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Paediatric pineal region cysts: Enigma or impaired glymphatic neurofluid system?

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HCL and HCB wrote the manuscript, and SDK added and completed the data with the results of real-time MRI investigations. HCL, HCB and SDK reviewed the manuscript.

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Abstract

Proposal: Pineal region cysts (PCs) may affect the tectum and aqueduct and cause deep central vein congestion and endocrine dysfunction. In addition to headaches, PC often causes a broad range of symptoms, leading to prolonged diagnosis and therapy. The aims of this study are to reveal parameters that might explain the ambiguity of the symptoms and to identify factors association with the respiration driven neurofluid preload system.

Methods: This retrospective study included 28 paediatric patients (mean age 11.6 years) who received surgical treatment for pineal region cysts and 18 patients (mean age 11.3 years) who were followed conservatively. Multiple clinical patient characteristics, such as symptoms, time to neuroimaging diagnosis, cyst size, ventricular indices, head circumference and postoperative outcome, were analysed. Four patients were investigated for CSF dynamics with real-time MRI. The mean follow-up time was 1.6 years.

Results: The most common early onset symptoms were headaches (92%), blurred vision (42.8%), sleep disturbances (39.3%) and vertigo (32.1%). Tectum contact was observed in 82% of patients, and MRI examinations revealed that imaging flow void signals were absent in 32.1% of patients. The mean cyst diameters were 13.7 mm for the axial axis and 15.6 mm for the longitudinal axis. Together with a postoperative flow void signal, 4 patients recovered their respiration-driven CSF upward flow, which was not detectable before OP. After operation in 92.1% of patients, the leading symptoms improved without any mortality or morbidity.

Conclusion: Despite proximity to the tectum and aqueduct with frequently absent aqueductal flow void signals, hydrocephalic ventricular enlargement was never detected. Data from real-time MRI depicted a reduced preoperative filling of the ventricular CSF compartments, indicating a diminished fluid preload, which recovered postoperatively.

Key words: Pineal cyst, hydrocephalus, microsurgery, real-time MRI, respiration, glymphatic system

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Introduction

Pineal cysts (PC) can often be completely asymptomatic and present as incidental findings in children and young adults, with a prevalence of 0.6-23% in the general population and a prevalence of up to 40% in autopsies (Michielsen, Benoit, Baert, Meire, & Caemaert, 2002). Sometimes, neurosurgeons see patients with a wide range of complaints and a pineal cyst on MRI, which makes decisions about surgical or conservative therapy difficult (Jenkinson, Mills, Mallucci, & Santarius, 2021), (Kalani et al., 2015). Some reports, studies and meta-analyses have examined PC; however, the data on paediatric patients are scarce. Chocque-Velaszquez (Choque-Velasquez et al., 2019) examined 109 paediatric patients from 43 study records (see Table 2 for an overview). Altogether, there are few reports in the literature regarding PCs among children, and evidence-derived standards for PC management or treatment are still not available. Pineal cysts derived from the pineal parenchyma cannot be easily distinguished from arachnoid cysts of the pineal region cisterns and 3rd ventricle. In contrast to other tumorous spaces requiring volumes in the pineal region (Böhrnsen et al., 2015), (Schulz et al., 2021), PCs are rarely accompanied by hydrocephalus despite aqueductal stenosis (Milton, Pelargos, & Dunn, 2020). Some researchers have attributed PCs to elevated venous pressure (Eide & Ringstad, 2017) and elevated CSF pulsatility (Eide & Ringstad, 2016). Aqueductal stenosis is expected to enlarge the supratentorial ventricular volumes. Implying an up-to-date view on hydrocephalus pathophysiology over the last 5 years (Steffi Dreha-Kulaczewski et al., 2015, 2017; H. Ludwig et al., 2021; H C Ludwig, Bock, & Dreha-Kulaczewski, 2020; H. Ludwig, Kulaczewski, & Bock, 2022; Hans C. Ludwig, Dreha-Kulaczewski, & Bock, 2021), symptomatic pineal cysts seem to offer a further understanding of related fluid dynamics. Since Klarica et al. (Klarica et al., 2009) demonstrated nonelevated ICP during 2 hours of measurement in a cat model following iatrogenic aqueductal stenosis, it has become obvious that the traditional Dandy concept has been turned towards another role for aqueduct and centripetal ventricular fluid filling by inspiration (Hans C Ludwig et al., 2020). We have recently published experiences from ETV procedures in which we showed CSF filling upward through the opened stoma (Hans C Bock, Dreha-Kulaczewski, Alaid, Gärtner, & Ludwig, 2019), (Hans C Ludwig, Dreha-Kulaczewski, & Bock, 2021b). Several clues have been identified regarding the concept of a strong regulatory role for the aqueduct with a small radial diameter, whose value accounts for the 4th power according to the law of Hagen-Poiseuille. This means that any small deviation of its diameter induces laminar fluid flow alterations in the fourth power. Because no alternate bypassing pathway exists for fluid conductance, inspiration-induced CSF flow can only enter the ventricles by the aqueduct, thereby functioning as a control valve to adapt to body positions and activity. Because of the transtentorial connection of the quadrigeminal cistern to the 3rd

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ventricle, intracranial or intraventricular pressure can be applied to the aqueduct for adaptation purposes. This mechanism allows pressure adaptations by the aqueductal diameter and a sort of fine tuning (Hans C Bock et al., 2019).

If such a mechanism exists, any adjacent cyst volume at the surrounding aqueductal environment should lead to the deterioration of the valve function like an added offset value in a regulatory pathway.

Therefore, the current single-centre study aimed to examine paediatric patients with fenestrated and nonfenestrated PC to identify different exploratory variables that might further elucidate the pathophysiology. In addition to clinical data, we concentrated on the symptomatology, duration of symptoms before diagnosis, geometry of the cysts and ventricular sizes. In a small group of patients, we performed additional imaging (i.e., real-time MRI) to analyse the CSF-flow dynamics.

Patients and methods

The retrospective study was conducted from 2007 to 2021 in a university hospital centre using prospectively collected data from our institutional paediatric neurosurgical patient registry (Hans Christoph Bock, Kanzler, Thomale, & Ludwig, 2018).

Most patients were referred directly for surgical consideration. Four patients with headaches and sleep disorders were treated with 2-4 mg melatonin at night. Patients who received microneurosurgical cyst fenestration via a suboccipital midline craniotomy underwent operations in a “sitting prayer position”, as described by Choque-Velasquez (2017) (Choque-Velasquez et al., 2017). The head was fixed in a Mayfield clamp, and patients were equipped with a centrally positioned venous line and transoesophageal ultrasound probe to detect air bubbles in case of aspiration. Postoperative ICU care was performed overnight, and the mean hospital admission time was 9 days. Postoperative control was performed after 4 hours by CCT. Each patient underwent postoperative MRIs at 3-month intervals. Four patients were investigated further pre- and postoperatively via real-time MRI (Steffi Dreha-Kulaczewski et al., 2015), (Steffi Dreha-Kulaczewski et al., 2017). Patients without specific complaints and surgical therapy did not receive further follow-up. Statistical calculations and graphics were performed with Statistica™ (TIBCO Software Inc. Palo Alto, CA 94304 USA) using ANOVA. Informed consent was obtained from patients or their caregivers. The institutional review board of the Georg August-University Goettingen approved the study (12-9-17), and the study complied with the Declaration of Helsinki.

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Real-time phase-contrast flow MRI

All datasets were acquired on a 3 Tesla scanner (Magnetom Prisma Fit, Siemens Healthcare) using real-time phase-contrast flow MRI based on highly undersampled radial FLASH sequences as described (Unterberger & Holzapfel, 2014), (Joseph et al., 2012), (Steffi Dreha-Kulaczewski et al., 2015, 2017; H. Ludwig et al., 2021) Measurements in sagittal or coronal orientation to the stoma in the floor of the 3rd ventricle were conducted with a 64-channel head coil.

RT-MRI data analysis

Real-time flow MRI datasets were quantitatively analysed using CaFuR software (Fraunhofer Mevis, Bremen, Germany) (Chitiboi et al., 2014) designed to accomplish automatic segmentation of flow signals in real-time image series. Manual definition of an initial ROI for the determination of through-plane flow was based on both signal intensities in magnitude images and corresponding phase difference values in velocity maps. Further data processing was performed using MATLAB (Mathworks, Massachusetts, USA), including net flow calculation and data visualization.

Results

The surgically treated children (N=28) were between 10 months and 17 years old, the mean age was 11.6 years, and the female/male ratio was 1.15. The mean time interval from diagnosis to operation was 11.8 months, with a follow-up interval of 1.3 years. Nonoperated children (N=18) were 11.3 years old, with a female/male ratio of 3.5. For this group, the follow-up interval was shorter, with a mean of 0.97 years. The interval between symptoms and first admission was 11.6 (11.3) months, reaching a maximum of 5 years. BMI was similar in both groups, with 20.21 and 23.1, and the mean head circumference was 66 P (63 P for nonoperated children). Symptoms leading to admission included headaches (92%), blurred vision (42.8%), sleep disturbances (39.3%), and vertigo (32.1%). Two patients had a papilledema preop. Direct contact of the PC to the tectum was counted in 82%, and a missing flow void signal was found in 32.1%. The mean cyst diameters were 13.7 mm for the axial axis and 15.6 mm for the longitudinal sagittal axis. For nonoperated patients, cyst diameters and lengths were estimated as 8.1 x 9.1mm, each below one centimetre. Ventricular sizes were never hydrocephalic, instead “normal” or even classified “small” with mean ER (0.26) and FOHR (0.33). Physical strain during sportive activity (25%) and educational schooling disorders were estimated as 21%. Together with a postoperative flow void signal in 64.3%, 4 patients re-established their respiration-driven CSF upward flow by real-time MRI, which was not detectable before OP. The mean ER (0.25) and FOHR (0.33) were not significantly altered at postoperation. Indicating communication, the occurence of air inside the ventricles 4 h after

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the operation was 75% (Table 2 for details). Among the 4 patients treated with melatonin, 2 (2 mg/night) had complete headache relief.

In nearly all cases (93%), the leading symptoms improved or remained stable after the operation.

Nine patients showed a patent flow void inside the aqueduct on the postoperative MRI, in which no flow void could be distinguished preoperatively. There was no mortality or morbidity. The mean length of hospital stay was 9.4 days.

Author	Year	Period (years)	N	Centres	Age	Children	f>m
Uschold	2011	?	6	1	26	2	y
Kalani	2015	14	18	1	24	few	y
Majovski	2017	16	110	1	?	no	?
Majovski	2017		4	1	?	no	?
Choque-Velasquez	2019	18	60	1	29	?	y
Koziarski	2019		28	1	31	few	y
Pitskhelani	2019	21	25	1	> 18	no	y
El Damaty	2019	15	43	3	25,6	few	y
Milton	2020		24	11	50	few	y
Yeung	2021	?	97	1	?	?	y
Mendoza	2021		84	1	?	no	y
Jenkinson	2021	Review		1		no	y

Table 1: Overview of the literature on PC in adults and children (Uschold, Abla, Fusco, Bristol, & Nakaji, 2011), (Kalani et al., 2015) , (Májovský, Netuka, & Beneš, 2017; Májovský, Řezáčová, et al., 2017), (Choque-Velasquez et al., 2019), (Koziarski, Podgórski, & Zieliński, 2019), (Pitskhelauri et al., 2019), (Damaty, Fleck, Matthes, Baldauf, & Schroeder, 2019), (Milton et al., 2020), (Yeung et al., 2021), (Mendoza et al., 2021), (Jenkinson et al., 2021).

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Variable	OP		Non-OP		
		%		%	p value
Patients	28		18		
f/m	1.15		3.5		0.10
Age OP (mean)	11.68		-		-
Age (years) at time of decision (mean)	11.68		11.3		0.38
Height (cm) (mean)	160.3		149.7		0.20
Weight (kg) (mean)	47.66		60.8		
BMI (mean)	20.21		23.1		0.14
FU (years) (mean)	1.37		1.02		-
Interval (mean)	11.8		7.8		0.48
Progression of complaints	3	10.70	0	0.00	0.18
Head circumference (mean P)	66		70		0.95
MRI presentation					
Cyst diameter (mm) (mean)	13.7		8.1		0.01
Cyst length (mm) (mean)	15.6		9.1		0.01
Contrast enhancement of cyst wall	2	0.07	0	0.00	0.26
Multiple compartments	4	14.20	4	22.22	0.50
Tectum contact	23	82.10	15	83.33	0.01
Aqueductal Flow void pre	9	32.00	12	66.67	0.21
ER pre (mean)	0.26		0.23		0.04
FOHR pre (mean)	0.33		0.31		0.79
Complaints/Symtoms					
Headache	26	92.8	12	66.67	0.01
Nausea/Vomiting	3	10.70	5	27.78	0.63
Vertigo	9	32.00	4	22.22	0.72
Vision	12	42.8	5	27.78	0.20
Dizziness	6	21.00	4	22.22	0.78
Sleep disorder	11	39.2	9	50.00	0.74
Sport disorder	6	21.40	1	5.56	0.13
Education disorder	7	25.00	3	16.67	0.29
Seizures	3	10.70	0	0.00	0.17
Treatment and Outcome					
Melatonin treatment	0		4	22.00	-
Flow void postoperation	18	64.30	-	-	-
ER postoperation (mean)	0.25	-	-	-	-
FOHR postoperation (Mean)	0.33	-	-	-	-
Headache postoperation	5	7.10	-	-	-
Vomiting postoperation	0	-	-	-	-
Vertigo postoperation	0	-	-	-	-
Vision disorder po postoperation st	2	7.10	-	-	-
Sleep disorder po postoperation st	0	-	-	-	-
Air inside ventricles at 4 h postoperation	21	75.00	-	-	-

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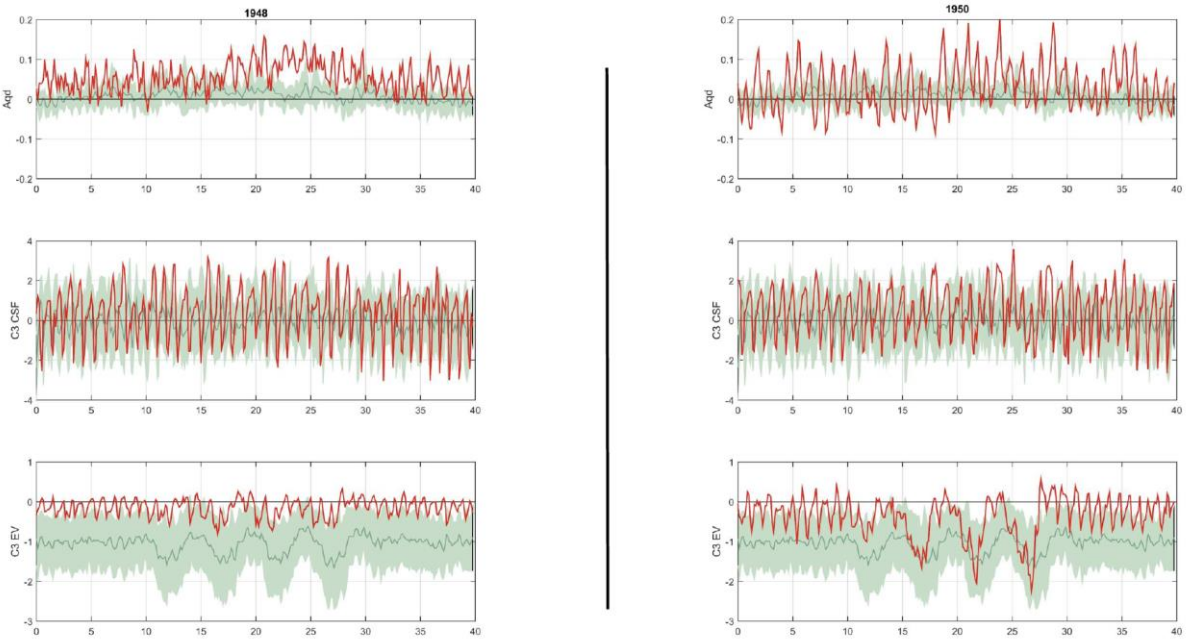
Table 2: Descriptive statistics

The real-time MRI data showed significantly higher CSF upward flow inside the aqueduct at postoperation than at preoperation.



RT-MRI data showing **one** individual (red line) with (left) preoperative periods of normal breathing followed by deep inspiration after 12 sec with consecutively altered venous blood dynamics at the level of C3 and CSF dynamics at level C3 and measured at the aqueduct (Aqd) for 16 seconds. On the right side, equal parameters at level C3 but higher CSF flow through the aqueduct. The green coloured mantle curves are an individual overlay on data from a healthy study group (H. Ludwig et al., 2022).

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Statistics

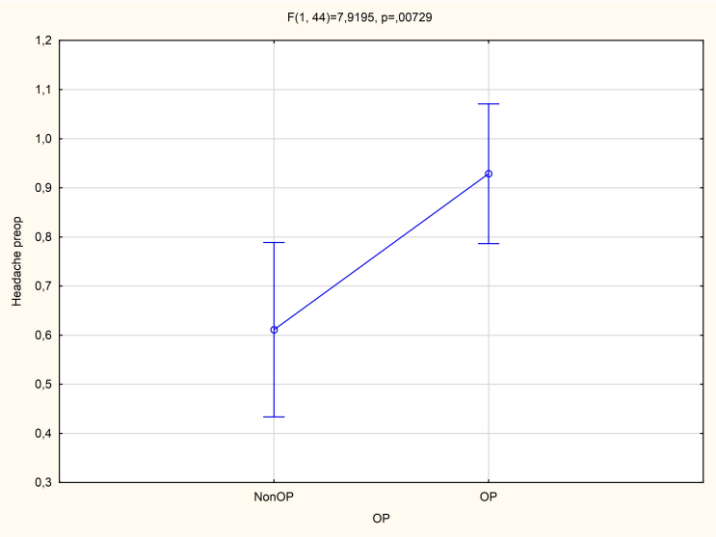

Diagram 1: Headache as a significant (p=0.07) main symptom in patients with and without microsurgical fenestration

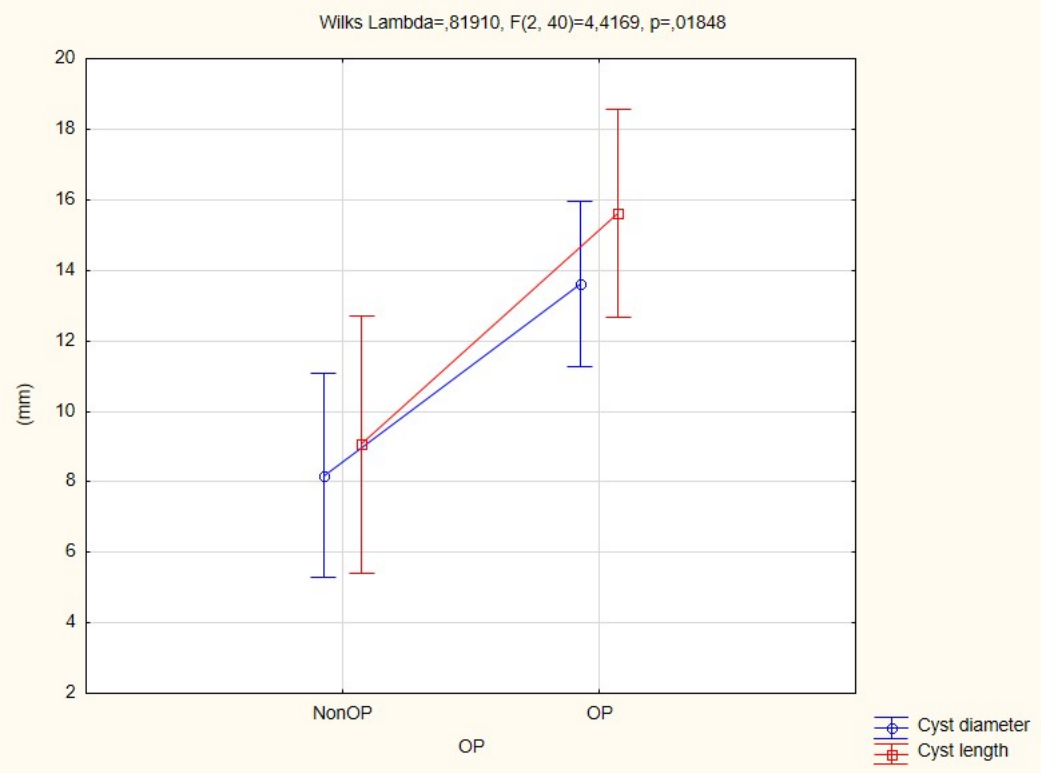

Diagram 2: Diameter and sagittal length for operated and nonoperated cysts (p=0.018)

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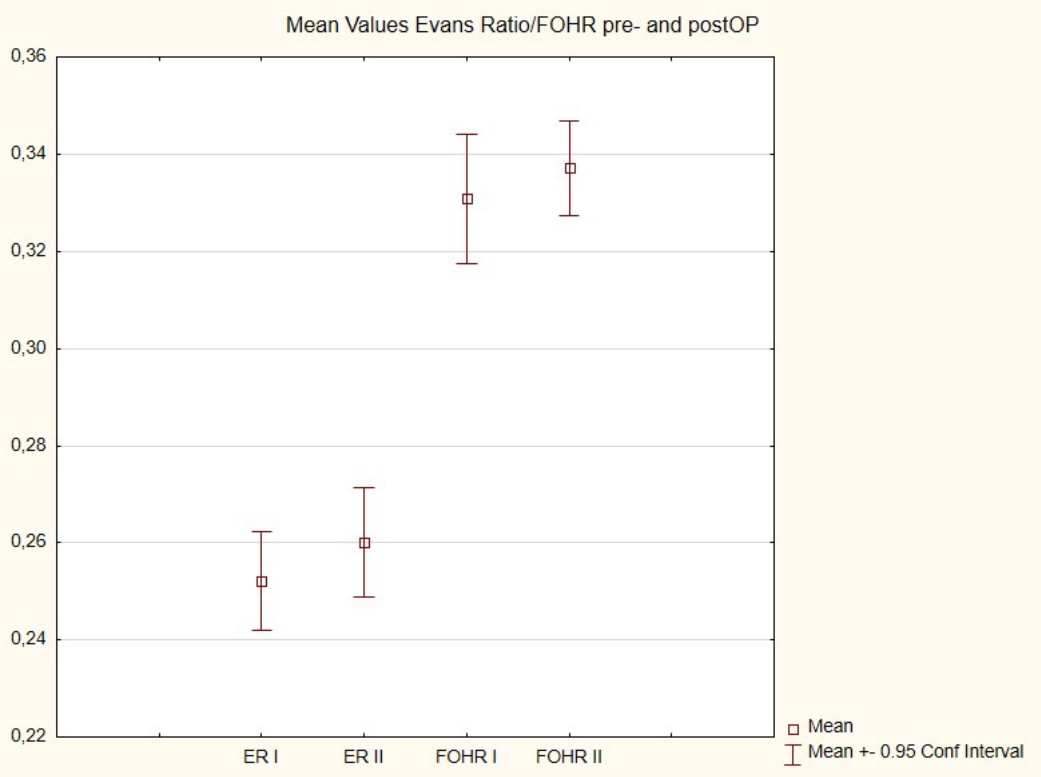

Diagram 3: Evans's ratio (ER) and FOHR for patients who received microsurgical fenestration preoperation (I) and postoperation (II), not significant

Discussion

Pineal cysts occur in children and adults (Pu et al., 2007). They are considered to be of benign character without any symptomatology and without the need for further follow-up.

Pineal cysts could be detected incidentally by MRI in children at a rate of 57% with a mean diameter of not more than 6 mm, and they are often multicystic parenchymal cysts without thickened walls or contrast enhancement (Whitehead, Oh, & Choudhri, 2013). Usually, females are more likely to be affected than men, with a female/male ratio of 1.5. For several years, a growing number of studies have described (Table 1) pineal cyst disease, which is attributed to headache, nausea and vomiting, dizziness and vertigo, sleep disturbances with deferred sleep induction and daytime sleepiness. Some patients report blurred vision, and in childhood, some patients develop educational difficulties with school annoyance and sporting aversion. Most patients lack clinical signs of hydrocephalus. Differentiation from other types of headaches, which belong to the main burden of diseases in school-aged children and young adolescents, is rather difficult (Leonardi et al., 2021). Melatonin deficiency has been identified by some authors as a reason for symptomatology of PCs (Májovský, Řezáčová, et al., 2017), but the results were inconsistent. Usually, clinical management of these patients is carried out by

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neurologists, and in the case of MRI imaging, radiologists and neurologists deny any further indication in regard to the usually small ventricular dimensions and the missing Parineaud syndrome. This diagnostic path may be the main reason for the long diagnostic delay after the beginning of complaints. If those patients are presented occasionally to the neurosurgeon, some of the reported symptoms resemble those of patients with arachnoid cysts or idiopathic intracranial hypertension (IIH). Indeed, the leading symptoms are severe and frequent headaches. Getting aware of this symptomatology, a growing number of neurosurgeons tend towards microsurgical fenestration, which often and statistically significantly resolves or at least weakens complaints (Yeung et al., 2021) (Milton et al., 2020). The indication for surgery should consider reported cases with severe surgical morbidity and even mortality (Choque-Velasquez et al., 2019) despite higher grades of surgical experience. A common feature for the broad symptomatology is the lack of any hydrocephalus and Parineaud syndrome, which belong to the main classic cornerstones of space-occupying lesions of the pineal region. Given the anatomical specialties of this region, four main pathophysiological systems seem closely related. (1) The close vicinity to the aqueduct interferes with the CSF passage. (2) The close vicinity to the central veins could challenge venous drainage. (3) Contact with the quadrigeminal plate could affect visual accommodation, hearing sensations and proprioception. (4) Finally, the endocrine function for secretion and distribution of melatonin could be affected. In contrast to the pineal gland, any cystic alteration of the pituitary gland of similar size would be expected to cause severe symptomatology. We cannot explain why any cystic space-occupying process inside the pineal region with densely packed content and densely sealed arachnoid membranes (Fig. 3) of appropriate size contacting the deep veins and the tectal plate is not able to cause aqueductal stenosis with elevated mean ICP and hydrocephalus. In such investigations, only ICP pulsatility scores were elevated(Eide & Ringstad, 2016) (Eide: 2016kk) but not ICP mean values themselves. Eide and Ringstad reported shunt therapy in some cases with PC and addressed a higher central venous pressure as a main cause of the disease (Eide & Ringstad, 2017). We therefore searched for parameters in our patient cohort with pineal cysts treated surgically or followed conservatively, which could further explain the specificities of the disease. Decision-making in such cases, as long as no clear evidence exists, is partly led by the “gut feeling”. To enhance the insights into the underlying pathophysiology, we have tried to include our experience with neurofluid flow (Hans C. Ludwig et al., 2021). In contrast to traditional concepts, sustainable CSF upward flow caused by inspiration is the most important part of the fluid exchange system of CSF with interstitial fluid and its entrance into the glymphatic system, which was traditionally called the “minor pathway” (Oi & DiRocco, 2006) (Hans C. Ludwig et al., 2021), (Hans C Ludwig, Dreha-Kulaczewski, & Bock, 2021a). Sustainable flow is caused by deep inspiration during non-REM sleep (Fultz:2019dq), whereas cardiac triggered oscillations cause fast but ineffective fluid

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movements that are visible on conventional MRI scanners as flow void signals. Conventional scanners must quench low-frequency breathing signals (Takizawa, Matsumae, Sunohara, Yatsushiro, & Kuroda, 2017) due to the processed cardiac triggered high-volume signals. This has been outlined recently in detail by our group (S Dreha-Kulaczewski et al., 2018). An important part of this fluid flow passes the aqueduct in the upward direction. The aqueduct is the unique fluid conducting element with a small diameter and a characteristic curve, which is regulated by the 4th power according to Hagen and Poiseuille's statute. This tuning element is severely disturbed in aqueductal stenosis, for example, by membranes or tumours. Whereas pure stenosis always leaves a tiny residual hole for at least some fluid passage, in the case of tumour-related complete stenosis, ventricular autonomy can be reached without any ventricular enlargement. Hydrocephalic triventricular dilatation, on the other hand, appears to be the result of incomplete stenosis due to a CSF trapping mechanism (Hans C Bock et al., 2019). If a similar mechanism is the underlying cause of a cystic space-occupying process with contact to the tectal plate and aqueductal flow hindrance, the equilibrated system should deteriorate in regard to its regulating function. We have therefore emphasized in our study those parameters, which might agree with this hypothesis in a cohort of 28 surgically treated children compared to the second cohort, in which the decision for conservative treatment was favoured. Similar ages, similar female/male ratios, body weight and height, BMI, ventricular indices ER and FOHR and similar symptoms were analysed. The main significant differences were the severity and frequency of headache, cyst diameter, and detectable aqueductal flow void signal in T2 MRI imaging. In accordance with the recent literature, nearly all reported patients did not suffer from hydrocephalus, but headaches, blurred vision nausea, disturbed sleep induction were the main symptoms (Damaty et al., 2019). After surgical treatment, more than 90% of patients experienced the disappearance of complaints. Focusing on children, we can confirm the reported experiences by our data. The most convincing details were the significant difference regarding the frequencies of headaches, the size of the cyst and the ventricular dimensions in those patients who received surgery compared to the children who decided to receive conservative therapy. We did not expect any certain or significant increase in ventricular size after the operation. The visible widening of the frontal horns postoperatively, as shown in Figure 1, is below the threshold of the ventricular indices. Therefore, the results of the real-time MRI investigations are most important, as they could show a certain inspiration triggering CSF flow movement upwards through the postoperatively unhindered aqueduct. This upward stream is necessary for the preload of the interstitial fluid flow system and the termination of complaints. This could already be shown by our group for ETV in the treatment of obstructive hydrocephalus (H. Ludwig et al., 2022) (Ludwig, 2021) and confirms our hypothesis of a deregulated aqueductal function as the main cause of the disease.

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Conclusion

Our data of 28 children with microsurgical fenestration of PC compared to a cohort of 18 conservatively observed children could show striking evidence for differences in regard to the main symptom headache and the significance of the cyst diameters. Only a few patients experienced headache relief with sleep induction by melatonin. After microsurgical fenestration of pineal cysts preserving the pineal gland, most children were free of headaches, nausea, vomiting, blurred vision, or cognitive deficits. Part of the pathophysiology seems to be a disturbed fluid exchange system by any offset to the tuning features of the aqueduct, in which its diameter counts for the 4^{th} power according to Hagen-Poiseuille's law. Therefore, most patients had a slight elevation of the postoperative ventricular indices, even if the data were not significant. Similar mechanisms of the disturbed neurofluid system are involved in obstructive hydrocephalus and might be directly involved in pseudotumor cerebri. Our experiences could lead to more differentiated decision-making in treating this PC disease.

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