## What do we already know about
★ **Syndromic craniosynostosis**

Craniosynostosis refers to the premature fusion of one or several calvarian sutures. For transient skull distortion during birth, as well as to facilitate growth of the brain, the seven bones of the calvarian are separated by six major calvarian sutures[1] (Figure 1). The sutures function as growth centers. The center of the suture deposits proliferating cells, which gradually undergo osteogenetic differentiation. Migration towards the skull bone results in growth of the cranial vault. This is an important requisite to allow the brain quadrupling its volume during the first two years of life. The posterior fontanel will close first at an age of two months. The metopic suture will close next within the first year of life, followed by closure of the anterior fontanel at the age of two years. Although the other sutures only close in adulthood, they lose their function in skull growth after the age of six years.[2]
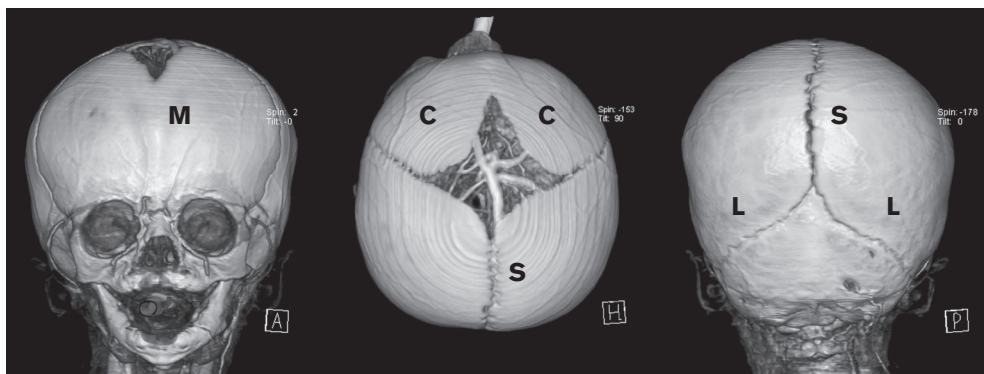
Figure 1: *Open calvarian sutures.* **Six-months-old patient with Crouzon syndrome with open calvarian sutures. Note the physiological synostosis of the metopic suture (M), and the open coronal sutures (C), lambdoid sutures (L) and sagittal suture (S).**

In the congenital anomaly of craniosynostosis, the cranial vault develops quite differently. The disorder is characterized by either premature fusion or agenesis of the calvarian sutures. Normal development is usually disrupted at 15 to 18 weeks of gestation.[3] It results in a restricted growth of the skull perpendicular to the suture. Compensatory growth occurs in the other directions to accommodate the growing brain. This abnormal development result in a deformity of the cranial vault. It may be associated with facial anomalies.

Craniosynostosis affects 1 in 2500 births. In 40% of all cases,[4] 1 in 6250 births, it is part of a syndrome. Genetic mutations most often concern the fibroblast growth factor receptor (FGFR) genes and may develop de novo or by autosomal dominant inheritance. FGFR's regulate cell proliferation and differentiation of mesenchymal and neuroectodermal cells.[5-6] Experimental research shows that they are not only expressed in
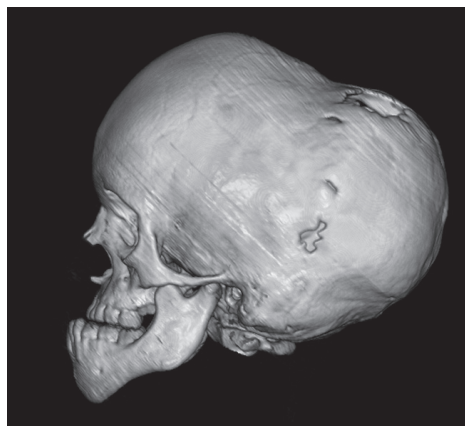
Figure 2: *Midface hypoplasia in a 5-years-old patient with Crouzon syndrome.*

the calvarian sutures, but also in the skull base, face and upper airway.[7-8] Dysregulation of the growth factors receptors are thought to be causally related to the anomalies associated with syndromic craniosynostosis. However, in few cases of syndromic craniosynostosis the calvarian sutures may be unaffected.

The syndromes that feature craniosynostosis include Apert syndrome, Crouzon syndrome, Pfeiffer syndrome, Muenke syndrome[9] and Saethre Chotzen syndrome[9-10] (Table 1). In over 50% of all cases a genetic cause is unknown, but expected, since the craniosynostosis involves multiple sutures or affects multiple members of a family.[4,11-12] These cases are referred to as 'complex' craniosynostosis. The MSX2 gene[13] and more recently the IL-11RA[14] gene were found in our population of complex craniosynostosis patients. Ongoing research should and will define more genetic causes in the future.[15]

Syndrome	Apert	Crouzon / Pfeiffer
Genetic cause	FGFR 2 gene Chromosome 10 - S252W - P253R - 1372 BP deletion	FGFR 1 gene Chromosome 8 - P252R FGRF 2 gene Chromosome 10 - Several mutations FGFR 3 gene Chromosome 4-A391E
Incidence	1 / 180.000	1 / 25.000
Phenotype	Craniosynostosis (majority bilateral coronal suture with enlarged anterior fontanel) - Exorbitism - Midface hypoplasia* - Class III malocclusion - Crossbow-shaped or trapezoidal lips - Symmetric, complex syndactyly hand and feet	Craniosynostosis (majority bilateral coronal suture) - Exorbitism - Midface hypoplasia* - Class III malocclusion - Acanthosis nigricans in FGFR 3 mutation - Pfeiffer syndrome can be distinguished by limb anomalies (ankylosis, broad first digits)
IQ**	75	98
Neuropsychological development	Variable, possible developmental delay Behavioral problems, mainly in boys	Variable, some developmental delay may be present

Syndrome	Muenke	Saethre Chotzen	Complex
Genetic cause	FGFR 3 gene Chromosome 4 - P250R	TWIST I gene Chromosome 7 - Several mutations/deletions	Currently unknown
Incidence	1 / 30.000	1 / 25.000	1 / 25.000
Phenotype	Craniosynostosis (majority bilateral coronal suture) - Hearing loss - Behavioral disturbances	Craniosynostosis (majority bilateral coronal suture) - Downward slanting of the palpebral fissure - External ear anomalies - Blepharoptosis of the upper eyelid - Incomplete, simple syndactyly	Craniosynostosis - Broad spectrum of possible additional features
IQ**	77	102	
Neuropsychological development	Possible learning disabilities Language delay	Normal Possible retardation in TWIST gene deletions	

Table 1: *Overview of syndromic craniosynostosis.*
*As illustrated by Figure 2.
**Own unpublished data. Patients who had an IQ too low to be tested were excluded.

Early fusion of the calvarian sutures and subsequent deformity of the skull and face may be related to increased intracranial pressure, hindbrain herniation, exorbitism, obstructive sleep apnea, malocclusion and esthetic anomalies. Further introduction of this thesis will focus on intracranial pressure, hindbrain herniation and obstructive sleep apnea.

Figure 3: *From top down and left to right showing Apert syndrome, Crouzon syndrome, Muenke syndrome, Saethre Chotzen syndrome and complex craniosynostosis.*

What do we already know about
★ **Craniosynostosis and Intracranial Pressure**

Intracranial pressure (ICP) is a delicate equilibrium between the rigid skull and its contents. The intracranial content comprises the brain parenchyma (80%), cerebrospinal fluid (CSF) (10%) and blood (10%), which is covered by the cranial vault.[16] ICP develops as a function of volume and compliance of the content. According to the Monro-Kellie hypothesis, the sum of the intracranial volume of blood, brain,

CSF, and other pathologic components if present is constant.[17] A mismatch in the skull's volume and intracranial volume or a limited ability to adapt to changes may consequently result in an increased ICP.

Adaptation to small changes in ICP is mainly dependant on absorption or transposition of CSF to or from the spinal compartment. In addition, blood flow may be variable too. Cerebral perfusion pressure can be defined as the difference between the mean arterial pressure and the ICP. If blood flow increases, the cerebral perfusion pressure increases, although this relationship is not linear. This dynamic cascade can be used to intercept changes in ICP.

There is only little evidence about intracranial compliance in craniosynostosis. It is affected in the majority of patients with multi-suture synostosis,[18] but it is unknown which part the compliance exactly fails in this population. Generally, a small increase in ICP may be compensated by a decreased blood flow or CSF flow, but once the compensation mechanism is exhausted, the compliance is overcome and a steep increase in ICP occurs.[19] In a hypercapnic and hypoxic condition for example, cerebral perfusion pressure has to be increased to avoid brain tissue hypoxia and metabolic crisis[20] which is associated with an increase in ICP.

> **What do we already know about ICP:**
> ★ The sum of intracranial volume of blood, brain and CSF is constant.
> ★ Compliance to maintain normal ICP mainly depends on absorption or transposition of CSF
> ★ This may be altered in syndromic craniosynostosis due to craniocerebral disproportion, venous hypertension, hindbrain herniation, hydrocephalus and OSAS

Patients with syndromic craniosynostosis have a craniocerebral disproportion, may suffer from venous hypertension, hindbrain herniation, hydrocephalus and possibly a failing compliance regarding CSF (Figure 1). This puts them at major risk for developing increased ICP. Compensatory mechanisms, such as cerebral flow and the interstitial fluid equilibrium, are depleted giving rise to a typical pattern of nocturnal waves of increased ICP,[16] especially during REM sleep[21] during which brain perfusion increases. In these patients, ICP is often normal during daytime.

The normal range of ICP varies with age but true values in the pediatric population have not been well established. Thresholds for initiating treatment vary according to etiology and within single conditions there is a continuous debate about the appropriate upper limit of normal. It is generally accepted that values above 15 mmHG are considered to be pathologic and values between 10 and 15 mmHg are considered borderline.[17]

Craniocerebral disproportion
ICP may increase if the brain grows faster than the skull.[22] In otherwise healthy children, the biggest growth of the skull is accomplished during the first two years of life (77%). At the age of five years, 90% of the maximum volume is achieved.[23] In syndromic craniosynostosis however, the volumes seem to be significantly smaller at birth,[24] which justifies cranial vault expansion and remodelling during the first year of life. Contrary, preoperative volumes are often at least 2 SD above the mean of healthy individuals.[25] After cranial vault remodelling, patients with Apert and Crouzon syndrome develop an intracranial volume which often even exceeds 2 SD as compared to age and gender matched controls.[25] This may partially be ex-

plained by an altered shape of the skull due to the craniosynostosis or cranial vault remodelling which may be associated with a larger volume. Moreover, the volume of CSF may be increased.[26] In our population of patients with syndromic craniosynostosis, the intracranial volume is normal on average. Ventricular volume however, is increased in children with Apert syn-drome and Chiari I malformations, which is most commonly found in Crouzon syndrome.[26]

A decreased skull volume has no direct correlation with increased ICP.[27] In a study of 41 craniosynostosis patients, over 90% had an increased ICP but only 10% of them had a decreased skull volume. Volume measurement alone is not a reliable predictor for increased ICP.[27-28] The biologic explanation remains unclear.

Venous Hypertension

Extensive venous collaterals have been found in patients with syndromic craniosynostosis, especially occipitally.[22] The presence of collaterals is a sign of abnormal intracranial-to-extracranial venous drainage[29] which is regarded to be a significant attributor to increased ICP.[22, 30] A suggested explanation is stenosis of the jugular foramen[30] and stenosis or absence of the sigmoid sinus and jugular vein.[31-32] These anomalies may increase CSF pressure and venous pressure which stimulate the formation of collateral veins and the development of early signs of increased ICP.[32] We found a bigger jugular foramen in patients with signs of increased ICP (own unpublished data). This is in line with a study by Booth and co-workers who studied craniosynostosis patients regardless of the ICP.[33] It appears that emissary veins develop to maintain a normal ICP during the first years of life. Since these emissary veins may be the only venous drainage, they are very important to take into consideration when planning (sub)occipital surgery. The veins are critical to maintain normal ICP and their division may be fatal.[34]

Hindbrain herniation

Hindbrain herniation is a frequent finding in syndromic craniosynostosis. It is found in up to 72% in Crouzon syndrome.[35] In contrast, only 0.1% of the general population[36] demonstrates hindbrain herniation. Several theories have been proposed to explain the mechanism by which hindbrain herniation in craniosynostosis could develop. Some authors have suggested that it might be related to the small size of the posterior fossa, especially after premature closure of the lambdoid sutures.[35] Others have suggested that the causes lie in anomalies of the cerebellum and brain stem, venous hypertension, hydrocephalus and/or increased ICP.[37-38] It is unknown what may be a cause and what may be a consequence of hindbrain herniation, but it seems that hindbrain herniation precedes hydrocephalus.[35, 39] In Crouzon patients,
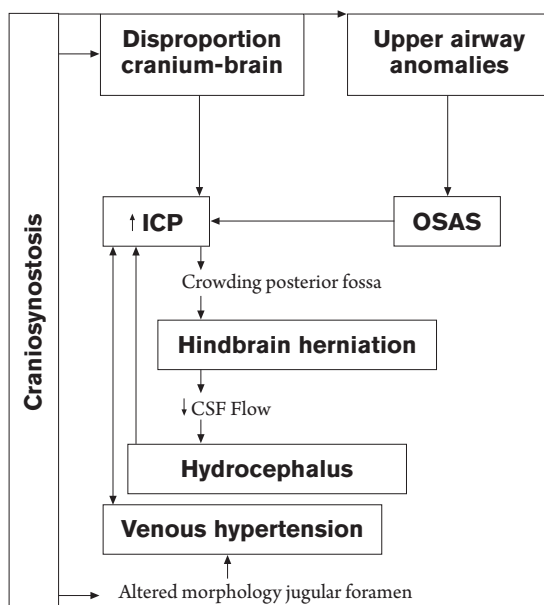
Figure 4: *The etiology of increased ICP in syndromic craniosynostosis.*

we found that hindbrain herniation occurs independent of lambdoid synostosis and that the cerebellum is actually smaller compared to other syndrome diagnoses (own unpublished data).

The position of the hindbrain is assessed on a sagittal MRI study. An imaginary line is drawn between the basion and occiput, which represents the foramen magnum. A herniation of < 5 mm is referred to as *tonsillar hernation* and a herniation of ≥ 5 mm is referred to as *Chiari I malformation*.[40]

Hindbrain herniation may result in compression of the brain stem, cranial nerves and upper spinal cord, resulting in i.a. impairment of the respiratory centres.[36, 40] Data on the symptomatology of hindbrain herniation in patients with craniosynostosis are contradictory.[38, 41]

Hydrocephalus

The majority of all patients with Apert and Crouzon syndrome have ventricular dilatation.[37, 42] It is not often observed in Muenke and Saethre Chotzen syndrome,[42] although the literature on this topic is limited. Ventricular dilatation may be due to venous obstruction as discussed previously, which results in a limited resorption of CSF. On the other hand, outflow of CSF to the spinal canal may be obstructed by hindbrain herniation. It is referred to as hydrocephalus when it is progressive and ventriculomegaly when it is stable.[42] Ventriculomegaly is most frequent observed in patients with Apert syndrome and explains most of their increased intracranial volumes.[26] It is unsure whether the increased skull's volume is the cause or consequence. It may even be a congenital anomaly of the brain or a (FGFR2-related) deviant CSF production.

From previous cohort studies, it is well known that up to 35-80% of all patients with syndromic craniosynostosis eventually develop increased ICP.[27, 43-48] Before initial cranial vault remodelling, increased ICP is already observed in 45% of patients with Apert syndrome and 63% of patients with Crouzon syndrome.[21, 49] It puts the optic nerve at risk which is associated with visual impairment[50] and even blindness.[51] Furthermore, increased ICP has been related to white matter abnormalities which decreases functional outcome.[52] Neuropsychological deficits have also been attributed to increased ICP,[53] even in non syndromic craniosynostosis.[54] For that reason, we perform cranial vault remodelling before the age of one year by protocol. Even after initial cranial vault remodelling, up to 35-52% of our patients with syndromic craniosynostosis develops a second period of increased ICP.[44] It occurs mainly in Apert and Crouzon syndrome, but a second episode of increased ICP also presents in Muenke and Saethre Chotzen syndrome and complex craniosynostosis.[44, 55] Therefore annual screening is required up to the age of six years. Invasive ICP monitoring is only performed when symptoms and signs are not conclusive for increased ICP, because it includes an operation under anesthesia and admittance to the intensive care unit. Clinical symptoms and signs such as headaches, nausea, vomiting and loss of vision are often not present or difficult to objectify in a pediatric population. Most commonly, screening consists of fundoscopy to assess the presence of papilledema. The sensitivity of papilledema in children with craniosynostosis younger than 8 years old has been debated.[56] Other craniofacial teams therefore suggest the use of visual evoked potentials (VEP) with good results.[55] There is a need for an objective and sensitive diagnostic tests to screen for ICP.

What do we already know about
★ **Craniosynostosis and Sleep Disordered Breathing**

Respiration is a complex interplay between upper airway, lungs and chest wall anatomy and central nervous control. Any disturbance in this interaction may result in (sleep) disordered breathing. It may present as abnormalities in frequency and tidal volume or obstructive and/or central apneas, which are closely related in clinical practice. Both types may occur together in the same patient over the same night. The pathogenesis of the phenomena arise from anatomic and functional factors, which may both exist in syndromic craniosynostosis. *Obstructive sleep apnea* and *Central sleep apnea* will be discussed separately after a general introduction on the physiology of respiration.

The upper airway is commonly defined as the soft tissue region bounded by the nasopharynx superiorly, the epiglottis inferiorly, the maxillomandibular complex anteriorly and the spinal column posteriorly.[57] The lower respiratory tract consists of the trachea and the lungs and together with the chest wall and diaphragm, the respiratory tract accomplishes inspiratory and expiratory flow and gas exchange. For adequate respiration, airway patency is required. It is influenced by the actual anatomic size, resistance of the upper airway, upper-airway neuromuscular tone and sensitivity to hypercapnia, hypoxia and airway occlusion. Pressure from the parapharyngeal tissue works as a collapsing force. Pharyngeal muscles may be activated which acts as a dilating force on the pharyngeal airway. The genioglossus muscle of the tongue, which is innervated by the hypoglossus nerve (XII), functions as the most important airway dilator. A certain degree of collapsibility is required for phonation and swallowing, but generally the tone of the upper airway muscle decreases with sleep onset. In infants the upper airway is generally more compliant and therefore collapsible.

> **What do we already know about sleep disordered breathing:**
>
> ★ **Airway patency is achieved by the actual anatomic size, resistance of the upper airway, upper-airway neuromuscular tone and sensitivity to hypercapnia, hypoxia and airway occlusion.**
>
> ★ **If the critical closing pressure gets too low, there should be a physiologic response by the loop-gain system based on chemosensitivity in order to stabilize respiration.**
>
> ★ **Due to maxillary and pharyngeal anomalies, children with syndromic craniosynostosis are at risk for developing OSAS.**
>
> ★ **Due to brain distortion, hindbrain herniation and severe OSAS, children with syndromic craniosynostosis are at risk for developing CSA.**

All collapsing and dilating forces create the critical closing pressure (P_{crit}), which the airway pressure at the flow-limiting site below which the flow-limiting site collapses. According to the Starling resistor mechanism,[58] inspiratory airflow through the upper airway during sleep is determined by the pressure at which a flow-limiting site within the upper airway collapses (P_{crit}). Therefore, inspiratory flow does not equal downstream pressure and expiratory flow does not equal upstream pressure.[59] Airway patency is preserved as long as the inspiratory 'downstream' pressure 1) overcomes the expiratory 'upstream' pressure and 2) is bigger than the critical closing pressure. If only the downstream pressure is below the P_{crit} and the upstream pressure is not, the airway does not collapse, but instead a state of flow-limitation arises. If the intra-luminal pressure gradually decreases below P_{crit} during expiration, the airway collapses.[57]

This disturbance in respiration can be corrected by a feedback loop known as *loop-gain*. The loop-gain system induces a response to stabilize the respiration, which is proportional to the disturbance.[57, 60] The respiratory loop-gain system is based on chemosensitivity. Abnormalities in the rate and depth of breathing can lead to hypercapnia and hypoxia which is sensed via peripheral chemoreceptors in the carotid body and central chemoreceptors in the brainstem. Respiration is activated by a central response if the upper threshold is reached. The chemoreceptor-induced ventilator drives decrease during sleep, which allow a limited increase in $paCO_2$ and decrease in paO_2.

The loop-gain system functions worst during REM-sleep.[57] Responses on hypercapnia delay through which the physiologic compensatory tonic input to the upper airway dilator muscle motor neurons fails to occur.[61] A high gain system on the other hand generates a rapid but unstable change in respiration.[62] This brisk response may manifest as periodic breathing. It occurs in newborns up to the age of one year old and may also be present in patients with brainstem pathology.

Eventually, autonomic activation may eventually increase airway activity. This may be associated with an arousal. If an arousal occurs, a transient change in sleep state occurs and cortical provocation does not only open the upper airway[63-64] but fragments sleep too. Arousals further contribute to respiratory instability and upper airway collapsibility and they have also been associated with co-morbidity due to sleep disordered breathing.[58, 65]

In conclusion, sleep apnea is a complex cycle from apnea, recovery and re-entry into apnea. Airway anatomy and collapsibility are controlled by a loop gain system based on chemosensitivity. Syndromic craniosynostosis may be associated with maxillary hypoplasia, palatal abnormalities, trachea rings, pharyngeal collapse and brainstem abnormalities. Hence, it is important to study the severity and co-morbidity of both obstructive and central sleep apnea in patients with syndromic craniosynostosis.

Obstructive sleep apnea

No one less than Charles Dickens (1812-1870) was the first to describe obstructive sleep apnea in 1836 in *The Posthumous Papers of the Pickwick Club*. Sir William Osler portrayed the classical presentation of obstructive sleep apnea syndrome in children in 1892, describing "loud and snorting respirations, prolonged pauses followed by deep, noisy inspirations, and wake ups in paroxysm of shortness of breath."[66] The first series of pediatric patients with OSAS was reported by Guilleminault.[67] The interest in breathing disturbances among craniofacial patients was raised by Schafer in 1982.[68]

Obstructive breathing is more and more contemplated as the following spectrum of disease. The P_{crit} is progressively higher with increasing severity.[58]

★ *Habitual snoring*
Although primary snoring does not include apneic episodes or desaturations it has been linked to neurocognitive impairments.[69]

★ *Upper airway resistance syndrome* (UARS)
Incowmplete obstruction of the airway during sleep. It is characterized by periods of sleep associated with inspiratory flow limitation, increased inspiratory effort and arousal.[70] Because it may result in hypercapnia and sleep fragmentation, co-morbidity may be equal to that of OSAS.

★   *Obstructive sleep apnea syndrome* (OSAS)
    Characterized by episodic upper airway obstruction and resultant cessation of airflow. It results in three major components that cause co-morbidity, being episodic hypoxia, intermittent hypercapnia and sleep fragmentation.

OSAS may be associated with symptoms of disrupted sleep, noctural sweating, sleep terror, (persistence of) bed-wetting, abnormal sleeping positions, sleep walking and fatigue. Children with OSAS are at risk for developing deficits of executive functions due to dysfunction of the prefrontal areas of the brain.[71] This includes more aggressive, hyperactive and inattentive behavior. If the executive functions are affected, it interferes with cognitive abilities and learning. Physically, OSAS is related to failure to thrive and abnormal growth patterns. Patients often show mouth breathing during the day, which results in secondary impairment of maxillomandibular growth.[72-73] Cognitive deficits and cardiovascular co-morbidity are negatively influenced by oxidative stress and systemic inflammation due to arousals and hypoxemia and re-oxygenation.[74-75] It is unknown to what extent this occurs in patients with craniofacial anomalies. Finally, OSAS may result in pulmonary hypertension which can eventually lead to cor pulmonale.[76] Sudden death may occur but is rare.[77]

OSAS is highly prevalent in children with syndromic craniosynostosis. Previous studies revealed prevalences of up to 40% in patients with Apert, Crouzon and Pfeiffer syndrome[78-79] but these data are derived from clinical observations only without diagnoses by means of objective sleep studies.
Several explanations can be given:
1. Abnormal upper airway anatomy due to narrowing of the nose due to septum deviation and choanal atresia, hypoplasia of the maxilla, palatal deformities and tracheal cartilage anomalies.[80] Hypertrophia of the adenoid and tonsils or pharyngeal edema/inflammation reduces the diameter of the upper airway.[81]
2. Increased upper airway resistance due to pharyngeal collapse of the lateral pharyngeal wall and/or supraglottic collapse.[82] This has never been studied extensively in craniosynostosis patients, but has been reported in craniosynostosis patients with persistent OSAS.[83] Potentially, in craniosynostosis patients, the hypoglossus nerve is compressed by hindbrain herniation. This might result in upper airway resistance and subsequently OSAS, as described previously[84] in a heterogeneous group of patients with Chiari I or II malformations.

Diagnostics
Questionnaires on the common associated symptoms, such as *Brouillette scoring*.[85] Previous research has shown that more than 75% of all children with syndromic craniosynostosis snore.[86] It has been proposed to use the single question regarding difficulty in breathing during sleep instead of the traditional Brouillette scoring. Additionally, the OSA 18 questionnaire has been tested in patients with syndromic craniosynostosis. It was found to be a valid tool in assessing OSAS. Sleep disturbance and physical suffering was more frequently reported for children with moderate OSAS compared to those without.[87]
      Quantitative assessment of OSAS can be performed at four levels:
IV: *Noctural Oximetry* and/or *airflow registration*.
III: *Home monitoring* of cardiac and respiratory variables, sometimes accompanied by videotaping (Figure 5).

II: *Polysomnography*, including respiratory recordings with monitoring of sleep/wake states through electroencephalography (EEG), electro-oculography, chin and/or leg electromyography, electrocardiography (ECG) and body position. In level II it is performed outside a sleep laboratory without technical assistance.

I: *Polysomnography*, including technical and medical support and capillary blood sampling to analyze $paCO_2$ levels.

Oximetry studies can be used to compute an oxygenation desaturation index (ODI), which reflects the number of desaturations of 4% or more from baseline saturation. If cardiac and respiratory variables are also registered, the number of apneas and hyponeas (Figure 6) can also be scored, which can be summarized in the obstructive apnea hyponeas index (oAHI). The most complete way to diagnose OSAS is by polysomnography, which includes oximetry, cardiac and respiratory variables but also EEG registration and laboratory examination of $paCO_2$ levels. The extensive information that can be derived from polysomnography creates additional options to analyze for example heart rate variability and quality of sleep, which has not yet been studied in children with craniofacial anomalies.

For OSAS diagnoses, ODI and oAHI are used. There is no consensus on the thresholds for abnormality, but values of 1 or bigger are generally considered to be abnormal.[85, 88] Different gradings are presented in Table 2.[89-90] In this thesis, we used the conventional grading as presented by Guilleminault and co-workers in 1995 based on 12-hour nocturnal polygraphic recording in the sleep laboratory. Ideally, a combination of the presented indices would be used to estimate the severity of OSAS, like recently proposed by Dayyat et al.[91] They are the first to integrate the full spectrum from simple snoring to severe OSAS in their classification.

Children with UARS may have normal sleep study outcomes according to these criteria but it may indeed have an impact on health and neurocognitive development of a child.[92] Subtle changes however may be hard to study in syndromic craniosynostosis since they may be affected by extensive co-morbidity which also influences neurocognitive outcome.

Treatment of OSAS in syndromic craniosynostosis

Airway obstruction in Apert, Crouzon or Pfeiffer syndrome may be so severe that a tracheostomy is required during the early months of life. Subsequently, advancement of the midface may be necessary to improve the airway volume. This procedure is preferably postponed up to after the age of eight years old if airway obstruction or exorbitism allows waiting. Nocturnal oxygen or continuous or bi-level positive airway pressure may be required.[93]

The benefit of midface advancement is variable.[83, 94-95] In our cohort it was unsatisfactory in 5/11 patients in the short term.[83] A surgically successful procedure does not self-evidently have a sufficient respiratory benefit to overcome OSAS. Preoperative endoscopy of the upper airway is an important investigation to determine the level of obstruction in children with craniosynostosis and OSAS. Obstruction is often found to be present at multiple levels. If one affected level is addressed by a certain surgical procedure, another level of obstruction may even become more apparent. Moreover, a high degree of pharyngeal collapse cannot be overcome with midface advancement.

Like in otherwise healthy children, (adeno)tonsillectomy (ATE) might be an appropriate treatment if hypertrophy of the lymphoid tissue is present. A study by Amonoo-Kuofi et al showed that there was a significant improvement in the mean number of saturation dips and in the mean minimum saturation after ATE in 26 children with syndromic craniosynostosis and moderate to severe OSAS.[96] It is unsure whether mild OSAS should be treated too and what the best treatment would be. Nasal corticosteroids can be used to decrease nasal mucosal swelling especially during upper airway infections. The benefit of nasal corticosteroids for craniosynostosis patients has not been studied yet.

|	Mild OSAS	Moderate OSAS	Severe OSAS
Guilleminault 1995			
Apnea and hyponeas / hour	1 − 5	5 − 24	>24
Sheldon 2005 (Book: Principles and practice of pediatric sleep medicine)			
Apnea and hyponeas / hour	1 − 4	5 − 10	>10
Lowest saturation	86 - 91%	76 - 85%	≤75%
Peak end tidal pCO_2	>53	>60	>65
End tidal pCO_2 >50 mmHg; % TST	10 − 24	25 − 49	≥50
Arousals / hour	>11	>11	>11
New Zealand 2006 (Guideline)			
Apneas / hour or	1 − 4	5 - 9	>10
Desaturation associated with respiratory obstruction	87 − 91%	76 − 85%	<75%
Hypoventilation; % TST	10 − 24%	25 − 49%	>50%
Goroza 2009			
Apnea and hyponeas / hour	5 − 15	16 - 30	>30
Lowest saturation	81 - 90%	71 - 90%	<71%
Dayyat 2007 oAHI	2- 5	5- 10	>10
Lowest saturation	88-92	80-88	<80
End tidal pCO_2 >50 mmHg; % TST	10-15	15-20	>20
Arousal/ hour	2-5	5-8	>8

Table 2: *Different gradings of OSAS severity.*[87-89]
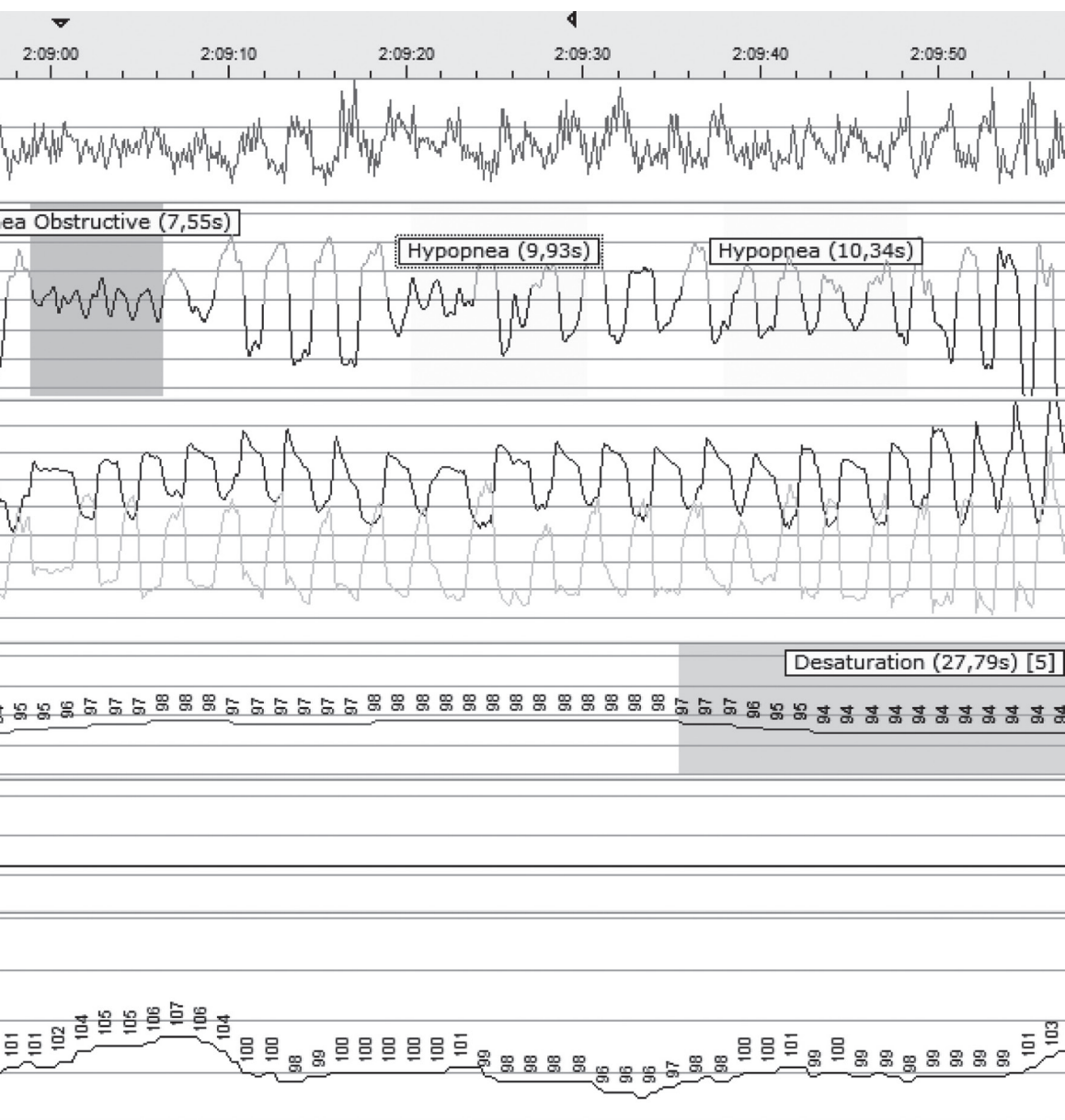
Central sleep apnea

An abnormal control of breathing may present as central sleep apnea. Neuronal input of chemoreceptors and mechanoreceptors innervates the pons and medulla which induce ventilation and coordinate airway activity. Even in healthy individuals, autonomic ventilatory responses decrease during sleep.[57] Secondly, the respiratory drive may be suboptimal during the first year of life. This may persist if a child is born prematurely or in case of developmental delay.[57] Thirdly, brainstem pathology may result in an abnormal respiratory control due to an abnormal loop-gain control. The latter may be the case in the previously described phenomenon of hindbrain herniation, which is highly prevalent in syndromic craniosynostosis.[35,97] Ultimately, severe OSAS may be associated with central sleep apnea secondary to severely abnormal loop-gain function.[98-99] Up to present it is unknown if central sleep apnea occurs in patients with syndromic craniosynostosis.

Diagnostics

Central sleep apnea (CSA) may also be associated with symptoms of disrupted sleep as decribed in the previous section. The diagnoses cannot be made using questionnaires since they concentrate on signs related to obstructive breathing patterns such as snoring and difficulty in breathing. Oximetry cannot differentiate in an obstruc-
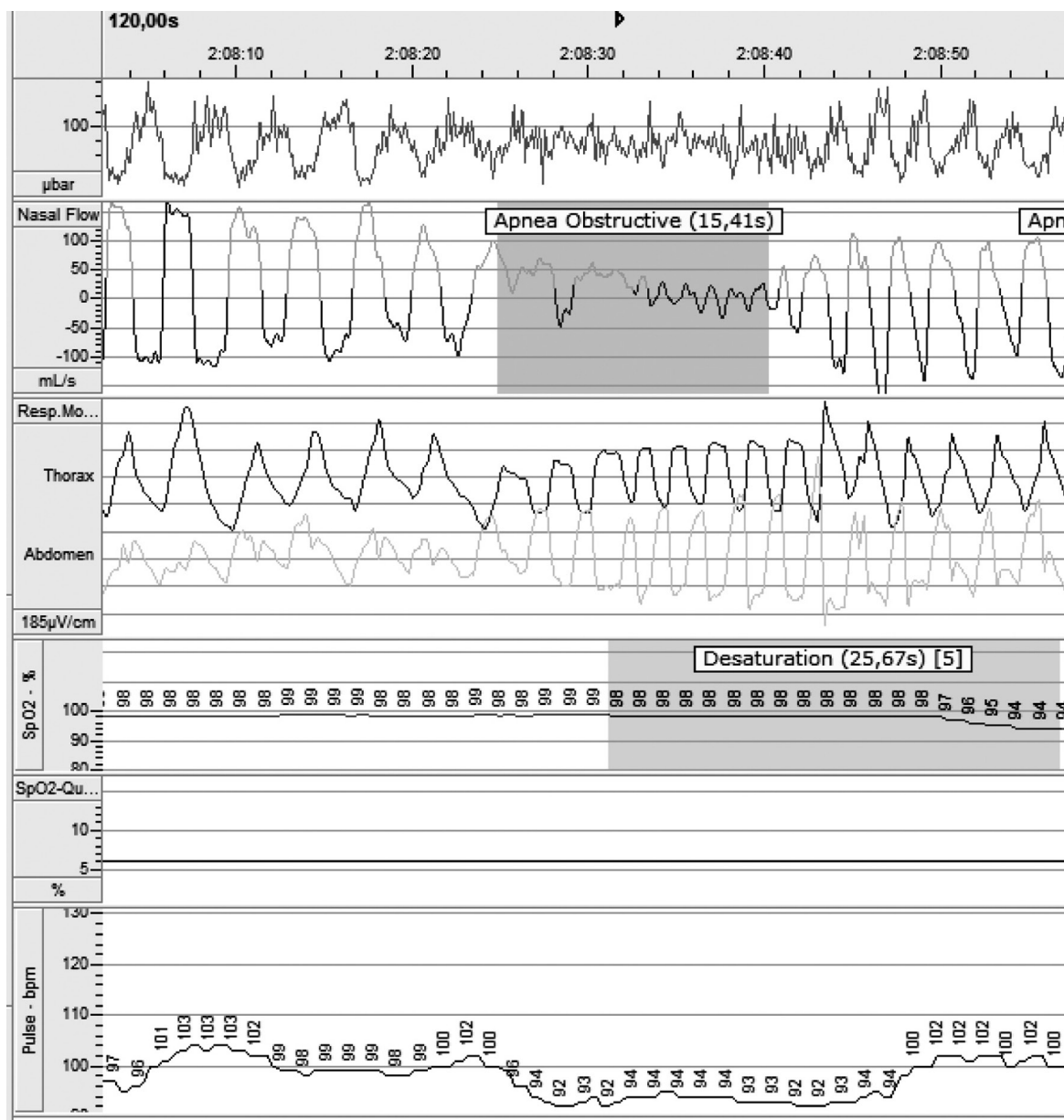
Figure 5: *Level III quantitative assessment of OSAS by means of a home monitoring device.*
Including the following traces starting from the top: 1) snoring, which is derived from 2) a nasal cannula pressure transducer. 3) The respiratory movements are registered by an elastic trace belt. 4) A peripheral saturation profile is generated which is checked for 5) technical artifacts and used as a source for 6) heart rate analysis. An obstructive apnea is defined as a reduction in nasal flow of ≥80% with paradox respiratory movements of the chest and abdomen and hyponeas are defined as a 50% - 80% flow reduction.

tive or central cause of sleep apnea. Respiratory monitoring (Level III), preferably including EEG registration to monitor arousals (Level IV), is required to distinguish between an obstructive and a central cause of sleep apnea (Figure 6).

There is a lack of uniform literature about the length of a central apnea and the number of events per hour needed to diagnose CSA. The American Association of Sleep recommends to only include apneas which last longer than 20 seconds or central events that are followed by a desaturation or arousal.[100] A central apnea index (CAI) bigger than 1 is then considered pathologic.[100]
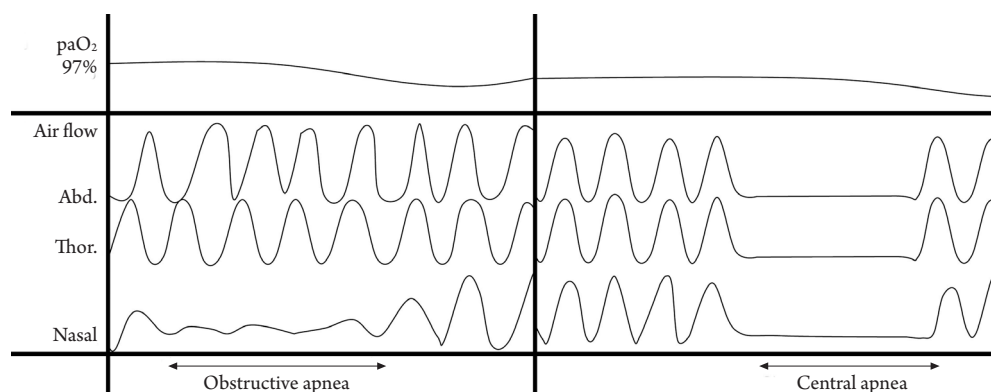
Figure 6: *Obstructive and central apnea.*

Treatment of CSA

If CSA is present, treatment would depend upon the cause of an abnormal respiratory control. Foramen magnum decompressions have been performed abroad to release the hindbrain herniation in syndromic craniosynostosis. We are unsure whether this surgery is required since the symptomatology, including central sleep apnea, has never been evidentially confirmed.

What would we like to know about
★ **Craniosynostosis, ICP and sleep disordered breathing**

Patients with syndromic craniosynostosis are at risk to develop both increased ICP and sleep disordered breathing. These problems may be interrelated, but the causal relationship between increased ICP and airway obstruction is not fully understood.

During REM sleep the activity and perfusion of the brain peaks.[101] Moreover, airway collapsibility is greatest[57] as a result of which number of apneic episodes is highest during this phase of sleep.[102] Apneas may result in hypercapnia and hypoxia which is associated with cerebral vasodilatation. ICP increases are seen synchronously with the apneas.[102] In the morning, baseline ICP is increased but the pressure increases are no longer observed.[102]

The response of the arterial flow and ICP to can be phased as following,[102] in which the pCO_2 and pO_2 play a crucial role. 1) In the beginning of the apnea there is a decrease in flow and ICP. 2) During the apnea, the ICP slightly increases as a result

of hypercapnia and hypoxia. 3) At termination of the apnea there is a steep increase in both flow and ICP. The steep increase is not yet completely understood but may be caused by an increased intrathoracic pressure at termination of the apnea. Also, recovery from pulmonary blood pooling due to a decreased cardiac output as a result of negative intrathoracic pressures during an apnea may influence cerebral flow and thus ICP.[102] Venous flow varies according to respiratory movements. Variation in arterial flow is correlated to the length of the apnea and the correlation between ICP and length of the apnea was found to show a similar linear correlation.[102] Arterial flow and ICP are highly correlated too.[102]

After a rise in ICP, cerebral perfusion decreases to compensate for the high pressures, resulting in retention of CO_2 and hypoxia. This may consequently result in cerebral vasodilatation,[48] which brings us back to step 2) of the sequence of anomalies as described above.

In conclusion, OSAS may have an important implication for cerebral blood flow and pressure dynamics in a population of patients who is already at risk for developing increased ICP.[48,103] It is currently unknown how often OSAS and to what extent sleep disordered breathing contributes to increased ICP.
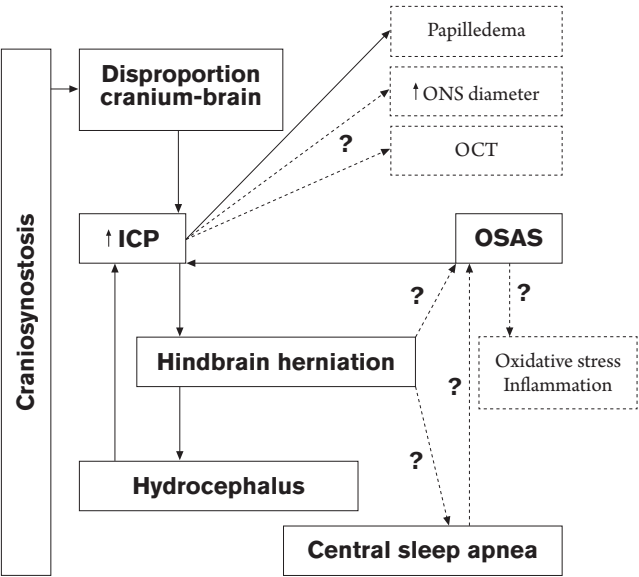

Figure 7: *Outline of the thesis.*

Hypothesis and objectives

This thesis aims at clarifying the dynamic equilibrium between ICP and OSAS in children with syndromic craniosynostosis (Figure 7). Therefore, we performed a prospective, ongoing study which includes extended history taking, physical examination, ophthalmological examination, sleep studies and blood sampling. The majority of these studies were performed parallel to their regular hospital visits from birth to adulthood.

The following objectives will be addressed:

★ **Objective 1: To improve diagnostic means to assess increased ICP in children with syndromic craniosynostosis.**

Papilledema is a late finding 1 and a subjective observation, which highly depends on the experience of the ophthalmologist. Invasive intracranial monitoring is only performed if papilledema intermittently occurs or if other clinical signs suspicious for increased ICP arise. To improve the screening for and follow up of increased intracranial pressure, two new techniques are described, using the eye as a window to the brain. We studied:
1. Ultrasound measurements of the optic nerve sheath diameter during the day as compared to CT and papilledema.
2. Ultrasound measurements of the optic nerve sheath diameter at night as compared to invasive intracranial pressure measurement.
3. Optical coherence tomography to measure retinal thickness of the papilla as compared to papilledema.

★ **Objective 2: To elucidate the natural course and consequences of OSAS in children with syndromic craniosynostosis.**

4. A longitudinal study was performed to study the course of OSAS over time.
5. A laboratory study on the occurrence of oxidative stress and systemic inflammation was performed.

★ **Objective 3: To study the presence and severity of central sleep apnea in children with syndromic craniosynostosis.**

OSAS, hindbrain herniation and developmental delay have been associated with central sleep apnea in other patient populations. This thesis describes
6. A cross-sectional study on the association between hindbrain herniation and sleep disordered breathing.
7. A cross-sectional study on the phenomenon of central sleep apnea in relation to its possible causal factors.

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