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ANALYSIS OF CEREBROSPINAL PULSE WAVE AMPLITUDE AND CORRELATION WITH OPTIC DISC MORPHOLOGY IN IDIOPATHIC INTRACRANIAL HYPERTENSION

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Relatore

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The present work was carried out at the Neurological Clinic, Policlinico University Hospital, Catania, Italy.

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Abbreviations

ABBREVIATIONS

IIH: Intracranial Idiopathic Hypertension,

ICP: Intracranial Pressure

MRI: Magnetic Resonance Imaging,

MRV: Magnetic Resonance Venography,

Ts: Transverse sinuses,

CSF: Cerebrospinal Fluid,

CSFp: Cerebrospinal Fluid Pressure,

CSFop: Opening Cerebrospinal Fluid Pressure,

PWA: Pulse Wave Amplitude,

OCT: Optic Coherence Tomography,

ONH: Optic Nerve Head,

RNFL: Retinal Nerve Fiber Layer,

BMI: Body Mass Index,

ONSAS: Optic Nerve Subaracnoid Space,

IOP: Intraocular Pressure;

C/D: Cup-to-disc ratio.

Abstract

Aims: Aims of this thesis are to evaluate the features of cerebrospinal fluid (CSF) pulse wave amplitude (pwa) of IIH by lumbar measurements of CSF pressure during intracranial pressure (ICP) monitoring, and to correlate the CSF pwa magnitude to the level of optic disc damage in patients suffering from IIH.

Methods: The thesis consists of two parts. Part I assesses the CSF pwa value in IIH by short-term (1-hour) monitoring by lumbar puncture and compared with an age-matched control group. CSF pwa values were collected with the same method of analisys in age-matched controls and IIH patients. Part II assesses optic disc morphology in the same patients by using Optic Coerence Tomography and than describes Optic disc parameters associated with raised CSF pressure and raised CSF pwa values in IIH with and without papilledema groups.

Results: We found that the 75% of IIH patients have raised CSF mean pwa as compared to control group. Of the 75% of IIH patients that presented raised CSF pwa during short-term monitoring, the 57.3% was suffering from IIHWP and the 42.7% was IIHWOP. OCT measurements collected in IIHWP patients, suffering from both raised CSF mean pressure and raised CSF mean pwa values, showed all abnormal neuroretinal parameters: rim area (mean ± SD:1.8 ± 0.2 mm^2, normal value: 1.6 ± 0.0; p=0.009) and thickness (776.8 ± 168.7 μm, normal value: 325.2 ± 7.7; p=0.009), cup volume (0.02 ± 0.0 mm^3, normal value: 0.2 ± 0.0; p=0.008) and cup-to-disc ratio (C/D) (0.02 ± 0.01, normal value: 0.6 ± 0.1; p=0.008), retinal nerve fiber

layer (RNFL) (221 ± 91.1 μm, normal value: 101.2 ± 2.4; p=0.009). OCT measurements collected in IIHWOP patients suffering from raised CSF mean pressure, showed abnormal both rim area (1.5 ± 0.2 mm^2, normal value: 1.6 ± 0.0; p=0.009) and thickness (640.2 ± 142.8 μm, normal value: 325.2 ± 7.7; p=0.009), cup volume (0.1 ± 0.06 mm^3, normal value: 0.2 ± 0.0; p=0.04) and C/D (0.1 ± 0.01, normal value: 0.6 ± 0.1; p=0.008), but rather normal RNFL (101.6 ± 5.6 μm, normal value: 101.2 ± 2.4; p=0.7). Furthermore, we found statistical significance when we correlated CSF mean pressure with RNFL (r=0.60, p=0.042) and CSF pwa with RNFL (r=0.77, p=0.028; Fig.3b) collected form all participants. No correlation was found for CSF opening pressure and RNFL (r=0.34; p=0.06) among patients.

Conclusions: Our data show that, during CSF short-term monitoring by lumbar access, both CSF mean pressure and CSF mean pwa are increased in IIH group if compared to control group as expression of reduced intracranial compliance. Neuroretinal structures are more damaged in IIH patients suffering from both raised CSF mean pressure and CSF mean pwa.
The lumbar CSFP pwa could be used to evaluate the intracranial compliance and the evolution of optic nerve head damage in IIH patients.

SECTION I:

CSF MEAN PRESSURE AND MEAN PULSE WAVE AMPLITUDE DURING SHORT-TERM MONITORING WITH LUMBAR PUNCTURE

Background

Intracranial idiopathic hypertension (IIH) is a syndrome characterized by raised intracranial pressure (ICP) without space occupying lesions or other known causes. In 1893, Quincke for the first time described a group of patients suffering from signs and symtoms of raised intracranial hypertension without any CSF pathological changes that he defined “meningitis serosa” (Quincke H. 1893). Later, Dandy in 1937 described another group of patients not dissimilar to Quincke’s patients group (Dandy WE. 1937).

The syndrome can develop at any stage of life, but IIH is most frequently observed in young women of childbering age (Wall M. 2010. Digre KB. 2010). Although it is considered a rare disorder of CSF pressure, IIH is extimated to become more frequent according to the increased prevalence of obesity in the world (Caballero B. 2007). However, patients who present raised ICP after administration of some medications, or who showed bilateral transverse venous sinus stenosis in MR venography (MRV) are conventionally defined IIH (Higgins JNP, et al. 2004. Frab RI, et al. 2003. Bono F, et al. 2006).

IIH typically presents with severe headache, pulsatile tinnitus, transient visual obscuration, blurred or double vision. Papilledema is the most common sign of IIH and can be detected by a routine ophtalmologic examination. Papilledema can evolve in an insidious and slowly progressive visual loss and if not treated, as it happens in chronic condition, can be associated to optic atrophy and permanent visual loss (Digre KB. 2003).

Cerebrospinal fluid (CSF) opening pressure value is the main parameter used to make the diagnosis in patients suffering from IIH (box 1.) (Headache Classification Committee of the International Headache Society (IHS) 2013).

Box 1. Diagnostic criteria for adult IIH*

a) Papilloedema

b) Normal neurological examination except for cranial nerve abnormalities.

c) Neuroimaging: Normal brain parenchyma without hydrocephalus, mass or structural lesion and no abnormal meningeal enhancement or venous sinus thrombosis on MRI and MR venography; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used.

d) Normal CSF composition

e) Elevated CSF opening pressure (≥25 cmH_2O) in a properly performed lumbar puncture.

f) A diagnosis of IIH is definite in patients fulfilling A–E; the diagnosis is probable if A–D are met but the CSF pressure is lower than specified.

*Adapted from the 2013 revised diagnostic criteria for IIH (IHS, 2013).

CSF pressure during opening phase represents the mean value obtained in a 6 seconds window, after 4 minutes from the beginning of CSF recording but, sometimes this short time period is not enough to observe the raised CSF pressure in these patients. Since CSF pressure is not a static but a dynamic circulatory system, some Authors used to record ICP during a long-term monitoring of 7 hours (overnight) (Gucer G. Vierenstein L. 1978. Czosnyka M, Pickard JD. 2004) or 24 hours to improve this analysis (Torbey MT, et al. 2004). But, in these cases, the technique used to record CSF pressure could be rather invasive by using intracranial or lumbar epidural catheters. Recently, Bono et al. have decribed a lesser invasive techique for monitoring CSF mean pressure at lumbar level in a shorter period of about 1-hour (Fig. 1) that improves CSF analysis by recording pathological waves often observed in IIH patients (Bono F, et al. 2010).

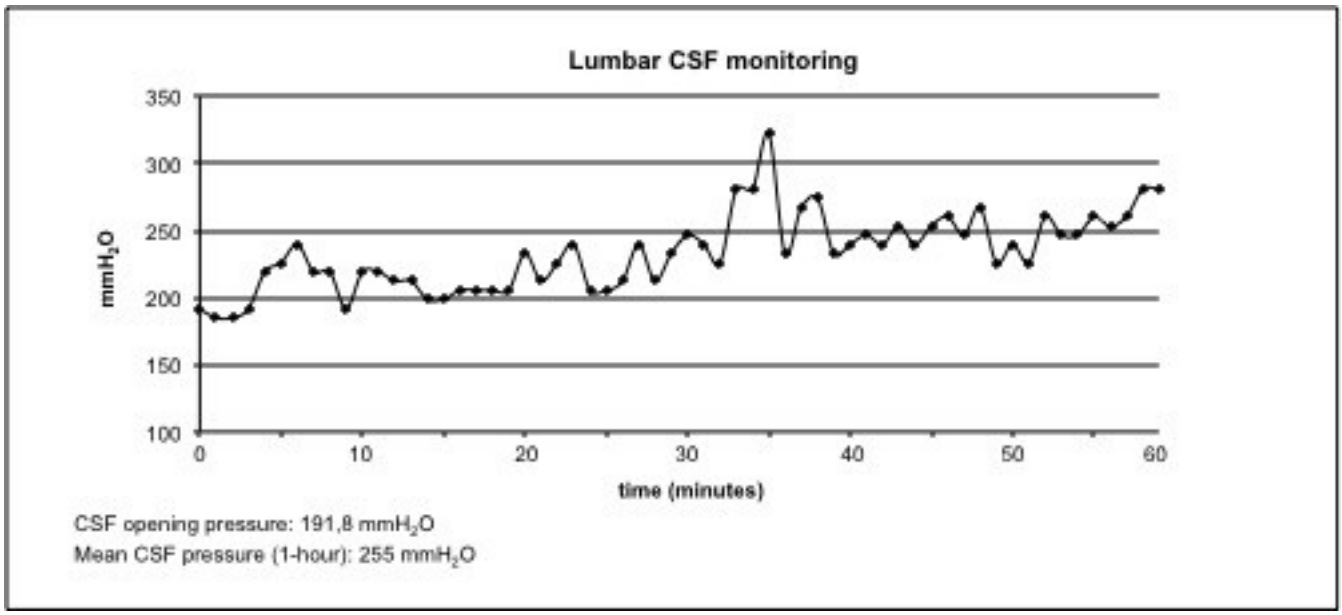


Figure 1. CSF pressure monitoring (1-hour) through the lumbar access in a patient suffering from IIH. After starting the procedure, CSF opening pressure evaluated at the 4th minute showed values under normal limits (normal value<200 mmH_2O) (Bono F, et al. 2010. Eide PK, Kerty E. 2011). Twenty minutes later, the CSF pressure increased progressively until it reaches pathological values above 250 mmH_2O.

Although CSF opening and CSF mean pressure have been exhaustively studied in IIH, fewer data about CSF pulse wave amplitude (pwa) parameter in IIH have been reported.

CSF pwa represents the intracranial pressure pulsation closely related to systolic and diastolic components of arterial pressure (Bering EA Jr.1962), and it is considered a helpful CSF parameter to estimate intracranial compliance. It consists of three components: P1 is the main component of CSF pwa and it is the analogous of the arterial pulse wave of carotid artery so called “Percussion Wave” (Hurst JW, Schlant RC. 1974). Other two smaller waves have been described: P2 is named “Tidal Wave” that is the reflection wave to P1, and P3 the “Dicrotic Wave” that corresponds to the closing time of aortic valve (Gega A, et al. 1980). These smaller waves are considered the result of the “Water Hammer Phenomenon” by the venous pressure (Bering EA. 1955).

Based on its relationship with the pressure-volume curve, CSF pwa increases linearly with intracranial CSF pressure when this curve changes from the flat to the exponential zone, showing a transition from

a status of good to poor compensatory reserve (Marmarou A, et al. 1975).

Cardoso and collegues have firstly studied changes in CSF pwa shape in a group of 3 IIH patients, but their analysis consisted in the careful description of the three main components of the shape during standardized manouvers to alter the intracranial dynamic. They observed a decrement in magnitude of the P2 and P3 components in respect to P1 resulting in a change of the shape of the CSF pwa with hyperventilation or CSF withdrawal until a drop of ICP, reflecting variations in the cerebral bulk compliance (Fig. 2) (Cardoso ER, et al. 1983).

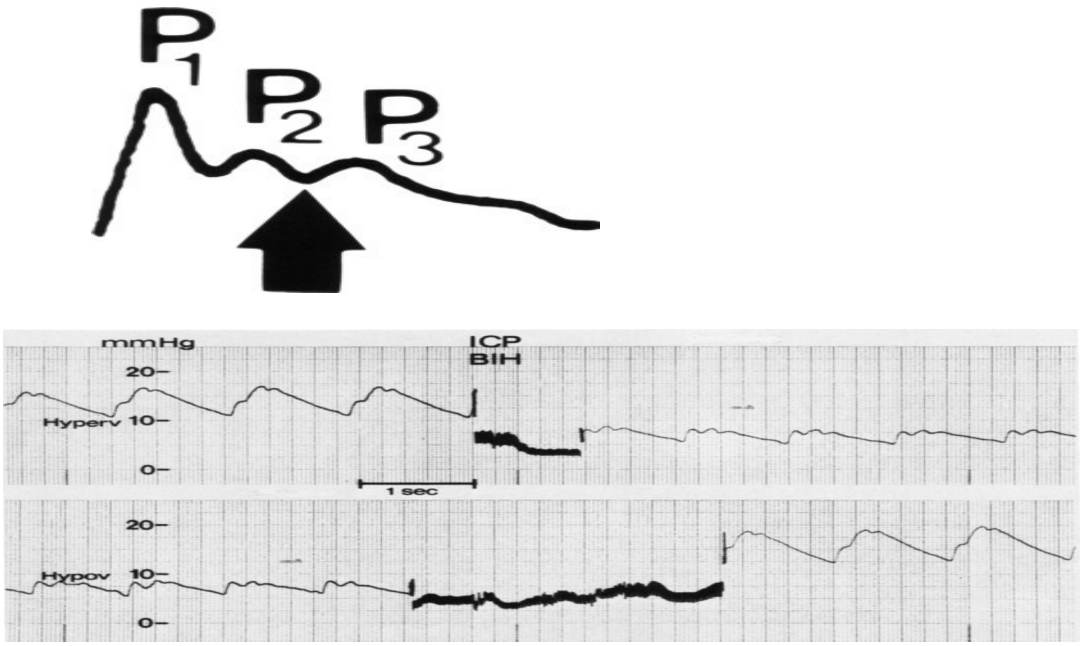


Figure 2. Images of cerebrospinal fluid pulse wave amplitude (CSF pwa). P1, P2, P3 are components of the shape of CSF pwa. P1 is the percussion wave, P2 the "Tidal wave" and P3 the dicrotic wave (A). Effect of ICP decrement after hyperventilation in a IIH patient. During intracranial hypertension P2 and P3 components are better represented than P1. Hyperventilation causes decrement of ICP that is followed by a decrease in magnitude of P2 and P3 (B). *From Cardoso ER, Rowan JO, Galbraith S. Analysis of the cerebrospinal fluid pulse wave in intracranial pressure. J Neurosurg 1983; 59:817-821.*

Recently, Eide and collegues have reported, after an over-night CSF monitoring by using an intracranial catheter, raised values of CSF pwa in 100% of IIH patients pharmacologically treated although the 50% of them had had normal ICP pressure values (Eide PK, Kerty E. 2011).
However, even though long-term monitoring is well recognized to study ICP trend and CSF pwa in CSF dynamic disorders (Eide PK, Brean A.2006. Eide PK. 2006), this invasive procedure can restrict the diffusion of the diagnostic tool in clinical practice. So far, there are no avaliable data about CSF pwa of IIH patients collected via lumbar access by using short-term (1-hour) monitoring.

Object of the study

The aim of the present study was to evaluate the CSF pwa value during opening phase and the mean value during short-term monitoring (1-hour) via lumbar access in suspected IIH patients.

Materials

Sixteen IIH patients (females, mean age ± standard deviation: 32.3 ± 10.7 years; range 21-53) underwent a CSF short-term (1-hour) monitoring, performed at the Neurological Clinic, Policlinico-University Hospital, Catania, Italy, between January 2013 and September 2015.
All patients were given the same standardized form to obtain general and neurological evaluations also incluting Body Mass Index (BMI) (weight in chilograms divided by the square of height expressed in metres).

Inclusion Criteria:

- Patients without central nervous system disease;
- Eligible patients had a normal brain MRI;

- Absence of psychoactive, cardiac, antihypertensive, or other drugs interfering with the CSF pressure;

- No evidences of current or previous cerebral venous thrombosis documented by cerebral MRV;

- CSF opening pressure >250 mmH_2O or CSF mean pressure from short-term monitoring >200 mmH_2O;

- Patients selected for the study included those with IIH with or without papilledema (confirmed by an ophtalmologic consultation);

- All patients had to provide written informed consent to participate in the study.

Patients results were compared with 12 normal age-matched subjects, selected from the database of the Department of Neurological Clinic, Policlinico-University Hospital, Catania, Italy.

Methods

The same operator performed the lumbar short-term monitoring on each patient. The lumbar puntcure was conducted with a pre-treatment with local anaesthesia (subcutaneous Lydocaine) at the L3-L4 level in lateral decubitus position. Quincke 20-Gauge needle with a three way stopcock was used during the CSF monitoring (Fig. 3a).

When the needle was introduced in the subarachnoid space at lumbar level, the hub of the needle was attached to the invasive pressure tranducer throughout a 20 centimeters long flexible tube (Fig. 3b). Then, the transducer was linked to the multiparametric monitor (Passport 2, Datascope Corporation, Mahwah, NJ, USA) and after positioned at the same horizontal level of the head, was zeroed. The monitoring was done in a silent room and the lateral decubitus was mantained for all the duration of the examination.

Figure 3. Quincke's needle for lumbar puncture has a diameter of G-20, 90 mm long and a three way stopcock (A). Invasive pressure transducer used for CSF monitoring via lumbar space, is linked both to the multiparametric monitor by a cable and to the lumbar needle by a 20-cm flexible tube.

The CSF pressure monitoring, was performed to study CSF pressure and CSF pwa in two different phases:

1. Opening pressure phase: four minutes after the beginning of the CSF pressure monitoring, CSF opening pressure (oCSFp) was recorded. The upper normal limit considered was ≤ 200 mmH_2O (Bono F, et al. 2010).
2. Short-term monitoring: from the end of the opening phase to the sixteenth minute, both the mean CSF pressure (CSF mean pressure) and the CSF mean pwa were recorded. CSF pwa was calculated as the peak to peak amplitude, where the maximum peak was the systolic peak and the minimum peak was diastolic peak of CSF pressure. The upper normal limit of CSF pwa was 54.6 mmH_2O (Eide PK, Kerty E. 2011).

   These parameters obtained from the 60-minutes monitoring were analyzed according to above mentioned normal values. The values of CSF pressure and pwa collected during artefacts period (moviments of the head or of the arms, etc.) were excluded from the CSF pressure analysis.

Statistical analisys

The computer program PC-STATA version 11 (Statcorp 4905 Lakeway Drive, College Station, Texas, USA), performed the stastical analysis. For continuos variables, the two group of patients were compared with the unpaired t-test. Significance was accepted at the 0.05 level.

Results

During the time period from 2013 to 2015, 16 IIH patients and 12 patients suffering from psychiatric and neurological diseases not related to CSF dynamic disorders, considered as control group, were studied by using CSF short-term (1hour) monitoring as a part of the diagnostic work-up. The characteristics of the 16 IIH patients are summarized in Table 1 and Table 3. Ten out of the 16 IIH patients were obeses (87.5%), 4 were overweight (25%) and 2 had normal weight (12.5%). Duration of symthoms was 14.2 ± 10.2 months (range 3-36). Fourteen out of 16 patients reported headache and all of them complained transient visual loss. Only 2 patients had permanent visual loss, and 8 patients had papilloedema (50%) as reported by the ophtalmologist consultation (Table 1). Cerebral MRV displayed bilateral stenosis in the midlateral portion of transverse sinuses (Ts) in 14 out of 16 patients, meanwhile 2 patients had normal bilateral Ts (Table 3).

Table 1.

Patient number	Age (years)	Sex	BMI	Symtoms Duration	Headache	Transient visual obscuration	Visual loss	Papilloedema
1	52	F	37	2 years	+	+	-	-
2	25	F	43	6 months	+	+	-	+
3	53	F	35,6	4 months	+	+	-	-
4	21	F	27,1	9 months	+	+	-	+
5	22	F	39,1	3 months	+	+	+	+
6	53	F	36,4	5 months	+	+	-	-
7	22	F	26,7	10 months	+	+	-	+
8	34	F	20,3	1 year	+	+	-	+
9	22	F	24,2	1 year	+	+	+	+
10	22	F	30	2 years	+	+	-	-
11	40	F	27,6	2 years	+	+	-	-
12	33	F	33,6	2 years	+	+	-	-
13	22	F	34,9	5 months	+	+	-	+
14	46	F	26,8	2 years	-	+	-	+
15	27	F	35,3	5 monyhs	+	+	-	-
16	22	F	34	3 years	+	+	-	-

BMI, Body Mass Index.

Table 2. Demografic and clinical features of controls.

Charatteristics	Results
Number Age, mean ± SD (years)	12 39.4± 12.9
Females, n (%)	9 (75)
Diseases, n (%)	Atypical facial pain, 1 (8.3) Multicranial neuropathy, 4 (33.3) Anxious and depressive syndrome, 5 (41.7) Episodic migraine, 2 (16.7)
Associated disorders, n (%)	Arterial Hypertension, 2 (16.7) Hypotiroidism, 1 (8.3)

Table 3. Radiological features and CSF analysis data of IIH patients and controls.

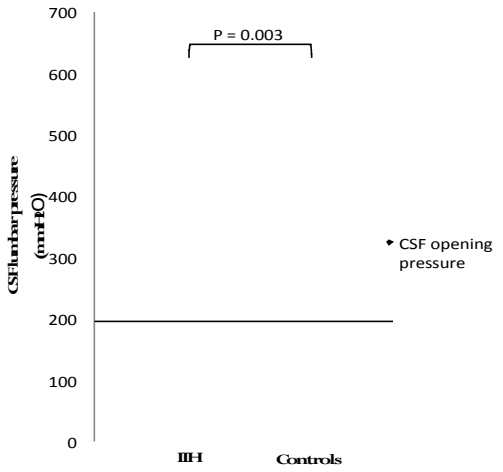
	Controls (n=12)	IIH (n=16)	P-value
Age, mean±SD	39.4±12.9	32.3±10.7	0.151
Sex, F/M	9/3	16/0	
BMI, Kg/m^2	25.6±4.8	30.8±6.9	0.006
MRI brain normal, n(%)	12 (100)	16 (100)	
MRV			
Normal bilateral transverse sinuses, n (%)	10 (83.3)	2 (12.5)	
Unilateral transverse sinus stenosis, n (%)	2 (16.7)	0	
MRV with bilateral trasverse sinuses stenosis, n (%)	0	14 (83.3)	
CSF opening pressure (mmH_2O), mean±SD	117.6±37.1	268.7±141.9	0.003
CSF mean pressure (mmH_2O), mean±SD	121.8±31.9	265.7±112.8	0.0001
CSF mean pwa (mmH_2O), mean±SD	33.4±15	108.3±87.2	0.007

BMI, Body Mass Index. MRI, Magnetic Resonance Imaging. MRV, Magnetic Resonance Venography. CSF, Cerebrospinal Fluid.
Significant differences between patients groups IIH and controls: $p<0.05$ (Mann-Whitney's U test).
Recording from 9:00 a.m. to 1:00 p.m.

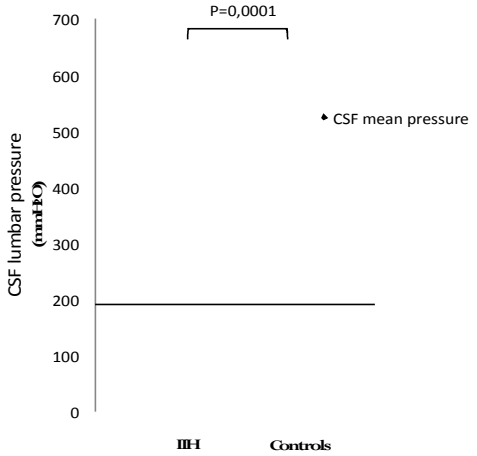
Demographic data and charatteristics of control group are reported in Table 2. One patient was obese, 4 out of 12 patients were overweight and 7 were of normal weight. However, as shown in Table 3, weight was higher in the IIH than in control group.

The CSF pressure results are shown in Table 3. At the group level, in IIH the CSF opening pressure (Fig. 4a), CSF mean pressure (Fig. 4b) and CSF mean pwa (Fig. 4e) were elevated when compared to control group.

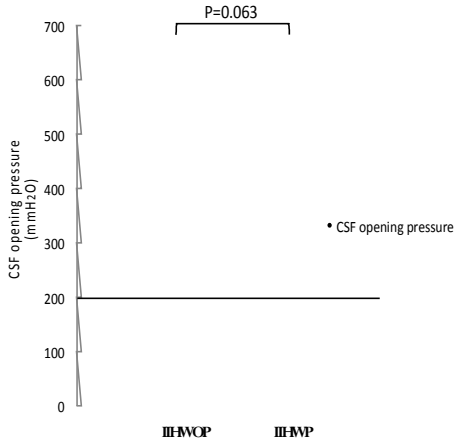
A


P = 0.003
CSF opening pressure
IIH
Controls

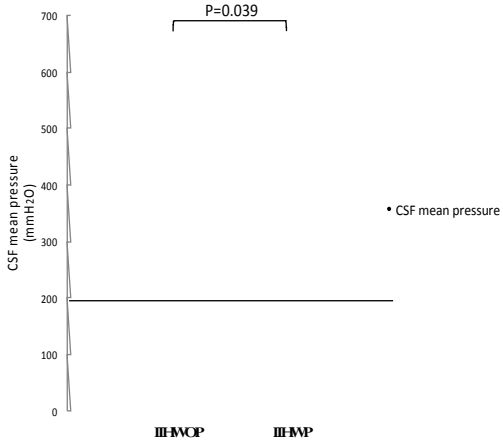
B


P=0,0001
CSF mean pressure
CSF lumbar pressure (mmH2O)
IIH
Controls

C


P=0.063
CSF opening pressure
CSF opening pressure (mmH2O)
IIHWOP
IIHWP

D


P=0.039
CSF mean pressure
CSF mean pressure (mmH2O)
IIHWOP
IIHWP

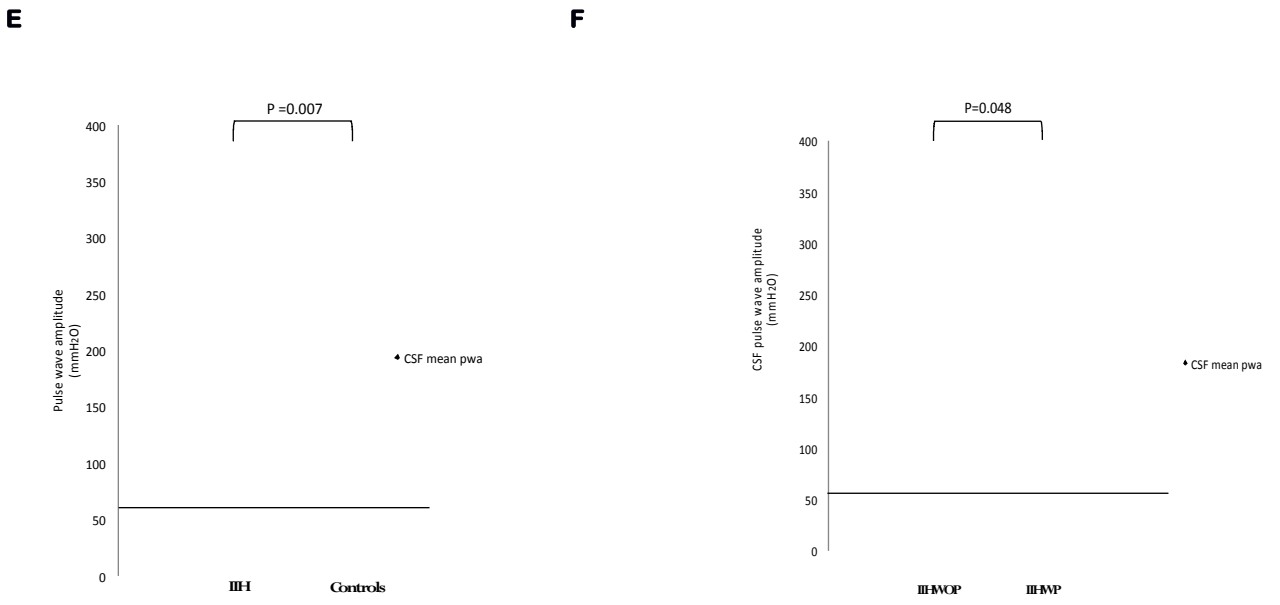


Figure 4. CSF short-term (1-hour) monitoring results of IIH and control groups are plotted. CSF pressure values in the IIH and control groups showed statistical difference both for CSF opening pressure (A) and CSF mean pressure (B). Statistical difference was observed for CSF mean pwa (E) between IIH and control groups. We divided the IIH patients into two groups according to the presence of papilloedema and the analysis showed a further significant difference as far as the CSF mean pressure and CSF mean pwa between the two groups (D-F) regards. No statistical difference was found for CSF opening pressure (C). All values were expressed in mmH_2O. Dotted horizontal lines (A-F) represent the upper normal limits.

At individual level, we reported normal CSF opening pressure (<200 mmH_2O) in 5 out of 16 IIH patients (31.3%, Fig. 4a). CSF mean pressure was elevated in all IIH patients (Fig. 4b). We founded elevated CSF mean pwa in 12 (75%) of the 16 IIH patients (Fig.4e).

When IIH patients group was divided into two subgroups according to the presence of papilloedema, at group level, both CSF mean pressure and CSF mean pwa showed significant difference since higher values were found in IIHWP (Fig. 4d-f). No differences were observed for CSF opening pressure between the two subgroups (Fig. 4c).

At the individual level, we observed that CSF mean pwa was elevated in 5 (62.5%) out of 8 IIH patients without papilloedema (WOP) and in 7 (87.5%) out of 8 IIH patients with papilloedema (WP)(Fig. 4d).

Discussion

In our IIH group, although only the 68.8% of IIH patients had raised CSF pressure during the opening phase, pathological increment of CSF mean pressure (>200 mmH_2O) was confirmed in all IIH patients after 1-hour monitoring via lumbar access. Pathological CSF mean pwa was showed in the 75% of patients in respect to the control group. Most of them, the 43.8% had IIHWP and 31.2% had IIHWOP. Our data, as reported, are not completely similar to Eide's results (Eide PK, Kerty E. 2011). These results can be explained probably with the selection of IIH group: in our group IIH patients showed a minor clinical severity (8/16 patients had papilloedema against 13/14 of Eide's work), our patients had not ever had pharmacological treatment before the CSF analysis, and after the diagnosis was made, during the follow-up, only two of them underwent the ventriculoperitoneal shunt (all patients underwent shunt surgery in Eide's work).

Abnormal CSF pwa is a typical sign of impaired intracranial compliance as already observed in Idiopathic Normal pressure Hydrocephalus (INPH) (Eide PK, Sorteberg W. 2010). According to the model of pressure-volume compensatory reserve, when intracranial compliance decreases, CSF pwa raises linearly with increment of ICP. CSF pwa originates from the intracranial blood circulation and is closely related to the R-wave of electrocardiogram (Zee CM, Shapiro K.1987) and any cerebral volume stress that acts on lateral ventricles such as brain water inbalance or increased ICP, can generate elevated CSF pwa (Zee CM, Shapiro K. 1987).

In IIH there are different potential causes responsible for the increment of CSF pwa:

1. Increased ICP leads to compression of cerebral bringing veins and as a consequence a raised venous resistence to outflow (Yada K, et al. 1973).
2. The BTSs observed in most of IIH contributes to increase CSF resistance outflow by reducing the CSF absorption into the Pacchioni's granulations (De Simone R, et al. 2010. Farb RI, et al. 2003).

3. In IIH patients, obesity can be associated to ventricular hypertrophy, increase in blood flow and circulating volume that may increase velocity of arterial blood pressure pulse wave in carotid arteries (Luaces M, et al. 2012. Urbina EM, et al. 2011).

In our cohort, the method used to study the CSF dynamic parameters was less invasive because of the lumbar access. Some Authors (Eide PK, Brean A. 2006) reported that lumbar CSF pwa recording could be considered as reliable as the ICP wave amplitude recording. Lumbar CSF pressure has already been used to study CSF dynamic disorders in INPH. In INPH, long-term monitoring of 24h or over-night monitoring for reserching raised CSF pwa (pathological values >54.6 mmH2O) (Eide PK, Brean A.2006) associated with lumbar infusion test, improve the predictive value of shunt surgery efficacy (Eide PK, Brean A. 2006). Even though lumbar measurement could understimate true CSF pwa by approximally 12.3 ± 13.7 mmH_2O as a consequence of dampening of the pulse wave traveling down the spinal canal, this understimation is lower at higher pressures so that the difference between ICP and lumbar pressure can be considered irrelevant (Eide PK, Brean A. 2006).

Furthermore, because of higher values of CSF mean pwa have been reported in pediatric patients suffering from IIHWP (Eide PK, et al. 2007), we can hypothesize that the increment of this parameter as observed in our patients, is expression of a more severe score of disease.

Conclusioni

1. CSF pressure short-term (1-hour) monitoring could be considered a good test to evaluate not only the CSF mean pressure but also the CSF mean pwa for the diagnosis of IIH. Its utility is based on the improvement of CSF analysis by catching short-term physiological fluctuation of pressure pulse amplitude.
2. Lower invasivity of this recording method could promote its use in neurological department by reducing adverse events and time of hospitalization.
3. CSF pwa could be considered a further physiological data to evaluate the severity score in IIH.