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REVIEW PAPER

Ventricular volume and neurocognitive outcome after endoscopic third ventriculostomy: is shunting a better option? A review

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Abstract
Background Shunts are generally associated with a smaller post-treatment ventricular size in comparison to endoscopic third ventriculostomy (ETV).
Methods To determine whether such a difference in ventricular size has neurocognitive implications, we reviewed the current literature pertaining to the (1) neurocognitive sequelae of hydrocephalus, (2) neurocognitive outcome after ETV, (3) extent of reversal of neurocognitive changes associated with hydrocephalus after shunting, and (4) data on correlation between post-treatment ventricular volume and neurocognitive outcome after ETV.
Results Collectively, the results of the available studies should call into question the correlation between the residual postoperative ventricular volume and neurocognitive outcome.
Conclusion The available literature is so far in support of ETV as a valid and effective treatment modality in hydrocephalic patients. No sufficient evidence is available to justify resorting to shunting on the premise that it is associated with a better neurocognitive outcome.

Keywords Diffusion tensor imaging · Endoscopic third ventriculostomy · Neurocognitive · Shunt · Ventricle · Ventricular size · Volume

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Introduction

It is well established that endoscopic third ventriculostomy (ETV) offers several potential advantages over shunting in select patients with hydrocephalus, including possibly lower long-term failure rates and avoidance of shunt hardware with its well-known associated complications [1].

Notwithstanding, shunting is generally associated with a smaller post-treatment ventricular size in comparison to ETV [2]. Controversy has recently emerged on whether such a difference has functional or developmental implications. As a matter of fact, the existing literature on neurocognitive outcome after ETV is limited. Notably, the majority of works fail to recruit an adequate number of patients and controls, are uncontrolled, are retrospective, or lack detailed comparative pre- and postoperative data [3–8]. Furthermore, combined endoscopic third ventriculostomy and choroid plexus coagulation (ETV-CPC) has emerged as a promising modality for treatment of infantile hydrocephalus [9, 10]. However, long-term neurocognitive outcome after the procedure is currently unknown. Owing to the currently accumulating evidence on the role played by the choroid plexus in brain development [11], neurocognitive outcome after ETV-CPC is expected to be an area of controversy that is likely to exist for years.

In this article, we review the (1) currently available knowledge on neurocognitive sequelae of hydrocephalus, (2) neurocognitive outcome after ETV, (3) evidence that shunting does not fully reverse neurocognitive changes associated with hydrocephalus (experimental and MRI studies), and (4) current literature on correlation between post-treatment ventricular volume and neurocognitive outcome after ETV.

Neurocognitive sequelae of hydrocephalus

Despite the existing discrepancies in the literature on the exact neurocognitive deficits associated with hydrocephalus, many seem to agree on memory impairments, decreased attention span, and visual perception deficits [4, 6, 12, 13]. Deficits in intelligent quotient (IQ) are controversial [13–16]. Moreover, children with infantile hydrocephalus display a high frequency of non-verbal learning disabilities [14] associated with a cognitive profile notable for a verbal IQ that is significantly higher than the performance IQ, as well as difficulties of planning and organization [17].

These neurocognitive abnormalities are believed to be a consequence of brain parenchymal damage [18] whose severity is affected by the age at onset, the rate of ventricular enlargement, the size of the ventricles, the intracranial pressure (which in turn dictates the cerebral perfusion pressure), the coexisting pathological changes, and probably the duration of hydrocephalus [19]. Impaired cerebral blood flow, alterations of neuronal cell metabolism, axonal loss, and pathological neurotransmission have been reported in association with hydrocephalus [13, 15, 19]. Damage of nerve cell processes and synaptic contacts observed in the hydrocephalic cortex implies nerve cell circuit alterations, which may explain the decline of intellectual functions and learning disabilities observed in patients with hydrocephalus. [18].

Specific neurocognitive deficits have been found to be associated with peculiar anatomical culprits. Memory and learning disabilities have been correlated with changes in the septo-hippocampal system in experimental animals [20] and in humans [21]. Partial agenesis of the corpus callosum with absent splenium and hypoplastic body has been shown to be associated with difficulty of transferring patterned visual information from one hemisphere to another [22].

The majority of the hydrocephalic patients with spina bifida demonstrate neuropsychological abnormalities that include impaired verbal learning ability, verbal recall, spatial working memory, attentional set shifting, and psychomotor speed on complex tasks involving sequencing [23]. These impairments have historically been thought to be a direct consequence of hydrocephalus. Recent investigations into the neuropsychological correlates of tectal beaking suggest that such specific neuropsychological impairments cannot be attributed solely to the effects of ventricular enlargement and rather result from the characteristic midbrain and posterior fossa malformations in these patients [24, 25]. Covert orienting responsible for the unobservable internal shifts of attention without engaging eye, head, or body movements is particularly defective in this patient subpopulation [24]. Impairment of the orienting network responsible for engaging, disengaging, and shifting attention is also well-established [26]. It is of note that individuals with spina bifida and a beaked tectum have more difficulty disengaging attention from a current stimulus and redirecting it towards a new stimulus when compared to normal individuals or those with spina bifida without tectal beaking [27]. Furthermore, the executive control network which is predominantly responsible for cognitively driven attention functions like conflict resolution and attentional control has also been demonstrated to be impaired in individuals with spina bifida [24, 28, 29].

Cognitive outcome after ETV

There is a notable paucity in the literature of studies elaborating on the neurocognitive outcome after ETV. The available information is by far incongruous. Some reports claim no resolution of cognitive deficits while others report improvement and normal cognition after the procedure [3, 4, 6, 7, 12]. Indeed, solid conclusions are very difficult to be drawn thereof owing to a multitude of limitations of these studies including for instance small sample sizes, lack of details of preoperative neurocognitive deficits, unavailability of postoperative long-term results of neurocognitive testing, failure to recruit control groups, and presence of confounders.

In 2002, Burtscher et al. prospectively evaluated the neurocognitive results of ETV in six adult patients with late onset idiopathic aqueduct stenosis. Pre- and postoperative neuropsychological assessments were undertaken and revealed multiple cognitive abnormalities in all patients preoperatively. The preoperative abnormalities included anterograde memory deficits, decreased list learning and confabulations, and impairment of executive functioning. Postoperative neuropsychological assessment demonstrated improved cognitive functions in all patients. Two patients showed complete resolution of preoperative deficits, three showed good recovery with occasional errors, and one patient was still suffering a deficit in verbal memory despite improvement. An important limitation of the study was the small sample size which clearly decreased its statistical power [4]. These findings are consistent with the findings of a more recent study by Hader et al. who reported successful ETV being capable of producing reliable objective improvements in cognitive dysfunction related to obstructive hydrocephalus. The majority of patients demonstrated benefits across a variety of cognitive domains including intelligence, attention and concentration, verbal and visual memory, and executive function. Limitations of the study included its retrospective nature and the variation of neuropsychological tests completed in each domain. Furthermore, in some cases, not all of the same tests were completed in the pre- and post-ETV assessments [5]. In the largest study so far available, Warf et al. evaluated the neurocognitive outcome in 93 children with spina bifida and ages ranging from 5 to 52 months using the modified Bayley Scales of Infant Development, third edition (BSID-III). Fifty-five of these children had been treated by ETV-CPC, 19

received ventriculoperitoneal (VP) shunts, and 19 had required no treatment for hydrocephalus. Ventricular volume was assessed by frontal-occipital horn ratio (FOR) calculated from postoperative CT scans. The mean scale scores of untreated patients were not different from normative scores in all portions of the BSID (excluding gross motor) and were generally significantly better than the scores of patients in the VP shunt-treated or in ETV-CPC groups. The ETV-CPC-treated patients had non-significantly better mean scores than patients treated with VP shunts in all portions of the BSID except receptive communication, which was significantly better for the ETV-CPC group. The authors concluded that the ETV-CPC and VP shunt groups had similar neurocognitive outcomes. It is of note that the VP shunt group in the study was biased because most patients had a failed ETV-CPC procedure (which might have been associated with cisternal scarring) or they suffered shunt infection. Therefore, the developmental outcome of the VP shunt group might be more attributable to these factors than the shunt treatment itself. However, within the group of VP shunt-treated patients, no significant difference of the mean BSID scale scores was found between patients with or without cisternal scarring or history of shunt infection [8].

Takahashi evaluated the long-term development of 25 pediatric patients with obstructive hydrocephalus treated with ETV versus VP shunting. All patients were 9 months of age or less by the time of intervention and were stratified based upon MRI findings. It was found that in infants without secondary brain damage and a cerebral morphology that is close to normal, ETV was sufficiently effective and achieved normal development although after a slightly longer period than after shunting. Nevertheless, in infants with poor cerebral development or secondary brain damage, shunting was more effective because ETV alone would not improve development [7]. Al-Jumaily et al. studied 20 adult patients with symptomatic long-standing overt ventriculomegaly (LOVA). All patients underwent ETV with two patients only requiring shunt insertion. Patients were assessed for childhood symptoms including memory impairment. Seven patients reported childhood memory problems, while nine patients reported memory problems during adulthood. Objectively, patients were mainly assessed using the repeatable battery for the assessment of neuropsychological status (RBANS). All patients scored well below normal in all test subcategories. Postoperatively, some patients reported subjective improvement in memory; however, objective test results revealed no improvement in cognitive function following ETV [3]. Looking into the results of Takahashi [7] and Al-Jumaily et al. [3], the possibility of irreversible parenchymal damage arguably stands as an explanation for the ineffectiveness of ETV in some or all of their patient populations. This is supported by the statement of Lacy et al. who argued that while ETV resolves intracranial hypertension and restores almost normal CSF pressure, long-term disruption of subcortical-frontal networks due to enlarged ventricles and subsequent stretching of axons may have taken place prior to intervention. Therefore, deficits persist despite both normalization in CSF dynamics and even reduced ventricular size [6]. Seemingly, the duration of the ventricular dilatation before the CSF is diverted by an ETV or a shunt plays a critical role in determining the ultimate neurocognitive outcome after the procedure. Evidence in support of such temporal relationship is discussed further in the following section.

Evidence that shunting does not fully reverse neurocognitive impairment associated with hydrocephalus

A relevant consideration to be addressed within the context of neurocognitive outcome after CSF diversion procedures is the effect of shunting on pre-existing neurocognitive deficits and the extent of their subsequent reversal. Abundant evidence from experimental animal studies is clearly in support of only a partial reversal of the progressive neuronal damage caused by infantile hydrocephalus after shunting. Aoyama and coworkers induced progressive hydrocephalus in experimental animals that were subsequently divided into pre-, post-, and non-shunt groups depending on whether the hydrocephalic animals underwent a ventriculoperitoneal shunting. Immunostaining for neurofilaments, glial fibrillary acid protein (GFAP), and synaptophysin was performed. Cortical morphological deformation and heterogeneous neurofilament immunoreactivity of the apical dendrites became pronounced as hydrocephalus progressed and remained after shunt insertion. The cytoskeletal damage of neurons was most significant in the periventricular white matter. Swollen and fragmented axons increased in number along with progression of hydrocephalus and were incompletely repaired by ventricular shunt placement. The GFAP-positive astrocytes observed around repaired axons after shunting were seen more prominently in comparison to untreated hydrocephalic groups [30]. Especially with reference to cortical neuronal damage, these findings are in concordance with the findings of Miyazawa and Sato who demonstrated a persistent learning disability following VP shunting in rats with arrested shunt-dependent hydrocephalus. Microscopic examination revealed partial development of dendrites and spines of cortical neurons after shunting, but normal spine density could not be restored [31]. At the neurotransmitter level, progressive functional injuries in the cholinergic, dopaminergic, and noradrenergic systems were found to parallel the development of hydrocephalus. Shunt placement for CSF drainage reversed such a functional injury only after

early but not after late placement [32]. Experimental evidence further supports the likely existence of a critical time window during which functional neuronal injury in hydrocephalus is reversible by shunt insertion. Beyond this period, irreversible neuronal impairment may occur [19, 32].

From another perspective, important insights into the question of the effect of CSF diversion procedures on the brain parenchyma can be gained from diffusion tensor imaging (DTI) studies. Diffusion tensor imaging is currently the most advanced and sensitive method for assessing white matter injury in vivo [33]. This modality has been demonstrated to be sensitive to the deleterious effects of hydrocephalus on the brain parenchyma including neuronal and axonal disruption, neuronal migration defects, and cellular death [34]. DTI parameter improvements have been found to correlate better with neuropsychological improvement and to serve as a more sensitive method for assessing patients after ETV than ventricular size alone [1]. Furthermore, DTI studies enabled delineation of the anatomical and functional alterations associated with specific neurocognitive deficits in hydrocephalic patients. For instance, tectal beaking in spina bifida patients was associated with parameter changes along all pathways emanating from the colliculi. This is uniquely related to the developmental malformation of this structure and not simply to the mechanical effects of hydrocephalus providing a potential mechanism for spatial attention deficits in spina bifida [35]. Importantly, evidence from recent DTI studies is in support of continuation of the early disruptive effects of hydrocephalus in treated children after shunting [34].

Correlation between post-treatment ventricular volume and neurocognitive outcome after ETV

Normal ventricular size is not always associated with normal cognitive functions. Lacy et al. reported that 40 % of the patients undergoing ETV displayed memory and or executive dysfunction 2 years post-intervention. Specifically, mild-to-moderate deficits were documented on tasks evaluating processing speed, cognitive flexibility, and short-term memory skills. These deficits continued despite the relatively normal ventricular size in the group [6]. Mandell et al. serially quantified both brain growth and ventricular volume in normal versus hydrocephalic experimental animals. The calculated total brain and ventricle volumes were then subjected to linear discriminant analysis. Two different patterns were observed; in the first pattern, brain growth was normal despite accumulation of CSF, while in the second pattern, abnormal brain enlargement was accompanied by increased CSF volume along with parenchymal edema. Clinically relevant measurements of head circumference or frontal and occipital horn ratios (FOR) were unable to discriminate between these patterns [36]. This is important because it offers evidence that brain and ventricular volumes are not necessarily inversely proportional. The same group of investigators carried out a subsequent clinical study in which they found that a normal brain volume was more important in neurocognitive development than fluid volume in hydrocephalic pediatric patients. Patients with severe accumulation (40–100 times normal) of fluid volume did cognitively worse than patients with lesser degrees of CSF accumulation. Below this level of CSF accumulation, results have shown that normal ventricle size is not necessarily crucial for normal development. In their study, FOR correlated significantly with CSF volume and not with brain volume [37]. These findings are supported by other studies investigating the relation between ventricular volume and neurocognitive outcome. Hanlo et al. demonstrated a high correlation between intracranial pressure (ICP), myelination, and neurodevelopmental testing scores in hydrocephalic infants. However, CSF volume correlated poorly with ICP, degree of myelination, and neurodevelopmental testing scores. Long-term follow-up showed a significant correlation between the early progress of myelination and later developmental level. Notably, delay in myelination was only partially reversible following VP shunting [38]. Warf et al. used linear regression analyses to demonstrate the lack of significant association between ventricle size and any neurocognitive developmental category measured by the BSID-III scale, regardless of treatment. It is of note that in this study, the mean FOR was similar among groups, with no significant difference between the untreated group and either the VP shunt or ETV-CPC groups [8]. More recently, Kulkarni et al. studied 23 children with hydrocephalus due to aqueductal stenosis or tectal glioma who were treated at least 2 years earlier and were asymptomatic by the time of evaluation. Seventeen children had undergone ETV, and six had received a shunt. Detailed DTI and a full battery of neuropsychological tests were performed. Correlation analysis was carried out to assess the relationship between DTI parameters, neurocognitive tests, and ventricular size. After adjusting for multiple comparisons, there were no significant correlations between any neurocognitive test and ventricular volume, any DTI parameter and ventricular volume, or any DTI parameter and a neurocognitive test. Post hoc analysis also revealed no obvious differences between patients who received ETV or shunting regarding white matter integrity on DTI or neurocognitive outcomes [33]. It is of importance that only aqueduct stenosis or tectal glioma were the salient anatomical abnormalities in this study. This negates the possibility of contribution from other brain parenchymal malformations to either neurocognitive outcome or DTI parameter changes. Collectively, the results of the aforementioned studies should call into question the correlation between the residual postoperative ventricular volume alone and neurocognitive outcome. The available literature is so far in support of ETV as a valid

and effective treatment modality for hydrocephalus. No sufficient evidence is available to justify resorting to shunting on the premise that it is associated with a better neurocognitive outcome. Although prospective randomized studies are ideal, they are difficult to carry out on hydrocephalic children. Large-scale multicenter studies utilizing unified and extensive neurocognitive evaluation methodologies and long-term follow-up periods are required for a definitive answer to be obtained. Enrolment of patients undergoing ETV as well as ETV-CPC procedures is needed because the two procedures may have different neurocognitive outcomes.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

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