Normal pressure hydrocephalus (NPH): ischaemia, CSF stagnation or both

Normal pressure hydrocephalus (NPH) is a clinical and radiographic syndrome first described by Hakim and Adams in 1965 (Hakim and Adams, 1965) and characterized clinically by gait apraxia ('magnetic gait'), incontinence and dementia, and diagnosed predominantly among people over the age of 60 years. Only a minority of patients present with the complete triad of symptoms, gait apraxia being the most common presenting complaint. On brain imaging, one sees ventricular enlargement without significant cerebral atrophy. The radiographic observation that best distinguishes the ventriculo-megaly of NPH from the 'hydrocephalus ex vacuo' of advanced Alzheimer's disease is the degree of dilatation of the peri-hippocampal fissures (PHFs). PHFs are normal or only minimally dilated in NPH, and typically markedly dilated in Alzheimer’s disease.

The ‘normal pressure’ aspect of NPH is something of a misnomer. While CSF pressure may be within the normal range when measured by manometry at lumbar puncture, continuous CSF pressure measurements reveal waves of increased pressure, particularly during rapid eye movement (REM) sleep, and CSF infusion studies reveal abnormal CSF circulation.

Sceptics may doubt the existence of NPH as a clear-cut clinical–pathological entity (Bret et al., 2002). Among ‘believers,’ most accept CSF shunting as a reasonably effective treatment for the gait disorder of NPH. The effectiveness of CSF shunting as a useful treatment for the dementia of NPH has never been demonstrated, and many doubt that there is a rationale for such an approach among NPH patients for whom dementia is a chief complaint (Thomsen et al., 1986; Vanneste et al., 1992). A better understanding of the physiopathological changes in NPH is needed to guide treatment, an understanding furthered by an excellent paper by Momjian et al. (2004), from the Cambridge group, in this volume.

The authors demonstrate significantly reduced cerebral blood flow (CBF) in the deep white matter of patients with NPH, compared with control subjects. The maximal decrease is seen at the ventricular wall, with an increase in CBF as one moves laterally. Among subjects with NPH, a more profound decrease in CBF follows the induction of increased CSF pressure, in a U-shaped distribution: the nadir of CBF shifts laterally from the ventricle by ~9 mm under these conditions, and normalizes as one moves toward the cortex. Cerebral vascular autoregulation was also impaired among subjects with NPH, suggesting less capacity to compensate for increases in CSF pressure.

A similar decrease in white matter blood flow has also been observed in experimental (kaolin-induced) chronic hydrocephalus in the rat (Klinge et al., 2003). Along with a persistent decrease in white matter blood flow, immunohistochemical changes were suggestive of ischaemic neuronal injury. While there is currently no animal model for the NPH-associated dementia, it is reasonable to speculate that chronic, low-grade ischaemia, with damage to cortical and hippocampal neurons, may play an important role in the human syndrome.

The dementia of NPH, however, still remains something of a conundrum. If, in human series, one applies strict entry criteria for the diagnosis of NPH, and strict psychometric test criteria for measuring cognitive improvement following shunt placement, CSF shunting does not appear to be effective in improving the dementia of NPH (Savolainen et al., 2002). The overall poor clinical outcome after shunting with regard to dementia, when contrasted with responses in gait and continence, suggests differences in aetiology or reversibility of the pathology underlying these symptoms.

The cause of the gait disturbance and incontinence may well be related to structural aspects of ventriculo-megaly, such as stretching of frontal fibres subserving micturition and those affecting executive motor function. Ischaemic changes leading to axonal injury to these fibres may also play a significant role. As the authors point out, the ischaemia may be due to a number of causes, including direct vascular compression, distortion of the brain, increase in the interstitial fluid pressure, the presence of vasoactive peptides, impaired autoregulation and the concomitant vasculopathies common in these patients. The dementia may also be caused or exacerbated by a number of factors, including ischaemia, frank infarction and relative CSF stasis with decreased clearance of various macromolecules (Tullberg et al., 2002; Klinge et al., 2003; Silverberg et al., 2003). An inability to clear potentially toxic metabolic products, such as amyloid β-peptides (Aβ) and tau (τ) protein, could lead to an increase in
their concentration in brain interstitial fluid, creating a potentially hostile milieu for neuronal function and survival.

In NPH and in normal ageing, there is evidence for both a decrease in CSF production and an increase in the resistance to CSF absorption (May et al., 1990; Czosnyka et al., 1996; Albeck et al., 1998; Silverberg et al., 2002) Both events lead to a decrease in CSF turnover and, in turn, a decreased clearance of macromolecules. In NPH, the decrease in clearance of Aβ and Õ is suggested by the higher than expected coincidence of Alzheimer’s disease pathology in cortical biopsies taken from NPH patients at the time of shunt implantation. From 30 to 50% of NPH patients will exhibit plaques and tangles consistent with Alzheimer’s disease, and, in the severely demented NPH patients, 75% will show Alzheimer’s disease (Silverberg et al., 2003). It therefore seems likely that an inability to clear potentially toxic molecules, such as Aβ and Õ and probably other toxic products of brain metabolism, contributes primarily to the dementia of NPH, as well as secondarily by vasoconstriction, as suggested by the authors.

In considering the multifactorial nature of the dementia in NPH, it is no wonder that simply controlling CSF pressure by a hydrocephalus shunt in patients having, by definition, normal CSF pressure much of the time would lead to varying, and often disappointing, results. It is intriguing to speculate that what one needs to accomplish is to increase CSF turnover and macromolecular clearance. In the Dutch hydrocephalus study, the authors note that the best results were found in the subjects treated with low-pressure valves (Boon et al., 1998).

Low-pressure valves would be expected to have the highest flow rates and provide the greatest CSF turnover. Unfortunately, they also provided the greatest number of subdural fluid accumulations.

Expectations for improvement in the dementia of NPH must be tempered by the knowledge that there may be fixed tissue damage prior to treatment. It may be that stabilizing the progression of the dementia is all that is realistic in the majority of patients, and that any demonstrable improvement must be considered an added bonus. It would also be helpful in defining stabilization or improvement in the dementia of NPH if there were a simple, relatively inexpensive and easily administered psychometric test battery that accurately reflected the state of the dementia pre- and postoperatively. It would, of course, have to be available in many languages and would require validation in each language, not an easy task. However, until we recognize that the dementia of NPH may be a combination of fixed and potentially treatable pathologies, and that there needs to be a standard way of expressing the psychometric deficits in order to evaluate different therapies, the results of shunting for the dementia of NPH will continue to be disappointing.

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References