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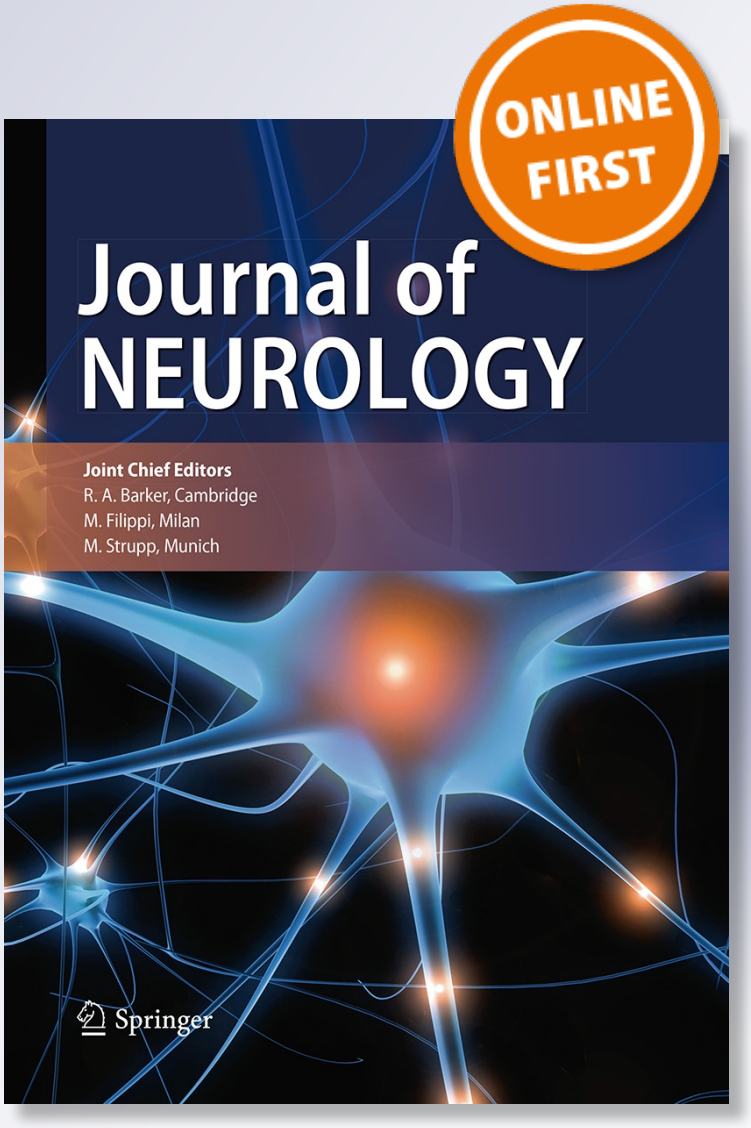

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ORIGINAL COMMUNICATION

CSF pressure, papilledema grade, and response to acetazolamide in the Idiopathic Intracranial Hypertension Treatment Trial

Jorge C. Kattah[1] · John H. Pula[2] · Luis J. Mejico[3] · Michael P. McDermott[4] · Mark J. Kupersmith[5] · Michael Wall[6]

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Abstract Previous reports suggest an association between the degree of optic nerve head edema and CSF pressure (CSFp) in idiopathic intracranial hypertension (IIH). We hypothesized that CSFp would be associated with Frisén papilledema grade (FPG) and other clinical features, and that FPG would modify the CSFp response to acetazolamide in participants in the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT). In the IIHTT, eligible patients underwent lumbar puncture (LP) prior to enrollment and were randomly assigned to one of two treatment groups: acetazolamide plus supervised diet or placebo plus supervised diet. Trial eligibility required baseline CSFp $\geq$250 mm H_2O or $\geq$200 mm H_2O with compelling clinical or imaging IIH findings. Associations between CSFp and FPG and other clinical features were examined at baseline. The effect of acetazolamide on 6-month change in CSFp was examined in those with low FPG (grades I–III) and those with high FPG (grades IV–V) at baseline. All 165 enrolled subjects had a baseline LP and 85 had an LP at 6 months. There was an association between CSFp and FPG at baseline: CSFp was more elevated in subjects with high FPG (378 $\pm$ 90 mm H_2O, $n = 50$) than in subjects with low FPG (331 $\pm$ 77, $n = 115$, $p = 0.002$). At 6 months, acetazolamide had a similar effect on CSFp in subjects with high FPG (-79.9 mm H_2O) and in subjects with low FPG (-50.9 mm H_2O, $p = 0.50$). We found a modest association between CSFp and FPG. Acetazolamide had a beneficial effect on CSFp regardless of baseline FPG.

Keywords CSF pressure · Idiopathic intracranial hypertension · Papilledema grade · Mild visual field loss · Effect of acetazolamide

Introduction

In the Idiopathic Intracranial Hypertension Treatment Trial (IIHTT), significant reductions in cerebrospinal fluid opening pressure (CSFp) and Frisén papilledema grade (FPG), and significantly improved quality of life measures and visual field perimetric mean deviation (PMD) at 6 months provided clear evidence of the beneficial effect of acetazolamide in IIH patients with mild visual loss [1–3]. Reports of case series have described that higher CSFp is associated with worse FPG and optical imaging measures of optic nerve head swelling [4, 5]. Furthermore, clinicians often consider the degree of CSFp elevation important for judging the severity of the disease and the treatment needed. To our knowledge, there are no prospective studies in patients with IIH and visual field loss which have examined the associations between elevated CSFp and IIH symptoms

For the NORDIC Idiopathic Intracranial Hypertension Study Group.

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and findings. In a retrospective study of fulminant IIH with significant vision loss at presentation, the mean CSFp was 541 mm H_2O with a range of 290–700 mm H_2O [6].

We acknowledge that in individual patients CSF pressure varies substantially throughout the day [7, 8], but our large cohort of prospectively collected data from the IIHTT provided an opportunity to examine the relationships between CSFp and the clinical features of IIH. We hypothesized that higher CSFp would be associated with higher FPG and worse IIH characteristics, as well as worse clinical outcome. We also examined the effect of acetazolamide on CSFp in two subgroups of participants: low FPG and high FPG.

Methods

This IIHTT was registered prior to official enrollment (identifier NCT01003639). The study was approved by the local IRB at each site and was performed in accordance with the ethical standards outlined in the Declaration of Helsinki. Newly diagnosed IIH patients with mild visual loss who satisfied eligibility criteria for the IIHTT [1–3] were randomized to receive acetazolamide (ACZ) or matching placebo; all participants also received low sodium, weight reduction diet. All participants underwent MRI with exclusion of other causes of increased intracranial pressure (ICP) and all had normal CSF contents. CSFp was measured in all participants via lumbar puncture (LP). The procedure was performed via the study protocol using one of three procedures for needle placement: (1) under fluoroscopic guidance in the prone position; (2) direct viewing at the bedside with the subject in the lateral decubitus position; and (3) direct viewing with the subject in the sitting position. After needle placement, the subject was placed in the lateral decubitus position with legs extended and head at the height of the needle, and the pressure was read via a manometer perpendicular to the horizontal. Study entry required opening pressure $\geq$250 mm H_2O, but an opening pressure of 200–250 mm H_2O was permitted if the subject had associated compelling clinical and/or MRI findings suggestive of IIH [1–3]. Subjects were encouraged to undergo a second LP at 6 months with the goals of assessing the effect of ACZ on CSFp and examining the associations between CSFp and other clinical outcomes.

The associations between CSFp and clinical IIH features at baseline were evaluated using Spearman's rank correlation coefficients; the clinical features examined included FPG, PMD, and visual acuity (number of correct letters with ETDRS charts) in the study eye (defined as the eye with the worst PMD at baseline), optical coherence tomography (OCT) measurement (in 126 subjects) of optic nerve head volume (ONHV), retinal nerve fiber layer (RNFL) thickness, and total retina thickness (TRT), number of headache days per month, and average headache severity (measured on a 0–10 scale). Mean CSFp was compared between groups of subjects defined by FPG (low grade, I–III vs. high grade, IV–V) and by presence/absence of pulsatile tinnitus, esotropia, and transient visual obscurations (TVO) at baseline using *t* tests. A Chi-square test was used to compare the percentages of subjects with CSFp $\geq$350 mm H_2O between those with FPG I–III and those with FPG IV–V at baseline. An analysis of covariance model was used to assess the effect of ACZ on 6-month change in CSFp in those with low FPG and those with high FPG; the model included treatment group, FPG (low vs. high), the interaction between treatment group and FPG, and baseline CSFp.

Results

The average age of the 165 IIHTT participants (161 women and 4 men) was 29 years (range 18–52 years). Baseline characteristics were comparable in the ACZ and placebo groups [1–3]. The distribution of FPG in the study eye was as follows: grade I, 12 %; grade II, 33 %; grade III, 24 %; grade IV, 27 %; grade V, 3 %. The mean baseline opening CSFp was 345.6 ± 83.5 mm H_2O overall, 348.9 ± 94.1 mm H_2O in the ACZ group ($n = 86$), and 342.0 ± 70.7 mm H_2O in the placebo group ($n = 79$). There was a mild correlation between baseline CSFp and FPG in the study eye ($r = 0.28$, $p = 0.0002$). The mean baseline CSFp was more elevated for subjects with high FPG (378.3 ± 89.9 mm H_2O, $n = 50$) than for subjects with low FPG (331.3 ± 76.8 mm H_2O, $n = 115$, $p = 0.002$) in the study eye (Fig. 1). The CSFp was $<$350 mm H_2O in 92 subjects (56 %) and $\geq$350 mm H_2O in 73 subjects (44 %) at baseline. A baseline CSFp $\geq$350 mm was more frequent with high FPG (29 subjects, 58 %) than with low FPG (44 subjects, 38 %, $p = 0.02$). The CSFp showed mild correlations at baseline with OCT ONHV ($r = 0.23$, $p = 0.01$), RNFL thickness ($r = 0.22$, $p = 0.02$), and TRT ($r = 0.23$, $p = 0.01$) in the study eye. The CSFp at baseline was not associated with headache days per month ($r = 0.06$, $p = 0.46$), headache severity ($r = 0.11$, $p = 0.17$), study eye PMD ($r = -0.07$, $p = 0.40$) or visual acuity ($r = 0.11$, $p = 0.15$), or the presence of pulsatile tinnitus [343.0 ± 81.0 with pulsatile tinnitus ($n = 86$) vs. 348.4 ± 86.6 without pulsatile tinnitus ($n = 79$), $p = 0.68$]. The mean CSFp at baseline was higher in subjects with esotropia (403.0 ± 102.9, $n = 7$) than in those without esotropia (343.0 ± 82.0, $n = 158$, $p = 0.18$) and in subjects with transient visual obscurations (TVO) (353.2 ± 85.6, $n = 112$) than in those without TVO (329.4 ± 77.4, $n = 53$, $p = 0.08$), but these differences were not statistically significant.

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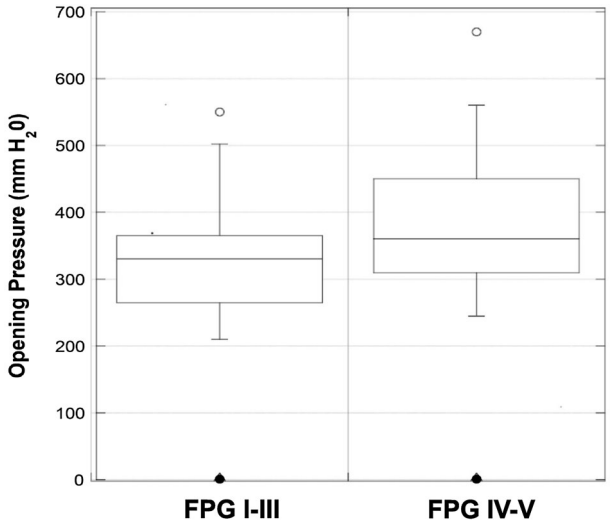

Fig. 1 Distribution of CSF opening pressure by Frisen papilledema grade (FPG) (I–III vs IV–V) in the worst affected eye at baseline. The distributions are represented by *boxplots*, with the *line* inside the box indicating the median, the bottom and top of the box indicating the 25th and 75th percentiles, respectively, and the *lines* protruding from the *box* indicating the range of the data. *Outliers* are displayed as *circles* outside the range if they fall more than 1.5 interquartile ranges beyond the nearest quartile

As previously reported [1], the adjusted mean CSFp at month 6 was 244.9 mm H_2O in the ACZ group ($n = 47$) and 304.8 mm H_2O in the placebo group ($n = 38$). The mean change in CSFp was −112.3 mm H_2O in the ACZ group and −52.4 mm H_2O in the placebo group (treatment effect −59.9 mm H_2O; 95 % CI −96.4 to −23.4 mm H_2O, $p = 0.002$). This treatment effect was fairly consistent in those with low FPG (mean change of −99.5 mm H_2O with ACZ vs. −48.6 mm H_2O with placebo; treatment effect −50.9 mm H_2O; 95 % CI −92.7 to −9.2 mm H_2O, $p = 0.02$) and in those with high FPG (mean change of −141.9 mm H_2O with ACZ vs. −62.0 mm H_2O with placebo; treatment effect −79.9 mm H_2O; 95 % CI −154.9 to −5.0 mm H_2O, $p = 0.04$), with no significant difference between these treatment effects ($p = 0.50$).

A total of 250 lumbar punctures were performed (165 at baseline and 85 at month 6). No significant LP complications occurred. Eighteen subjects reported a post-LP headache and 12 of these were reported within the first 24 h after LP. All patients with post-LP syndrome recovered, except one in whom recovery status was unknown.

Discussion

The CSFp was mildly but significantly associated with FPG in the study eye at baseline. In addition, the OCT outcomes, selected to reflect swelling in the optic nerve head and peripapillary retina due to papilledema, also showed mild but significant correlations with CSFp at baseline [4, 5]. None of the other clinical features of IIH, including visual acuity and PMD, were associated with CSFp. Our results suggest that structural changes in the optic nerve may be a more sensitive indicator of higher CSFp, although the associations between CSFp and OCT outcomes should be interpreted with some caution given the limitations of multiple statistical testing.

IIHTT subjects with high FPG more frequently had very high CSFp (≥350 mm H_2O) than subjects with low FPG. We found a greater CSFp decline after treatment with acetazolamide among subjects with high FPG than among subjects with low FPG; however, the subgroup difference in treatment effect did not reach statistical significance ($p = 0.50$). The power to detect a modest subgroup difference in treatment effect was quite low, particularly given the small number of subjects who agreed to an LP at month 6 ($n = 85$). Our observations are limited to patients who have mild visual field deficits. A different approach may be appropriate in treating high FPG and high CSF pressure IIH patients if the visual field is worse than that specified in our study entry criteria. Similarly, other indicators of afferent visual function impairment might prompt CSF shunting or optic nerve sheath decompression. The optimal management of IIH patients with moderate to severe visual loss awaits further investigation.

Although IIH symptoms and findings are associated with raised ICP, the amount of elevation, as measured by a single lumbar puncture, does not appear to parallel their frequency or severity. CSFp can fluctuate widely over 24 h in IIH and in conditions with other causes of increased ICP [7, 8], and it is possible that prolonged ICP recording would detect stronger associations. Given our data and the ability of ACZ to improve FPG grade and CSFp, having a high CSFp or high FPG is not an indication for early surgical intervention in IIH patients with mild vision loss.

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Conflicts of interest There is no conflict of interest for any of the authors.

Ethical standard This study was approved by the appropriate Ethics Committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

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