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Could there be any merit in lumping primary open-angle glaucoma, idiopathic intracranial hypertension and Meniere's disease into a novel and discrete category of fluid tension disorders?

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ABSTRACT

Open-angle glaucoma, idiopathic intracranial hypertension, and Meniere's disease are disorders managed by different specialties in medicine viz. ophthalmology, neurology, and otorhinolaryngology respectively. By working in silos, the similarity of these disorders is overlooked. Close inspection of these disorders reveals the presence of signs and symptoms triggered by fluid under high pressure within relatively closed chambers. There is a similarity in the capillary production of fluid, which then circulates and drains into the venous system. Management practices that reduce fluid production, decrease fluid pressure or enhance fluid drainage are employed for the treatment of all three disorders. A search for a unifying mechanism explaining the pathophysiology of all three disorders may unlock effective and perhaps curative measures for these disorders.

Introduction

Primary open angle glaucoma, Meniere's disease and Idiopathic intracranial hypertension (IIH) are heterogeneous disorders of the nervous system. However, the similarities in pathophysiology and management of these disorders appear remarkable. High fluid pressure within a closed chamber is the main shared feature. The fluid containing chambers located within the anterior segment of the eye, the cochlea of the ear and the ventricles of the brain result in symptoms that are chiefly visual, auditory or cerebral, respectively. Conceivably, formation, circulation and drainage of the fluid within these compartments must play a role in their pathophysiology. Which begs the question whether there could be any merit in lumping these disorders together into a single closed chamber disorder. If so, does it plausibly offer a better understanding of the pathophysiology of these disorders or even extrapolate to aspects of management as well? A brief discussion regarding their similarities is presented and perhaps some heuristic food for thought.

All three disorders relate to high pressure within a fluid filled chamber producing symptoms referable to the part of the head where they are located. In each chamber, a colorless fluid is produced by a vascular structure and drainage occurs by a passive process. In Table 1, similarities and differences in the composition of cerebrospinal fluid (CSF), aqueous humor and endolymph that occupies these three chambers are compared. All are clear and colorless, with similar pressure and specific gravity. However, differences in their chemistry especially that of endolymph is evident and points to its specialized role in hearing unlike the other fluids, which provide a supportive role (structural, nutritive and immunological).

Hypothesis

The similarity of fluid hypertension within closed fluid chambers viz. the anterior and posterior chambers of the eye in primary open angle glaucoma, the cochlear duct in Meniere's disease and the ventricular system in idiopathic intracranial hypertension, suggest a common pathophysiological mechanism in their aetiology. A search for a common channelopathy seems most prudent with implications for diagnosis and management. Leaky water channels induced by autoimmune or microbial infection may be implicated. The lack of co-occurrence of these disorders propose different genetic susceptibilities of these three closed compartments to environmental triggering events.

Empirical data

Primary open angle glaucoma: (Fig. 1) The aqueous humor within the eye is produced by vascular endothelium of the ciliary process (pars plicata). Fluid circulates from the posterior chamber via the pupil to the anterior chamber. The canal of Schlemm mediates re-absorption into the venous circulation passively. In primary open angle glaucoma, the

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Table 1
Fluid chemistry.

	CSF	Aqueous Humor	Endolymph
Origin	Choroid plexus and transependymal flow	Ciliary process	Stria vascularis and diffusion from perilymph
Pressure	8–18 mmHg/10–25 cmCSF	8–18 mmHg	Unknown. Probably similar to CSF and Perilymph[†]
Chemistry			
Sodium	135–150 mmol/L	142 mmol/L	1 mmol/L
Potassium	2.7–3.9 mmol/L	2.2 – 4 mmol/L	150 mmol/L
Glucose	40–85 mg/dL	88 – 124 mg/dL	9 mg/dL
Protein	0.15–0.45 g/L	0.05 – 0.15 g/L	0.15 g/L
Specific gravity	1.006–1.009	1.002 – 1.004	1.0087
pH	7.28–7.32	7.6	7.4
Osmolarity	295 mosm/L	304 mosm/L	315 mosm/L
Red cells	0–10 cells/μL		
White cells	0–5 cells/μL		0
Disorder from elevated pressure	Idiopathic Intracranial Hypertension	Primary open angle glaucoma	Meniere's Disease

[†] Perilymph is continuous with CSF at the oval window. Perilymph and endolymph pressure are postulated to be similar as they are in equilibrium. CSF – cerebrospinal fluid.

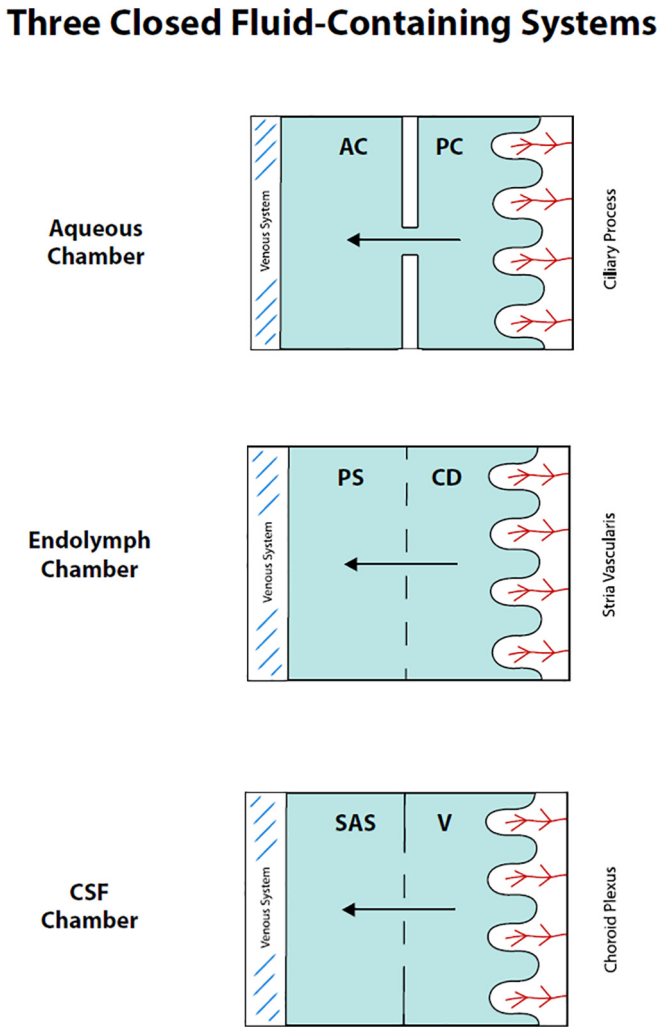

Fig. 1. Showing the three closed fluid-containing chambers. After production of aqueous, endolymph and CSF by vascular endothelium, fluid is conveyed within the closed compartment to venous drainage sites. AC – anterior chamber, PC – posterior chamber, PS – perilymphatic space, CD – cochlear duct, SAS – subarachnoid space, V – ventricles, CSF – cerebrospinal fluid.

pressure of these chambers is noticeably elevated in relation to the peri-optic space [1]. Increased production of aqueous humor is more plausible as no obvious obstruction to drainage via the canal of Schlemm has been demonstrated. A pressure gradient between the intra-ocular compartment and the peri-optic nerve space is more likely and currently more popular as it explains cases of normal intra-ocular pressure, appropriately called normal tension glaucoma [2]. The impact of this pressure gradient is most endured by the susceptible retinal ganglion cells and retinal nerve fibers are consequently lost [3]. Additionally, the pressure gradient results in cupping of the optic nerve head which is visualized as an increased vertical cup-to-disc ratio. Secondary inflammatory, toxic and barotrauma are factors implicated in the ischaemia to the optic nerve head and neurodegeneration [4]. In symptomatic patients, peripheral vision is especially affected. Ocular pain, headaches and visual haloes seen around lights are late features and more common in angle closure glaucoma. Relative elevated fluid pressure within the optic globe triggers the disorder.

Meniere's disease (MD) [5]: The endolymph within the cochlear duct (scala media) of the inner ear also lies within a closed system. Production of endolymph occurs via vascular endothelium of the stria vascularis (Fig. 1). Whilst perilymph has chemistry very similar to extracellular fluid and CSF, endolymph is rich in potassium, very poor in sodium and is positively charged (+80 mV) in relation to perilymph. In MD, the pressure within the cochlear duct and otoliths is elevated. Such elevated endolymphatic pressure (endolymphatic hydrops) either results from increased production of endolymph or decreased drainage via the endolymphatic sac. The 'leakage theory' postulates that membrane rupture and leakage of potassium rich fluid into the perilymph is primarily responsible for MD symptoms. A new theory postulates a mechanism similar to benign paroxysmal positional vertigo (BPPV) whereby detached saccular otoconia are responsible for stasis of endolymphatic flow [6]. In BPPV, it is the detached utricular otoconia, which are implicated. Regardless, the elevated endolymphatic pressure is associated with fluctuating hearing loss, episodic vertigo, tinnitus and aural fullness. With the apex of the cochlear duct being particularly susceptible to the high pressure, low frequency hearing mediated by the apex is particularly affected. Elevated pressure within the closed endolymphatic compartment triggers the disorder.

Idiopathic intracranial hypertension [7]: In idiopathic intracranial hypertension (IIH) CSF pressure within the ventricles is elevated but the ventricles usually remain undilated as there is no obstruction to the flow of CSF through to the arachnoid granulations from their site of production by the choroid plexus (Fig. 1). Pressure surrounding the brain and within the ventricles hypothetically reach an equilibrium thus preventing the formation of ventriculomegaly. The elevated pressure stretches the meninges with their associated vascular structures thereby producing headaches and symptoms of raised intracranial pressure. Pressure that is conveyed to the peri-optic nerve sheath produces papilloedema; to the peri-vestibulocochlear nerve produces tinnitus and downward pressure on the brainstem produces diplopia. Stretching of the sixth cranial nerve as it angulates into

Table 2
Some similarities between Idiopathic intracranial hypertension, Primary open angle glaucoma and Meniere's disease.

	Idiopathic intracranial hypertension	Primary open angle glaucoma	Meniere's disease
Defining Symptoms	RICP headaches, transient visual obscurations, tinnitus, diplopia	Headaches, ocular pain, haloes around lights, visual field loss. But most are asymptomatic	Fluctuating hearing loss, episodic vertigo, tinnitus, aural fullness
Pathogenic Mechanism unknown but postulated mechanisms	1. Increased CSF production 2. Increased CSF outflow obstruction at arachnoid granulations or [g] lymphatic drainage sites 3. Transverse venous sinus stenosis and venous hypertension	1. Increased aqueous production 2. Current hypothesis: Intra-ocular pressure > peri-optic nerve CSF pressure. 3. Decreased aqueous outflow	1. Endolymphatic hydrops from increased production 2. Membrane rupture with leakage of potassium rich fluid into perilymph 3. Blockage at the endolymphatic sac or duct by detached otoconia
Diagnosis	Modified Dandy Criteria 1. Symptoms and signs of RICP 2. No other neurological abnormalities 3. High CSF pressure. Normal CSF composition 4. Brain imaging showing no cause for RICP	1. Raised IOP in < 50% 2. Cupping of optic nerve head. Thinning of RNFL 3. VF defects. Arcuate, nasal step, paracentral scotoma 4. Open anterior chamber angle	1. Two spontaneous episodes of vertigo lasting 20mins 2. Sensorineural hearing loss on audiometry 3. Tinnitus and or perception of aural fullness
MRI	Vertical tortuosity of optic nerve. Dilated optic sheath, flattening of posterior sclera, slit like ventricles	Not indicated	Used to exclude secondary disease. Less visible endolymphatic duct in MD
Mainstay of treatment: Lowering of fluid pressure and shunting procedures	Lower intracranial pressure by decreasing CSF production, CSF tapping, CSF shunting, ONSF	Lower intra-ocular pressure by decreasing aqueous production. Aqueous shunting by filtration blebs or mechanical shunts	Lower intra-cochlear pressure by decreasing endolymph production eg diuretics. Vestibular suppressants. Endolympatic sac shunting.
Common drug used	Acetazolamide	Acetazolamide	Acetazolamide
Lifestyle modification	Weight loss program, Low salt diet	Low salt diet	Low caffeine intake. Low salt diet

RICP- raised intracranial pressure, CSF – cerebrospinal fluid, ONSF – optic nerve sheath fenestration, IOP - intra-ocular pressure. VF – visual field. RNFL- retinal nerve fibre [fiber] layer

Dorello's canal results in diplopia as a false localizing sign. The symptoms and signs of IIH are primarily caused by raised intracranial pressure in the absence of space occupying lesions and venous sinus thrombosis. Reasonably, transverse venous sinus stenosis and venous hypertension should be considered secondary causes of pseudotumour cerebri rather than a possible mechanism for the idiopathic condition [8]. Elevated CSF pressure as detected by lumbar puncture within the CSF compartments of the ventricles and subarachnoid space, trigger the disorder.

Discussion and consequence of the hypothesis

Table 2 summarizes the similarities between disorders of elevated pressure involving these closed fluid-containing compartments. In none of them has obstruction been unequivocally demonstrated. However, an increased production of fluid with resultant pressure increase within a relatively closed compartment is principally responsible for the disease entity and the symptoms that follow. The use of acetazolamide, a carbonic anhydrase inhibitor for all three conditions lends tentative support for increased fluid production as the primary pathogenic mechanism. Acetazolamide supposedly decreases CSF, aqueous and endolymph production within these closed chambers. Other mechanisms have been credibly argued for and perhaps support secondary causes for these three conditions; for example transverse venous sinus stenosis in IIH, pseudo-exfoliation in glaucoma and an autoimmune mechanism in Meniere's syndrome [8,9]. Nevertheless, the absence of secondary causes and similarities of elevated pressure within a closed compartment does warrant further scrutiny into these idiopathic disorders.

The similarities favour a search for a common group or class of mechanisms acting on fluid production within the closed chambers. Leaky water channels at blood-fluid barriers in these closed systems might be the eventual process initially induced by autoimmune or infective mechanisms. While the lack of co-occurrence of these entities in a single patient argues against a shared channelopathy or common triggering event exposing the greater susceptibility of any one chamber thereby allowing them to present separately. Whether to lump or to split these disorders does have implications on management, the responsibility by the primary care physician and on medical lexicon. Nevertheless, the similarities and response to pressure lowering therapy does beg the questions. Is there an all-encompassing mechanism such as a channelopathy shared between these disorders that we are missing? Is there merit in classifying these disorders under the banner of fluid tension disorders allowing for a more rigorous search for a unifying mechanism? No doubt, the similarities are striking and warrant experimental scrutiny.

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Declaration of Competing Interest

The authors report no conflict of interest in the drafting of this article or anything that pertains to it.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109361.

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