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The Dilemma of Hydrocephalus in Prolonged Disorders of Consciousness

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Abstract

Prolonged disorders of consciousness (DOC) are considered to be among the most severe outcomes after acquired brain injury. Medical care for these patients is mainly focused on minimizing complications, given that treatment options for patients with unresponsive wakefulness or minimal consciousness remain scarce. The complication rate in patients with DOC is high, both in the acute hospital setting, as in the rehabilitation or long-term care phase. Hydrocephalus is one of these well-known complications and usually develops quickly after acute changes in cerebrospinal fluid (CSF) circulation after different types of brain damage. However, hydrocephalus may also develop with a significant delay, weeks, or even months after the initial injury, reducing the potential for natural recovery of consciousness. In this phase, hydrocephalus is likely to be missed in DOC patients, given that their limited behavioral responsiveness camouflages the classic signs of increased intracranial pressure or secondary normal-pressure hydrocephalus. Moreover, the development of late-onset hydrocephalus may exceed the period of regular outpatient follow-up. Several controversies remain about the diagnosis of clinical hydrocephalus in patients with ventricular enlargement after severe brain injury. In this article, we discuss both the difficulties in diagnosis and dilemmas in the treatment of CSF disorders in patients with prolonged DOC and review evidence from the literature to advance an active surveillance protocol for the detection of this late, but treatable, complication. Moreover, we advocate a low threshold for CSF diversion when hydrocephalus is suspected, even months or years after brain injury.

Keywords: cerebrospinal fluid disorders; disorders of consciousness; secondary normal pressure hydrocephalus; traumatic brain injury; ventriculoperitoneal shunt

Introduction

Prolonged disorders of consciousness (DOC) are considered to be among the most severe outcomes after acquired brain injury. A large proportion of patients with severe brain injury who survive the initial acute phase show (minimal) signs of consciousness during the first months after injury.[1] As time passes, a significant subgroup of patients fails to recover, developing a chronic state of impaired consciousness.[1–3] Distinct clinical syndromes have been identified subsequent to the acute comatose phase after brain damage, such as unresponsive wakefulness syndrome (UWS), a condition of unresponsiveness in the presence of wakefulness (previously known as the vegetative state), and the minimally conscious state (MCS), a state characterized by partial preservation of consciousness with reproducible signs of minimal awareness.[1,4,5] The complication rate in these patients is high, especially during the early months after injury, but also at a later phase if consciousness remains impaired.[6,7]

Cerebrospinal fluid (CSF) disorders are one of these well-known complications and are associated with a wide variety of brain injuries. Hydrocephalus is usually well recognized in the acute phase after brain injury through a combination of acute ventricular enlargement on computed tomography (CT)/magnetic resonance imaging (MRI) studies and evidence of elevated intracranial pressure by means of diagnostic procedures.[8] Consequently, it is usually treated accordingly with temporary or permanent CSF diversion techniques. Abnormalities in CSF absorption may also develop subacutely, such as weeks or months after injury.[9,10] This type of hydrocephalus may limit or even prevent the process of natural recovery, impairing functional brain networks, but is difficult to recognize in patients with prolonged DOC given that their limited behavioral responsiveness camouflages the classic signs of hydrocephalus. Moreover, the radiological diagnosis of hydrocephalus is challenging after severe brain injury, given that ventricular enlargement is often compensatory to progressive loss of

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brain tissue rather than a reflection of abnormalities in the equilibrium of CSF production and absorption.

In this article, we discuss the dilemmas in both the diagnosis and treatment of CSF disorders which may arise in patients with prolonged DOC after severe acquired brain injury and review evidence from the literature to propose a protocol for the evaluation and treatment of this complication.

Definition of Hydrocephalus after Severe Acquired Brain Injury

Hydrocephalus is a common complication in patients with severe acquired brain injury, especially in patients with traumatic brain injury (TBI) and cerebrovascular injuries, such as subarachnoid hemorrhage (SAH) or intracerebral bleeding.[9,11–13] Depending on the timing of onset, hydrocephalus is divided into an acute (hours), subacute (days), or a late-onset (weeks-months) type.[13] Late multi-factorial changes in CSF hydrodynamics may cause hydrocephalus to emerge weeks or months after the initial injury. In contrast to acute forms of hydrocephalus, late-onset hydrocephalus may also present with a normal intracranial pressure, which is sometimes referred to as secondary (sNPH) normal pressure hydrocephalus (NPH).[9,10]

Incidence of late-onset hydrocephalus seems relatively high in the literature, especially in patients with TBI and SAH. For instance, incidence of post-traumatic hydrocephalus (PTH) presenting with a normal or elevated intracranial pressure has been described to occur in up to 29% of patients with severe TBI.[14,15] PTH is often a late-onset form of hydrocephalus, which develops during the initial weeks after discharge from the hospital. In a prospective analysis of patients with TBI and PTH, $\sim$75% of PTH emerged within 8 weeks of rehabilitation.[16] Other studies report that a significant proportion, $\sim$10%, is even discovered at a later phase, between 4 and 6 months after the initial injury.[17] Looking at the specific group of patients with prolonged DOC after TBI, it is estimated that $\sim$18–20% develop PTH, with 50% eventually being discovered during the late rehabilitation phase.[18–20]

This makes PTH a significant secondary complication during the course of prolonged DOC. In SAH, it is estimated that 10–20% of all patients with SAH develop signs of late-onset hydrocephalus.[21] Patients with prolonged DOC after SAH have a relatively high chance of developing late-onset hydrocephalus, given that SAH patients with severe neurological deficits are more at risk for late disturbances in CSF dynamics, even if no signs of hydrocephalus are present on initial admission.[21,22]

Dilemmas in Diagnosis

Clinical assessment of hydrocephalus in patients with prolonged disorders of consciousness

First of all, it remains challenging to make a diagnosis of clinical hydrocephalus in patients with prolonged DOC. Most classic warning signs of CSF disorders, such as headache, altered arousal, cognitive deterioration, loss of continence, and walking difficulties, are usually camouflaged by the fact that DOC patients show limited behavioral responsiveness, have fluctuations in arousal, and remain bedridden or wheelchair-bound.[18] Likewise, secondary deterioration of consciousness or slow functional recovery could be merely the result of the severity of the brain damage itself or subsequent neuronal atrophy.[23] Further, consciousness itself is notoriously challenging to quantify. Several clinical scales have been developed for the neurobehavioral assessment of patients with DOC.[24] Of these, the Coma Recovery Scale-Revised (CRS-R) is the internationally accepted gold standard for diagnosis of consciousness disorders in patients with severe brain injury.[25]

Ideally, multiple CRS-R assessments are performed within a short interval (e.g., 2 weeks) to account for behavioral fluctuations and detect subtle differences in arousal in patients with DOC.[26] Administration of these clinical scales is time-consuming and requires professional training to perform in daily practice. Therefore, they are difficult to incorporate into the clinical setting of a nursing home or standard rehabilitation facility. Still, up to 41% of patients with DOC receive an incorrect diagnosis if consensus is used instead of standardized assessments.[27,28] Although significant deterioration in neurological functioning, increased hypertonia, or slow functional recovery could be used as arguments to examine the possibility of a concurrent hydrocephalus, it is likely that late-onset hydrocephalus is missed, especially if it develops slowly and after the period of regular follow-up.[7,18,29]

Neuroradiological assessment of ventricular enlargement: Hydrocephalus or atrophy?

The diagnosis of hydrocephalus in DOC is primarily based on a mixture of careful serial clinical assessments and evidence of sequential ventricular enlargement on multiple CT or MR scans.[14,18] Ventricular enlargement is a common finding in the acute phase of severe brain damage. It is estimated that the incidence of ventricular enlargement after TBI might be as high as 30–86%.[30] However, the neuroradiological diagnosis of hydrocephalus after severe acquired brain injury is controversial, because it is difficult to determine whether ventriculomegaly after severe acquired brain injury is related to an atrophic process, or to a ''true hydrocephalus'' resulting from an imbalance between CSF production and absorption.[15,31] To differentiate between hydrocephalus and loss of brain tissue, a wide variety of radiological diagnostic criteria have been suggested. Different quantitative radiological measures, such as the callosal angle and Evan's index, have been developed to differentiate brain atrophy from hydrocephalus.[32,33]

Further, other morphological MR-imaging markers, such as transependymal edema (i.e., interstitial periventricular edema observed as periventricular hyperintensities on T_2-weighted or fluid-attenuated inversion recovery sequences), a disproportionately enlarged subarachnoid space, enlarged Sylvian fissures/basal cisterns, and aqueductal or fourth ventricular flow voids, are sometimes used to identify signs of hydrocephalus.[9,33–35] However, these markers have long been a subject of debate, and, although they may be indicative of idiopathic NPH (iNPH), they might have limited diagnostic value in patients with severe acquired brain injury and concomitant sNPH.[36] Moreover, there are no standard values of these markers in patients with severe brain injury or in those who received a neurosurgical intervention, such as a decompressive hemicraniectomy.

More recently, several volumetric techniques have been described to quantitatively measure hydrocephalus. Advanced imaging techniques, such as arterial spin labeling, a measure for cerebral perfusion changes in different types of hydrocephalus, and magnetic resonance elastography, a measure for tissue viscoelasticity, could further improve hydrocephalus diagnosis, though they remain experimental, especially in patients with severe brain injury, and are difficult to incorporate into standard clinical practice.[37,38]

Diagnostic cerebrospinal fluid diversion

Several invasive methods are used to detect the presence of hydrocephalus, including spinal tap tests, temporary external lumbar drainage, lumbar infusion tests, and long-term intracranial pressure monitoring. The gold standard to detect the presence of an increased intracranial pressure remains a lumbar puncture. However, the detection of sNPH is far more difficult. Most previous studies on the value of invasive diagnostic procedures have focused on the idiopathic form of NPH, which represents a subset of patients with a different etiology and vastly different underlying pathophysiology.[9,10] For iNPH, the spinal tap test, which involves removing 40–50 mL of CSF through a lumbar puncture, remains the most widely used diagnostic technique, though it cannot be used as an exclusionary test, because of its low sensitivity (26–61%).[33,34] A positive tap test in iNPH patients who are awake usually results in prompt improvement of walking difficulties. However, DOC patients are bedridden or wheelchair-bound and often experience spasticity, which makes the assessment of these motor improvements difficult.

Normally, the effects of a single tap test on cognitive functioning in iNPH is minimal.[39,40] Therefore, the predictive value of a single or serial tap test in DOC patients with ventricular enlargement is presumably limited, though this has never been thoroughly studied. More prolonged (usually 72 h) drainage of lumbar spinal fluid through an external lumbar drain (ELD) has been used for >20 years to detect iNPH and has a relatively high sensitivity (50–100%) and high positive predictive value (80–100%).[33,41] However, the predictive value of a negative ELD is deceptively low, because of a high rate of false-negative results. This might also limit the use of a temporary ELD in patients with prolonged DOC. It remains unknown whether temporary drainage affects arousal and for how long drainage is necessary to assess a positive or negative effect. Arousal effects after temporary drainage might also present at a later stage, when the ELD has already been removed.

In addition to lumbar puncture and ELD, a lumbar-infusion test has been developed to dynamically assess abnormalities in CSF hydrodynamics in iNPH. It involves infusion of artificial fluid through one spinal needle while simultaneously recording CSF pressure through a second spinal needle.[33,41,42] It has a slightly higher sensitivity (57–100%) and a similar positive predictive value for iNPH compared to a spinal tap test. However, the costs and invasiveness of the test, and the possibility of serious test-related complications, further limits its usefulness in managing hydrocephalus in DOC patients.[33,41,43] This also applies for other invasive techniques, such as continuous intraventricular pressure monitoring.[44] Not surprisingly, these techniques are rarely applied in standard care, and the value of these invasive techniques in patients with DOC and ventricular enlargement has not been studied.

Dilemmas in Treatment

As a result of the difficulties in clinical and neuroradiological assessment of patients with hydrocephalus after severe acquired brain injury, the response to CSF shunting procedures in these patients is difficult to predict.[9] Usually, acute and subacute hydrocephalus with a high intracranial pressure are readily recognized in the acute phase after brain injury and treated accordingly, using temporary or permanent CSF diversion techniques. In patients who present with a combination of hydrocephalus and large skull defects after decompressive craniectomy, cranioplasty is known to benefit the restoration of CSF circulation and should be considered as a first step in the treatment of hydrocephalus.[9,45,46] In patients without large skull defects, treatment of late-onset hydrocephalus usually relies on conventional neurosurgical interventions, most commonly ventriculoperitoneal (VP) and lumboperitoneal (LP) shunting.[9]

Up until now, only three prospective studies have been performed that evaluated the specific effects of shunting in patients with prolonged DOC and late-onset hydrocephalus. First of all, Kim and colleagues, described the clinical course of 39 patients with UWS and concomitant hydrocephalus on follow-up CT after different types of severe brain injury (see Table 1).[47] Of these patients, 13 of 39 were treated conservatively, whereas the majority (26 of 39) received a VP or LP shunt. Shunt procedures were performed relatively soon, within weeks after the initial injury and loss of consciousness. After a follow-up period of 6 months, Glasgow Coma Scale (GCS) scores of patients were compared between the different study groups. In the shunt group, GCS scores were significantly better with a mean 6-month change of 2.38 versus 0.54 compared to the conservative group. Whereas younger patients and those with TBI in the shunt group had better Glasgow Outcome Scale (GOS) scores at follow-up, no significant differences were found in GOS scores between the two study groups on group level.

Second, Chen and colleagues performed VP shunting in 35 SAH patients with impaired consciousness and concomitant sNPH.[48] Twenty-four (68.5%) of these patients gradually recovered after shunt placement, as demonstrated by significant GCS score changes at the 3-month follow-up screening. They revealed a significant difference in GCS scores after 3 months between DOC patients who received VP shunting (mean change from 7 to 12) compared to the conservatively treated group (mean change from 6 to 7). Third, Huang and colleagues performed a prospective study of VP shunting in 13 patients with suspected late-onset PTH without using a control group.[49] Seven of 13 patients showed improvements in GOS or modified Barthel Index (MBI) scores during a 2-year follow-up period after shunting.

In addition to the above-described prospective studies, several retrospective studies have been performed in patients with secondary NPH after TBI, including subgroups of patients with DOC.[9] However, most studies report no clear criteria for the measurement of consciousness and contain a heterogeneous variety of patient profiles, which makes it difficult to extrapolate results for patients with DOC. In the study of Tribl and colleagues, 48 patients with PTH underwent shunt implantation.[50] Before the shunt implantation, 18 (38%) patients were diagnosed with ''coma.'' After 3 months of follow-up, the number of patients with coma decreased to 12. GOS scores improved in 33% of coma patients, remained unchanged in 61%, and deteriorated in 6% after shunting. Further, Licata and colleagues described 83 patients who underwent shunt implantation for subacute or late PTH after TBI, of which 58 were reported to have a comatose state before treatment.[17] At long-term follow-up, 33% of these patients eventually experienced good recovery, 9% retained partial disability, 50% remained comatose, and 8% of patients were dead at follow-up.

Although most prospective and retrospective studies show some promising results of shunting in DOC patients, all have significant methodological limitations. Most important, it is difficult to distinguish natural recovery from recovery as a result of CSF diversion, given that most shunting procedures were performed within 6 months after brain injury, which is well within the known time frame wherein spontaneous recovery usually occurs

Table 1. Intervention Studies in Patients with Prolonged Disorders of Consciousness and Concomitant Hydrocephalus

Authors/year	*Design*	*Sex M/F*	*Mean age*	*No. DOC/total*	*Diagnosis*	*Etiology*	*Intervention*	*Valve*	*Timing of surgery*	*Follow-up months*	*Outcome*
Kim e.a. 2006	Prospective	26/13	52	39/39	UWS: 39	TBI: 19 Vascular: 18 Other: 2	Conservative: 13 VPS: 22 LPS: 4	NM	± weeks	±10–11	Δ GCS shunt group 2.38 ± 0.48 Δ GCS conservative group 0.54 ± 0.14 GOS: no differences
Huang e.a. 2014	Prospective	11/4	47	15/15	UWS: 2 MCS: 13	TBI: 15	VPS	PA: 5 MP: 10	1–3 months: 8 4–6 months: 5 >6 months: 2	24	GOS improved in 1 of 13 patients MBI improved in 6 of 13 patients
Chen e.a. 2014	Cross-sectional	35/16	59	51/51	UWS: 44 Coma: 7	Vascular: 51	Conservative: 16 VPS: 35	PA: 35	3 weeks to 3 months	3	GCS improved in 68.5% shunt group Δ GCS shunt group from 7 to 12 Δ GCS conservative group from 6 to 7
Tribl e.a. 2000	Retrospective	40/8	36	18/48	UWS: 18	TBI: 18	VPS	NM	±27 weeks	3	GOS improved in 33% GOS remained unchanged in 61% GOS deteriorated in 6%
Licata e.a. 2001	Retrospective	82/16	39	58/98	UWS: 26 Coma: 32	TBI: 61	VPS 56 VAS: 2	Mixed	Weeks-months	NM	Good recovery in 33% Partial disability in 9% Persistent coma in 50% Death in 8%

[a]Studies above the horizontal dividing line only included patients with DOC. Studies beneath the horizontal dividing line contain a subset of DOC patients in all studies.

DOC, disorders of consciousness; GCS, Glasgow Coma Scale score; GOS, Glasgow Outcoma Scale score; LPS, lumboperitoneal shunt; MBI, Modified Barthel Index; MP, median pressure; PA, pressure adjustable; NM, not mentioned; VPS, ventriculoperitoneal shunt; VAS, ventriculoatrial shunt.

in DOC.[3,45] This is especially relevant in studies with small patient groups or studies without control groups. For example, in the study of Huang and colleagues, 2 of the 7 patients who regained signs of consciousness after VP shunting improved relatively late, between the fourth and sixth month after shunting, which makes a causal relationship between shunt implantation and improvement unlikely.[49]

In the other studies, the time frame between shunting and improvement remains unclear. Moreover, none of the above studies used structured and repeated CRS-R assessments, the gold standard for clinical evaluations of consciousness, which leads to possible misdiagnosis and might cause bias, given that arousal notoriously fluctuates throughout the day in DOC patients.[26] It is now recommended to perform multiple CRS-R assessments within a short time interval to make an accurate clinical diagnosis and estimate of the level of consciousness in DOC patients. Further, there remains significant heterogeneities in underlying etiologies, age, surgical timing, and outcome measures in previous studies, which makes it difficult to draw definite conclusions about the effectiveness of shunting in DOC.

In a large recent review of the literature on CSF diversion for sNPH, 74.4% of all patients were found to have signs of clinical improvement in their neurological status after a shunting procedure.[9] In general, patients with sNPH have a better outcome after shunting than patients with the idiopathic form of hydrocephalus.[10] Therefore, it is conceivable that VP shunting might eventually result in an improvement of neurological function if used in a selected group of DOC patients with sNPH. Patients that present with relative early ventricular dilatation in the course of prolonged DOC, additional neurological deficits rather than ceased clinical improvement, and increased hypertonia are known to show the most favorable results from shunting.[17] As with any invasive procedure, risks are involved when applying diagnostic interventions or treatment with VP shunts. Well-known complications of VP shunting are hardware infections and shunt malfunction.[51,52] Especially, the latter has to be considered if secondary clinical deterioration occurs. A switch to shunts with a lower opening pressure or pressure-adjustable valves might be necessary in patients with evident signs of sNPH that deteriorate or fail to recover.

Follow-up with neuroimaging is necessary to exclude other complications that might go otherwise unnoticed, such as the presence of subdural effusions.[53] In general, the complication rate in patients with prolonged DOC after extensive brain injury may be higher, given that these patients are more subject to secondary complications.[6] However, these risks must be weighed against the risk of a conservative attitude.[54] Not resolving potential hydrocephalus could severely impair the recovery of the patient and would go against the ethical principle of beneficence, which requires to give patients the best chance of improving their condition.[55]

Future studies have to address whether treatment will effectively result in a clinically significant difference and increased quality of life. After all, a small improvement of consciousness might lead to increased pain perception levels and higher disease self-awareness among patients, which could mean more suffering. However, a small gain of functional capacity can contribute to major differences in daily care and might support the deployment of rehabilitation interventions or assistive devices that facilitate reliable communication and environmental control strategies. To date, a high-quality trial evaluating the effects of CSF diversion on both consciousness and quality of life in patients with prolonged DOC is still to be performed.

Future Prospects

Patients with prolonged DOC face substantial challenges. Despite encouraging technological developments and improvements in accurate diagnosis and prognosis techniques for patients with DOC, there remains a scarcity of treatment options.[1,56] In general, medical care usually includes intensive and adapted rehabilitation therapy (physiotherapy, speech therapy, or occupational therapy) and is focused on minimizing secondary complications of neurological damage.[7,29] Hydrocephalus is one of these complications. Recognizing and treating clinical (normal-pressure) hydrocephalus might be ''low-hanging fruit'' for this vulnerable group of patients. A better outcome is to be expected when hydrocephalus is recognized and treated at the earliest possible moment.[48,57]

Future studies should address the dilemmas in both detection and treatment of hydrocephalus, as well as its effects on rehabilitation and quality of life, over prolonged periods of time. Intervention studies, with a prospective, controlled, randomized design and standardized use of validated scales in both initial assessment and follow-up, are necessary to clarify the effectiveness of CSF diversion in patients with prolonged DOC. Moreover, it remains important to study the underlying mechanisms of delayed hydrocephalus in patients with severe brain injury, and, in this context, neuroimaging modalities and neurophysiological evaluations could help to better understand the pathogenesis of this disease and may lead to more accurate non-invasive ways to detect hydrocephalus.

Proposed evaluation and treatment of hydrocephalus in prolonged disorders of consciousness

To minimize the chance of missing late-onset hydrocephalus and optimize the chance of recovering residual cognitive capacity in patients with prolonged DOC, a vigilant surveillance protocol is necessary after patients leave the hospital setting. Regular checkups by experts in administering the CRS-R, follow-up with sequential neuroimaging, and multi-disciplinary consultations between post-acute, long-term, and hospital experts are vital. To ensure that such care is provided to patients with prolonged DOC we propose the following protocol:

1. Regular, preferably multi-disciplinary, evaluation of the present state of consciousness and evolution of neurological recovery; at least involving multiple behavioral screenings using the CRS-R.
2. Regular outpatient follow-up with serial neuroradiological assessments of ventricular size using CT or MRI; preferably 6–8 weeks and 6 months after hospital discharge, or at the request of caregivers in case of clinical deterioration.
3. In patients with suspected hydrocephalus, a single lumbar puncture needs to be performed to exclude the presence of high-pressure hydrocephalus. There seems to be no evidence for temporary external lumbar drainage, although, if used, it seems rational to perform CRS-R assessments, both during treatment as well as in the first days after drainage of CSF to measure delayed changes in consciousness.
4. In patients with suspected hydrocephalus and concomitant post-operative skull defects, subsequent cranioplasty has to be considered as a first step to restore CSF hydrodynamics, before considering shunting.
5. CSF diversion should be considered in patients with radiological signs of progressive ventricular enlargement and when the medical team suspects the presence of ''true'' hydrocephalus, for instance, because of clinical deterio-

ration, increased hypertonia, otherwise inexplicable failure to recover, or based on the results of procedures described in point 3.

6. Before and after treatment (points 4 and 5), frequent neurobehavioral assessments, including the CRS-R, need to be performed in order to monitor neurological recovery and detect the occurrence of postoperative complications, such as shunt dysfunction or subdural effusions.

Conclusion

Hydrocephalus in patients with prolonged DOC is probably underdiagnosed while the presence of hydrocephalus can be of significant clinical importance, given that it may well prevent meaningful functional recovery. The diagnosis of permanent MCS or UWS should not be made before hydrocephalus is excluded and treated accordingly. Several controversies exist regarding the clinical and radiological assessment of these patients. Active surveillance and early treatment of late-onset hydrocephalus in patients with prolonged DOC might prevent the fatalistic acceptance of unfortunate outcomes and could result in significant improvements of functional outcome after acquired brain injury. Combining standardized behavioral assessments, regular follow-up with neuroimaging and multi-disciplinary evaluations may lead to valuable new treatment insights that are necessary to fine-tune the care for these vulnerable patients.

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