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Bilateral hyperplasia of choroid plexus with severe CSF production: a case report and review of the glymphatic system

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Abstract

Background An important feature of hydrocephalus is the alteration of the cerebral spinal fluid (CSF) homeostasis. New insights in the understanding of production, secretion, and absorption of CSF, along with the discovery of the glymphatic system (GS), can be useful for a better understanding and treatment of hydrocephalus in disorders with CSF overproduction.
Case description A 1-year-old patient was diagnosed with communicating hydrocephalus; ventricle peritoneal shunt (VPS) is installed and ascites developed. VPS is exposed, yielding volumes of 1000-1200ml/day CSF per day. MRI is performed showing generalized choroidal plexus hyperplasia. Bilateral endoscopic coagulation of thechoroid plexus was performed in 2 stages (CPC) however the high rate of CSF production persisted, needing a bilateral plexectomy through septostomy, which finally decreased the CSF outflow.
Discussion New knowledge about the CSF physiology will help to propose better treatment depending on the cause of the hydrocephalus. The GS is becoming an additional reason to better study and develop new therapies focused of the modulation of alternative CSF reabsorption.
Conclusion Despite the current knowledge about hydrocephalus, we remain without a complete understanding of the pathophysiology of this condition. GS could be more important than conventional concept of reabsorption of CSF in the arachnoid villi, therefore GS could be a new key point, which will guide future investigations.

Keywords Choroid plexus hyperplasia · Hydrocephalus · Glymphatic system · Cerebrospinal fluid

Introduction

Hydrocephalus is a diverse integration of conditions characterized by a disorder on cerebral spinal fluid (CSF) physiology that usually drives to an abnormal enlargement of the cerebral ventricles and is regularly linked with raised intracranial pressure [1, 2]. If untreated, hydrocephalus could produce brain herniation and subsequent decease [1]. In addition, it is a frequent cause of pediatric disease and death, representing a foremost monetary burden on health care budget [3]. In the pediatric population, hydrocephalus acquires complexity in its anatomy and mechanisms [4, 5]. Clinical manifestations are linked to the age of onset; children in early infancy complain more commonly for headache, usually associated with progressive macrocephaly and visual disturbances, and older kids present impairment and decreased levels of consciousness due to raised intracranial pressure [2, 5]. Hydrocephalus might disturb cerebral development and prompt motor, sensitive, and cognitive deficits [6]. The management of hydrocephalus aims to relieve the symptoms that regularly implicates the placement of ventricle-peritoneal shunts (VPSs) which require neurosurgical intervention [3]. Current paradigm of impairment in the reabsorption of CSF in arachnoid villi could be renewed because of increasing knowledge of CSF dynamics. Alternative pathways of CSF

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drainage are under extensive research, and their relevance in the management of hydrocephalus could be higher than we think. Besides, management alternatives for hydrocephalus remain unchanged during the last years [7]. Nevertheless, evidence shows that in order to describe its pathogenesis, genetic factors get a relevant role in several types of hydrocephalus [8]. Therefore, we report a bilateral hyperplasia of choroid plexus (CP) with severe CSF production in a 1-year-old boy, and we review the underlying physiology of the CSF in children and new insights about the relation between hydrocephalus and the glymphatic system (GS).

Case description

A 1-year-old patient, product of preterm gestation because of premature rupture of membranes, and previously healthy, presents with vomiting and irritability. Communicating hydrocephalus is evident in computed tomography (CT); VPS is placed, and 45 days after surgery, the patient developed ascites. CT abdomen shows free fluid in the cavity, without a solid or hollow viscera lesion. VPS is externalized, reporting drainage volumes of 1000–1200 ml/day of CSF, without signs of infection. Given such high output, magnetic resonance imaging (MRI) is performed showing bilateral CP hyperplasia (Figs. 1 and 2). The bilateral endoscopic procedure is performed in 2 stages: first, only CP cauterization (CPC). Subsequently, CSF flow decreases by 800 ml/day, and bilateral plexectomy was performed using a right frontal approach and performing a posterior septostomy, decreasing CSF outflow to 120 ml/day. It is decided to install VPS. A biopsy confirmed the diagnosis of CP hyperplasia.

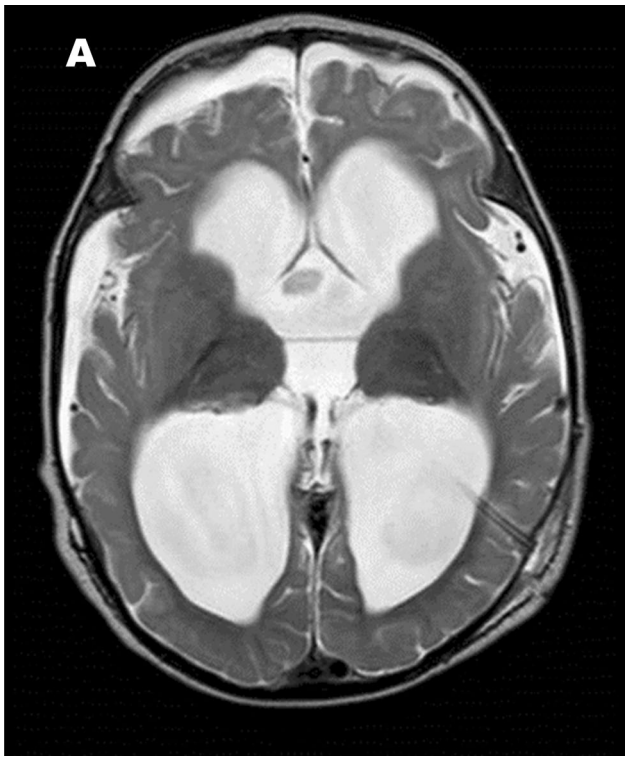

Fig. 2 Postoperative MRI. (**A**) Axial section showing enlarged ventricles persisted, and prominent choroid plexus tissue disappeared

Historic model of CSF physiology

In the last century, the "bulk-flow" model of CSF homeostasis was the standard in which pathogenesis of hydrocephaly had the best understanding [5, 9]. In this paradigm, the CSF is excreted in the CP in the brain ventricles, then leaves into

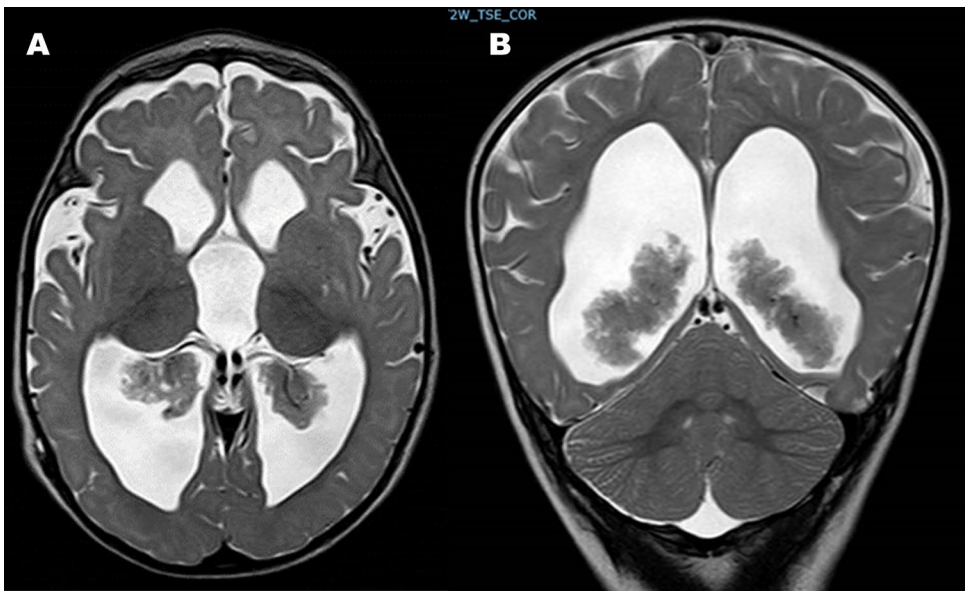

Fig. 1 Preoperative MRI. Enlarged ventricles and prominent choroid plexus. (**A**) Axial section; (**B**) Coronal section

the subarachnoid space where it flows and is absorbed by the arachnoid granulations in the deep vein draining. This model states hydrocephalus is due to the obstruction of CSF circulation anywhere along the aforementioned pathway.

Relatively new, another "hydrodynamic model" where the role of the atypical intracranial pulsations might cause the pathological condition [10]. Better accounts for annotations cannot be explained with the bulk flow model and are founded in the following premises:

1. Functional arachnoid granulations cannot be found in some pediatric populations (infants < 2 years) [11].
2. The ependyma and other structures different from CP might supply a significant quantity of CSF [12].
3. Increasing the intra-ventricular CSF osmolarity is sufficient to cause experimental hydrocephalus [13].
4. Despite unobstructed flow and normal mean CFS pressures, increasing intra-ventricular fluid pulsation amplitudes by itself are enough to produce hydrocephalus [14].

Some types of hydrocephalus appear (mostly) in the pediatric population in which pathogenesis has been neglected toward CSF production; rather, it is attributed, lastly, to an anomalous accumulation of CSF. Nevertheless, pharmacological (e.g., acetazolamide) and non-conservative (e.g., CPC) alternatives that reduce CSF excretion have demonstrated effectiveness for particular hydrocephalus types.

CSF secretion and production

The CP is a vastly vascularized capillary bed of fenestrated vessels fenced by polarized cube-shaped epithelial cells faced through tight junctions [15]. In contrast to the blood–brain barrier (BBB), which is constituted by tight junction, the blood-CSF barrier is constituted by the tight junctions of CP epithelia. The fenestrated capillaries of the CP have the feature of not being completely impermeable and, unlike the brain endothelial cells, willingly allow the diffusion of ions and other smalls particles [16]. Epithelial cells in the CP have diverse ion channels and transporters that are responsible for most of CSF secretion: [17]

1. Na/K-ATPase is disposed toward the lumen (apical membrane), is central to CSF production, and prompts the hydro-electrolytic gradient for Na^+ that is imported utilizing: (a) Na^+/H^+ exchanger, (b) NHE, (c) $Na+/HCO_3^-$ cotransporter, (d) NCBE basolaterally
2. Co-import of HCO_3^- via NCBE and hydration of CO_2 by carbon anhydrase (CA) increases the concentrations of HCO_3^- intracellularly, which prompts a hydro-electrolytic gradient which modulates the efflux of HCO_3^- basolaterally situated Cl/HCO_3^- exchanger, AE_2, and apically expressed HCO_3^- channels
3. The role of AE_2 prompts an increment in Cl^- concentrations intracellularly, modulating the apically Cl^- exporter employing the NKCC1 and Cl^- channels

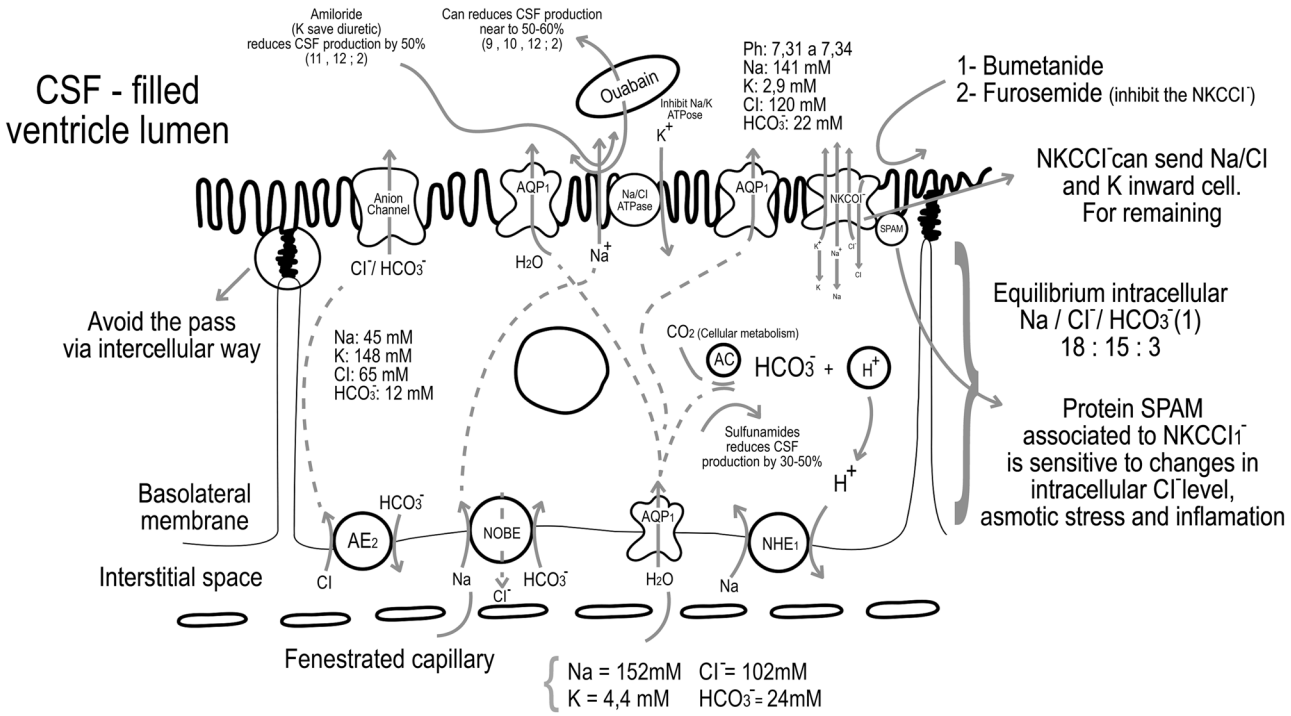

Fig. 3 CSF production. Amiloride (K-save diuretic) reduces CSF production by 50%. Ouabaina inhibits K/Na ATPase and can reduce CSF production near to 50–60%. NKCCl can send sodium, clorum, and potassium inward cell for the remaining intracellular equilibrium: Na/Cl/HCO3:18/15/3. These NKCCls are associated to a special protein named SPAK which is sensitive to changes in intracellular clorum level, osmotic stress, and inflammation

The ending outcome of the aforementioned procedures at the CP epithelial cells is a net flux of Na^+, HCO_3^-, and Cl^-, from the vascular compartment through the epithelial cells of the cerebral ventricles, which prompts the hydro-electrolytic gradient that induces water diffuse across AQP1, thus generating the CSF (Fig. 3).

The transcellular pathway is the main transporter for CSF [18], and ending solute concentrations of the CSF are carefully modulated and persist quite unchanged [19].

The terminal membrane of CP epithelial cells has vast water leak [20], and the passive movement of water through the transcellular way from the vascular compartment to the ventricles is performed mostly through AQP1 [21]. That is demonstrated thanks to animal studies with AQP1 knockout mice where the permeability of CPE is reduced by 80% [21]. However, an increase in AQP1 expression does not always lead to a rise in the excretory capacity of the CPE by itself, given that water movements require a driving force (osmotic force made by Na/K ATPase and others) [1].

CSF absorption

The CP epithelium (CPE) produces about 80% of CSF, while the remaining 20% is generated from brain interstitial fluid (BIF) [22]. The CPE is between the main competent excretory epithelium in the human organism. It generates a rate of 0.4 ml/min/g of tissue and an excretion rate that is just matched by the proximal tubule of the nephrons and the canals of the exocrine pancreas [19]. The entire amount of CSF is around 150 ml; nevertheless, it is calculated that 500–600 ml is excreted daily. Then, the CSF is reabsorbed by arachnoid granulations. Nonetheless, several of the non-human models which attain to study hydrocephalus [23] and early infancy [24] do not appear to express functional arachnoid granulations. So, there must be other factors, such as BIF, which generate approximately 20% of CSF volume, as aforementioned [25]. The flow of the BIF is estimated between 0.1 and 0.29 µg/g of tissue/min [25]. Besides, BIF is dynamic; it pursues a mostly periventricular pathway and crosses the intricate microanatomy of Virchow-Robin spaces (VRS) [22]. It has been demonstrated that the circulation of BIF is not in a single direction and might influence equally the net CSF excretion and absorption. Therefore, there is persistent intercommunication among BIF and CSF [17]; the makeup of this dynamic system is termed glymphatic system (GS), which is a paravascular path which eases the flow of subarachnoid CSF into BIF and, thus, out through the deep vein draining [17] (Fig. 4).

These paravascular networks are attached by astrocyte feet expressing Aquaporin 4 (AQP4) [26], which, once it is dysfunctional, can influence or worsen the progression of hydrocephalus [26]. The CP owns the maximum rate of water and ion diffusion of any epithelia in humans [19].

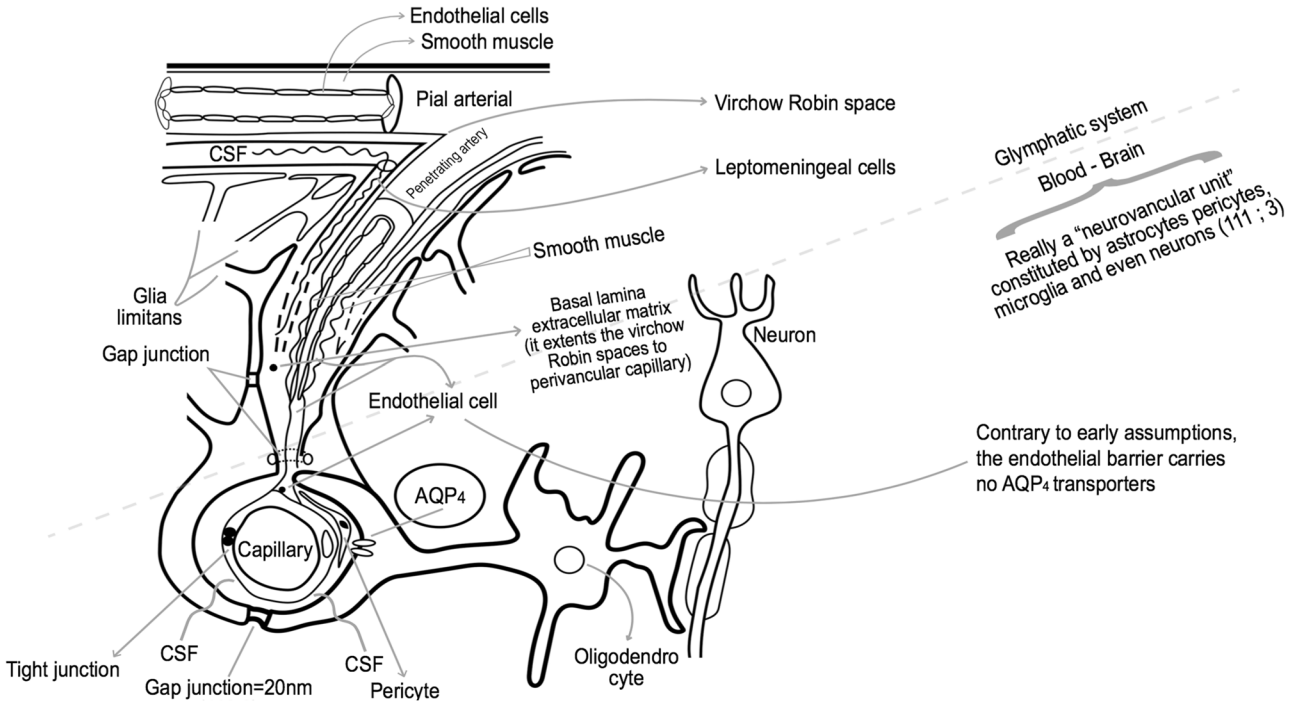

Fig. 4 Neurovascular unit. The "neurovascular unit" is constituted by astrocytes, pericytes, microglia, and even neurons. Contrary to early assumptions, the endothelial barrier carries no AQP4 transporters. Instead, water may cross the endothelium by diffusion, vascular transport, and even against osmotic gradients by means of co-transport with ions and glucose. CSF, cerebrospinal fluid; AQP, aquaporin

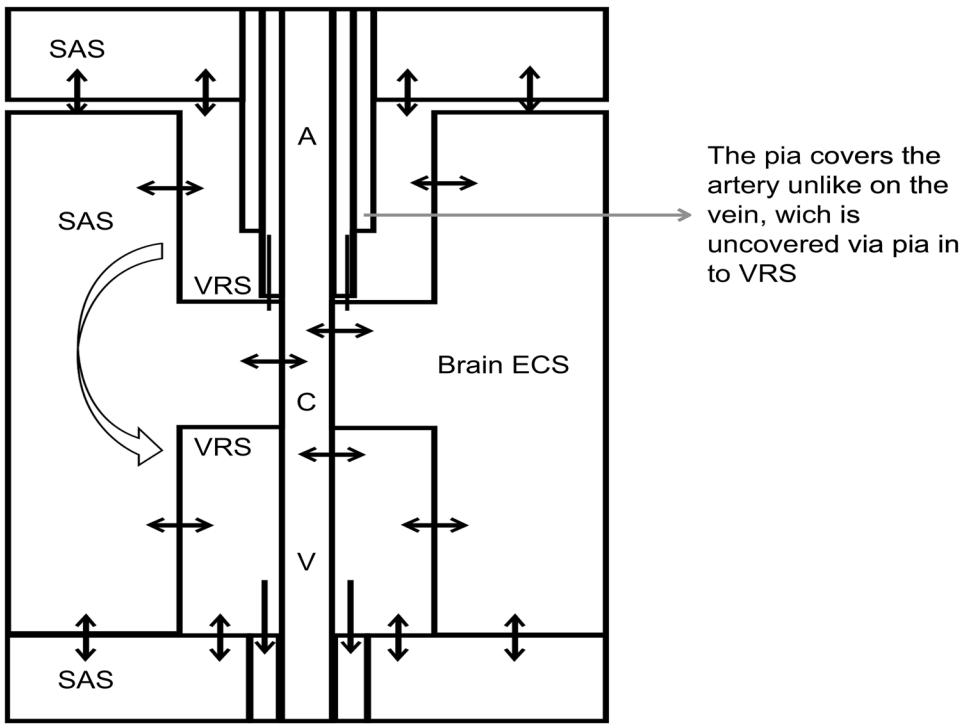

Fig. 5 Virchow-Robin space microanatomy. VRS, Virchow-Robin space; SAS, subarachnoid space; A, artery; C, capillary; V, vein; ECS, extracellular space

Microscopic anatomy of the Virchow–Robin space

The pia covers the artery unlike on the vein, which is uncovered by pia in the VRS (Fig. 5). The pia sheathes the arteries, but not venous vessels extend into the VRS. In studies of rodents, the VRS space is filled by fluid, electron-microscopic–dense material [27] macrophages, and other blood-borne inflammatory cells [28]. The pia in humans is a barrier constituted by a seemingly continuous stratum of cells, which are united by desmosomes and gap junctions but have no apparent tight junctions [29]. Notably, the injection of tracers into the brain shows no drainage throughout the perivenous canals except if there is a distraction of circulation in cerebral amyloid angiopathy when entering some tracer through the perivenous spaces [30].

The glymphatic system

The dense distribution of lymph vessels is proportional to the rate of tissue metabolic function in each tissue [31]. While the brain and spine are differentiated by a dissimilarly great metabolic rate [32] and the synaptic transmission is finely susceptible to variations in their situations, these lack of traditional lymphatic vessels. CSF is drained into the conventional lymphatic system (lymphatic nodes) by efflux via the olfactory bulb and throughout peripheral nervous fibers [33]. Lately, the relevance of arachnoid granulations in CSF reabsorption has been interrogated [34]. Therefore, efflux throughout peripheral nerve fibers and the olfactory path can signify the most important efflux ways for CSF [33].

The discovery of the glymphatic system

A lymphatic drainage percentage of 50% was calculated based on injections of radio-iodinated albumin (RISA) in the brain of rabbits. Remarkably, considerable RISA presented a draining through the brain perivenous spaces along with that by the route from the subarachnoid space of olfactory lobes into the submucosal spaces of the nose (therefore to the lymphoid vessels) [35].

The dynamics of the glymphatic system

CSF flows into the tissue, then it diffuses by convection through BIF within the tissue on the way to the perivascular space and flows out of the brain into the cervical lymphoid structures [33].

In 2012, employing two-photon microscopic was characterized for the first time in vivo in a mouse model [34]. Moreover, using injected fluorescent tracers in the CSF within the cisterna magna, a study demonstrated CSF quickly arrives at the brain via pial blood vessels situated in the cortex. This penetration was followed by influx into the VRS throughout penetrating arterioles. It was obvious that CSF tracers, instead of being widely and randomly spread in the tissue, arrived at the tissue via periarterial route neighboring the muscle cells in vessels united by perivenous

astrocytic end-feet, and ex vivo suggestion demonstrated that tracers quickly left the brain mostly throughout the central deep vessels and the anterolateral caudal rhinal veins [34]. The paravascular glymphatic route guided by AQP4 bulk flow-dependent represents a foremost elimination route of interstitial fluid substance from the nervous tissue [36].

AQPs and other models of water transport

It is well-known that diffusion transportation lacks specificity and is a very low way to move; in contrast, water canals such as the AQPs confer a quick way to diffuse and own a great competence and a high selectivity to transport molecules [37]. There are five different types of AQPs [5]. Trials assessing the structure and function of AQPs showed data suggesting that whether the AQP channels are permeable or not might be modulated and can also present compromise in pathologic states of the brain [38]. Remarkably, AQP1 is found in cells of endothelium along with the organism but cannot be found in the BBB, except in the structures adjacent to ventricles. AQP1 is expressed in the cells disposed into ventricles of CP epithelia, signifying an important role in this structure for CSF production.

Controversially, literature stated that extrachoroidal CSF secretion was notably higher than CSF generated in CP, rather be the most important producer of CSF [39]. The posterior concept is reinforced by the comment that after its intravenous administration, the infiltration and stable concentration of $H_2{}^{17}O$ are markedly decreased in ventricular CSF in AQP4 but not in AQP1 knockout mouse models. The authors comment that in conclusion, AQP4 is a higher CSF producer than AQP1 [40]. AQP4 is vastly found in astrocyte foot processes located in the BBB, glia limits with brain surface and VRS, ventricular ependymal cells and subependymal astrocytes [41], and astrocytic end-feet at the presynaptic space of nerve cells and is expressed in the olfactory epithelial cells [42]. Nowadays, it is well known that water penetrates the endothelial cells by simple diffusion and vesicular transport and through the astrocyte foot processes mainly via AQP4 channels [43].

Implications in hydrocephalus

Clinical presentation

The rhythms of CSF secretion and reabsorption have to be balanced. The excess of production can be seen in:

(a) *CP hyperplasia* [44] (our case)

It is also named diffuse villous hyperplasia or villous hypertrophy. It is a rare congenital disorder that yields enlarged and hyper-secreting CSF. There is an increase in the number of CPE cells [1], which denotes an increase in blood flow to choroid plexus, a wider surface of filtration, and, therefore, a higher rate of production of CSF. As we detailed in this case, once ascites were reported, EVD quantified an output rate as high as 1000–1200 ml per day, which doubles the normal production and saturates the drainage systems of CSF we aforementioned. To note, rates of arachnoid villi drainage are pressure-dependent essentially following a kind of first-order kinetic model of reabsorption. When intracranial pressure is 0, 10, 20, or 30 mmH_2O, then reabsorption rate is up to 0, 1.52, 6.44, and 18.04 ml/min, respectively. This rate of reabsorption was even more sensitive to changes in pressure in the glymphatic drainage system, which results in a more pronounced reabsorption activity in hydrocephalus [45]. This data reinforces the idea that possibly, the glymphatic pathway becomes even more relevant than arachnoid villi in reabsorption of CSF when there is intracranial hypertension, and therefore, in the onset of communicating hydrocephalus, the modulation of the glymphatic system could be a potential therapeutic target in the management of this disease.

(b) *CP papilloma (CPP)* [46]

It represents 1–4% of all cerebral neoplasm in children. It is a different bulk separated from the CPE and is regularly seen within 2 years of birth [1].

The diagnosis of hydrocephalus with CPP or CP hyperplasia origin is decisive given that the standardized management for them is not a VP shunt; in contrast, tumor or excessive CPE should be resected [44]. The diagnosis is challenging and usually can be confirmed when a performed shunt fails or there is development of ascites, and if the shunt is externalized, the excessive amount of CSF makes the diagnosis [1]. The normal secretion of CSF is 500 mL/day. If CPP or CP hyperplasia appears, then the rate could be as high as 5000 mL/day, and a higher rate is associated with worse hydrocephalus [44]. After surgery (CP cauterization or tumor resection), the rates of CSF production decrease [44], and in some cases, there was no further need for a shunt [46].

Management

Conservative treatment of hydrocephalus by targeting CSF production

Diuretics are the medications more frequently used [1]; however, these drugs are regularly non-effective, develop adverse effects, and have off-target properties in the kidney [1].

(a) Sulfonamide-type acetazolamide generates about 30–60% reduction in CSF rate and 24-h excretion [47]. The fractional result of this inhibitor is described by the expression of a group of CAIII receptors which are not sensible to acetazolamide. This subtype of receptors has been isolated in normal persons and different species models [48].

(b) Loop diuretics: There is evidence showing that furosemide as a KCC inhibitor and bumetanide as an NKCC1 inhibitor, single or combined with the aforementioned, reduce the CSF rate of output in dog and cat models [49].

Animal information also exposes the result of furosemide in interrupting ion transport along the blood-CSF barrier, which decreases the rate of CSF excretion [50]. Given that the outcomes of these drugs were also described in animal-based models in which nephrectomy was performed, there was reported likely secondary diuretic or hemodynamic alterations prompted by renal hydro-electrolytic dysregulation as well as the apparition of acid-base disorders, which uncertainly explicate the reduction in CSF secretion [51].

Even with the theoretical success and hopeful outcomes from animal models, furosemide and acetazolamide have been administered in patients where the posterior period of hemorrhagic hydrocephalus has been reached ($n = 177$). The outcome unexpectedly showed a representative crossover to the shunt surgery and an augmented rate of neurological manifestations in this group [52]. The literature stated that a representative fraction of the pediatric population progressed into nephron-calcinosis as a consequence of the administration of this drug [53].

Then, according to the Cochrane review, the combination of acetazolamide + furosemide is not effective and neither safe in managing post-hemorrhagic hydrocephalus.

Modulation of CSF production by the surgical intervention of the CP

Surgical procedures that compromise targeting CSF are widely defined by several authors in the last century. Dandy [54] illustrated the first surgery for managing hydrocephalus by ablating the CP.

Current techniques are:

(a) Plexectomy: Some authors informed 37% of successful cases, as dodging of CSF deviation interventions [55]. The first animal study was performed by Milhorat et al. [56], and it was done on monkeys and demonstrated a reduction of CSF production near to 37–40%.

(b) Cauterization (CPC): The study of Pople et al. demonstrated that 36% of the cohort did not crossover to shunt surgery in the mean follow-up period of 10.5 years; the best outcome was in those cases that developed communicating hydrocephalus and in cases with decelerated evolution of ventriculomegaly [57].

Warf et al. [58] in Uganda have used ETV (endoscopic third ventriculostomy) and CPC surgery using an elastic endoscope and monopolar cautery to coagulate the whole CP through both lateral ventricles; they emphasize that ETV might serve as a pulsation absorber.

In comparison with single-ETV, ETV-CPC generated greater outcomes in infants < 1 year of age [58] and in all mentioned etiology subtypes [59–61]. The efficacy of ETV-CPC is related to the quantity of CP cauterized [62] and does not harmfully affect cognition in comparison to shunt placement or single-ETV [63]. Physiological adjustment to a modification in the regular secretion of CSF could suggest compensation by the residual CP tissue not cauterized in typical procedure or by upregulation of secondary mechanism of production.

Conclusions

There are several types of hydrocephalus, and its differential diagnosis is a major concern, such as what happens in CP hyperplasia and CPP diagnosis. This kind of hydrocephalus commonly leads to high rate of CSF production. The best mechanism of diagnoses is the MRI; the ideal treatment according to our experience corresponds to total plexectomy followed by total CPC. Despite the current knowledge about hydrocephalus, we remain without a complete understanding of the pathophysiology of this condition. GS could be more important than conventional concept of reabsorption of CSF in the arachnoid villi; therefore, GS could be a new key point, which will guide future investigations. The new concepts of AQPs 1 and 4 are involved in the physiology of the CSF production and open the possibilities of new pharmacological approaches. It is even possible that disorders in AQP1 on endothelial cells in specialized circumventricular organs like subcommisural structure might be associated with congenital hydrocephalus. There are few cases like ours written in the literature; we believe this kind of example switches on the alarms and should be taken into account always in the mind of the neurosurgeons. Further studies are required to corroborate these premises and elucidate the pathophysiological mechanisms underlying CSF circulation diseases.

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Declarations

Conflict of interest The authors declare no competing interests.

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