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Outcome predictors for normal-pressure hydrocephalus

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Summary

The objective of this prospective study was to find outcome predictors for better selection for treatment of normal-pressure hydrocephalus (NPH) patients. A total of 125 patients were evaluated and provided with a gravitational shunt.

Cerebrospinal fluid hydrodynamics provided better predictive values if an algorithm to shunt all patients with a pressure/volume index of <30 mL or resistance to outflow > 13 mmHg/mL × min was used. In general, outcome became worse with increasing anamnesis duration, worse preoperative clinical state, and increasing comorbidity. If one of these parameters was lower than a critical value, the shunt-responder rate was about 90% and the normally negative influence of older age was not seen. The well-known paradigm of a worse prognosis with NPH is not the result of the hydrocephalus etiology itself, but the consequence of a typical accumulation of negative outcome predictors as a consequence of the misinterpretation of normal aging and delayed adequate treatment.

Keywords: Normal-pressure hydrocephalus; outcome; resistance to outflow; pressure/volume index; comorbidity; shunts.

Introduction

Responder rates after treatment of normal-pressure hydrocephalus (NPH) are suboptimal [9, 22]. Up to 70% of patients with NPH suffer further neurodegenerative diseases, which may cause symptoms similar to those of NPH [1, 20]. On one hand these patients may benefit from shunting, but on the other, the decision whether to shunt or not is more demanding.

One objective of this prospective study was to find outcome predictors which improve with the indication for shunting. Another objective was to re-evaluate the paradigm that NPH, and especially idiopathic normal-pressure hydrocephalus (iNPH), has a worse outcome than other forms of chronic hydrocephalus [22].

Materials and methods

Patients, clinical management

A total of 125 patients (68 female, 57 male) were included in the study: 64 iNPH, 19 secondary NPH (sNPH), 42 non-communicating hydrocephalus (aqueduct stenosis: n = 40; Chiari I malformation: n = 2). Patients with at least 2 symptoms of Hakim's triad and an Evans Index > 0.3 received gravitational valves: 82 Aesculap-Miethke Dual-Switch valve (Christoph Miethke GMBH & Co. KG, Potsdam, Germany), 18 Aesculap-Miethke gravity-assisted valve (Christoph Miethke GMBH & Co. KG, Potsdam, Germany), and 25 received a combination of an adjustable Codman-Hakim valve (Codman and Shurtleff, Inc., Raynham, MA) and Aesculap-Miethke Shunt-Assistant (Christoph Miethke GMBH & Co. KG, Potsdam, Germany) [12, 17]. Complications were treated as described earlier [12]. Average follow-up was 4.3 ± 2.4 years.

Indication policy

Shunt indication was based on intracranial pressure monitoring. If mean intracranial pressure was >20 mmHg or B-wave frequency > 50%, shunt implantation was indicated. Additionally, a constant-volume infusion test was performed, but without influence on indication for surgery [12, 16].

Documentation

Each patient was examined clinically and by magnetic resonance imaging or cranial computed tomography preoperatively, at 1 and 12 months postoperatively, and yearly thereafter. To document the clinical state and the ventricular size, we used the Kiefer Index (KI) [12, 16], the Recovery Index [12, 16] and the Evans Index. Comorbidity was documented according to a new grading scale (Table 1).

Statistics

Mann-Whitney U, Spearman, analysis of variance, and Kruskal-Wallis tests at a significance level of $\alpha = 0.05$.

Table 1. *Comorbidity Index. Each mentioned symptom or disease has to be assigned according to the indicated parameter-values (1–3 points). The sum represents the individual comorbidity index*

	1 Point	2 Points	3 Points
Vascular risk factors	– Hypertension	– Diabetes mellitus	
Peripheral vascular occlusions	– Aortofemoral bypass – stent – ICA stenosis	– Peripheral vascular occlusion	
Cerebrovascular disease	– Posterior circulation insufficiency	– Vascular encephalopathy – TIA – PRIND	– Cerebral infarct
Heart	– Arrhythmia – Valvular disease – Heart failure (coronal) – Stent – Aortocoronary bypass – Infarction		
Others		– Parkinson's disease	

ICA Internal carotid artery; *PRIND* prolonged reversible ischemic neurologic deficit; *TIA* transient ischemic attack.

Results

Preoperative clinical state

The worse the clinical state was at admission, the worse the clinical outcome ($p = 0.003$). A mild clinical obstruction at admission (0–5 KI points) indicated an excellent prognosis (89% shunt-responder rate). In contrast, if severe preoperative obstructions were present (>12 KI points), responder rate dropped to 64%.

Comorbidity

From a statistical viewpoint, hypertension ($p = 0.015$), cerebrovascular diseases ($p < 0.001$), peripheral/coronary vascular occlusion ($p < 0.001$), diabetes mellitus ($p < 0.001$), and Parkinson's disease ($p < 0.003$) had a negative influence on outcome, while non-coronary heart failure ($p = 0.226$) and a history of alcohol abuse ($p = 0.738$) had none. However, each disease alone could not be taken as an independent variable of outcome, but only the combination of several diseases. To value the influence of all comorbidities, the usage of the Comorbidity Index (CMI) has been valuable. Three CMI points seemed to represent a critical value. Patients with 0–3 CMI points had a shunt-responder rate > 90% (age-independent), while beyond 3 CMI points the chance for a clinical benefit from shunting decreased to 65% ($p = 0.002$) overall with worse values for older patients.

Age

In general, outcome was worse with increasing age ($p < 0.001$); however, age was not an independent outcome predictor. A clear correlation between comorbidity and age was found ($p = 0.002$), because comorbidity normally increased with age. The influence of age on outcome has been mediated mainly by comorbidities.

Anamnesis duration

Shunt-responder rate decreased the longer the period between first hydrocephalus symptoms and treatment initiation ($p = 0.002$). Shunt-responder rates were higher (86%) for a shorter anamnesis (critical value: 1 year) than with a longer one ($p < 0.001$). Comorbidity plays an important role: at 0–3 CMI points the typical influence of the anamnesis duration seemed meaningless (responder rate > 90% independent from the anamnesis duration). In contrast, patients with >3 CMI points and a short anamnesis had responder rates of 80%, while those with an anamnesis of >1 year had responder rates < 60%.

Cerebrospinal fluid (CSF) hydrodynamics

Using CSF resistance to outflow (ROF) > 13 mmHg/mL × min as an independent outcome predictor alone, the positive predictive value (PPV) was 75%, the negative predictive value (NPV) 40%,

with a sensitivity of 96% and a specificity of 7%. At a critical value > 18 mmHg/mL $\times$ min, the specificity increased to 33%, PPV did not increase, while NPV and sensitivity decreased. Similar predictive values could be found regarding pressure/volume index (PVI) alone at varying critical values as an independent outcome predictor. However, combining both, according to an algorithm whereupon all patients with a PVI < 30 mL or a ROF > 13 mmHg/mL $\times$ min are shunted, provided a specificity and sensitivity $> 90\%$, PPV $\sim 80\%$. Only NPV remained at a clinically unsatisfying 60%.

Impact of hydrocephalus etiology

NPH patients responded to shunt surgery in 71% of the cases (iNPH, 66% responders; sNPH, 82% responders), while 87% of ''non-NPH'' responded; however, this narrowed perspective may lead to a wrong assumption about the meaning of hydrocephalus etiology. Shunt-responder rates of NPH and non-NPH with similar favorable preconditions such as mild (KI < 6 points) preoperative obstruction ($p = 0.643$), short (<1 year) anamnesis ($p = 0.114$), mild (CMI < 3 points) comorbidity state ($p = 0.082$), were not significantly different. NPH patients with favorable preconditions had a similar or better prognosis than non-NPH patients with worse preconditions (responder rates, CMI value: iNPH 83%, sNPH 85%, non-NPH 66%; anamnesis duration: iNPH/sNPH 82%, non-NPH 80%; KI value: iNPH 84%, sNPH 86%, non-NPH 81%). Some influence of the hydrocephalus etiology could be seen with worse preconditions only. With a longer anamnesis ($p = 0.0109$) and a worse preoperative clinical condition ($p = 0.021$), NPH had a 20% lower responder rate than non-NPH sufferers with similarly worse preconditions. However, for a worse CMI (>3 points), NPH and non-NPH shared the same worse prognosis of 66% and 65% of responders ($p = 0.856$), respectively. Considering independent outcome predictors, the paradigm of a worse NPH prognosis no longer held true.

We found a worse NPH prognosis compared to non-NPH simply from an accumulation of negative influences in the NPH group such as older age ($p < 0.001$), longer anamnesis ($p < 0.001$), worse clinical state at admission ($p < 0.001$), more comorbidity ($p < 0.001$).

Discussion

An important finding of this study is that iNPH does not mean a worse prognosis, as is often assumed [9, 22]. When taking into account similar favorable preconditions, the post-interventional outcome of NPH may be as good as with non-communicating hydrocephalus or better compared to non-communicating hydrocephalus with worse preconditions. From a pathophysiological viewpoint, the worse prognosis of NPH remained an enigma. Apparently it is not the hydrocephalus type which results in worse clinical outcome in NPH patients, but the generally worse precondition they have when first seen. Because the first symptoms of NPH are often neglected or misinterpreted as a natural consequence of older age, a drop in rehabilitation chances occurs.

Whether old age automatically results in a worse prognosis is controversial [7, 10, 18, 19]. According to our data, age must not be the determining factor for outcome; rather, it is a pseudo-correlation between age and outcome mediated by comorbidity, which normally becomes worse with older age. Accordingly, elderly persons (>80 years) with a low CMI (0–3 points) could have an excellent prognosis (responder rates $> 90\%$).

The clinical state at admission is typically not a discussion point. Mostly, specific symptoms are mentioned as good or bad outcome predictors instead of a global approach to the clinical state. We showed that grading allows an outcome prediction. A milder preoperative obstruction (5 KI points seems to represent a critical value) due to hydrocephalus allows better rehabilitation chances. Our grading system contrasts with earlier assumptions focusing on complete Hakim's triad and outcomes related to purity of the triad [2, 14, 20, 22]. However, other findings point in the same direction as ours in that a worse prognosis occurs with advanced mental deficits or the presence of urinary incontinence [2, 14, 20].

Additional diseases, especially cerebrovascular diseases, vascular occlusions, and Parkinson's disease, are important comorbidities [3, 13, 21], which can be seen in our data as well. There was previously no method established to value comorbidities as a prognostic instrument such as our Comorbidity Index, which allows gathering and valuing the influence on outcome of all additional diseases. Beyond a critical value of 3 CMI points, prognosis becomes worse even if other outcome predictors point to a favorable prognosis.

Our data indicates that both disputed viewpoints, an existing [3, 19] and a non-existing [2] influence of anamnesis duration on outcome, can be correct. Generally, prognosis becomes worse with longer anamnesis; however, this no longer holds true under favorable preoperative preconditions (CMI value < 4 points, KI < 6 points).

While the value of the ROF or PVI has been studied extensively with inconsistent results [4–6, 9, 11, 15, 16, 22], the recent trend to elevate the critical ROF value [3] may not be supported by our data. The infrequent use of PVI is astonishing, because recent data suggests that compliance is the initially disturbed parameter at the beginning of hydrocephalus, while ROF is only an epiphenomena [8]. Against this background, the mentioned algorithm may be found to be a better outcome predictor than those typically mentioned [9].

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