Leaders

Pathological approach to the diagnosis of hydrocephalus

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Hydrocephalus is defined as excess fluid in the cranium. This may result from increased production, reduced resorption, or obstruction to the flow of CSF, or from increase in volume of CSF spaces following loss of tissue or failure of brain growth. Underlying disorders form a highly heterogeneous group, the nature of which will determine age of onset, prognosis, and management.

Congenital hydrocephalus has an incidence of 0.8 to 3 per 1000 live births.^{1,2} In term infants prenatal causes predominate. In pre-term infants over half are thought to acquire their hydrocephalus in the perinatal period, reflecting the susceptibility of these infants to haemorrhage and ischaemic injury at this time. Haemorrhage, infection, and tumours are rare in congenital hydrocephalus but are the most common causes of postnatally acquired hydrocephalus³ (table 1). The very poor prognosis of babies with hydrocephalus of prenatal onset is due to the frequent association with other malformations and with chromosome anomalies in this group.

Diagnosis

Ventriculomegaly is usually identified by ultrasound scan. The normally developing cerebral ventricles undergo considerable variations in

size during the second trimester, with rapid decrease in size from 15 to 20 weeks, gradually slowing until 28 weeks of gestation. In order to establish the diagnosis, serial assessments of ventricular size are needed and the diagnosis cannot be made with certainty until 17 to 20 weeks of gestation.

Specific diagnosis depends on finding a ventricle to hemisphere ratio of more than 0.5 or an anterior or posterior horn diameter of more than 10 mm after 20 weeks.

The natural history of fetal ventriculomegaly is closely related to the presence or absence of other malformations. Over 75% of fetal ventriculomegaly is associated with other malformations, either within or outside the CNS.^{4,5} In some the fetal head enlarges, but an increased biparietal diameter is not usually identifiable before 24 to 30 weeks. Occasionally the biparietal diameter is reduced, indicating tissue loss or failure of brain growth. Chromosome analysis reveals anomalies in about 30% of these malformed fetuses, compared with less than 6% in isolated ventriculomegaly.⁶ α Fetoprotein and cholinesterase assay of amniotic fluid may provide supportive evidence of associated CNS malformation.

In about one quarter of cases, ventriculomegaly is isolated and remains stable. These fetuses have a much better prognosis: half will develop normally and three quarters have an IQ of over 70, the condition occasionally resolving before birth.^{5,7}

Pathological confirmation

If pregnancy is terminated after ultrasound diagnosis of ventriculomegaly it is clearly important that sonographic diagnosis is confirmed. The cause of the hydrocephalus and any associated malformations must be identified by careful necropsy examination. This is essential for genetic counselling and for the management of future pregnancies.

The general necropsy examination should include a complete skeletal survey with particular reference to midline defects such as spina bifida and skull base malformations. Anomalies such as arthrogryposis, polydactyly, or adducted thumbs may give clues to associated malformation syndromes.

The fetal brain at 17 to 20 weeks is tiny and fragile and collapses readily on handling.

Table 1 Causes of postnatally acquired hydrocephalus

Increased production of CSF	Choroid plexus papilloma
Reduced resorption of CSF	-Damage to arachnoid villi by haemorrhage or infection -Congenital absence of arachnoid villi ²⁵
Obstruction to CSF flow	-Tumour -Infection -Haemorrhage -Aqueduct stenosis -Skull base deformity, eg mucopolysaccharidosis, achondroplasia
Loss of brain tissue	-Ischaemia -Infarction -Haemorrhage -Infection -Trauma
Failure of brain growth	-Isolated ventriculomegaly -Ventriculomegaly with other malformations, eg Arnold-Chiari malformation, agenesis of corpus callosum, Dandy-Walker malformation, lissencephaly, cerebellar hypoplasia

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Figure 1 Twenty week fetus. View of normal posterior fossa structure after fixation in situ. The cranium has been opened along suture lines before fixation. The cerebellar hemispheres are small at this age and the caudal part of the fourth ventricle remains visible (arrow).

Ideally the brain should be fixed in situ after carefully opening the cranium along the suture lines to allow entry of fixative. Examination of the contents of the posterior fossa and their relations in situ is particularly important in identifying obstruction to CSF flow at this site and is much more reliably done after fixation (fig 1). Once the cranium has been opened the fixed brain is easily removed. Removal before fixation is much more difficult because of the extreme softness of the fetal brain. It is facilitated by immersing the fetus in water to float the brain out, or by delivering it into a wide container of formalin in hypertonic saline which supports the brain as it leaves the cranial cavity. The practical aspects of brain removal are described in detail by Keeling.⁸

Macroscopic photographs of the fixed brain can avoid the need for extensive descriptive reports and provide a valuable archive for later case review. Reference to such photographs is helpful in preparing a final report.

Cutting the immature brain, even after fixation, usually causes the cerebral hemispheres to collapse, and it can be extremely difficult to recognise ventriculomegaly. Objective measurement of ventricular size in fetal necropsy material has not proved reliable or reproducible.

The first cut should be a high horizontal cut through the cerebral peduncles to detach the brainstem. The hemispheres should be cut coronally and representative blocks taken. The brainstem and cerebellum require careful examination and the entire midbrain must be blocked for histology if the aqueduct is to be fully assessed. The small fetal hindbrain can be examined in two blocks obtained by cutting

Figure 2 Ventricular lining from a child with chronic hydrocephalus. The ependyma is thin with focal deficiencies overlying small glial cushions (haematoxylin and eosin, $\times 44$).

through the pons and cerebellum at right angles to the brainstem. These blocks are embedded on end so that step sections through the rostral block contain the entire midbrain and aqueduct. Levels through the caudal block will display cerebellum, pons, and medulla. In larger brains the cerebellum has to be blocked separately.⁹

Any degree of maceration makes neuropathological examination even more difficult. However, even in very macerated cases, it is worth recovering fragments for histology. These can show surprisingly good preservation and reveal such diagnoses as cortical malformation, infection, haemorrhage, or tumour.

Fetal neuropathological examination reveals a cause for ventriculomegaly in over 80% of cases¹⁰ but in the remaining 20% it may not be possible to make a diagnosis or even to establish the presence of ventriculomegaly.

General pathology of hydrocephalus

The effects of hydrocephalus are borne mainly by the white matter. In the acute phase there is ependymal disruption, extracellular oedema of the periventricular white matter, reactive gliosis, and axonal degeneration. Myelination appears normal on remaining axons and may even be excessive, with ectopic myelination of glial processes.¹¹ The cortex shows minor changes such as decreased dendritic density.

Ultrasound images of acutely oedematous white matter show flares which eventually evolve into cysts or atrophy associated with ventricular dilatation.¹²

Later on the white matter is atrophic and gliosed. The ependyma is stretched and thin with focal deficiencies and cushions of glia bulging through them (fig 2). Ependyma may be totally lost over large areas of the ventricular wall. Simple loss of ependyma without gliosis is a common finding in otherwise normal infant brains.

Causes of fetal hydrocephalus

Neuropathological studies of fetuses with ventriculomegaly diagnosed by ultrasound have

Table 2 Ninety four cases of fetal hydrocephalus (HC) diagnosed by neuropathology among 1601 consecutive necropsies¹⁰

HC with other malformations (n=85)	CNS and other malformations, 47 CNS malformation only, 32 Extra-CNS malformation only, 6
Isolated HC (n=9)	Post-haemorrhage, 6 Post-infection, 3

Figure 3 Part of the lining of the fourth ventricle (IV) in a baby who had a prenatal intraventricular haemorrhage. There is a cushion of gliotic tissue containing many haemosiderin bearing macrophages. The overlying ependyma is partly deficient. Reactive ependymal proliferation is seen as a row of rosettes (arrowheads). (Haematoxylin and eosin, $\times 46$).

confirmed its frequent association with other malformations. In the largest published neuropathological series of 101 fetuses,¹⁰ 90% had other abnormalities, 84% involving the nervous system and 56% involving other systems (table 2). Only nine of the 101 cases had isolated hydrocephalus; all of these were the result of haemorrhage or infection.

Both *haemorrhage* and *infection* may cause hydrocephalus by several mechanisms:

(1) CSF flow may be obstructed, usually in the long narrow aqueduct of Sylvius in the midbrain, at the outflow foramina of the fourth ventricle, or in the basal cisterns where blood clots and inflammatory debris may accumulate. Blood and infection in the CSF cause ependymal damage and proliferation of glia which form cushions that encroach on and narrow the CSF pathways. Gliosis and blood pigment persist for many years as evidence of previous inflammation or haemorrhage (figs 3 and 4).

(2) There may be damage to the arachnoid granulations with consequent reduction in resorption of CSF.

(3) Blood in the CSF is a potent cause of vasospasm¹³ which can cause parenchymal ischaemia. Babies who develop severe germinal matrix haemorrhages are also at risk of infarction in the periventricular white matter.¹⁴ In these cases parenchymal loss exacerbates the hydrocephalus, causing *hydrocephalus ex vacuo*.

Tumours are rare causes of developmental hydrocephalus. They are usually rapidly growing, destructive tumours and enlargement of the fetal head is due to volume of tumour rather than true hydrocephalus.

Figure 4 Aqueduct stenosis in the same case as fig 3. The outline of the original aqueduct is represented by an irregular band of proliferated ependymal cells (arrowheads). The lumen is obstructed by glial tissue containing haemosiderin. A few small patent channels remain. (Haematoxylin and eosin, $\times 34$.)

Aqueduct stenosis

Aqueduct stenosis is rare and was found in only two of Roume's 101 cases.¹⁰ Narrowing by tumour is rare in the fetus. Aqueduct obstruction may result from intrauterine infections or haemorrhage, when ependymal proliferation and rosette formation accompany gliosis. Calcification and residual haemosiderin are sometimes seen. In experimental animals vitamin deficiencies and viral infections can induce non-inflammatory aqueduct obstruction.¹⁵ Reactive ependymal proliferation can result in aqueduct branching or forking as described originally by Russell.¹⁶ CSF follows an irregular pathway through these channels, some becoming dilated and others stenotic. Rarely a thin septum may form across the aqueduct which can be demonstrated on magnetic resonance imaging (MRI), but true septae are rarely found in necropsy material.

Aqueduct stenosis not only causes hydrocephalus but is probably more often the *result* of hydrocephalus.^{17 18} Hydrocephalic cerebral hemispheres compress the midbrain laterally, narrowing the aqueduct into a dorsoventral slit, sometimes with lateral branching (fig 5). The same lateral forces also cause compression or beaking of the quadrigeminal plate and the bodies of the thalamus are pushed together, enlarging the normal area of adhesion between them to produce the effect of midline fusion of the thalamus.

Figure 5 Aqueduct of Sylvius in a 19 month baby with chronic hydrocephalus. (A) There is little gliosis and no evidence of haemorrhage or reactive ependymal proliferation. The ventral part is a narrow slit while dorsally there is a channel with small lateral branches (PTAH $\times 20$). The starred area is seen in (B). (B) Higher power pictures in an adjacent section of (A). There is complete fusion of the lateral walls of the ventricle. The absence of reactive change suggests this is the result of lateral compression or malformation. (Haematoxylin and eosin, $\times 60$.)

Pathogenesis of hydrocephalus with malformations of the central nervous system

When hydrocephalus is associated with brain malformations it is not usually possible to identify a cause for altered CSF hydrodynam-

Figure 6 Nineteen week fetus with Dandy-Walker malformation, viewed from behind. The grossly dilated fourth ventricle is seen bordered by small splayed cerebellar hemispheres, with remnants of the ruptured cyst at their edges. The anterior vermis is intact (arrow). cp = choroid plexus.

ics to account for the ventriculomegaly. More often this is a matter of speculation and ventricular enlargement is assumed to result from inadequate brain growth.

ARNOLD-CHIARI MALFORMATION

In this malformation there is a commonly associated triad of hydrocephalus, spina bifida, and caudal displacement of the medulla and cerebellar tonsils into the cervical spinal canal. Midline bony malformations causing spinal dysraphism and a small posterior fossa with herniation of its contents are described. It has also been suggested that the spinal lesion causes traction on the cord, or lowered spinal pressure, allowing downward displacement of the hindbrain. Impaction of the displaced hindbrain structures in the foramen magnum is thought to obstruct the outflow foramina of the fourth ventricle with subsequent development of hydrocephalus.¹⁷

Studies of human fetal brains, however, have shown that the hindbrain malformation does not consistently precede ventricular dilatation, and the cause for hydrocephalus is unresolved.¹⁹

AGENESIS OF THE CORPUS CALLOSUM

This malformation is often associated with ventricular enlargement, but nothing is known of the hydrodynamics in human cases.² Rarely there are associated midline cysts. These, as with other meningeal cysts, may act as space occupying lesions and alter CSF pressure, causing hydrocephalus.²⁰

DANDY-WALKER MALFORMATION

In this condition there is a large cystic expansion of the fourth ventricle, with partial or complete agenesis of the midline cerebellar vermis (fig 6). The tentorium is raised and the posterior fossa enlarged. Hydrocephalus is presumed to result from increased pressure in the posterior fossa but does not always develop until the first year of life.

CORTICAL MALFORMATIONS

When hydrocephalus develops in or after the third trimester it may disrupt the pattern of cortical gyri, which appear more numerous

than usual and mimic polymicrogyria "redundant gyration", but the histology of the cortex is normal.²¹

However, true primary malformation of the cortex is often associated with gross enlargement of the ventricles. In lissencephaly syndromes the brain surface remains smooth, because of cortical dysplasia resulting from disordered neuronal migration. In type I lissencephaly the cortex is simple and poorly endowed with neurones, while in type II, nests of ectopic neurones are found among proliferated blood vessels and connective tissue in the leptomeninges. This type is characteristic of the Walker-Warburg syndrome, when there are associated muscle and eye malformations.

The reason for increased ventricular size is unclear but it may result from failure of brain growth.

CEREBELLAR HYPOPLASIA

Defective cerebellar growth is frequently associated with ventriculomegaly. A possible mechanism is failure of formation of the cerebellar outflow foramina.

From the above discussion it is clear that hydrocephalus is not always the result of obvious pathology, such as alteration in CSF flow dynamics or loss of brain tissue. Recognition and description of syndromes where hydrocephalus is associated with other malformations is important in clinical practice and particularly in genetic counselling. However, this exercise adds little to our understanding of how, or why, the ventricles enlarge.

Recent advances in the fields of genetics and molecular biology may help to make progress in tracing developmental aberrations which result in hydrocephalus.

X linked hydrocephalus is one condition where such attention has recently been focused. The syndrome is also called HSAS (Hydrocephalus with Stenosis of the Aqueduct of Sylvius) and is responsible for 2–15% of primary "idiopathic" hydrocephalus in males. Hydrocephalus develops after 20 weeks of gestation, often too late for detection by routine ultrasound scan.

Clinical features include mental retardation and lower limb spasticity. This contrasts with other forms of hydrocephalus where intelligence may be normal and motor impairment is unusual.

Recently the gene responsible for this condition has been mapped to a locus at Xq 28.²² Other neurological disorders located here include MASA syndrome, SPG1 (spastic paraplegia, type 1), and most recently, X linked epilepsy with periventricular heterotopias.²³ This locus also contains the gene for the L1 neural cell adhesion molecule. This is a surface glycoprotein, part of the immunoglobulin superfamily and expressed on developing axons. It appears to have a role in neurite extension, formation of axon bundles, and neuronal migration.

The predominant neuropathological findings in X linked hydrocephalus are ventricular dilatation, slit-like narrowing of the aqueduct, absence of the pyramidal tracts in the medulla,

midline fusion of the thalamus, and absence of the corpus callosum. Detailed examination of several cases now suggests that the slit-like malformation of the aqueduct is most likely to be secondary to development of hydrocephalus in early life. This is possibly also the cause of thalamic midline fusion. The sequence of origin of these abnormalities remains unknown.

Impairment of formation of axonal bundles may underlie failure of formation of the corpus callosum and pyramidal tracts in X linked hydrocephalus. Studies of the expression of L1 NCAM in developing brains from normal humans and those with X linked hydrocephalus may determine whether L1 NCAM has a role in development of axon bundles in vivo. We still do not know why the ventricles enlarge.

There are various transgenic animal models of neurodevelopmental disorders which show similarities to human syndromes with hydrocephalus. One such example is a mouse with absence of the MARCKS protein (myristoylated, alanine-rich C kinase substrate), a cellular substrate for protein kinase C. In this model there is absence of the corpus callosum, ventriculomegaly, and dysplasia of the cerebral cortex and retina.²⁴ These malformations suggest a defect in neuronal migration resembling that seen in lissencephaly.

Studying these models allows us to benefit from recent advances in genetics and molecular biology in the attempt to unravel the processes involved in human brain development at a molecular level and so begin to explain the abnormalities which have long been described by traditional neuropathology.

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