Brain Research 1644 (2016) 161–175

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/brainres

Research Report

Cortical astrogliosis and increased perivascular aquaporin-4 in idiopathic intracranial hypertension

Per Kristian Eide [a,b,*], Vigdis Andersen Eidsvaag [a,c], Erlend A. Nagelhus [b,c], Hans-Arne Hansson [d]

[a] Department of Neurosurgery, Oslo University Hospital - Rikshospitalet, Oslo, Norway
[b] Faculty of Medicine, University of Oslo, Oslo, Norway
[c] Institute of Basic Medical Sciences, University of Oslo, Norway
[d] Institute of Biomedicine, University of Gothenburg, Göteborg, Sweden

ARTICLE INFO

Article history:
Received 28 January 2016
Received in revised form
7 April 2016
Accepted 12 May 2016
Available online 14 May 2016

Keywords:
Pseudotumor cerebri
Benign intracranial hypertension
Pulsatile intracranial pressure
Astrogliosis
Aquaporin-4
Interstitial fluid disturbance

ABSTRACT

The syndrome *idiopathic intracranial hypertension* (IIH) includes symptoms and signs of raised intracranial pressure (ICP) and impaired vision, usually in overweight persons. The pathogenesis is unknown. In the present prospective observational study, we characterized the histopathological changes in biopsies from the frontal brain cortical parenchyma obtained from 18 IIH patients. Reference specimens were sampled from 13 patients who underwent brain surgery for epilepsy, tumors or acute vascular diseases. Overnight ICP monitoring revealed abnormal intracranial pressure wave amplitudes in 14/18 IIH patients, who underwent shunt surgery and all responded favorably. A remarkable histopathological observation in IIH patients was patchy astrogliosis defined as clusters of hypertrophic astrocytes enclosing a nest of nerve cells. Distinct astrocyte domains (i.e. no overlap between astrocyte processes) were lacking in most IIH biopsy specimens, in contrast to their prevalence in reference specimens. Evidence of astrogliosis in IIH was accompanied with significantly increased aquaporin-4 (AQP4) immunoreactivity over perivascular astrocytic endfeet, compared to the reference specimens, measured with densitometry. Scattered CD68 immunoreactive cells (activated microglia and macrophages) were recognized, indicative of some inflammation. No apoptotic cells were demonstrable. We conclude that the patchy astrogliosis is a major finding in patients with IIH. We propose that the astrogliosis impairs intracranial pressure-volume reserve capacity, i.e. intracranial compliance, and contributes to the IIH by restricting the outflow of fluid from the cranium. The increased perivascular AQP4 in IIH may represent a compensatory mechanism to enhance brain fluid drainage.

1. Introduction

Idiopathic intracranial hypertension (IIH), previously also named pseudotumor cerebri and benign intracranial hypertension, is a syndrome characterized by signs and symptoms associated with increased intracranial pressure (ICP) in an overweight, alert and oriented patient (Ball and Clarke, 2006). The predominant clinical symptoms are headache and visual disturbances, but tinnitus and dizziness may as well be present. Serious long-term consequences are visual impairments, including blindness. IIH has recently been associated with cognitive impairment (Kharkar et al., 2011; Yri et al., 2014), and olfactory dysfunction (Bershad et al., 2014; Kunte et al., 2013; Schmidt et al., 2012). For many victims, IIH has a large impact on the quality of life (Friesner et al., 2011; Kleinschmidt et al., 2000; Yri et al., 2012).

IIH is predominantly diagnosed in overweight fertile women (Ball and Clarke, 2006). The incidence is 1–2 per 100,000 but raises to 19/100,000 among women aged 20–44 years who are overweight. It can, however, also occur in men (about 10% of IIH cases) and in children. With increasing weight in the population and increased frequency of obese people, the incidence of IIH has increased dramatically over the recent years (Kesler et al., 2014). Hence, from 1988 to 2002, in the USA the rate of shunting for IIH increased with 320% (Curry et al., 2005), and the annual economic costs of IIH exceed 444 million US$, mostly because of frequent hospital admissions, unsatisfactory treatment options and lost productivity (Friesner et al., 2011).

The diagnostic criteria for IIH was initially specified by Dandy

Abbreviations: AQP4, aquaporin-4; AU, arbitrary units; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; ICP, intracranial pressure; IIH, idiopathic intracranial hypertension; ISF, interstitial fluid; IR, immunoreactivity; VRS, Virchow-Robin paravascular space

* Corresponding author at: Department of Neurosurgery, Oslo University Hospital – Rikshospitalet, Pb 4950 Nydalen, N-0424 Oslo, Norway.
E-mail addresses: p.k.eide@medisin.uio.no, peide@ous-hf.no (P.K. Eide).

http://dx.doi.org/10.1016/j.brainres.2016.05.024
0006-8993/

(1937), but the pathogenesis remains an enigma. It has been suggested that IIH may be caused by deficient water homeostasis, parenchymal edema, increased cerebral blood volume, excessive CSF production, compromised cerebrospinal fluid (CSF) absorption, or cerebral venous outflow obstruction (Kerty et al., 2013; Skau et al., 2006). Lumbar puncture or overnight ICP monitoring may demonstrate increased ICP, despite normal or small ventricles (Corbett and Mehta, 1983). It has been questioned whether IIH is basically a disease of the visual system or a disorder of the brain.

The main treatment of IIH includes weight reduction and/or medication with acetazolamide and furosemide to reduce the ICP. In patients with progressive or stationary visual disturbances, or intractable headache, surgical intervention may be considered, and includes shunt implantation with diversion of CSF, or optic nerve sheet fenestration (Ball and Clarke, 2006). The headache is frequently recurring even though surgical interventions may improve visual disturbances. In addition, shunt surgery is associated with complications (McGirt et al., 2004).

There is an urgent need to understand the pathogenesis to establish more efficient and specific treatment. Previously, we have monitored ICP and ICP waves invasively in IIH patients, which has provided evidence that impaired pressure-volume reserve capacity (i.e. reduced intracranial compliance) is characteristic for the disease (Eide and Kerty, 2011). We have in the present study paid special attention to the structure and organization of astrocytes by light microscopy and immunohistochemistry of brain biopsies. We hypothesized that IIH involves histopathological alterations in astrocytes that might impair cerebral water homeostasis in IIH. As astrocytic aquaporin-4 (AQP4) water channels play key roles in brain ion and water homeostasis (Nagelhus and Ottersen, 2013; Oberheim et al., 2012; Papadopoulos and Verkman, 2013; Verkhratsky and Butt, 2013), we hypothesized that AQP4 expression was altered in IIH subjects. In addition, we looked for insult to neurons given the fact that some IIH patients report subjective cognitive impairment. In the present study, a tissue sample was gathered from the brain cortex wherein an ICP sensor was placed. Striking histopathological findings were patchy astrogliosis with loss of distinct astrocyte domain organization, and increased perivascular AQP4 immunoreactivity (IR).

2. Results

2.1. Patients

During the study period from January 2010 to November 2012, 18 IIH patients meeting the modified Dandy criteria (Friedman and Jacobson, 2002) were consecutively enrolled in the study. In all patients, both brain biopsy and over-night ICP monitoring were performed. In addition, brain biopsy was obtained from 13 reference patients (Table 1). The IIH patients were somewhat younger than the reference patients (33.1±11.2 vs. 42.3±15.2 years, $P=0.06$). Body mass index (BMI) was significantly higher in the IIH patients (30.8±6.2 kg/m^2 vs. 26.2±4.2 kg/m^2, $P=0.03$; Table 1).

The pre-operative symptoms and signs of the IIH patients are presented in Table 2. All 18 patients had severe headache while 15/18 also had visual symptoms and signs. Notably 6/18 patients (33%) reported cognitive impairment. For the whole group, symptoms had lasted median 2 years prior to assessment. At the time of assessment 16/18 patients were on medication (acetazolamide, furosemide or topiramate; Table 2).

2.2. Surgical results

2.2.1. No complications to brain biopsy/ICP monitoring were observed

Shunting was done in 14/18 IIH patients. Among the 4 patients managed conservatively (non-surgery group), one already had a shunt for IIH and underwent ICP monitoring for assessment of shunt failure. Among the 14 shunted patients, one received a LP shunt, while the others received a VP shunt (opening pressure 12–18 cm H_2O; Table 2). Complications to shunting required shunt revision(s) in 5/14 patients (36%), that is, shunt infection (n=1), ventricular catheter malfunction (n=2), distal catheter obstruction (n=1), or over-drainage (n=1).

Outcome of management is presented in Table 2. While visual disturbances were normalized in 14 of 15 patients, complete relief of headache was obtained in only about one third of patients.

Table 1.
Demographic data of patients (total cohort).

Patient	Gender (F/M)	Age (yrs)	BMI (kg/m^2)	Diagnosis
1	F	38	29.0	IIH
2	F	27	25.2	IIH
3	F	22	29.3	IIH
4	F	34	34.0	IIH
5	F	29	28.6	IIH
6	F	24	27.5	IIH
7	F	48	22.8	IIH
8	F	25	24.6	IIH
9	F	37	26.4	IIH
10	F	47	33.1	IIH
11	F	22	37.7	IIH
12	M	21	34.6	IIH
13	F	24	36.5	IIH
14	M	55	24.3	IIH
15	F	52	39.1	IIH
16	F	37	43.7	IIH
17	M	31	22.7	IIH
18	M	22	35.2	IIH
19	F	40	32.5	Aneurysm
20	M	64	29.6	Aneurysm
21	M	24	34.7	Epilepsy
22	M	27	22.0	Cerebral tumor
23	F	54	26.8	Aneurysm
24	F	25	23.1	Epilepsy
25	M	22	26.0	Epilepsy
26	F	40	22.2	Epilepsy
27	M	43	24.4	Epilepsy
28	M	67	24.4	Aneurysm
29	F	58	29.4	Epilepsy
30	F	40	20.9	Epilepsy
31	M	46	24.1	Epilepsy

F: Female; M: Male; BMI: Body Mass Index.

2.3. The scores of pulsatile and static ICP

The ICP scores are presented in Table 3. Based on our previous experience (Methods section), we consider the pulsatile ICP (ICP wave amplitude and rise time coefficient) as abnormal in 14/18 patients, while the static ICP was abnormal in 3/18 patients (Table 3). Hence, according to our criteria, we considered the ICP scores as abnormal in 14/18 IIH patients (within normal ranges in patients 2, 5, 8, and 14; Table 3). Necessary medication was not stopped prior to monitoring.

2.4. Histopathological findings

2.4.1. General observation

The specimens used in the present study comprised at least the 3 superficial layers of the cerebral cortex (stopping at layer 3) and had a width of up to 0.9 mm (Fig. 1A). No obvious brain edema, hemorrhages or deformations were observed (Fig. 1), except for along parts of cut margins. No necrosis or scar tissues were