Measuring changes in the optic nerve sheath diameter in patients with idiopathic normal-pressure hydrocephalus: a useful diagnostic supplement to spinal tap tests

Michael Ertl, R. Aigner, M. Krost, Z. Karnasová, K. Müller, Markus Naumann, F. Schlachetzki

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Measuring changes in the optic nerve sheath diameter in patients with idiopathic normal-pressure hydrocephalus: a useful diagnostic supplement to spinal tap tests

M. Ertl[a], R. Aigner[a], M. Krost[a], Z. Karnasová[a], K. Müller[b], M. Naumann[a] and F. Schlachetzki[c]

[a]*Clinic for Neurology and Neurophysiology, Klinikum Augsburg, Augsburg;* [b]*Center for Clinical Studies, University Medical Center Regensburg, Regensburg; and* [c]*Department of Neurology, Clinic for Neurological Rehabiliation II, University of Regensburg, Regensburg, Germany*

Background and purpose: Cerebrospinal fluid (CSF) removal improves clinical symptoms of many patients with idiopathic normal-pressure hydrocephalus (iNPH). The aim of this study was to investigate the correlation of changes in the optic nerve sheath diameter (ONSD) with patient responses to CSF removal.

Methods: Transorbital ultrasonography was performed to obtain ONSD measurements in 31 patients with iNPH before and after lumbar puncture. Measurements were obtained while patients were supine and upright. Changes in the ONSD between supine and upright positions [ONSD variability (ONSD-V)] were assessed and compared with those in 60 healthy volunteers. ONSD-V was correlated with relative changes in a validated iNPH severity (Boon) score.

Results: Mean pre-puncture ONSD-V was significantly lower in healthy volunteers and patients with no response to CSF removal (Fisher test) [0.05 ± 0.14 mm (SD)] than in responsive patients [0.37 ± 0.20 mm (SD), $P < 0.001$]. ONSD-V predicted response to the spinal tap test (odds ratio, 0.30; 95% confidence interval, 0.12–0.75 mm, $P = 0.011$). The higher the ONSD-V, the better the therapeutic effect ($\chi^2 = 14.980$, $P < 0.001$). The post-spinal tap test ONSD-V correlated significantly with clinical severity in the motor portion of the Boon score [0.16 ± 0.23 mm (SD), $P = 0.003$].

Conclusions: The ONSD-V before and after spinal tap test correlated well with the clinical effects of CSF removal. Transorbital ultrasonography seems to be a reliable, safe add-on to the Fisher test and may support selection of patients for shunt intervention.

Introduction

Idiopathic normal-pressure hydrocephalus (iNPH) is defined by the clinical triad of a characteristic gait disturbance, incontinence and dementia [1], which is supported by a specific neuroimaging pattern [2]. The therapy of choice is continuous or regular removal of cerebrospinal fluid (CSF). To evaluate the need for and effectiveness of permanent shunting, the spinal tap test, also known as the Fisher test, is regarded as the diagnostic gold standard [3].

Despite thorough patient selection, some patients do not respond sufficiently to CSF removal [4].

Transorbital ultrasonography (TUS) with measurements of the optic nerve sheath diameter (ONSD) is an elegant non-invasive technique used to monitor changes related to intracranial pressure (ICP) [5]. These changes can be monitored quickly [6], even when a patient shifts from the supine (sONSD) to upright (uONSD) position [hereafter called ONSD

Correspondence: M. Ertl, Clinic for Neurology and Neurophysiology, Klinikum Augsburg, Stenglinstrasse 2, Augsburg 86156, Germany (tel.: +49 821 400 2991; fax: +49 821 400 2691; e-mail: Michael.Ertl@klinikum-augsburg.de).

variability (ONSD-V), defined as sONSD – uONSD], as was demonstrated in a study with patients suffering from spontaneous intracranial hypotension (SIH) [7].

The aim of this study was to investigate the correlation of changes in ONSD with the clinical severity of the disease and the effect of CSF removal trials.

Here we provide data from a prospective study involving 91 individuals (31 patients with iNPH and 60 healthy volunteers) showing that TUS with ONSD measurements may be a useful non-invasive supplement to the spinal tap test for selection of patients suitable for shunt surgery.

Materials and methods

Study population

Between September 2014 and March 2016, 31 patients were enrolled in this prospective study. The diagnosis of iNPH was made according to established clinical and neuroimaging criteria [8]. The clinical criteria consisted of 'magnetic' gait disturbance, cognitive impairment and urinary incontinence; at least two of these criteria had to be met, with gait disturbance being the obligatory criterion [9]. Clinical diagnoses were made by a senior neurologist (M.E.). The neuroimaging (computed tomography-based or magnetic resonance imaging-based) criteria included temporal horn enlargement, periventricular signal changes, periventricular edema and an aqueductal/fourth ventricular flow void [2]. Neuroimaging evaluations were conducted by specialized neuroradiologists.

Control group

Data from the patients with iNPH were compared with data collected from a group of 60 healthy volunteers who were previously enrolled in an epidemiological study to establish age-related reference values of ONSD dynamics (data not published). All patients and volunteers were more than 60 years old.

Transorbital ultrasound examination and safety considerations

The TUS was performed as previously described [5]. The examination was conducted prior to the spinal tap test first with the patient lying supine and then with the patient standing upright for 2 min. ONSD-V was calculated as sONSD – uONSD. A layer of acoustic gel was applied to closed eyelids, after which the transducer was placed on the upper lid with the examiner's hand resting on the patient's orbital margin. The ONSD was measured 3 mm behind the optic disc; the diameter was determined by measuring the distance between the hyperechogenic borders of the ONS. The investigation was repeated within 3 h after the spinal tap test had been conducted, and ONSD values were compared before and after CSF removal.

Measurements were performed by an experienced examiner (M.E.), who was accredited by the German Medical Ultrasound Society, and three other senior neurologists (R.A., M.K. and Z.K.). Three of the four investigators (except M.E.) were blinded for the clinical test and radiological findings of the patients. The correctness of measurements on all scans was re-evaluated by another experienced neurologist (F.S.), who was blinded to each patient's specific clinical outcome.

To reduce measuring intolerances, the ONSD was measured three times in each eye and the mean values from both eyes were calculated. Intraobserver reliability was also calculated. A good interobserver reliability has been previously reported [10].

For safety considerations and machine parameters, see Ertl *et al.* [5].

Spinal tap test

Lumbar puncture was performed, while the patient lay supine, using the usual hygienic precautions. The cerebrospinal opening pressure was recorded and a standardized quantity of 40 mL CSF was removed.

Outcome measures and statistics

We applied a standardized iNPH scale (Boon score) to quantify and compare the outcomes of patients with iNPH after CSF removal [11]. Briefly, the score consists of both motor and cognitive evaluations. The motor severity score [number of steps and time (in s) required for a 10-m walk, and eight gait characteristics (e.g. start hesitation, wide-based stride, etc.)] ranges from 2 to 40. The cognitive severity score (based on a 10-word recall test after 5 min, trail-making test and finger-tapping test) was modified to a range of 3–30 points. Higher numbers indicate greater clinical severity. In total, a maximum score of 70 can be achieved.

By calculating the relative improvement in the Boon score, patients were categorized according to their responses to CSF removal: Group 1 (<15%), no improvement; Group 2 (>15%), relevant improvement [12]. A further subdivision depending on the rate of improvement was omitted due to the relatively small number of patients.

The ONSD-V before and after therapy was regarded as a marker for ventricular compliance and ICP.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 (SPSS, Inc., Chicago, IL, USA), including descriptive analysis [frequencies (n), percentages, means and SD], median and quartiles (Q1 and Q3). Study groups were compared with regard to sociodemographic and clinical variables using chi-square test, t-test, U-test and Kruskal–Wallis test based on scale level, distribution of metric variables and number of groups.

Intraclass correlation (ICC) was used to examine the intraobserver reliability of the pre-puncture ONSD-V measurement.

To analyze statistical differences in the ONSD-V (between patient groups and healthy volunteers), we performed a univariate ANOVA as the ONSD-V was normally distributed within each group. Post-hoc analysis (using Games–Howell due to the heterogeneity of the variances) was performed to evaluate which groups differentiated. Binary logistic regression was performed to predict responsiveness to CSF removal (response versus no response) by pre-puncture ONSD-V. Moreover, the cut-off value of ONSD-V was calculated to predict responsiveness to CSF removal. Linear regression analyses were used to predict clinical severity measured by Boon scores by pre-puncture ONSD-V. To analyze the correlation between the pre-puncture ONSD-V and clinical severity (Boon scores), as well as post-puncture ONSD-V and clinical severity (Boon scores), we used the Pearson correlation coefficient for normally distributed scores and Spearman correlation coefficient for non-normally distributed scores. A P-value of 0.050 was regarded as statistically significant.

Ethical aspects

The study protocol was approved by the ethics committee at the Clinic of Augsburg (no. 2014/14) in accordance with guidelines of the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Results

Study population

The median age was 72 years (Q1, 66; Q3, 76; range, 60–85 years; $n = 91$), and 55 patients (60%) were male. Patient groups and healthy volunteers did not significantly differ in terms of gender ($\chi^2_{2,90} = 0.927$, $P = 0.629$). However, groups differed significantly in age ($\chi^2_{2,89} = 26.476$, $P < 0.001$). Healthy volunteers were significantly younger than patients with response to CSF ($P < 0.001$). Table 1 presents characteristics of the study population.

Intraobserver reliability

The ICC showed excellent intraobserver reliability [ICC, 0.93 (95% confidence interval, 0.85–0.97), $F_{15,30} = 38.568$, $P < 0.001$].

Differences in the optic nerve sheath diameter variability between patient groups and healthy volunteers

Univariate ANOVA showed that patients with no response to CSF removal ($n = 7$), patients with response to CSF removal ($n = 24$) and healthy volunteers ($n = 60$) significantly differed in pre-puncture ONSD-V ($F_{2,90} = 8.629$, $P < 0.001$). Patients with response to CSF removal had significantly higher pre-puncture ONSD-V (-0.37 ± 0.20 mm) than patients with no response to CSF removal (-0.05 ± 0.14 mm, $P = 0.001$) and healthy volunteers (-0.05 ± 0.37 mm, $P < 0.001$) (Fig. 1).

Prediction of response to cerebrospinal fluid removal and clinical severity by pre-puncture optic nerve sheath diameter variability

Binary logistic regression analysis revealed that the ONSD-V was a significant predictor of the response to CSF removal (odds ratio, 0.30; 95% confidence interval, 0.12–0.75, $P = 0.011$). The higher the ONSD-V, the better the therapeutic effect ($\chi^2_{1,31} = 14.980$, $P < 0.001$, Nagelkerke's $R^2 = 0.582$). Receiving operating characteristic curve analysis showed that ONSD-V was an excellent predictor of responsiveness to CSF removal (area under the curve, 0.93). An ONSD-V of -0.23 mm (Youden index, 0.83) could be calculated as a reliable cut-off value to predict a significant improvement in response to CSF removal, having a sensitivity of 83% and a specificity of 100% (Fig. 2).

Linear regression analyses showed that pre-puncture ONSD-V predicted clinical severity measured by Boon scores (Table 2). Figure 3 presents the scatter plot of the association between ONSD-V and total Boon score.

Correlation of optic nerve sheath diameter variability with clinical severity

As a potential marker for ventricular compliance, the difference of ONSD-V before lumbar puncture correlated significantly with clinical severity in the total Boon score ($r = -0.78$, $P < 0.001$) as well as with the motoric ($r = -0.83$, $P < 0.001$) and cognitive ($r = -0.49$, $P = 0.005$) subscores. The ONSD-V after spinal tap

Table 1 Characteristics of study population

	Patients with no response to CSF removal (n = 7)	Patients with response to CSF removal (n = 24)	Healthy volunteers (n = 60)	P
Sociodemographic information				
Sex				
Female	2	8	25	0.629
Male	5	16	35	
Age (years)	70 (68, 80)	79 (75, 81)	70 (64, 74)	<0.001
Clinical information				
Boon total score	2 (0, 5)	30 (20.25, 35.75)	–	<0.001
Boon motoric score	4 (0, 6)	34 (21.25, 51.75)	–	<0.001
Boon cognitive score	2 (0, 4)	14.50 (6.25, 20.00)	–	0.001
Pre-puncture ONSD-V	−0.10 (−0.15, 0.10)	−0.33 (−0.50, −0.26)	−0.06 (−0.27, 0.17)	<0.001
Post-puncture ONSD-V	−0.10 (−0.20, −0.10)	−0.15 (−0.29, −0.10)	–	0.241

For ease of presentation, median (med) and quartiles (Q1 and Q3) for metric variables are presented as some variables were normally distributed [Boon total score, Boon motoric score, pre-puncture optic nerve sheath diameter variability (ONSD-V)] and some were not normally distributed (age, Boon cognitive score, post-puncture ONSD-V). Chi-square test showed that the groups did not significantly differ in sex ($\chi^2_{2,90}$ = 0.927, P = 0.629). However, Kruskal–Wallis test revealed that the groups differed significantly in age ($\chi^2_{2,89}$ = 26.476, P < 0.001). Healthy volunteers were significantly younger than patients with response to cerebrospinal fluid (CSF) removal (P < 0.001). Patients with response to CSF removal had significantly higher Boon total score (T_{29} = −6.187, P < 0.001), Boon motoric score (T_{29} = −5.123, P < 0.001) and Boon cognitive score ($U_{7/24}$ = 11.325, P = 0.001) than patients with no response to CSF removal. Patient group did not significantly differ in post-puncture ONSD-V ($U_{7,24}$ = 1.376, P = 0.241). ANOVA was used to compare study groups regarding pre-puncture ONSD-V. Patient groups and healthy volunteers did significantly differ in pre-puncture ONSD-V ($F_{2,90}$ = 8.629, P < 0.001). Values are given as n or med (Q1, Q3).

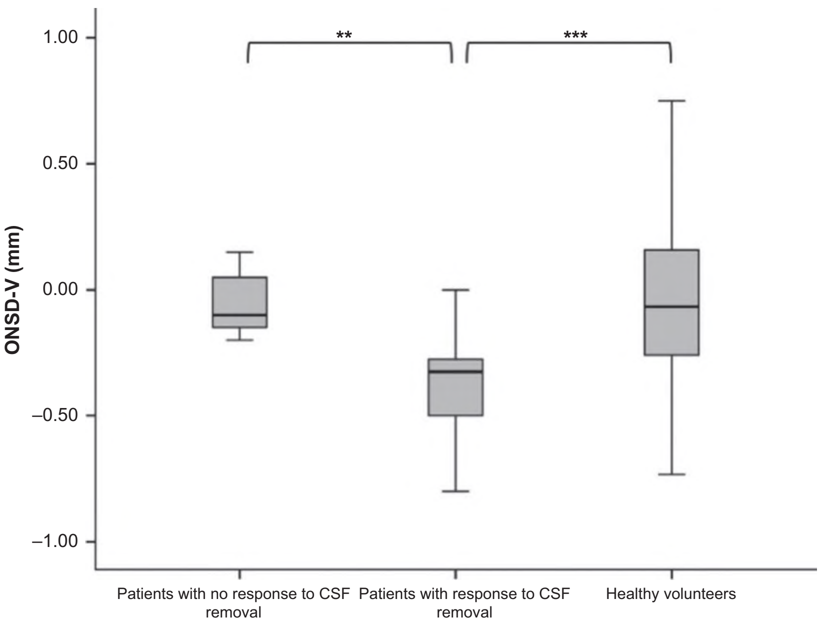

Figure 1 Differences in the optic nerve sheath diameter variability (ONSD-V) between patient groups and healthy volunteers. Patients with response to cerebrospinal fluid (CSF) removal had significantly higher ONSD-V than patients with no response to CSF removal and healthy volunteers. ***P < 0.001, **P < 0.010.

correlated with the motoric subscore (r = −0.40, P = 0.027) (Table S1). Figure 4 depicts the ultrasound technique and a typical ONSD-V of a responsive patient.

Discussion

The pathophysiology of idiopathic iNPH is still not entirely clear. The most conclusive theory seems to be that chronic hypertension and white-matter disease may lead to periventricular ischemia, which increases compliance of the ventricle wall and causes gradual ventricle enlargement [13,14]. Therefore, in patients with iNPH, we can probably assume that there is increased ventricular compliance and that it may be the basis of the clinical effect exhibited after CSF removal.

In this prospective study, this theory was substantiated for the first time using TUS with dynamic ONSD measurements.

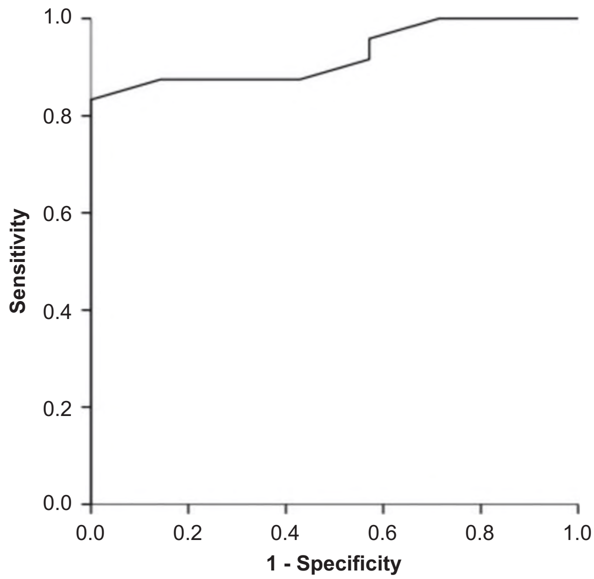

Figure 2 Receiving operating characteristic curve. Area under the curve, 0.93; pre-puncture optic nerve sheath diameter variability cut-off, −0.23 mm (Youden index, 0.83).

Table 2 Prediction of clinical severity by pre-puncture optic nerve sheath diameter variability (ONSD-V) (n = 31)

Dependent variable	Predictor (ONSD-V) *B*	95% CI	Adjusted R^2	*F*	*P*
Boon total score	−49.90	−64.90, −34.91	0.602	46.348	<0.001
Boon motoric score	−75.48	−94.96, −56.00	0.673	62.830	<0.001
Boon cognitive score	−19.36	−36.75, −1.97	0.122	5.182	0.030

Linear regression analyses showed that pre-puncture ONSD-V is a significant predictor of clinical severity measured by Boon scores. CI, confidence interval.

In patients with iNPH, a significant correlation between the post-puncture ONSD-V and the motor severity score was identified.

The mean pre-puncture ONSD-V in patients with iNPH was significantly higher than the ONSD-V in healthy volunteers. The better the patient response to the spinal tap test, the greater the reduction of the ONSD upon upright positioning. An ONSD-V of 0.23 mm predicted a relevant effect of spinal fluid removal with 83% sensitivity. Even more striking was the specificity of 100%, which means that not one patient with an ONSD-V lower than 0.23 mm responded to the spinal tap test.

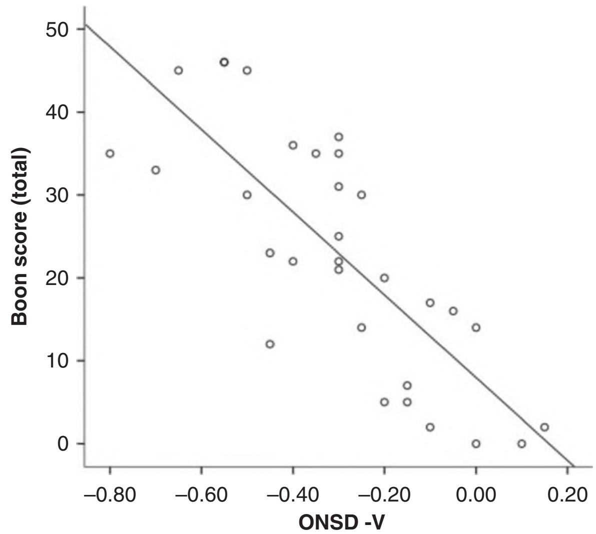

Figure 3 Association between pre-puncture optic nerve sheath diameter variability (ONSD-V) and Boon total score. R^2 linear = 0.615. $y = 7.96 - 49.9{*}x$.

We found a significant correlation between clinical improvement and CSF removal, which could be quantified by applying a validated iNPH severity score. As expected, the short time effect of this improvement was mainly exhibited in the motor subsection of the test; cognitive deficits were not significantly affected [15].

However, a reduction of ONSD in the upright position compared with the supine position has also been found in SIH [14]. In SIH, this effect was caused by a spinal CSF fistula resulting in a loss of pressure in the spinal CSF column, followed by a reduction of ICP in the upright position, whereas in iNPH, ONSD may be related to changes in ventricular compliance that are directly associated with the pathophysiology of iNPH and not with the baseline ICP [13,14].

In this study, ONSD-V may reflect pathological ventricular compliance in iNPH rather than a reduction of ICP as found in SIH [7]. Prior to this study, ONSD had mainly been used to identify and monitor circumstances of raised intracranial [16–19] or intraspinal [20] pressure.

Although data collected from the healthy volunteers (Group 3) on the ONSD-V were more or less in line with those mentioned in the existing literature [10,21], data from the patients with iNPH showed a strikingly greater reduction of ONSD upon positional changes, an effect that was not expected to be so great.

The Fisher test has an excellent positive predictive value of 90–100%; however, it has only a limited negative predictive value (18–50%) [22]. A significant number of patients who display no response to removal of CSF still improve with time after surgery

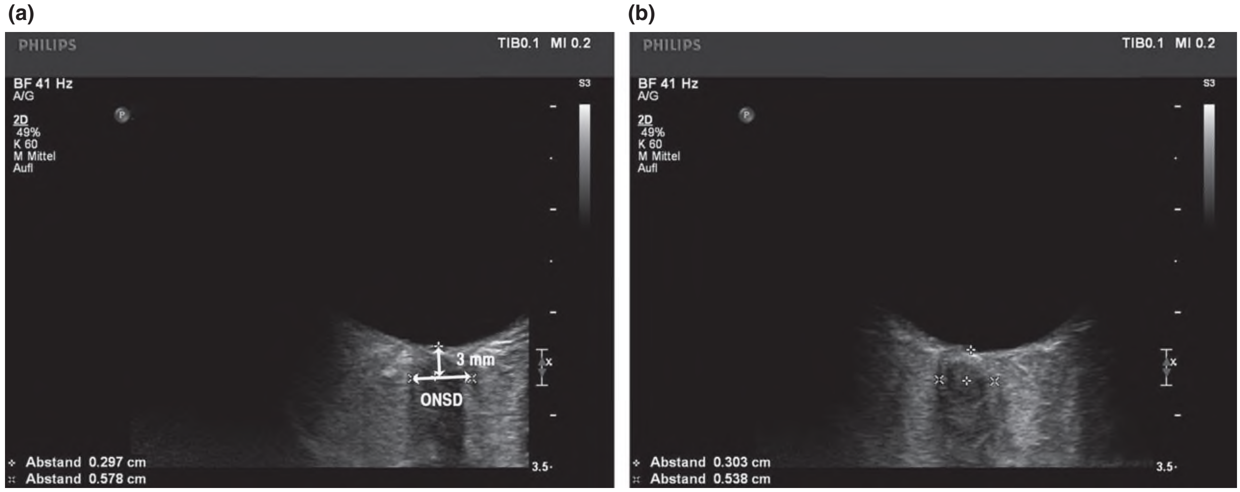

Figure 4 Optic nerve sheath diameter (ONSD) of a representative patient with an excellent response to therapy. (a) Supine and (b) upright position. ONSD is measured 3 mm beyond the surface of the retina. The diameter is determined by measuring the distance between the hyperechogenic borders of the optic nerve sheath.

[23,24]. One reason may be inadequate patient selection, as symptoms of iNPH can easily be mimicked by a variety of other pathological disorders, such as Alzheimer's disease, Parkinson's disease or subcortical atherosclerotic encephalopathy [15].

We were able to demonstrate that the ONSD-V reliably predicts a gain in function after the Fisher test and to show that a low ONSD-V is associated with a lack of response to CSF removal. Use of TUS may be helpful to spare patients from repeated invasive and potentially harmful spinal tap tests, and may identify patients appropriate for shunt implantation, even after a spinal tap test has proved non-diagnostic. The combination of a good ONSD-V and a poor reaction to CSF removal might signify the eligibility of the patient for shunt placement.

In summary, dynamic TUS is a clinical adjunct to the spinal tap test with high prognostic value for the short-term effect of CSF removal and may be related to ventricular compliance. Whether this translates into higher long-term success rates after shunting is a question that future prospective studies should address. In addition, the ONSD-V after the spinal test correlated in particular with the Boon score.

Study limitations

As mentioned above, a possible bias inherent in this study lies in patient selection, as all major symptoms of iNPH can be caused or mimicked by a variety of other, much more frequently occurring diseases. This is reflected by the fact that new consensus criteria for the diagnosis of iNPH differentiate between 'probable,' 'possible' or 'unlikely' improvement of diagnostic accuracy [1].

Finally, the study population was rather small. This investigation was aimed to be a 'proof of principle' study. This means that our findings need to be validated in clinical practice and further prospective studies.

Conclusion

To the best of our knowledge, this is the first study in which ONSD measurements were used diagnostically in patients with iNPH. The ONSD-V had a striking correlation with the clinical effects of CSF removal, giving us the opportunity to predict a patient's individual outcome even before implementation of the spinal tap test. TUS seems to be a reliable and safe add-on to the Fisher test and may be used to support the selection of patients for shunt intervention.

Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Correlations between pre-puncture and post-puncture optic nerve sheath diameter variability and clinical severity.

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