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# Influence of sex and disease etiology on the development of papilledema and optic nerve sheath extension in the setting of intracranial pressure elevation in children

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ABSTRACT

*Introduction:* Dilatation of the optic nerve sheath diameter and swelling of the optic disc are known phenomena associated with intracranial pressure elevation.
*Research question:* Do sex and disease etiology have an impact on the development of optic disc elevation and optic nerve sheath extension in children in the setting of ICP elevation? Fundoscopic papilledema and point-of-care-ultrasound techniques-optic nerve sheath diameter (US-ONSD) and optic disc elevation (US-ODE) - were compared in this regard.
*Material and methods:* 72 children were included in this prospective study; 50 with proven pathology (e.g. pseudotumor cerebri, tumor), 22 with pathology excluded. Bilateral US-ONSD and US-ODE were quantified by US using a 12-MHz-linear-array-transducer. This was compared with fundoscopic optic disc findings and in 28 patients with invasive ICP values, stratified for sex and etiology.
*Results:* In patients with proven disease, significant more girls (69%) had fundoscopic papilledema compared with boys (37%, $p < 0.05$). Girls had also larger US-ODE values ($0.86 \pm 0.36$ mm vs. $0.65 \pm 0.40$ mm in boys). 80% of tumor patients had initial papilledema (100% girls, 79% boys), compared with 50% in pseudotumor cerebri (PTC) (83% girls, 30% boys). US-ONSD had no sex- and no etiology-specificity.
*Discussion and conclusion:* Presence of papilledema appears to be influenced by sex and etiology, whereas US-ONSD is not. Girls seem more likely to develop papilledema under similar conditions. Male sex and PTC appear as risk factors for being undetected by fundoscopic findings. US-ONSD and US-ODE seem useful tools to identify pathologies with potentially increased ICP requiring treatment in children regardless of sex and etiology.

## 1. Introduction

Rapid and reliable detection of increased intracranial pressure (ICP) is an essential skill in medical institutions treating children. To date, fundoscopic examination of the eye ground to detect or exclude papilledema is still the gold standard of non-invasive ICP diagnosis (Bartsikhovsky et al., 2019; Passi et al., 2013). However, it is known that the diagnostic quality of papilledema is limited, partly due to the fact that papilledema takes an average of 7 days to develop (Liu et al., 2020), and 1.5–2.5 months to regress (Reier et al., 2022). Fundoscopic presence of papilledema is of high specificity to indicate raised ICP but its sensitivity is often reported to be reduced, as elevated ICP can be associated with absent papilledema (Aylward et al., 2016; Masri et al., 2022; Nazir et al., 2009; Nuijts et al., 2022). An alternative method of non-invasive ICP estimation is transorbital point-of-care-ultrasound measurement of the optic nerve sheath diameter (US-ONSD). A high correlation of US-ONSD to invasively measured ICP has been described in children (Kerscher et al., 2019a; Padayachy et al., 2016a), and quantifiable ONSD cut-off values (Kerscher et al., 2019a; Padayachy et al., 2016b) can be used as a first-line and follow-up diagnostic tool in children with elevated ICP. Elevation of the optic disc can be measured by point-of-care US (US-ODE) as well. A recent study revealed, that the combination of US-ONSD and US-ODE might be a promising diagnostic tool to monitor

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**Abbreviations**

| | |
|---|---|
| ONSD | Optic nerve sheath diameter |
| ONS | Optic Nerve Sheath |
| ODE | Optic disc elevation |
| ICP | intracranial pressure |
| US | ultrasound |
| PTC | Pseudotumor cerebri |
| FU | follow up |
| Y | year(s) |

elevated ICP in adults (Yu et al., 2023).

Although there are numerous studies in the literature on ONSD and papilledema in children, very little research has been done on whether sex and the underlying disease driving ICP elevation influence the development of papilledema and optic nerve sheath (ONS) dilatation.

Recent MRI and CT-based studies on ONSD in children described an age dependency of the width of the ONSD and boys generally had significantly wider ONSD values than girls (Bardak et al., 2023; Raffa et al., 2023). There is also evidence that the type of ICP-increasing disease in children might affect the width of the ONSD (Padayachy et al., 2016a).

Young age has been identified as a factor limiting the susceptibility of papilledema (Lee et al., 2017; Tuite et al., 1996), and pseudotumor cerebri (PTC) was described as a major cause of papilledema in cohorts of pediatric (Hyde et al., 2019), and adult (Crum et al., 2020) patients.

This study investigates whether sex and etiology influence the development of papilledema (optic disc elevation) and ONS dilation in children and compares fundoscopic with transorbital point-of-care ultrasound techniques to identify conditions with potentially increased ICP in children, that might require treatment.

## 2. Material and Methods

### 2.1. Study design

This is a prospective observational study. Pediatric patients were enrolled from 2018 to 2021 according to the following inclusion criteria: All patients had clinical signs and symptoms indicating elevated ICP (headache, vomiting, irritability, macrocephaly, developmental delay, visual disturbance, e.g., blurred/double vision), some of them were presented to us for the first time, others were already known with known, already treated disease. Based on the symptomatology, the initial diagnosis or a relapse of a disease was suspected. Further evaluation followed according to duration or severity of symptoms. All patients underwent fundoscopy by independent ophthalmologists (during in-house stays or on an outpatient basis). Additionally, all patients underwent transorbital US examination of ONSD and ODE by an investigator blinded to the clinical and fundoscopic findings and US findings were not included in decision making regarding treatment. Only patients, who tolerated US investigation without sedation were included. The maximum time interval between fundoscopy and transorbital US was 24 h, with no ICP-affecting therapy in between. Depending on kind, duration and severity of the symptoms and the fundoscopic findings, further work-up was performed by US, X-ray, CT or MRI.

In 28 patients an additional invasive ICP measurement (by lumbar puncture or intraparenchymal ICP probe) was performed, either because the diagnostic criteria required it (in case of PTC) (Friedman et al., 2013), or the preceding diagnostic procedures did not yield clear findings (e.g. arachnoid cyst or clinical suspicion of recurrent craniosynostosis in the absence of papilledema).

According to the findings and treatment decisions patients were divided into 2 groups: 1) treatment group (TG) and 2) non-treatment group (NTG). Inclusion criteria for TG included in addition to the existing symptoms of all patients as described above: 1) imaging evidence of intracranial disease/disease-recurrence associated with increased ICP (hydrocephalus, space-occupying arachnoid cyst or brain tumor, craniosynostosis with copper-beaten skull or involvement of multiple sutures, imaging signs of PTC, e.g. empty sella, flattened ocular bulb, hypoplasia/stenosis of venous sinus) and/or 2) evidence of intracranial pressure ≥18.5 mmHg/25cmH20 (≥20.5 mmHg/28cmH20 if child was sedated and/or obese) and/or 3) diagnosis of PTC according to the Friedman criteria (Friedman et al., 2013).

Inclusion criteria for NTG encompassed: 1) absence of fundoscopic papilledema and absence of radiological evidence of a disease associated with increased ICP or 2) absence of fundoscopic papilledema, absence of imaging findings and intracranial pressure <18.5 mmHg/25cmH20.

Informed consent was obtained from parents and children old enough to understand the study prior to investigation. According to the written ophthalmologic reports, fundoscopic findings were classified into A) papilledema (in any manifestation) and B) no papilledema.

The term sex in this paper generally refers to a set of biological characteristics associated with physical and physiological traits (e.g. chromosomal genotype, anatomy). The use of a binary sex classification (male/female) refers to the sex usually determined and assigned at birth and is usually based solely on the visible external anatomy of a newborn.

All procedures performed in this study were in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the institutional ethics committee (180/2018BO2). The study met the STROBE guidelines for reporting observational studies (https://www.equator-network.org/reporting-guidelines/strobe/).

### 2.2. Study population

Seventy-two patients, aged 9 months to 18 years, (mean age 9.3 ± 4.7 years), were included, among those 69 children were >1 year. 46 children were male (64%), 26 were female (36%).

The diagnoses within the overall cohort included: PTC (n = 21), brain tumor (n = 16), arachnoid cyst (n = 8), craniosynostosis (n = 9), other intracranial pathologies (hydrocephalus, sinus vein thrombosis, intracranial hemorrhage; n = 14), patients without proven disease (n = 4).

Fifty patients met the inclusion criteria for TG and were thus diagnosed with a disease/recurrence of a previously treated disease associated with an increase in ICP. Twenty-two met the inclusion criteria for NTG, thus disease requiring treatment or recurrence of such disease with increased intracranial pressure was excluded.

Diagnoses of the TG encompassed pseudotumor cerebri (PTC) (19/50), space-occupying brain tumors or tumors with hydrocephalus (13/50), craniosynostosis (6/50), space-occupying arachnoid cysts (7/50) and other pediatric neurosurgical/neurological pathologies like hydrocephalus of different origin (5/50). According to the diagnosis patients were treated with tumor-resection, endoscopic cyst fenestration, expansion cranioplasty, lumbar CSF drainage, VP-Shunt or acetazolamide medication.

In 12 tumor and 16 PTC patients of TG, fundoscopy, US-ONSD and US-ODE were acquired before and after ICP decreasing therapy. In 8 tumor and 12 PTC patients at least one further follow-up investigation was performed over a maximum follow-up period of 50 weeks.

### 2.3. Ultrasound measurement of ONSD and ODE

One examiner (SRK) with five years of experience in transorbital US performed all ultrasound investigations. US was performed in patients in supine position, head straight and not elevated. A 12 MHz-linear-transducer (Epiq 5G US system; Philips Healthcare, Best, The Netherlands) was used in B-mode and ONSD determination was performed 3 mm behind and with an angle of 90° to the optic nerve

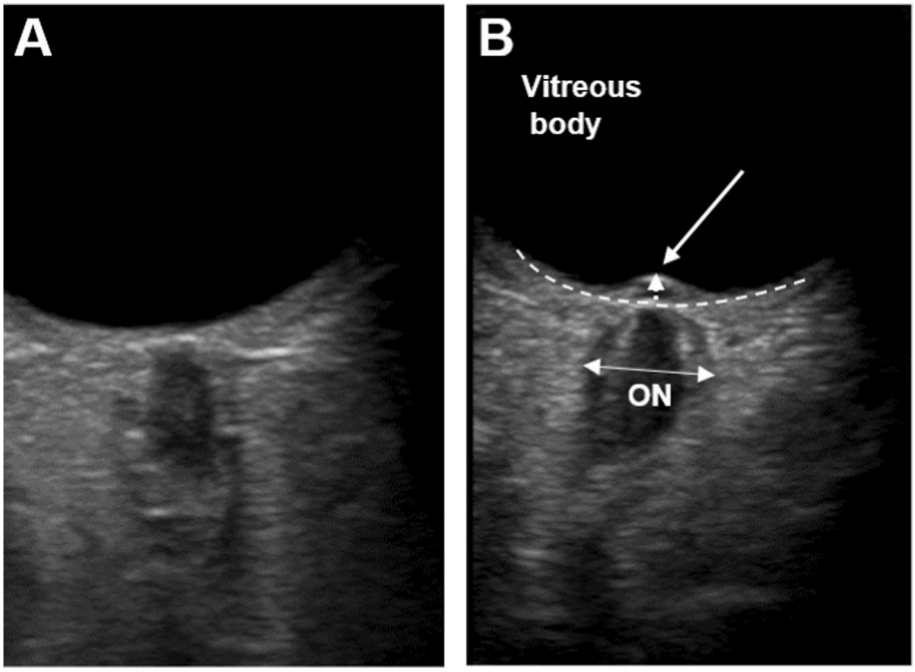


**Fig. 1.** B-scan-ultrasound of the orbit A Transorbital US-image of a child without acute intracranial pathology with small values for US-ONSD and US-ODE. **B** Transorbital US-image of a child with acute intracranial pathology needing treatment. The optic nerve (ON) appears hypoechogenic and is surrounded by the hyperchogenic optic nerve sheath. The white double-arrow shows the region where US-ONSD is measured 3 mm behind the retina (dotted line). The white arrows show the elevated optic disc and the area where US-ODE is measured.

(Fig. 1B). Three measurements were acquired in an axial plane, mean ONSD of each side and resulting mean binocular ONSD was calculated, as previously described in detail (Kerscher et al., 2021). In addition, the elevation of the optic disc at the exit of the optic nerve was measured three times on each side and the mean binocular US-ODE was calculated (Fig. 1B).

The investigator was blinded to the fundoscopic findings, if they were acquired prior to the US examination.

### 2.4. Sample size calculation

The estimated sample size for the comparison of US-ONSD means was calculated to be 16 patients per group to achieve 99% power with an alpha of 0.1 ($p < 0.001$). The estimated sample size for the comparison of US-ODE means was calculated to be 22 patients for each group to achieve 95% power with an alpha of 1 ($p < 0.01$). With an estimated loss of 10% due to exclusion criteria and data loss, at least 51 patients should be recruited for the study.

### 2.5. Statistical analysis

The statistical analyses were done using SPSS software (PASW Statistics 27, IBM Corp., Armonk, NY, USA). Data were tested for normality of distribution using Shapiro-Wilk test. Parametric data were reported as means and standard deviation (sd). Depending on normality of distribution, the correlation of the parametric variables was tested using Pearson's or Spearman's correlation. Point-biserial correlation r was used to compare parametric and nominal data. Mann-Whitney-U-test was used for comparing mean values, the dependent student's *t*-test or Wilcoxon sign-rank test for paired samples. Chi-Quadrat-test (Fisher's exact test) was applied for comparing nominal parameters. Statistical significance was set at $p < 0.05$.

## 3. Results

### 3.1. Sex-specific differences in US-ONSD, US-ODE and fundoscopic findings

#### 3.1.1. Non-treatment group (NTG)

In the NTG ($n = 22$, mean age 8.9 ± 5.4 years) boys ($n = 9$) had a mean US-ONSD of 5.32 ± 0.3 mm, girls ($n = 13$) had 5.30 ± 0.44 mm, ($p > 0.05$). Mean US-ODE was 0.31 ± 0.25 mm in boys and 0.32 ± 0.21 mm in girls, respectively ($p > 0.05$). None of these patients had papilledema. The patients were all scheduled for short-term follow-up, and in all of them, the original symptoms had disappeared in the interim and had not recurred.

#### 3.1.2. Treatment group (TG)

In children with indication for treatment ($n = 50$, mean age 9.5 ± 4.3y) the mean duration of symptoms prior to diagnosis was 2.9 ± 2.0 months in girls ($n = 13$, mean age 9.8 ± 4.1y) compared to 2.6 ± 2.4 months in boys ($n = 37$, mean age 9.4 ± 4.5y), $p > 0.05$. There was no significant difference in age-distribution ($p > 0.05$).

#### 3.1.3. Fundoscopic papilledema

In the TG 9/13 girls (69.2%) had papilledema, compared to 14/37 boys (37.8%). This difference was significant ($p < 0.05$, Fig. 2A).

#### 3.1.4. US-ONSD

Mean US-ONSD was 6.50 ± 0.5 mm for boys and 6.51 ± 0.77 mm for girls, $p > 0.05$. US-ONSD values were insignificantly larger in patients with papilledema (6.59 ± 0.77 mm-girls, 6.60 ± 0.69 mm-boys) compared to those without (6.32 ± 0.64 mm-girls, 6.44 ± 0.50 mm-boys). Fig. 2B.

#### 3.1.5. US-ODE

Girls in general had insignificantly larger values for US-ODE (0.86 ± 0.36 mm vs. 0.65 ± 0.40 mm-boys). However, patients with papilledema (1.03 ± 0.25 mm-girls, 1.07 ± 0.27 mm-boys) had significantly

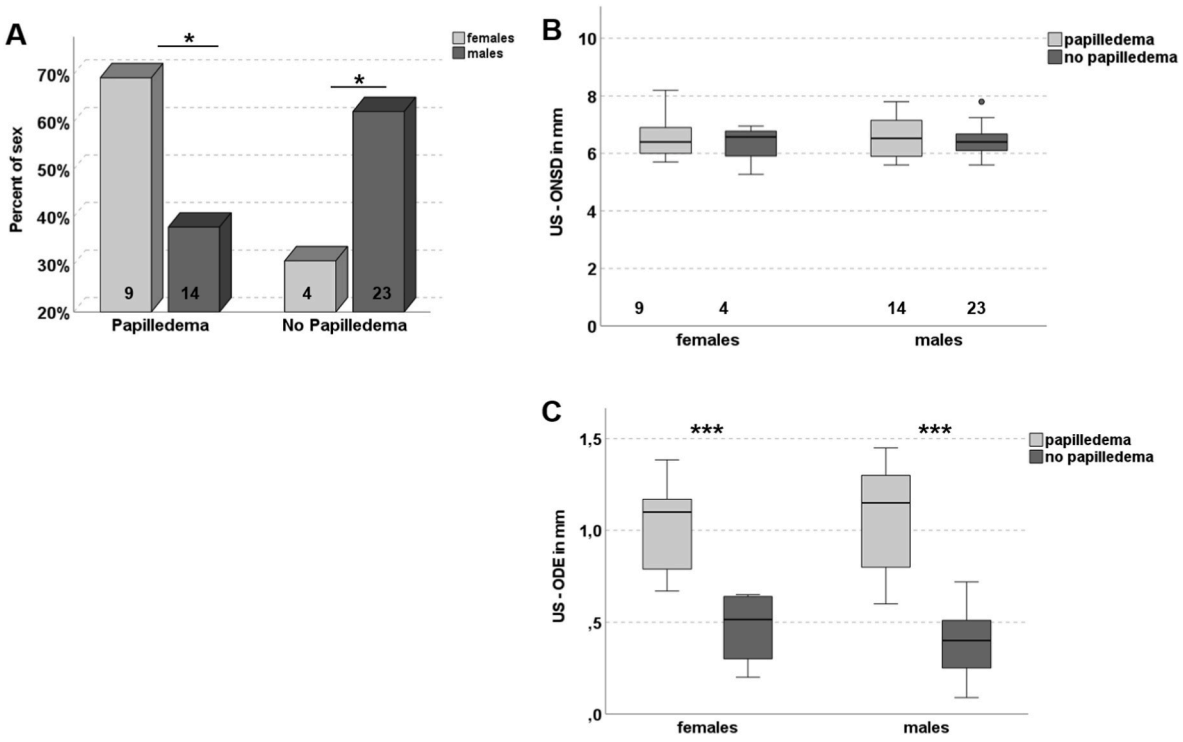


**Fig. 2.** US-ONSD, US-ODE and fundoscopic findings in children with proven treatment-indication for diseases with potentially elevated ICP considering sex-distribution A Sex-specific percentage distribution of patients with and without papilledema in the cohort with proven disease **B** US-ONSD in patients with proven disease considering fundoscopic aspects and sex **C** US-ODE in patients with proven disease considering fundoscopic aspects and sex.

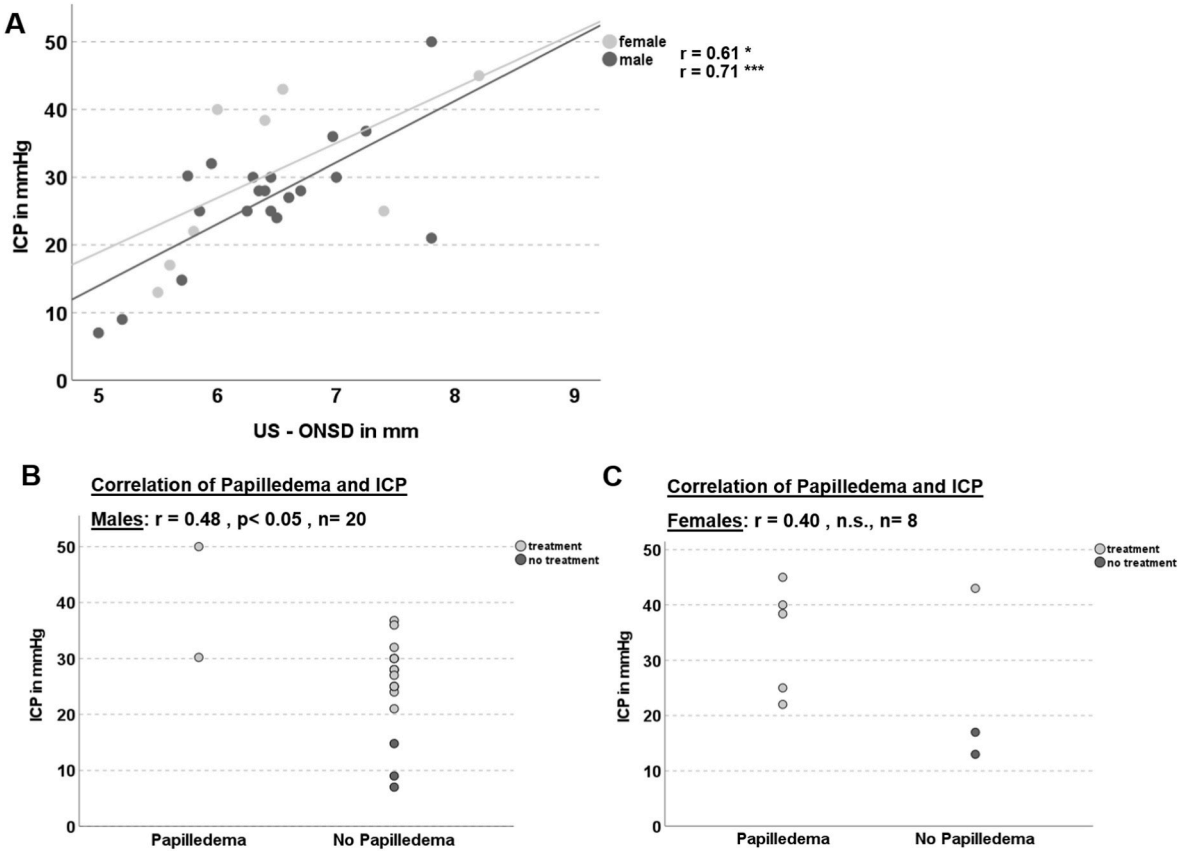


**Fig. 3.** Correlation of US-ONSD and fundoscopic papilledema with ICP considering sex A Correlation of US-ONSD and ICP considering sex. **B** Correlation of fundoscopic papilledema and invasively measured ICP in boys considering treatment indication **C** Correlation of fundoscopic papilledema and invasively measured ICP in girls considering treatment indication. n.s. = not significant. * = $p < 0.05$; *** = $p < 0.001$.

($p < 0.001$) larger US-ODE values compared to patients without papilledema (0.47 ± 0.18 mm-girls, 0.39 ± 0.19 mm-boys). Fig. 2C.

*3.1.6. Correlation analyses of US-ONSD, US-ODE and papilledema*

The correlation between US-ODE and papilledema was good (girls $r = 0.74$, boys $r = 0.83$, $p < 0.01$). It was poor for US-ONSD and US-ODE (girls $r = 0.17$, boys $r = 0.019$, $p > 0.05$) and for US-ONSD and papilledema (girls $r = 0.15$, boys $r = 0.13$, $p > 0.05$).

*3.1.7. Correlation analyses of invasively measured ICP, US-ONSD, US-ODE and papilledema*

Twenty-eight children (20 boys, mean age 7.8 ± 3.2y, 8 girls, mean age 8.7 ± 4.3y) of the entire cohort underwent invasive ICP measurement during the diagnostic work-up. 17/20 boys (mean ICP 29.8 ± 6.6 mmHg) and 6/8 girls (mean ICP 35.6 ± 8.8 mmHg, $p > 0.05$) had an increased ICP and thus an indication for treatment. Mean ICP of girls with papilledema ($n = 5$) was 34.1 ± 10.0 mmHg, compared to 43.0 mmHg in one girl without papilledema. Mean ICP of boys with papilledema ($n = 2$) was 40.1 ± 14 mmHg, compared to 28.4 ± 4.3 mmHg in 15 boys without papilledema. Mean ICP in 2 girls without treatment indication was 15.1 mmHg vs. 10.3 mmHg in 3 boys.

The correlation analysis between US-ONSD and ICP revealed a good correlation independently of sex (girls $r = 0.61$, $p < 0.05$, boys $r = 0.71$, $p < 0.001$, Fig. 3A).

Correlation between US-ODE and ICP was relatively poor with $r = 0.35$ or $r = 0.22$ for girls and boys, respectively ($p > 0.05$). Correlation of fundoscopic papilledema and ICP was as well poor with $r = 0.40$ and $r = 0.48$, $p < 0.05$, for girls and boys respectively.

Fig. 3B + C with scatter plot demonstrate, that 15/17 boys (88.2%) with proven ICP above 20 mmHg and indication for treatment had no fundoscopic papilledema (mean US-ONSD 6.61 ± 0.6 mm), whereas only 1/6 (16.7%) girls with ICP above 20 mmHg had no papilledema (mean US-ONSD 6.73 ± 0.9 mm). The difference in US-ONSD between boys and girls without papilledema that received treatment was not significant, $p > 0.05$.

The main results of this section 3.1. are summarized in Table 1.

*3.2. Etiology-specific differences in US-ONSD, US-ODE and fundoscopic findings*

In the entire cohort 16 patients were diagnosed with a tumor and 21 with a pseudotumor cerebri. For the remaining diagnoses, the groups were too small to be studied separately.

*3.2.1. Children with brain tumors*

*3.2.1.1. Correlation analyses of US-ONSD, US-ODE and papilledema.* In 16 children (mean age 10.6 ± 4.6y, duration of symptoms prior to diagnosis: 4.7 ± 5.2months) diagnosed with tumor (5 girls, mean age 10.3 ± 3.8y, 11 boys, mean age 8.9 ± 4.3y) the correlation analysis for US-ODE and papilledema ($r = 0.86$, $p < 0.001$), US-ODE and US-ONSD ($r = 0.68$, $p < 0.01$) as well as for US-ONSD and papilledema ($r = 0.72$, $p < 0.01$) depicted good correlations.

12/16 patients underwent US and fundoscopic investigation straight before and within 1–14 days after surgery. In 8/12 the investigations were repeated after a follow-up period of 2–50 weeks. All patients benefited from therapy, relapse was excluded clinically and/or radiologically.

*3.2.1.2. Fundoscopic papilledema.* Before surgery 10/12 (83.3%) of the tumor patients had papilledema (100% of girls, 78% of boys, Fig. 4A+B). Papilledema persisted in all patients at the first investigation after therapy and in 2 patients (1 girl, 10 years old, 2 months symptom duration and 1 boy, 14 years old, 5 months symptom duration) papilledema persisted during follow-up (girl: 24 weeks, boy: 11weeks after surgery, Fig. 4C).

**Table 1**
Comparison of US-ONSD, US-ODE, fundoscopic papilledema, age, mean ICP and mean duration of symptoms prior to initial diagnosis in females and males under consideration of treatment indication. There was no significant difference ($p > 0.05$) in the US-ONSD for females and males between patients with (+) and without (-) papilledema. At US-ODE, there was a significant difference ($p < 0.001$) between patients with (+) and without (-) papilledema regardless of sex. NTG = non-treatment group. TG = treatment group. n.a. = not available if the group size is too small.

| | Females | Males | p-value |
|---|---|---|---|
| NTG | | | |
| **Number** | 13 | 9 | |
| **Age** | 7.77 ± 3.71 years | 6.17 ± 2.92 years | >0.05 |
| **Mean ICP (n = 5/22)** | 15.1 mmHg (n = 2) | 10.3 mmHg (n = 3) | >0.05 |
| **US-ONSD** | 5.30 ± 0.44 mm | 5.32 ± 0.3 mm | >0.05 |
| **US-ODE** | 0.32 ± 0.21 mm | 0.31 ± 0.25 mm | >0.05 |
| **Fundoscopic Papilledema** | 0 | 0 | >0.05 |
| TG | | | |
| **Number** | 13 | 37 | |
| **Age** | 9.8 ± 4.1 years | 9.4 ± 4.5 years | >0.05 |
| **Duration of symptoms** | 2.9 ± 2.0 months | 2.6 ± 2.4 months | >0.05 |
| Mean ICP (n = 23/50) | 35.6 ± 8.8 mmHg | 29.8 ± 6.6 mmHg | >0.05 |
| + **papilledema** | 34.1 ± 10.0 mmHg (n = 5) | 40.1 ± 14 mmHg (n = 2) | n.a. |
| **- papilledema** | 43.0 mmHg (n = 1) | 28.4 ± 4.3 mmHg (n = 15) | n.a. |
| US-ONSD mean | 6.51 ± 0.77 mm | 6.50 ± 0.5 mm | >0.05 |
| + **papilledema** | 6.59 ± 0.77 mm | 6.60 ± 0.69 mm | |
| **- papilledema** | 6.32 ± 0.64 mm | 6.44 ± 0.50 mm | |
| US-ODE mean | 0.86 ± 0.36 mm | 0.65 ± 0.40 mm | >0.05 |
| + **papilledema** | 1.03 ± 0.25 mm | 1.07 ± 0.27 mm | |
| **- papilledema** | 0.47 ± 0.18 mm | 0.39 ± 0.19 mm | |
| **Fundoscopic Papilledema** | 9/13 ≈ 69.2% | 14/37 ≈ 37.8% | **<0.05** |

*3.2.1.3. US-ONSD.* Mean initial US-ONSD was 6.54 ± 0.51 mm (6.62 ± 0.52 mm vs. 6.15 ± 0.49 mm, respectively with vs. without papilledema) and decreased significantly straight after therapy (5.92 ± 0.59 mm, $p < 0.01$) and during follow-up (5.31 ± 0.38 mm, $p < 0.001$) independently of fundoscopic findings (Fig. 4C).

*3.2.1.4. US-ODE.* US-ODE values strongly correlated to the fundoscopic findings (see also 3.1.). Patients with papilledema in general had distinctly larger US-ODE values and US-ODE values significantly decreased after therapy and during follow-up in patients with and without papilledema (Fig. 4D).

*3.2.2. Children with pseudotumor cerebri*

*3.2.2.1. Correlation analyses of US-ONSD, US-ODE and papilledema.* In 21 children (mean age 8.9±4y, duration of symptoms: 2.7 ± 3.5months) with PTC (8 girls, age 10.8 ± 2.7y, 13 boys, age 8.8 ± 4.1y) the correlation between US-ODE and papilledema was good ($r = 0.82$, $p < 0.001$), but the correlation between US-ONSD and US-ODE ($r = 0.07$, $p > 0.05$) and US-ONSD with fundoscopic papilledema ($r = 0.13$, $p > 0.05$) was poor.

In 16/21 children repeated US and fundoscopic investigations were performed before and after therapy (1–14days) and during follow-up (2–24weeks).

*3.2.2.2. Fundoscopic papilledema.* 8/16 (50%) of the patients had papilledema (83% of girls, 30% of boys) at initial presentation (Fig. 5A/B). In 6/8 papilledema persisted after therapy and 2 patients (1 girl, 9 years old, 12 weeks later, 1boy, 13 years old, 8 weeks later) had persistent

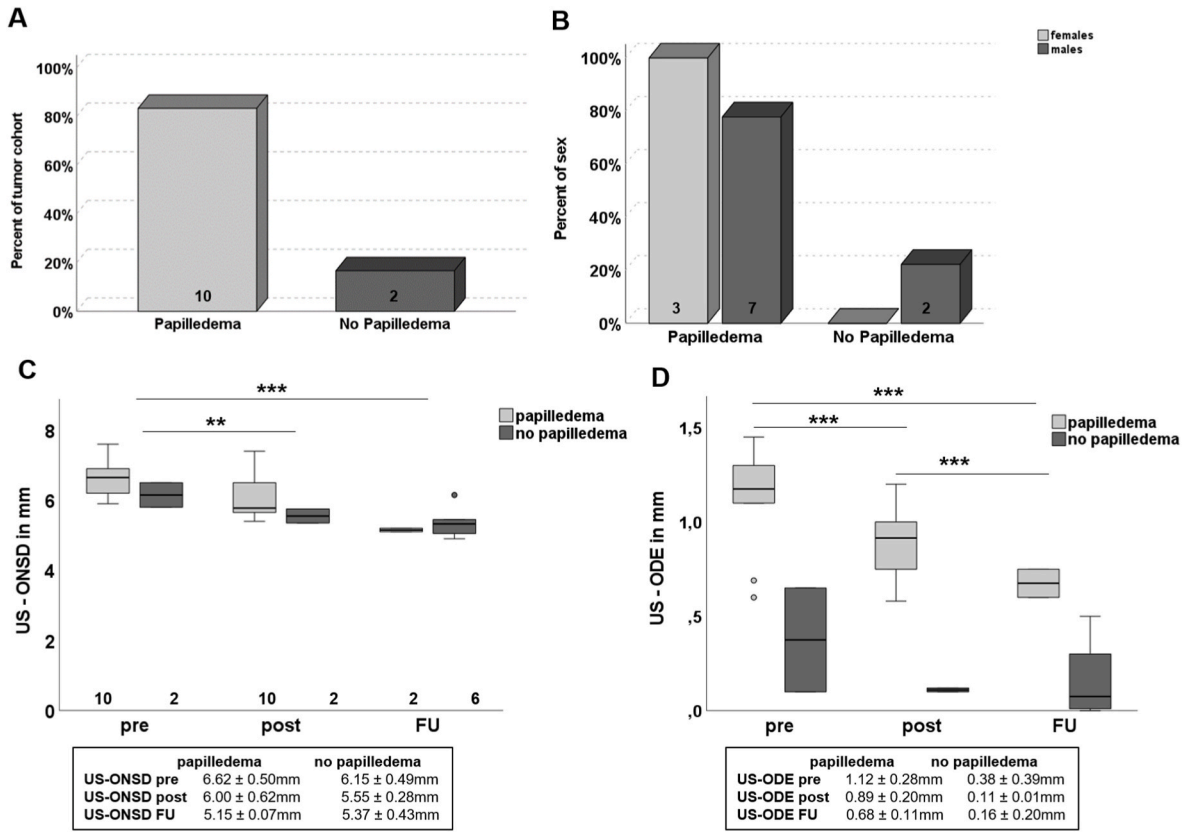


**Fig. 4.** US-ONSD, US-ODE and fundoscopic papilledema in children with brain tumor before and after therapy A Distribution of patients (%) with and without papilledema **B** Sex-specific distribution of patients with and without papilledema **C** US-ONSD before and after tumor removal considering fundoscopic aspects **D** US-ODE before and after tumor removal considering fundoscopic aspects.

papilledema during long-term evaluation (Fig. 5C).

*3.2.2.3. US-ONSD.* US-ONSD was, independently of papilledema, enlarged (6.66 ± 0.79 mm) and decreased significantly after therapy (5.70 ± 0.53 mm, $p < 0.05$) and during follow-up (5.34 ± 0.52 mm, $p < 0.001$)) (Fig. 5C).

*3.2.2.4. US-ODE.* US-ODE was significantly ($p < 0.001$) larger in patients with papilledema and decreased slowly and insignificantly after therapy and during follow-up in both patients with and without papilledema (Fig. 5D).

In both tumor and PTC, difference in age, sex distribution and duration of symptoms prior to diagnosis was marginal and not significant ($p > 0.05$).

The main results of section 3.2. are summarized in Table 2.

## 4. Discussion

This study is the first one in the literature to describe the influence of sex and disease etiology on the development of papilledema and ONS dilation following ICP elevation in children. In addition, this is the first study to compare the use of US-ONSD and US-ODE with fundoscopic findings to identify treatment-emergent conditions with potentially elevated ICP in children, with particular attention to the influence of sex and etiology. We provide a sex-specific correlation analysis of invasively measured ICP with US-ONSD, US-ODE, and fundoscopic papilledema. In addition, the etiology-specific regression behavior of US-ONSD, US-ODE, and papilledema after therapy was analyzed.

### *4.1. Sex and etiology as influencing factors for the development of papilledema*

#### *4.1.1. Influence of sex on papilledema development*

In our treatment cohort, only 23/50 (46%) patients had fundoscopic papilledema, which is consistent with previous studies that also showed limited diagnostic reliability of fundoscopic papilledema for detecting increased ICP in children (Nazir et al., 2009; Shi et al., 2019). Whether sex influences the development of papilledema has not yet been adequately clarified. Cavuoto et al. recently published a retrospective study on 213 pediatric patients presenting to an ophthalmologic emergency department with suspected optic head elevation (Cavuoto et al., 2022). The majority of all patients with papilledema (52.6%) were female (76.8%) and only 23.2% were male, but it has to be considered, that the majority of the entire cohort was as well female (73.2%). In our study, the difference in sex-distribution was significant as 69.2% of girls and only 37.8% of boys with proven treatment indication for ICP-increasing disease had papilledema. Age as an influencing factor was excluded. This sex-dependency was also evident in the sub-grouping according to pathology. In the tumor-cohort 100% of females vs. 78% males had initial papilledema compared to the PTC-cohort with 83.3% of the girls and 30% of the boys with papilledema. There were no sex-differences with regard to the tendency to regression after successful therapy. 2 patients in the tumor and PTC cohort respectively had persistent papilledema in the long-term FU (8–24 weeks), one girl and one boy in each group. The long persistence of papilledema in our cohort is consistent with findings of other studies, reporting on average persistence of 1.5–2.5 months (Hayreh, 2016; Reier et al., 2022).

As expected, the correlation analysis of papilledema and invasively measured ICP in 28 children showed a weak correlation independently of sex. Pollak et al. found a similar correlation ($r = 0.33$, $p < 0.01$) in a

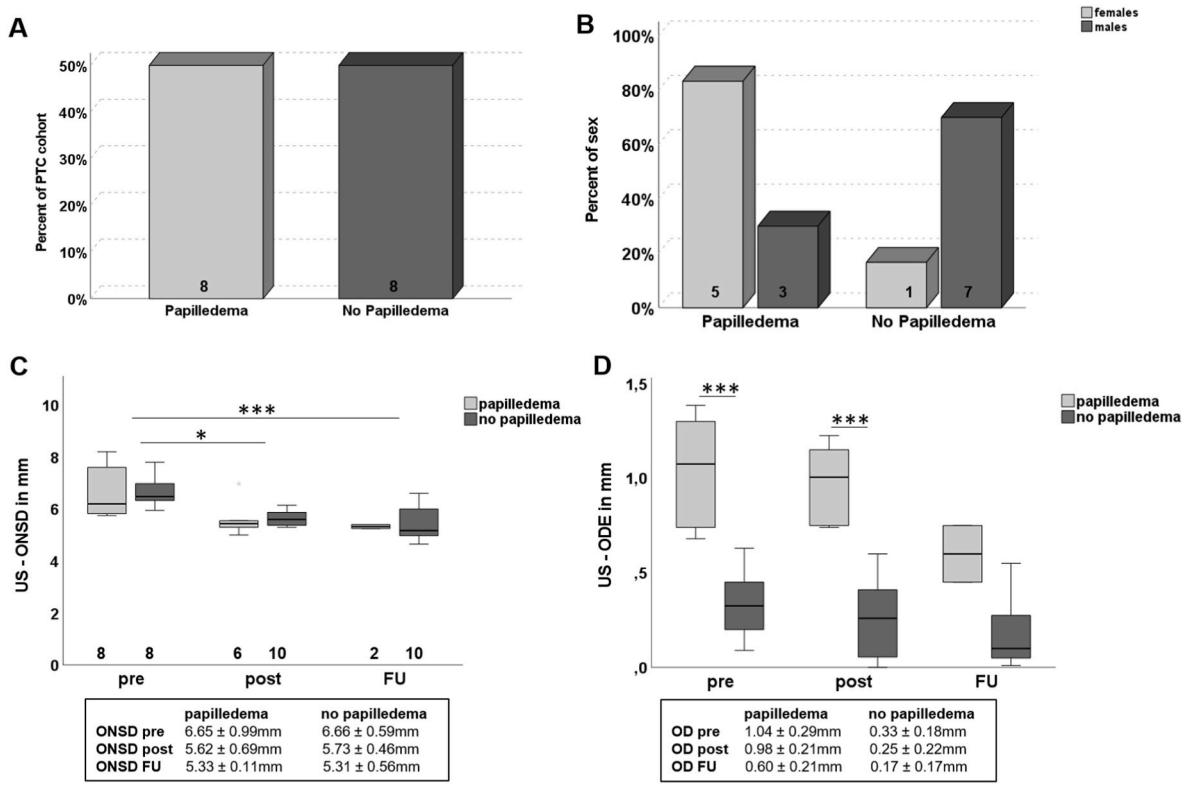


**Fig. 5.** US-ONSD, US-ODE and fundoscopic papilledema in children with PTC before and after therapy A Percentage distribution of patients with and without papilledema **B** Sex-specific percentage distribution of patients with and without papilledema **C** US-ONSD before and after treatment considering fundoscopic aspects **D** US-ODE before and after treatment considering fundoscopic aspects.

**Table 2**
Comparison of US-ONSD, US-ODE, fundoscopic papilledema, age, mean ICP and mean duration of symptoms prior to initial diagnosis in patients with brain tumor and pseudotumor cerebri. There was no significant difference ($p > 0.05$) in the US-ONSD for the tumor and the PTC group patients with (+) and without (-) papilledema. At US-ODE, there was a significant difference ($p < 0.001$) between patients with (+) and without (-) papilledema regardless of etiology. NTG = non-treatment group. TG = treatment group. n.a. = not available if the group size is too small.

| | Tumor | PTC | p-value |
|---|---|---|---|
| **Number** | 16 | 21 | |
| **Age** | 10.6 ± 4.6 years | 8.9 ± 4 years | >0.05 |
| **Duration of Symtpoms** | 4.7 ± 5.2 months | 2.7 ± 3.5 months | >0.05 |
| US-ONSD mean | 6.54 ± 0.51 mm | 6.66 ± 0.79 mm | >0.05 |
| + **papilledema** | 6.62 ± 0.52 mm | 6.65 ± 0.69 mm | |
| **- papilledema** | 6.15 ± 0.49 mm | 6.66 ± 0.59 mm | |
| US-ODE mean | 1.10 ± 0.61 mm | 0.79 ± 0.25 mm | >0.05 |
| + **papilledema** | 1.12 ± 0.28 mm | 1.04 ± 0.29 mm | |
| **- papilledema** | 0.38 ± 0.39 mm | 0.33 ± 0.18 mm | |
| Fundoscopic Papilledema | 10/12 ≈ 83.3% | 8/16 ≈ 50% | |
| **females** | 3/3 ≈ 100% | 5/6 ≈ 83% | n.a. |
| **males** | 7/9 ≈ 78% | 3/10 ≈ 30% | n.a. |

retrospective analysis of 82 adult patients with idiopathic intracranial hypertension, even though in this study ICP was correlated to the grade of papilledema (Pollak et al., 2013). Strikingly, however, among the boys in our cohort, more than 80% of patients with treatment indication did not have papilledema at all, although they had ICP values between 21 and 37 mmHg. In girls, only one girl with high ICP (43 mmHg) did not have papilledema, however the smaller group size is somewhat limiting. In girls and boys with treatment indication, mean age, duration of symptoms before diagnosis, and ICP were without significant difference (see Table 1). This is suggesting that girls seem to develop papilledema earlier and faster than boys under very similar conditions. In a retrospective study on 46 children with hydrocephalus, only 59% had papilledema (65.4% of boys and 50% of girls) and the mean duration of symptoms was similar in patients with vs. without papilledema (Lee et al., 2017), comparable to our results. There was, in contrast to our results, an association between presence of papilledema and magnitude of ICP.

### 4.1.2. *Influence of disease etiology on papilledema development*

Regarding etiology, there have been some studies investigating which disease entities are prominent in patients with papilledema. Accordingly, PTC has been identified as one of the main causes of existing papilledema in adults (Crum et al., 2020), and children (Maheswaran et al., 2020). Hyde et al. reported, that most of the children presenting with papilledema had PTC (42.1%) or tumor (15.8%) (Hyde et al., 2019).

In our cohort 80% of all tumor patients had papilledema at initial investigation, persistence early after surgery in all and in 20% in the long-term. In another recently published retrospective study on 90 children with brain tumors only 44.1% of the cohort and 15% of patients with tumor-associated hydrocephalus had papilledema (Nuijts et al., 2022). In our PTC cohort only 50% of the children had papilledema with persistence after therapy in 6/8 (75%) and during FU in 2/8 (25%). In both groups age, sex distribution and especially duration of symptoms was similar, so that no influence from these factors can be assumed. Our results are consistent with retrospective studies of pediatric PTC, in which only 50% (Gerstl et al., 2017), and 66%, respectively, had initial papilledema that regressed in only 34% of patients (Masri et al., 2022). The male:female ratio was 2.1:1, similar to us.

These results suggest that male children have a higher risk to develop PTC and for going undetected by fundoscopic findings during the diagnostic work-up.

### 4.2. US-ODE is a quantifiable option to detect papilledema in the context of ICP elevation in children - regardless of sex

#### 4.2.1. Comparison of fundoscopy and US to detect papilledema

Besides fundoscopy, US is another technique to detect, and in contrary to fundoscopy, measure optic disc elevation (Marchese et al., 2015; Tamburrelli et al., 2000). Although fundoscopy and US examine the same pathologic feature - optic disc elevation - their diagnostic quality appears to be different, with US-ODE appearing to be more sensitive in children for detecting disease with potentially elevated ICP needing treatment. This is probably due to the fact that US measures exact, repeatable values as numbers, whereas fundoscopy can only make a qualitative statement about papilledema. Even if a fundoscopic graduation of papilledema exists (Frisén, 1982, 2017), ophthalmological expertise and a higher level of instrumentation is required as compared to US imaging of the ocular fundus. Furthermore, the Frisén-classification seems to be applied mainly scientifically, since, at least to our experience, it does not play a major role in everyday clinical practice and is usually not contained in opthalmological reports. It also has been demonstrated, that reproducibility and discriminating power of the Frisén-classification is limited even among ophthalmologists (Sinclair et al., 2012). Thus, fundoscopy, unlike point-of-care US, cannot be performed by every physician, independently of the discipline, reliably, rapidly and at the bedside. In the presented study US-ODE showed similar results to fundoscopic findings as expected. This was also reflected in the poor correlation between US-ODE and ICP, which was very similar to the poor correlation of ICP and fundoscopic papilledema.

#### 4.2.2. US-ODE indicates an increase in ICP requiring treatment regardless of sex

Children with proven treatment indication and visible papilledema presented significantly higher US-ODE values compared to the children without papilledema (e.g. girls with vs. without papilledema 1.03 ± 0.25 mm vs. 0.47 ± 0.18 mm, see Fig. 2C). However, those children with treatment indication and without manifest fundoscopic papilledema also had higher US-ODE values than those of the non-treatment group (e.g. boys of TG without papilledema vs. boys of NTG- 0.39 ± 0.19 mm vs. 0.31 ± 0.25 mm). Among boys in particular, a large number (>60%) harboring high ICP requiring treatment had not been detected by fundoscopy. Therefore, US-based measurement of ODE may provide a higher diagnostic potential in assessing optic disc elevation than fundoscopy alone, as US can provide quantifiable values of optic disc elevation also in absence of fundoscopically visible papilledema. Such quantitative values can make dynamic changes and tendencies more tangible and repeatable than purely qualitative findings, especially in the course of the individual case. Further research in larger cohorts is necessary to investigate the role of US-ODE in children, when raised ICP is clinically suspected.

#### 4.2.3. US-ODE and disease etiology

The stratification according to etiology demonstrates that US-ODE has the same etiology-specific features as fundoscopy, however, the existence of quantitative values may allow a much better assessment especially of patients without fundoscopic papilledema. Figs. 4 and 5D clearly show that the US-ODE continues to slowly decrease after treatment also in patients without initial papilledema and can thus indicate a quantifiable tendency of a regressing optic disc elevation and thus an increasing normalization of the intracranial pressure situation. It should be noted, however, that depending on the initial findings, normalization of the US-ODE may be very slow or may not occur at all (compare Fig. 4D/5D, US-ODE FU in patients with papilledema), according to a hysteresis theory (Choudhari et al., 2009; Hansen and Helmke, 1997; Hayreh, 2016). Therefore, follow-up examinations and comparison with initial findings are recommended.

### 4.3. The reliability of US-ONSD as an initial and follow-up diagnostic tool to estimate ICP is independent of sex and underlying etiology

Numerous studies have already shown that US-ONSD is a very reliable tool for non-invasive and rapid assessment of intracranial pressure in children (Kerscher et al., 2019a; Padayachy et al., 2016a), and adults (Wang et al., 2018). It has already been described that the reliability of US-ONSD is limited in very small babies with a patent fontanel (Padayachy et al., 2016b), and that a transorbital US examination is often poorly tolerated in children <3 years of age (Kerscher et al., 2019b). Padayachy et al. found a putative relationship between the level of US-ONSD, its response to ICP elevation, and the underlying etiology, and constructed ONSD-cut-off values for different etiologies (Padayachy et al., 2016a).

#### 4.3.1. The width of the ONSD is not dependent on sex

There has been little research on the sex-specificity of ONSD in children, however. Lan et al. showed in a study of term neonates that boys in the mean had a slightly larger US-ONSD than girls (Lan et al., 2021). Another recently published CT-based study on children found significant differences in CT-ONSD between boys (median right ONSD 5.5 mm) and girls (median right ONSD 5.21 mm) in 332 children with a normal cranial CT (Bardak et al., 2023). In our NTG, the sex differences in US-ONSD were marginal, but one has to take into account the small number in that group.

In the presented cohort, US-ONSD could, independently of sex, distinguish between children not needing treatment acutely or later (5.32 ± 0.3 mm-boys, 5.30 ± 0.44m-girls) and disease affected children requiring treatment (6.50 ± 0.5 mm-boys, 6.51 ± 0.77 mm-girls), independently of existence of papilledema. The US-ONSD of the healthy subjects corresponded to the published ONSD cut-off values for low = normal ICP values (Kerscher et al., 2019a; Padayachy et al., 2016b). The correlation between ICP and US-ONSD demonstrated good values for males and females and was clearly superior to the correlation of ICP with fundoscopic papilledema or US-ODE. Mean US-ONSD in the treatment group was 6.61 ± 0.6 mm and 6.73 ± 0.9 mm for boys and girls, respectively with a mean ICP of 29.8 ± 6.6 mmHg in boys and 35.6 ± 8.8 mmHg in girls ($p > 0.05$). These results fit well to published ONSD-cut-off values for ICP>20–30 mmHg (5.75–5.91 mm) (Kerscher et al., 2019a; Padayachy et al., 2016b).

#### 4.3.2. The width of the ONSD is not dependent on disease etiology

Regarding etiology, initial US-ONSD was similar in patients with PTC (6.67 ± 0.79 mm) compared with tumor patients (6.54 ± 0.51 mm), with a greater difference between patients with vs. without papilledema in the tumor cohort. In the tumor and PTC cohorts, ONSD regression/normalization was delayed in line with the known hysteresis of the optic nerve sheath (Hayreh, 1977) after chronic ICP elevation, but showed a clear and significant decrease regardless of etiology. At the end of FU, all patients had normal US-ONSD values.

Using the published ONSD cut-off values for defined ICP scores in children (Kerscher et al., 2019a; Padayachy et al., 2016b), all patients in this study, regardless of sex and etiology and whether or not they had papilledema, would have been identified by US-ONSD as having pathologically raised ICP or a disease associated with raised ICP and would have been reliably distinguishable from the healthy patients. This makes US-ONSD, in contrast to fundoscopy, an excellent screening and follow-up tool for identifying increased ICP in children regardless of sex and disease etiology.

### 4.4. Limitations

Although this is a prospective study, it is limited by the relatively small cohort, especially in terms of sex distribution, which complies nevertheless to the generally expected sex distribution in many neurologic/neurosurgical disorders in children (Bennett et al., 2016; Masri

et al., 2022; Williams et al., 2019). Larger, ideally multicenter studies, should be conducted, to give general recommendations on the topic. However, the relative percentage distribution should not change significantly with higher total numbers.

A further limitation is that fundoscopic findings were dichotomized in two groups (papilledema vs. no papilledema). However, in clinical routine, especially at initial presentation, the Frisén classification (Sinclair et al., 2012) does not play a role and the most relevant (and often only) message of the ophthalmologist is presence or absence of papilledema, which is justified by the high specificity of papilledema.

## 5. Conclusions

Fundoscopic papilledema and ultrasound determined optic disc elevation (US-ODE) appear to be features significantly influenced by sex and etiology of the raised ICP, whereas US-ONSD is not. Girls seem to be more likely to develop papilledema and do so possibly faster than boys under very similar conditions. Male sex and PTC seem to be risk factors for going undetected with respect to diagnosis of raised ICP by fundoscopy. Transorbital point-of-care US, particularly US-ONSD, can quickly and reliably identify children with treatment-emergent elevated ICP, regardless of sex and underlying etiology. US-ODE may have greater potential than fundoscopy for papilledema because the extent of elevation is easier to quantify and ophthalmic expertise is not required for its assessment.

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## Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Author contributions

SRK contributed to the conception/design of the study, acquisition, analysis and interpretation of data, writing of the first draft, revision and final approval of the version to be published. JZ, JT, KHL and AB contributed to data acquisition, critical revision for important intellectual content and final approval. MUS was responsible for study conception, data interpretation, critical revision and final approval of the version to be published.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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