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ORIGINAL PAPER

Cerebro-venous hypertension: a frequent cause of so-called "external hydrocephalus" in infants

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Abstract

Introduction External hydrocephalus (eHC) is commonly defined as a subtype of infant "hydrocephalus" consisting of macrocepahly associated with enlarged subarachnoid space and no or mild ventriculomegaly. This status is thought to be related to impaired CSF absorption because of arachnoid villi immaturity. However, other factors like the venous system might be involved in the development of the clinical picture.

Methods All patients diagnosed with eHC received prospectively contrast-enhanced 3D MR phlebography. Venous sis abnormalities were graded depending on the number of affected sinus segments and type. External CSF space volume was quantified planimetrically.

Results Seventeen patients with the typical clinical feature of eHC were included. In 15, venous sinus abnormalities were found. There was a significant correlation between the volume of the widened cortical subarachnoid space (CSAS) and the number of venous sinus segments affected. Conversely, ventricular volume was not correlated.

Conclusion These results support the hypothesis that impaired venous outflow plays a major role in external hydrocephalus development. Raised venous pressure increases intracranial pressure accelerating head growth, resulting in an enlargement of the cortical subarachnoid space. Increased venous pressure increases the capillary bed pressure and brain turgor preventing ventricular space to enlarge forcing displacement of ventricular CSF to the subarachnoid space. As a result, ventriculomegaly is rarely found. The descriptive term "external hydrocephalus" implying a primary etiology within the CSF system is misleading and this work supports the notion that venous hypertension is the leading cause of the clinical picture.

Keywords Benign idiopathic macrocephaly · Subarachnoid space · Venous sinuses · MR phlebography

Introduction

The so-called external hydrocephalus is defined as a subtype of hydrocephalus consisting of a large or fast-growing head circumference associated with enlarged subarachnoid spaces and no or mild ventriculomegaly [19]. Other clinical and radiological findings attributed to high intracranial pressure are usually not present [14]. It presents in infants with a mean age of 6 months at onset. Radiological widening of the subarachnoid spaces progressively subsides spontaneously in the majority of patients; some of them remaining macrocephalic.

Many theories and different etiological factors have been described for this pathology. The common theory for external hydrocephalus suggests that it is produced by impairment of CSF absorption at immature arachnoid villi [1, 12]. In infants with opened fontanels and sutures, accumulation of CSF would result in widening of subarachnoid spaces fostered by the growing skull. However, arachnoid villi immaturation is present in all infants [25]. In addition, a primary CSF absorption problem, in the classical sense, would be expected to lead predominantly to a ventricular enlargement (communicating hydrocephalus) and not to an expansion of the external subarachnoid spaces.

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The hypothesis this work supports, that has been published, states that in the majority of the so-called "external hydrocephalus" patients, the cerebro-venous outflow is impaired leading to an increased venous pressure, impaired CSF absorption, and increased ICP. In infants with open sutures and fontanelles, this leads to macrocephaly due to a low resistance to skull expansion. Since the skull thus is bigger than the brain and has different compliance, the surplus in intracranial volume fills with accumulated CSF, thus enlarging subarachnoid extraaxial spaces [5].

To investigate this understanding of external hydrocephalus further, this study analyzes the relation between cerebro-venous system abnormalities and the volume of the subarachnoid space.

Methods

All patients with diagnosis of macrocephaly of infancy received as part of the routine work-up a diagnostic cranial MRI and, in case an external hydrocephalus was present, a contrast-enhanced 3D MR phlebography. Twenty patients with external hydrocephalus were studied. Three patients were excluded from final analysis because of incomplete information; therefore, a total of 17 infants were included in this analysis, 6 males and 11 females.

Retrospectively, the main clinical presentation, signs and symptoms, and radiological findings were analyzed. Based on the radiological report, MR phlebography abnormalities were graded according to several features: number of segments affected (up to 7: sagittal, transverse right, transverse left, sigmoid right, sigmoid left, jugular right, jugular left), main impaired segment, type of abnormality (focal or diffuse) and if abnormalities were bilateral or not. (Fig. 1).

The ventricular space was assessed with the Evans index (EI) and the fronto-occipital horn ratio (FOHR). The subarachnoid space width was analyzed at the frontal convexity, sylvian fissure and interhemispheric frontal fissure. To measure these parameters, the maximum frontal width was measured at the MRI slice were EI and FOHR were also measured. The interhemispheric width was measured at the tip of the falx in the same plane.

The extraaxial space volume was outlined and computed using BrainLab 2.0 with semiautomatic volume outline from the anterior to posterior commissure plane to the vertex. (Fig. 2).

To evaluate the relation between measured variables and subarachnoid space volume, an ANOVA test was performed. For resulting significant variables, the Pearson correlation coefficient was computed. Mean and standard deviation were obtained for each quantitative variable.

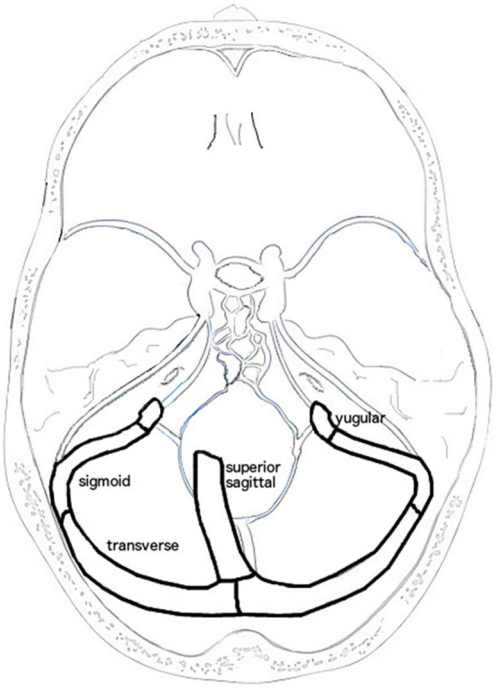

Fig. 1 Venous abnormalities grading. The number of affected segments encountered is noted up to seven according to the following segmentation: jugular left, jugular right, sigmoid left, sigmoid right, transverse left, transverse right, superior sagittal sinus

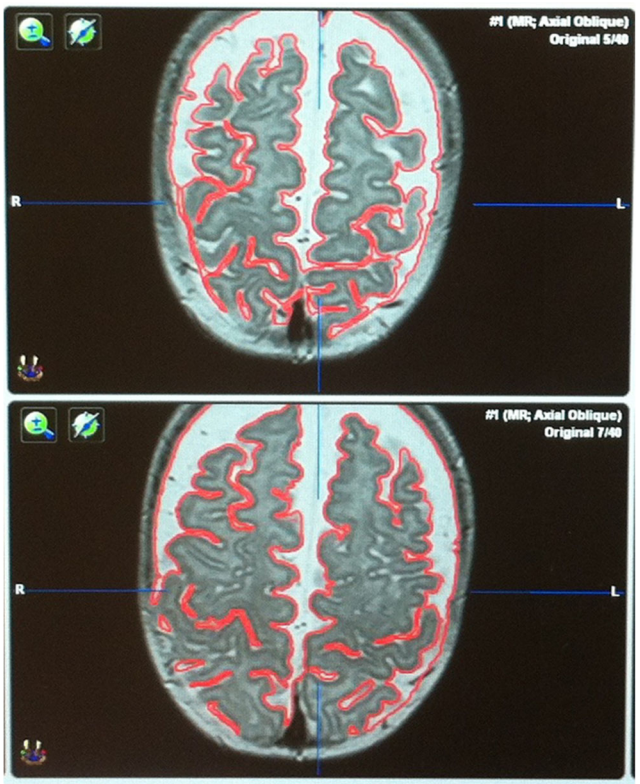

Fig. 2 Subarachnoid space volume outline accomplished with BrainLab 2.0 from the anterior to posterior commissure plane to the vertex

Results

Seventeen patients ranging from 3 to 24 months of age were studied, with a mean age of 12 months at diagnosis. Considering the distribution of ages, there was a single outlier of 24 months at diagnosis. If this patient was removed from calculation, the resultant mean age at diagnosis was 7 months. Male:female ratio was 11:6. All patients except one presented with macrocephaly or fast head growth with crossing percentiles. Thereby, head circumference percentile at diagnosis was over 97th in 14 cases. Six patients presented with other concomitant pathology or radiological features as extracranial collection (2), an arachnoidal sylvian cyst (1), lypomyelomeningocele (1), tethered cord (1), and a IV ventricle cyst (1).

Mean EI was 0.29 ± 0.04 and mean FOHR was 0.36 ± 0.04. Four patients were considered to have ventriculomegaly. Average interhemispheric width was of 5.79 mm ± 1.64 mm. For maximum frontal convexity width, the average was 8.54 ± 2.98 mm. Finally, the subarachnoid space volume at diagnosis had an average of 194.48 ± 59.02 cm^3.

Regarding treatment, in the majority of cases, a conservative approach was taken (76.5%, 13 of 17). After appropriate counseling, the remaining were treated more aggressively: two with a ventriculoperitoneal shunt because of neurological development delay respect to siblings, two received repeated CSF lumbar tapping, and two were treated with acetazolamide.

In 15 of 17, an abnormal cerebral phlebography of the large sinuses was found. These findings ranged from slight hypoplastic sinus segments to severe sinus stenosis based on neuroradiologist assessment. Quantitative data on the extent of the stenosis were not available from the radiological report and the 3D reconstruction deemed to be unfit for more than a descriptive analysis. The most frequently affected sinus segment was the sigmoid sinus (53.0%) followed by the transverse sinus.

Plotting the subarachnoid volume against the number of affected venous segments in the 15 patients with sinus abnormalities a positive linear correlation was found with a Pearson correlation coefficient of 0.57. As the number of affected venous segments increased, the volume of subarachnoid space among patients was also higher (Fig. 3). The ANOVA test for variables correlating with the volume of subarachnoid space showed only a significant correlation for the number of affected venous segments ($p = 0.028$).

Ventricular width as measured by EI and FOHR were not related to number of affected segments or subarachnoid space volume.

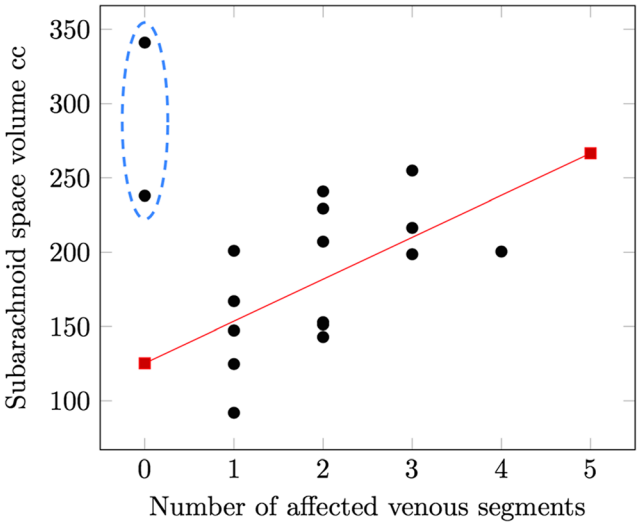

Fig. 3 Plot of subarachnoid space volume against number of affected segments. Excluding the two patients without any affected sinus segment (dashed blue ellipse), the patient data show a positive linear correlation clustering (red line) with a Pearson coefficient of 0.57

Discussion

Besides the outlier of two years of age, the mean age at diagnosis tallies other studies for external hydrocephalus [26]. There is controversy about what is considered to be normal width for subarachoid space in infants. Suggested upper limits based on healthy subjects are 4 mm for craniocortical width and 6 mm for interhemispheric width [17]. Nevertheless, these studies are based in ultrasound measurements with different measurement protocols and not available for MRI. In this study, all infants with external hydrocephalus except two showed cerebro-venous sinus abnormalities. Prevalence of these MR venogram abnormalities in healthy subjects is unknown. However, there was a linear correlation between the number of affected sinus segments and the amount of external CSF volume. The correlation between the extent of venous sinus alterations and the subarachnoid space volume was highly significant ($p = 0.028$).

There is mounting evidence that there is indeed a relation between the venous system and CSF dynamics. CSF pressure correlates with pressure measurements in the sagittal superior sinus and is high in (internal) hydrocephalic infants [21]. Pathologies like achondroplasy with known fixed venous sinus stenosis at the skull base are related to hydrocephalus, including the external variant. Even when venous pressure is raised acutely, compromising venous outflow, it may result in both external and internal hydrocephalus [9, 15].

Furthermore, arachnoid villi appear not to be the main outflow pathway for CSF neither in adults [13] nor in infants [23], challenging the common theory for external hydrocephalus. Studies on arachnoid granulations reveal that the immature state is common among all infants regardless their CSF condition [25]. Quantitative studies analyzing CSF flow conclude that the capillary bed must play an active role in CSF dynamics, specially relevant in infants, were the net aqueduct flow is into the ventricles [4, 18]. Non-obstructive variants of hydrocephalus in children are likely to be a problem of capillary bed pressure and thereby potentially can be affected by

changes in the cerebro-venous system. Moreover, direct changes in jugular flow and hence, pressure in the venous system, have been related to changes on the cortical subarachnoid space [10, 24].

Likewise, arterial inflow, if abnormally high, may also increase capillary bed pressure and result in a relative increase in venous outflow resistance (too high resistance for the large amount of blood to be transported), without venous stenosis. This mechanism is thought to produce in adults the less common form of hyperemic pseudotumor cerebri (as opposed to stenotic pseudotumor cerebri) and appears related to findings in some cases of idiopathic hydrocephalus in infants [2]. In this study, the two cases of macrocephaly with external hydrocephalus that presented no MR phlebographic sinus abnormalities are thought to represent a hyperemic form of external hydrocephalus as described by Bateman (5). However, we did not perform arterial inflow calculation to substantiate this possible explanation. A further cause could be an extra cranial venous flow stenosis at the level of the jugular veins, which were not investigated in this study.

In keeping with a venous pathophysiology of external hydrocephalus, the ventricular space was not correlated with CSAS volume. Molecular and cellular studies have revealed CSF circulation more complex than previously expected. At the core of the new concept is the Virchow Robin space, the unit were an active and regulated exchange of substances takes place in what has been called the "third circulation" acting as a clearance pathway for the interstitial fluid [6]. These structures are at the border between vessels, neural tissue and CSF space. Taking into account the proportion of perforating vessels in CSF compartments, the CSAS arises as a relevant compartment independent from ventricular space. It becomes particularly evident in those clinical settings where ventricular size remains unchanged.

Regarding external hydrocephalus in infants below 1 year, as sutures and fontanelles are open, CSAS increases also on account of the pressure driven skull expansion. Likewise, adult patients with a decompressive craniectomy, with equivalent less rigid skull, frequently develop subarachnoid CSF collections. These correlate to the extent of midline exposure and therefore proneness of the sagittal sinus to collapse under atmospheric pressure increasing venous outflow resistance [7].

In our study, ventriculomegaly was described by the neuroradiologist in only four cases. The FOHR, which is considered to be the best index of ventricular volume [22] was above normal (>0.37) in 5 patients, with a cohort mean of 0.36 ± 0.04. Ventricular size did not correlate with subarachnoid space volume in our study. This implies that eHC differs from classical obstructive internal hydrocephalus in that the ability of ventricular CSF to flow to the CSAS is unimpaired, making possible for this compartment to change in response to cerebral blood volume [24].

The core finding of this study is that the relation between cortical subarachnoid space volume and extent of venous impairment is positive, proportionate, and highly significant. This result supports the hypothesis that the impairment of venous outflow is a main driving factor in "external hydrocephalus" and first and foremost that it is related with its severity (Fig. 3).

The exact timeline of pathological steps in external hydrocephalus development remains unknown. It is not entirely clear from our data if venous abnormalities are the cause or the consequence of subarachnoid widening or both.

Dynamic venous stenosis due to collapsible sinus has been described and reported to improve after CSF pressure reduction through shunt insertion or after resolution of a CSF infection, revealing certain dynamic component of stenosis [3]. In our study, both patients who received a shunt due to clinical consequences of external hydrocephalus had a second MR phlebography showing a clear improvement of sinus stenosis (Fig. 4). This indicates that at least in some of those children a collapsible form of sinus stenosis was present. We

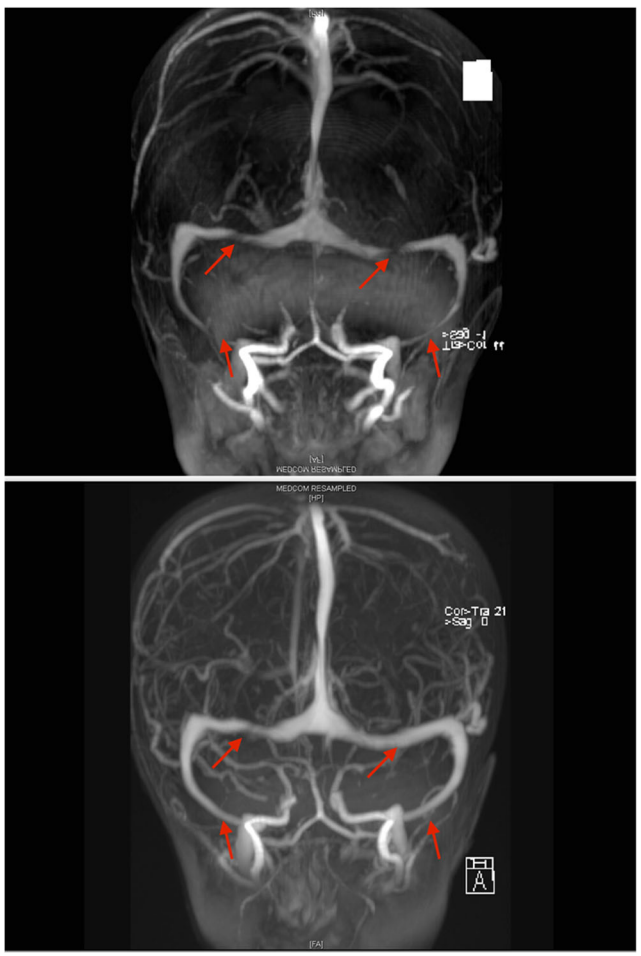

Fig. 4 MR phlebography of a patient with external hydrocephalus and stenotic sinuses before (up) and after (below) CSF shunting (red arrows) showing a reversible stenosis of the sinuses after shunting

hypothesize that the venous pathology is the origin of the disease, resembling the mechanism described in adults in pseudotumor cerebri [8]. Since the majority of children had a benign clinical course and did not receive a shunt, a discrimination of collapsible versus fix sinus stenosis cannot be made in this cohort.

Regardless of the initial cause for the venous sinus pressure to increase, CSF pressure in CSAS will increase accordingly and further compromise venous outflow in a positive feedback loop. Other studies have the same findings and conclude that there must be a dynamic component of obstruction.

The hypothesis for the development of cerebro-venous hypertension of infancy as the underlying pathophysiological momentum of external hydrocephalus is based on impairment of cerebro-venous outflow, increasing cerebral venous pressure. In turn, this produces increase in the capillary bed pressure affecting CSF absorption. Furthermore, the increase in ICP forces the growing infant skull to expand accordingly, contributing to CSAS widening since the brain growth is not equally enlarging by venous pressure. Thus, a mismatch between skull volume and brain volume develops.

Finally, the increased capillary bed pressures will produce an increase in cerebral blood volume augmenting brain turgor (Kb). Consequently, the CSF accumulation as a result of impaired CSF reabsorption does not lead to a ventricular widening, since the brain turgor prevents their expansion and forces ventricular CSF to be displaced to the cortical subarachnoid space [24]. Therefore, at least in an initial phase, ventricular volume will remain normal. Increased CSF pressure may trigger a secondary collapse of the venous sinuses fostered in case of wall instability, completing a vicious cycle (Fig. 5).

Considering this condition as benign has prevented invasive pressure recordings in the intracranial compartment or the sinuses in those infants. As venous occlusive factors are present in this pathology as demonstrated in this study

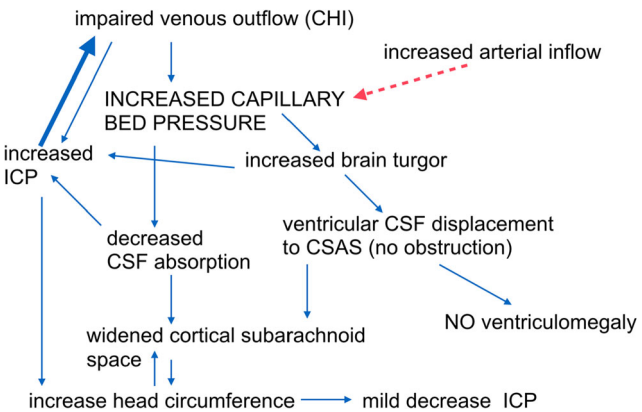

Fig. 5 Pathophysiological development of cerebro-venous hypertension of infancy (CHI). An increased venous pressure with impaired venous outflow would trigger elevation of the capillary bed pressure. Other forms of external hydrocephalus with no phlebography abnormalities may correspond to increased arterial inflow cases resembling the hyperemic form of pseudotumor cerebri in adults [2] (red dashed arrow)

and related literature, there is a high likelihood that indeed intracranial pressure is increased. None of the studied infants was classically symptomatic for raised intracranial pressure, probably because the skull expansion prevents very high pressures. However, pathological consequences may appear in the long run due to chronically abnormal venous and CSF dynamics after exhausting compensative mechanisms. Increased intracranial pressure is known to have a severe impact on development. Brain tissue undergoes mild hypoperfusion [16] and compromises myelination relating to developmental outcome [11]. In the external hydrocephalus condition, brain tissue may be affected during a critical time of development, interfering with the acquisition of certain skills, giving rise to permanent although subtle deficits. Functional long-term outcome studies in patients with external hydrocephalus show that although the majority is within the normal range of performance, a significant proportion presents with impaired attention skills and low borderline visuo-motor scanning performance [20].

Therefore, the issue of chronically raised intracranial pressure and low compliance as the result of venous outflow impairment should be clarified for external hydrocephalic infants in future studies. It is unclear how these venous anomalies evolve over time in these children. There is some inkling from single observation that they may attenuate or even resolve when subarachnoid collections subside either with treatment or spontaneously [5].

We conclude that impaired drainage of venous blood resulting in both (a) initially raised ICP, leading to skull expansion, and (b) impaired CSF dynamics with impaired capillary bed pressure constitute the main factors underlying the pathophysiology of the so-called "external hydrocephalus." Since "hydrocephalus" is a misleading term which automatically implies a primary CSF disorder, we suggest to use instead the term "Cerebro-venous Hypertension of Infancy" or CHI.

CHI is then the infant form of cerebrovenous hypertension which in older children, adolescents, or adults is commonly called pseudotumor cerebri (PTC), benign intracranial hypertension (BIH), or idiopathic intracranial hypertension (IIICH). The main difference between CHI and the adult form is the age at onset of the venous hypertension and thus the presence of open sutures and fontanels, leading to a rapid skull expansion, and thus to enlarged external CSF spaces. In the adult form, without skull expansion, external CSF spaces appear normal and high intracranial pressure usually develops.

The principal limitation of this study is the lack of quantification of the venous anomalies in terms of flow or degree of stenosis in comparison with healthy infants. Still, the relation found between graded venous anomalies and the extent of increased subarachnoid volumen and its proportionality indicates a strong pathophysiological dependence and not just an incidental concomitant finding.

Conclusions

The descriptive term "external hydrocephalus" is related in most cases to venous outflow stenosis and appears as an early onset analog of pseudotumor cerebri. It may thus be replaced by the pathophysiologically defined term of Cererbo-venous Hypertension of Infancy (CHI), as an age-related infant condition with self-limiting radiological enlargement of external CSF spaces and macrocephaly.

Considering the new evidence on pathophysiology as outline herein and missing systematic long-term outcome reports, further investigations are needed to assess the duration of venous sinus alterations over time (transient or permanent) and developmental consequences of venous outflow impairment and enlarged CSAS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Barlow CF (1984) CSF dynamics in hydrocephalus—with special attention to external hydrocephalus. Brain Dev 6:119–127
2. Bateman GA (2010) Hyperemic hydrocephalus: a new form of childhood hydrocephalus analogous to hyperemic intracranial hypertension in adults. J Neurosurg Pediatr 5(1):20–26
3. Bateman GA, Alber M, Schuhmann MU (2014) An association between external hydrocephalus in infants and reversible collapse of the venous sinuses. Neuropediatrics 45:183–187
4. Bateman GA, Brown KM (2011) The measurement of CSF flow through the aqueduct in normal and hydrocephalic children: from where does it come, to where does it go? Childs Nerv Syst 28:55–63
5. Bateman GA, Napier BD (2011) External hydrocephalus in infants: six cases with MR venogram and flow quantification correlation. Childs Nerv Syst 27:2087–2096
6. Brinker T, Stopa E, Morrison J, Klinge P (2014) A new look at cerebrospinal fluid circulation. Fluids Barriers CNS 11:10
7. De Bonis P, Pompucci A, Mangiola A, Rigante L, Anile C (2010) Post-traumatic hydrocephalus after decompressive craniectomy: an underestimated risk factor. J Neurotrauma 27:1965–1970
8. De Simone R, Ranieri A, Montella S, Bilo L, Cautiero F (2014) The role of dural sinus stenosis in idiopathic intracranial hypertension pathogenesis: the self-limiting venous collapse feedback-loop model. Panminerva Med 56(3):201–209
9. Dillon T, Berman W Jr, Yabek SM, Seigel R, Akl B, Wernly J (1986) Communicating hydrocephalus: a reversible complication of the mustard operation with serial hemodynamics and long-term follow-up. Ann Thorac Surg 41:146–149
10. Frydrychowski AF, Winklewski PJ, Guminski W (2012) Influence of acute jugular vein compression on the cerebral blood flow velocity, pial artery pulsation and width of subarachnoid space in humans. PLoS One 7(10):e48245
11. Hanlo PW, Gooskens RJ, van Schooneveld M, Tulleken CA, van der Knaap MS, Faber JA, Willemse J (1997) The effect of intracranial pressure on myelination and the relationship with neurodevelopment in infantile hydrocephalus. Dev Med Child Neurol 39:286–291
12. Hellbush LC (2007) Benign extracerebral fluid collections in infancy: clinical presentation and long-term follow-up. J Neurosurg 107(2 Suppl Pediatrics):119–125
13. Kapoor KG, Katz SE, Grzybowski DM, Lubow M (2008) Cerebrospinal fluid outflow: an evolving perspective. Brain Res Bull 77:327–334
14. Kumar R (2006) External hydrocephalus in small children. Childs Nerv Syst 22:1237–1241
15. Kendall B, Holland I (1981) Benign communicating hydrocephalus in children. Neuroradiology 21:93–96
16. Leliefeld PH, Gooskens RHJM, Vicken KL, Ramos LM, van der Grond J, Tulleken CAF et al (2008) Magnetic resonance imaging for quantitative flow measurement in infants with hydrocephalus: a prospective study. J Neurosurg Pediatrics 2:163–170
17. Libicher M, Tröger J (1992) US measurement of the subarachnoid space in infants: normal values. Radiology 184(3):749–751
18. Maki Y, Kokubo Y, Nose T, Yoshii Y (1976) Some characteristic findings of isotope cisternograms in children. J Neurosurg 45:56–59
19. Maytal J, Alvarez LA, Elkin CM, Shinnar S (1987) External hydrocephalus: radiologic spectrum and differentiation from cerebral atrophy. AJR Am J Roentgenol 148:1223–1230
20. Muenchberger H, Assaad N, Joy P, Brunsdon R, Shores EA (2006) Idiopathic macrocephaly in the infant: long-term neurological and neuropsychological outcome. Childs Nerv Syst 22(10):1242–1248
21. Norrell H, Wilson C, Howieson J et al (1969) Venous factors in infantile hydrocephalus. J Neurosurg 31:561–569
22. O'Hayon BB, Drake JM, Ossip MG, Tuli S, Clarke M (1998) Frontal and occipital horn ratio: a linear estimate of ventricular size for multiple imaging modalities in pediatric hydrocephalus. Pediatr Neurosurg 29(5):245–249
23. Oi S, Di Rocco C (2006) Proposal of "evolution theory in cerebrospinal fluid dynamics" and minor pathway hydrocephalus in developing immature brain. Childs Nerv Syst 22:662–669v
24. Rekate HL, Nadkarni TD, Wallace D (2008) The importance of the cortical subarachnoid space in understanding hydrocephalus. J Neurosurg Pediatr 2(1):1–11
25. Turner L (1961) The structure of arachnoid granulations with observations on their physiology and pathophysiological significance. Ann R Coll Surg Engl 29:237–264
26. Wiig US, Zahl SM, Egge A, Helseth E, Wester K (2017) Epidemiology of benign external hydrocephalus in Norway-a population-based study. Pediatr Neurol 73:36–41