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Research report

Cerebral microvascular abnormalities in patients with idiopathic intracranial hypertension

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ABSTRACT

Aim: Idiopathic intracranial hypertension (IIH) is characterized by symptoms indicative of increased intracranial pressure (ICP), such as headache and visual impairment. We have previously reported that brain biopsies from IIH patients show patchy astrogliosis and increased expression of the water channel aquaporin-4 (AQP4) at perivascular astrocytic endfeet.
Methods: The present study was undertaken to investigate for ultrastructural changes of the cerebral capillaries in individuals with IIH. We examined by electron microscopy (EM) biopsies from the cortical parenchyma of 10 IIH patients and 8 reference subjects (patients, not healthy individuals), in whom tissue was retrieved from other elective and necessary brain surgeries (epilepsy, tumors or vascular diseases). IIH patients were diagnosed on the basis of typical clinical symptoms and abnormal intracranial pressure wave amplitudes during overnight ICP monitoring.
Results: All 10 IIH patients underwent shunt surgery followed by favorable clinical outcome. EM revealed abnormal pericyte processes in IIH. The basement membrane (BM) showed more frequently evidence of degeneration in IIH, but neither the BM dimensions nor the pericyte coverage differed between IIH and reference tissue. The BM thickness increased significantly with increasing age. Reference individuals were older than IIH cases; observations may to some extent be age-related.
Conclusion: The present study disclosed marked changes of the cerebral cortical capillaries in IIH patients, suggesting that microvascular alterations are involved in the evolvement of IIH.

1. Introduction

The syndrome of idiopathic intracranial hypertension (IIH), also referred to as pseudotumor cerebri or benign intracranial hypertension, is characterized by headache and visual disturbances, and is associated with a range of other clinical symptoms such as tinnitus and dizziness. Most frequently overweight fertile women are affected (Ball and Clarke, 2006). According to recent studies, IIH may also cause cognitive impairment (Kharkar et al., 2011; Yri et al., 2014), and substantially reduces life quality (Friesner et al., 2011; Kleinschmidt et al., 2000; Yri et al., 2012; Yri et al., 2014).

The incidence of IIH has increased dramatically over the past years due to a growing frequency of obesity (Kesler et al., 2014). Accordingly, the rate of shunting for IIH in the United States has increased with 320% from 1988 to 2002 (Curry et al., 2005). Annual costs for IIH have risen up to 444 million USD ($), mostly because of frequent hospital admissions, unsatisfactory treatment options and lost productivity (Friesner et al., 2011).

Even though the diagnostic criteria for IIH were specified by Dandy 80 years ago (Dandy, 1937), its pathogenesis remains largely unknown. It is known, however, that intracranial pressure (ICP) may be increased, as measured by lumbar puncture or overnight ICP monitoring. Yet paradoxically cerebral ventricles usually are normal or small sized (Corbett and Mehta, 1983; Eide and Kerty, 2011). Female IIH patients show increased prevalence of diabetes and arterial hypertension compared with the general population (Frič et al., 2017).

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We recently showed that brain biopsies of individuals with IIH provided evidence of patchy astrogliosis (Eide et al., 2016). In addition, the expression of the water channel aquaporin-4 (AQP4) was increased at astrocytic perivascular endfeet tentatively suggesting that increased AQP4 expression was compensatory to disturbed brain fluid drainage. It is well established that AQP4 plays key roles in brain ion and water homeostasis and thereby might influence the ICP (Nagelhus and Ottersen, 2013; Oberheim et al., 2012; Papadopoulos and Verkman, 2013; Verkhratsky and Butt, 2013).

The aim of the present study was to explore the ultrastructural changes of the cerebral cortical capillaries in human brain samples of IIH patients, and compare with those from reference (Ref) individuals. It was addressed whether structural changes of the cerebral cortical capillaries could provide a basis for the evolvement of the disease IIH.

2. Results

2.1. Patients

The study included 10 IIH patients meeting the modified Dandy criteria (Friedman and Jacobson, 2002) and 8 Ref patients (Table 1). The occurrence of pre-operative symptoms and signs of the IIH patients are presented in Table 1. Headache and visual impairment was significantly more prevalent in IIH than Ref patients (Table 1); the occurrence of other symptoms did not differ significantly.

No complications to brain biopsy/ICP monitoring were observed. All 10 IIH patients underwent shunt surgery. While normalization of visual impairment occurred in 8/10 patients, 5/10 reported no improvement of headache (Table 1).

2.2. The scores of pulsatile and static ICP

The scores of pulsatile and static ICP in IIH patients are presented in Table 2. While mean wave amplitude (MWA) was abnormal (>4 mmHg) in 10/10 IIH patients, the static ICP (mean ICP) was >10 mmHg in 7/10 patients and >15 mmHg in only 2/10 patients.

Table 1
Demographic, clinical, management and outcome data of the IIH and Ref groups.

	IIH Group	Ref Group
No	10	8
Sex (F/M)	8/2	6/2
Age mean at inclusion (yrs)	32.0 ± 10.6	44.8 ± 17.0
Co-morbidity		
Arterial hypertension, n (%)	1 (10%)	2 (25%)
Diabetes mellitus, n (%)	1 (10%)	0 (0%)
Pre-operative symptoms		
Headache, n (%)	10 (100%)[b]	3 (30%)
Visual disturbances, n (%)	9 (90%)[c]	0 (0%)
Dizziness, n (%)	2 (20%)	1 (10%)
Tinnitus, n (%)	1 (10%)	1 (10%)
Unsteady gait, n (%)	1 (10%)	1 (10%)
Cognitive impairment, n (%)	4 (40%)	4 (40%)
Duration of symptoms (yrs)	4.8 ± 2.9[a]	15.3 ± 13.4
Management		
Shunt surgery, n (%)	10 (100%)	
Cranial surgery (epilepsy, aneurysm, tumor), n (%)		10 (100%)
Clinical improvement - Surgery group		
Normalization of visual impairment, n (%)	8 (80%)	0 (0%)
Total freedom from headache, n (%)	2 (20%)	0 (0%)
Partial relief of headache, n (%)	3 (30%)	0 (0%)
No improvement of headache, n (%)	5 (50%)	0 (0%)

Categorical data presented as numbers; continuous data presented as mean ± standard deviation (std). [a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$; significant differences as compared to Ref group (independent samples *t*-test).

Table 2
The pre-operative pulsatile and static ICP scores of IIH patients.

	IIH Group (n = 10)
Pulsatile ICP	
Mean wave amplitude (MWA)	
Average (mmHg)	6.4 ± 2.5
Percentage ≥ 5 mmHg	60 ± 31
Mean wave rise time (RT)	
Average (sec)	0.18 ± 0.08
Percentage ≥ 0.20 sec	41 ± 45
Mean wave rise time coeff. (RTC)	
Average (mmHg/sec)	41.6 ± 11.5
Percentage ≥ 30 mmHg/sec	79 ± 32
Static ICP	
Mean ICP	
Average (mmHg)	12.2 ± 4.6
Percentage ≥ 15 mmHg	26 ± 32

*ICP parameters recorded from 11 pm to 7 am. ICP. Data presented as mean ± standard deviation.

Hence, the increase of mean ICP was modest, but the elevated pulsatile ICP was considered as indicative of impaired intracranial compliance.

2.3. Capillaries, capillary basement membrane, pericytes and endothelial cells

Fig. 1 illustrates how assessment of basement membrane (BM) thickness was performed. Regarding the BM thickness, we differentiated between the BM between the astrocytic endfeet and peripheral endothelial cells (BM_E), and the BM between endfeet and pericytes (BM_P). Fig. 2 presents electron micrographs from IIH patients and Fig. 3 from Ref individuals. Most endothelial cells

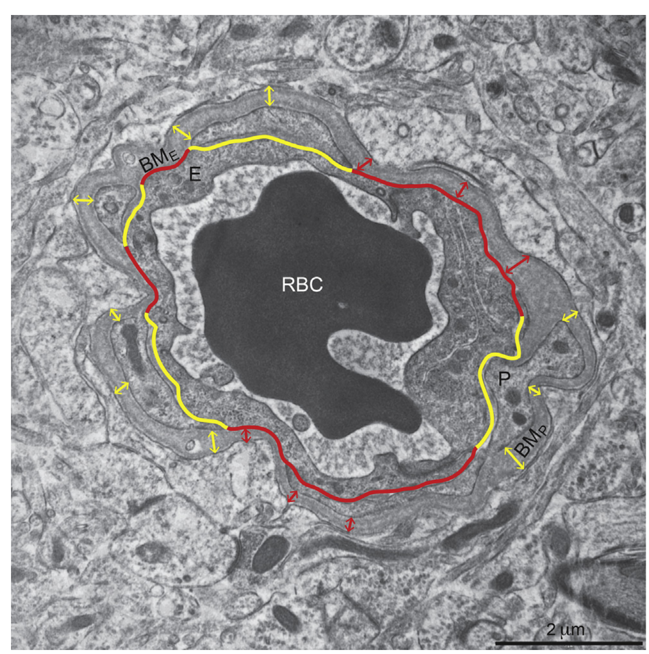

Fig. 1. Procedure for quantification of BM thickness and pericyte coverage. The thickness of the basement membrane peripheral to pericytes (BM_P) and peripheral to endothelial cells (BM_E) was measured approximately every 1 μm and is indicated by yellow and red double arrows, respectively. Pericyte coverage was measured as the percentage of the endothelial cell perimeter covered by pericytes. The endothelial cell perimeter is indicated in yellow when covered by a pericyte, elsewhere in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)