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Original article

Changes of third ventricle diameter (TVD) mirror changes of the entire ventricular system after initial therapy and during follow-up in pediatric hydrocephalus

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ABSTRACT

Purpose: Regular measurement of ventricular size is important in children with hydrocephalus. After closure of the fontanelle this is currently addressed by repetitive cranial MRI or CT imaging, coming along with risks of anaesthesia or radiation. As the third ventricle is accessible via the temporal bone window using ultrasound, determination of its diameter might be an easy and radiation-free alternative to assess the ventricular system. An essential precondition is that changes of the third ventricle diameter (TVD) mirror changes of the whole ventricular system. This study compares changes of TVD with changes of ventricular indices before and after initial treatment of hydrocephalus and during the following evolution.

Methods: MRT/CT images from 117 children with hydrocephalus were evaluated at time of diagnosis, after initial therapy and during follow-up with functional shunts. Measurements included axial TVD and three standard linear measures of the lateral ventricles (Evans Index - EI, fronto-occipital horn ratio - FOHR Index, and Cella Media Index - CMI). Furthermore, a correlation within subjects was calculated in 8 patients over the entire available follow-up.

Results: Relative changes of TVD were significantly correlated to relative changes of all ventricular indices ($r = 0.48$, $r = 0.68$ and $r = 0.701$ for EI, FOHR and CMI, respectively, $p < 0.01$). The correlation within subjects was outstanding for EI ($r = 0.988$), FOHR ($r = 0.99$) and CMI ($r = 0.99$).

Conclusion: TVD showed a significant correlation with all three linear indices at the time of diagnosis and during follow-up changes independently of age, aetiology and ventricular

Abbreviations: TVD, Third ventricle diameter; Sd, standard deviation; CSF, cerebrospinal fluid.

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width. TVD and its changes are therefore a reliable surrogate of changes in ventricular size in pediatric hydrocephalus undergoing treatment.

1. Introduction

Hydrocephalus is one of the most common pathologies in pediatric neurology and neurosurgery.[1,2] Besides clinical assessment, a regular evaluation of the ventricular size is an essential component in routine follow-up care of these patients. In children with patent anterior fontanelle, imaging diagnostic of the ventricles is easy to perform using trans-fontanelle ultrasound.[3,4] After closure of the anterior fontanelle, CT and MRI scans remain, so far, as the most commonly used imaging techniques to visualize the intracranial ventricular system.

Therapy for hydrocephalus is known to be associated with some morbidity and therapy failure.[5,6] Furthermore, children often present with nausea and vomiting for harmless reasons, symptoms that are mimicking shunt-dysfunction. Thus, repetitive MRI/CT scans are used in clinical routine to determine ventricular width in children with hydrocephalus. In patients below an age of 5 years, MRI scans are often tolerated with general anaesthesia or analgo-sedation only. In consequence, repeated MRI/CT scans come along with known risks of exposure to radiation or anaesthesia. Another radiation- and anaesthesia-free technique for ventricle investigation is fast-brain MRI,[7] but this is also associated with a certain effort, not feasible with very small or incompliant children and it is also uneconomical when more frequently used.

An alternative imaging technique is the visualization of the third ventricle using ultrasound via the trans-temporal bone window. This method has mainly been described for evaluation of brain structures and ventricles in patients with neurodegenerative[8–11] and psychiatric[11] disorders but also for investigation of ventricle enlargement in hydrocephalus[12,13] of adults. The accessibility rate of intracranial structures via trans-temporal ultrasound is mainly limited by thickness of the temporal bone and is described to 80–95% in the adult population.[14] As temporal bone windows in children are at least as penetrable for ultrasound, ultrasound-based measurement of the third ventricle has the potential to be a reliable and radiation-free method to assess the ventricular system in children with hydrocephalus.

An essential precondition therefore is, that changes of third ventricle diameter correlate to changes of the whole ventricular system and thus represent the situation of the entire intracranial ventricles correctly and reasonably.

This study compares changes of third ventricle diameter (TVD) to changes of three standard ventricle indices in MRI/CT images after initial therapy and during chronic evolution in pediatric hydrocephalus, considering the influence of age, aetiology, ventricle configuration and ventricular width.

2. Materials and methods

2.1. Study design

This study was performed as a retrospective observational study. Pediatric patients between newborn and 16 years, treated at the University Hospital of Tuebingen, Department of Neurosurgery, Division of Pediatric Neurosurgery were enrolled into the study if they underwent a diagnostic or surgical procedure for diagnosis or therapy of hydrocephalus. Patients with rare forms of occlusive hydrocephalus above the third ventricle were not included in this study.

The study protocol was approved by the institutional ethics committee (project number: 476/2017BO2).

2.2. Study population

The overall cohort included 117 patients aged newborn to 16 years with a median age of 1.4 years; 60 children were >1 year, 57 ≤ 1 year. 68 children were male (58.1%), 49 were female (41.9%).

Diagnoses encompassed aqueduct stenosis (17.1%), posterior fossa (PF) obstructive hydrocephalus (27.4%, including Dandy Walker Malformations, Blake's Pouch, Blake's Pouch like Hydrocephalus and Chiari Malformation), posthemorrhagic hydrocephalus (25.6%), tumor-associated hydrocephalus (17.1%) and other forms of hydrocephalus (12.8%), such as brain anomalies and post-infectious hydrocephalus.

A total of 394 imaging scans were analyzed, 352 of whom were MRI scans and 42 were CT scans. CT scans were only used, when MRI scans were not available.

2.3. Measurement of third ventricle diameter (TVD) and standard ventricle indices

All measurements were done by one examiner (L.L.S), experienced in cranial MRI/CT assessments. Measurements were mainly performed on high resolution T1 MRI scans or in few cases on CT scans of the brain and included axial third ventricle diameter[15] and three standard linear measures - Evans Index (EI), FOHR (frontal occipital horn ratio) Index and Cella Media Index (CMI).[16–18] The measurements were performed as described in Fig. 1. The third ventricle diameter was measured on the axial plane underneath the Foramen of Monro but above the mesencephalon on the thalamic level straight in the middle of the fronto-occipital direction.

Measurements were done at initial diagnosis, after therapy (time range between pre- and post-operative MRI-imaging was 0–48 months, dependent on age of the child and possibility of transfontanellar ultrasound imaging) and within the

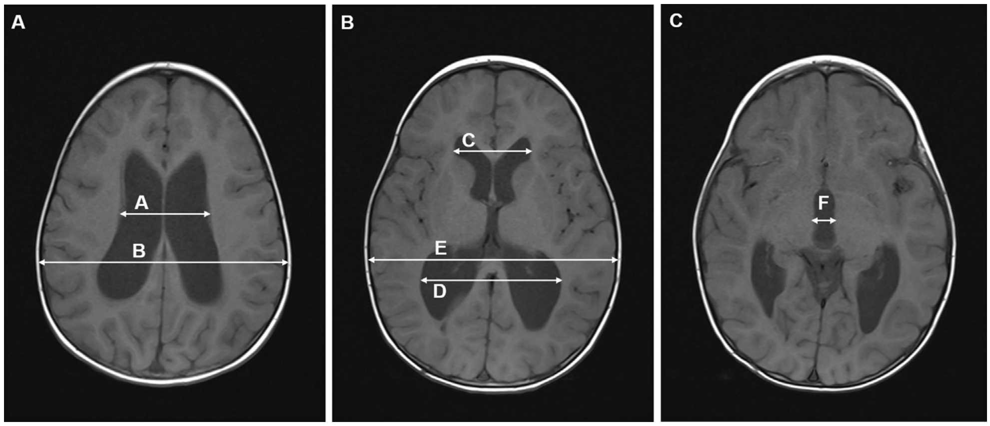

Fig. 1 – A Representative illustration of CMI determination on axial T1 MRI of the brain; CMI = A/B B Representation of measurement of Evans Index (EI) and FOHR Index; EI = C/E, FOHR Index = (C + D)/2E C Illustration of axial TVD determination.

further course of the patient. The relative differences of TVD and index values in-between those different time points were calculated and compared. Relative differences were calculated in percent using the formula $\frac{(A-B)}{A}$ x100 (A = initial value, B = value post therapy). 8 patients received a minimum of 3 measures, so that an observation of the long-term development of the ventricular system was possible.

2.4. Statistical analysis

Data were tested for normality of distribution using Kolmogorov-Smirnov or Shapiro-Wilk test. Parametric data were reported as means and standard deviation (sd). The analyses were done using SPSS (PASW Statistics 18, IBM) statistical software. Depending on normality of distribution, the correlation of the variables was tested using Pearson's or Spearman's correlation coefficient. Bland-Altmanś Analysis was used to test for correlation within subjects. Statistical significance was set at $p < 0.05$. The independent Student's t-test was used for comparing mean values.

3. Results

3.1. Third ventricle diameter (TVD) and lateral ventricles decrease significantly after initial therapy of pediatric hydrocephalus

64 patients underwent therapy after initial diagnosis of hydrocephalus. 27 (42.2%) patients were female, 37 (57.8%) were male. Patients with rare occlusive forms of hydrocephalus above the third ventricle were excluded. At the time of diagnosis, children were aged between newborn and 13 years, median age was 1.7 years. 34 children were >1 year, 30 ≤ 1 year. 14 (21.9%) children had aqueduct stenosis, 13 children had PF (20.3%) and posthemorrhagic hydrocephalus (20.3%), 15 patients had a tumor-associated hydrocephalus (23.4%) and 9 patients had other forms of hydrocephalus (including brain anomalies). 44 children received a ventriculo-peritoneal-Shunt (68.8%), in 11 patients (17.2%) an endoscopic, laser-assisted ventriculostomy was performed and in 9 children (14%) a resection of an intracranial tumor-mass treated the occlusive hydrocephalus as well.

Patients were divided into subgroups regarding pathology. TVD and ventricle indices were measured before and after hydrocephalus therapy. Mean differences between pre- and post-operative values were calculated.

Mean TVD ranged between a minimum of 10.88 ± 5.27 mm (PF obstructive hydrocephalus) and a maximum of 14.21 ± 5.84 mm for other forms of hydrocephalus. Mean normal TVD values according to the literature are 5.54 ± 1.29 mm for boys and 4.98 ± 1.08 mm for girls, respectively[15]). Detailed pre- and post-operative values as well as mean differences for hydrocephalus subgroups are summarized in Table 1. In Fig. 2 box plots of pre- and post-operative TVD, EI, FOHR and CMI are illustrated.

The subgroup "others", encompassing patients with post-infectious hydrocephalus or brain anomalies, revealed the largest ventricles at initial diagnosis with a TVD of 14.21 ± 5.84 mm, an EI of 0.44 ± 0.12, a FOHR of 0.58 ± 0.1 and a CMI of 0.58 ± 0.14. FOHR index showed a significant decrease in all aetiologies, whereas in the subgroup with PF hydrocephalus TVD, CMI and EI showed a non-significant decrease.

3.2. Changes of TVD correlate to changes of lateral ventricles after initial therapy of pediatric hydrocephalus

To evaluate if a decrease of TVD after initial hydrocephalus therapy correlates to the decrease of the lateral ventricle width, relative differences between pre-and post-operative TVD and all ventricle index values were calculated in percent.

In 64 patients, that underwent therapy of hydrocephalus, the mean relative decrease of TVD after therapy was 34 ± 22% (±sd), compared to 13.6 ± 11% for EI, 15.1 ± 12.5% for FOHR and 20.4 ± 15.6% for CMI. The relative decrease of TVD was significantly higher than relative decrease of the ventricular indices ($p < 0.001$). Results according to different hydrocephalus aetiologies are summarized in Table 1.

In the entire cohort, relative changes of TVD revealed a significant correlation to relative changes of all three

Table 1 – Mean (±sd) TVD and ventricle indices before and after hydrocephalus therapy and mean TVD and ventricle index differences after therapy with p-values considering different hydrocephalus aetiologies.

Aetiology	TVD pre in mm (mean ± sd)	TVD post in mm (mean ± sd)	TVD difference in mm (mean ± sd)	TVD difference in % (mean ± sd)	p- value
Aqueduct stenosis	13.04 ± 7.57	10.07 ± 7.1	2.97 ± 2	27.05 ± 19.16	<0.001***
PF Hydroc.	10.88 ± 5.27	9.13 ± 6.28	1.74 ± 5.9	31.09 ± 18.7	n.s.
Posthemorrh. Hydroc.	12.27 ± 5.16	8.27 ± 6.2	3.99 ± 3.8	36.66 ± 33.71	<0.01**
Tumor ass. Hydroc.	11.35 ± 4.7	6.61 ± 2.76	4.74 ± 2.8	40.59 ± 12.17	<0.001***
Others	14.21 ± 5.84	9.84 ± 6.17	4.37 ± 2.55	34.45 ± 23.12	<0.01**
Aetiology	**EI pre (mean ± sd)**	**EI post (mean ± sd)**	**EI difference (mean ± sd)**	**EI difference in % (mean ± sd)**	**p- value**
Aqueduct stenosis	0.37 ± 0.09	0.32 ± 0.09	0.046 ± 0.04	13.66 ± 12.28	<0.001***
PF Hydroc.	0.35 ± 0.09	0.32 ± 0.08	0.031 ± 0.06	11.47 ± 12.6	n.s.
Posthemorrh. Hydroc.	0.39 ± 0.07	0.31 ± 0.05	0.08 ± 0.06	19.17 ± 12.24	<0.001***
Tumor ass. Hydroc.	0.32 ± 0.05	0.28 ± 0.04	0.04 ± 0.03	10.38 ± 7.99	<0.01**
Others	0.44 ± 0.12	0.37 ± 0.11	0.07 ± 0.04	14.83 ± 7.42	<0.01**
Aetiology	**FOHR pre (mean ± sd)**	**FOHR post (mean ± sd)**	**FOHR difference (mean ± sd)**	**FOHR difference in % (mean ± sd)**	**p- value**
Aqueduct stenosis	0.53 ± 0.1	0.46 ± 0.1	0.067 ± 0.06	12.71 ± 11.74	<0.01**
PF Hydroc.	0.48 ± 0.08	0.42 ± 0.1	0.067 ± 0.1	16.74 ± 15.42	<0.05*
Posthemorrh. Hydroc.	0.55 ± 0.7	0.44 ± 0.08	0.11 ± 0.09	19.14 ± 14.44	<0.01**
Tumor ass. Hydroc.	0.43 ± 0.06	0.39 ± 0.05	0.04 ± 0.03	9.99 ± 5.59	<0.001***
Others	0.58 ± 0.1	0.47 ± 0.12	0.11 ± 0.07	19.01 ± 13.01	<0.01**
Aetiology	**CMI pre (mean ± sd)**	**CMI post (mean ± sd)**	**CMI difference (mean ± sd)**	**CMI difference in % (mean ± sd)**	**p- value**
Aqueduct stenosis	0.51 ± 0.15	0.42 ± 0.17	0.089 ± 0.06	18.67 ± 13.83	<0.001***
PF Hydroc.	0.46 ± 0.15	0.4 ± 0.12	0.075 ± 0.13	19.04 ± 14.66	n.s.
Posthemorrh. Hydroc.	0.54 ± 0.08	0.4 ± 0.13	0.14 ± 0.13	25.49 ± 21.05	<0.01**
Tumor ass. Hydroc.	0.34 ± 0.07	0.28 ± 0.06	0.06 ± 0.05	18.21 ± 11.27	<0.001***
Others	0.58 ± 0.14	0.46 ± 0.16	0.13 ± 0.11	21.61 ± 18.18	<0.01**

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

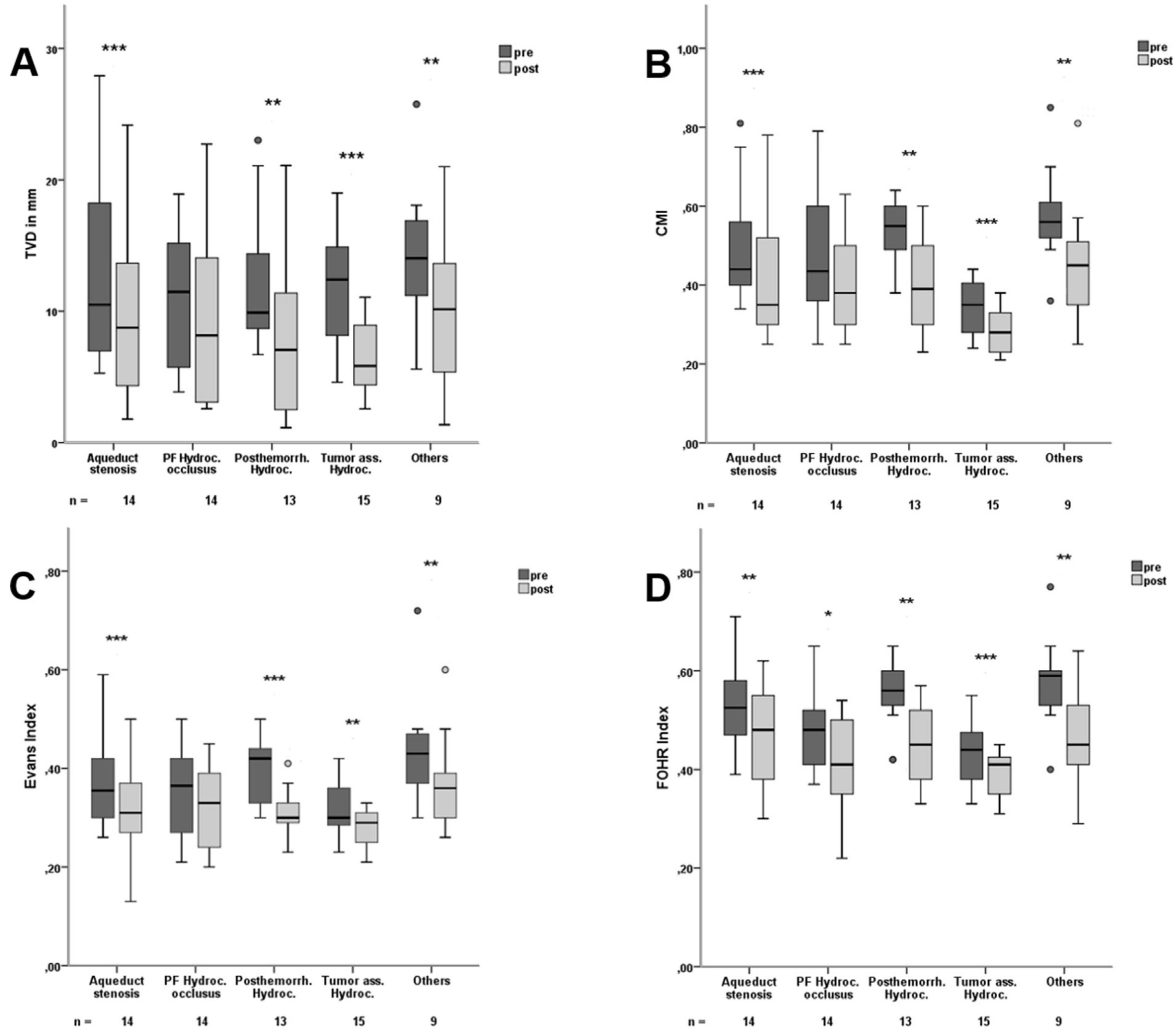

Fig. 2 – Box plots show TVD and lateral ventricle indices before and after initial therapy of pediatric hydrocephalus. Dark grey plots illustrate values at initial diagnosis (pre therapy) and light grey plots mark values after initial therapy (post therapy). Aetiologies are represented on x-axis. * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$. A Third ventricle diameter (TVD) in mm decreased significantly after therapy of different forms of hydrocephalus in children. B Decrease of Cella media Index (CMI), C Evans Index and D FOHR Index after therapy of pediatric hydrocephalus.

ventricular indices, with $r = 0.48$, $r = 0.68$ and $r = 0.701$ for correlation with EI, FOHR and CMI, respectively ($p < 0.01$). An exemplary scatter plot for correlation between decrease of TVD and CMI after therapy is shown in Fig. 3.

3.3. *Age does not affect TVD-lateral-ventricle correlation*

34 children of the cohort that underwent initial therapy of hydrocephalus were >1 year and 30 children were ≤1 year. To investigate if age has an influence on TVD-lateral-ventricle correlation, correlation coefficients for relative changes of TVD and relative changes of lateral ventricle indices were calculated for both age subgroups.

For children >1 year mean initial TVD was 13.7 ± 6.4 mm and for children ≤1 year 10.7 ± 4.4 mm (mean normal TVD values according to the literature are 5.54 ± 1.29 mm for boys and 4.98 ± 1.08 mm for girls and ranging between 4.11 and 4.97 mm in children < 3 years and 3.55 mm–4.32 mm for children > 3 years[15]).

TVD decrease correlated well to decrease of FOHR and CMI independently of age (r ranged between 0.6 and 0.83, $p < 0.01$) and for EI in children ≤ 1 y. The correlation between TVD and EI was poor for the cohort >1 year ($r = 0.21$), Correlation coefficients for different age groups are summarized in Table 2.

3.4. *Influence of aetiology on TVD-lateral-ventricle correlation*

We investigated if aetiology affects development of third and lateral ventricles after hydrocephalus therapy.

To address this, patients were allocated to subgroups regarding underlying aetiology of hydrocephalus. 14 patients

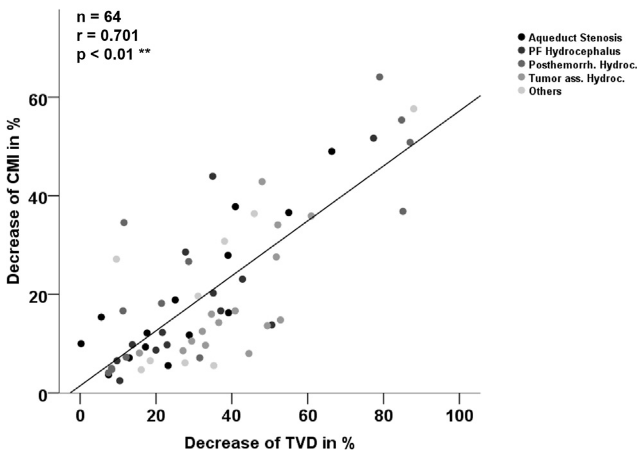

Fig. 3 – Correlation of percental TVD and CMI decrease after therapy of hydrocephalus in children.

suffered from aqueduct stenosis, 13 from posterior fossa (PF) hydrocephalus (including Dandy-Walker Malformation, Blake's Pouch, Blakes pouch like, and Chiari Malformation with and without spina bifida), 13 children had a post-hemorrhagic hydrocephalus, 15 patients had a tumor-associated hydrocephalus and 9 children had other forms of hydrocephalus (including post-infectious forms and brain anomalies).

Decrease of TVD after therapy correlated well to decrease of ventricle indices independently of pathology (Table 3). Regardless of aetiology, the correlation between TVD and EI changes was poorest. The best correlation was found between TVD and CMI changes followed by TVD and FOHR changes.

3.5. *Influence of ventricle configuration on TVD-lateral-ventricle correlation*

Some patients develop asymmetric ventricle configurations during course of their disease. In our cohort 7 patients presented with asymmetric lateral ventricles and 57 children had a symmetric ventricle configuration. We calculated correlation coefficients for TVD and ventricle indices for patients with symmetric and asymmetric ventricles to illustrate differences.

Compared to previous investigations, we found the best correlation for TVD and CMI changes and the poorest for TVD and EI changes (Table 4). Patients with asymmetric ventricles were without disadvantage and showed even slightly better correlations.

Table 2 – Correlation between change of TVD and change of ventricle indices in % after initial therapy of pediatric hydrocephalus for patients > and ≤1 year. $^{**}p < 0.01$.

Age	Number	Correlation TVD-EI	Correlation TVD-FOHR	Correlation TVD-CMI
>1 year	34	0.21	0.60^{**}	0.83^{**}
≤1 year	30	0.56^{**}	0.78^{**}	0.78^{**}

3.6. *Impact of ventricle width on correlation of TVD and lateral ventricles*

For evaluation if the initial width of ventricles does influence the correlation between TVD and lateral ventricle decrease after therapy of hydrocephalus, the patient cohort was subdivided into 4 groups regarding width of third ventricle at presentation.

The first group included patients with a width of the third ventricle between 4 and 10 mm (n = 28). The mean TVD (±sd) was 7.18 ± 1.86 mm with a mean EI of 0.32 ± 0.06, FOHR of 0.46 ± 0.09 and a mean CMI of 0.42 ± 0.14 respectively.

The second group encompassed 17 children with a TVD ranging between 11 and 15 mm. The mean TVD (±sd) was 12.86 ± 1,2 mm, with a mean EI of 0.37 ± 0.05, mean FOHR of 0.51 ± 0.07 and a mean CMI of 0.48 ± 0.12 respectively.

The third group included 14 patients with a TVD between 16 and 20 mm. Mean TVD (±sd) was 17.36 ± 1.38 mm, mean EI was 0.43 ± 0.05, mean FOHR 0.56 ± 0.05 and mean CMI 0.55 ± 0.12.

In the fourth group were only 5 patients with a TVD ranging from 21 to 26 mm and a mean TVD of 24.77 ± 2.72 mm. Mean index values were 0.51 ± 0.14 for EI, 0.64 ± 0.10 for FOHR and 0.67 ± 0.11 for CMI, respectively.

Evaluating the correlation between relative decreases of TVD and lateral ventricles after hydrocephalus therapy within these different subgroups, the correlation between TVD and CMI was best (r ranging between 0.695 and 0.859, p < 0.01) and the best correlation was found for patients with a TVD between 11 and 15 mm. The poorest correlation was found for TVD and EI with r values ranging between 0.33 and 0.785.

Patients with relatively wide ventricles (TVD between 16 and 20 mm in width) had the best overall correlation between TVD and all three lateral ventricle indices.

In summary, independently of width of the ventricles, changes of TVD correlate well to changes of lateral ventricles after therapy of pediatric hydrocephalus (Table 5).

3.7. *Changes of lateral ventricles correlate to changes of TVD during long-term follow up of pediatric hydrocephalus*

8 children underwent repetitive MRI imaging as part of a follow-up routine or due to symptoms suspicious of shunt failure. 4 children were male and 4 patients were female; At the time of initial measurement 6 children were >1 year and 2 children were ≤1 year. Diagnoses encompassed aqueduct stenosis (n = 2), PF hydrocephalus (n = 1), posthemorrhagic hydrocephalus (n = 3), tumor-associated hydrocephalus (n = 1) and other forms of hydrocephalus (n = 1).

In each individual comparative measurements of TVD and ventricle indices were performed at 4 different time points (ranging from 0 to 57 months in between) and TVD in mm was compared to each ventricle index.

The correlation within subjects for TVD was outstanding with all three lateral ventricle indices (EI (r = 0.988), CMI (r = 0.99) and FOHR (r = 0.99)). A representative illustration of correlation within subjects for TVD and FOHR is shown in Fig. 4A.

To test for intra-individual correlations of TVD and indices, correlation-coefficients and -curves of TVD and FOHR were

Table 3 – Correlation between change of TVD and change of ventricle indices in % after initial therapy of pediatric hydrocephalus for different hydrocephalus forms. *p < 0.05, **p < 0.01.

Aetiology	Number	Correlation TVD-EI	Correlation TVD-FOHR	Correlation TVD-CMI
Aqueduct Stenosis	14	0.65*	0.82**	0.87**
PF Hydroc.	13	0.67*	0.70**	0.77**
Posthemorrh. Hydroc.	13	0.5	0.81**	0.86**
Tumor ass. Hydroc.	15	0.52*	0.75**	0.69**
Others	9	0.071	0.69*	0.79*

Table 4 – Correlation between change of TVD and change of ventricle indices in % after initial therapy of pediatric hydrocephalus considering ventricle configuration. **p < 0.01.

Ventricle configuration	Number	Correlation TVD-EI	Correlation TVD-FOHR	Correlation TVD-CMI
symmetric	57	0.48**	0.68**	0.71**
asymmetric	7	0.69**	0.8**	0.87**

Table 5 – Correlation between change of TVD and change of ventricle indices in % after initial therapy of pediatric hydrocephalus considering ventricle width. *p < 0.05, **p < 0.01.

TVD width in mm	Number	Correlation TVD-EI	Correlation TVD-FOHR	Correlation TVD-CMI
4–10	28	0.49**	0.64**	0.695**
11–15	17	0.33	0.73**	0.859**
16–20	14	0.785**	0.698**	0.799**
21–26	5	0.35	0.478	0.810*

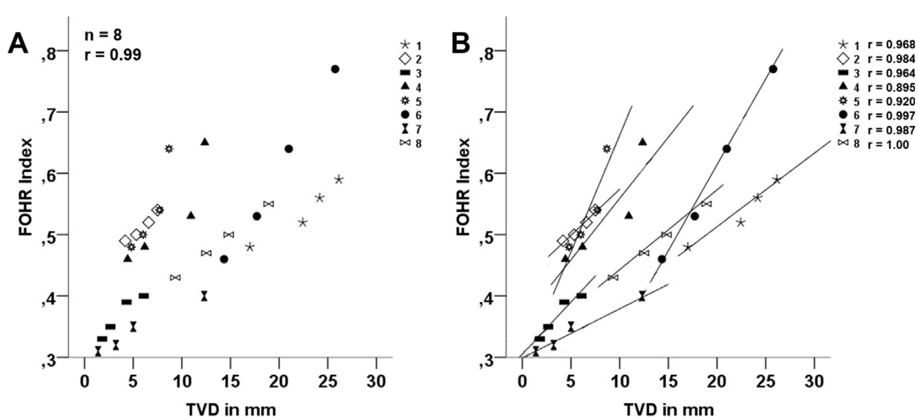

Fig. 4 – A Correlation within subjects of TVD and FOHR in 8 children during repeated follow-up investigations. Different icons highlight individual patients. B Intra-individual correlation of TVD and FOHR in 8 different patients with hydrocephalus. Calculation of correlation coefficients demonstrates excellent correlation for each subject.

calculated exemplary for each patient. Individual correlations of TVD and FOHR were excellent, correlation-coefficient r ranging from 0.895 to 1.00 (Fig. 4B).

4. Discussion

This study is the first and only in the current literature, that investigates the correlation of changes of the third ventricle to changes of lateral ventricles after therapy and during long-term follow-up of pediatric hydrocephalus considering the influence of age, aetiology, ventricle configuration and ventricle width. It is furthermore the first study of its character that reports on the influence of hydrocephalus aetiology on initial width of lateral ventricles and third ventricle. Additionally, it is the only study of this kind, where it can be shown that changes of third ventricle diameter directly reflect changes of the lateral ventricles in pediatric hydrocephalus, especially in the intra-individual course (which is the most important result regarding the clinical use), where correlation coefficients were close to 1 in all patients.

When using ultrasound-based, transtemporal measurement of the third ventricle for monitoring of hydrocephalus, it is essential that changes of the third ventricle diameter directly correlate to changes of the lateral ventricles. The third ventricle must be a reliable surrogate of the entire ventricular system, to be measured alone and representatively for all ventricles together. Rare occlusive hydrocephalus forms due to occlusion of the foramina of Monro leading to a separation of the third and lateral ventricles, are, of course, exempted of this consideration.

In the current literature, there are several studies reporting on the reliability of ventricular indices regarding assessment of ventricle size or comparing ventricular indices with intraventricular volume and intracranial pressure.

In one study an excellent correlation between the standard ventricle indices (FOHR, EI, CMI and bicaudate index) and ventricular volume was found in a pediatric cohort.[19] FOHR and CMI could reflect ventricle volume better than EI and bicaudate index could. O'Hayon, who was the first to define FOHR index, also revealed that FOHR correlates much better to ventricular volumes than EI does.[17] Using EI for assessment of ventricular width also bears a risk for missing hydrocephalus cases where occipital lateral horns expand earlier than the frontal horns,[20] what is not a rare scenario in children with hydrocephalus. In most of these studies, third ventricle diameter or third ventricle index was not considered and only one study defined normal values for ventricular indices including third ventricle diameter for pediatric patients.[15]

There is, to our knowledge, so far, no study in the literature where dynamic changes of lateral ventricles and the third ventricle were investigated and compared.

Measurement of ventricle volume would be, of course, the gold standard to investigate changes of the ventricles. But in the clinical routine ventricle volume determination to detect changes in ventricle configuration is not feasible since it is very time consuming and requires special computerized segmentation algorithms. Therefore, it is substituted by ventricle index measurement in the majority of all publications on pediatric hydrocephalus. There are several studies showing excellent correlations between ventricle indices and ventricle volume.[17,19] Thus, we decided relative differences of TVD not to compare to ventricle volumes but to relative differences of FOHR, CMI and EI in this study.

After initial therapy of hydrocephalus, the relative decrease of TVD revealed a good correlation to all three standard ventricle indices. In the entire cohort, the best correlation was found between TVD and CMI ($r = 0.701$), followed by TVD and FOHR ($r = 0.68$). As might have been expected from the above cited literature, EI had the poorest correlation to TVD for the entire cohort ($r = 0.48$, $p < 0.01$).

The overall correlation between TVD and lateral ventricle indices was independent of age and form of hydrocephalus.

Interestingly, the ventricle configuration did also not affect the correlation between TVD and lateral ventricle indices. Even if the number of children with asymmetric ventricle configuration was quite low ($n = 7$), this cohort showed even a slightly better TVD-ventricle-index-correlation. This is a remarkable and significant finding, as asymmetric ventricle configurations are a common phenomenon in pediatric hydrocephalus.

There is also one study in the previous literature comparing ventricle indices with ventricle volumes regarding ventricle size and symmetry.[21] Here, in patients with asymmetric ventricles, ventricle indices could also reliably reflect real ventricle volume.

We furthermore found that the initial width of ventricles seems not to affect the correlation between decrease of TVD and lateral ventricles after therapy. According to the literature, normal values for EI are below 0.3[22] and normal TVD values range between 5.54 ± 1.29 mm for boys and 4.98 ± 1.08 mm for girls.[15] In our hydrocephalus cohort, mean TVD was 7.18 ± 1.86 mm for the hydrocephalus subgroup with the smallest ventricles (subgroup 1, mean EI 0.32 ± 0.06) with an incremental increase of both TVD and lateral ventricle indices to a maximum of 24.77 ± 2.72 mm for TVD and 0.51 ± 0.14 for EI in subgroup 4. According to the previous results, correlation between TVD and EI was poorest except for subgroup 3 with a TVD between 16 and 20 mm ($r = 0.785$, $p < 0.01$).

In the individual assessment, the correlation within subjects for TVD and all ventricular indices ($r = 0.988–0.99$) and the intra-individual correlation during long-term follow up was outstanding (r ranging from 0.895 to 1.00). This information is of high value, since it allows TVD to be used for reliable assessment of ventricular size during long-term follow-up instead of “whole cranium” imaging with CT or MRI.

The intra-individual correlation between TVD and FOHR index was higher than the overall correlation of TVD and lateral ventricle indices (r ranging from 0.48 to 0.701). This underscored, that the reliability of TVD to represent the entire ventricular system, is best in the intra-individual application, what thus should be considered as the main purpose of this technique.

It is conspicuous, that the statistical variation of TVD measurements was higher compared to the ventricular indices and spread from ±41–58% for initial TVD values and from ±14.8–33% for initial CMI values. Moreover, the relative decrease of TVD after therapy was 34 ± 22% as compared to the relative decreases of EI (13.6 ± 11%), FOHR (15.1 ± 12.5%) and CMI (20.4 ± 15.6%). Fig. 3 shows that small decreases of CMI are usually associated to stronger TVD decrease. There are few cases where CMI decreased stronger or similar as TVD did.

These results indicate, that TVD does react more sensitive to hydrocephalus therapy regarding the relative decrease than the lateral ventricles indices do. This is largely because TVD is a direct measurement on a relative short distance. A decrease of e.g. 2 mm from 8 mm to 6 mm already means a decrease of 25%, whereas a decrease of the lateral ventricular width of 2 mm will not have a big effect in all ventricular indices, where the whole head diameter, that will not change, is taken into calculation.

Provided that an ultrasound technique for determination of third ventricular diameter is as precise and reliable as MRI, TVD monitoring by ultrasound might be even more sensitive to detect smaller changes in ventricular size than standard assessment of EI, FOHR or CMI on the basis of MRI or CT scans is. For clinical usage, one should thus keep in mind that TVD tends to “over-react” to hydrocephalus therapy and that marked changes of TVD can be associated with only small changes of the lateral ventricles.

In summary, these results demonstrate, that the third ventricle and changes of its axial diameter reliably mirror changes of the lateral ventricle indices. Thus, TVD and its changes may be considered as a valid surrogate parameter of changes of whole ventricular volume in pediatric hydrocephalus.

Patients were, moreover, divided into subgroups according to the underlying hydrocephalus aetiology and decrease of TVD and indices was recorded in number and percent.

Tumor patients (with acquired hydrocephalus) presented with the tightest lateral ventricles (mean ± sd: EI 0.32 ± 0.05, FOHR 0.43 ± 0.06, CMI 0.34 ± 0.07); TVD was the second tightest with 11.35 ± 4.7 mm. The patients of the subgroup "others" including congenital brain anomalies and post-infectious hydrocephalus, presented the largest initial ventricle size, regarding lateral and third ventricles.

With regard to ventricle decrease after therapy, patients with tumor-associated hydrocephalus showed, despite smaller initial TVD values, the strongest decrease of TVD after therapy (mean percental TVD decrease 40.59 ± 12.17%, $p < 0.001$), but the smallest decrease in all lateral ventricle indices. An overall strong decrease of TVD and lateral ventricles could be found for patients with posthemorrhagic hydrocephalus.

The smallest reduction of TVD and the second smallest reduction of lateral ventricles was found in patients with aqueduct stenosis.

These results indicate, that width of ventricles is not merely determined by presence of hydrocephalus but also by the underlying pathophysiological mechanism, the period of life, in which the hydrocephalus emerged and duration of hydrocephalus. All these aspects seem to influence initial size and extent of reduction of ventricles after therapy.

Other factors that might influence ventricle width are for example brain atrophy, brain edema and idiopathic intracranial hypertension (IIH).[23]

It was demonstrated, that in children with large ventricular volume, the ventricle decrease was stronger within 3–6 months after ETV, than in patients with initial small ventricle volume.[24] In this study all patients had abnormal high ventricle volumes in the long-term follow up after ETV. Moreover, there are further studies reporting, that a decrease of ventricular size after ETV was not necessary to be equal to a clinically effective treatment of the hydrocephalus.[25,26]

In summary, these results demonstrate, that pathophysiology and relationship between CSF dynamics, intracranial pressure and intracranial ventricles are complex and most probably affected by many different aspects. Initial ventricle size as well as extent of ventricle decrease after therapy seem to be influenced by the form of hydrocephalus and its underlying pathophysiological mechanism.

5. Conclusion

This study demonstrates, that changes of TVD reliably and coherently reflect changes of the lateral ventricles after initial therapy of pediatric hydrocephalus and during long-term evolution. Furthermore, it could be shown, that initial ventricle width and extent of ventricle reduction after therapy is influenced by the underlying hydrocephalus aetiology.

Axial Third Ventricle Diameter (TVD), which can potentially be determined apart from standard imaging techniques like CT and MRI by high resolution trans-temporal ultrasound in children, is thus a reliable parameter to assess changes of ventricle width/size after initial therapy and during long-term follow up in pediatric hydrocephalus. This opens up the avenue to ultrasound determination of TVD to partially substitute MRI and CT imaging in clinical practice for the assessment of ventricular size in pediatric hydrocephalus. This approach can be applied to all forms of hydrocephalus except rare occlusive forms of hydrocephalus above the third ventricle.

Conflicts of interest

The authors have no potential conflict of interests to declare.

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