Brain Injury in the Premature Infant: Current Concepts

J.J.

Joseph J.

Volpe

Department of Neurology, Children's Hospital, Harvard Medical School, Boston, Mass., USA

Prof. Joseph Volpe, MD, Department of Neurology, Children's Hospital, Harvard Medical School, Boston, MA 02115 (USA)

The magnitude of the problem of brain injury in the premature infant and, particularly, the prevention of that injury is enormous. Approximately 50,000 infants are born yearly in the United States with a birth weight of $\leq 1,500$ g. Approximately 85% of these infants survive and, of the survivors approximately 5-15% later exhibit major spastic motor deficits, grouped under the rubric, 'cerebral palsy', and an additional 25-50% exhibit cognitive/behavioral deficits that result in school failure. The major neurological manifestations of brain injury in the premature infant are, firstly, spastic motor deficits. These consist primarily of spastic quadripare-sis, characteristically with the lower extremities being more affected than the upper extremities (thus, the term 'spastic diplegia'), or spastic hemiparesis, or both. Intellectual deficits are frequent accompaniments. Less severe disturbances of motility and cognition occur, as noted above, in 25-50% of survivors. The major neuropathologies for the spastic motor deficits, with or without accompanying intellectual deficits, are periventricu-lar hemorrhagic infarction and periventricu-lar leukomalacia. In the following we will consider periventricular hemorrhagic infarction and periventricular leukomalacia in sequence in terms of the neuropathology, the means of identifying this pathology in vivo, the relation of this pathology to the subsequent neurological deficits noted above, the pathogenesis, the probable cause(s), and the possibilities for prevention.

Periventricular Hemorrhagic Infarction

Periventricular hemorrhagic infarction refers to hemorrhagic necrosis of periventricular white matter that is usually large and almost invariably asymmetric. The lesion most often coexists with severe inträventricu-lar hemorrhage and, indeed, approximately 10-15% of all infants with intraventricular hemorrhage also exhibit periventricular hemorrhagic infarction. The neuropathology of periventricular hemorrhagic infarction is striking and consists of a relatively large region of hemorrhagic necrosis in the periventricular white matter, just dorsal and lateral to

the external angle of the lateral ventricle. The necrosis is strikingly asymmetric – in the largest series reported 67% of such lesions were exclusively unilateral and in virtually all of the remaining cases, grossly asymmetric, even though bilateral. The principal diagnostic procedure utilized to identify periventricular hemorrhagic infarction in vivo is cranial ul-trasonography. Although CT and MRI are useful and effective in the imaging of this lesion, the excellent sensitivity, resolution and portable capability make ultrasonography the much preferred

approach. The major long-term correlates of periventricular hemorrhagic infarction are spastic hemiparesis (or asymmetric quadriplegia) and intellectual deficits. The spastic hemiparesis characteristically affects the lower extremities as much as the upper extremities, presumably because the periventricular locus of the lesion affects the descending fibers emanating from the lower extremity as well as the upper extremity region of the motor cortex. The pathogenesis of periventricular hemorrhagic infarction relates to the fact that in general the lesion has the pathological characteristics of a venous infarction. A direct relation to germinal matrix-intraventricular hemorrhage seems likely in most cases on the basis of three clearly defined facts. First, approximately 80% of the parenchymal lesions are observed in association with large (and usually asymmetric) intra-ventricular hemorrhage. Second, essentially the parenchymal lesions invariably occur on the same side as the larger amount of intra-ventricular blood. Third, the parenchymal lesions develop and progress after the occurrence of the intraventricular hemorrhage. The peak time of their occurrence is the 4th postnatal day, i.e., when 90% of cases of intraventricular hemorrhage have already occurred. The minority of periventricular hemorrhagic lesions may represent unilateral or asymmetric hemorrhagic periventricular leukomalacia

or, even less commonly, infiltration of blood into the periventricular white matter from a large intraventricular hemorrhage, or a combination of these possibilities.

Periventricular Leukomalacia

The neuropathology of periventricular leukomalacia consists of focal necrosis of periventricular white matter, with a particular predilection for the periventricular tissue at the level of the optic radiation adjacent to the trigone of the lateral ventricles and at the level of the frontal cerebral white matter near the foramen of Monro. Microscopically, axonal disruption with coagulation necrosis, i.e., the appearance of an infarction, is the major early finding. Oligodendroglial cell death and subsequent myelin deficiency are the usual sequelae. Lateral ventricular dilation reflects the paucity of myelin at the sites of injury. On ultrasound scan, in the coronal projection the lesions appear as bilateral, primarily linear echodensities just adjacent to the external angles of the lateral ventricles. Many examples of less severe periventricular leukomalacia are not detectable acutely by cranial ultrasonography. Whether early MRI scans would be useful in this setting remains to be established. The logistical difficulties in testing this possibility are not trivial. The major long-term clinical correlates of periventricular leukomalacia are spastic diplegia and intellectual deficits. Spastic diplegia is a type of spastic quadriplegia in which the lower extremities are affected more than the upper extremities.

The pathogenesis of periventricular leukomalacia relates to three principal factors:

periventricular vascular anatomic factors;

pressure-passive cerebral circulation, and

enhanced vulnerability of actively differentiating and/or myelinating periventricular glial cells.

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Delineation of a causative relationship between a pressure-passive cerebral circulation and the occurrence of periventricular leukomalacia has been hindered by the lack of a method for essentially monitoring cerebral blood flow continuously. Recent data to be shown in this presentation suggest that the advent of near-infrared spectroscopy will overcome this problem. The characteristics underlying the particular vulnerability of the differentiating oligodendroglia, which are the principal cellular targets of the lesion, have been addressed in recent studies of the

human brain by immunocytochemical methods and oligodendrocytes in culture by cellular biological approaches. These data will be reviewed in the presentation.

Conclusions

There are two principal lesions that underlie the brain injury and the neurological manifestations thereof in the premature infant, i.e., periventricular hemorrhagic infarction and periventricular leukomalacia. Periventricular hemorrhagic infarction may be largely preventable, i.e., by averting germinal matrix-intraventricular hemorrhage. Periventricular leukomalacia may be preventable in part by deterring impaired cerebral blood flow, e.g., secondary to systemic hypotension. However, further insights into the mechanisms of the vulnerability to cell death in differentiating oligodendroglia and the interruption of these mechanisms are necessary before this lesion can be eliminated.

Extended Abstracts

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