Increased ICP is a well-known feature of craniosynostosis, especially in syndromic cases.9,17,19 Prolonged increased ICP can lead to loss of vision due to optic nerve atrophy. An objective screening method is required because the classic symptoms of increased ICP such as headache, changes in behavior, or vomiting are unreliable in patients with craniosynostosis.2

The gold standard for measuring ICP is invasive intracranial monitoring, but this requires a surgical procedure and admittance to the hospital,25 and therefore cannot be used as a regular screening tool. For many years, funduscopny has been accepted as an alternative, noninvasive method to screen for increased ICP.5,22 However, papilledema is a late sign of raised ICP. Furthermore, children with syndromic craniosynostosis often do not have severely increased ICP, but suffer from peaks in pressure during the night with a normal or slightly elevated baseline. It is not known at which stage this results in papilledema. Therefore, a more sensitive and objective way of detecting increased ICP might be beneficial for the patients with syndromic and complex craniosynostosis.

Another possible noninvasive method to monitor ICP indirectly is measurement of the ONS diameter using ultrasonography. Transorbital sonography can show a significant increase in the ONS diameter when increased ICP

Abbreviations used in this paper: ICP = intracranial pressure; ONS = optic nerve sheath.
expands the dura mater and enlarges the subarachnoid space.\textsuperscript{10–12,15,16} This might even occur before any changes in the optic disk\textsuperscript{a} and thus precede the onset of papilledema. The measurement can easily be learned\textsuperscript{16} and has been used successfully in the diagnosis and monitoring of ICP in a broad setting of critically ill children, characterized by a sudden onset of a high increase in ICP.\textsuperscript{3,6,12}

The aim of this prospective study was to evaluate whether measuring the ONS diameter using ultrasonography is an early predictor of increased ICP in children with syndromic or complex craniosynostosis. To assess its predictive value in detecting increased ICP, the ultrasonography findings were compared with measurements of the ONS on CT and funduscropy.

**Methods**

**Study Population**

The study was undertaken at the Craniofacial Center of the Sophia Children’s Hospital in Rotterdam, The Netherlands, from January 2007 to December 2009. In a prospective setting, 175 transorbital ultrasonography scans were performed in children with Apert syndrome, Crouzon syndrome, Muenke syndrome, Saethre-Chotzen syndrome, and complex craniosynostosis. The syndromic diagnosis of the patients with craniosynostosis was based on genetic analyses. Informed consent was obtained from all participants, and the study was approved by the Erasmus MC Medical Ethics Committee.

**Measurements and Assessments**

All measurements were captured with the Acuson Sequoia 512 scanner (Siemens) by a single investigator using a hands-free 8.5-MHz linear array probe on the patient’s upper eyelid, after applying a gel pad and transmission gel with the patient placed supine and with closed eyelids. The ONS diameter was measured bilaterally at 3 mm posterior to the papil in the axial transbulbar view (Fig. 1). The measurements were performed during regular hospital visits during the daytime and never while patients were sleeping. All assessments were obtained twice and the mean of these measurements (per eye) was used for statistical analyses. Measurements on the images were made by hand by one of the investigators (N.B.), who was blinded to the results of the CT and funduscropy. An age-dependent cutoff point for abnormality was used: > 4.0 mm for those patients younger than 4 years, or > 4.5 mm for those at least 4 years old.\textsuperscript{1,11}

To validate the ultrasonography assessment of the ONS, the measurement was repeated on the available CT scans. Computed tomographic angiography was performed using a Siemens CT scanner according to a 3D craniosynostosis protocol. Measurements on the images were made by hand by one of the investigators (C.D.), who was blinded to the results of the ultrasonography and funduscropy. Reference values of the ONS diameter on CT are not available. Only investigations with a maximum time difference of 1 year were included in the analysis.

Funduscropy was performed on patients annually up to 6 years of age and on demand if necessary. Funduscopy was performed by a pediatric ophthalmologist by indirect ophthalmoscopy after mydriasis of the pupil with 2.5% phenylephrine and 0.5% tropicamide. Papilledema was defined as any grade of blurring of the margins of the optic disk. Objective refraction (retinoscopy) was performed in the children with an abnormal funduscopy to exclude pseudopapilledema caused by hyperopia. Only funduscopies that were performed on the same day as the ultrasonography measurement were included in the analysis.

Because of intrapatient variation in left and right outcomes on ultrasonography, CT, and funduscopy, the unilateral left and right assessments were analyzed as separate findings. Invasive intracranial monitoring was performed if papilledema was found intermittently or if a high clinical suspicion arose based on headaches, vomiting, delayed skull growth, or change in behavior without papilledema.

**Statistical Analysis**

Statistical analysis was performed using Prism 5 (GraphPad Software, Inc.). Normal distribution of the data was confirmed using a Kolmogorov-Smirnov test before parametric tests were used. Correlation of the ultrasonography measurements with CT measurements was calculated using a Pearson correlation coefficient. The means of the ultrasound images per year of age were compared using a linear regression analysis. Paired measurements were analyzed using the Wilcoxon signed-rank test. Multivariable testing was performed using linear regression as well. A Kruskal-Wallis test was used to analyze the difference in mean values between the 5 diagnostic groups. Different outcomes and diagnoses were compared using an unpaired t-test. If the groups were not normally distributed, the Mann-Whitney U-test was used to identify differences between the groups. All tables and figures are represented as means ± SDs unless otherwise noted. Statistical significance was defined as p < 0.05.
Optic nerve sheath measurements in children with craniosynostosis

TABLE 1: Patient characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>M:F Ratio</th>
<th>Mean Age ± SD (yrs)</th>
<th>No. of Ultrasonography Measurements</th>
<th>No. of Abnormal Measurements (no. of patients)</th>
<th>Mean ONS Diameter ± SD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apert syndrome</td>
<td>19</td>
<td>8:11</td>
<td>8 ± 5.3</td>
<td>44</td>
<td>0</td>
<td>2.9 ± 0.4</td>
</tr>
<tr>
<td>Crouzon/Pfeiffer syndrome</td>
<td>32</td>
<td>16:16</td>
<td>8 ± 4.4</td>
<td>82</td>
<td>6 (4)</td>
<td>3.3 ± 0.6</td>
</tr>
<tr>
<td>Muenke syndrome</td>
<td>20</td>
<td>8:12</td>
<td>7 ± 5.2</td>
<td>60</td>
<td>2 (2)</td>
<td>3.0 ± 0.5</td>
</tr>
<tr>
<td>Saethre-Chotzen syndrome</td>
<td>25</td>
<td>11:14</td>
<td>6 ± 5.5</td>
<td>72</td>
<td>1 (1)</td>
<td>3.1 ± 0.4</td>
</tr>
<tr>
<td>complex craniosynostosis</td>
<td>32</td>
<td>16:16</td>
<td>5 ± 4.4</td>
<td>92</td>
<td>2 (2)</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>syndromic* or complex craniosynostosis (all patients)</td>
<td>128</td>
<td>59:69</td>
<td>6 ± 5.0</td>
<td>350</td>
<td>11 (9)</td>
<td>3.1 ± 0.5</td>
</tr>
</tbody>
</table>

* Diagnosis based on genetic analyses.

Results

A total of 128 children (Table 1) with syndromic or complex craniosynostosis accounted for 175 ultrasound images of both optic nerves. The mean ultrasonography ONS diameter in 350 measurements was 3.1 ± 0.5 mm. The ultrasonography investigations were easily performed, even in very young children, and lasted only a few minutes.

The distribution of mean ONS diameter was analyzed (Fig. 2). Regression analysis showed a mean slope of 0.0046 ± 0.010 (p = 0.65), indicating no significant relationship between increase in diameter and age in our population. In 11 measurements (3%), the ONS was enlarged with a mean of 4.4 ± 0.3 mm, and the largest ONS was 5.0 mm (Table 2). The abnormal measurements were captured in 9 patients (Table 3).

Thirty-nine patients underwent repetitive (2 or more) ultrasonography measurements with a maximum interval of 2 years. A total of 48 paired measurements were available, which were not significantly different (mean 3.1 ± 0.5 mm vs 3.1 ± 0.4 mm; Z = -0.53, p = 0.59). In 15 cases, 5 of whom underwent operations because of increased ICP, these measurements were captured before and after cranial vault remodeling, which also did not make a significant difference (mean 3.0 ± 0.4 mm preoperatively vs 3.0 ± 0.4 mm postoperatively; Z = -0.065, p = 0.95). The ONS diameters were related to the child’s diagnosis and analyzed. Table 1 shows the range of measurements in different subtypes of craniosynostosis. There was a significant difference between these subtypes (p = 0.008). Patients with the Crouzon/Pfeiffer subtype had the highest average mean ONS diameter, which was significantly different from that of patients with Apert syndrome (p = 0.0009), Muenke syndrome (p = 0.013), and complex craniosynostosis (p = 0.018).

Validation of the Ultrasonography ONS Measurement

Thirty-seven CT scans were available to validate the ultrasonography measurements. The mean ONS diameter on 37 CT scans in 35 patients was 4.4 ± 0.9 mm. Ultrasonography and CT measurements correlated significantly (r = 0.41, p < 0.001).

Predictive Value of the Ultrasonography ONS Measurement

In 125 patients a funduscopy was performed on the same day as the ultrasonography measurement, accounting for 250 unilateral eye assessments. Papilledema was detected in a total of 38 eyes in 23 patients. In 8 patients in whom a funduscopy was available, 10 ONS diameters were too large if the conventional ONS cutoff points of 4.0 mm (for those younger than 4 years) and 4.5 mm (for

TABLE 2: Range of ultrasonography measurements

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Measurements</th>
<th>Mean ONS Diameter ± SD (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>all measurements</td>
<td>350</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td>normal ultrasound scan</td>
<td>339</td>
<td>3.0 ± 0.4</td>
</tr>
<tr>
<td>abnormal ultrasound scan*</td>
<td>11</td>
<td>4.4 ± 0.3</td>
</tr>
<tr>
<td>all fundoscopies</td>
<td>250</td>
<td>3.1 ± 0.5</td>
</tr>
<tr>
<td>normal fundoscopy</td>
<td>212</td>
<td>3.1 ± 0.5†</td>
</tr>
<tr>
<td>papilledema</td>
<td>38</td>
<td>3.3 ± 0.5†</td>
</tr>
</tbody>
</table>

* Abnormal ultrasound images include measurements > 4.0 mm in children younger than 4 years old and > 4.5 mm in children at least 4 years.
† Significantly different (p = 0.039).

Fig. 2. Graph of age-specific mean ONS diameters of all patients (mean slope = 0.0046 ± 0.010; p = 0.65).
those at least 4 years old) were used. Thirty-four of 38 eyes with papilledema had a normal ONS on ultrasound imaging; sensitivity was 11%, specificity was 97%, and positive and negative predictive values were 40% and 86%, respectively.

The mean ONS diameter in patients with papilledema was $3.3 \pm 0.5$ mm, which was significantly larger compared with the mean ONS diameter of $3.1 \pm 0.5$ mm in patients with a normal funduscopy ($p = 0.039$). Multivariate analysis, however, revealed that the diagnosis of Crouzon syndrome was the determinant ($b = 0.183, p = 0.005$) rather than papilledema ($b = 0.076, p = 0.249$).

Six patients with an enlarged ONS diameter on at least 1 side did not develop papilledema simultaneous to the abnormal ultrasound scan or during follow-up. The mean follow-up duration was 18 months (range 0–41 months). The enlarged ONS diameter in these patients did not appear to be a sign of future papilledema (Table 3). Three patients with papilledema had an enlarged ONS on ultrasound on at least 1 side. In all 3 patients, intracranial monitoring was performed, and was found to be abnormal in 2 patients (1 with Crouzon syndrome and 1 with Muenke syndrome) (Table 3). The patient with Crouzon syndrome had a baseline ICP of $< 10$ mm Hg. During 7 plateaus, the ICP was $> 35$ mm Hg for $> 20$ minutes. The patient with Muenke syndrome had a baseline ICP of 5 mm Hg while awake, which increased slightly from 10 to 15 mm Hg during the night. Furthermore, she developed 5 plateaus during REM sleep with pressures up to 27 mm Hg. This result was regarded as borderline by definition, but it was considered abnormal because the girl was only 19 months old. The third intracranial monitoring was performed in a boy with Crouzon syndrome and did not show any abnormalities. The baseline ICP during sleep was 8 mm Hg with few short plateaus up to a maximum of 20 mm Hg. An enlarged ONS and papilledema had a similar predictive value in these 3 cases.

**Discussion**

Measuring the ONS on ultrasound images is a reliable way to assess the diameter of the optic nerve. Moreover, the measurement on ultrasound images is easy to perform and does not have the disadvantages of funduscopy such as the use of eye drops, blurry vision afterward, and resistance of the child due to irritation and fear. In contrast to funduscopy, ultrasonography measurement is a quantitative assessment that is useful for follow-up measurements.

The mean value of our ONS measurements on ultrasound in children without other signs of elevated ICP confirms previous research. The correlation of the ultrasonography ONS diameter with its diameter on CT is significant and is thus a valid method to assess the optic nerve in our population. We measured no very high values, and the maximum value of 5.0 mm was only slightly abnormal. Over time, there was no significant change in ONS diameter, even in children who underwent cranial vault remodeling. As expected, the ONS was bigger in children with papilledema. This can mainly be attributed to the fact that the ONS diameter is bigger in children with Crouzon/Pfeiffer syndrome compared with other diagnoses. Children with Crouzon/Pfeiffer syndrome in particular are at risk for developing raised ICP or hydrocephalus, and at this stage we cannot conclude whether diagnosis, ICP, and/or hydrocephalus are causally related.
to an enlarged ONS. Compared with funduscopes, the sensitiv-
ty of the ONS diameter is too low to screen for raised ICP.
Also, an increase in ONS diameter does not appear to preceede
the occurrence of papilledema. Because papille-
edema is not only a sign of increased ICP, but also an
important cause of vision loss, daytime ultrasound scans are
unable to replace funduscopes. Patients with acute raised
ICP do not have papilledema in the acute setting. From
animal experimental studies, we know that papilledema
does not develop immediately after ICP increases. Glew7
was the first to insert subdural balloons into 6 monkeys,
resulting in papilledema in 2 monkeys. This study was
repeated in 1963,14 when tissue expanders were inserted
into a hole in a monkey’s skull and repeatedly inflated to
achieve sustained increased ICP. This method required 4
to 12 days of continuous increased ICP to develop papil-
edema in 7 of 19 monkeys. Five monkeys were believed
to be blind, and papilledema was observed in only 1 of
these monkeys. In the other 4 cases no other explanation
(such as lesions of the optic nerves, chiasm, or optic tract)
was found in postmortem examination.

In previous studies, the ONS measurement was per-
fomed in patients with an acute onset of raised ICP, con-
trary to our cohort that consisted of children suffering
from a more chronic increase in ICP.3,13,15 The exact re-
ponse of the diameter and structure of the optic nerve
to repetitive or chronic ICP elevation is unknown. Intra-
cranial pressure is a highly dynamic process, dependent
on the growing brain, cranial cavity, and CSF flow, which
is determined by cardiac and respiratory pulsatility.23
Transcranial or fontanel Doppler flow has been studied
extensively as a noninvasive alternative for ICP monitor-
ing. Although the resistive velocity indexes of the ante-
rior cerebral artery are increased in multisuturine synosto-
sis,24 the correlation of this vascular parameter with ICP
is weak.8,24 Cerebrospinal fluid dynamics are difficult to
map, but ultrasonography measurements of the ONS pro-
vide a clue in the acute situation3,6,12,16 and possibly in this
chronic population.

Children with syndromic craniosynostosis may have
a normal or slightly elevated baseline ICP during the day
with recurrent plateaus of increased pressures during the
night.29 This worsens when a child suffers from obstruc-
tive sleep apnea.3 If the ONS diameter reflects actual ICP,
the diameter might be normal during daytime and only
increased during the nocturnal plateaus of increased pres-
ures. This might explain why the daytime measurements
did not exceed 5.0 mm. In parallel with this hypothesis,
we were not surprised by the daytime agreement in ONS
diameter over time and before and after cranial vault re-
modelling. Unfortunately, we were unable to correlate the
ultrasound scans to a significant number of invasive in-
tracranial monitoring results. If ONS diameter is found to
be a main predictor of ICP, this study has created a large
database of patients with syndromic craniosynostosis, the
majority of whom did not have elevated ICP at the time
of measurement.

Limitations of this study include the lack of ICP mea-
urements to compare with ONS measurements, instead of
the suboptimal funduscopes. The range of ONS responses
to repetitive ICP elevation is unknown and it would be of
great interest to improve our understanding of the suscep-
tible equilibrium of ICP in children with craniosynostosis.
There is a need for further research to explore the noctur-
nal response of the optic nerve to a chronic or repetitive
increase of ICP synchronous to invasive monitoring.

Conclusions
We found a significantly enlarged ONS diameter in
children with either papilledema or Crouzon syndrome.
Furthermore, we were able to map ONS diameters in a
large cohort of children with syndromic craniosynostosis
without suspicion of increased ICP. At this stage, we be-
lieve the results of this study show that ultrasonography
measurements of the ONS cannot replace conventional
funduscopy. Instead, nocturnal measurements may be the
key to noninvasive ICP monitoring in patients with syn-
dromic or complex craniosynostosis.

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Critically revising the article: all authors. Reviewed submitted
version of manuscript: all authors. Approved the final version of
the manuscript on behalf of all authors: Driessen. Statistical analy-
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