General discussion and future perspectives

How do OSAS and ICP interact?

Increased ICP and OSAS are both highly prevalent in syndromic craniosynostosis. The correlation between increased ICP and sleep was first addressed in 1982 by Renier and co-workers.[1] In their series of untreated patients, epidural ICP monitoring was performed in 75 patients with single or multiple suture synostosis. They differentiated between the baseline ICP value during slow-wave sleep and the waves of increased ICP during REM sleep. According to their observations waves of increased ICP were recorded during each period of REM sleep. In 22 cases ICP was found to be borderline and in 30 patients ICP was found to be normal, as defined by a baseline <10 mmHg. Even in these cases, the mean ICP increased during REM sleep with peaks of 25-30 mmHg which were considered to be normal. A total of 23 of 75 patients (31%, mainly cases with multiple suture synostosis) had increased ICP, as defined by a baseline >15 mmHg. Figure 1 shows a typical pattern of increased ICP monitoring of one of our patients with complex craniosynostosis, moderate OSAS and increased ICP.

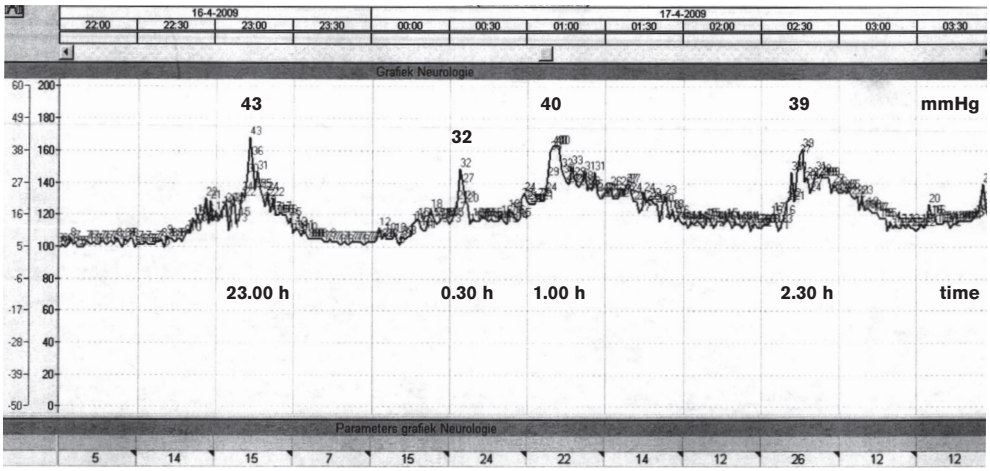

Figure 1: ***Invasive ICP monitoring in a three years-old patient with complex craniosynostosis, moderate OSAS and increased ICP.***
It represents a partial night from 22 pm to 3.30 am with 4 peaks of increased ICP and a slight increase in baseline during the night. No EEG registration available.

How does OSAS result in increased ICP?

1. **Hypercapnia and hypoxia**
2. **Negative intrathoracic pressure → enhanced venous return → pooling of blood in the cerebral veins**
3. **Increased sympathetic nerve activity → increased arterial pressure**
4. **Positive intrathoracic pressure → transmission of pressure**
5. **Increased brain metabolism during REM sleep**

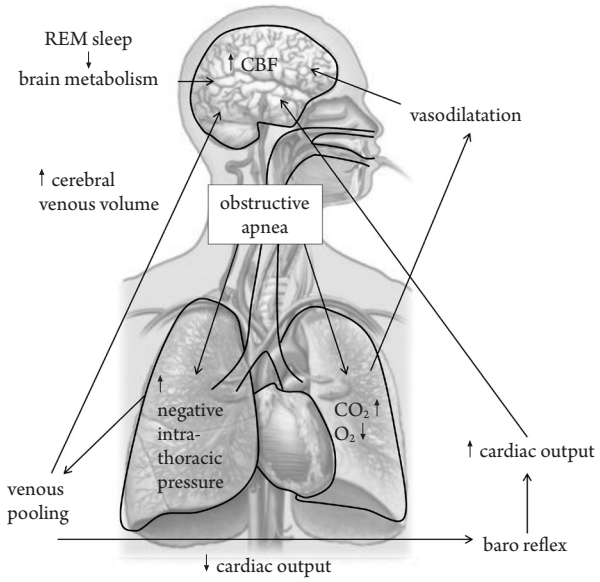

Figure 2: *How does OSAS result in increased ICP?* Where CBF is cerebral blood flow.

The pathophysiology of the intracranial vault is extraordinarily complex. The possible effect of OSAS on the intracranial volume and pressure is only one of the contributive factors to increased ICP. The ICP-equilibrium may be influenced by:[2]

1. In obstructive sleep apnea, there may be an increase in CO_2-levels which may result in cerebral vasodilatation and thus increase cerebral blood flow and flow velocity. The cardiovascular effects only affect the brain if cerebral auto-regulation is overridden.
2. There is a negative intrathoracic pressure which can be as low as -80 cm H_2O, during inspiration with obstructed airway. Negative intrathoracic pressure enhances venous return, which results in pooling of blood in the pulmonary circulation. Since there are no valves in the veins between the brain and the heart, the pooling results in stasis of blood in the cerebral venous system, which may result in an additional increase in ICP.[3] Although the venous return is enhanced, the cardiac output initially decreases.[4] This may be caused by an increase in afterload, probably due to the negative intrathoracic pressure.
3. Consequently, there is an increase in heart rate due to the baroreflex, which results in an increased arterial pressure.[5] If cerebral auto-regulation is overridden, this results in an increase in cerebral blood flow and flow velocity.
4. At the termination of apnea, resumption of ventilation results in a less negative intrathoracic pressure which is conducted to the brain.
5. Finally, OSAS occurs most during REM sleep, during which the metabolic rate of the brain is highest, which results in an increased cerebral arterial blood volume.[6] All together, this cycle of apnea and resumption may result in increased cerebral blood flow and flow velocity during an obstructive apnea if auto-regulation is overridden[3] (Figure 2).

Clinical evidence for the effect of OSAS on ICP was first reported by Sugita et al in 1985 in three patients suffering from sleep apnea hypersomnia syndrome.[6] These patients had episodic marked elevations of CSF pressure during an episode of sleep apnea or hypopnea. Significant correlations were found between the duration of an apnea and the increase in CSF pressure, and between the oxygen-desaturation and the increase in CSF pressure. In 1989, six patients with severe OSAS were analyzed by means of a sleep study, intra-arterial pressure monitoring, central venous pressure monitoring, and an epidural pressure sensor.[7] In addition to the effect of changes in oxygen saturation, these authors acknowledge an additional steep increase in ICP. According to the preceding explanation, this may either be caused by a simultaneous rapid increase in arterial pressure and the transmission of positive intrathoracic pressure after resumption of breathing. The causal effect of OSAS on increased ICP was confirmed in syndromic craniosynostosis by Gonsalez and co-workers,[8] who demonstrated that the ICP-baseline was increased and significant elevations in ICP were observed as a result of apneic episodes.

From previous studies we know that the risk of a recurrent peak in ICP is highest in children with Crouzon syndrome (62.5%), who also have the highest risk of developing OSAS.[1] It is hard to say how often OSAS is a contributive factor to increased ICP. It was shortly addressed in the study of the natural course of OSAS in 97 children (Chapter 5). In 2/97 (2%) cases, OSAS was confirmed to further increase ICP. This was first attempted to be managed by ATE in both patients. This was not sufficient to reduce ICP back to normal values and secondary cranial vault remodelling was still required. Of the study cohort of 188 patients, 24 patients underwent secondary cranial vault remodelling for increased ICP (Table 2).

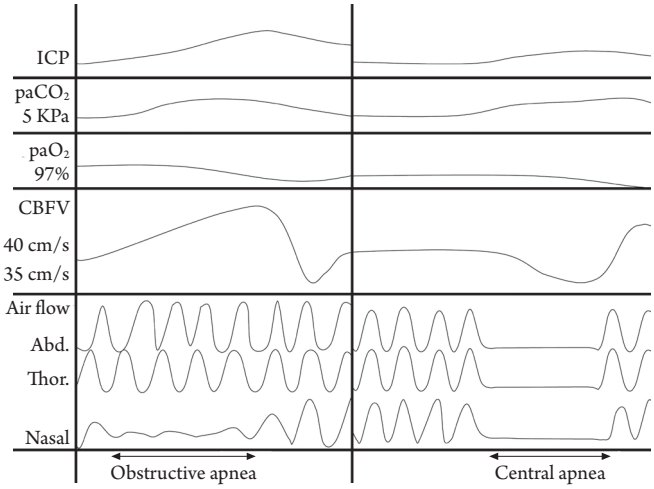

Figure 3: ***Cerebral blood flow in sleep disordered breathing.*** **Where CBFV is cerebral blood flow velocity and ICP is intracranial pressure. Contrary to the hemodynamic responses after an obstructive apnea, there is a decreased blood flow velocity during a central apnea and an increase after termination of the central apnea.**

In 13 of the 24 patients, invasive ICP monitoring was performed which was combined with a parallel sleep study in only five cases. In three patients with Crouzon syndrome a clear association between increased ICP and OSAS was observed. One of them was adequately treated by ATE and did not need secondary cranial vault remodelling; two others needed secondary cranial vault remodelling eventually despite OSAS treatment. In four other patients, moderate or severe OSAS was diagnosed previously by a separate sleep study and this may have contributed to increased ICP. However, based on retrospective data, a causal relationship cannot be confirmed. It remains unsure if these patients happen to be affected independently by both increased ICP and OSAS, for example because of a more severe phenotype, or if these patients have increased ICP secondary to OSAS. A minor share of 6% of

the total study population is younger than 3 years old at the time of analysis, meaning that a second episode of ICP elevation can still arise.

Based on our results, OSAS-related increased ICP has an estimated prevalence of 0 -12%, which depends on the syndrome diagnosis and on the uncertainty of to what extent OSAS is a causal factor for increased ICP. The fact that OSAS is generally stable in patients with Apert, Crouzon and Pfeiffer syndrome as presented in Chapter 5, makes it unlikely that it is the main cause of increased ICP. However, the evidence on the effect of OSAS on ICP stresses that respiratory obstruction should be eliminated to allow a fair cerebral perfusion pressure without immediate increased ICP as a consequence, especially in Crouzon syndrome. The vicious circle of OSAS, cerebral perfusion and ICP should be addressed in future research. The association between increased ICP and OSAS could be further explored using transcranial Doppler (TCD) to quantify alterations in cerebral blood flow or cerebral oximetry by means of near-infrared spectroscopy (NIRS).[9]

	Secondary cranial vault remodelling necessary due to elevated ICP		Secondary cranial vault remodelling prevented by OSAS treatment	Total (possibly) OSAS-related ↑ICP (% of total study population)
Syndrome diagnosis	Total (% of total study population)	(possibly) OSAS-related ↑ICP		
Apert (n = 28)	**6 (21%)**	**0**	**1**	**1 (4%)**
Crouzon / Pfeiffer (n = 43)	**9 (21%)**	**4**	**1**	**5 (12%)**
Muenke (n = 29)	**1 (3%)**	**0**	**0**	**0 (0%)**
Saethre Chotzen (n = 32)	**3 (9%)**	**1**	**0**	**1 (3%)**
Complex (n = 56)	**5 (9%)**	**1**	**0**	**1 (2%)**
Total (n = 188)	**24 (13%)**	**6**	**2**	**8 (4%)**
1	2	3	4	5

Table 2: *Patients with increased ICP due to OSAS.*
The total number of patients in whom secondary cranial vault remodelling due to increased ICP was necessary is reflected in column 2. The patients in whom OSAS was a (possibly) contributive factor for increased ICP are presented in column 3. Moreover, there are two patients who did not need secondary cranial vault remodelling since their papilledema disappeared after ATE (column 4). Column 5 represents the total number of patients in whom OSAS may have contributed to increased ICP.
Data are presented as: number of cases (% of total study population (column 2 and 5).

How can we quantify the effects of OSAS on ICP?

1. Transcranial Doppler

In 1982, Aaslid first described the use of TCD.[10] He provided a non invasive technique for the investigation of the vascular component of intracranial physiology which is able to monitor rapid changes of cerebral blood flow velocity. Since then, it has been applied as a method of intracranial monitoring in a broad spectrum of neurological anomalies. Most often, the middle cerebral artery is addressed since it carries 80% of the hemispheric blood and the changes in blood flow velocity in this artery reflect changes in the total cerebral blood flow as well.[10] Importantly, intracranial vessels lack autonomic innervation and thereby the diameter of the cerebral arteries is not commonly influenced by systemic changes in sympathic activity and arterial pressure.[11]

★ *TCD: ICP*

Klingerhöfer and co-workers showed in 1988 that increased ICP results in a decrease in cerebral blood flow velocity as measured by means of TCD.[12] Their findings were confirmed by Bellner and co-workers (including pediatric patients) and Moreno and co-workers who both focused on the pulsatility index (peak systolic velocity – end diastolic velocity / mean flow velocity), which increases with increasing ICPs.[13-14]

A decrease in cerebral blood flow velocity results in a decrease in cerebral perfusion pressure due to increased resistance in the brain. This can be estimated by subtracting the end-diastolic velocity from the peak systolic velocity and dividing this by the peak systolic velocity, according to Pourcelot's formula.[15] The use of resistance indices has been described previously in craniosynostosis. Rifkinson-Mann and co-workers[16] presented 31 patients with different types of single and multiple suture synostosis. In 22 of 31 children (71%), there was an increased resistance index indicating increased ICP. This is much higher than the overall prevalence of increased ICP of 11% as previously reported by Renier[1] using invasive intracranial pressure monitoring. It is well possible that TCD provides an overall estimation of resistance of the brain and cerebral perfusion pressure rather than a local direct reflection of ICP which is obtained by invasive intracranial pressure monitoring. Iqbal and co-workers first evaluated cerebral hemodynamic changes before and after cranial vault surgery.[17] He already suggested using TCD to measure effect of surgery. In a Chinese study by Wang and co-workers,[18] 11 cases of single and multiple suture synostosis were also studied using TCD before and after cranial vault surgery. This small group was stratified according to age. Both systolic and diastolic blood flow velocities increased in the children aged 0 – 3 and 4 – 7 years old with a concomitant decrease in resistance index. There were two 11-years old children, in whom postoperative changes were not significant. These results support the hypothesis that increasing the cranial volume is beneficial for cerebral blood flow, mainly in children under 7 years of age.

★ *TCD: OSAS*

It was previously published that cerebral auto regulation may fall short in OSAS3, resulting in a subsequent increase in blood flow velocity of 19 - 219%.[19] After termination of the apnea and onset of breathing, cerebral blood flow velocity decreased. Even in snoring, otherwise healthy children with mild OSAS (AHI < 5) the blood flow velocity was significantly higher than in 17 non-snoring controls. In this population, processing speed, visual attention and executive functions were also significant different. Although there was no direct correlation, correcting for blood flow velocity eliminated the differences between the groups. Given these results, cerebral blood flow velocities may be abnormal already in mild OSAS and a possible association with neuropsychological setback exists.[20]

The abnormalities regarding cerebral blood flow velocity in patients with OSAS may be the key in finding out in which children OSAS may be a contributive factor to increased ICP. The relatively simple, non invasive technique of TCD would be of great interest in a population who is at risk for both increased ICP and OSAS. Up to present it is unknown if the morphology of the acoustic window in the temporal bin is altered by the craniosynostosis. This could be an important radiological study to start off with. If the acoustic window is open, TCD appears to be an appealing method to study cerebral hemodynamics as a reflection of increased ICP, OSAS and its correlation in syndromic craniosynostosis.

How can we quantify the effects of OSAS on ICP?
2. NIRS

Near-infrared spectroscopy is a non-invasive technique used to estimate regional cerebral oxygenation saturation.[21] An oximeter sensor is placed on the forehead and it emanates and recollects near-infrared light (800 nm - 2500 nm). It passes extracranial tissues (such as the scalp and skull) to reach the underlying cerebral tissue. Hemoglobin is a light-absorbing chromophore, and the absorption spectra of oxyhemoglobin (660 nm) and deoxyhemoglobin (940 nm) differ, which enables NIRS to evaluate the estimated oxygen saturation. It works by means of spatial resolution, which is based on the principle that the depth of tissue interrogation is proportional to the distance between the light emitter and the detector. Hence, one light detector is placed close to the light emitter so that it perceives the saturation results from the extra cranial tissue and one light detector is placed so that it perceives the saturation results of the cerebral tissue. By subsequent automated algorithmic subtraction, extra-cranial contamination is overcome. Most often, two oximeters are placed paramedian on the forehead. NIRS can thus be only used to estimate cerebral oxygenation of the frontal regions. It is extremely important not to place the oximeter over the sagittal sinus. Since venous blood flow may be altered in syndromic craniosynostosis[22] this should be kept in mind during application and with interpretation of the results. NIRS' first applications were mainly in the peri-operative care. Several studies have shown that patients with substantial cerebral oxygen desaturations during surgery have adverse outcomes post-operatively, including neuropsychological dysfunction, prolonged hospital length of stay, major organ morbidity and mortality.[23] Although cerebral oximetry is increasingly being used, it has not yet been adopted as a standard of care during surgery or observation on the intensive care.

The decrease in cerebral perfusion pressure as a result of increased ICP, as well as the hypoxemia due to OSAS make NIRS of potential interest for research in the field of syndromic craniosynostosis. Previous studies on the use of regional cerebral oxygenation saturation and auto regulation in the context of ICP and OSAS provided the following results.

★ *NIRS: ICP*

Cerebral perfusion as measured by 3 different oximetry technologies varies from 73% - 76% on average in healthy individuals with an average arterial oxygenation of 99% as measured on the finger.[23] Changes in ICP result in decreased cerebral oxygenation saturation after a median time of 7.1 seconds.[24] In a pilot study of adults with severe brain trauma,[25] it was found that cerebral oxygenation saturation was significantly decreased in cases of increased ICP. Even after 3 minutes of artificial hyperoxygenation (50% oxygen therapy), cerebral oxygenation saturation was significantly lower in cases of increased ICP, indicating impaired cerebral perfusion pressure. It is striking that cerebral blood flow velocities were comparable both before and after oxygen therapy. In children who underwent invasive ICP monitoring for a range of neurologic diagnoses it was also found that cerebral oxygen saturation decreased during episodes of increased ICP.[26] During periods of normal ICP's, the mean cerebral oxygen saturation was 75% as compared with a mean cerebral oxygen saturation of 71% if the ICP was >20 mmHg. The mean difference of 4% is small in comparison to the standard deviation of 10-13%. The values of absolute ICP nor the change in cerebral oxygen saturation were significantly associated with intracranial pressure. Contrary, there was a significant correlation between absolute

values and changes in end-tidal CO_2 and cerebral regional oxygen saturation. After stratification for underlying cause of increased ICP, it was found that only in patients with intracranial hemorrhage there was an increase in cerebral oxygen saturation. Therefore, the authors conclude that there might be a decreased cerebral oxygen saturation in pediatric patients with increased ICP, but the relationship is strongly influenced by diagnosis. It is unknown how a possibly altered compliance of ICP in craniosynostosis will affect the cerebral perfusion and cerebral oxygenation.

★ *NIRS: OSAS*

With regard to OSAS, it was shown that mean cerebral oxygen saturation is significantly lower (57.1% versus 61.5%) in adult patients with OSAS (median AHI 55) compared to controls.[27] Additionally, a study in adult snoring patients, mild OSAS patients and severe OSAS patients evaluated the effect of events on oxygen saturation.[28] The authors showed that hypopneas were associated with an average decrease of peripheral oxygenation of 3.6%, whereas the mean decrease in cerebral oxygenation was only 0.6%. For obstructive apneas the peripheral decrease in oxygenation was 7.2% as compared to a decrease in cerebral oxygenation of 1.7%. The decreases were most pronounced in cases of severe OSAS. Subtle changes in oxygenation due to UARS or mild OSAS may be hard to discriminate and mainly the less severe part of the spectrum of sleep disordered breathing is highly prevalent in syndromic craniosynostosis as we showed in our prospective cohort study. Moreover, changes in perfusion during non REM sleep and REM sleep may contribute to further diagnostic inaccuracy.

In summary, it appears that during severe OSAS, the transient increase in cerebral blood flow measured by means of TCD, is not fully able to prevent cerebral hypoxia as measured by means of NIRS. Although the concept is interesting, there are many practical and financial burdens that make the use of NIRS in syndromic craniosynostosis not too appealing.

Is OSAS a problem in syndromic craniosynostosis?

Respiration is most often not severely affected in syndromic craniosynostosis. We repeatedly found, that the severity of OSAS is predominantly 'only' mild. In about 1 in 4 cases of syndromic craniosynostosis, OSAS is moderate or severe; in about 2 in 4 cases, OSAS is mild at worst and in the remaining OSAS is not present at all. Patients with severe OSAS and syndromic craniosynostosis are a challenge for the craniofacial team. Previous studies showed that midface surgery often is insufficient to completely resolve OSAS.[29-30] Hence, there is a big population of children with syndromic craniosynostosis and long-lasting mild OSAS.

One of the main findings of the prospective cohort study was that OSAS was also highly prevalent in patients without midface hypoplasia. A recent study by Alsaadi and co-workers[31] showed that even six (one unilateral coronal suture synostosis, two sagittal suture synostosis, three multi-suture synostosis) of 10 non-syndromic patients have abnormal sleep studies in absence of complaints. A different morphology of the skull and cranial base may have (subtle or more pronounced) effects on the facial morphology as well. In addition to the underdevelopment and a lack of growth of the maxilla presenting as a class III malocclusion, the mandible may be affected too. Moreover, the nose may also be affected with possible nasal septum deviation, increased size of the inferior nasal turbinates and choanal atresia. Anoma-

lies of the soft palate include (submucosal) cleft, differences in characteristics of the uvula and soft tissue redundancy; the hard palate may be high and narrow arched.[32] Finally, there are case reports presenting solid cartilaginous tracheal sleeves due to fusion of rings in Crouzon and Pfeiffer syndrome.[33-34] All these characteristics have never been studied in different syndromes associated with craniosynostosis. We are unsure how often these additional anomalies are present, and to what extent they relate to primary OSAS and persisting OSAS after midface advancement. For clinical care we now mainly perform endoscopies in patients with Apert, Crouzon and Pfeiffer syndrome. To be able to explain the high prevalence of OSAS in patients without midface hypoplasia, standardized endoscopies would be a logic next step to improve the understanding of OSAS. It is known that in otherwise healthy children with OSAS, deviant anatomy of the nose and palatal anomalies are risk factors for persistent OSAS after ATE.[35] Of our cohort, 20% undergoes an ATE but it was previously reported that only 60% of them have a significant benefit of the procedure,[36] which is somewhat less than the 75-100% of otherwise healthy children.[37] Possibly, thorough examination of the upper airway using endoscopy may help us predicting in which craniosynostosis patients ATE is an appropriate treatment.

How should we ideally diagnose OSAS in syndromic craniosynostosis?

It is not easy to quantify mild OSAS using ambulatory sleep studies. The regular indices including apneas or desaturations are often insufficient to diagnose minor obstruction or upper airway resistance (UARS). Since total collapse of the pharyngeal wall and oxygen-desaturations are not present, the traditional oAHI in these cases has a low sensitivity. Currently, the most common way to accurately diagnose UARS is by means of esophageal pressure measurement. An increase in intra-thoracic and intra-esophageal pressure is observed during progressive flow limitation.[38] In our study population, we did not yet use esophageal pressure measurements, nor quantify flow limitation. We sometimes observe a typical pattern of flattening of the respiratory peak as measured by the nasal cannula pressure transducer.[39] The wave contour is asymmetric, which reflects flow limitation. These observations have been previously objectified with the same material and also in a paediatric population[40] and it might be a valuable contribution to the current diagnostics. UARS may also adversely affect quality of sleep due to a high number of respiratory-effort related arousals (RERAs) on EEG-monitoring. In the study, we did not yet have all fancy additional analyses available. From parental observations, we know that many patients suffer from respiratory effort and snoring.[41] This may be associated with RERAs,[38] which results in sympathic activation via the baroreflex leading to subtle increases in pulse transit time[42] and blood pressure.[43-44] Pulse transit time is the time taken for the arterial pressure wave to travel from the aortic valve to the periphery (measured by finger photopletsymography). It is used as an index of autonomic (dys)function.[45] It was previously shown that the pulse transit time significantly correlates with the AHI in children with sleep disordered breathing.[46] This has triggered our interest in using heart rate variability (HRV), which may be another index for autonomic dysfunction in sleep disordered breathing.

HRV can be analyzed by computing the time between two beats, but it can also be analyzed by determining the frequency of changes among multiple beats.[47] The high frequency (HF) bands represent the fast periodicity that depends on the parasympathic control, and the low frequency (LF) bands represent both the sympathic and the parasympathic control.[47] The ratio between the low and high frequency

bands (LF/HF) is a measure for sympathovagal balance, with a bigger ratio indicating a tilt toward the sympathetic component.[48] OSAS appears to have an adverse effect on HRV.[47,49-50] A pediatric study showed that in patients with moderate – severe OSAS (AHI > 5), parasympathic control diminishes which results in an increase in HRV.[51] Patients with mild OSAS (AHI 1-5) also have a minor increased HRV as compared to healthy control subjects. Regarding mild OSAS or snoring, the sympathetic component was indeed increased, but autonomic balance was undisturbed without treatment.[52] Otherwise, there is a lack of thorough evidence on chronic changes in HRV in patients with primary snoring, UARS or mild OSAS. Therefore, we conducted a pilot study on 4 patients with UARS using Kubios HRV software[53] on the ECG signals that were recorded parallel to a clinical sleep study. Our methods to generate the HRV-parameters was comparable to a previous study by Muzumdar and co-workers,[48] who analyzed 10 controls without OSAS and 18 patients with OSAS (AHI 31.9 ± 24.8). Table 3 represents the parameters regarding heart rate variability which were obtained during S1 and S2 stages sleep.

HRV						
Frequency domain	**Controls[48]**	**UARS 1 Apert**	**UARS 2 Crouzon**	**UARS 3 Apert**	**UARS 4 Crouzon**	**Severe OSAS[48]**
Age	**5.6 ± 3.5**	**1 year, 10 months**	**5 years, 9 months**	**6 years, 3 months**	**8 years, 7 months**	**4.9 ± 2.4**
Mean HR	**77.9 ± 9.2**	**102.1**	**84.6**	**76.8**	**73.6**	**99.8 ± 16.9**
Mean RR	**800 ± 100**	**598.9**	**720.4**	**804.5**	**838.4**	**630 ± 120**
LF (ms^2)	**564.1 ± 331.7**	**1254**	**958**	**2248**	**2226**	**360.4 ± 342.1**
HF(ms^2)	**3226.3 ± 3299.8**	**2738**	**1329**	**6490**	**5965**	**902.4 ± 1202.8**
LF/HF	**0.3 ± 0.2**	**0.46**	**0.72**	**0.35**	**0.37**	**1.6 ± 2.7**

Table 3: ***Heart rate variability in controls, severe OSAS and four cases with syndromic craniosynostosis and upper airway resistance syndrome.***
Where HR is heart rate, RR is the time between two R waves, LF is low frequency, HF is high frequency, UARS is upper airway resistance syndrome and OSAS is obstructive sleep apnea syndrome.

HF (parasympathetic input) in UARS seems to be comparable to values in healthy controls. Different than in both controls and OSAS patients, LF (parasympathetic and sympathetic input) is extremely high as a result of an increase in HRV. Autonomic balance, as reflected by the LF/HF ratio, impresses to be close to normal in our 4 UARS patients. HRV is an interesting topic for future research, definitely concerning UARS.

UARS and mild OSAS are also associated with OSAS-related co-morbidity.[38] It has been proposed that the RERAs, and not hypoxemia, are the causal factor of cardiovascular morbidity and altered quality of life. Repetitive arousals for example, have been related to increases in systolic and diastolic blood pressure, even in the absence of hypoxemia.[43] Research in otherwise healthy children has also shown that even mild OSAS is associated with an increased cerebral blood flow velocity.[20] Moreover, animal studies and previous research in adult subjects suggests that the vibrations associated with heavy snoring are an independent, significant risk factor for carotid artherosclerosis.[54-55] The latter has been indirectly correlated with cognitive inabilities. Moreover, OSAS in syndromic craniosynostosis is associated with diminished quality of life and behavioral problems.[56]

Next to all abnormalities in patients with syndromic craniosynostosis, it was very interesting to report that CSA is not a significant problem. Apparently, the effects of hindbrain herniation, white brain matter anomalies and OSAS are subtle. In combination with a great plasticity of the developing brain, this possibly results in an unaffected innervation of respiration.

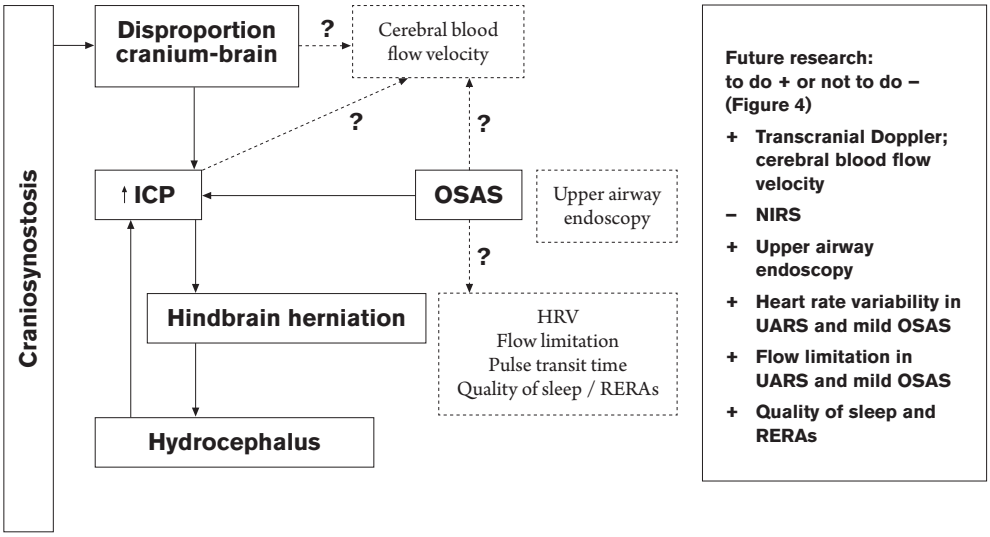

Figure 4: ***Future research.***

Strongholds and limitations

The strongholds of this research project were the large population of patients with a rare congenital anomaly and the longitudinal set up of the study; something which was never performed before. Referral bias is overcome by including all patients with syndromic and complex craniosynostosis and we have no indication that the 51 not-included patients are distinct from the study group.

A first limitation is that a daytime, indirect measurement of ICP is unable to fully reflect the dynamics of the actual swings in pressure, if present. In healthy individuals, only rapid, big increases in for example thoracic pressure after coughing result in a temporary increase in ICP which is soon enough overcome. Contrary, in syndromic craniosynostosis, compliance mechanisms may fail. Increased ICP, due to for example hypercapnia associated with OSAS[57] or an abnormal CSF circulation due to hindbrain herniation,[58] cannot be compensated by the usual ways of compliance. The lack of compliance mainly presents at night, when the ICP gets highest. It is thus comprehensible that daytime ONS measurements are not so valuable as compared to measurements during the night. Papilledema, as well as abnormalities on OCT, may be sooner or later after ICP increases, but most commonly not straight away, as presented in figure 5.

The low sensitivity of daytime ultrasounds requested additional analysis. A more dynamic overview was created by performing multiple ultrasounds in one single patient at different times and at different ICP levels. The ONS was found to be enlarged during the night and sometimes already recovered to a normal size in the morning.

It seems that the ONS diameter is more dynamic as compared to the currently used measure of papilledema. We know from early monkey-studies in which subdural tissue expanders were inflated,[59] as well as from trauma cases,[60] that papilledema only develops after persistent or intermittent ICP increases. OCT scanning may be more sensitive to detect subtle changes that may not be seen by an investigator's eye during fundoscopy, such as a minor increase in the retinal nerve fiber layer thickness.

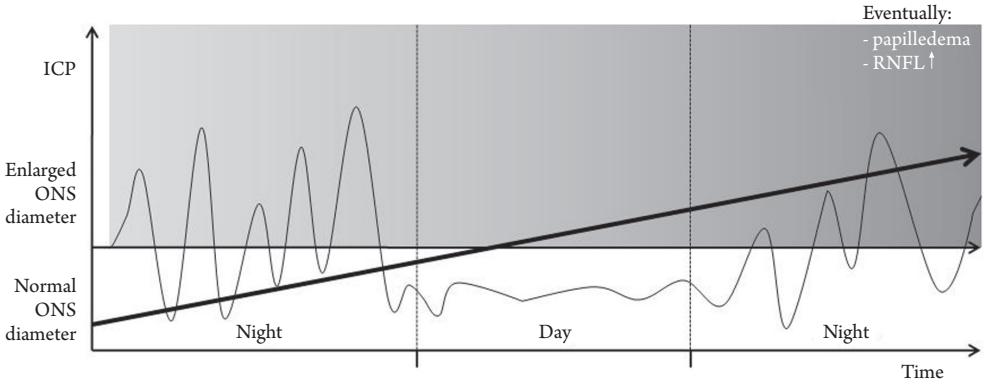

Figure 5: ***Acute and long-term effects of increased ICP.***
Where ONS is optic nerve sheath.

A second shortcoming is the use of level III sleep studies for diagnosing sleep disordered breathing. Ideally, diagnostic tests for sleep abnormalities should include esophageal pressure measurement to determine upper airway resistance, $paCO_2$ analysis to analyse hypercapnia in the absence of oxygen desaturations EEG registration to analyze the quality of sleep. Hyponeas with arousals, but without desaturation, could not be scored since EEG registration was unavailable. Upper airway resistance, hypercapnia and arousals could be abnormal and missed although we know that mild OSAS, and possibly also UARS, have a high prevalence in syndromic craniosynostosis. Moreover, the estimated sleeping time was based on the regularity of respiratory parameters. This may result in an overestimation of the effective sleeping time. All in all the severity of sleep disordered breathing in syndromic craniosynostosis may have been underestimated.

Since the second half of 2011, EEG registration has been integrated in clinical sleep studies. The upcoming results regarding quality of sleep as well as HRV in syndromic craniosynostosis patients with (close to) normal saturation profiles are promising. Finally, in retrospect it would have been of great interest to also know about oxidative stress and inflammation during the night to exclude false negative results.

By means of a multidisciplinary approach, we aimed at combining the physiology of intracranial pressure, ophthalmologic changes and respiration. We feel that we have contributed significantly to the evidence based scientific knowledge on the most important morbidities in children with syndromic craniosynostosis. The clinical relevance can be found in 1) the availability of objective derivations of ICP by means of optic nerve sheath ultrasound measurements and OCT analyses, 2) the importance of performing a sleep study in all patients with syndromic craniosynostosis before the age of one year old and 3) generally a low prevalence of central sleep apnea.

The Dutch craniofacial center in Rotterdam has over 40 years of dedicated experience. With the start of this prospective project on ICP and OSAS in syndromic craniosynostosis in 2006 by Dr. Natalja Bannink, Dr Koen Joosten and professor Irene Mathijssen and the continuation as reported in this thesis, many questions regarding understanding, prevalence and optimal screening have been answered. It is a dynamic and fascinating field of research with a variety of new hypotheses to be put under pressure.

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