highly specific

and sensitive marker of severe brain anoxia in term babies though its etiology remains unclear.

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