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Dynamics of Intracranial Venous Flow Patterns in Patients with Idiopathic Intracranial Hypertension

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Key Words
Cerebral flow · Headache · Pseudotumor cerebri · Duplex sonography

Abstract
Objective: To examine the dynamics of intracranial venous flow patterns in patients with idiopathic intracranial hypertension (IIH). ***Methods:*** Nonrandomized controlled trial analyzing the difference in cerebral perfusion in 13 IIH patients and 12 healthy controls using contrast-enhanced duplex sonography. In patients, an additional 3D gradient echo magnetic resonance venography (MRV) using a new technique was performed to quantify stenosis of the cerebral sinus. The cerebral perfusion parameters, including cerebral transit time (CTT) and time to peak (TTP), were analyzed. ***Results:*** IIH patients had a higher BMI (29.3 [95% CI 26.4, 32.2] vs. 23.3 [95% CI 20.7, 25.9], p = 0.003) and an increased prevalence of headache, but all other clinical characteristics were comparable. The CTT did not differ significantly. The TTP was significantly longer in IIH patients compared to controls (8.5 [95% CI 7.6, 9.4] vs. 7.3 s [95% CI 6.3, 8.1], p = 0.04). Twelve of 13 (92%) IIH patients showed stenosis of the cerebral sinus. ***Conclusions:*** Our study is the first to report an altered cerebral venous flow in IIH patients compared to controls using a dynamic ultrasonographic technique. A simplified MRV technique confirms the high prevalence and reliable detection of venous stenosis in IIH patients.

Introduction

The syndrome of an increased intracranial pressure without hydrocephalus or mass lesion is called idiopathic intracranial hypertension (IIH) or pseudotumor cerebri. The etiology of this syndrome still remains unknown. The diagnosis is mainly found in young obese women. The clinical symptoms are headache and visual disturbance, which commonly resolve spontaneously over months or years. A number of pathogenic mechanisms leading to the increased intracranial pressure have been discussed including altered cerebrospinal fluid (CSF) dynamics, obesity, sex hormones and an underlying prothrombotic abnormality [1–3]. The most accepted theory for the raised CSF pressure is an alteration in CSF dynamics. Some authors favor an impaired CSF absorption as a possible explanation [4, 5], which could be caused by pathology of the intracranial venous drainage system, for example sinovenous stenosis. Increasing evidence of a

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Table 1. Clinical characteristics of the IIH patients and controls

	Control group	IIH patients	p value
Number	12	13	
Age, years	37.8 [28.8, 46.7]	42.0 [32.6, 51.3]	NS
Sex (m/f), n	0/12	3/10	NS
BMI	23.3 [20.7, 25.9]	29.3 [26.4, 32.2]	0.003
Headache, n	3 (25%)	9 (69%)	0.03
Visual disturbances, n	0	7 (54%)	0.03
Hypertension, n	3 (25%)	6 (46%)	NS
Diabetes mellitus, n	1 (8%)	1 (8%)	NS
Smoking, n	6 (50%)	3 (23%)	NS
Hypercholesterolemia, n	1 (8%)	4 (31%)	NS
CTT, s	7.0 [6.3, 7.6]	7.2 [5.9, 8.6]	NS
ΔTTP, s	7.3 [6.3, 8.1]	8.5 [7.6, 9.4]	0.04

Values in square brackets indicate 95% CI.

high prevalence of stenosis of the transverse sinus was recently demonstrated. Higgens et al. [6] detected bilateral sinus stenosis in 13/20 patients with IIH and Farb et al. [7, 8] observed a high prevalence of sinovenous stenosis using a new and more simplified magnetic resonance venography (MRV) technique.

In order to analyze whether the cerebral perfusion is altered in IIH patients as compared to controls and to examine the possible pathogenetic role of cerebral sinus alterations for intracranial hemodynamic changes, we analyzed cerebral venous hemodynamics using echo-contrast bolus tracking power duplex sonography. A second aim of our study was to confirm the high incidence of sinus stenosis in patients with IIH using a new MRV technique without auto-triggering.

Methods

Patients and Controls

Twelve healthy control persons (12 women, mean age 37.8 [95% CI 28.8, 46.7] years) and 13 patients with IIH (10 women, mean age 42.0 [95% CI 32.6, 51. 3] years) were included in the study. The diagnosis of IIH was established using the recently proposed criteria for IIH [9] and the updated modified Dandy criteria [10].

Ten patients fulfilled all criteria, whereas in 3 patients not all criteria could be verified (table 1). One patient refused lumbar puncture, but improved after administration of acetazolamide. In the second patient, the CSF opening pressure was only 21 cm of water. However, this patient also improved after lumbar puncture. In the third patient, the CSF opening pressure was not measured; however, the patient improved after removal of 40 ml CSF.

The exclusion criteria for this study were pregnancy, extra- or intracranial arterial stenosis, ischemic heart disease, heart failure, stable and instable angina pectoris, history of myocardial infarction or ischemic stroke, severe arterial hypertension, pulmonary hypertension or other kind of pulmonary diseases. For further sub-analyses, IIH patients were divided into a symptomatic (persistent headache and visual disturbances) and an asymptomatic group. Informed consent was obtained according to the Declaration of Helsinki. The local ethics committee approved the study.

Duplex Sonography

We used a handheld 7.5-MHz linear array probe (Elegra®; Siemens, Erlangen, Germany). The common carotid artery (CCA) and the internal jugular vein (IJV) were simultaneously insonated using a longitudinal plane. Measurement was performed once on both sides. After achievement of an optimal position the color-coded flow was lowered until it was hardly visible and the perfusion imaging program of the Siemens Elegra (Axius ACQ®) was started. The parameters were: 7 images/s and a sub-sampling rate of 5 images. We injected a 1-ml bolus of a sulfur hexafluoride dispersion (SonoVue®; Bracco International BV, Germany) followed by 10 ml of saline in the right antecubital vein. Time intensity curves were analyzed in predefined regions of interest in the CCA and IJV offline using a computerized analyzing system provided by Siemens (Axius ACQ). The arrival time was defined as the point where the intensity changes achieved 10% of the maximum intensity changes compared to baseline. The CTT was defined as the time interval between venous and arterial arrival time. This method is comparable to the technique recently described by Schreiber at al. [11]. Additionally, we analyzed the difference in time to peak (TTP) interval between the IJV and CCA (ΔTTP). The investigator was blinded to the results of the MRV. An example of the method is given in figure 1.

Magnetic Resonance Venography

All MR examinations were performed with a 1.5 MRI (Magnetom Symphony, Siemens Medical Systems, Erlangen, Germany) using a standard 8-channel head coil. MRV was started after obtaining an axial plane located at the level of the cavernous carotid

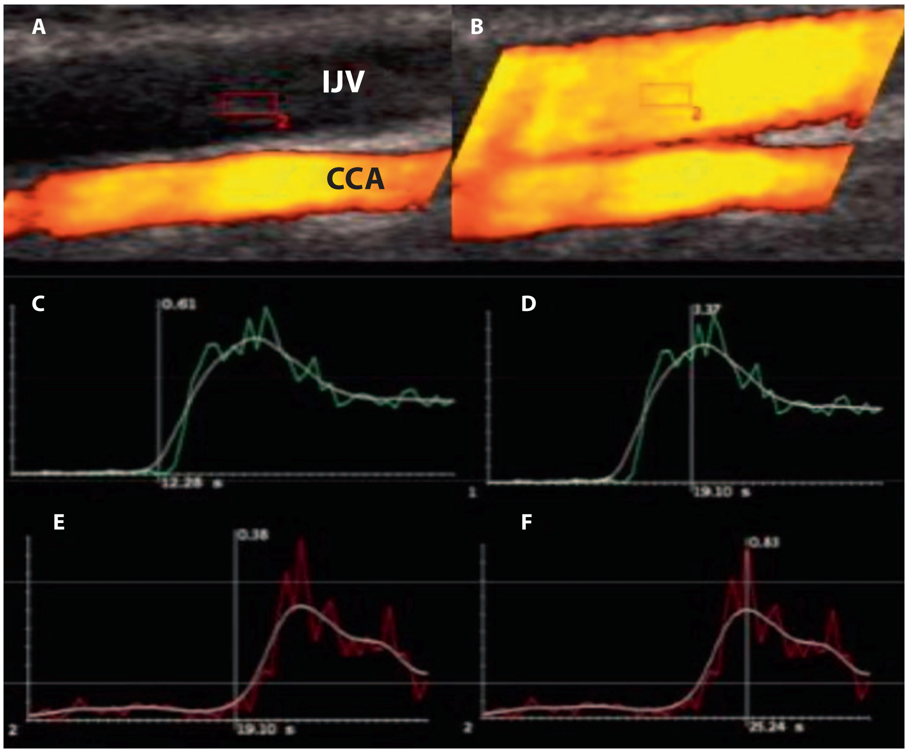

Fig. 1. Measurement of cerebral hemodynamics using duplex sonography. Exemplary CTT and ΔTTP measurements using Axius ACQ® (Siemens, Elegra, Germany). Arrival of the contrast agent in the common carotid artery (CCA) after 12.3 s (**A**, **C**). The time to peak is reached after 19.1 s (**D**). Arrival of the contrast agent in the internal jugular vein (IJV) after 19.1 s (**B**, **E**) with a time to peak of 25.2 s (**F**). The CTT for this example is 6.8 s and the ΔTTP is 6.1 s.

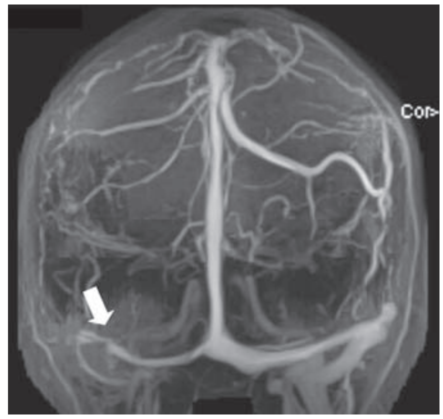

Fig. 2. Example of the MRV. Three-dimensional gadolinium-enhanced MRV of a patient with a left-sided hypoplasia and a mild right-sided stenosis (arrow).

artery. Forty seconds after a bolus of gadolinium contrast agent (Magnevist; 0.1 ml/kg) a fast 3D gradient echo MRV sequence oriented in the sagittal plane was started in every subject. The parameters were: TR 4.3 ms; TE 1.5 ms; 128 slices; field of view 280 cm; matrix 320 × 320; bandwidth 490 Hz; section thickness 1.25 mm; scan time 62 s; voxel dimensions 0.9 × 0.9 × 1.3 mm. Source images were transferred to a 3D workstation (Syngo 2000B®; Siemens). One example is given in figure 2. Additionally we performed a semiquantitative grading of the left and right transverse-sigmoid conduit as described recently by Farb et al. [8]: 0 = aplastic or discontinuity segment; 1 = hypoplasia or severe stenosis (>75%); 2 = moderate stenosis (50–75%); 3 = mild stenosis (25–50%), and 4 = stenosis <25% or normal sinus. As already proposed by these investigators, the sum of the left and right score was named the combined conduit score (CCS) [7].

Statistical Analysis

All values are given as mean and 95% CI, as median and interquartile range (IQR; range from the 25th to the 75th percentile) or as counts and percentages. We used the χ^2 test, the independent t test and the median test. Calculations were performed with JMP 5.01 software (SPSS Inc.). A calculated difference of $p < 0.05$ was considered statistically significant.

Results

Clinical Characteristics

We observed a significantly increased prevalence of headache (69 vs. 25%; p = 0.03) and a higher BMI (29.3 vs. 23.3; p = 0.003) in the IIH group as compared to the control group. Concerning other clinical characteristics both groups were comparable (table 1).

Duplex Sonography and MRV

The CTT measurement revealed no significant differences on each side separately or for the mean of both sides as compared to the controls (table 1). Interestingly, the mean ΔTTP was clearly longer in patients as compared to controls (8.5 vs. 7.3 s; p = 0.04). In the IIH group, 12/13 (92%) of the patients showed cerebral sinovenous stenosis or hypoplasia and the median CCS score was 4.0 (IQR 3.0, 5.5). In 9 IIH patients a bilateral stenosis was found.

Table 2. Clinical characteristics of symptomatic and asymptomatic IIH patients

	Symptomatic patients	Asymptomatic patients	p value
Number	7	6	
Age, years	48 [34.1, 61.9]	35 [20.4, 49.6]	NS
Sex (m/f), n	1/6	2/4	NS
BMI	31.3 [27.8, 34.8]	27.0 [21.4, 32.5]	NS
Sinus stenosis >50%, n	7 (100%)	4 (67%)	NS
Hypertension, n	3 (43%)	3 (50%)	NS
Diabetes mellitus, n	1 (14%)	0	NS
Current smoking, n	0	2 (30%)	NS
Hypercholesterolemia, n	4 (57%)	0	0.03
CCS	4.0 [2.8, 5.3]	4.7 [2.8, 7.3]	NS
CTT, s	7.4 [4.8, 10.0]	7.0 [5.6, 8.4]	NS
ΔTTP, s	9.1 [7.6, 10.6]	7.8 [6.7, 8.9]	NS

Values in square brackets indicate 95% CI.

IIH Subgroups

The mean CTT was longer (7.3 vs. 6.1 s, p = 0.07) in patients with a stenosis of ≥50%. Additionally, on the stenotic side the CTT increased with lower CCS scores from 6.3 (CCS = 4) to 7.9 s (CCS = 1). However, due to the small sample size no statistical test could be done. The CTT and the TTP at the stenotic side were increased compared to the contralateral side (7.5 vs. 6.6 s; p = 0.06 and 8.9 vs. 7.5 s; p = 0.07). However, both values did not reach statistical significance.

Seven of 13 IIH patients reported persistent headache and visual disturbances. The patients of this symptomatic subgroup were older (48 vs. 35 years) and more obese (BMI 31.3 vs. 27.0; table 2). Additionally, we found a higher prevalence of moderate and severe stenosis (50–100%) in this subgroup (100 vs. 67%) but the mean CCS did not differ significantly (4.0 vs. 4.7; table 2). The mean CTT and ΔTTP were also comparable between both subgroups.

Discussion

A high prevalence of hypoplasia and stenosis of the cerebral venous sinus was found in patients with IIH [6, 7]. Invasive studies already documented an alteration in cerebral venous flow with a high pressure in the venous sinus in these patients [12, 13]. Therefore, we analyzed the cerebral perfusion time in IIH patients as compared to controls using a noninvasive dynamic duplex sonography technique. Cerebral perfusion can be measured using color-coded duplex sonography either transcranially [14, 15] or extracranially [16]. Compared to controls, Liebetrau et al. [15] observed prolonged CTT in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Moreover, a reduced global CTT in patients with arteriovenous malformations was demonstrated [17]. More recently, Schreiber et al. [11] described a novel technique to assess the global cerebral circulation using power duplex sonography with echo-contrast bolus tracking.

We observed comparable values for the CTT in IIH patients and controls on both sides. The mean CTT of about 7 s in both groups is comparable with the results of Schreiber et al. [11]. The TTP interval was significant prolonged in IIH patients compared to controls. This finding strongly points to an alteration in venous cerebral blood flow in patients with IIH. One explanation for this finding might be the high prevalence of sinus stenosis in IIH patients. To the best of our knowledge, this is the first study analyzing these hemodynamic parameters using duplex sonography. However, further studies are needed to verify these findings and the clinical implications of these results.

One might hypothesize that the stenosis is more pronounced and the cerebral perfusion is more affected in symptomatic IIH patients. Interestingly, we observed that all symptomatic patients had severe stenosis; however, the overall CCS was comparable in both groups. This finding might indicate that a disturbance in venous outflow in IIH patients is more important for symptom persistence than the degree of stenosis. This assumption might be supported by the clinical improvement in 5 IIH patients after venous stenting as reported by Higgins et al. [13]. Moreover, Baryshnik and Farb [18] described 2 cases with normalization of venous sinus appearance following medical treatment.

Another intention of our study was to reproduce the findings of Farb et al. [7] who reported a high prevalence of hypoplasia and stenosis of the cerebral venous sinus in patients with IIH using an even easier MRI technique without auto-triggering. We were able to detect altered cerebral venous sinus in 12/13 IIH patients, which is comparable to the results of Farb et al. [7] reporting sinovenous stenosis in 27/29 patients with IIH. For a better comparison of both MR techniques, we used the same grading of the transverse sigmoid conduit as described by Farb et al. [7] and observed a comparable stenosis score in our group. Therefore, we consider that using an even easier and faster MRV technique without auto-triggering, the quality of our MRV protocol is sufficient for the detection of cerebral sinovenous pathology.

Higgins et al. [6] described a significantly higher prevalence of bilateral flow gaps in IIH patients as compared to controls. In our investigation, bilateral abnormalities were also detected in a high proportion of patients (9/13). Despite the improvement in diagnosis of cerebral venous abnormalities using an advanced MRV technique in IIH patients, it is still unclear whether the cranial venous outflow obstruction is the primary or a secondary process in IIH. Further studies using combined measurements of CTT and manometry in IIH patients might help to identify patients who improve after invasive treatment. Nevertheless, as all asymptomatic IIH patients in our study could successfully reduce their weight, we propose that the motivation of the patients to lose weight is of particular importance.

In summary, the two most important findings of our study were the detection of an altered cerebral venous flow in IIH patients compared to controls using a noninvasive dynamic ultrasonography technique and the confirmation of the recently published high prevalence of venous stenosis in IIH patients using a similar but simplified MR technique. However, it is not clear whether the detection of altered cerebral perfusion makes a difference in treatment in IIH patients, but this technique might help to generate further hypothesis.

References

1 Fishman RA: The pathophysiology of pseudotumor cerebri. An unsolved puzzle. Arch Neurol 1984;41:257–258.

2 Donaldson JO: Pathogenesis of pseudotumor cerebri syndromes. Neurology 1981;31: 877–880.

3 Sussman JD, Sarkies N, Pickard JD: Benign intracranial hypertension. Pseudotumour cerebri: idiopathic intracranial hypertension. Adv Tech Stand Neurosurg 1998;24: 261–305.

4 Johnston I, Hawke S, Halmagyi M, Teo C: The pseudotumor syndrome. Disorders of cerebrospinal fluid circulation causing intracranial hypertension without ventriculomegaly. Arch Neurol 1991;48:740–747.

5 Janny P, Chazal J: Intracranial pressure and sagittal sinus pathology. J Neurosurg 1981; 54:424.

6 Higgins JN, Gillard JH, Owler BK, Harkness K, Pickard JD: MR venography in idiopathic intracranial hypertension: unappreciated and misunderstood. J Neurol Neurosurg Psychiatry 2004;75:621–625.

7 Farb RI, Vanek I, Scott JN, Mikulis DJ, Willinsky RA, Tomlinson G, TerBrugge KG: Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. Neurology 2003;60:1418–1424.

8 Farb RI, Scott JN, Willinsky RA, Montanera WJ, Wright GA, terBrugge KG: Intracranial venous system: gadolinium-enhanced three-dimensional MR venography with auto-triggered elliptic centric-ordered sequence – initial experience. Radiology 2003;226:203–209.

9 Friedman DI, Jacobson DM: Diagnostic criteria for idiopathic intracranial hypertension. Neurology 2002;59:1492–1495.

10 Dhungana S, Sharrack B, Woodroofe N: Idiopathic intracranial hypertension. Acta Neurol Scand 2009;121:71–82.

11 Schreiber SJ, Kauert A, Doepp F, Valdueza JM: Measurement of global cerebral circulation time using power duplex echo-contrast bolus tracking. Cerebrovasc Dis 2003;15: 129–132.

12 King JO, Mitchell PJ, Thomson KR, Tress BM: Cerebral venography and manometry in idiopathic intracranial hypertension. Neurology 1995;45:2224–2228.

13 Higgins JN, Cousins C, Owler BK, Sarkies N, Pickard JD: Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting. J Neurol Neurosurg Psychiatry 2003;74:1662–1666.

14 Puls I, Hauck K, Demuth K, Horowski A, Schliesser M, Dorfler P, Scheel P, Toyka KV, Reiners K, Schoning M, Becker G: Diagnostic impact of cerebral transit time in the identification of microangiopathy in dementia: a transcranial ultrasound study. Stroke 1999; 30:2291–2295.

15 Liebetrau M, Herzog J, Kloss CU, Hamann GF, Dichgans M: Prolonged cerebral transit time in CADASIL: a transcranial ultrasound study. Stroke 2002;33:509–512.

16 Hoffmann O, Weih M, Schreiber S, Einhaupl KM, Valdueza JM: Measurement of cerebral circulation time by contrast-enhanced Doppler sonography. Cerebrovasc Dis 2000; 10:142–146.

17 Schreiber SJ, Franke U, Doepp F, Staccioli E, Uludag K, Valdueza JM: Dopplersonographic measurement of global cerebral circulation time using echo contrast-enhanced ultrasound in normal individuals and patients with arteriovenous malformations. Ultrasound Med Biol 2002;28:453–458.

18 Baryshnik DB, Farb RI: Changes in the appearance of venous sinuses after treatment of disordered intracranial pressure. Neurology 2004;62:1445–1446.