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REVIEW

Brain metabolism in adult chronic hydrocephalus

Daniel Kondziella,*,† Ursula Sonnewald,† Mats Tullberg*,‡ and Carsten Wikkelso*,‡

*Department of Neurology, Sahlgrenska University Hospital, Göteborg, Sweden
†Department of Neuroscience, Norwegian University of Science and Technology, Trondheim, Norway
‡Institute of Neuroscience and Physiology, The Sahlgrenska Academy, Göteborg University, Göteborg, Sweden

Abstract

Normal pressure hydrocephalus (NPH) is the most frequent form of chronic hydrocephalus in adults. NPH remains underdiagnosed although between 5% and 10% of all demented patients may suffer from this disorder. As dementia is an increasing demographic problem, treatable forms such as in NPH have become a central issue in neurology. Despite the traditional perception of hydrocephalus being a disorder of disturbed CSF dynamics, in NPH metabolic impairment seems at least as important. So far, the only valid animal model of NPH is chronic adult kaolin hydrocephalus. In this model, opening of alternative CSF outflow pathways leads to normal or near-normal intracranial pressure and CSF outflow resistance. Yet, various metabolic disturbances cause ongoing ventricular enlargement and characteristic symptoms including cognitive decline and gait ataxia. Delayed hippocampal neuronal death, accumulation of beta-amyloid and disturbed cholinergic neurotransmission may contribute to memory dysfunction. Compromised periventricular blood flow, decreased dopamine levels in the substantia nigra and damaged striatal GABAergic interneurons may reflect basal ganglia symptoms. At least in human hydrocephalus cerebrovascular co-morbidity of the white matter plays an important role as well. It seems that in hydrocephalus from a certain 'point of no return' metabolic impairment becomes decoupled from CSF dynamics and, at least partly, self-sustained. This is probably the reason why despite restored CSF circulation by shunting many patients with chronic hydrocephalus still suffer from severe neurological deficits. The present paper offers a comprehensive review of the experimental and clinical data suggesting metabolic disturbances in chronic hydrocephalus.

Keywords: cerebral blood flow, cerebrospinal fluid, dementia, intracranial pressure, white matter.
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Chronic hydrocephalus can be defined as a disorder in which radiologically verified ventricular enlargement occurs together with normal or low-grade elevation of intracranial pressure (ICP; Edwards *et al.* 2004). This review will focus on normal pressure hydrocephalus (NPH), which is the most frequent form of chronic hydrocephalus in adults. NPH is either classified as idiopathic (INPH) or, when there is an obvious cause such as traumatic brain injury, as secondary (SNPH; Relkin *et al.* 2005). Ventriculomegaly arises despite unrestricted communication between the ventricular system and subarachnoidal space. Gait ataxia, cognitive disturbances, and urine incontinence develop (Blomsterwall *et al.* 1995, 2000; Tisell *et al.* 2005; Hellström *et al.* 2007). Mortality may be increased by 2.5 times (Malm *et al.* 2000; Tisell *et al.* 2006). NPH is more common than earlier estimated (Edwards *et al.* 2004). Up to 10% of all demented patients may have NPH (Hakim *et al.* 2001; Vale and Miranda 2002). A recent surveillance from Norway showed an INPH prevalence of 22/100 000 inhabitants with an incidence of 5.5/100 000 (Brean and Eide 2008). However, < 2 NPH patients in 100 000 inhabitants per year receive

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Address correspondence and reprint requests to Daniel Kondziella, MD, PhD, Department of Neurology, Sahlgrenska University Hospital, SE-41345 Göteborg, Sweden. E-mail: daniel.kondziella@vgregion.se

Abbreviations used: ADC, apparent diffusion coefficients; AQP4, aquaporin 4; CBF, cerebral blood flow; ICP, intracranial pressure; INPH, idiopathic normal pressure hydrocephalus; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NPH, normal pressure hydrocephalus; SAE, subcortical arteriosclerotic encephalopathy; SNPH, secondary normal pressure hydrocephalus.

surgery (Krauss and Halve 2004; Tisell *et al.* 2005). The discrepancy between high NPH incidence and low treatment frequency has been attributed to lack of awareness in physicians (Stein *et al.* 2006; Conn 2007). Symptoms often resemble those of other brain disorders such as subcortical arteriosclerotic encephalopathy (SAE, or Binswanger disease). Bilateral white matter changes and ventricular enlargement seen on magnetic resonance imaging (MRI) in SAE patients may be indistinguishable from findings in NPH (Tullberg *et al.* 2001, 2002). Furthermore, the available diagnostic tools have limited sensitivity and specificity and predict post-operative outcome often poorly. Diagnosis is still largely based on measuring CSF dynamics. The most common approaches include evaluation of CSF outflow resistance (Rout; Eklund *et al.* 2007) and of clinical improvement following temporary CSF drainage (Wikkelso *et al.* 1986; Marmarou *et al.* 2005). CSF diversion with a ventriculo-peritoneal or -artrial shunt device is the treatment of choice. All symptoms, including cognitive, may improve post-operatively (Larsson *et al.* 1994; Iddon *et al.* 2004). Short-term outcome is positive in roughly 80% of patients (Tisell *et al.* 2006), whereas long-term benefits are seen in only 26–60% (Malm *et al.* 2000; Savolainen *et al.* 2002; Tisell *et al.* 2006).

As dementia is an increasing demographic problem, reversible dementias such as in NPH will receive considerable interest in the future. Despite more than 40 years of research, our understanding of chronic hydrocephalus remains sparse. Have we focused too much on CSF dynamics and forgotten metabolic aspects of the disorder? This review summarizes the experimental and clinical data of brain metabolism in adult chronic hydrocephalus and outlines important areas for future research.

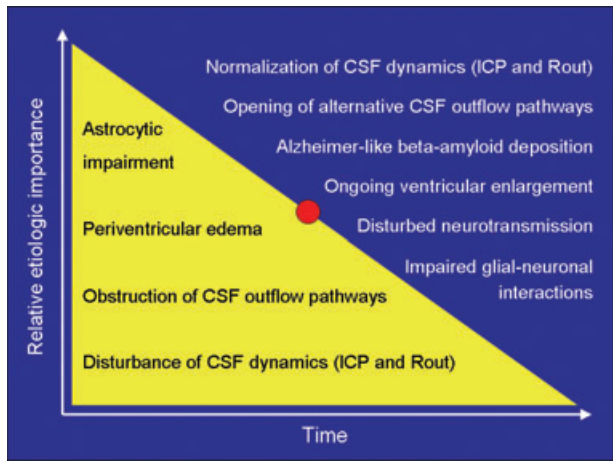

Fig. 1 Schematic depiction of pathophysiological mechanisms in kaolin-induced hydrocephalus. In acute hydrocephalus (yellow, left) 4 weeks after kaolin-treatment impairment of CSF dynamics dominates, but from week 6 ICP and Rout normalize because of opening of alternative CSF outflow pathways. Yet, increasingly important metabolic disturbances lead to ongoing ventricular enlargement and the characteristic clinical symptoms of chronic hydrocephalus (blue, right). It is therefore postulated that from a certain 'point of no return' (red circle, center) metabolic impairment becomes self-sustained and, at least partly, irreversible.

Evidence of metabolic disturbances in experimental hydrocephalus

Is there a valid animal model of NPH?

Normal pressure hydrocephalus is, as far as we know, a strictly human phenomenon. It seems therefore wise to consider the validity of animal models of hydrocephalus before reviewing the knowledge we have gained from them. Criteria for animal models include: (i) face validity (how well are human symptoms modeled?), (ii) causative validity (how well does the disease-inducing factor match current pathophysiological theories?), and (iii) predictive validity (how well does treatment applied to patients reverse symptoms in animals?). Disturbances of brain structure and metabolism in experimental hydrocephalus depend on several factors such as etiology, age of onset, CSF outflow resistance (Rout), ICP, progression and amount of ventricular enlargement and severity of mechanical stretching of periventricular structures. Consequently, different animal models of hydrocephalus are difficult to compare. The largest part of literature on experimental hydrocephalus involves genetic models (Crews *et al.* 2004) and kaolin-induced hydrocephalus in neonatal or juvenile animals (Fukushima *et al.* 2003; Del Bigio 2004; Khan *et al.* 2006). This is not very relevant to NPH. However, adult chronic kaolin-induced hydrocephalus seems to satisfy face validity as an NPH model (Fig. 1). Adult rats with chronic kaolin hydrocephalus show cognitive impairment such as decreased learning and spatial memory (Del Bigio *et al.* 1997a,b; Del Bigio *et al.* 2002; Del Bigio *et al.* 2003; Egawa *et al.* 2002) and psychomotor symptoms including gait ataxia and bradykinesia comparable to NPH patients (Del Bigio *et al.* 1997a,b; Del Bigio *et al.* 2002; Del Bigio *et al.* 2003). Ventriculomegaly continues in chronic hydrocephalus 6 weeks after kaolin treatment despite normalizing Rout and ICP (Kondziella *et al.* 2002), which is in good agreement with human NPH. Additionally, MRI often shows a flow-void phenomenon similar to the one seen in NPH (Del Bigio *et al.* 1997a,b), and β-amyloid accumulates in hydrocephalic rat brain as it does in NPH patients (Klinge *et al.* 2006). The good predictive validity of the kaolin model has been established as well: shunting of hydrocephalic rats leads to significant clinical improvement (Del Bigio *et al.* 1997a,b; Del Bigio and Massicotte 2001) and attenuates biochemical disturbances (Tashiro *et al.* 1997a,b). As in NPH, the degree of ventriculomegaly does not predict the level of behavioral impairment (Del Bigio *et al.* 2003) nor does the regression of ventriculomegaly after shunting

Table 1 Clinical features of NPH and chronic adult kaolin hydrocephalus

	Cognitive disturbances	Gait ataxia, motor dysfunction	Urinary incontinence	Etiology	Shunt responsiveness
NPH	Yes	Yes	Yes	Idiopathic or secondary	Yes
Kaolin hydrocephalus	Yes	Yes	Not known	Secondary	Yes

See text for details. NPH, normal pressure hydrocephalus.

necessarily correspond to the degree of clinical improvement (Del Bigio *et al.* 1997a,b). However, causative validity is obviously a drawback when it comes to modeling of INPH. Instillation of kaolin into the cisterna magna causes aseptic inflammation of the basal meninges, which obstructs the outlet foramina of the fourth ventricle. Non-communicative hydrocephalus develops. Low doses of intracisternal kaolin causing slower ventricular enlargement are probably preferable. In the acute phase 4 weeks after kaolin treatment ICP and Rout are highest, while 2 weeks later in the chronic phase ICP becomes normal and Rout declines (Kondziella *et al.* 2002). This is at least partly because of the establishment of compensatory CSF outflow pathways along spinal and cranial nerves (Brinker *et al.* 1998; Luedemann *et al.* 2002; Voelz *et al.* 2007). Thus, chronic kaolin-induced hydrocephalus may be an adequate model of SNPH only. However, we obviously have no means to create a model of INPH with high causative validity, as INPH still *is* idiopathic and our knowledge about the underlying causes so limited. For the time being we have to accept animal models with low causative validity and of these, adult rats with chronic kaolin hydrocephalus appear to be the best choice (Table 1).

Development and absorption of brain edema in adult kaolin hydrocephalus

Magnetic resonance imaging and magnetic resonance spectroscopy (MRS) enable non-invasive longitudinal monitoring of transformation from acute into chronic hydrocephalus and have been used in neonatal, juvenile and adult rats with kaolin hydrocephalus. If not explicitly stated otherwise, all cited studies in the following paragraphs involve *adult* kaolin hydrocephalus.

During acute kaolin hydrocephalus apparent diffusion coefficients (ADC) and T_2 values in the striatum and cortex decrease. This, together with reduced total water and impaired diffusion, is consistent with compression of gray matter secondary to a raise in ICP (Massicotte *et al.* 2000). In contrast, in white matter ADC values increase because of accumulation of free extracellular water and edema development. Cerebral blood flow (CBF) is unaltered in gray matter, but reduced in white matter (Massicotte *et al.* 2000). Interestingly, changes in CBF do not seem to correlate with ventricular size, T_1, T_2, or ADC values, indicating that other parameters, possibly including ICP, may be important. White matter hypoperfusion may in addition to vasogenic extracellular edema lead to cytotoxic edema secondary to impaired cell energy metabolism (Massicotte *et al.* 2000), which is reflected by increased lactate levels detected by MRS (Braun *et al.* 1997, 1999). Release of the intracellular osmolyte taurine during acute hydrocephalus may temporarily compensate for cellular edema (Kondziella *et al.* 2002). However, this remains speculative as ADC values do not allow clear distinction between intracellular and extracellular water (Ebisu *et al.* 1993). During the chronic stage of kaolin hydrocephalus white matter edema gradually decreases (Braun *et al.* 1997, 1998, 1999), although the ventricles continue to expand up to 6 weeks after kaolin instillation or even longer (Braun *et al.* 1997; Kondziella *et al.* 2002). As discussed below, changes in gray and white matter CBF are important for metabolic derangement in the different stages of hydrocephalus development.

It can be concluded that MRI has convincingly demonstrated dynamic changes of water diffusion in the hydrocephalic brain. Increases in Rout and ICP in the acute phase of kaolin hydrocephalus explain the compression of gray matter, initial ventriculomegaly and subsequent white matter edema. Ventricular enlargement continues in chronic experimental hydrocephalus because of unknown reasons despite normal ICP. However, normalization of CSF dynamics (Kondziella *et al.* 2002) and alternative CSF outflow pathways (Luedemann *et al.* 2002; Voelz *et al.* 2007) probably contribute to the resolution of white matter edema. Moreover, yet speculative but intriguing suggestions stem from recent research on pediatric hydrocephalus involving aquaporin 4 (AQP4). This water channel permits bidirectional water transport across cell membranes (Verkman *et al.* 2006). Up-regulation of AQP4 has been documented in juvenile hydrocephalus (Lehmann *et al.* 2004; Mao *et al.* 2006). In the hydrocephalic brain CSF is thought to move from the ventricular to the parenchymal extracellular space causing white matter edema (Hochwald 1985). Part of this CSF is cleared via a transparenchymal route into the cerebral microvasculature (Bloch *et al.* 2006; Mao *et al.* 2006; Shen *et al.* 2006). APQ4 may therefore play a role in both generation and resolution of hydrocephalic brain edema (Manley *et al.* 2000; Papadopoulos and Verkman 2005; Mao *et al.* 2006; Zador *et al.* 2007). Increased expression of AQP4 has been associated with spontaneously arrested

congenital hydrocephalus and development of alternative CSF absorption from the interstitial space into periventricular tissue capillaries (Shen *et al.* 2006). Lack of increased APQ4 expression in contrast has been related to hydrocephalus progression (Bloch *et al.* 2006). It must be borne in mind that none of the cited studies (Bloch *et al.* 2006; Mao *et al.* 2006; Shen *et al.* 2006) examined adult chronic kaolin hydrocephalus, but it seems obvious to suggest that the function of AQP4 in NPH is worth exploring. Reversed water transport via AQP4 into the vasculature may contribute to white matter edema resolution during the chronic phase of kaolin hydrocephalus.

Cerebral ischemia, lactate production, and neuronal damage in adult kaolin hydrocephalus

In both acute and chronic adult kaolin hydrocephalus ^{1}H MRS *in vivo* studies have shown increased lactate concentrations in voxels containing CSF and adjacent brain tissue (Braun *et al.* 1997, 1998, 1999). Lactate is the end product of anaerobic glycolysis and a sensitive marker of cerebral ischemia and hypoxia. It has been suggested that compromised periventricular CBF (Klinge *et al.* 2003) is followed by lactate accumulation within the ventricular system. CBF in acute kaolin hydrocephalus assessed by ^{14}C iodoantipyrine autoradiography was decreased by 13–53% in cortex, hippocampus, and periventricular white matter, but only in the latter below the ischemic threshold (Klinge *et al.* 2003). Reduced CBF and cerebral ischemia in acute hydrocephalus probably result from increased ICP. When kaolin hydrocephalus becomes chronic, CBF is restored in hippocampus and cortex, but remains slightly decreased in the periventricular region (Klinge *et al.* 2003). As ICP normalizes (Kondziella *et al.* 2002) and as ventricular size is not correlated with lactate levels (Braun *et al.* 1999) and only loosely with periventricular CBF (Klinge *et al.* 2003), other still unknown mechanisms are necessary to explain the decreased periventricular CBF and lactate production in chronic hydrocephalus. At the stage of greatest ventricular enlargement during chronic hydrocephalus CBF is already normalizing (Klinge *et al.* 2003). Interestingly, simultaneous ^{31}P MRS revealed no changes in high-energy phosphate metabolism or pH (Braun *et al.* 1999). The findings from ^{1}H and ^{31}P MRS may seem contradictory at first, but could be explained by differences in voxel positions, macrophage-induced lactate production or, most noteworthy, by the assumption that in mild ischemia lactate production occurs before levels of adenosine triphosphate and phosphocreatine fall (Sutton *et al.* 1987).

In both acute and chronic kaolin hydrocephalus ^{1}H MRS revealed decreased ratios of *N*-acetyl aspartate/choline and total creatine/choline, implicating neuronal injury or functional impairment respectively changes in membrane phospholipid metabolism as seen in myelin damage and gliosis (Braun *et al.* 1997, 1999). It should be noted that these studies were hampered by the fact that only one large, single voxel and a weak 4.7 T magnet were used, which made it neither possible to clearly distinguish between metabolite levels of CSF and brain parenchyma nor to quantify metabolic disturbances in more confined brain regions. However, neuronal impairment was confirmed by immunohistochemistry revealing increased immunoreactivity for nitric oxide synthase in cortical and hippocampal neurons 2 weeks after kaolin treatment, which suggested an early global neuronal ischemic response (Klinge *et al.* 2003). At 4 weeks, when ICP and Rout reach maximal levels (Kondziella *et al.* 2002), the most salient finding was an increase in neurofilament staining of the periventricular white matter, consistent with reactive axonal changes secondary to mechanical stretching (Klinge *et al.* 2003). In line with this, calcium-mediated proteolytic white matter damage has been detected in acute kaolin hydrocephalus (Del Bigio 2000). In chronic hydrocephalus, periventricular immunoreactivity was no longer apparent. In contrast, the CA1 hippocampus subfield displayed a strong increase of nitric oxide synthase immunostaining and a loss of neurofilament reactivity, suggesting cytoskeletal neuronal injury and the onset of reactive dendritic and axonal changes (Grady *et al.* 1993). In the CA3 subfield increased staining of neurofilament and synaptophysin were noticed. As hippocampal CBF at that time was already normal and never had been below the ischemic threshold, the authors concluded that these findings were compatible with delayed neuronal death in the hippocampus of chronic hydrocephalic rats (Klinge *et al.* 2003). Selective and delayed neuronal injury of hypoxia-sensitive structures such as the hippocampus also occurs in other brain disorders (Kirino 2000). Delayed hippocampal neuronal injury might indeed be an intriguing explanation for some of the dementia observed in NPH patients (Hellström *et al.* 2007).

Disturbances of neurotransmitter metabolism and glial–neuronal interactions in adult kaolin hydrocephalus

Neurotransmitter disturbances in adult kaolin hydrocephalus are complex and include cholinergic (Tashiro *et al.* 1997a,b; Egawa *et al.* 2002), dopaminergic (Miwa *et al.* 1982; Tashiro *et al.* 1997a; Del Bigio *et al.* 1998), serotonergic (Del Bigio *et al.* 1998), noradrenergic (Miwa *et al.* 1982; Egawa *et al.* 2002), glutamatergic and GABAergic (Tashiro *et al.* 1997b; Kondziella *et al.* 2002, 2003; 2008 unpublished results) systems. Changes have been described in cerebellum (Kondziella *et al.* 2002), basal ganglia (Tashiro *et al.* 1997a,b), hypothalamus, mesencephalon, pons, medulla oblongata (Tashiro *et al.* 1997a,b; Del Bigio *et al.* 1998; Kondziella *et al.* 2002, 2003; 2008 unpublished results), nucleus caudatus (Miwa *et al.* 1982), hippocampus (Egawa *et al.* 2002) and cortex (Miwa *et al.* 1982; Del Bigio *et al.* 1998, Egawa *et al.* 2002 and Kondziella *et al.* 2002, 2003; 2008 unpublished results). Some of the

reported neurotransmitter decreases may be attributed to damage of related axonal projection systems, whereas accumulation of metabolites because of reduced CSF clearance may explain some of the increases. Decreased hypothalamic and mesencephalic dopamine levels (Del Bigio *et al.* 1998), especially in the substantia nigra (Tashiro *et al.* 1997a), together with damaged striatal GABAergic interneurons (Tashiro *et al.* 1997a) may reflect Parkinsonian symptoms in NPH. Progressive injury to cholinergic systems (Tashiro *et al.* 1997a,b; Egawa *et al.* 2002) in combination with the above cited delayed neuronal death in hippocampus (Klinge *et al.* 2003) may contribute to hydrocephalic dementia. Disturbances of serotonergic (Del Bigio *et al.* 1998) and noradrenergic (Miwa *et al.* 1982; Egawa *et al.* 2002) systems could impair mood and long-term potentiation required for learning (Bliss *et al.* 1983). As a general rule, transmitter disturbances tend to increase in chronic adult kaolin hydrocephalus suggesting development of structural neuronal damage (Tashiro *et al.* 1997a; Klinge *et al.* 2002; Kondziella *et al.* 2002, 2003), but disturbances may be functional in acute hydrocephalus. In some cases biochemical and behavioral changes are rapidly reversible by surgical treatment (Tashiro *et al.* 1997a).

Interplay between astrocytes and neurons are crucial for energy metabolism (Pellerin 2005) and information signaling (Verkhratsky and Toescu 2006). Gial–neuronal interactions in experimental hydrocephalus have recently been reviewed (Sonnewald and Kondziella 2003). Whereas in the acute stage 2 weeks after kaolin-injection changes of amino acid levels were minimal, in chronic hydrocephalus glutamate and glutamine were decreased in the cerebellum and glutamine was increased in the cerebrum. As glutamine synthesis in the brain is an exclusively glial process (Norenberg and Martinez-Hernandez 1979), increased cerebral glutamine can suggest reactive gliosis (Kondziella *et al.* 2002). Altered astrocytic glutamate handling was also confirmed in another study, which examined label incorporation in neurotransmitter amino acids and other compounds in kaolin hydrocephalus using ^{13}C MRS (Kondziella *et al.* 2003). With this method it is possible to study astrocytic and neuronal metabolism simultaneously (Sonnewald and Kondziella 2003). In kaolin hydrocephalus labeling of most amino acids derived from neuronal metabolism was largely unchanged, whereas labeling from astrocytic metabolism was affected (Kondziella *et al.* 2003). Four weeks after kaolin installation cerebral transport of astrocytic glutamine to glutamatergic neurons was clearly impaired, suggesting disturbed glial–neuronal interactions. Only in chronic hydrocephalus neuronal glutamatergic metabolism became affected as well (Kondziella *et al.* 2003). Using the same animal model, glial–neuronal injury has also been reported by Klinge *et al.* (2002) who showed that in the acute stage expression of selected glial and neuronal enzymes increased, whereas in chronic hydrocephalus sustained changes in structural proteins occurred.

Evidence of metabolic disturbance in human NPH

Although the precise mechanisms remain largely unknown it is believed that initial ventricular enlargement in NPH is due to disturbed CSF absorption into the venous blood. A mild temporary increase in ICP is generally seen, but ventriculomegaly may also be associated with increased amplitude of intracranial pulsatile pressure alone (Di Rocco *et al.* 1979). As force equals pressure multiplied by area, ventricular pressure tends to normalize with expanding ventricles (Hakim and Adams 1965). Transcapillary CSF absorption in the periventricular white matter and absorption via spinal nerves into the lymphatic system may contribute to normalization of ICP (Deo-Narine *et al.* 1994; Edsbagge *et al.* 2004), but also these mechanisms are still very unclear. Pathologically the periventricular tissue is characterized by interstitial edema, ependyma disruption, microvascular infarctions, gliosis, and neuronal degeneration (Weller *et al.* 1971; Akai *et al.* 1987). Injury to neurons may result from various mechanisms such as mechanical stretching of periventricular tissue by the enlarging ventricles and disturbed elimination of metabolic end products because of parenchymal edema, impairment of the blood brain barrier and reduced CSF turnover.

Evidence for metabolic disturbance in NPH comes from neuroimaging studies of CBF, MRS of neuronal and glial function and analysis of CSF markers of brain damage. Single photon emission computed tomography and positron emission tomography studies have shown a global reduction of CBF (Owler and Pickard 2001). In addition, regional CBF is decreased in the frontal lobe, hippocampus (Larsson *et al.* 1994), thalamus, basal ganglia (Owler *et al.* 2004) and periventricular white matter (Corkill *et al.* 2003; Momjian *et al.* 2004). CBF is maximally reduced periventricularly and gradually increases towards the subcortical white matter and cortex. The decrease in CBF in the thalamus, basal ganglia and white matter correlates with changes in CSF pressure (Owler *et al.* 2004). In line with this, reduced oxygen metabolism in the basal ganglia, possibly contributing to motor symptoms, has been described in NPH (Miyamoto *et al.* 2007). Disturbances of CBF and oxygen metabolism suggest chronic ischemia in NPH, which is reflected by the detection of lactate in some, but not all, studies. Microdialysis revealed increased lactate concentrations and anaerobic glycolysis in periventricular white matter (Agren-Wilsson *et al.* 2003). Another microdialysis study showed that a sudden increase of ICP in NPH patients acutely impaired periventricular white matter energy metabolism, which was completely reversible when ICP was reduced again (Agren-Wilsson *et al.* 2005). However, normal lactate levels in the periventricular tissue and CSF of NPH were found in one MRS studies (Braun *et al.* 2003). These contradicting findings may either be explained by methodical limitations and the very heterogenous patient group (Braun *et al.* 2003)

or, more likely, by the assumption that only a subset of NPH patients has increased lactate levels. Indeed, normal cerebrovascular autoregulation without compromised energy metabolism may be characteristic for NPH patients without significant cerebrovascular co-morbidity or white matter lesions on MRI (Tullberg *et al.* 2002). Conversely, the presence of lactate and impaired cerebrovascular autoregulation in other NPH patients may be explained by the high degree of cerebrovascular co-morbidity in both SNPH and INPH (Czosnyka *et al.* 2002; Haubrich *et al.* 2007). In these patients white matter lesions on MRI associated with cerebrovascular disease are more common than in age-matched controls (Tullberg *et al.* 2002). Moreover, they often show evidence of co-existing cerebrovascular disorder at biopsy (Bech *et al.* 1997; Bech-Azeddine *et al.* 2007) and of hypertensive encephalopathy at autopsy (Akai *et al.* 1987; Newton *et al.* 1989). The frequent co-existence of cerebrovascular disease and NPH constitutes a major clinical challenge, but seems important to the pathophysiology of chronic hydrocephalus and will be discussed further below.

A number of CSF biomarkers such as tumor-necrosis factor (Tarkowski *et al.* 2003), tau protein, amyloid beta 42 (Agren-Wilsson *et al.* 2007), sulfatide (Tullberg *et al.* 2000), and neurofilament triple protein (Tullberg *et al.* 1998) are promising diagnostic markers for chronic hydrocephalus (Tarnaris *et al.* 2006). Sulfatide is a marker for demyelinisation, differentiating between irreversible and reversible tissue damage in NPH (Tullberg *et al.* 2000). Neurofilament protein, phospho-tau, and amyloid beta 42 in combination may distinguish between INPH, SAE, and healthy elderly controls (Agren-Wilsson *et al.* 2007). Increased turnover or accumulation of neurofilament protein and other structural proteins in axons may lead to release of these metabolites into the ventricular CSF which therefore serve as markers of neuronal injury (Agren-Wilsson *et al.* 2007). Likewise, probably as a result of global neuronal dysfunction, neuropeptides in CSF such as delta-sleep-inducing peptide, peptide YY and somatostatin, corticotropin-releasing factor are decreased in NPH (Wikkelso *et al.* 1991; Poca *et al.* 2001).

Restoration of CSF circulation by a shunt device or endoscopic third ventriculostomy not only leads to clinical improvement but also to normalization of many metabolic parameters. Thus, in the mesencephalon, hippocampus, frontal, and parietal lobes CBF is restored after shunting (Mamo *et al.* 1987; Larsson *et al.* 1994; Owler and Pickard 2001; Tullberg *et al.* 2004). Post-operative normalization of CSF biomarkers suggests a restitution of axonal function (Tullberg *et al.* 1998, 2000 and Tullberg *et al.* 2007). Reduced ventricular CSF tau indicates that cortical neuronal function improves after surgery (Agren-Wilsson *et al.* 2007; Tullberg *et al.* 2007). Furthermore, increased *N*-acetyl aspartate/Cr values are related to improved cognition (del Mar Matarín *et al.* 2007). Also neuropeptide levels (Wikkelso *et al.* 1991; Poca *et al.* 2001), monoaminergic neurotransmission (Malm *et al.* 1991) and glucose metabolism (Agren-Wilsson *et al.* 2003) increase following CSF drainage or shunting.

Although human studies strongly support the concept of hydrocephalus being a disorder of altered CSF dynamics, various metabolic disturbances and frequent cerebrovascular co-morbidity, our knowledge remains superficial. Ventriculomegaly *per se* is insufficient to explain the clinical symptoms of chronic hydrocephalus (Table 2). Unchanged post-operative ventriculomegaly does not exclude significant clinical improvement (Fukuhara *et al.* 2000). Conversely, despite decreasing ventricular size after shunting, often severe cognitive and motor deficits remain (Malm *et al.* 2000; Savolainen *et al.* 2002; Tisell *et al.* 2006). Much attention has therefore been paid to the possible association of NPH with Alzheimer and SAE (Silverberg *et al.* 2003; Edwards *et al.* 2004; Bech-Azeddine *et al.* 2007). In the elderly both production and absorption of CSF is decreased (Edwards *et al.* 2004) and CSF outflow resistance is increased (Albeck *et al.* 1998; Czosnyka *et al.* 2001). Increased Rout may result from impaired clearance via alternative CSF outflow pathways secondary to enhanced venous pressure (Rubenstein 1998), capillary thickening because of amyloid deposition (Zekry *et al.* 2003) and leptomeningeal fibrosis (Bech *et al.* 1997; Albeck *et al.* 1998). Reduced CSF turnover possibly leads to decreased clearance of neurotoxic substances such as β-amyloid, tau-protein, and pro-inflammatory cytokines (Kudo *et al.* 2000;

Table 2 CSF dynamics and MRI phenomenology in NPH and chronic adult kaolin hydrocephalus

	ICP	Rout	Ventricular enlargement	MRI flow void	CSF outflow pathways	Periventricular edema	WM hyperintensities
NPH	Normal (near)	Elevated (slightly)	Yes	Common	Opening of alternative pathways	Yes	Yes
Kaolin hydrocephalus	Normal (near)	Elevated (slightly)	Yes	Common	Opening of alternative pathways	Yes (resolving)	No

See text for details. ICP, intracranial pressure; MRI, magnetic resonance imaging; NPH, normal pressure hydrocephalus; Rout, CSF outflow resistance; WM, white matter.

Table 3 Brain metabolism in NPH and chronic adult kaolin hydrocephalus

	Neurotransmitter levels	Periventricular CBF	CSF biomarkers	^{1}H MRS	Astrocytic function	Delayed neuronal death	β-amyloid accumulation
NPH	Various changes	Decreased	Various changes	NAA↓ Cho↑	Probably disturbed	Not known	Yes
Kaolin hydrocephalus	Various changes	Decreased	Not known	NAA↓ Cho↑	Disturbed	Yes	Yes

See text for details. CBF, cerebral blood flow; Cho, choline; ^{1}H MRS, proton magnetic resonance spectroscopy; NAA, *N*-acetyl aspartate; NPH, normal pressure hydrocephalus.

Silverberg *et al.* 2003; Tarkowski *et al.* 2003; Tisell *et al.* 2004). Accumulation of parenchymal β-amyloid and age-related loss of neuroprotective mechanisms (Dröge and Schipper 2007) may contribute to cognitive deterioration seen in elderly patients with decompensated chronic hydrocephalus. Indeed, β-amyloid accumulation because of decreased CSF clearance may also explain the high co-occurrence of Alzheimer-like changes in the cortex of NPH patients (Del Bigio *et al.* 1997a,b; Golomb *et al.* 2000; Savolainen *et al.* 1999) and of rats with chronic hydrocephalus (Klinge *et al.* 2006). This finding has led to speculations whether Alzheimer disease and NPH may just be the extremes in a cluster of disorders characterized by a continuum of CSF circulatory failure with subsequent neurodegeneration (Silverberg *et al.* 2003). As NPH also has a strong relation to cerebrovascular disorders (Boon *et al.* 1999; Tullberg *et al.* 2001) and NPH-related dementia often is of the subcortical type (Hellström *et al.* 2007), it seems obvious to speculate that SAE or Binswanger disease belongs to this cluster of neurodegenerative disorders as well (Tullberg *et al.* 2002). Consequently, it has been suggested that shunting in SAE (Tullberg *et al.* 2002) and even Alzheimer disease (Edwards *et al.* 2004) may be worth exploring (Table 3).

Synopsis

Establishment of alternative CSF outflow pathways into spinal and cranial nerves probably initiates the transformation from acute into chronic kaolin hydrocephalus (Fig. 1). In addition, transparenchymal water transport into periventricular capillaries supports CSF clearance in both experimental and clinical hydrocephalus. Whether or not the membrane water-channel APQ4 plays a role in this respect needs to be addressed by future studies. MRI has clearly demonstrated continuing ventriculomegaly in chronic experimental hydrocephalus, despite normalization of CBF, Rout and ICP and resolution of white matter edema. Despite the fact that CBF is reduced only temporarily below the ischemic threshold and only in the white matter, at least in experimental hydrocephalus delayed neuronal death occurs in the hypoxia-sensitive hippocampus and may contribute to hydrocephalic dementia. Impairment of cholinergic neurons and accumulation of β-amyloid probably adds to cognitive decline and is part of a complex derangement of various neurotransmitter systems including monoaminergic metabolites and amino acids. Also glial–neuronal interactions and astrocytic handling of glutamate seem disturbed. Early shunting may reverse or ameliorate metabolic and behavioral alterations in experimental and human hydrocephalus by preventing transformation from functional to structural damage. It can be concluded that in chronic hydrocephalus increasing metabolic impairment leads to ongoing ventricular enlargement and characteristic clinical symptoms. We therefore hypothesize that from a certain 'point of no return' metabolic disturbances become decoupled from CSF dynamics and, at least partly, self-sustained (Fig. 1). This is probably the reason why despite restored CSF circulation by shunting many patients with chronic hydrocephalus still suffer from severe neurological deficits.

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