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ORIGINAL COMMUNICATION

Idiopathic intracranial hypertension is not benign: a long-term outcome study

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Abstract Idiopathic intracranial hypertension (IIH) primarily affects young obese females, and potentially causes visual loss and severe headache. The aim of this experiment is to examine relapse rate and long-term outcome in IIH patients. The methods involved in this experiment include a prospective controlled study of 18 newly diagnosed IIH patients followed for a mean observation period of 21.1 (±8.0) months. Treatment regime included diuretics, dietary recommendations and check-up visits at a dietician. Baseline and follow-up included neurological examination, detailed headache history and comprehensive neuro-ophthalmological examination, including fundus photography, Humphrey visual fields, and measurement of the retinal thickness (RT) and retinal nerve fiber layers (RNFL) by optical coherence tomography (OCT). Relapse was defined as recurrence of either: (1) papilledema or (2) symptoms and demonstrated raised ICP. The result of this experiment is that relapse was found in 28%. Visual function improved from baseline to follow-up and was generally favorable. In patients without relapse of papilledema RT and RNFL were significantly thinner than in healthy controls ($p = 0.003$ and 0.02), although atrophy was clinically detectable in only one patient. Headache was still present in 67% of the patients at follow-up. Headache was heterogenic and unrelated to relapse. After an initial reduction, weight increased again in the relapse group compared to reduced weight in the non-relapse group ($p = 0.013$). Thus, the conclusions drawn are that headache was persistent, difficult to classify, and equally represented in relapse and non-relapse patients. Headache was thus a poor marker of active disease. Relapse rate was high and clinically undetectable optic disc atrophy was discovered in apparently well treated IIH patients.

Keywords Headache · Idiopathic intracranial hypertension · OCT · Papilledema · Relapse · Recurrence

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Introduction

Idiopathic Intracranial Hypertension (IIH) is a condition of raised intracranial pressure (ICP) in the absence of space occupying lesions or other known etiology. Symptoms include severe headache, pulsatile tinnitus, transient visual obscuration (TVO), blurred vision and diplopia [15, 31, 41]. Some reports of dizziness [10, 25] or cognitive deficits [3, 38] have also been published. Signs are papilledema [5, 20, 21] and occasionally sixth nerve palsy. The papilledema may be asymmetric, unilateral or in some cases even absent [23].

The main morbidity of IIH is the risk of visual impairment and high recurrence rates have been reported [17]. If treated, visual prognosis is usually good [12]. Untreated the papilledema may cause a progressive and irreversible visual loss due to secondary optic disc atrophy. Unfortunately, visual loss may be insidious and asymptomatic until irreversible damage has occurred. Mainly visual fields are affected while visual acuity and color-vision are relatively spared [32, 33].

IIH primarily affects young obese women. The estimated incidence is this group is 20 times higher (19.4/100.000) than in the general population (0.9–1.0/100.000) [11, 28, 29]. As the worldwide prevalence of obesity is rapidly increasing the

incidence of IIH is likely to follow. Even though the incidence at this point is relatively low, the socio-economic consequences of the disease are substantial [13].

A standardization of the acute and long term management of IIH patients is lacking, and further information on the natural history of the disorder is needed to establish a sufficient clinical follow-up regime. The aim of the present study was to investigate the relapse rate and long term clinical outcome, with respect to visual function and headache, in a prospective case–control study of 18 patients with confirmed IIH.

Materials and methods

A prospective long-term follow-up study of 20 newly diagnosed IIH patients, were consecutively recruited among patients referred to the Danish Headache Center from Dec 2006 to Dec 2008. All met the diagnostic criteria of IIH according to the International Headache classification (criteria B, Table 1 [1]). Exclusion criteria were other significant medical, psychiatric or ocular disorders. A group of 20 healthy individuals, matched in terms of age, gender and body mass index (BMI) served as control [37].

The Danish Headache Center is a tertiary referral resource for patients with rare or severe headache disorders referred from private neurologists, outpatient neurology clinics and hospitals. IIH patients are diagnosed and treated in close collaboration with the Department of Ophthalmology, Glostrup Hospital, a tertiary eye care center receiving patients from other Danish ophthalmological departments and private ophthalmologists.

At baseline patients underwent a detailed interview on headache symptoms and had a standardized neurological and ophthalmological examination including pressure measurement by lumbar puncture, Humphrey visual field testing (30-2 SITA standard), measurement of RNFL and RT by peripapillary and macular OCT (Stratus OCT 3000, fast RNFL 3.4 protocol) and fundus photography (Zeiss, FF 450 plus, red and red-free light). Baseline results are described in previous publications [36, 37].

Treatment regime included dietary recommendations to induce weight loss and medication with per oral acetazolamide in individualized dosages (maximum 2,250 mg/day). The treatment goal was to reduce papilledema and eliminate visual dysfunction, and to relieve symptoms while minimizing medical side-effects. If acetazolamide alone was insufficient, a dose of furosemide (40–120 mg/day) combined with potassium was added. Topiramate served as a second-line treatment and replaced acetazolamide in case of intolerable side-effects.

During the follow-up period patients were seen at regular neuro-ophthalmological and neurological control visits. Number of visits varied depending on the severity of the disease and patient compliance. The neuro-ophthalmological evaluation included best corrected visual acuity (Snellen), Ishihara color vision test, assessment of pupillary function and eye motility, slit-lamp examination, Goldman intraocular pressure measurement, dilated fundoscopy, fundus photography and Humphrey visual field testing. At final follow-up the examination program was similar to the one at baseline (except from pressure measurement that was only repeated in two patients).

Visual fields were graded from grade 0 (normal) to grade 4 (extensive defects) on a visual field grading scale. The grading scale is based on the presence of nerve fiber layer type of visual field defects and mean deviation values (see the Iowa experience [34]). Papilledema was graded according to the Frisén grading scale [14].

Relapse of IIH was defined as (1) recurrence of previously resolved papilledema or (2) recurrence of clinical symptoms (e.g. headache, TVO, tinnitus) and increased ICP measured by repeated lumbar puncture.

Statistics

Demographic data were summarized. Differences between controls and patients were evaluated by *t*-test for age and Mann–Whitney test for BMI. Wilcoxon sign test for matched pairs compared BMI at baseline and follow-up. Weight-changes and duration of treatment in the relapsing and non-relapsing group were tested by Mann–Whitney test for unrelated groups.

As papilledema is often asymmetric, follow-up evaluation and treatment in clinical practice is based on the most affected eye. Thus, statistical analyses of OCT in this study were based on measurements of the eye presenting with the thickest RNFL and RT at baseline.

The RNFL and RT from baseline to follow-ups were analyzed by the Wilcoxon sign test for matched pairs. RNFL and RT values for patients and controls were compared by Mann–Whitney test. In non-parametric tests immeasurable eyes were assigned a value above the highest measurable value. Data are expressed as mean ± SD. p-Level < 0.05 was chosen as the level of significance.

Results

Demographics

Baseline

Two of the 20 patients included at baseline were lost to follow-up. Eighteen patients were re-evaluated. Fourteen had IIH with papilledema (IIHWP) and four were

diagnosed with IIH without papilledema (IIHWOP). Baseline ICP exceeded measure limits (>50 cmH_2O) in three patients. Mean ICP in the remaining 15 patients was 32.1(±6.4) cmH_2O. The demographic characteristics are shown in Table 2.

Mean follow-up time was 21.1 ± 8.0 months. Mean number of visits between baseline examination and follow-up was 8.5 (range from 4 to 16 visits). An average of 1.9 ± 2.4 telephone consultations were offered.

Follow-up

At final follow-up five IIHWP patients (28%) presented with papilledema. Four patients had relapse of a papilledema previously reported to be resolved. One patient had a persistent papilledema from baseline examination to final follow-up. In one IIHWOP patient relapse was suspected by recurrence of headache and cognitive symptoms. Relapse was confirmed by lumbar puncture (opening ICP of 30 cmH_2O). In total, relapse was found in five of 18 patients (28%). All IIH relapses occurred among patients in whom medical treatment was discontinued due to clinical remission.

The remaining 12 patients had no signs of relapse at final follow-up. Nine had IIHWP and remission was supported by normal optic nerve heads. Of the three IIHWOP patients, one had severe continuous headache and significant visual field defects. Relapse was ruled out by 24-h continuous ICP measurement showing a pressure of 5–9 mmHg (7–12 cmH_2O).

Systematic ICP measurement was not repeated at follow-up, but performed only in those two IIHWOP patients with suspected relapse. Neither duration of treatment nor medication free interval differed significantly between the relapsing and non-relapsing group. Mean duration of treatment in the relapsing group was 9.5 (±4.4) months versus 11.7 (±5.9) months in the non-relapsing group ($p = 0.6$). The five relapsing patients had been off medication for an average at 11.6 (±5.3) months. Seven of 12 patients in the non-relapsing group were off medication [mean time 14 (±11) months ($p = 0.9$)].

Table 1 Diagnostic criteria of IIH

Idiopathic intracranial hypertension, ICHD-II criteria B [1]
1. Alert patient with neurological examination that either is normal or demonstrates any of the following abnormalities:
a) Papilledema
b) Enlarged blind spot
c) Visual field defect (progressive if untreated)
d) Sixth nerve palsy
2. Increased CSF pressure (>200 mmH_2O [non-obese], >250 mmH_2O [obese]) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring
3. Normal CSF chemistry (low CSF protein acceptable) and cellularity
4. Intracranial diseases (including venous sinus thrombosis) ruled out by appropriate investigations
5. No metabolic, toxic or hormonal cause of intracranial hypertension

Table 2 Demographic data of IIH patients (at baseline and follow-up) and healthy controls

	Baseline ($n = 18$)	Follow-up ($n = 18$)	Controls ($n = 20$)
IIHWP/IIHWOP	14/4	14/4	
Age (y)	25.7 ± 7.9	27.4 ± 7.9	35.5 ± 12.5
Sex (F/M)	16/2	16/2	19/1
BMI (kg/m^2)	36.4 ± 7.1[a]	35.7 ± 8.8[b]	30.6 ± 3.8[c]
ICP (cmH_2O)	32.1 (±6.4)*		17.1 (±2.4)

IIHWP Idiopathic intracranial hypertension with papilledema; *IIHWOP* Idiopathic intracranial hypertension without papilledema

* $n = 15$ (ICP values were above measurable limits (>50 cmH_2O) in three patients. These were not included in calculation of mean value)

Difference in BMI from baseline to follow-up: [ab]$p = 0.8$. Baseline BMI compared to controls: [ac]$p = 0.01$. Follow-up BMI compared to controls: [bc]$p = 0.06$

Headache

Baseline

At baseline headache was present in 17 of 18 patients (94%) (Table 3). The single patient without headache reported a mild pressure (but no pain) above the right orbit. The phenotypical presentation resembled migraine in eight and tension-type headache in six patients. Three patients had an underlying tension-type like headache with intermittent migraine-like attacks. Of the headache patients, 16 reported continuous headaches while the remaining patient reported intermittent headache (1–2 days/week). Mean headache intensity of continuous headaches was 6.3 on a 0–10 VAS-scale. In addition they suffered intermittent peak intensities of 6–10, 2–4 days/week.

Headache location was holocranial in eight patients while the remaining nine patients reported a single frontal (4), temporal (5) and occipital (4) location or in a combination. In two patients (non-migraineurs) the headache was strictly unilateral. Specific retrobulbar pain/pressure was present in eight patients. All 17 patients reported a pressing/tightening quality of their headache; in addition, five reported intermittent pulsatile aggravations. Only three patients reported aggravation of their headache in the morning and/or on bending forward.

Table 3 Headache and other symptoms at baseline and follow-up

	Baseline total *n* (%) *n* = 18	Follow-up	
		Relapse *n* (%) *n* = 6	Non-relapse *n* (%) *n* = 12
Headache	17 (94)	4 (67)	8 (67)
Throbbing	5 (29)	2 (50)	3 (38)
Pressing	17 (100)	2 (50)	7 (88)
Related to position	3 (18)	1 (25)	2 (25)
Photophobia	11 (65)	1 (25)	3 (38)
Phonophobia	7 (41)	0	3 (38)
Pulsatile tinnitus	12 (67)	3 (50)	5 (42)
Visual disturbances			
Diplopia	8 (44)	1 (17)	0
Blurred vision	12 (67)	1 (17)	1 (8)
TVO	8 (44)	2 (33)	1 (8)
Other			
Retrobulbar pain	8 (44)	1 (17)	0
Dizziness	10 (56)	0	5 (42)

Symptoms at baseline and follow-up. At follow-up symptoms are displayed according to occurrence in, respectively, relapse and non-relapse patients.

* Data from the patient with continuous disease is included in the relapse group

Five patients had a history of episodic headache, respectively migraine (2), tension-type headache (2) or post-traumatic headache type (1) prior to symptoms of IIH. In addition two patients had suffered from chronic tension-type headaches and chronic migraine on a daily basis during >4 years prior to the diagnosis of IIH. The remaining 11 patients reported no headaches prior to debut of IIH.

Follow-up

At follow-up six patients were completely headache free. Twelve patients still experienced headaches, 8 of which had no headache history prior to IIH. One patient had suffered from a constant headache since baseline. One patient had a relapse of continuous headache the last month prior to follow-up after a period of 19 headache-free months. A daily although intermittent headache was reported in three, episodic headache (1–4 days/week) in five and infrequent headache 2–4 days/month in two patients. Totally, the mean intensity of headache (VAS-scale 0–10) was decreased from 6.8 at baseline to 5 at follow-up. Location of pain was very variable. Holocranial in three, frontal alone or in combination with other locations in six, and retrobulbar, parietal and temporal, respectively in the remaining three. In respect to quality, nine and five patients reported, respectively, tightening and/or pulsatile, widely unchanged from baseline.

Headache was reported in four of six (67%) patients with relapse, and in eight of 12 (67%) patients without relapse. Neither duration nor intensity of headaches differed between the groups.

One patient from the non-relapsing group reported a constant high intensity headache. Relapse was out ruled by 24-h continuous ICP measurement. In another patient presenting with a constant headache at follow-up, the headache was classified as chronic tension-type headache and resolved almost completely after physiotherapy.

Papilledema

Baseline

Fourteen of 18 patients had clinically detectable papilledema at baseline, bilateral in 13 and unilateral in one. Mean edema grade was 2 on the Frisén scale [14]. In one case the edema was very subtle and upon the subsequent grading (fundus photography) both optic discs were graded as normal.

Follow-up

At final follow-up a complete resolution was found in nine patients. Mild papilledema grade 1–2 (mean 1.7) was found in five cases, two bilateral and three unilateral. Four of these were relapses of a previously resolved papilledema. All had been off medical treatment for at least 3 months (3–14 months). One patient had persistent papilledema from baseline examination to final follow-up. During the observation period of 24 months this patient had 10 clinical follow-up visits. Complete resolution was never detected despite an initial improvement. Deterioration was observed 4 months before the final follow-up visit after a period of 12 months with poor compliance, self-administered tapering of acetazolamide to 250 mg/day and no clinical controls.

Mean time from diagnosis of papilledema to clinical resolution (as documented in the medical records) was 5.4 ± 2.6 months. In three cases the edema resolved within 3 months, in another six cases within 6 months. In two cases the exact time of clinical resolution was uncertain due to a tight optic nerve head structure complicating the distinction between genuine edema and blurred disc margins due to congenital optic disc morphology.

OCT

OCT data are displayed in Table 4. In the relapse group RNFL and RT values were above the 97.5 percentile of the

healthy controls in seven eyes. Papilledema was detectable clinically in only six eyes.

IIHWP patients with resolved papilledema at follow-up had a significant reduction in RNFL and RT values from the 3-month follow-up visit to the final follow-up (RT: $p = 0.011$ and RNFL: $p = 0.03$). At final follow-up RNLF and RT were significantly thinner than in healthy controls (RT: $p = 0.003$ and RNFL: $p = 0.02$) although atrophy was clinically detectable in only one patient.

Visual fields

Visual fields from six (baseline) and three eyes (follow-up) were excluded due to poor cooperation.

Baseline

Normal visual fields (grade 0) were found in 15 eyes (48%). Eleven eyes (35%) graded ≥2 and three eyes (10%) graded 3 or 4 (Table 5).

Follow-up

Visual fields were normal in and 26 eyes (79%). Thirty of 33 eyes (91%) graded ≤1 and no eyes rated higher than grade 2. In eyes of IIHWP without relapse at follow-up visual fields were normal (grade 0) in 15 eyes and grade 1 in 2 eyes.

Peripheral visual field defects in 11 eyes resolved completely during the observation period. Eyes with peripheral visual field defects at follow-up had similar or even higher graded defects at baseline. Thus, no deterioration was seen in visual fields from baseline to final follow-up.

Best corrected visual acuity (BCVA)

BCVA at follow-up was >0.8 in all eyes, and >1.0 in 34 of 36 eyes. Five eyes had improved from a BCVA of 0.8–0.9 at baseline to >1.0. Two eyes remained stable at 0.8 and 0.9, respectively (Table 5). BVCA at baseline was only affected in one of the 10 eyes that presented with a high-grade edema (Frisén grade 4, BCVA = 0.9).

At follow-up BCVA was >1.0 in all 10 eyes. In total, mean BCVA improved from baseline to follow-up ($p = 0.01$) and none decreased in BCVA.

Other signs

Color vision was not significantly affected. Apart from two patients suspected of functional vision loss, only two patients presented with errors in the Ishihara test (≤2 errors) at baseline and follow-up. No relative afferent pupil deficit (RAPD) was found.

Six patients presented with sixth nerve palsy at baseline. All were resolved at follow-up. In two cases without initial sixth nerve palsy a subtle bilateral abduction deficit was suspected at follow-up. Only one of these had other signs of raised ICP.

Other symptoms

Pulsatile tinnitus was reported in three of the six (50%) patients with relapse and in five of the 12 (42%) non-relapsed patients. A clear reduction of other symptoms was noted (Table 3). TVO was only reported by three patients (two with and one without papilledema). One patient in each group reported blurred vision.

Table 4 OCT from baseline to final follow-up

OCT	Baseline	3-month follow-up	Final follow-up	Controls	^{ac}p	^{bc}p	^{cd}p
Non-relapse							
Eyes	9	9	9	20			
RNFL (μm)	256.1 ± 112.1[a]	104.8 ± 13.4[b]	94.4 ± 8.8[c]	101.1 ± 7.5[d]	0.008	0.03	0.02
RT (μm)	521.3 ± 222.1[a]	282.7 ± 31.1[b]	258.9 ± 14.9[c]	278.9 ± 9.9[d]	0.008	0.01	0.003
Relapse[a]							
Eyes	5	5	5	20			
RNFL (μm)	307.6 ± 84.6[a]	136.1 ± 38.4[b]	183.4 ± 46.0[c]	101.1 ± 7.5[d]	0.08	0.08	0.001
RT (μm)	824.3 ± 235.9[a]	318.7 ± 42.0[b]	415 ± 122.0[c]	278.9 ± 9.9[d]	0.08	0.1	0.01

Data are expressed as mean ± SD.

The table shows RNFL and RT values of healthy controls and IIHWP patients with and without relapse of papilledema at final follow-up. OCT values were immeasurable due to extensive edema in respectively six (RNFL) and four (RT) eyes at baseline and one (RNFL and RT) eye at final follow-up. Immeasurable eyes were assigned to values above highest measurable value

[a] The patient with continuous papilledema was included in the relapse group. ^{ac}p difference from baseline to final follow-up; ^{bc}p difference from 3-month follow-up to final follow-up; ^{cd}p final follow-up compared to healthy controls

Table 5 Neuro-ophthalmological signs at baseline and final follow-up

	Baseline total eyes ($n = 36$)	Follow-up	
		Relapse eyes ($n = 12$)	Non-relapse eyes ($n = 24$)
Papilledema	22	7	0
Frisén grade 0	12	5	24
Frisén grade 1	3	2	0
Frisén grade 2	7	5	0
Frisén grade 3	4	0	0
Frisén grade 4	10	0	0
Frisén grade 5	0	0	0
Visual fields			
Grade 0	15	7	19
Grade 1	4	2	2
Grade 2	8	1	2
Grade 3	2	0	0
Grade 4	1	0	0
Snellen visual acuity			
≥1,0	28	12	22
0.8–0.9	7	0	2
<0.8	1	0	0
Ishihara			
17	24	10	19*
≥15	9	2	3
<14	3	0	0
RAPD	0	0	0

Ishihara: number of correctly identified plates out of 17 possible. * One patient (non-relapse) was not re-tested at follow-up

Visual fields are graded according to the IOWA grading scale

Autoperimetry result from, respectively six and three eyes at baseline and follow-up were excluded due to poor cooperation

Weight and BMI

At baseline 15 patients were obese and three were overweight. Mean BMI was 36.7 kg/m^2. At follow-up mean BMI had not changed significantly (Table 2). Only one patient had achieved a normal BMI (<24.9 kg/m^2). Three patients were overweight with BMI between 24.9 and 29.9 kg/m^2. Fourteen patients were obese with BMI > 30 kg/m^2. Only five had lost >5 kg (or 5% of body weight). Two of these had major weight loss of 45 kg (37.5%) and 24 kg (20.3%) due to Bariatric surgery and major depression, respectively.

In the relapse group three of five patients had gained weight of 17.5, 18 and 24.8 kg, respectively (13.8–17.3% of body weight). All of these were now morbidly obese with BMI > 40 kg/m^2. The one patient with prolonged disease course had a weight gain of 5 kg (4.6%). In the 12 patients without signs of relapse seven had lost weight (2.2–37.5%), one was stable and four had had minor weight gains (1.1–5.7%). In total the relapsed patients have had a significant weight gain (in % of body weight) compared to the non-relapsed patients ($p = 0.013$) (Fig. 1).

Discussion

In general IIH is considered a benign condition with a favorable long-term outcome. It may, however, be complicated by severe visual loss [9]. An overall rate of visual impairment between 10 and 20% is indicated by prior studies [9, 29]. As the disease and associated progressive visual loss can be asymptomatic for a long time, it poses a challenge in patient follow-up. Signs and symptoms at time of diagnosis cannot predict the risk of recurrence or visual deterioration [41] and further knowledge is thus needed to establish recommendations for future disease management and follow-up.

The relapse rate in this prospective long-term study of 18 IIH patients was 28%. This is somewhat less than a relapse rate of 38.4% reported by Kesler et al. [17]. The mean observation period in their study, however, was 6.2 years compared to 21.1 months in our study. In another retrospective study by Shah et al. covering an observation period of 10 years the recurrence rate was only 15% [34]. The lower rate can probably, and at least partly, be explained by a more strict definition of relapse. Shah et al. defined relapse as a return of signs and symptoms after resolution of papilledema and being off medication for at

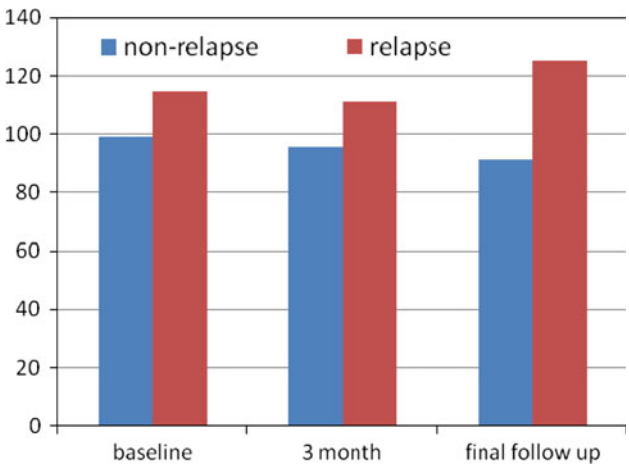

Fig. 1 Weight changes in kg from baseline to follow-up. Mean body weight (kg) at baseline, 3-month and final follow-up displayed for respectively relapse and non-relapse patients. The patient with continuos disease is included in the relapse group

least 6 months. The present study and the one by Kesler et al. did not request any medication free period in the relapse definition. Relapse rates of IIH have been reported in yet other and older studies (1966–1990) (with less well defined criteria of relapse) at levels between 6 and 19% [2, 9, 22, 43].

Among the five patients with relapse in our study only one experienced symptoms (relapse of continuous headache of moderate to high intensity and deficits in memory and concentration) at a level that caused the patient to consult a physician. Two patients were completely asymptomatic and the remaining two had paid no attention to their symptoms (intermittent headaches and episodes of TVO).

In contrast daily or frequent headaches were reported by 42% of patients in the non-relapse group as was pulsatile tinnitus. Unfortunately, the headache profile of IIH is not pathognomic as it mimics the primary headaches. Like previous studies [24, 40, 42] we found no features that separated the initial IIH-headaches from episodic migraine or chronic tension-type headache. Detailed characteristics of headache in prior follow-up studies are lacking. We hypothesize that headache and other symptoms are poor markers of disease activity.

IIH is closely associated with obesity, and weight reduction has been shown to improve the rate of recovery and prognosis in overweight patients [18, 26, 35, 41, 44]. At baseline patients entered a course of dietary recommendations and follow-up visits resulting in an overall initial weight loss [37]. Despite continuous information of the correlation between weight loss and prognosis the long-term effect was poor. Apart from two patients with major weight losses due to either bariatric surgery or psychiatric illness, only another two had a sustained weight loss of >4%. Only one patient achieved a normal BMI while 14 (78%) were still obese (BMI > 30 kg/m^2). Three patients presenting with a relapse had even gained significant weight >17 kg (>13% of body weight). Patients presenting with relapse at final follow-up had higher baseline BMI and in addition gained significant weight compared to patients without relapse. This demonstrates the importance of and the difficulties in achieving and maintaining long-term weight loss. Far more detailed and controlled weight reduction programs are needed if weight loss is aimed to be a realistic and consistent treatment strategy.

The main risk of IIH is irreversible visual impairment. Visual loss caused by IIH is often insidious and may appear months or years after initial symptoms. Long-term studies report visual impairment at rates between 10 and 20% [9, 29]. In the present study visual function in terms of visual fields and visual acuity improved from baseline to follow-up and in general the outcome was good. At follow-up VA was normal in 94% of eyes and subnormal in the remaining 6%. Visual fields were normal in 79% of eyes and subnormal in 12%. In the remaining three eyes (9%) visual fields were moderately affected. Only one of the eyes were, however, considered to have true visual field affection, as defects in one patient (two eyes) were suspected to be functional.

At final follow-up RNFL and RT of IIHWP patients without relapse of papilledema were significantly thinner than in the healthy controls, although optic nerve atrophy was only clinically detectable in one patient. This important finding indicates that axonal loss might be more widespread than previously suspected and might occur even in apparently effectively treated IIH.

Axonal nerve fiber loss becomes evident on OCT only after papilledema resolves. The point at which atrophy appears is, therefore, difficult to define. Most likely it appears initially before papilledema has resolved significantly. Our study and similar findings reported by Laemmer et al. [19], indicating early retinal axonal nerve fiber loss, suggest that early and aggressive treatment of IIH is indicated even in cases of unaffected visual parameters.

The present study did not include surgical interventions. CSF diversion procedures (ventriculoperitoneal and lumboperitoneal shunting) and optic nerve sheath fenestration (ONSF) are currently the mainstay of interventions when medical therapy is insufficient. In patients with acute visual deterioration or progressive visual loss unresponsive to medical therapy surgical interventions should be considered promptly [39].

The procedures are, however, invasive and associated with potential complications that may require multiple additional procedures [4, 6–8, 16, 27, 30]. In patients without detectable visual defects the overall benefit of surgical intervention thus most likely does not outweigh the disadvantages.

The present findings with subclinical optic atrophy and unfavorable prognosis in a subset of IIH patients do, however, prompt reconsiderations and randomized controlled studies of medical versus surgical treatment are desirable.

Limitations of the present study are the small patient cohort and the individualized number of clinical follow-up. The follow-up did not include systematic ICP measurement and undetected relapse of intracranial hypertension cannot be completely excluded. The strength of the study is the controlled prospective design, the detailed reports of headache, and the standardized neuro-ophthalmological examination.

In conclusion, this 21-month prospective follow-up study of 18 IIH patients showed a high relapse rate. Prevalence of chronic headache was high whereas the clinical visual outcome was good. Significant headache (≥14 days/month) persisted in 42% of patients without

signs of active disease. Neither headache nor other symptoms were reliable indicators of relapse. Patients with relapse were more obese and had gained weight compared to patients without relapse.

Although the visual outcome was favorable, subclinical optic nerve atrophy was detected by OCT in apparently well treated patients. Along with the high relapse rate, our findings underline that IIH is not a benign disease and suggest that intensified medical treatment may be essential even in the absence of detectable visual field defects. Furthermore, as symptoms of relapse were vague, long term follow-up for years after initial remission is mandatory.

Acknowledgments The studies have been approved by the appropriate ethics committee and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. (2004) The International Classification of Headache Disorders: 2nd edn Cephalalgia 24 (Suppl 1):9–160
2. Arienta C, Caroli M, Balbi S, Parma A, Calappi E, Massei R (1990) Clinical evaluation and long-term follow-up in 16 patients with pseudo tumour cerebri. Acta Neurochir Suppl (Wien) 51:369–371
3. Arseni C, Simoca I, Jipescu I, Leventi E, Grecu P, Sima A (1992) Pseudotumor cerebri: risk factors, clinical course, prognostic criteria. Rom J Neurol Psychiatry 30:115–132
4. Banta JT, Farris BK (2000) Pseudotumor cerebri and optic nerve sheath decompression. Ophthalmology 107:1907–1912
5. Binder DK, Horton JC, Lawton MT, McDermott MW (2004) Idiopathic intracranial hypertension. Neurosurgery 54:538–551
6. Borgbjerg BM, Gjerris F, Albeck MJ, Borgesen SE (1995) Risk of infection after cerebrospinal fluid shunt: an analysis of 884 first-time shunts. Acta Neurochir (Wien) 136:1–7
7. Borgbjerg BM, Gjerris F, Albeck MJ, Hauerberg J, Borgesen SE (1995) Frequency and causes of shunt revisions in different cerebrospinal fluid shunt types. Acta Neurochir (Wien) 136:189–194
8. Brazis PW (2009) Surgery for idiopathic intracranial hypertension. J Neuroophthalmol 29:271–274
9. Corbett JJ, Savino PJ, Thompson HS, Kansu T, Schatz NJ, Orr LS, Hopson D (1982) Visual loss in pseudotumor cerebri. Follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss. Arch Neurol 39:461–474
10. Digre KB, Nakamoto BK, Warner JE, Langeberg WJ, Baggaley SK, Katz BJ (2009) A comparison of idiopathic intracranial hypertension with and without papilledema. Headache 49:185–193
11. Durcan FJ, Corbett JJ, Wall M (1988) The incidence of pseudotumor cerebri. Population studies in Iowa and Louisiana. Arch Neurol 45:875–877
12. Friedman DI (2008) Pseudotumor cerebri presenting as headache. Expert Rev Neurother 8:397–407
13. Friesner D, Rosenman R, Lobb BM, Tanne E (2011) Idiopathic intracranial hypertension in the USA: the role of obesity in establishing prevalence and healthcare costs. Obes Rev 12:e372–e380
14. Frisen L (1982) Swelling of the optic nerve head: a staging scheme. J Neurol Neurosurg Psychiatry 45:13–18
15. Giuseffi V, Wall M, Siegel PZ, Rojas PB (1991) Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. Neurology 41:239–244
16. Goh KY, Schatz NJ, Glaser JS (1997) Optic nerve sheath fenestration for pseudotumor cerebri. J Neuroophthalmol 17:86–91
17. Kesler A, Hadayer A, Goldhammer Y, Almog Y, Korczyn AD (2004) Idiopathic intracranial hypertension: risk of recurrences. Neurology 63:1737–1739
18. Kupersmith MJ, Gamell L, Turbin R, Peck V, Spiegel P, Wall M (1998) Effects of weight loss on the course of idiopathic intracranial hypertension in women. Neurology 50:1094–1098
19. Laemmer R, Heckmann JG, Mardin CY, Schwab S, Laemmer AB (2010) Detection of nerve fiber atrophy in apparently effectively treated papilledema in idiopathic intracranial hypertension. Graefes Arch Clin Exp Ophthalmol 248:1787–1793
20. Lepore FE (1992) Unilateral and highly asymmetric papilledema in pseudotumor cerebri. Neurology 42:676–678
21. Lipton HL, Michelson PE (1972) Pseudotumor cerebri syndrome without papilledema. JAMA 220:1591–1592
22. Lysak WR, Svien HJ (1966) Long-term follow-up on patients with diagnosis of pseudotumor cerebri. J Neurosurg 25:284–287
23. Marcelis J, Silberstein SD (1991) Idiopathic intracranial hypertension without papilledema. Arch Neurol 48:392–399
24. Mathew NT, Ravishankar K, Sanin LC (1996) Coexistence of migraine and idiopathic intracranial hypertension without papilledema. Neurology 46:1226–1230
25. Murphy TP (1991) Otologic manifestations of pseudotumor cerebri. J Otolaryngol 20:258–261
26. Newborg B (1974) Pseudotumor cerebri treated by rice reduction diet. Arch Intern Med 133:802–807
27. Plotnik JL, Kosmorsky GS (1993) Operative complications of optic nerve sheath decompression. Ophthalmology 100:683–690
28. Radhakrishnan K, Ahlskog JE, Cross SA, Kurland LT, O'Fallon WM (1993) Idiopathic intracranial hypertension (pseudotumor cerebri). Descriptive epidemiology in Rochester, Minn, 1976–1990. Arch Neurol 50:78–80
29. Radhakrishnan K, Thacker AK, Bohlaga NH, Maloo JC, Gerryo SE (1993) Epidemiology of idiopathic intracranial hypertension: a prospective and case-control study. J Neurol Sci 116:18–28
30. Reddy GK, Bollam P, Shi R, Guthikonda B, Nanda A (2011) Management of adult hydrocephalus with ventriculoperitoneal shunts: long-term single-institution experience. Neurosurgery 69:774–781
31. Round R, Keane JR (1988) The minor symptoms of increased intracranial pressure: 101 patients with benign intracranial hypertension. Neurology 38:1461–1464
32. Rowe FJ (2011) Assessment of visual function in idiopathic intracranial hypertension. Br J Neurosurg 25:45–54
33. Rowe FJ, Sarkies NJ (1998) Assessment of visual function in idiopathic intracranial hypertension: a prospective study. Eye (Lond) 12(Pt 1):111–118
34. Shah VA, Kardon RH, Lee AG, Corbett JJ, Wall M (2008) Long-term follow-up of idiopathic intracranial hypertension: the Iowa experience. Neurology 70:634–640
35. Sinclair AJ, Burdon MA, Nightingale PG, Ball AK, Good P, Matthews TD, Jacks A, Lawden M, Clarke CE, Stewart PM, Walker EA, Tomlinson JW, Rauz S (2010) Low energy diet and intracranial pressure in women with idiopathic intracranial hypertension: prospective cohort study. BMJ 341:c2701
36. Skau M, Milea D, Sander B, Wegener M, Jensen R (2011) OCT for optic disc evaluation in idiopathic intracranial hypertension. Graefes Arch Clin Exp Ophthalmol 249:723–730

37. Skau M, Sander B, Milea D, Jensen R (2011) Disease activity in idiopathic intracranial hypertension: a 3-month follow-up study. J Neurol 258:277–283
38. Sorensen PS, Thomsen AM, Gjerris F (1986) Persistent disturbances of cognitive functions in patients with pseudotumor cerebri. Acta Neurol Scand 73:264–268
39. Thambisetty M, Lavin PJ, Newman NJ, Biousse V (2007) Fulminant idiopathic intracranial hypertension. Neurology 68:229–232
40. Wall M (1990) The headache profile of idiopathic intracranial hypertension. Cephalalgia 10:331–335
41. Wall M, George D (1991) Idiopathic intracranial hypertension. A prospective study of 50 patients. Brain 114:155–180
42. Wang SJ, Silberstein SD, Patterson S, Young WB (1998) Idiopathic intracranial hypertension without papilledema: a case-control study in a headache center. Neurology 51:245–249
43. Weisberg LA (1975) Benign intracranial hypertension. Medicine (Baltimore) 54:197–207
44. Wong R, Madill SA, Pandey P, Riordan-Eva P (2007) Idiopathic intracranial hypertension: the association between weight loss and the requirement for systemic treatment. BMC Ophthalmol 7:15