Level of IL-6 in cerebrospinal fluid is a preoperative predictor of short-term outcome in acquired hydrocephalus

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Research

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Abstract

**Background:** Acquired hydrocephalus (AH) is a common complication in patients with severe brain injury. Brain tissue injury has been proposed to induce a neuroinflammatory reaction reflected by cytokines release, particularly interleukin-6 (IL-6), which associates with early brain damage. The present study measured IL-6 in the cerebrospinal fluid (CSF) of AH patients and determined its relationship to functional outcome following shunt operation.

**Methods:** The study included a total of 32 patients with a shunt operation due to hydrocephalus. CSF samples from 26 AH subjects and 6 iNPH patients were collected via lumbar puncture before surgery. IL-6 level was measured using the micro ELISA immunoassay method. AH subjects were dichotomized into good versus poor outcomes based on modified Rankin Scale (mRS) at 3 months after shunting.

**Results:** CSF analysis demonstrated that IL-6 was significantly elevated in the CSF of the AH group compared to controls (p = 0.023). Within the AH group, eighteen (69.2%) had a good outcome while eight (30.8%) patients had a poor outcome. Mean IL-6 level in the good outcome group was approximately four-times higher than the poor outcome group (p = 0.004). Glasgow Coma Scale (GCS) on admission was significantly different between the two groups (p = 0.014). IL-6 level and admission GCS were significantly correlated with improvement of mRS score (r = 0.473, p = 0.015 and r = 0.691, p<0.0001, respectively). Receiver operating characteristic curve analysis showed that both factors can accurately differentiate between patients with good versus poor functional outcome (AUC = 0.861, p = 0.0039 and AUC = 0.823, p = 0.0098, respectively).

**Conclusions:** The CSF level of IL-6 is elevated in AH patients and higher levels correlate with improvement of post-shunt functional outcome. Therefore, IL-6 CSF level might serve as a complementary surrogate parameter for operative indication. A possible IL-6 threshold in clinical routine might be a 6.98-pg/ml cutoff value to rule out unresponsive and poor outcome AH patients that are under the 6.98-pg/ml threshold.

Background

Acquired hydrocephalus (AH) is a common complication in patients with severe brain injury, especially in patients with traumatic brain injury (TBI) and cerebrovascular disorders, such as subarachnoid hemorrhage (SAH) or intracerebral bleeding.[1, 2] AH is regarded as one of the main causes of disability in those patients and serves as an important clinical predictor of adverse outcomes after brain injury, since it may hamper the process of functional recovery and rehabilitation, impairing functional brain networks.[3–6] In recent decades, the development and implementation of evidence-based medicine into clinical practice reduced the mortality of patients in the acute period of severe brain injury, but increased in the number of patients with AH and did not significantly improve long-term outcomes in survivors.[7]

The diagnosis of AH is primarily based on a mixture of careful serial clinical assessments and evidence of sequential ventricular enlargement on multiple computed tomography (CT) or magnetic resonance
imaging (MRI) scans.[7, 8] Nevertheless, it remains challenging to make a diagnosis of clinical hydrocephalus in patients with severe brain injury since their limited behavioral responsiveness camouflages the classic signs of hydrocephalus, and ventricular enlargement on images is often compensatory to progressive loss of brain tissue rather than a reflection of imbalance of CSF production and absorption.[2] Although several invasive methods are used to detect the presence of hydrocephalus, including spinal tap tests and temporary external lumbar drainage,[2] changes in the mental status or consciousness level are not always observed in these patients and may be biased by doctors and patient’s relatives, especially in the vegetative and minimally conscious state. Therefore, the diagnostic value of those indicators is presumably limited in these vulnerable group of AH patients, which may lead to underdiagnosis or overdiagnosis of hydrocephalus in patients with severe brain injury.

Surgical cerebrospinal uid (CSF) diversion remains the standard of care for many patients with AH, most commonly ventriculoperitoneal shunts (VPS).[7] In recent review, 74.4% of patients with secondary normal pressure hydrocephalus were found to have signs of clinical improvement after a shunting placement, suggesting that CFS shunting might eventually result in an improvement of neurological function if used in a selected group of brain injury patients with AH.[9] Nevertheless, the number of unreasonable surgical interventions and unsatisfactory outcomes of treatment is still high since it is often difficult to recognize AH and determine indications for surgical treatment, especially in patients with vegetative and minimally conscious state. Given that clinicians often make therapeutic decisions on the basis of their prognosis assessment, to accurately evaluate the prognosis is of great significance. Unfortunately, there is a lack of specific and reliable agreement on how to prognosticate outcome in AH.

There is mounting evidence that neuroinflammation following brain injury plays an important role in the pathophysiological events of early brain injury.[10, 11] Measuring CSF biomarkers may be particularly useful in the setting of brain injuries due to their ability to reflect changes occurring within the brain parenchyma.[12] Recently, many potential biomarkers of neuroinflammation were determined by analysis of CSF cytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-α.[13, 14] IL-6 is a multi-functional cytokine that activates various cell types and has chemotactic effects.[15] Numerous clinical and experimental studies have reported the involvement of IL-6 in the pathology of SAH and contribute to the pathogenesis of post-SAH complications such as vasospasm and delayed ischemic deficits.[14, 16] Moreover, elevated CSF IL-6 levels can predict an unfavorable clinical outcome in SAH patients.[16] Recently, it has been proposed that IL-6 levels may be regarded as a predictive marker for the development of chronic hydrocephalus after SAH.[17] However, no previous study has analyzed the relationship between levels of IL-6 in CSF and post-shunt outcome in AH patients secondary to various brain injuries. We hypothesized that levels of IL-6 is elevated in AH patients and that it is associated with treatment effectiveness. Consequently, we measured IL-6 in the CSF of AH patients and determined its relationship to functional outcome after shunt implantation.

Materials And Methods

Study Population
AH patients treated with CSF shunting from January 2019 to December 2020 were recruited at the First Affiliated Hospital of Nanchang University. Patients were eligible for enrollment if they were 18 years of age or older, had intracranial hemorrhage (ICH) or TBI confirmed by CT or MRI, and later developed post-hemorrhagic hydrocephalus (PHH) or post-traumatic hydrocephalus (PTH). Exclusion criteria were as follows: (1) initial neuroimaging scan showed the presence of hydrocephalus, (2) previous neurological disability (defined as preadmission modified Rankin Scale (mRS) ≥ 2), (3) brain tumor, intracranial surgery or meningitis, (5) multiple injuries (abbreviated injury score ≥ 3), and (4) lost contact in the follow-up period. Control subjects were idiopathic normal pressure hydrocephalus (iNPH) patients 18 years of age or older with no previous craniocerebral disorders who underwent CSF analysis and CSF shunting.

**AH Diagnosis**

AH was defined as neuroimaging evidence of progressive ventricular dilatation (Evans index > 0.3) accompanied by periventricular interstitial edema, together with clinical characteristics of AH hydrocephalus, such as neurobehavioral and cognitive impairment, increased flap tension in patients undergoing decompressive craniectomy, and no improvement or deterioration of consciousness in patients with coma. All patients with clinical and radiological signs of AH were treated with a shunt. VPS using a programmable valve was the first-choice surgical procedure. Ventriculoatrial shunt (VAS) is a preferred alternative when VPS are contraindicated or not successful.

**Data and Variables**

The following patient, treatment, and hospitalization variables were determined for all AH cases included in the study cohort: patient age, gender, preoperative intracranial pressure (ICP), days until surgery (duration from injury to shunt implantation), etiology (ICH vs TBI), Glasgow Coma Scale (GCS) at presentation, Evans index, shunt type (VPS vs VAS), skull defect, hospitalization time, shunt complication (shunt infection, inadequate placement of ventricular or distal catheters requiring revision, hemorrhage, exposed hardware, inadequate shunting from valve malfunction), mRS.

**Cerebrospinal Fluid Collection and Analysis**

CSF samples of all patients were collected through a lumbar puncture before shunt surgery. Approximately 5 ml of CSF was collected and centrifuged (2500 rpm for 6 min) at room temperature. Supernatants were collected, aliquoted into cryovials, and stored at -80°C for experimental analysis. The concentration of IL-6 was measured using the micro ELISA immunoassay method in the clinical laboratory of the First Affiliated Hospital at Nanchang University.

**Outcome**

Given the different baseline status of the patients enrolled, the overall clinical outcome was calculated by subtracting preoperative and postoperative mRS to achieve an outcome point at 3 months after shunt surgery, namely improved mRS (imRS, imRS = preoperative - postoperative mRS). Results were then
dichotomized into good versus poor outcomes. Good outcome was considered as imRS ≥ 1 points, and ≤0 indicated poor outcome.

**Statistical Analysis**

Descriptive variables are presented as either percentages, mean ± standard deviation (SD), or median and interquartile range (IQR). Continuous variables were analyzed by the Mann–Whitney U test. Categorical variables were compared by the Fisher Exact test or Chi Square test. The correlation between IL-6 level and imRS were analysed using the Spearman's rank correlation coefficient. Univariable logistic regression analyses were performed to identify factors significantly associated with functional outcome. Factors with a P < 0.10 were entered into a multivariate logistic regression analysis to determine independent predictors of the aforementioned clinical endpoint. Receiver operating characteristic (ROC) curves were created to evaluate the effect of these parameters on functional prognosis. Youden's index was calculated to determine optimal cut-off point and corresponding sensitivity and specificity. Statistical significance was defined as P < 0.05. Data were analyzed using SPSS (SPSS, Inc., Chicago, Illinois, USA). Figures were made using GraphPad Prism (Version 8.3.0, La Jolla, California, USA).

**Results**

In the present study, we collected a total of 32 CSF samples, six of which were obtained from control patients (iNPH patients) and 26 from AH patients. Baseline characteristics are displayed in Table 1. The shunt type was VPS in 28 (87.5%), and VAS in 4 (12.5%). As expected, the control group patients were older (mean age 71.0 vs 55.2 yr; p = 0.002); had higher GCS scores (mean 14 vs 10.5; p = 0.001); and lower preoperative mRS (mean 2 vs 5; p < 0.0001) and hospitalization time (mean 12.8 vs 22.2; p = 0.008). There was no difference in sex, ICP, Evans index, shunt type, and shunt complications between AH patients and controls (all p ≥ 0.1).

**TABLE 1.** Patient characteristics.

GCS, Glasgow Coma Scale; VPS, ventriculoperitoneal shunt; VAS, ventriculoatrial shunt, IL-6, interleukin-6; ICP, intracranial pressure; ICH, intracranial hemorrhage; TBI, traumatic brain injury; mRS, modified Rankin Scale; SD, standard deviation; IQR, interquartile range.

In AH group, the interval time between brain injury outset and shunt operation was nearly all within 6 months in our study. The mRS score at admission and follow-up postoperatively in the patient with AH are shown in Fig. 1. AH patients were then stratified into those with good or poor functional outcome based on imRS (preoperative - postoperative mRS). Eighteen (69.2%) had a good outcome (imRS ≥ 1) while eight (30.8%) patients had a poor outcome (imRS ≤ 0). There were no significant between-group differences in age, sex, ICP, Evans index, days until surgery, hospitalization time, skull defect, shunt type, and etiology (all p ≥ 0.05). Notably, the only clinical score on admission that was different between good and poor outcome groups was the GCS (p = 0.014, Fig. 2a). Good outcome patients had a median baseline GCS of 11.5 while those with poor outcomes had a median baseline GCS of 9. There were no
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>AH</th>
<th>All</th>
<th>P value</th>
<th>Good outcome (imRS ≥ 1)</th>
<th>P value</th>
<th>Poor outcome (imRS ≤ 0)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n (%)</td>
<td>6</td>
<td>26</td>
<td>—</td>
<td>—</td>
<td>18 (69.2)</td>
<td>8 (0.002)</td>
<td>18 (69.2)</td>
<td>8 (0.002)</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>71 (8.9)</td>
<td>55.2 (10.9)</td>
<td>0.002</td>
<td>55.6 (10.8)</td>
<td>54.5 (11.8)</td>
<td>0.78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>2 (33.3)</td>
<td>12 (46.2)</td>
<td>0.568</td>
<td>7 (38.9)</td>
<td>5 (62.5)</td>
<td>0.401</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative ICP, mean (SD)</td>
<td>90.8 (27.3)</td>
<td>132.9 (61.6)</td>
<td>0.114</td>
<td>137.8 (70.4)</td>
<td>121.9 (36.1)</td>
<td>0.956</td>
<td></td>
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<tr>
<td>Etiology, n (%)</td>
<td>—</td>
<td>—</td>
<td>15 (57.7)</td>
<td>12 (66.7)</td>
<td>3 (37.5)</td>
<td>0.218</td>
<td></td>
<td></td>
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<tr>
<td>ICH</td>
<td>—</td>
<td>15 (57.7)</td>
<td>12 (66.7)</td>
<td>3 (37.5)</td>
<td>0.218</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>TBI</td>
<td>—</td>
<td>11 (42.3)</td>
<td>6 (33.3)</td>
<td>5 (62.5)</td>
<td>0.218</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Evans index, median (IQR)</td>
<td>0.4 (0.3-0.4)</td>
<td>0.4 (0.3-0.4)</td>
<td>0.754</td>
<td>0.4 (0.3-0.4)</td>
<td>0.4 (0.3-0.4)</td>
<td>0.824</td>
<td></td>
<td></td>
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<td>GCS, median (IQR)</td>
<td>14 (14-15)</td>
<td>10.5 (9-12.3)</td>
<td>0.001</td>
<td>11.5 (9-13.3)</td>
<td>9 (8-9.8)</td>
<td>0.014</td>
<td></td>
<td></td>
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<tr>
<td>Days until surgery, median (IQR)</td>
<td>150 (31.8-408.8)</td>
<td>81.5 (59-140.3)</td>
<td>0.411</td>
<td>105 (62.3-157.5)</td>
<td>71.5 (54.8-102.3)</td>
<td>0.578</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shunt type, n (%)</td>
<td>—</td>
<td>—</td>
<td>0.242</td>
<td>0.619</td>
<td>0.242</td>
<td>0.619</td>
<td></td>
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<tr>
<td>VPS</td>
<td>6 (100)</td>
<td>22 (84.6)</td>
<td>16 (88.9)</td>
<td>6 (75)</td>
<td>16 (88.9)</td>
<td>6 (75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAS</td>
<td>0</td>
<td>4 (15.4)</td>
<td>2 (11.1)</td>
<td>2 (25)</td>
<td>2 (11.1)</td>
<td>2 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization time, mean (SD)</td>
<td>12.8 (3.1)</td>
<td>22.2 (10.4)</td>
<td>0.008</td>
<td>21.8 (11.7)</td>
<td>22.9 (7.3)</td>
<td>0.388</td>
<td></td>
<td></td>
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<tr>
<td>Shunt complication, n (%)</td>
<td>0(0)</td>
<td>7 (26.9)</td>
<td>0.15</td>
<td>5 (27.8)</td>
<td>2 (25)</td>
<td>0.883</td>
<td></td>
<td></td>
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<tr>
<td>Skull defect, n (%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>0.877</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>—</td>
<td>20 (76.9)</td>
<td>14 (77.8)</td>
<td>6 (75)</td>
<td>14 (77.8)</td>
<td>6 (75)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>—</td>
<td>6 (23.1)</td>
<td>4 (22.2)</td>
<td>2 (25)</td>
<td>4 (22.2)</td>
<td>2 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative mRS,</td>
<td>2 (2-3)</td>
<td>5 (4-5)</td>
<td>4.5 (4-5)</td>
<td>5 (4.3-5)</td>
<td>5 (4.3-5)</td>
<td>0.186</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
differences in preoperative mRS score (p = 0.186) between groups, suggesting that preoperative functional status was comparable between the two groups. Additionally, no significant differences were observed in the number of patients who developed shunt complication (p = 0.883).

We next evaluated differences in IL-6 between AH patients and controls. AH patients had higher IL-6 in CSF compared to controls (p = 0.023, Fig. 2b). Whereafter, we determined whether differences could be noted in IL-6 levels amongst AH patients when stratified by imRS at 3 months following shunt surgery. Average IL-6 level in good outcome patients (n = 18) was 21.2 pg/mL while that in poor outcome patients (n = 8) was 5.2 pg/mL, corresponding to a near four-fold increase in good outcome patients compared to poor outcome patients (p = 0.004, Fig. 2c). Moreover, there was a significant correlation between imRS and IL-6 levels (r = 0.473, p = 0.015, Fig. 3a), demonstrating that as IL-6 level in CSF increased, functional outcome improved. IL-6 levels were not correlated with admission scores including mRS or GCS (all p > 0.05). Additionally, the correlation between the admission GCS score and imRS was observed (r = 0.691, p < 0.0001, Fig. 3b).

Table 2 details the logistic regression analyses for predictors of short-term functional outcome of AH patients after shunt surgery. In multivariate logistic regression, level of IL-6 in CSF (p = 0.02) and admission GCS (p = 0.031) were independent predictors of short-term functional outcome. ROC curves analysis revealed that IL-6 level and admission GCS were able to significantly differentiate between those with good versus poor functional outcome (Fig. 4) (AUC = 0.861, p = 0.0039 and AUC = 0.823, p = 0.0098, respectively, Table 3). The optimal cut-points were 6.98 pg/mL and 10.5, respectively; the sensibilities were 0.833 and 0.667, respectively; the specificities were 1 and 0.875, respectively (Table 4).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>29.8</td>
<td>1.37 - 646.80</td>
<td>0.031</td>
</tr>
<tr>
<td>IL-6</td>
<td>19.4</td>
<td>1.61 - 235.26</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Table 3
Area under curve (AUC) of receiver operating characteristic curve of IL-6 and GCS.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Area under curve</th>
<th>Standard error</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>0.823</td>
<td>0.081</td>
<td>0.663-0.982</td>
<td>0.0098</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.861</td>
<td>0.077</td>
<td>0.711-1.000</td>
<td>0.0039</td>
</tr>
</tbody>
</table>

IL-6 and admission GCS had better predictive ability.

Table 4
Youden's J statistic of GCS and IL-6.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cut-off point</th>
<th>Youden's J statistic</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS</td>
<td>10.5</td>
<td>0.542</td>
<td>0.667</td>
<td>0.875</td>
</tr>
<tr>
<td>IL-6</td>
<td>6.98</td>
<td>0.833</td>
<td>0.833</td>
<td>1</td>
</tr>
</tbody>
</table>

Youden's J statistic yielded a cutoff value for IL-6 levels that would be indicative of improvement of outcome after surgery.

Discussion

Our study demonstrated that varying extent of clinical improvement occurred in 69.2% of AH patients. IL-6 level are significantly elevated in the CSF of AH patients compared to controls and are correlated with functional outcome. ROC analyses revealed that elevated IL-6 CSF level could serve as a objective prognostic marker for predicting functional outcome of AH following shunt operation. A difference ≥ 6.98-pg/ml for IL-6 CSF level was highly correlated with the improvement of outcome after the treatment of AH. Therefore, the assessment of IL-6 levels in CSF seems to be a promising strategy for treatment stratification and a step toward personalized medicine in AH patients. Additionally, the present study also validated the correlation between the GCS score at admission and the post-shunt outcome of AH.

AH may occur in the short-term or long-term after initial brain injury, and is divided into an acute (hours), sub-acute (days), or a late-onset (weeks-months) type.[18] The incidence of late-onset hydrocephalus seems relatively high in the literature, especially in patients with TBI and SAH.[2] Similarly, AH in the present study occurred within 3 months after the initial injury in most patients, and within 6 month in nearly all patients. The interval from injury onset to shunt surgery may be an important issue in shunt surgery. However, we failed to find a significant correlation between time to shunt placement and functional outcome in AH.

IL-6 is a pleiotropic cytokine with hormone like activity. In pathological conditions, elevated IL-6 CSF level stimulates the neuroinflammatory response that may contribute to the disease progression.[13, 14] Some preliminary data supported feasibility of measurement and potential association between IL-6 and poor
neurological outcome of SAH patient.[16] Moreover, the assessment of CSF IL-6 levels may be regarded as a valuable diagnostic indicator for shunt dependency in patients with PHH.[17] However, few studies have focused on the association between levels of IL-6 in CSF and other relevant endpoints, such as functional outcome in patients with AH after brain injury. We therefore aimed to assess the contribution of IL-6 level in CSF to functional outcome in AH patients at 3 months postoperatively and evaluate its prognostic capacity.

During a 3-month follow-up, 69.2% of the patients with AH were found to have signs of clinical improvement in their neurological status after a shunting procedure, suggesting that CSF shunting surgery seems to be an important step in surgical rehabilitation of AH patients. Most notably, the positive effect of shunting surgery in cases with gross impairment of consciousness is associated with transition to higher levels of consciousness (Fig. 1). This is consistent with previous study.[19] Although the mRS score of all AH patients improved merely by an average of 1.1 points in the study, a small gain of functional capacity can contribute to major differences in daily care and might support the deployment of rehabilitation interventions.[7] Further, we investigated the possible factors affecting short-term functional outcome after shunting in AH patients. Knowledge of such factors could possibly aid in the preoperative decision-making process by enhancing both operative indications and patient informed consent. We confirmed that IL-6 was elevated in the CSF of the AH group compared to the iNPH group, suggesting that inflammatory responses mediated by IL-6 may play an important role in hydrocephalus development and progression after brain injury. Consistent with this, previous studies reported that increased IL-6 levels in CSF could be a direct cytokine reaction facilitating microgliosis and scar formation within the CSF system, thereby resulting in chronic CSF obstruction.[13, 17] In subgroup analysis, our results showed that CSF levels of IL-6 were higher in good outcome group compared to poor outcome group and had a positive correlate with improvement of mRS score. Collectively, these results suggested that elevated IL-6 CSF level may reflect the effectiveness of shunt operation in AH patients and may hold significant promise as a clinical biomarker to predict functional outcome of AH.

To visualize the prognostic capacity of changes in CSF level of IL-6, a ROC analysis based on functional outcome yielded a IL-6 cut-off value with high sensitivity and specificity which resulted in sub-populations with significantly different therapy response and post-shunt functional outcomes of AH. Concluding from our data, the optimal threshold of 6.98-pg/ml for the exclusion of non-response and poor outcome patients might help to further characterize AH patients above the 6.98-pg/ml threshold as good outcome, which is of clinical relevance, especially in cases of unclear indications prior to therapy. We therefore consider that IL-6 might serve as a complementary surrogate parameter which might be of interest to differentiate between the atrophic process and normotensive AH, reducing unnecessary operations, especially in cases with ventriculomegaly and impaired consciousness.

Coi

Incidentally, a study in animal models reported similar results. The authors observed that distension of the ventricles is accompanied by an increase of CSF IL-6, and IL-6 concentrations decreased significantly
after reduction of lateral ventricular volume using an indwelling VPS system. [20] This suggests that IL-6 in CSF can be indicators of ventriculomegaly and of improvement after the treatment of hydrocephalus. However, in addition to involving in the development of hydrocephalus, IL-6 still mediates a variety of pathological brain injuries. For example, increased IL-6 levels in CSF could significantly elevate the number of glial fibrillary acidic protein-immunoreactive astrocytes and ionized calcium-binding adaptor molecule-1-reactive microglia, causing a massive reactive gliosis, which results in ubiquitous cerebral hypertrophy. [13, 17] Moreover, changes in IL-6 concentrations in the CSF can contribute to damage of periventricular white matter injury. Damage to the white matter may influence brain integrity in hydrocephalus cases. [20] Therefore, it is conceivable that CSF shunt surgery could help to mitigate the deleterious effect of IL-6 in AH cases.

Taken together, our study expands upon these findings by showing that not only is IL-6 correlated to development of chronic hydrocephalus after brain injury, but it has an ability to predict shunt response and functional outcome of AH patients, especially in cases with the vegetative and minimally conscious state. Even if IL-6 only has a correlative — as opposed to causative — relationship with functional outcome, the identification of the measurable biomarker of outcome may allow objective prognostication of patients and facilitate addressing goals of care early for AH patients following brain injury.

Additionally, we observed a statistically significant difference between the two subgroups depending on GCS score at the time of admission, and logistic regression analysis revealed that GCS was associated with the post-shunt outcome of AH, indicating GCS at presentation could serve as a risk factor for predicting the unfavorable functional outcome of AH patients. In fact, patients with a worse baseline clinical status was more likely to undergo shunt failure due to the deleterious effects of primary brain injury on neurological presentation. [3, 21] Contrary to expectations, recent studies have reported GCS on admission and outcome in patients with AH, but the results are contradictory. [6, 8] Therefore, GCS obtained upon admission may have variable predictive value and is not entirely objective. Comparatively speaking, levels of IL-6 in CSF may be more stable and objective than admission GCS, and has therefore been emphasized as a more reliable test before surgery. Yet even that, when clinician have difficulties in the preoperative decision-making process, it is recommend admission GCS of 10.5 as a reference threshold for assessing the postoperative outcome of AH.

In summary, this study included an investigation of preoperative factors associated with short-term outcomes following shunt surgery in AH patients. Our results indicated that the CSF level of IL-6 and admission GCS were the most useful measures for predicting short-term outcome after shunt surgery. The identification of both factors may translate into better surgical patient selection, which may result in improvement of postoperative outcomes and a reduction in unnecessary operations.

Limitations

While this study has provided greater insight into the role of IL-6 in the treatment and prognosis of AH, there are several limitations. First, the sample size is relatively small. We recommend that further multi-
institutional, prospective studies in larger patient cohorts are warranted to fully address the role of IL-6 in association with outcomes in AH patients. Second, the degree of objectivity and accuracy of data collection may have been limited because of the variability and subjectivity of patient and family perceptions of therapeutic assessment. Finally, the duration of this study was short, and future studies with longer follow-up periods are needed to validate our findings.

Conclusions

The IL-6 CSF level was sharply increased in AH patients compared to controls. Moreover, levels of IL-6 and admission GCS correlate with post-shunt functional outcomes as measured by mRS. Importantly, CSF IL-6 level may be a very valuable laboratory test for the early recognition of AH patients requiring treatment after brain injury, and may be an objective prognostic tool to predict functional outcomes of AH following shunt operation. Therefore, the underlying mechanism is worth future investigations to improve our understanding of the molecular and cellular events influencing progression and prognosis of hydrocephalus after brain injury.

Abbreviations

AH, acquired hydrocephalus; IL-6, interleukin-6; CSF, cerebrospinal fluid; GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; AUC, area under curve; TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; CT, computed tomography; MRI, magnetic resonance imaging; VPS, ventriculoperitoneal shunt; VAS, ventriculoatrial shunt; PHH, post-hemorrhagic hydrocephalus; PTH, post-traumatic hydrocephalus; ICH, intracranial hemorrhage; iNPH, idiopathic normal pressure hydrocephalus; imRS, improved modified Rankin Scale; ROC, receiver operating characteristic; SD, standard deviation; IQR, interquartile range; ICP, intracranial pressure.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Nanchang University. Written informed consent was required from all patients or designated proxies.

Consent for publication

All authors read and approved the final manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests
The authors declare that they have no competing interests.

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**Authors’ contributions**

DJW and YHL drafted the manuscript and participated in its design. JJS and XLF collected the data for the study. LMX and ZYG analyzed the data. DHL performed the statistical analysis of the data.

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**References**


Figures
Figure 1

Modified Rankin Scale score (mRS) at admission and follow-up in the patients with acquired hydrocephalus. All (26) patients at admission had an mRS score of 3 or greater. 69.2% (18) of patients showed clinical improvement at follow-up postoperatively. 34.6% (9) cases with gross impairment of consciousness translated to higher levels of consciousness.

Figure 2
a Comparison of GCS score on admission between good (imRS ≤ 0, n = 18) and poor (imRS ≥ 1, n = 8) outcome group. b IL-6 level in control group (n = 6) compared to AH group (n = 26). c Comparison of IL-6 level in poor (n = 8) and good (n = 18) outcome groups. GCS, Glasgow Coma Scale; AH, acquired hydrocephalus; imRS, improved modified Rankin Scale (imRS = preoperative - postoperative mRS).

![Graph with labeled axes](image1)

**Figure 3**

IL-6 level (a) and GCS score (b) on admission were correlated with imRS in acquired hydrocephalus. GCS, Glasgow Coma Scale; imRS, improved modified Rankin Scale (imRS = preoperative - postoperative mRS).

![Graph with labeled axes](image2)
Figure 4

Receiver operating characteristic (ROC) curve of IL-6 for the prediction of improvement in functional outcome. ROC curves were generated from IL-6 levels in acquired hydrocephalus patients (n = 26, solid black line). ROC curve for Glasgow Coma Scale (GCS) ability to predict outcome was plotted as well (dashed gray line).