Hydrocephalus in children

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Hydrocephalus is a common disorder of cerebral spinal fluid (CSF) physiology resulting in abnormal expansion of the cerebral ventricles. Infants commonly present with progressive macrocephaly whereas children older than 2 years generally present with signs and symptoms of intracranial hypertension. The classic understanding of hydrocephalus as the result of obstruction to bulk flow of CSF is evolving to models that incorporate dysfunctional cerebral pulsations, brain compliance, and newly characterised water-transport mechanisms. Hydrocephalus has many causes. Congenital hydrocephalus, most commonly involving aqueduct stenosis, has been linked to genes that regulate brain growth and development. Hydrocephalus can also be acquired, mostly from pathological processes that affect ventricular outflow, subarachnoid space function, or cerebral venous compliance. Treatment options include shunt and endoscopic approaches, which should be individualised to the child. The long-term outcome for children that have received treatment for hydrocephalus varies. Advances in brain imaging, technology, and understanding of the pathophysiology should ultimately lead to improved treatment of the disorder.

Published **Online**
August 7, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60694-8

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Introduction

Although a precise definition is controversial, hydrocephalus generally refers to a disorder of cerebrospinal fluid (CSF) physiology resulting in abnormal expansion of the cerebral ventricles, typically associated with increased intracranial pressure. Although undoubtedly related, idiopathic normal pressure hydrocephalus causing ventriculomegaly without intracranial hypertension and idiopathic intracranial hypertension (or pseudotumour cerebri) causing intracranial hypertension without ventriculomegaly are beyond the scope of our Seminar. Here we discuss epidemiology, pathophysiology, diagnosis and treatment, controversies, and future research agendas for paediatric hydrocephalus—a surprisingly neglected topic given its prevalence and economic burden.

Epidemiology

Hydrocephalus is the most common disease treated by paediatric neurosurgeons and accounts for roughly US$2 billion in health expenditures in the USA every year.[1] The prevalence of infant hydrocephalus is roughly one case per 1000 births,[2] but this is probably greater in developing countries.[3] In sub-Saharan Africa alone the new cases of infant hydrocephalus might exceed 200 000 per year, mostly due to neonatal infection.[4] The most common causal mechanisms in high-income countries are post-haemorrhagic hydrocephalus of prematurity, congenital aqueduct stenosis, myelomeningocele, and brain tumours.[5,6]

Pathophysiology

Understanding of CSF physiology is evolving and incomplete. In the traditional bulk flow model, CSF is secreted by the choroid plexus epithelium in the cerebral ventricles, flows into the subarachnoid spaces, and enters the cerebral venous system via the arachnoid granulations. In this model, hydrocephalus results from obstruction to CSF flow anywhere from its origin to its most distal point of absorption, with a few exceptional cases in which CSF might be hypersecreted. Classically, obstruction of CSF flow within the ventricles is classified as obstructive or non-communicating hydrocephalus, whereas obstruction of CSF flow or its absorption in the subarachnoid spaces is known as communicating hydrocephalus.

Researchers have since developed an alternative hydrodynamic model that explains hydrocephalus as a disorder of intracranial pulsations.[7,8] In this model, arterial systolic pressure waves entering the brain are normally dissipated by the subarachnoid spaces, venous capacitance vessels, and intraventricular pulsations transmitted by the choroid plexus. The intraventricular pulsations are then absorbed through the ventricular outlet foramina. According to this model, dysfunction of these pulsation absorbers contributes to abnormally high pulsation amplitudes that result in ventricular expansion. Abnormal pulsations might have different effects based on age-dependent changes in brain compliance, resulting in a continuum of dysfunctional CSF physiology (eg, idiopathic hydrocephalus in infants, idiopathic intracranial hypertension in adolescents and young adults, and normal pressure hydrocephalus in elderly individuals).[9]

Causes

Irrespective of the model used to understand hydrocephalus, ventricular or subarachnoid space obstruction and raised cerebral venous pressures can all lead to hydrocephalus, with several potential causes for each

Search strategy and selection criteria

We searched PubMed, the Cochrane Library, and Embase for reports published in English from Jan 1, 2000, to Nov 14, 2014. The search terms "hydrocephalus" or "hydrocephalic" were combined with many search terms for epidemiology, pathophysiology, aetiologies, diagnosis, management, and current issues (appendix). In addition to the search results, we also hand searched the references of relevant articles retrieved by the search strategy. We excluded letters.

See **Online** for appendix

	Cause	Proposed mechanism
Acquired hydrocephalus		
Inflammatory		
Subarachnoid haemorrhage or infection	Arachnoid scar	Dysfunctional subarachnoid space
Intraventricular haemorrhage or infection	Ependymal scar	Ventricular obstruction
Neoplasm		
Parenchymal brain tumour	Mass effect	Ventricular obstruction
Spinal cord tumour	Altered CSF composition	Dysfunctional subarachnoid space
Disseminated tumour	Tumours with meningeal infiltration—eg, primitive neuroectodermal tumour	Dysfunctional subarachnoid space
Choroid plexus tumour	Altered CSF composition	Dysfunctional subarachnoid space
Choroid plexus tumour	Mass effect	Ventricular obstruction
Choroid plexus tumour or hyperplasia	Altered choroid plexus function	CSF overproduction—or hyperdynamic intraventricular pulsations
Vascular		
Vascular malformation	Ventricular obstruction—eg, vein of Galen malformation; venous hypertension—eg, arteriovenous malformation	Ventricular obstruction; decreased venous compliance—or decreased CSF absorption
Disordered cerebral venous function	Extrinsic venous obstruction—eg, skeletal dysplasias; intrinsic venous obstruction—eg, venous sinus thrombosis; idiopathic venous dysfunction—eg, congenital idiopathic hydrocephalus	Decreased venous compliance—or decreased CSF absorption
Congenital or developmental hydrocephalus		
Congenital aqueduct stenosis	Third ventricle outlet obstruction	Ventricular obstruction
Neural tube defects—eg, myelomeningocele and Chiari II malformation	Third or fourth ventricle outlet obstruction; altered venous compliance; arachnoid or ependymal scar	Variable
Posterior fossa malformations	Fourth ventricle outlet obstruction—eg Dandy-Walker complex; Chiari I malformation	Ventricular obstruction
Developmental cysts	Mass effect	Ventricular obstruction
Congenital foramen of Monro atresia	Lateral ventricle outlet obstruction	Ventricular obstruction

Table 1: **Causes of paediatric hydrocephalus**

	Putative genetic link
X-linked hydrocephalus with aqueduct stenosis (307000)	*L1CAM*
Non-syndromic autosomal recessive hydrocephalus (HYC; 236600 [HYC1]; 615219 [HYC2])	*CCDC88C*; *MPDZ*
Fried-type syndromic mental retardation (304340)	*AP1S2*
Walker-Warburg syndrome (multiple subtypes)	*POMT1*; *POMT2*; *POMGNT1*; and others
Neural tube defects (folate-sensitive [601634] and insensitive [182940] forms)	Multiple susceptibility genes involved in planar-cell polarity—eg, *FUZ*, *VANGL1/2*, *CCL2*, and others; folate-sensitive neural tube defects associated with genes in folate synthesis pathway (*MTR*, *MTRR*, *MTHFR*, *MTHFD*)
Primary ciliary dyskinesia's and other ciliopathies (including the many heterogeneous subtypes of Mekel-Gruber syndrome and Joubert syndrome)	Multiple genes involved in cilia structure, function, and regulation—eg, *CC2D2A*, *TMEM67*, *MKS1*, and others
RAS-opathies—eg, neurofibromatosis type 1, Noonan's syndrome, Costello's syndrome, cardio-facio-cutaneous syndrome	*NF1*; Ras-Raf-MEK-ERK pathway genes—eg, *KRAS*, *BRAF*, *PTPN11*, and others
VACTERL-H (association of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies plus hydrocephalus; 276950)	*PTEN*
X-linked VACTERL-H (300515)	*FANCB*

Numbers given are Online Mendelian Inheritance in Man (OMIM) identifiers.

Table 2: **Genetic abnormalities associated with paediatric hydrocephalus**

mechanism. Table 1 and table 2 present ways to broadly organise most of the known aetiological mechanisms of paediatric hydrocephalus.

Possible genetic origins

Recent progress has elucidated some of the genetic underpinnings of inherited congenital hydrocephalus.[2] Genetic factors are contributors to both syndromic and non-syndromic forms (table 2).[10] Population studies show familial aggregation of congenital hydrocephalus, with increased recurrence risk ratios for same-sex twins and first-degree and second-degree relatives.[11,12] More than 50 mutant loci or genes have been linked to non-syndromic congenital hydrocephalus in animals, but only three in humans.[2,13,14] Most patients with non-syndromic congenital hydrocephalus have aqueduct stenosis (figure 1).[14] Of these, X-linked hydrocephalus (OMIM number 307000) is the most common heritable form, accounting for about 10% of cases in boys (table 2).[14] Mutations in *L1CAM*, encoding the L1 cell adhesion molecule, are the most common cause.[14,15] Researchers have identified two additional gene mutations in severe autosomal-recessive forms: truncating mutations in *MPDZI* encoding MUPP-1, a tight junction protein

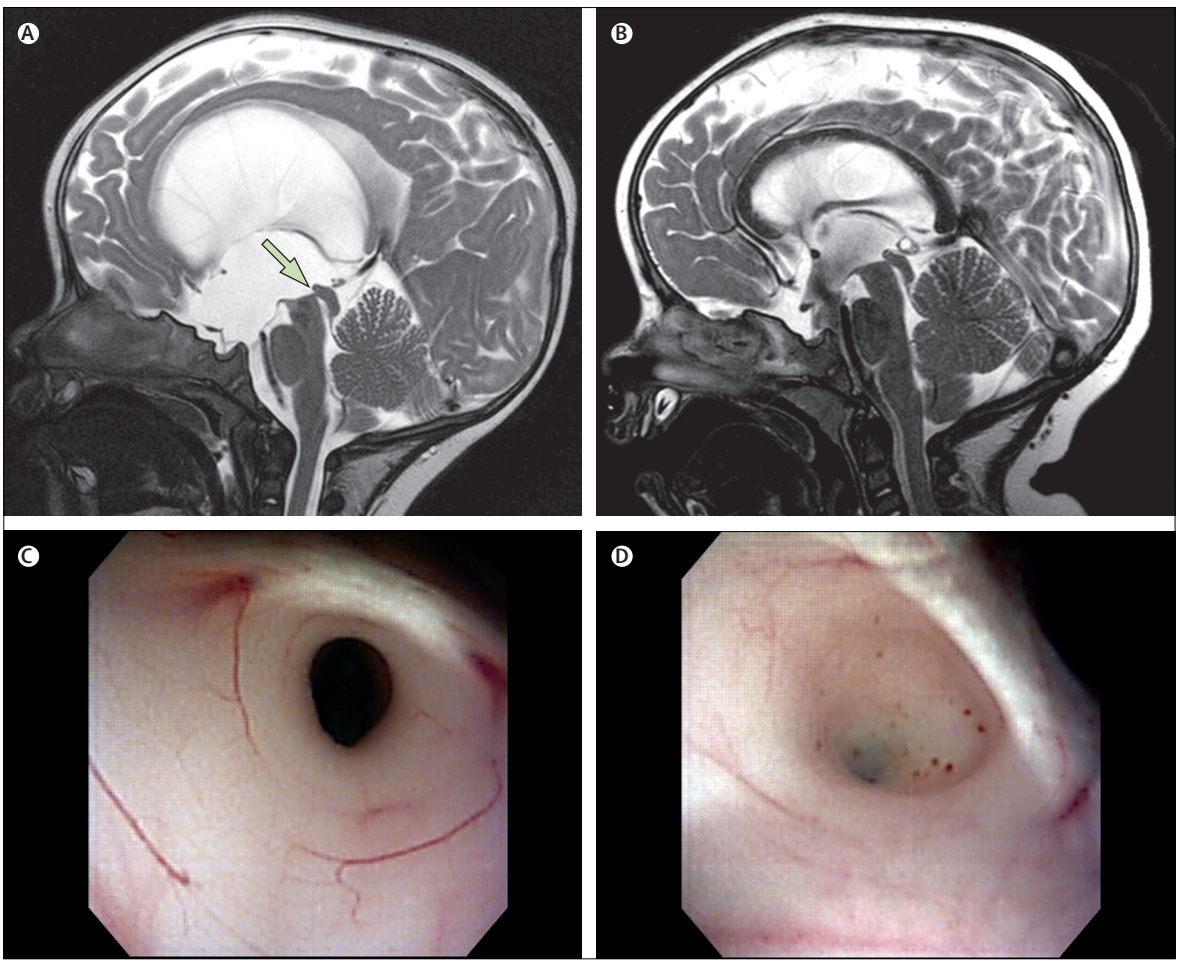

Figure 1: **Aqueduct stenosis**
(A) Sagittal brain T2 MRI of infant with hydrocephalus secondary to congenital aqueduct stenosis. Arrow indicates point of obstruction. (B) Same patient after endoscopic third ventriculostomy; note dark flow void indicating flow across endoscopic third ventriculostomy. (C) Endoscopic view of healthy patent aqueduct. (D) Endoscopic view of obstructed aqueduct in aqueduct stenosis; note posterior commissure at dorsal margin of the aqueduct ostium in both (A) and (B).

and planar cell regulator,[16] and mutations in *CCDC88C* encoding DAPLE, a regulator of cell migration via its interaction with *Dishevelled* in the non-canonical Wnt signalling pathway.[17–19]

Primary ciliopathies such as Joubert's syndrome and Meckel-Gruber syndrome are associated with congenital hydrocephalus in human beings.[20,21] Recent evidence suggests ependymal cell polarisation, which determines the orientation of ciliary beating and CSF flow, when disrupted, results in hydrocephalus and developmental anomalies.[22,23] In mice, eight of 12 novel genes that cause autosomal-recessive congenital hydrocephalus[24] code for ciliary-associated proteins.[21,25]

Together, human and animal molecular genetic data show that most hydrocephalus genes encode growth factors, receptors, cell-surface molecules (including cilia), and their associated intracellular signalling molecules that regulate brain growth and development.[13] When mutated, these molecules perturb neuroglial cell fate, proliferation, and survival, creating structural (anatomical) or functional impediments to CSF circulation or pulsatility or both.

Structural causes (developmental and acquired)

Ependymal denudation and subcommisural organ dysfunction can lead to closure of the fetal aqueduct and contribute to hydrocephalus as an isolated phenomenon or in combination with other congenital brain malformations (figure 1).[26] CNS malformations such as myelomeningocele and Chiari II malformation, Dandy-Walker complex, and encephalocele are also associated with hydrocephalus (table 1). Mass lesions such as tumours or developmental cysts can cause hydrocephalus through obstruction of CSF pathways. Tectal gliomas and other posterior third ventricle tumours can present with aqueduct obstruction and new-onset of hydrocephalus. The most common paediatric posterior fossa brain tumours, including cerebellar astrocytoma, medulloblastoma, and ependymoma, often present with hydrocephalus from fourth ventricle outlet obstruction.

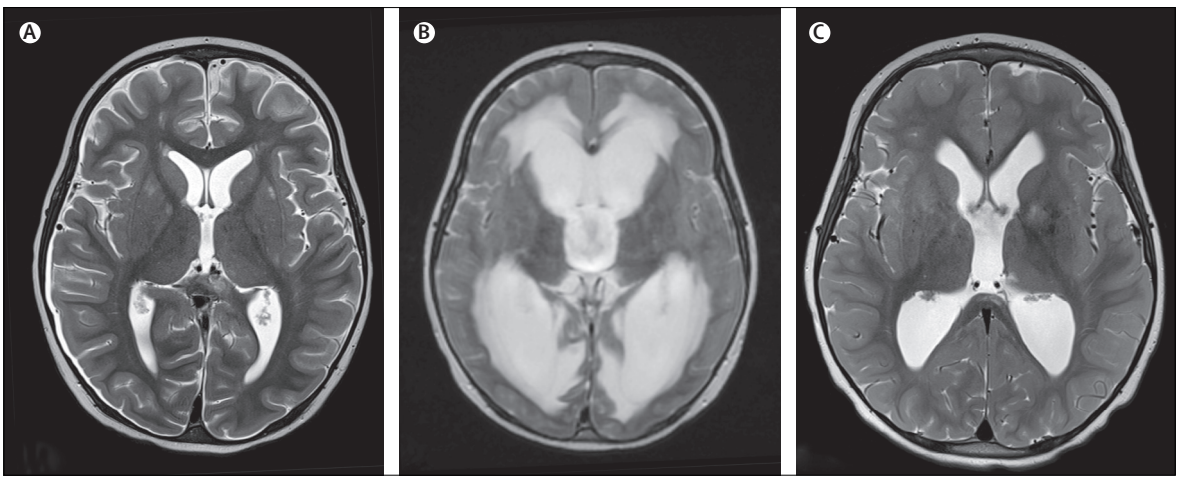

Figure 2: **MRI of child with post-meningitic hydrocephalus before and after treatment**
(A) Brain T2 MRI showing mild ventriculomegaly with very early stage hydrocephalus development in a child aged 22 months with meningitis. (B) Brain MRI of same child 2 weeks later showing severe hydrocephalus with severe ventriculomegaly and increased extracellular water in the periventricular white matter. (C) Brain MRI of same child 9 months after endoscopic third ventriculostomy and choroid plexus cauterisation with resolution of hydrocephalus and clinical recovery.

Inflammatory processes

Inflammation of the meninges or ventricles from infection or haemorrhage often leads to hydrocephalus through impairment of CSF circulation and absorption or the normal dampening of arterial pulsations (figure 2). Intraventricular haemorrhage of prematurity is one of the most common causes in developed countries[6] whereas neonatal ventriculitis with a climate-associated cyclical incidence pattern has recently emerged as the primary cause in Uganda and presumably other sub-Saharan African countries.[27] Ventriculitis can induce ependymal scarring, intraventricular obstruction, and multi-compartment hydrocephalus. Some congenital hydrocephalus can result from fetal ventriculitis that inhibits ependymal ciliary development and function,[28] or from the effect of blood-borne lysophosphatidic acid on neural progenitor cell adhesion and localisation along the ventricular surface.[29] Either of these mechanisms can lead to third ventricle or aqueduct occlusion.

Vascular dysfunction

Reduced venous compliance may be a primary cause of communicating hydrocephalus. For example, communicating hydrocephalus has been attributed to idiopathic venous outflow resistance and venous sinus collapse[9,30] as well as to venous thrombosis[31] and venous outlet stenosis at the skull base[32] associated with craniofacial dysostoses (eg, Crouzon's and Pfeiffer's syndromes). Cases of idiopathic infant hydrocephalus have also been attributed to cerebral hyperaemia.[33]

Dysregulated ion and water transport

The choroid plexus has the highest rate of ion and water transport of any epithelium in human beings[34,35] and this process is carried out by specific enzymes and ion transport molecules such as carbonic anhydrase, the bumetanide-sensitive Na-K-2Cl cotransporter NKCC1[36,37] and aquaporin (AQP) water channels, which are also present in ventricular ependymal cells.[38,39] These transport processes have been implicated in the pathogenesis and treatment of hydrocephalus.[38,40–43] For example, AQP4 is expressed in glia and ependymocytes, and a subset of AQP4-knockout mice develop obstruction of the aqueduct.[44] Conversely, ependymal AQP4 is upregulated in the late, but not early, stages of hydrocephalus, suggesting a compensatory role to maintain water homoeostasis.[45,46] A paravascular system that facilitates movement of water and solute from subarachnoid CSF into brain interstitial fluid and out through the deep draining veins, the so-called glymphatic system,[47,48] contains paravascular channels bounded by astrocytic endfeet containing AQP4.[49] Impairment of this system might contribute to the development of hydrocephalus.[49] CSF hypersecretion secondary to hyperplasia of the choroid plexus[50] or non-obstructive tumours of the choroid plexus can also cause hydrocephalus.

Secondary effects of hydrocephalus: mechanical disruption, ischaemia, and inflammation

Increased intraventricular pressure and ventriculomegaly can cause secondary neurovascular damage and inflammation, creating a crescendo of tissue injury that further compromises brain development.[26,51] Acute ventriculomegaly results in compression and stretch of periventricular tissue (including axons, myelin, and microvessels) causing ischaemia, hypoxia, inflammation, and increased CSF pulsatility.[26] Chronic ventriculomegaly elicits gliosis and chronic inflammation, demyelination, axonal degeneration, periventricular oedema, metabolic impairments, and changes to blood–brain barrier permeability.[26] Hydrocephalus is also accompanied by

www.thelancet.com Published online August 7, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60694-8

ependymal denudation, which exacerbates hydrocephalus and exposes the sensitive subventricular zone to toxic metabolites that can compromise neurogenesis.[52,53] Considerable compensation also probably occurs in response to hydrocephalus, including glymphatic absorption of CSF.[54]

Clinical presentation

Clinical presentation varies with age. Prenatal ultrasound can identify fetal ventriculomegaly, sometimes as early as 18–20 weeks' gestation.[55] Detection often prompts further studies, including a level two ultrasound scan, fetal MRI, TORCH (toxoplasmosis, rubella, cytomegalovirus, herpes simplex) screening, or amniocentesis.[56] In known maternal carriers of *L1CAM* mutation, chorionic villus sampling or amniocentesis can be offered for prenatal diagnosis of X-linked hydrocephalus.[56] In infants, hydrocephalus presents with an abnormally increasing head circumference, irritability, vomiting, bulging of the anterior fontanel, or splaying of the cranial sutures. True hydrocephalus must be distinguished from so-called benign external hydrocephalus or benign enlargement of subarachnoid space, which needs no treatment and is characterised by enlarged subarachnoid spaces, only mild or absent ventriculomegaly, and a clinically well child.[57] Beyond infancy, hydrocephalus typically presents with a constellation of findings that include some combination of headache, vomiting, loss of developmental milestones, diplopia (usually from a VI cranial nerve palsy), or papilloedema. Brain imaging is the most important diagnostic investigation. An infant with an open fontanel can be screened for ventriculomegaly by cranial ultrasonography, but an MRI study (preferred rather than CT because MRI avoids radiation exposure and provides more information) is typically indicated to elucidate the anatomy and cause (figure 1A). Cine MRI CSF flow imaging might provide insight into patient-specific changes in CSF hydrodynamics and, particularly in cases where a site of obstruction is questionable, these methods can inform surgical decision making and provide a means to assess treatment efficacy.[58–60]

Acute management

CSF shunts

Historically, hydrocephalus treatment has been based on the bulk flow model of CSF physiology detailed above. Early 20th century attempts to bypass obstructed CSF pathways via open craniotomy or reducing of CSF production with crude endoscopic methods were slightly successful but had unacceptable rates of morbidity and mortality.[61] With the advent of silastic tubing and early valve mechanisms, attention was directed toward mechanical conduits for CSF diversion, and, 60 years after its introduction, CSF shunting remains the standard treatment. The most common type of shunt diverts CSF from the ventricles to the peritoneal cavity (ventriculo-peritoneal shunt [VPS]), although other distal sites such as the right atrium of the heart and the pleural cavity are occasionally used. Shunts generally consist of silastic tubing that runs subcutaneously from the head to the abdomen, with a valve between the ventricular and distal catheters. Differential pressure (with fixed or programmable settings) or flow-regulating valve mechanisms are often paired with antisiphon or gravitational devices to prevent CSF overdrainage from posture-related siphoning. However, despite technological progress, valve design seems to have little if any effect on shunt efficacy or failure rates.[62–64]

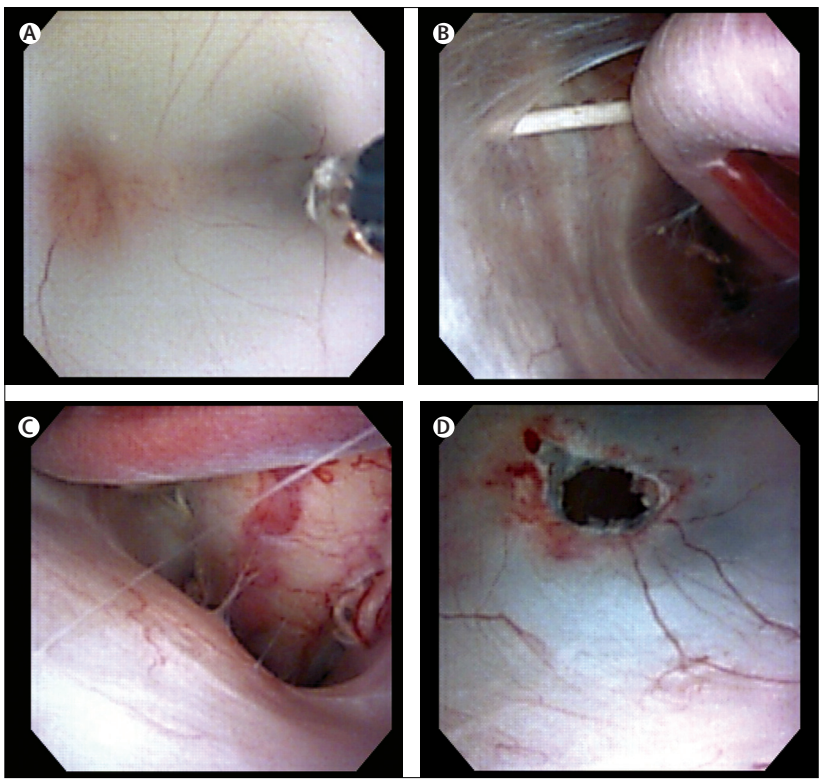

Figure 3: **Digital flexible ventriculoscopic images of endoscopic third ventriculostomy procedure**
(A) Endoscopic image of third ventricular floor with infundibular recess on left and tip of 1 mm Bugby wire poised to penetrate floor on right; anterior is left. (B) Endoscopic image of basilar artery on right and VI cranial nerve entering cavernous sinus on left after passing endoscope through the third ventriculostomy into the prepontine cistern; clivus is anterior at left. (C) More caudal intracisternal endoscopic image showing right vertebral artery and junction of upper cervical spinal cord and lower medulla at the level of the foramen magnum; clivus is anterior at lower left. (D) Endoscopic image of endoscopic third ventriculostomy opening in floor of third ventricle after withdrawing scope from prepontine cistern back into third ventricle.

Endoscopic third ventriculostomy and choroid plexus cauterisation

In the 1990s, endoscopic third ventriculostomy (ETV) emerged as an effective alternative treatment for hydrocephalus, particularly in patients with non-communicating hydrocephalus,[65] and is now routinely carried out at most major paediatric neurosurgical centres in high-income countries. The procedure involves passing an endoscope into the frontal horn of the lateral ventricle, then through the foramen of Monro, and into the third ventricle. An opening is then made in

the floor of the third ventricle, enabling direct communication into the prepontine cistern (figure 3). Although ETV is successful in many patients, there is a high rate of early failure, particularly in infants.[66] Beginning in the early 2000s, however, choroid plexus cauterisation (CPC) was added to ETV to improve efficacy of ETV alone in very young patients.[67]

In the early twentieth century results of small series in which CPC alone was used to treat hydrocephalus showed some success in patients with communicating hydrocephalus,[68,69] but with the available techniques, mortality and morbidity were substantial, and any long-term collateral effects of CPC were, and remain, unknown. The modern use of CPC has mostly been in combination with ETV, especially in sub-Saharan Africa.[67] According to the bulk flow model, ETV bypasses an obstruction and CPC reduces CSF production. In the hydrodynamic model, ETV acts to create a pulsation absorber and CPC reduces the intraventricular pulsation amplitude.[61,70] As described, the ETV and CPC procedure involves use of a flexible endoscope to cauterise the entire choroid plexus throughout both lateral ventricles.

Compared with ETV alone, ETV and CPC provided better results in children younger than 1 year[67] across many subgroups.[70–73] Further, the efficacy of ETV and CPC was proportional to the amount of choroid plexus cauterised[74] and, although preliminary findings, ETV and CPC did not seem to affect cognition negatively compared with shunting or ETV alone.[75] Based on these promising results from sub-Saharan Africa, ETV and CPC have been introduced in the USA and Canada and have had favourable results both in a single institution series[5] and in a preliminary study through the Hydrocephalus Clinical Research Network.[76]

Long-term management: complications and outcomes

Shunt complications

Children with treated hydrocephalus face many potential long-term complications, often relating to treatment. Shunt failure, usually from mechanical obstruction, needing some form of intervention occurs in 40% of children within the first 2 years after original placement[6] with continued risk of failure thereafter. Failure is diagnosed by imaging evidence of increased ventricle size compared with baseline (although this is not always the case) with symptoms of headache, vomiting, irritability, decreased level of consciousness, and, in infants, bulging fontanel and accelerated head growth. Randomised trial evidence suggests that the type of shunt valve used has no effect on failure incidence.[63,77] Shunt obstruction is treated with urgent surgery to identify and replace the obstructed component of the shunt (proximal catheter, distal catheter, or valve). In situations in which symptoms are more subtle (eg, chronic headache or deteriorating school performance) intracranial pressure monitoring can sometimes be helpful to establish if shunt obstruction is the cause. Perioperative mortality from shunt surgery is rare (0·5%).[78] The estimated 30 year shunt-related mortality is 5–10%.[79]

The rate of shunt infection is about 5–9% per procedure[80,81] and mostly occurs within 3 months of surgery,[82] and presenting with fever, irritability, wound erythema, or symptoms of shunt malfunction. Diagnosis is confirmed by positive microbiological culture from CSF obtained from a shunt tap (or blood culture in patients with a ventriculo-atrial shunt). The most common pathogens are cutaneous commensal organisms, including coagulase-negative *Staphylococcus* spp, *Staphylococcus aureus*, and, less commonly, *Propionibacterium* spp.[80,83,84] Uncommonly, VPS infection presents with abdominal symptoms from a peritoneal CSF pseudocyst.[85] Use of systemic prophylactic antibiotics[86] and following a standardised surgical protocol[81] seem to reduce the risk of infection. Shunt catheters impregnated with clindamycin and rifampicin might reduce the risk of infection,[80,87,88] but randomised data are pending from the ongoing British Antibiotic and Silver-Impregnated Catheters Study (the BASICS trial; ISRCTN 49474281), which is a three-arm study comparing antibiotic-impregnated catheters, silver-impregnated catheters, and standard catheters.[89]

Shunt overdrainage can present acutely with subdural hygroma or haematoma, or chronically with the so-called slit-ventricle syndrome.[90] The classic form of slit-ventricle syndrome is a child whose baseline ventricle size is very small (slit-like), often having chronic low-pressure headaches or acute intermittent symptoms of shunt obstruction, and whose ventricles expand only slightly or not at all with shunt failure. Options for treating these challenging patients are controversial and include revising the shunt to reduce CSF drainage, shunting the lumbar CSF space, and cranial vault expansion.[90]

ETV complications

Although in unselected cohorts the incidence of ETV failure at 2 years is about 35%,[91] the true incidence depends on individual prognostic factors, especially age and cause of hydrocephalus.[66] These have been quantified in the validated ETV Success Score,[66,92] which can accurately stratify patients into those with high (≥80%), moderate (50–70%), and low (≤40%) chance of ETV success.[93] Most ETV failures occur within the first 6 months of surgery.[66,94,95] When matched for prognostic factors, the overall temporal pattern of ETV failure differs from that of shunt failure (figure 4A), with the failure-free survival curves crossing between 2 and 3 years. Modelling of time-dependent hazard ratios shows a greater risk of early ETV failure (within about the first 3 months of surgery), after which the chances of a delayed ETV failure are lower than that of a delayed shunt failure (figure 4B).[91] Although rare, late ETV failures do occur, and can be fatal.[96] Infection after ETV is less common than with shunt procedures and occurs in fewer than 2% of procedures.[97] Other serious complications from ETV are

rare and include basilar artery injury (0·2%), permanent endocrinopathy (0·9%), hypothalamic injury or other brain injury (0·2%), and perioperative mortality (0·2%).[97]

Long-term clinical outcomes

The degree of long-term cognitive dysfunction is dependent on the causal mechanisms of hydrocephalus and any accompanying brain dysmorphology or primary injury from an inciting event such as infection or haemorrhage. For example, children with isolated aqueductal stenosis and no other brain anomaly have cognitive profiles that approach that of typically developing children.[98] However, in many children impairment in overall intelligence[99,100] along with verbal IQ,[100] spatial navigation,[101] executive functioning,[102,103] learning,[103] memory,[103] and processing speed[104] can be present.

Although quality of life is impaired in many children with hydrocephalus, nearly 20% have near-normal quality of life.[105] Epilepsy develops in as many as 34% of patients treated in infancy for hydrocephalus,[106] and has a major negative effect on quality of life. Headaches are reported to some degree in most children with shunted hydrocephalus, and are severe in 10–20% of those with shunted hydrocephalus.[105] Once in adulthood, serious chronic headaches are reported in over 40% of individuals with shunted hydrocephalus[107] and among patients treated in infancy, 45% needed treatment for depression, 43% were dependent on care, and 43% were unemployed.[108]

Controversies and uncertainties

The best treatment: shunt versus endoscopy

The optimum treatment for hydrocephalus is controversial. Aside from obstructive hydrocephalus in children older than 2 years and adults, in whom ETV is often used, VPS placement remains the standard of care. But the indications for performing ETV have recently broadened to communicating types of hydrocephalus[109–111] and the success of ETV in young infants for all causes of hydrocephalus has been increased by the addition of CPC (see above). Nonetheless, questions remain about the best first treatment for infant hydrocephalus and how to assess whether optimum treatment has been accomplished.

No completed randomised trials have compared endoscopic and shunt treatment for paediatric hydrocephalus. The IIHS (NCT00652470) began in 2004 as one of the first prospective direct comparisons of VPS versus ETV for infants (≤24 months of age) with aqueduct stenosis. Both a randomised group and a non-randomised group, based on parental preference, are included. It is unique in that the primary outcome is health status at 5 years. Recruitment ended in December, 2013, and results of the preliminary analysis are pending.

Another randomised prospective trial is currently underway at CURE Children's Hospital of Uganda to compare ETV plus CPC versus VPS alone in infants younger than 6 months of age with post-infectious hydrocephalus (NCT01936272). The primary outcome measure is the scaled cognitive score of the Bayley Scales of Infant Development, with other secondary outcome measures such as increase in brain volume.[112]

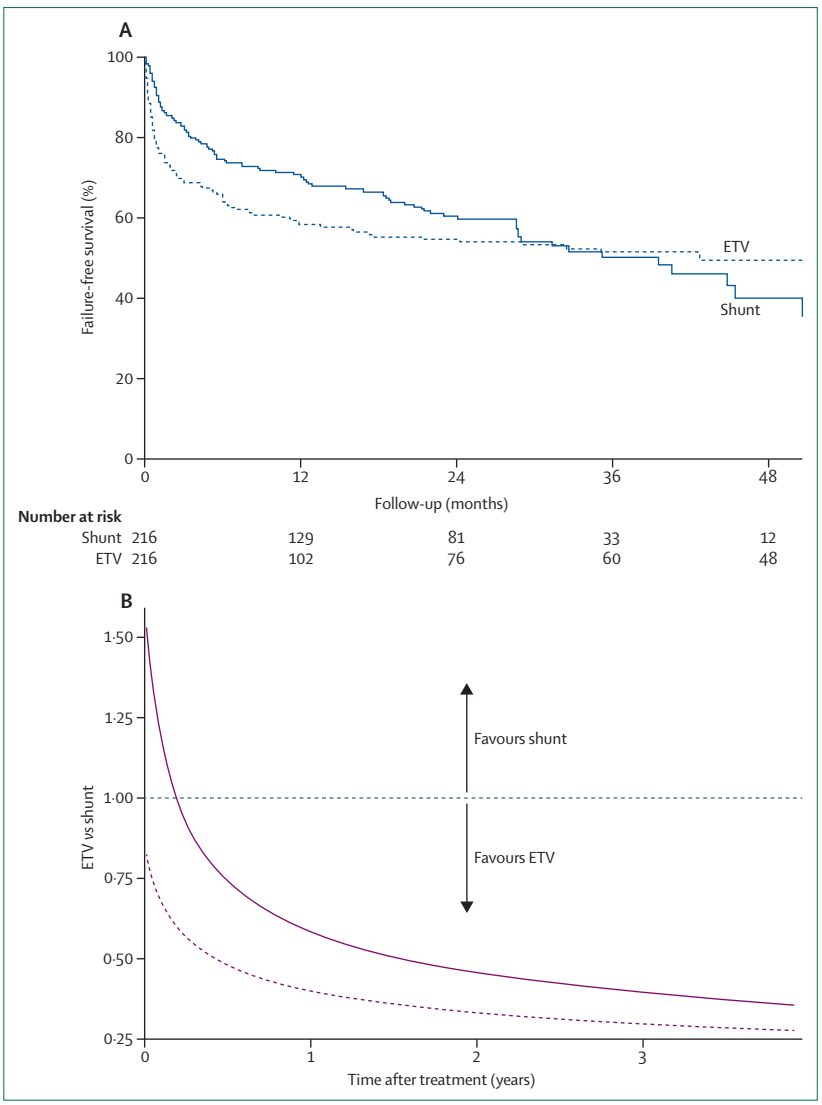

Figure 4: **Failure-free survival pattern for ETV and shunt**
(A) Survival curve showing failure-free treatment survival for patients treated with endoscopic third ventriculostomy (ETV; dotted line) and shunt (solid line). For these curves, patient prognostic factors have been balanced (adjusted for) with propensity score matching. (B) Graph showing the hazard ratios for ETV failure relative to shunt failure, modelled as a function of time, for an unadjusted model (dotted line) and a propensity score-matched model (solid line), which balances prognostic factors. Adapted from Kulkarni and colleagues.[91]

Determining when hydrocephalus is adequately treated

The best criteria to determine optimum hydrocephalus treatment are not known. Traditional criteria, including alleviation of the obvious signs and symptoms of intracranial hypertension and decreased ventricle size can be insufficient. Persistent ventriculomegaly, especially after treatment with ETV, is common even after symptom alleviation. It is not clear whether

persistent ventriculomegaly can in itself cause subtle white matter injury or impair cognitive outcome. Although some small clinical studies have shown no adverse outcome related to large ventricles,[75,113–115] animal models of compensated hydrocephalus have shown accumulation of phosphorylated tau protein in the cerebral cortex, suggested as a possible mechanism of later cognitive decline.[116] Findings of a recent study showed that brain volume correlates with cognitive outcome better than CSF volume suggests promotion of brain growth as the more important measure of truly successful treatment.[112]

Determining when and how to treat ventricular dilatation of prematurity

Of preterm infants (<30 weeks' gestation) who develop severe germinal matrix haemorrhage, about 30–50% develop some degree of ventricular dilatation.[117] A subset of these infants ultimately develops post-haemorrhagic hydrocephalus that needs permanent treatment. In preterm infants with ventricular dilatation, the decision of when to intervene and with what intervention (acetazolamide, lumbar punctures, ventricular access reservoir, ventriculo-subgaleal shunt, or external ventricular drain)[118] is controversial, with substantial variation in practice.[119] Traditionally, clinical signs of progressive ventriculomegaly and raised intracranial pressure have been used to start surgical intervention, but earlier treatment,[118] perhaps guided by neurophysiological assessment,[120] might be beneficial. A multicentre trial randomly assigning patients to an earlier versus later treatment threshold is ongoing (ELVIS, ISRCTN 43171322).

Research in hydrocephalus: a broad agenda for the next decade

Clinical research to optimise care of the child with hydrocephalus

The past 10–15 years of hydrocephalus clinical research have undergone a shift from small, single-centre reports, to large, prospective multicentre studies. The creation of patient registries and clinical research networks such as the UK Shunt Registry[121] and the Hydrocephalus Clinical Research Network (HCRN)[79] has enabled clinical studies with sufficient power to address important clinical questions and to provide a platform to standardise care across institutions. These efforts have already resulted in both lower infection rates[79] and improved shunt failure rates.[6] Despite this, a recent systematic literature review reported little high-quality data to guide best-treatment practices.[122] Going forward, research should emphasise long-term neurodevelopmental outcomes, in addition to surgical parameters such as shunt failure or infection rates.

Tenable near-term objectives for multicentre clinical research networks include addressing both surgeon-driven technical issues (eg, trial to identify optimum shunt entry, NCT02425761) and the efficacy of antibiotic-impregnated shunt catheters [BASICS trial, ISRCTN 49474281]), and global management approaches (eg, timing or type of intervention for post-haemorrhagic hydrocephalus [ELVIS trial, ISRCTN 43171322] and shunt outcomes of post-haemorrhagic hydrocephalus trial [SOPHH, NCT01480349], and the selection of endoscopy versus VPS [NCT00652470 and NCT01936272]).

For the **trial on entry methods** see http://www.pcori.org/research-results/2014/randomized-controlled-trial-anterior-versus-posterior-entry-site-cerebrospinal

Advancing diagnostic and prognostic methods for hydrocephalus

Conventional neuroimaging shows the presence of ventriculomegaly but provides little information about subtle microstructural pathology. Therefore, translational research into more sophisticated diagnostic methods is a priority. This is now greatly facilitated by coordinated, registry-associated repositories, which catalogue human biospecimens in parallel with clinical and radiographic data. Both conventional and high-throughput screening methods[123] have been used to identify potentially relevant CSF biomarkers for inflammation (eg, interleukin-18, interferon-γ, transforming growth factor [TGF-] β),[124–126] neurodevelopment (eg, amyloid precursor protein, *L1CAM*),[127] and neural injury (eg, tau, caspase-3).[128–130] Advanced MRI techniques can assist better clinical management of hydrocephalus. High-resolution MRI, augmented with volumetric analysis, surface morphometry, and gyrification indices,[131,132] are being used to define the short-term and long-term anatomical effects of hydrocephalus. Diffusion tensor imaging is being used to study microstructural effects that occur in the absence of gross anatomical changes and has already shown hydrocephalus-related injury to periventricular structures.[133] These injuries are now being investigated in conjunction with psychometrics to anticipate long-term neurodevelopment outcomes.[134] Investigators are now using magnetic resonance (MR) elastography to study changes in brain compliance that occur with hydrocephalus, particularly with overshunting.[135,136] MR angiography and venography,[30,137] phase-contrast MR,[138,139] and arterial spin labelling[140] are also likely to find roles in the study of the effects of hydrocephalus and its treatment on blood flow and CSF movement.

Innovation in technology and instrumentation for hydrocephalus treatment

Despite high failure and reoperation rates, CSF shunts have remained essentially unchanged in configuration and design since their introduction in the 1950s. Antibiotic-impregnated catheters, siphon-control devices, and programmable valves are available, but shunt management is still greatly limited by catheter obstruction, poor control of CSF flow, and the absence of feedback for shunt function. In recent years, demand has increased for a smart shunt capable of providing advanced flow control and real-time feedback of shunt function, but none are yet commercially available.[141] Building on the rationale of drug-eluting cardiac stents,

bioengineers are also investigating the materials, coating, and design of shunt catheters to limit obstruction via tissue ingrowth.[51]

Basic research in hydrocephalus

The next 10 years should yield important refinements to our model of hydrocephalus pathophysiology, including the roles of pulsation dysfunction and newly characterised water transport mechanisms in the brain. Further research should yield a better understanding of both the genetic basis of ciliary dysfunction in congenital aqueductal stenosis and the contribution of ependymal and ciliary disruption to acquired hydrocephalus. Recent findings that implicate lysophosphatidic acid[29] and TGF-β[142] in the pathogenesis of post-haemorrhagic hydrocephaly offer hope for pharmacological strategies of prevention or treatment.

Contributors

All authors contributed equally to the research, writing, and editing of this Seminar.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Alison Clapp of the Boston Children's Hospital medical library (MA, USA) for her invaluable assistance with the systematic literature search.

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