Chronic Hydrocephalus in Adults

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Chronic hydrocephalus is a complex condition, the incidence of which increases with increasing age. It is characterised by the presence of ventricular enlargement in the absence of significant elevations of intracranial pressure. The clinical syndrome may develop either as a result of decompensation of a "compensated" congenital hydrocephalus, or it may arise de novo in adult life secondary to a known acquired disturbance of normal CSF dynamics. The latter may be due to late onset acqueductal stenosis or disruption of normal CSF absorptive pathways following subarachnoid hemorrhage or meningitis ("secondary" normal pressure hydrocephalus (NPH)). In some cases the cause of the hydrocephalus remains obscure ("idiopathic" NPH). In all forms of chronic hydrocephalus the clinical course of the disease is heavily influenced by changes in the brain associated with aging, in particular cerebrovascular disease. Recent research has challenged previously held tenets regarding the CSF circulatory system and this in turn has led to a radical rethinking of the pathophysiological basis of chronic hydrocephalus.

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INTRODUCTION

Hydrocephalus has in the past been regarded predominantly as a disease of childhood, but recent improved recognition of the disorder in later adulthood through increased availability of neuro-imaging has led to greater interest in its pathophysiology, investigation and treatment. Ever since the first identification of the syndrome of "normal pressure" hydrocephalus (NPH) in adults by Hakim and Adams in 1965, controversies have existed regarding its pathogenesis(62) .

The transition from childhood hydrocephalus to an adult type has remained poorly understood, yet it is generally recognised that adults who develop hydrocephalus in later life have more robust compensatory mechanisms than children and the hydrocephalus tends to be more slowly progressive. In this article we describe a simple classification of the disorder and discuss some of the theories surrounding its pathogenesis, investigation and treatment.

CLASSIFICATION OF CHRONIC HYDROCEPHALUS

The term chronic hydrocephalus encompasses any condition in which ventriculomegaly, defined radiologically by an Evans index (the ratio of the frontal horn diameter to the maximum brain width from the inner skull) >0.3, occurs in association with a normal or chronic low-grade elevation of cerebrospinal fluid (CSF) pressure. This broad definition encompasses normal pressure hydrocephalus (NPH) (61, 62), compensated (arrested) congenital hydrocephalus, (148) adult-onset aqueduct stenosis (65, 112), and other forms of acquired hydrocephalus including those due to meningitis, subarachnoid hemorrhage and head trauma (30). NPH may be subdivided into that group of patients with a clear precipitating factor for the development of hydrocephalus (SAH, head trauma, meningitis, etc) where the term secondary NPH is used, and that group of patients with no obvious precipitating factors for whom the term idiopathic NPH is used (67, 153). It would also include *ex vacuo* hydrocephalus, a term reserved for patients in whom ventricular enlargement is secondary to (apparent) cerebral atrophy(23). The implied corollary of the latter definition is that *ex vacuo* hydrocephalus is due to a loss of brain parenchyma and is unrelated to disturbances in CSF dynamics. This view has recently been challenged (9, 133, 134).

Although chronic hydrocephalus may have a variety of precipitating causes, the clinical presentation and neuropathological changes that occur share many common features.

EPIDEMIOLOGY OF CHRONIC HYDROCEPHALUS

Epidemiological data on chronic hydrocephalus are limited. Data from Sweden suggest an incidence of adult-onset chronic hydrocephalus of 2.6 per 100 000 per year (69). Chronic hydrocephalus in adults is estimated to account for greater than 50% of the approximate 80 000 diagnoses of hydrocephalus made in the United States per year (17). The prevalence of chronic hydrocephalus is almost certainly underestimated. Between 5% and 10% of demented patients are thought to have a diagnosis of NPH (61, 144). However, this understates the true incidence, as NPH can manifest without cognitive impairment (50, 85).

CLINICAL PRESENTATION

The clinical presentation of chronic hydrocephalus in adults is dependent on both the age of the patient (Figure 1), the presence or absence of (chronic, low-grade) intracranial hypertension (more common in younger patients), and the co-existence of cerebrovascular disease (more common in elderly patients). Patients with decompensation of previously asymptomatic childhood hydrocephalus will usually have a head circumference over the 98th percentile. Modest elevations of intracranial pressure (ICP) are often present in younger patients and may manifest as chronic low-grade non-specific headache. Often the headaches do not have the "classic" features usually associated with raised ICP such as early morning exacerbation or

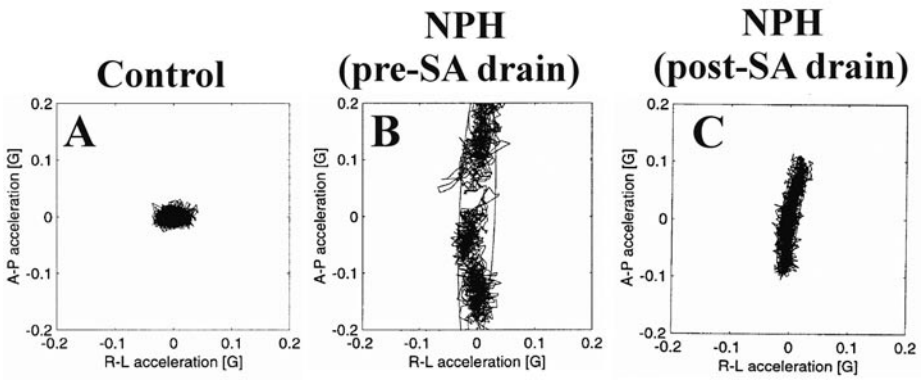

Figure 1. Preliminary findings using dual axis cranial accelerometry. Examples of measures of postural stability in a normal volunteer (**A**), a patient with NPH before and after trial lumbar subarachnoid CSF drainage (**B** and **C**, respectively). Differences in head acceleration, expressed in units of gravity G, were significantly greater in the anteroposteral (A-P) than mediolateral (R-L) dimensions in the NPH group compared to controls. Improvement in postural stability was observed immediately following trial lumbar CSF drainage.

associated nausea and vomiting (45, 47). These patients may also present with an insidious onset of visual failure secondary to chronic papilledema and optic atrophy (46). The majority of patients with chronic hydrocephalus will present with the NPH syndrome, first described by Hakim and Adams in 1965, features of which are outlined below (62).

Normal pressure hydrocephalus. The diagnosis of NPH is based on three groups of clinical symptoms: *gait disturbances*, urinary incontinence and cognitive changes. A consensus is emerging that gait disturbance is the principal symptom of NPH and it is around this feature that the overall clinical picture should be organized (61). Gait is the most likely symptom to improve in response to CSF shunting. The relative frequency of the other symptoms is variable and their presence is not a prerequisite for the diagnosis of NPH.

The gait disturbance is variable in its presentation. It is frequently broad-based, with a short stride length and diminished foot-floor clearance (135). The walking speed is slowed and the gait unsteady. Truncal instability, often with a tendency to fall backwards (16), is common, and patients often report a history of frequent falls (59). This has been evaluated in our institution (ML) using dual axis cranial accelerometry and preliminary results have demonstrated a significant decrease in seeking and maintaining postural stability that were alleviated by trial lumbar CSF drainage (Figure 1) (91). Patients may have difficulty in initiating walking ("magnetic phenomenon"). Parkinsonism may be present, with festination, hypokinesia and freezing (35, 52, 81). The latter may respond to visual cueing but Parkinsonian symptoms are typically not responsive to levodopa (145).

Eventually the patient becomes akinetic and wheelchair-dependent. Postural instability may be so severe that the patient is unable to maintain an upright position when seated. Because of the anatomical proximity of the axons innervating the legs to the lateral ventricles, the lower extremities tend to be preferentially affected (150). Upper extremity involvement may also occur, with handwriting deterioration, reduced finger motor speed, and difficulty in accomplishing complex fine motor tasks (15, 135, 142).

Urinary urgency is a common symptom in NPH. Urodynamic studies have demonstrated bladder hyperactivity with detrusor instability but no impairment of bladder sphincter control (1). In most patients, incontinence results from a combination of urgency coupled with a gait disturbance, which prevents the patient reaching proper facilities in time. In advanced cases, incontinence may be associated with a lack of concern for micturition due to severe frontal lobe dysfunction, with fecal incontinence also occurring in the most severe cases (61).

Cognitive impairment generally manifests later in the course of the disease. Most patients have only a mild to moderate cognitive deficit at presentation. An onset of dementia prior to the development of a gait disturbance or severe intellectual impairment are both associated with a lack of response to CSF shunting (55, 71). There may be noticeable fluctuations in cognitive function from day to day (61). The cognitive deficit is typically of the subcortical type seen in frontal lobe disorders. Frequent findings include inattention, paucity of thought, forgetfulness and diminished intellectual agility. Responses are globally slowed and patients lack spontaneity.

Other frontal lobe deficits such as apathy, emotional lability and disinhibition are often seen (92). Neuropsychological investigation of non-demented patients with NPH will often identify more subtle impairment of frontal lobe executive function (impairment in tasks requiring reasoning, anticipation, goal establishment, strategy formation, shifting mental set, and error monitoring) (71). Executive function deficits often fail to respond to CSF shunting, despite dramatic responses in some patients to more global measures of cognition such as the Mini-Mental Status Examination (MMSE) (71). Occasionally, paranoid psychosis or mania may be a presenting feature (87, 115). True depression is relatively uncommon but may be difficult to distinguish from the apathy, psychomotor slowing, and executive deficits of NPH (66, 124).

Patients with NPH are indifferent about activities of daily living and personal safety and therefore may require close supervision (98). Excessive daytime somnolence is frequently reported by patients or their families (92). The finding of depressed CSF levels of the hypothalamic neuropeptide hypocretin-1 in NPH suggests that the chronic ventriculomegaly may result in impaired function or depletion of the hypothalamic neurons involved in sleep regulation (32,39).

Uncommon presentations of chronic hydrocephalus. Rarely, hypothalamic-pituitary axis dysfunction, either with panhypopituitism, growth hormone deficiency or amenorrhoea, can be the sole mode of presentation of chronic hydrocephalus (7, 68, 86). Chronic tonsillar herniation may lead to the development of secondary syringomyelia (51, 104). Chronic CSF rhinorrhoea, due to erosion of the skull base secondary to chronic ventricular distension, has also been reported(94).

"Hydrocephalic attacks" and sudden death in chronic hydrocephalus. There

are reports of young adults with chronic hydrocephalus who die suddenly and unexpectedly without any preceding symptoms, in whom post-mortem examination reveals massive ventriculomegaly, but no uncal or tonsillar herniation and an absence of midbrain hemorrhage or necrosis (122). Many of these deaths may be attributable to epilepsy (14). However, sudden death may occur in chronic hydrocephalics with no history of seizures(122).

Syncopal attacks are occasionally encountered in chronic hydrocephalics, without grossly elevated intracranial pressure, and may be precipitated by modest exertion or straining (20, 43). They may be preceded by an overwhelming sense of doom or imminent death. Such "hydrocephalic attacks" may have a similar underlying pathogenic mechanism to that in the patients who suffer sudden death. Preliminary results in our (SD, ML) canine model of chronic obstructive hydrocephalus show evidence of ischemic damage to the cardio-respiratory centers within the brainstem (Figure 2) that lend weight to the concept of instantaneous "neurogenic" cardiac death in chronic hydrocephalus. Patients with apparently stable chronic hydrocephalus may have finely balanced CSF pathways with little or no functional reserve. Any further insult to the brain or CSF pathways, for example following minor head trauma, may result in an abrupt neurologic deterioration (42).

RADIOLOGICAL CHANGES

As stated above, radiological enlargement of the ventricles, in the absence of clinical symptoms and signs of significantly raised intracranial pressure, is a prerequisite for a diagnosis of chronic hydrocephalus. Beyond this, the usefulness of CT or MR imaging in determining the likelihood of a clinical response to CSF diversion is severely limited. Classically, the finding of ventricular dilatation out of proportion to the cortical sulcal enlargement, with ballooning of the frontal horns and enlargement of the temporal horns, has been used to describe the radiological appearance in chronic hydrocephalus. However, such changes may also be seen in the central atrophy that may, for example, follow near-drowning or multiple sclerosis (23). Furthermore, sulcal enlargement, consistent with a radiological diagnosis of cortical atrophy, has been reported in cases of shunt-responsive hydrocephalus (Figure 3) (61, 126, 138). Gross hippocampal atrophy on volumetric MR imaging is probably the best indicator of an unfavorable response to CSF diversion (70, 127).

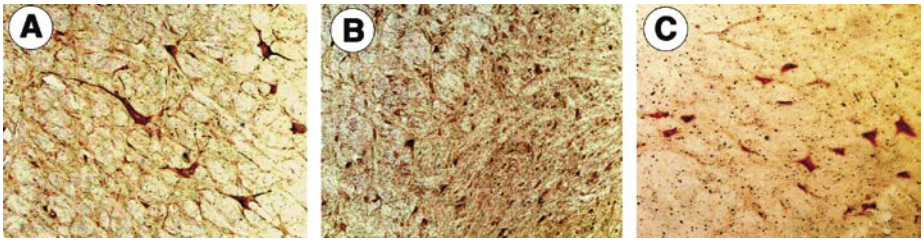

Figure 2. Photomicrographs showing ischemic changes in cardio-respiratory brainstem nuclei in an experimental model of chronic obstructive hydrocephalus: hypoglossal and vagal nuclei show an increase in staining for VEGF-R2 at 22 days post-hydrocephalus induction (**A**, **B**), and the solitary nucleus is positive for hypoxia-inducing factor-1 alpha (HIF-1α) at 112 post-hydrocephalus induction (**C**).

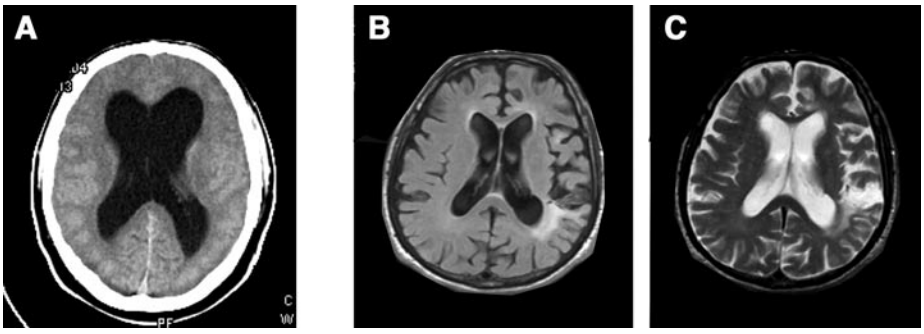

Figure 3. Examples of ventriculomegaly, a hallmark of chronic hydrocephalus, with cortical effacement as seen on CT (**A**), and cortical atrophy observed on T1 and T2 MRI (**B**, **C**).

Neuro-imaging has also identified disturbances of CSF dynamics in chronic hydrocephalus. An increase in the aqueductal CSF flow void is often seen on MR imaging, and more recently quantitative phase-contrast CSF velocity imaging has demonstrated an increase in aqueductal CSF flow velocities in shunt-responsive chronic hydrocephalus (24, 25, 72, 76), although again the absence of these findings does not preclude shunt responsiveness (48, 83, 93). Isotope cisternography has also been reported to show a disturbance of CSF flow in chronic hydrocephalus with a reversal of the normal distribution of the isotope, which normally accumulates over the cerebral convexities, but in hydrocephalics tends to accumulate in the ventricles (19). Again however, this finding is inconsistent and is not of sufficient diagnostic accuracy to predict a response to shunting (19).

Many studies have also demonstrated cerebrovascular abnormalities in chronic hydrocephalus. Periventricular deep white matter ischemia (DWMI) is a non-specific finding on MR imaging but is commonly seen in patients with chronic hydrocephalus and may be involved in its pathogenesis (18, 23, 26, 84). It is important for clinicians to appreciate that the presence of this radiological feature does not preclude a favorable response to CSF shunting(143).

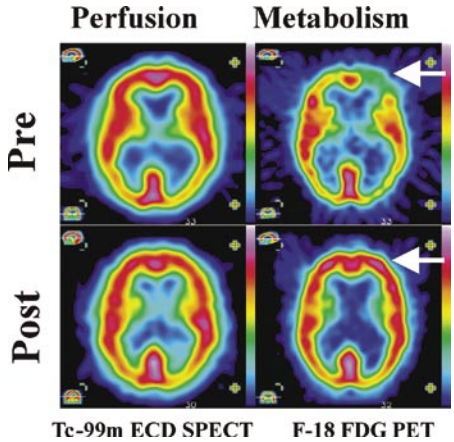

Figure 4. Use of PET and SPECT imaging revealed a mismatch in luxury perfusion as hypometabolism in the left frontal region (arrows) that was alleviated with endoscopic third ventriculostomy (ETV) surgical treatment.

Single positron emission computed tomography (SPECT) (56, 88, 146), transcranial Doppler ultrasonography (44) and positron emission tomography (PET) (77, 79, 80, 113) studies have all demonstrated abnormalities of cerebral blood flow (CBF) in chronic hydrocephalus: impairment of cerebral perfusion in the periventricular white matter, particularly in the frontal and

parietal regions (100), with an abnormal gradient from the lateral ventricles to the subcortical white matter (109). A combination of PET and SPECT imaging can also be utilized to demonstrate reversible mismatches in cerebral perfusion and metabolism (Figure 4) (75). Although such abnormalities of CBF are not specific for chronic hydrocephalus (130) they may provide an insight into the underlying pathogenic mechanisms involved (10, 23, 113).

PATHOGENESIS OF CHRONIC HYDROCEPHALUS

The pathogenesis of chronic hydrocephalus is not fully understood. Several theories have been put forward, but none has been fully substantiated. Any theory must explain the formation and maintenance of ventriculomegaly in the presence of a normal CSF pressure. Ventriculomegaly per se is insufficient to account for the clinical symptoms encountered in chronic hydrocephalus. After successful treatment of obstructive hydrocephalus by endoscopic third ventriculostomy, ventricular size may remain unchanged despite dramatic resolution of symptoms and normalization of ICP (53).

Patients with large ventricles secondary to known congenital precipitants may be both neurologically and cognitively intact, and may continue in some cases to function at a high intellectual level (45, 49). Other patients may remain stable both in terms of ventricular size and clinical performance, although the latter may be sub-optimal as evidenced by improvements following CSF shunting (89, 99). The terms "compensated" and "arrested" hydrocephalus are used interchangeably to describe these patients (102, 148). A significant proportion of patients with compensated hydrocephalus decompensate in adult life. Decompensation may occur decades after the initial arrest of hydrocephalus (46).

Explanation of the development of *symptomatic* chronic hydrocephalus requires an understanding of the changes in the brain parenchyma and CSF hydrodynamics that occur in association with cerebrovascular disease and as part of the normal aging process. In the context of ventriculomegaly these changes can precipitate decompensation. Possible mechanisms involved in the pathogenesis of chronic hydrocephalus are discussed below.

CSF production and absorption. Despite more than a century of research, the mechanisms involved in the normal production and absorption of CSF and how these are altered in the hydrocephalic state are still not fully understood. In recent years many of the central tenets, particularly those surrounding CSF absorption by the arachnoid granulations, have been challenged.

Cerebrospinal fluid (CSF) is secreted by the epithelial cells of the choroid plexus, by an energy-dependent process that involves the movement of Na^+, Cl^- and HCO^{3-} from the blood to the ventricles of the brain. This creates the osmotic gradient, which drives the secretion of water (40, 136). Aquaporin-1, a water channel heavily expressed on the apical membrane of the choroid plexus epithelial cells, is likely to facilitate the passage of water into the ventricles (6). Recent evidence suggests that Aquaporin-1 expression is down-regulated in pathological conditions in which cerebral perfusion is compromised and this may represent a homeostatic mechanism for the regulation of CSF production (96, 97). Approximately 80% of CSF production is thought to be by the choroid plexus, the remaining 20% is thought to be produced through trans-ependymal bulk flow of CSF from the brain parenchyma to the ventricle (105, 116). CSF is produced at a rate of approximately 0.35 ml/min, but there is a marked diurnal fluctuation in CSF production rates with night-time production approximately twice that of daytime (36, 111).

The arachnoid villi are traditionally regarded as the main site of CSF absorption (147), although physiological studies have questioned the extent to which CSF absorption takes place at the arachnoid villi (40, 74). CSF resorption via perineural lymphatic pathways and possibly through lymphatic pathways via the cribriform plate may constitute major CSF drainage routes (21, 107). It is also likely that a significant proportion of CSF absorption occurs via trans-ependymal pathways, with absorption through transcapillary or transvenular routes in the brain interstitial space (40, 57). In hydrocephalus it is likely that these alternative routes of CSF absorption become increasingly important, particularly the trans-ependymal route, ie, reverse bulk flow (10, 40, 58, 118). There is growing evidence that the arachnoid villi may in fact be a minor pathway of CSF absorption (74). It has been proposed that their major role is as a physiological regulator of the pulse pressure once the fontanel has closed, with an ability to vent CSF when intracranial pressure is pathologically elevated (152).

Age-related changes in the brain and choroid plexus. Age-related changes in the brain and choroid plexus have, until recently, received relatively little attention, yet it is becoming increasingly clear that they may have an important influence on the development of symptomatic chronic hydrocephalus. Production of CSF by the choroid plexus declines with increasing age (101), the decline being particularly pronounced in chronic hydrocephalus and Alzheimer disease (37, 132, 134). Elderly patients may also lose the normal circadian rhythms in CSF secretion rates (119). The effect of this is a reduction in the turnover of CSF (2). With increasing age, the resistance to CSF outflow (R_{out}) increases (37). The impairment of CSF absorption may reflect several pathogenic mechanisms associated with increasing age, including arachnoidal thickening (12), leptomeningeal fibrosis (2, 11), β-amyloid deposition (64), and increased venous pressure (29, 40, 125). The decline in CSF production may partly be caused by diminished arterial perfusion of the choroid plexus, which may in turn be a compensatory response to the reduction in absorptive capacity (37). Studies of alterations in the choroid plexus in response to experimental conditions, such as spaceflight and head-down tilt, which mimic reduced cerebral perfusion due to an increase in venous pressure, have demonstrated down-regulation of aquaporin-1 water channel expression on the choroid plexus cell apical surface and loss of microvilli on the apical surface of choroid plexus cells (96, 97). Reduction in CSF production may also in part be mediated by an increase in the levels of CSF vasopressin (a CSF protein known to be involved in the regulation of CSF production) which occurs with aging (73). Age-related thickening of the choroid plexus basement membrane and epithelial atrophy secondary to a decline in growth hormone binding sites on the choroid plexus may also impair CSF production(119, 128, 129).

The reduction in CSF turnover will impair the clearance from the CNS of any

substances that rely on bulk flow of CSF, such as large protein molecules (119). Potentially harmful substances such as β-amyloid may then accumulate in the CSF, meninges and brain parenchyma (134). Other neuroprotective mechanisms regulated by the choroid plexus, such the production of key antioxidant enzymes, particularly glutathione peroxidase, and active transport of the antioxidant vitamins C and E into the CSF by the choroid plexus, are also impaired in the aging brain, increasing oxidative stress and free radical neuronal damage (119, 128, 140). Age-related reductions in secretion by the choroid plexus of transthyretin, which sequesters β-amyloid and inhibits amyloid fibril formation, may lead to increased parenchymal β-amyloid deposition (27). In chronic hydrocephalus the accumulation of such substances may be accelerated and contribute to the cognitive decline seen in elderly chronic hydrocephalic patients.

With increasing age parenchymal changes such as dilatation of the Virchow-Robin perivascular spaces (*état criblé*), demyelination and perivascular gliosis become more common and more pronounced (4). *État criblé* is associated with vascular ectasia and sclerosis of arterioles. These changes are especially pronounced in patients with hypertension and may be indicative of a progressive loss of cerebral autoregulation (4, 123). The *état criblé* and associated changes correlate with the periventricular lucencies seen on MR imaging studies of the brains of elderly patients and patients with chronic hydrocephalus (5, 54).

Hydrodynamic changes also occur with increasing age. An increased resistance to CSF outflow (R_{out}) has already been discussed. The Monro-Kellie doctrine dictates that because the intracranial volume is constant, any increase in any of the intracranial contents must be compensated to avoid a rise in pressure. Cerebral compliance (dV/dP) is the change in volume observed for a given change in pressure and represents the accommodative capacity of the intracranial space. The veins are the major capacitance vessels, and as they are thin-walled, they account for between 70% and 80% of the capacitance in the brain (13, 33). With aging, cerebral compliance decreases (37), and this may reflect closure of parenchymal veins secondary to cerebrovascular disease (23). Other factors that contribute to loss of compliance include the diminished capacity for CSF resorption and possibly spinal degenerative disease, that may in turn reduce compliance in the spinal subarachnoid space (10, 95). This will reduce the capacity of the brain to damp arterial pulse pressure waves, and may further impair CSF absorption (9). With increasing age the brain may also be more susceptible to deformation by pulsatile forces due to *état criblé* and softening of the deep white matter (121).

Mechanisms of ventricular enlargement. It is not disputed that cerebral compliance is significantly decreased in both acute and chronic hydrocephalus (Figure 5) (10, 37, 61, 151). This may reflect either an obstruction to CSF flow from the ventricular system as in aqueduct stenosis or Chiari malformation, or a failure of CSF resorption as seen in communicating hydrocephalus caused by leptomeningeal fibrosis following subarachnoid hemorrhage or meningitis.

In idiopathic NPH the impairment of compliance remains obscure. We suggest that these patients have an underlying degree of CSF resorption failure, due either to an occult insult to the CSF absorptive pathways (such as a traumatic subarachnoid hemorrhage or unrecognised congenital intraventricular hemorrhage), or possibly a failure of maturation of the arachnoid villi manifesting itself in adulthood—a *form fruste* of neonatal external hydrocephalus (3). In younger life this is compensated by secondary CSF absorption pathways, in particular through reverse bulk flow of CSF and absorption via the parenchymal route. We suggest that with age, degenerative vascular changes in the parenchyma compromise this route of absorption, triggering decompensation. The less pronounced the deficiencies in absorption, the more severe the degree of cerebrovascular compromise required to initiate decompensation.

The mechanism through which such a reduction in compliance leads to the development of ventriculomegaly is disputed. It has been proposed that for ventricular enlargement to occur a trans-mantle pressure gradient (between the ventricles and subarachnoid space) must be generated, at least temporarily (34, 61, 63). With an increase in CSF pressure, due to either obstruction to flow or diminished absorption, the brain

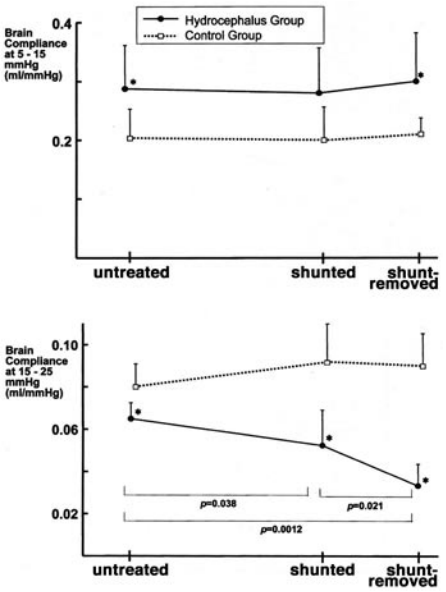

Figure 5. Changes in brain compliance (dV/dP) as it relates to low (5-15 mm Hg) and high (15-25 mm Hg) pressures in an experimental model of chronic obstructive hydrocephalus. At low pressure (**A**), compliance was higher in the hydrocephalic group than in controls, with no significant change after CSF shunting and shunt removal. By comparison, at high pressures (**B**), brain compliance was decreased in the hydrocephalic group and was further reduced after CSF shunting ($p = 0.038$) and shunt removal ($p = 0.021$). Reproduced with permission from Fukuhara T, Luciano MG, Brant CL, Klauscie JJ (2001) Effects of ventriculoperitoneal shunt removal on cerebral oxygenation and brain compliance in chronic obstructive hydrocephalus. *J Neurosurg* 94:573-581.

suffers non-hydrostatic loading of the parenchyma. As a result of these pressure changes parenchymal fluid is "squeezed out" into the extra-cranial venous system, reducing the volume occupied by the parenchyma with corresponding enlargement of the ventricles. Because force is the product of pressure multiplied by area, the ventricular pressure will tend to normalize as the ventricles expand (61). Once the brain has undergone such "bioplastic deformation" the ventricles will not return to a normal size unless the CSF pressure is lowered below that of the parenchymal pressure (61). This has been cited as a physiological example of hysteresis, predicted by the chaos theory of non-linear dynamics as a Hopf bifurcation, which explains how a system can exhibit 2 different states (ventricular size) at a single parameter value (ICP) (90). The existence of such a trans-mantle gradient has been disputed, particularly in the setting of communicating hydrocephalus (137). For a trans-mantle gradient to exist

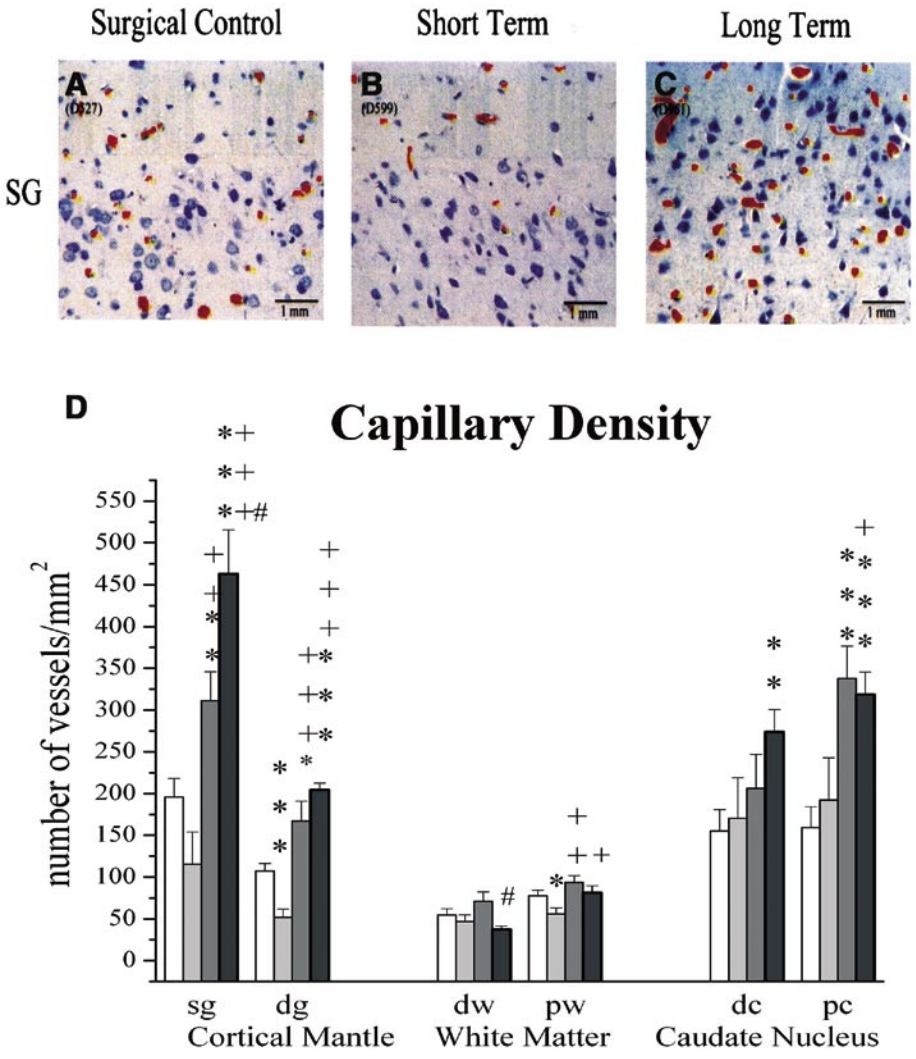

Figure 6. Angiogenesis, as shown by an increase in blood vessel density, has been reported in an experimental model of chronic obstructive hydrocephalus. Blood vessel density initially decreases in the first 3 to 5 weeks post-CH induction (**B**), then increases significantly ($p \leq 0.01$) in later weeks (8 and 10-12 weeks). Quantitative changes in blood vessel density (**D**) were most prominent in superficial and deep gray matter, followed by caudate nucleus, and also in deep and periventricular white matter. Reproduced with permission from Luciano MG, Skarupa DJ, Booth AM, Wood AS, Brant CL, Gdowski MJJ (2001) Cerebrovascular adaptation in chronic hydrocephalus. *Cereb Blood Flow Metab* 21:285-294.

there must be significant resistance to flow at the cerebral aqueduct and although this is present in obstructive hydrocephalus, in communicating hydrocephalus aqueductal resistance is decreased (24).

Portnoy et al (118) have demonstrated that what is actually present is a trans-cortical venous pressure gradient with higher pressures generated superficially in the cortical venous system, where (vascular) compliance is most impaired. As the subependymal brain parenchyma adjacent to the ventricles is at a lower pressure (close to the venous sinus pressure) in chronic hydrocephalus, absorption of CSF via the transependymal route can still occur in the periventricular region, and this may be sufficient to compensate the hydrocephalus and may explain why the CSF pressure does not rise. Although the mean intraventricular pressure in chronic hydrocephalus is usually normal, the loss of compliance results in an increase in the pulse pressure up to 6 times normal, giving a so-called "water hammer pulse" (49). Bateman (10), building on the above findings, proposed an alternative explanation for ventricular enlargement: under normal conditions the inner portions of the brain move least, but in NPH, owing to a combination of reduced compliance more superficially and larger arterial pulsations in the deeper territory, they move most. This has the effect of producing increased shear stresses and thus ventricular expansion through brain volume loss. The large floppy ventricles appear to be bowing outward due to the small but significant intraventricular water hammer pulse.

The development of symptoms with ventriculomegaly in the presence of a normal CSF pressure has been attributed to the shear stresses exerted on the white matter tracts (8, 61). However, this fails to take into account the lack of a strong correlation between ventricular size and symptom severity, nor does it explain the phenomenon of compensated hydrocephalus. Studies in our (ML, SD) experimental model of chronic hydrocephalus suggest that compensation is, in part, brought about through vascular proliferation in the deep white matter (Figure 6), which acts both to increase CSF clearance by the transependymal route and also to improve periventricular cerebral perfusion. Any subsequent compromise of these vascular changes may precipitate decompensation.

The role of cerebrovascular disease. There is now strong evidence for an association between chronic (symptomatic) hydrocephalus and cerebrovascular disease (18, 26, 28, 60, 82, 110, 131, 143). In particular, there is a strong association with hypertension (82). When arterioles are occluded due to cerebrovascular disease the associated veins also close; although this maintains the inflow-outflow balance for blood, the loss of veins further compromises CSF absorption which, as stated above, may be heavily dependent on the trans-ependymal pathways. This exacerbates the loss of compliance and may result in transient elevations of CSF pressure (B waves). The net effect is progression of ventricular dilatation and impairment of cerebral periventricular perfusion (22, 23, 108).

Cerebral blood flow (CBF) studies have demonstrated significant reductions in periventricular perfusion in association with chronic hydrocephalus (78, 109, 113). When cerebral perfusion is compromised in the presence of intact cerebral autoregulation, the arterioles will dilate as a result of local ischemia. If maximal arteriolar vasodilatation is already present then CBF will not improve following administration of acetazolamide (a carbonic anhy-

drase inhibitor which normally increases CBF). This loss of a vasomotor response has been used to evaluate patient suitability for shunting (31, 106). There is evidence that recovery of autoregulation after shunting in chronic hydrocephalus is associated with a better outcome (38). Furthermore, the severity of deep white matter ischemic changes on imaging is inversely correlated with the degree of improvement following CSF shunting (18), although this association is inconsistent and does not preclude a response to shunting (143). The implication is that with severe cerebrovascular disease, autoregulation is lost and therefore the ability to reperfuse the deep white matter bed following shunt placement is impaired. Furthermore, the more severe the cerebrovascular disease, the more likely it is that CBF will be critically reduced, with subsequent cerebral infarction. This will result in progressive cerebral atrophy, with a corresponding increase in compliance (as the transcortical pressure gradient is reduced) and reduction in CSF outflow resistance (10, 38). Arteriolar atherosclerosis increases the pulsatility of the arterial inflow resulting in pulsatile shear stress injury to the surrounding parenchyma (9, 10). Thus end stage "burnt out" chronic hydrocephalus reaches a point where it is no longer shunt responsive and may resemble subcortical arteriosclerotic encephalopathy (SAE, or Binswanger disease). Chronic hydrocephalus and SAE may therefore represent different ends of a single pathological spectrum with the relative degrees of 'true' hydrocephalus—ie, hydrodynamic disturbance versus the amount of cerebrovascular disease—determining the degree of reversibility with CSF shunting.

The role of CSF turnover. In addition to cerebrovascular disease, a reduction in CSF turnover may also have an important role in chronic hydrocephalus. As previously discussed, with increasing age CSF turnover declines and this may be more pronounced in patients with chronic hydrocephalus (132). Reductions in CSF turnover may exacerbate neuronal loss due to parenchymal accumulation of neurotoxins such as β-amyloid, tau protein, and pro-inflammatory cytokines such as TNF-α (134, 139, 141). A reduction of bulk flow in chronic hydrocephalus will tend to compound the parenchymal stasis of the interstitial fluid and further exacerbate any neurotoxicity. The accumulation of neurotoxins occurs regardless of the underlying cause of the hydrocephalus as the same common pathogenic mechanisms (reversed bulk flow, decreased CSF production) are involved. Tisell et al (141) recently demonstrated that ventricular CSF biochemical markers such as sulfatide, tau protein, and neurofilament light protein (NFL) accumulated to the same extent regardless of whether the patient had obstructive (aqueduct stenosis) or communicating idiopathic chronic hydrocephalus. Compensatory vascular proliferation in the deep white matter may initially facilitate clearance of neurotoxins, but with age-related cerebrovascular changes this may be compromised. If decreased CSF turnover does contribute to the development of symptomatic chronic hydrocephalus, one might predict a relative lack of efficacy for treatment options such as endoscopic third ventriculostomy or choroid plexus coagulation (117), that improve the hydrodynamic environment of the brain without increasing CSF turnover. CSF shunt placement, which increases CSF turnover, would be predicted to be more successful in improving symptoms of chronic hydrocephalus. This may be particularly true for cognitive function, which is more likely to reflect neurotoxic damage than is the case for disturbances of gait, which may be more closely related to pulsatile shear injury of the periventricular white matter (61, 134). The failure of 10 of 18 patients with chronic hydrocephalus due to aqueduct stenosis to respond to endoscopic third ventriculostomy and their subsequent clinical improvement following placement of a CSF shunt lends support to this theory (141).

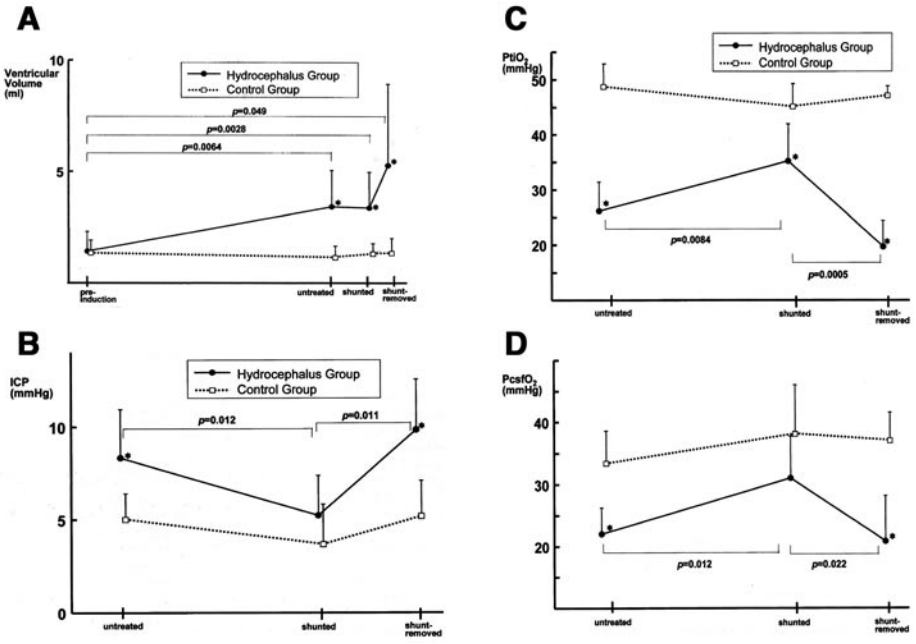

Figure 7. In an experimental model of chronic obstructive hydrocephalus, CSF shunting has been shown to be an effective surgical treatment. Specifically, shunting has been shown to significantly slow the progression of ventriculomegaly (**A**), and significantly reduce ICP (**B**). CSF shunting also significantly improved oxygen saturation in both brain parenchyma (**C**) and CSF (**D**). These improvements were reversible, and in some cases significantly worsened when shunting was removed. Asterisks indicate significant differences compared with corresponding values of the control group. Reproduced with permission from Fukuhara T, Luciano MG, Brant CL, Klauscie JJ (2001) Effects of ventriculoperitoneal shunt removal on cerebral oxygenation and brain compliance in chronic obstructive hydrocephalus. *J Neurosurg* 94:573-581.

CSF SHUNTING IN ALZHEIMER DISEASE

If the above arguments hold, there is possibly a role for CSF shunt placement in patients with a clinical diagnosis of AD or SAE, particularly in the presence of ventriculomegaly.

Recent reports suggest that ischemia may have a significant role in pathogenesis of AD (9, 41, 114) and the effect of shunting might be to decrease hydrodynamic stress and improve periventricular perfusion in these patients. Perhaps more importantly, it would increase turnover of CSF and brain tissue fluid, thus potentially reducing toxic cell damage (133). Although shunt-

ing would not be expected to improve the clinical condition, it might arrest or slow disease progression. Obviously, the risks of shunt placement in elderly patients with fragile cerebral vessels and often-significant co-morbidity would have to be weighed against the possible benefits in terms of improved quality of life and reduced cost of nursing care. The health economic arguments that might be used to justify shunts for AD would be similar to those used in recent debates regarding cholinesterase inhibitors, in which justification of their use was made on basis of marginal stabilization in cognition and reduced care needs (120, 149).

TREATMENT OPTIONS FOR ADULT HYDROCEPHALUS

Currently, the mainstay of treatment in symptomatic adult-onset hydrocephalus is the insertion of a ventriculo-peritoneal shunt. There are many different types of shunt valves, which regulate by various mechanisms the amount of CSF draining from the ventricles to the peritoneal cavity. For patients with normal-pressure hydrocephalus the amount of CSF drainage and valve pressure setting required to achieve therapeutic benefit varies considerably. Hence, it is convenient to have a valve that is adjustable in order for the pressure and CSF drainage to be tailored as precisely as possible to the individual's particular physiological requirements (153). Currently, these adjustable valves represent the 'gold standard' for treating patients with NPH, but other fixed pressure valves may sometimes be used as a cheaper alternative. Experimental studies from our laboratory (SD, ML) have shown CSF shunting to be an effective surgical treatment in the regulation of CSF volume and pressure (Figure 7A, B), as well as oxygen saturation in brain parenchyma ($PtiO_2$) and CSF ($PcsfO_2$) (Figure 7C, D). Additionally, these improvements are reversible, and in some cases significantly worse than prior to shunt placement which may correspond clinically to a state of shunt dependency.

Some of the potentially damaging complications associated with shunts in elderly patients have led neurosurgeons to try alternative therapeutic procedures, such as endoscopic third ventriculostomy and endoscopic choroid plexus cauterisation, in efforts to restore normal cerebral CSF dynamics without shunting (103, 117). However, in chronic hydrocephalus these techniques remain experimental and it is not yet known whether they will have any role in the future management of these patients.

Concomitant hypertension or diabetes must be carefully controlled in patients with adult-onset hydrocephalus, especially in more elderly patients, and regular low dose aspirin can reduce the risk of lacunar strokes from deep white matter small vessel disease. In patients who have experienced improvement in mobility following a shunt, but continue to deteriorate with dementia, there may be a role for cholinesterase inhibitors.

FUTURE RESEARCH

There needs to be a better understanding of the control of CSF production and its absorption in normal and hydrocephalic patients. Neurosurgeons with an interest in hydrocephalus need to collaborate to a greater extent with neuropathologists, physiologists, and engineers specializing in fluid mechanics to make real progress in this area. In the clinical arena, a wider role for CSF shunting is emerging and rigorous clinical and health-economic evaluations of new therapeutic strategies will be necessary.

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