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Cerebrospinal Fluid Physiology of the Developing Fetus

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Rapid advances in imaging techniques have made it possible to detect hydrocephalus early in gestation. In this article, no attempt has been made to cover the diagnosis, management or outcome of fetal hydrocephalus. Instead, this is a brief review focusing on the cerebrospinal fluid (CSF) physiology of the developing fetus and the pathophysiology of hydrocephalus.

CSF Pathways

Formation of the ventricular system begins at the time the neural groove closes to form a neural tube. Fluid is present within the tube, even before the choroid plexus anlage appears. This fluid serves as a structural support for the tube, as well as a pathway for diffusion of metabolites prior to the formation of blood vessels. In the small, thin-walled fetal brain, fluid movement is characterized by noncommunication between the ventricles and the meningeal fluid spaces. Ciliary action inside the ventricles produces directional streaming and fluid mixing which aid in diffusing substances from the outer surface of the brain through the extracellular spaces of the wall of the neural tube into the ventricular cavity, and vice versa.

The mesenchyme surrounding the brain thins out in a definite, organized pattern to form the pia-arachnoid membrane and the cisterns of the subarachnoid spaces. The residual mesenchyme forms the trabecular meshwork of the arachnoid. Ultrasonography can visualize fluid within the subarachnoid space at 15 weeks gestation. It has also been noted that the amount of fluid present at various regions in the subarachnoid space changes with development (1). The subarachnoid space and its configuration are virtually complete at birth (2). The subarachnoid space develops independently of the choroid plexus and does not require the presence of a CSF circulation. There is no movement of fluid out of the ventricular system during the early development of the subarachnoid space (3). The outlets to the fourth ventricle are covered with a membrane, even after the choroid plexus begins to create CSF. This membrane does not appear to impair outflow of CSF from the ventricle, since drainage occurs via intercellular pores (4) in the membrane. The membrane subsequently becomes progressively attenuated, and develops larger and larger holes until it is no longer present.

Outflow resistance from the ventricles increases as gestation progresses, but does not change to any degree after birth (5). The resistance to CSF drainage in turn is the end product of the differentiation of the cells that make up the pathways. Glycoconjugates appear to influence the development of the matrix of the drainage pathway and to determine the degree of resistance (6). Presumably impaired function or absence of normal glycoconjugates could lead to increased resistance which, if significant, would result in hydrocephalus.

Choroid Plexus

The choroid plexus of the third and fourth ventricles arises from invaginations of the roof plate, whereas the choroid plexus of the lateral

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ventricles arises from the choroidal fissure of the developing telencephalon. The choroid plexus consists of epithelium covering a stromal core. The stromal core, or tela choroidea, is derived from mesenchyme. The epithelium—and the ependyma—arise from the spongioblasts lining the ventricles. The epithelium is initially pseudostratified, but is subsequently transformed into a single layer of cuboidal cells. During development, the choroid plexus forms lobules, which in turn become fronds covered with microvilli. This process markedly increases the surface area of the choroid while reducing the proportional volume that the choroid plexus occupies within the ventricular system. The microvilli become progressively more convoluted. The degree of convolution may relate to secretory activity. In humans, the greatest bulk of the choroid plexus resides in the lateral ventricles; here it is attached to the medial ventricular walls, where it is supplied by branches of the anterior and posterior choroidal arteries. The remaining choroid plexus hangs from the roof of the third and fourth ventricles and is supplied by branches of the medial posterior choroidal artery and the anterior inferior/posterior inferior cerebellar arteries, respectively. The choroidal veins drain mainly into the internal cerebral vein, which is part of the deep venous or Galenic system.

Development of CSF Blood-Brain Barriers

The earliest CSF most likely is an ultrafiltrate of plasma. With the development of the CSF blood-brain barriers, the CSF becomes a secretion. The concept that these barriers are less developed in the fetus and infant is based upon observations that blood-borne dyes stain the immature brain more extensively, that the concentration of protein in the CSF is higher in newborns, and that metabolites and various solutes enter more readily and reach higher concentrations in the fetal brain than in the adult brain (7).

However, many problems exist in trying to determine the permeability of CSF blood-brain barriers in the immature brain, as there are many differences and continual changes occurring during gestation. The very early embryonic brain has no blood vessels, so exchanges with the blood in the external vessels must occur *indirectly*. After vascularization begins, the initially low density of the blood vessels increases steadily with gestation. The number of blood vessels and the cerebral blood flow increase in relation to metabolic needs. The extracellular space appears to be larger at certain stages, so restriction to free diffusion is less. The volume of the brain is initially small relative to its surface area, and the amount of CSF is proportionately higher. The kinetics of CSF circulation is different in the fetus, so the removal of dyes and other markers of permeability, such as inulin, is not the same as in the adult CNS.

Finally, the concentration of various substances in the central nervous system (CNS) will depend upon many different active transport mechanisms, which mature independently. All these factors will produce alterations that make it difficult to assess any changes in the passive permeability characteristics of the CSF blood-brain barriers (8). In spite of these complexities, experimental models have been designed and are able to answer some of the questions regarding the development of the barriers special to the CNS. This helps to increase our understanding of the mature brain.

The CNS barriers are indeed more permeable in the fetus, but this greater permeability does not relate to the tightness of the junctions at either the brain capillary endothelium (9) or at the choroid plexus epithelium (10, 11). Indeed, the intercellular junctions at these locations are well formed very early in fetal development and do not differ significantly from those in the adult. Saunders has shown that the degree of capillary permeability relates, instead, to the size of intracellular channels, which may be part of the endoplasmic reticulum, or even possibly transcellular vesicles (12). Evidence indicates that a decrease in the size and perhaps the number of these "pores" is what tightens the barrier.

In order for the barrier to tighten, however, it is necessary for astrocytes to be present. It has been shown that capillaries of CNS origin grown outside the CNS lose their normal barrier properties, whereas non-CNS capillaries grown in the CNS acquire the appropriate characteristics (13, 14). Additional evidence to support the contention of the inductive influence of the astrocytes is the loss of normal capillary barrier function in the mature brain at the site of tumors. There are no data as to the changes that occur in the permeability of the choroid plexus epithelium with gestation.

Statz and Felgenhauser studied the protein content in CSF of fetuses, premature infants, and infants (15). The total protein level reaches a peak concentration at 20 weeks gestation and

then falls steadily. For full-term infants less than 2 months of age it is normal to find a protein level up to 100 mg/mL. Premature infants show even higher protein levels. The concentration of protein in the CSF varies with conceptual age but not with birth weight or with postnatal life span, even if the infant is born prematurely, indicating that the maturation of the barrier, as reflected by decline in protein content, is not influenced by the timing of birth.

The protein level represents a steady state at the time of sampling and is dependent upon multiple factors (ie, CSF secretion rate, volume of distribution, CSF circulation, absorption rates of macromolecules). The protein level is not dependent solely on the degree of barrier permeability at the time of sampling. The protein does not appear to emanate from the brain side of the barrier. It has an electrophoretic pattern similar to that of plasma (12).

Although cited as an indication of barrier immaturity in the neonatal CNS, the focal deposition of bilirubin in the basal ganglia (ie, kernicterus) does not reflect an increased permeability to this substance. The *conjugated* form of bilirubin is not lipid soluble and does not cross the neonatal CNS to any significant degree. However, the *unconjugated* lipid-soluble form of bilirubin easily crosses into the CNS, as is also true in the adult. That the unconjugated lipid-soluble form does not usually enter the brain is due to the fact that it is bound to plasma protein. It is only when the binding capacity of plasma protein is exceeded that the free, lipid-soluble bilirubin enters the CNS. Overloading of the binding capacity of plasma protein may result from reduced numbers of available binding sites on the plasma protein secondary to competition from drugs or to lowered blood pH.

Why the bilirubin should selectively affect some regions more than others and why the developing brain is more sensitive to this substance is not known.

Formation of CSF

Normally about 80%–90% of CSF production is derived from the choroid plexus. Evidence suggests that the remaining portion most likely originates from the CNS parenchyma. The factors that have a direct bearing on the possibility that the parenchyma is the main source of nonchoroidal CSF formation include the presence of an extracellular space that is approximately 15% of the brain volume, lack of ependymal resistance to free exchange between the fluid in the extracellular space and the CSF, and the similar composition of extracellular fluid and CSF. The most likely candidate for the parenchymal source of CSF is the capillary endothelium, since its high mitochondria content could provide the metabolic energy required for such a function (16).

The first step in the formation of CSF is the passage of an ultrafiltrate of plasma through the non-tight junctioned choroid capillary endothelium into the connective tissue stroma beneath the epithelium of the villus. This passage is driven by hydrostatic pressure. The ultrafiltrate is subsequently transformed into a secretion (namely, CSF) by an active metabolic process within the choroidal epithelium (17). The precise mechanism of this active process is largely speculative (17). Current thinking is that the active process depends upon creating osmotic gradients by pumping sodium across the epithelial cell wall, first at the *basal* surface of the cell, ie, at that surface of the epithelial cell furthest from the ventricle, so that water enters the cell, and then, again, at the *apical* surface of the cell that abuts the ventricle, so that water leaves the cell to enter the ventricle. Apparently, sodium-potassium adenosine triphosphatase effectively pumps sodium into the basal side of the epithelial cell so that water enters the epithelial cell down the osmotic gradient created. Carbonic anhydrase then catalyzes the formation of bicarbonate in the cell, so that the proton is fed back to the sodium pump as a counter-ion with potassium. In a manner analogous to that involving the basal side of the epithelium, sodium-potassium adenosine triphosphatase located in the microvilli on the *apical* surface of the epithelium extrudes sodium from the epithelial cell into the ventricle, so that water passes from the cell into the ventricle down the osmotic gradient. Because the epithelial cells do not swell nor shrink, the sum of the two processes must be in balance.

The relation of CSF formation to brain maturation has been studied in several animal species but not in humans (18). The data indicate that CSF production increases at a rate greater than can be accounted for by a corresponding increase in choroid plexus weight or brain weight. Thus the increased production of CSF may reflect maturation of the enzyme systems involved.

Under normal physiologic conditions CSF formation can be considered independent of pressure. If intraventricular pressure becomes ele-

vated to such a degree that it reduces cerebral perfusion pressure, then CSF formation does diminish, because the increased back pressure reduces the quantity of ultrafiltrate formed from the choroidal capillaries in the first step in CSF production. Oversecretion of CSF does occur in the presence of a choroid plexus papilloma. In utero, hydrocephalus secondary to the presence of a choroid plexus papilloma has been recently demonstrated as well (1).

Absorption of CSF

The absorption of CSF and its constituents depends upon bulk flow, in addition to passive or facilitated diffusion and active transport of specific solutes. As hydrocephalus results exclusively from impairment of bulk flow of CSF, only this aspect will be covered.

The rate of CSF absorption is pressure dependent and linear over a fairly wide physiologic range. The only force proven to be responsible for CSF absorption is that of a hydrostatic gradient.

The arachnoid villus would seem to be ideally situated to drain CSF from the subarachnoid space into the major dural sinuses, since it consists of a cell cluster that projects from subarachnoid space into these venous structures. A point of controversy regarding the arachnoid villus is the existence—or absence—of open channels connecting the arachnoid side of the villus with the venous side of the villus. The presence or absence of such channels would indicate a basic difference in the physiology by which CSF and its constituents drain. The open villus model would be solely pressure responsive and would allow for passive escape of macromolecules. In the closed villus model where the cell would be covered by an endothelial membrane with continuous tight junctions, CSF drainage would also depend upon osmosis, filtration, and an active transport process by which macromolecules could cross the barrier. Accumulating physiologic and morphologic evidence fully supports the open channel model.

Until recently, scant consideration has been given to the fact that CSF might drain at sites other than the arachnoid villus under normal physiologic conditions. A number of recent laboratory investigations, to include primates, indicates that a significant quantity of CSF can drain into lymphatic channels (19). Although there have been no studies demonstrating lymphatic drainage of CSF in man, there would be no reason to suspect any difference from what has been found in the primate model.

Alterations of CSF Physiology in Hydrocephalus

With the single exception of CSF overproduction by choroid plexus papilloma, *hydrocephalus results from impaired CSF absorption.* Production of CSF in hydrocephalus is either normal or near normal. "Real time" estimation of CSF production shows considerable variation on a minute-to-minute basis, but confirms the fact that the average rate of production remains within normal limits even in the face of infantile hydrocephalus (20). In compensated hydrocephalus, the rate of absorption must equal the rate of formation. In noncompensated hydrocephalus only a minute fraction of the total amount of CSF secreted is retained. Thus, even in hydrocephalus, the overwhelming majority of CSF formed is still absorbed. As CSF formation is relatively constant, it is the change in resistance to absorption that determines CSF pressure and whether or not the hydrocephalus is progressive. Simpson et al (21) attempted to delineate the dynamics of fetal intracranial pressure in utero, at the time of therapeutic abortion. Although their study suffered from having only seven patients with diverse CNS malformations, they could not correlate the type of CNS lesion with the intracranial pressure found in fetuses with an excessive amount of CSF. In hydrocephalic fetuses, an attempt has been made to correlate ventricular size with the velocity waveforms of pulsed Doppler recordings of cerebral blood flow, but no correlation has been found to date (22, 23).

In utero imaging studies now make it possible to detect developmental abnormalities, mass lesions, evidence of infections, and hemorrhage, any of which can result in hydrocephalus. The antenatal diagnosis of hydrocephalus may influence the time of delivery, the mode of delivery, and the possibility of aborting the fetus. In a situation that is fairly analogous to in utero hydrocephalus, a retrospective analysis was undertaken to assess the efficacy of aggressive surgical management of progressive hydrocephalus in preterm neonates with intracranial hemorrhage. The overwhelming factor in determining the outcome in this patient group was the extent of the intracranial hemorrhage. Hydrocephalus and its treatment was not significant (24). There is no

evidence that early control of hydrocephalus significantly improves neurologic function, since the functional outcome is determined by the underlying insult to the CNS rather than the hydrocephalus.

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