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Ophthalmological findings in children operated for non-syndromic craniosynostosis

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Abstract

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Craniosynostosis, characterised by the premature fusion of one or more cranial sutures, can significantly affect orbital morphology, ocular development, and visual pathways in affected children. While syndromic craniosynostosis is known to cause severe ophthalmological complications, the visual risks associated with non-syndromic craniosynostosis, especially across different subtypes and longitudinally, remain largely unexplored. This thesis systematically assesses visual function, refractive errors, strabismus, and fundus changes in children with non-syndromic craniosynostosis, both pre- and postoperatively, with follow-up extending to preschool age.

The study included 122 children with Computed Tomography (CT)-confirmed non-syndromic craniosynostosis who underwent craniofacial surgery at the Uppsala Craniofacial Centre between 2012 and 2019. Follow-up examinations were conducted at 6–12 months, 3 years, and 5 years post-operatively. A control group of 33 healthy 5-year-old children was also included for comparison. Quantitative volumetric and morphometric analyses of orbital CT images were conducted in a subset of patients with unicoronal synostosis to explore associations between orbital morphology and ophthalmological outcomes.

Results revealed subtype-specific risks: children with sagittal synostosis showed a low prevalence of refractive errors and strabismus, while those with unicoronal synostosis exhibited the highest rates of persistent astigmatism, anisometropia, and strabismus, including new cases emerging post-surgery. Metopic synostosis was associated with increased hypermetropia. Variations in orbital shape were found to correlate with strabismus and astigmatism in unicoronal synostosis. Surgical intervention did not fully correct orbital deformities and, sometimes, precipitated new instances of strabismus.

These findings emphasise the importance of tailored ophthalmological follow-up and highlight the need for improved surgical strategies to address subtype-specific risks and optimise visual outcomes in children with non-syndromic craniosynostosis.

Keywords: non-syndromic craniosynostosis, craniosynostosis subtypes, ophthalmological outcomes, orbital morphology, craniofacial surgery, follow-up

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To my dad

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Ntoula E., Nowinski D., Holmstrom G., Larsson E. (2021) Ophthalmological findings in children with non-syndromic craniosynostosis: preoperatively and postoperatively up to 12 months after surgery. *BMJ Open Ophthalmol.* 2021 Apr 26;6(1): e000677. *Published open access.*
- II. Ntoula E., Nowinski D., Holmström G., Larsson E. (2024) Strabismus and refraction in non-syndromic craniosynostosis - A longitudinal study up to 5 years of age. *Acta Ophthalmol.* 2024 Aug;102(5):564-572. *Published open access.*
- III. Ntoula E., Nowinski D., Holmström G., Larsson E. Visual outcome in 5-year-old children operated for non-syndromic craniosynostosis. *Submitted August 2025*
- IV. Lif HM, Ntoula E., Larsson E., Nowinski DJ. (2024) Variations in orbital morphology, globe:orbit volume relation, and ophthalmological outcome in unicoronal synostosis. *J Plast Surg Hand Surg.* 2024 Dec 12;59: 162-170. *Published open access.*

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Abbreviations

| | |
|--------|--|
| CS | Contrast sensitivity |
| CT | Computed tomography |
| D | Dioptres |
| EOM | Extraocular muscles |
| ERF | ETS2 repressor factor |
| f | female |
| FGFR | Fibroblast growth factor receptor |
| FOAR | Fronto-orbital advancement/remodelling |
| HRR | Hardy Rand and Rittler |
| ICP | Intracranial pressure |
| IM | Intramembranous |
| LCVA | Low contrast visual acuity |
| LE | Left eye |
| LogMar | logarithm of minimal angle of resolution |
| m | male |
| n | number |
| OCT | Optical coherence tomography |
| PCA | Principal component analysis |
| PL | Preferential looking |
| RE | Right eye |
| SE | Spherical equivalent |
| TCF | Transcription factor |
| TWIST | Twist-related protein |
| UCS | Unicoronal synostosis |
| VA | Visual acuity |

Introduction

Craniosynostosis is a congenital condition characterised by the premature fusion of one or more cranial sutures, leading to deformity of the skull and numerous morphologic and functional abnormalities. The term was first used by Otto in 1830 to morphologically describe this clinical entity. Since then, several theories have attempted to explain the pathogenesis of the premature suture fusion and the interactive mechanisms between cranial growth and subsequent characteristic cranial maldevelopment (Lenton et al. 2005).

The first to describe patterns of compensatory skull growth in relation to the closure of individual sutures, and to attempt to classify predictable deformities, was Virchow in 1851 (Persing et al. 1989). Subsequent advances in molecular biology and genetics have improved the understanding of the cranial suture morphogenesis, pathology and genetic associations and have enabled the development of today's multidisciplinary care, conducted in expertise centres.

Classification into syndromic and non-syndromic forms, based on specific genetic variants and clinical features, reflects considerable variability in the severity of deformities and functional impairments, including ophthalmological disorders. While ophthalmic problems are well recognised in syndromic craniosynostosis, due to marked orbital deformities, their prevalence and characteristics in non-syndromic forms are less well understood. Surgical correction is essential to restore shape and prevent functional impairment; however, orbital reconstruction procedures also carry a risk of iatrogenic ophthalmic complications.

Follow-up protocols vary between centres, and few studies have systematically compared ophthalmic outcomes across the subtypes of non-syndromic craniosynostosis. Research is further limited by inconsistent assessment methods, short follow-up periods and a focus on selected subtypes.

This thesis presents a comprehensive, prospective evaluation of ophthalmological outcomes in children operated on for various types of non-syndromic craniosynostosis, aiming to identify subtype-specific patterns, follow their development over time, and inform and optimise ophthalmological care for affected children.

Background

Development of the normal cranial vault

The cranium (skull) is divided into the *neurocranium*, which encloses and protects the brain, and the *viscerocranium*, which forms the skeleton of the face. The neurocranium can be further subdivided into the cartilaginous part, which forms the skull base (*chondrocranium*), and the membranous part, which forms the cranial vault (*calvarium*).

The morphogenesis of the cranial vault is a prolonged process, with origin in early embryogenesis and completion during adulthood. It consists mainly of the flat bones: the paired frontal and paired parietal bones, the squamous parts of the temporal bones, and the superior part of the occipital bone. The calvarial bones differ in embryogenic origin, with the frontal bones deriving from the neural crest (ectoderm) and the more posterior cranial vault bones from the paraxial mesoderm. Development begins early in embryogenesis (within the first four weeks of gestation), through epithelial-to-mesenchymal cell transformation, mesenchymal cell migration, and condensation of mesenchymal cells that contain osteoprogenitor cells at the sites where bones are to be formed. By the sixth week of gestation, the membranous neurocranium surrounding the developing brain has formed (Jin et al. 2016).

At the end of the embryonic phase (7 weeks of gestation), bone formation begins through the differentiation of osteoprogenitor cells into osteoblasts and the direct placement of bone tissue into the primitive tissue (mesenchyme), a process called intramembranous (IM) ossification. As ossification progresses, the developing bones gradually approximate one another, and the cranial sutures begin to form as fibrous tissues, separating the adjacent bones. These sutures play a critical role as sites of IM ossification, responding to osteogenic signals from the underlying dura (Opperman et al. 2020).

The main cranial sutures include: the metopic suture, separating the frontal bones; the paired coronal sutures, separating the frontal and parietal bones; the sagittal suture, separating the parietal bones; the paired squamosal sutures, separating the temporal and parietal bones; and the paired lambdoidal sutures, separating the parietal and occipital bones (Figure 1).

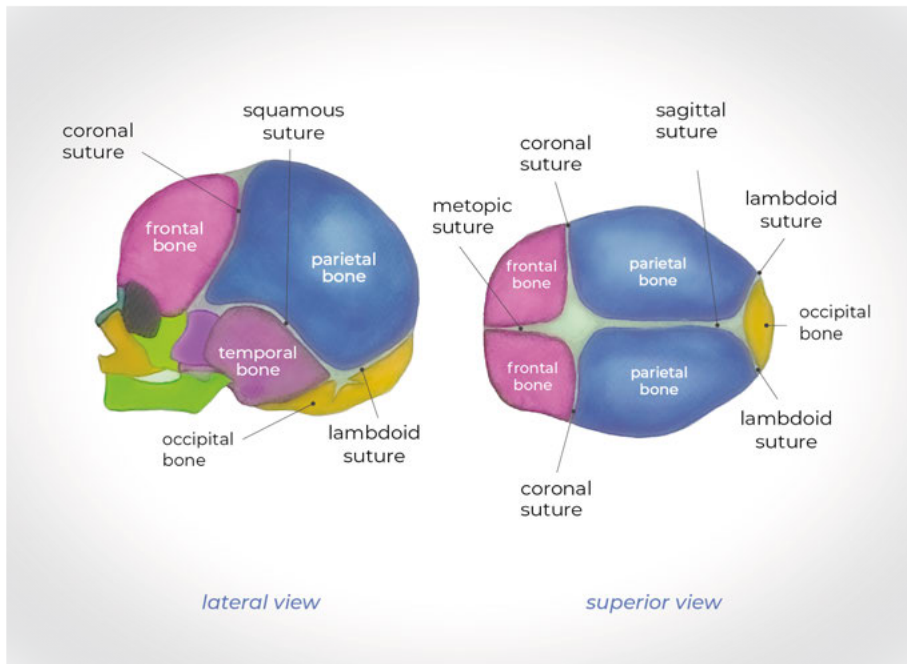


Figure 1. Image of the infant skull bones and respective separating sutures. (Illustration: Christina Dimaki)

The patency of the cranial sutures allows for cranial deformation through the birth canal. Postnatally, the sutures act as areas of growth and adjustment of the skull shape. In order for the sutures to serve their purpose, they must remain unossified. With the exception of the metopic suture, which normally fuses at around 8 months of age, the cranial sutures remain patent during the first years of life and persist as visible structures throughout life. Following the rapid natural brain growth during the first two years of life, the cranial vault bones are driven apart, stimulating osteoprogenitor cells to differentiate into osteoblastic cells in order to cause ossification at the osteogenic fronts and subsequent skull growth. Between 2 and 7 years of age, sutural growth slows down drastically, and cranial vault growth occurs mostly through bone remodelling, with epicranial bone deposition and endocranial bone reabsorption. Once the growth of the cranial vault is completed, most sutures undergo ossification (Jin et al. 2016).

Craniosynostosis

In craniosynostosis, one or more cranial sutures are already ossified at birth. The loss of these natural sites of skull growth prevents further bone formation at the osteogenic fronts along the affected sutures, making it difficult for normal expansive growth of the neurocranium and resulting in abnormal growth patterns (Opperman 2000). According to Virchow's Law, cranial growth in a child with craniosynostosis, is restrained perpendicular to the fused suture(s) and occurs compensatorily in the parallel direction (Lenton et al. 2005).

Classification of craniosynostosis

Craniosynostosis is divided into simple (single-suture) or complex craniosynostosis, where multiple sutures are involved. It is also classified as non-syndromic (isolated) or syndromic, depending on the presence of a known genetic variant and additional clinical characteristics.

Non-syndromic craniosynostosis typically involves a single suture and occurs without an identified genetic mutation or additional deformities (Garza et al. 2012). Conversely, syndromic craniosynostosis usually involves multiple sutures and is often accompanied by malformations of the cranial base and midface skeleton, which can result in severe orbital dysmorphology and functional impairment of the upper aerodigestive tract. In addition, complex visceral and skeletal anomalies are common (O'Hara et al 2019).

An anatomical classification based on the suture involved, the corresponding skull deformity and associated clinical characteristics is presented in Table 1 and Figure 2.

Table 1. Classification of craniosynostosis depending on the affected suture, corresponding deformities, and clinical characteristics.

| Affected suture | Deformity | Typical characteristics |
|------------------------|------------------------------|--|
| Sagittal | Scaphocephaly/Dolichocephaly | <ul style="list-style-type: none"> - Head elongated anterior-posteriorly and shortened in the bi-parietal direction - Frontal bossing - More common in boys |
| Metopic | Trigonocephaly | <ul style="list-style-type: none"> - Head triangular shaped - Forehead narrow and pointed, occipital region broad - Hypotelorism |
| Unicoronal | Anterior plagiocephaly | <ul style="list-style-type: none"> - Forehead flattened on the synostotic side - Forehead pushed forward on the contralateral side - High supraorbital margin on the synostotic side (Harlequin sign) - Nasal root deviation towards the synostotic side - Skull base asymmetry - More common in girls and on the right side |
| Bicoronal | Brachycephaly | <ul style="list-style-type: none"> - Short skull anterior-posteriorly - Forehead and occipital region flattened - Frontal bone prominent superiorly and elongated vertically - Hypertelorism - Bilateral Harlequin malformation of the orbits |
| Lambdoid | Posterior plagiocephaly | <ul style="list-style-type: none"> - Frontal and occipital bossing - Head shape may resemble a trapezoid when seen from above - Ipsilateral ear and mastoid displaced downward |

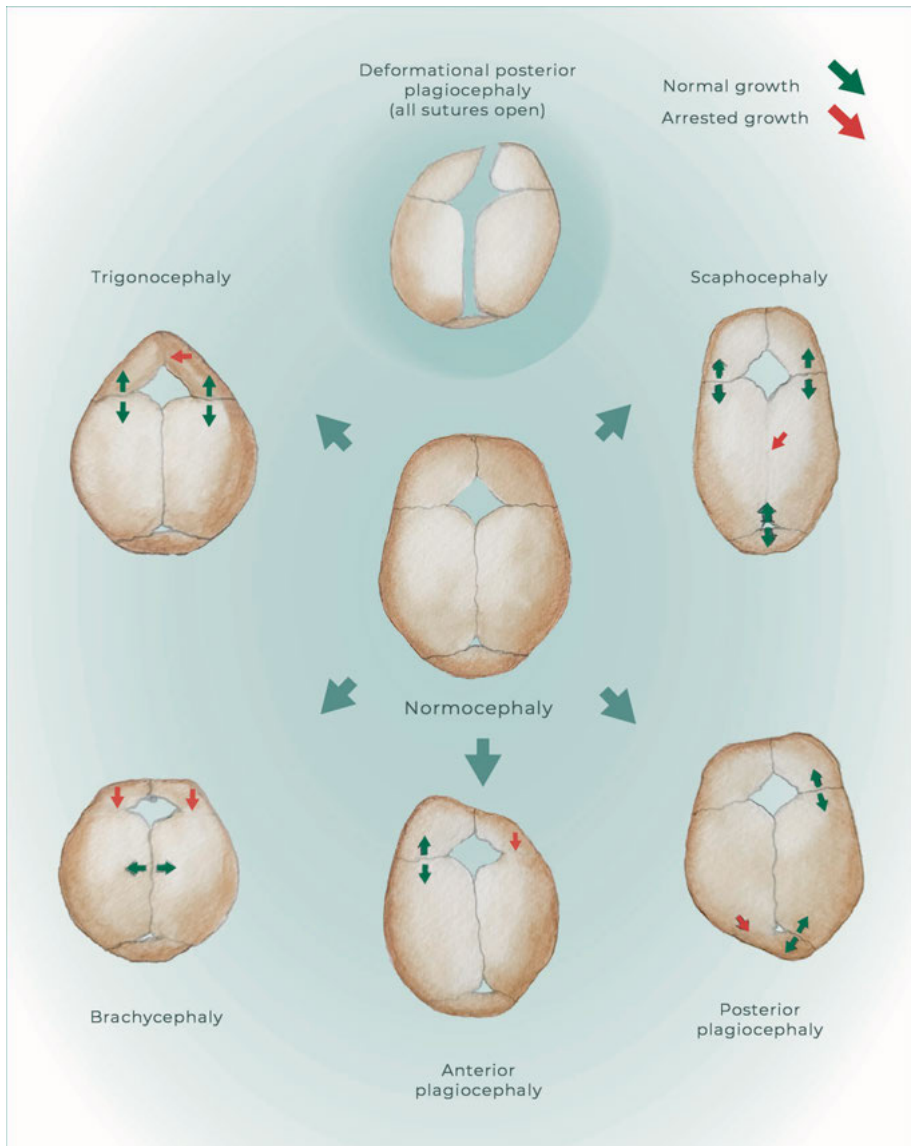


Figure 2. Types of cranial deformities. (Illustration: Christina Dimaki)

An important differential diagnosis for craniosynostosis is deformational posterior plagiocephaly, which usually occurs because of the infant lying in the same position consistently or secondarily to conditions such as torticollis or spinal malformations.

Epidemiology of craniosynostosis

Craniosynostosis occurs in approximately 1 per 2,000–2,500 births worldwide (Governale et al. 2015) with a prevalence of 7.7 per 10,000 births in Sweden (Tarnow et al. 2022).

In about 15% of the cases, the condition is associated with a craniofacial or rare genetic syndrome (Nagaraja et al. 2013). Over 100 syndromes associated with craniosynostosis have been identified, with the most common being Muenke, Crouzon, Apert, Pfeiffer, and Saethre-Chotzen syndromes (Khan et al. 2003).

Among single-suture craniosynostosis, sagittal synostosis is the most common, occurring in approximately 1 in 5,000 births, followed in frequency by metopic, unilateral coronal, and unilateral lambdoid craniosynostosis.

Pathogenesis of craniosynostosis

The pathogenesis of craniosynostosis is yet to be fully understood. Cranial suture ossification and the maintenance of suture patency appear to depend on the abnormal interaction between transcription factors, cytokines, growth factor receptors and the extracellular matrix. In the majority of syndromic craniosynostosis, a *de novo* gene mutation has been identified, which follows mainly an autosomal dominant inheritance pattern. Mutations in genes encoding fibroblast growth factor receptors, *FGFR 1-3*, have been associated with Crouzon (*FGFR 2*), Apert (*FGFR 2*), Pfeiffer (*FGFR 1* or *FGFR 2*), and Muenke (*FGFR 3*) syndromes, while Saethre-Chotzen syndrome results from a mutation in the *TWIST 1* gene, which encodes transcription factors involved in FGFR signalling (Governale et al. 2015). Other genes, more recently implicated in the pathogenesis of craniosynostosis, include *TCF12* and *ERF*, which also play a role in the regulation of osteoblastic differentiation and growth factor receptors pathway, respectively (Wilkie et al. 2017). These gene mutations lead to various alterations in the proliferation and differentiation of osteoblasts at the calvarial sutures, resulting in alterations in bone formation (Slater et al. 2008).

Unlike syndromic craniosynostosis, non-syndromic craniosynostosis occurs sporadically in over 95% of cases and typically lacks an identifiable genetic cause, therefore resulting in a low hereditary risk. Although specific associated genes have been identified in some patients with unilateral coronal synostosis, the majority of cases are classified as non-syndromic.

Reconstructive surgery for craniosynostosis

The fundamental goal of treatment for craniosynostosis is to normalise craniofacial form and allow for normal brain development and facial functions. Treatment protocols vary significantly between the different centres; however, there is a general consensus that reconstructive surgery performed prior to 1 year of age is preferable, in order to optimise correction of the deformity.

In Sweden, surgical care for all forms of craniosynostosis is centralised in two licensed national reference centres, one of which is the Uppsala Craniofacial Centre, at Uppsala University Hospital, established in 2012.

Sagittal craniosynostosis is preferably treated early, between 3 and 6 months of age, with relatively less invasive procedures. At our centre, the H-craniectomy technique was used until the end of 2019, after which spring-assisted cranioplasty became the standard approach. In children older than 6 months of age, more extensive remodelling of the cranial vault, typically involving forehead remodelling, is required. Metopic and unilateral coronal craniosynostosis are typically operated later, between 6 and 18 months of age, using fronto-orbital remodelling/advancement techniques. Lambdoid craniosynostosis is preferably treated before or around 6 months of age, with spring- or distractor-assisted distraction osteogenesis, or posterior vault remodelling in children older than 1 year of age.

Advocates of early surgical treatment argue that techniques performed at a younger age entail less surgical trauma, as the cranial bones are more malleable and reconstruction is attainable with less invasive methods based on dynamic reshaping. In contrast, the main rationale for later primary surgery is that the risk of recurrence is reduced and that the morphological correction is more stable when surgery is performed closer to the conclusion of neurocranial growth.

Multidisciplinary care of craniosynostosis

All patients referred to the Uppsala Craniofacial Centre receive multidisciplinary care pre-operatively with protocolised follow-up, at least until the completion of neurocranial growth at 8 years of age for non-syndromic cases and up to 18 years for syndromic craniosynostosis cases. The main objectives are to prevent harmful effects on brain development, normalise appearance, and furthermore, restore functionality.

The initial investigation and follow-up protocol for patients with non-syndromic craniosynostosis are presented in Table 2.

Table 2. Initial investigation and follow-up for patients with non-syndromic craniosynostosis treated at Uppsala University Hospital.

| | Pre-op | 1 year post-op | 3 years of age | 5 years of age | 8 years of age |
|--|---------------------------------------|--|--|----------------------|----------------------|
| CT scan | √ | | √ | | |
| Genetic analysis | √ (Unicoronal craniosynostosis) | | | | |
| Plastic surgeon Examination | √ | √ | √ | √ | √ |
| Neurosurgeon Examination | √ | In cases where raised ICP is suspected | | | |
| Neuropeadiatric Evaluation | √ | | | | |
| Ophthalmological Evaluation | √ | Every half year until 2 years of age | Every year until 4 years of age | √ (+OCT) | √ (+OCT) |
| Psychological Evaluation | | √ | √ | √ | √ |

CT scan: Computed Tomography scan, ICP: Intracranial pressure, OCT: Optical Coherence Tomography.

Visual development and amblyopia

Visual development is a complex, continuous process that begins from birth and extends throughout the first decade of life, with the most critical development occurring in the first 5–7 years of age.

The visual pathway starts with images of the visual world, transmitted through the anterior parts of the eye (cornea, anterior chamber, pupil, lens, vitreous), focusing to the retina of each eye, where they are encoded into neural signals by photoreceptor cells (rods and cones). These signals are then transported by the retinal ganglia cells network to the optic nerve fibres, which are routed so that signals from each eye are transmitted to interconnected areas at the visual cortex in the occipital lobe of the brain; see Figure 3. The stimuli from both eyes are then integrated by the visual cortex and transformed into a unique visual perception (binocular vision).

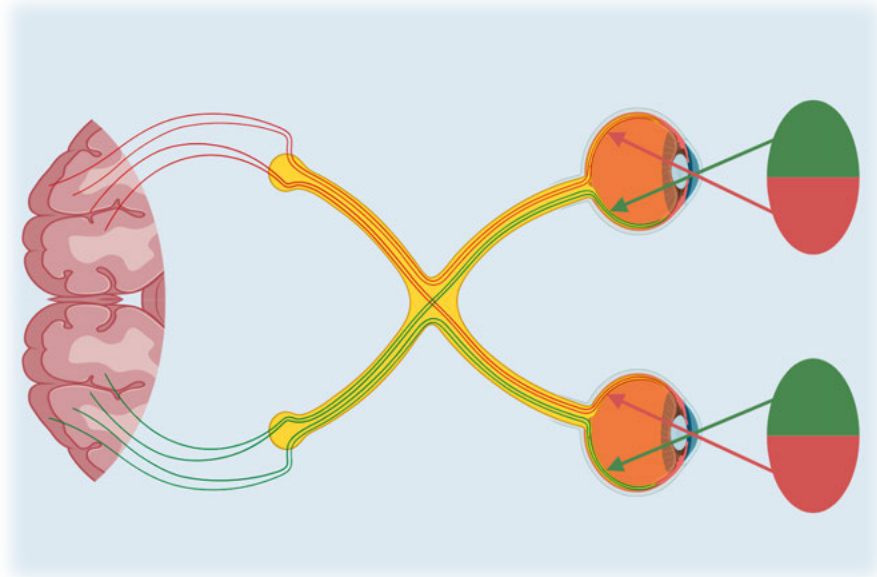


Figure 3. The visual pathway. (Illustration created with BioRender.com)

The capacity of the human visual system and central nervous system is not fully developed at birth. On the contrary, they undergo a maturation process, which is directly analogous to the child's cognitive and neuropsychomotor development. Through visual stimuli and interaction with the environment, myelination of the optic nerve fibres progresses and the synaptic density in the visual cortex increases, reflecting the improvement in visual perception, fixation, and functional coordination (Atkinson et al. 2020). Furthermore,

complex brain processing develops for the interpretation of perceived images through communication pathways between the visual cortex in the occipital lobe and the centres in the parietal and temporal lobes.

The first basic measure of visual development is Visual acuity (VA), which represents the fine detail (central) vision. The second is Contrast sensitivity (CS), which is the ability to identify differences in shading and pattern and to distinguish objects from the background contrast. For measurements of acuity and Contrast sensitivity in preverbal children, behavioural matching or searching tasks have been implemented (Teller acuity cards). In preschool children, standardised tests with symbols (LEA symbols test) are used (Hyvärinen et al. 1980; Atkinson et al. 2008). Colour vision, stereopsis (depth perception), and motion perception complement the assessment of Visual function (Bennet CR et al. 2019).

A decrease in best-corrected VA caused by visual stimuli deprivation or abnormal binocular interaction, for which no underlying organic causes can be detected in the eye, is called amblyopia. It is usually monocular, or less often binocular, with a prevalence of 2%–4% in developed countries (Atkinson et al. 2020). Most cases are associated with eye misalignment (strabismus), others with anisometropia (difference in the refraction between the eyes) or a combination of both, in infancy or early childhood. Amblyopia may also result from conditions that disrupt the visual axis and obstruct a clear image from reaching the retina, such as cataracts and eyelid ptosis. Visual loss in amblyopia can vary from mild to severe, but with early detection, it may be reversible, which confirms once again the plasticity of the developing visual system. Low contrast visual acuity (LCVA), is a sensitive measure for detecting subtle visual dysfunction particularly in amblyopia and neuro-ophthalmological disorders, where LCVA deficits often precede measurable VA loss (Jayaraman et al. 2024).

In strabismic amblyopia, where the loss of binocularity coexists, the “crowding phenomenon” also occurs. The condition is characterised by a reduced ability to discriminate letters or symbols presented closely together compared with when they are presented individually. A crowding ratio can be calculated by dividing the single optotype acuity by the linear acuity (Rydberg et al. 1999). Crowding is also a known developmental phenomenon in healthy young children (Jeon et al. 2010). A crowding ratio of approximately 1.2 has been reported in children aged 5 to 7 years (Dekker et al. 2012; Atkinson et al. 1998).

Refractive development in the paediatric population

The distribution of refraction varies with age. Most neonates are moderately hypermetropic, typically ranging from +2 to +4 diopters (D), while considerable levels of astigmatism can be noted as well. However, both hypermetropia and astigmatism tend to decrease significantly during the first two years of life, a process known as emmetropisation.

Emmetropisation occurs during the normal childhood growth, in which the refractive state of the eye changes from ametropia to emmetropia. The primary component of this process is the rapid increase in axial length during the first two years of life, driven by both physical and genetic factors associated with normal eye growth. The axial length increases by approximately 2–3 mm, mainly due to expansion of the vitreous chamber, leading to proportional interactive changes in the dioptric components. Moreover, an active developmental mechanism regulated by the retinal image is suggested to contribute to the control of refraction. Depending on the degree of retinal blur, the eye elongates or shortens proportionally until the retina and the image are fused. The amount of spherical ametropia tends to decrease by around one-third, and the amount of astigmatism by approximately two-thirds during the first two years of life (Yackle et al. 1999).

Ophthalmological manifestations in craniosynostosis

Premature fusion of the cranial sutures restricts skull growth and results in compensatory deformity, which also affects the osseous structures of the orbits, leading to orbital malformations (Rostamzad et al. 2022). Orbital anatomy appears to be most severely disrupted in the syndromic forms of craniosynostosis, due to multiple suture involvement and coexisting malformations of the cranial base and midface skeleton. In the different forms of single-suture craniosynostosis, orbital dysmorphology is generally less pronounced and varies depending on the type of the fused suture. Among these, unilateral coronal craniosynostosis (UCS) has a much more complicated effect on orbital anatomy compared to the other forms of non-syndromic craniosynostosis (Figure 4). UCS presents with great variability in morphological severity which, in some cases, is similar to that seen in less severe syndromic forms, such as Muenke syndrome. In addition, UCS is the most common type of synostosis associated with craniosynostosis syndromes.

Orbital asymmetry



Harlequin deformity

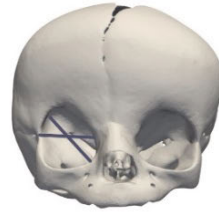


Figure 4. Orbital pathology in unicoronal craniosynostosis. A typical feature of unicoronal synostosis is the variability in asymmetry between the synostotic and contralateral sides. The orbit on the synostotic side is elevated superotemporally, known as the Harlequin deformity. (Illustration courtesy of Dr Hanna Lif)

Common ocular anomalies include eyelid ptosis and lacrimal dysfunction, and in some syndromic forms, such as Apert and Crouzon syndromes, proptosis, caused by the shallowing of the orbits. This predisposes to subsequent exposure keratitis, which, if left untreated, can lead to corneal scarring and subnormal vision, and in more severe cases, corneal perforation and endophthalmitis (Touze et al. 2019).

Motility disorders and strabismus are also very common among patients with craniosynostosis, with rates varying depending on craniosynostosis type. They are most frequent in UCS and syndromic types, where strabismus is reported in approximately 40% – 70% of cases (Touze et al. 2019). The typical presentation is vertical-torsional strabismus with a variable horizontal component. This is attributed to extraocular muscle (EOM) imbalance caused by increased interorbital distance (hypertelorism), and induction of divergent orbital axis, as well as orbital dystopia and trochlea displacement. In addition, hypoplasia or absence of EOM may be observed in craniosynostosis syndromes (Touze et al. 2019).

Further, refractive errors are well described in the literature, occurring most frequently in cases with most disturbed orbital anatomy, such as UCS and craniosynostosis syndromes (MacIntosh et al. 2007; Levy et al. 2007; Luo et al. 2020; Touze et al. 2022; Hinds et al. 2022; Khan et al. 2003). Commonly reported are astigmatism and anisometropia, secondary to the shape of the orbits and its effect on corneal curvature, as well as ptosis and corneal scarring.

Amblyopia due to ametropia, anisometropia, and strabismus is the main cause of visual impairment in patients with craniosynostosis, occurring in at least one eye in almost 65% of syndromic craniosynostosis patients (Khan et al. 2003). Khan et al. (2003) reported a best corrected visual outcome of equal or lower than 6/12 in the best eye, in 40% of cases. Similar results have also been reported by Tay et al. (2006).

Among patients with single-suture craniosynostosis, higher rates of amblyopia are documented in UCS (Tarczy-Hornoch et al. 2008; Luo et al. 2020; Touze et al. 2022). Nonetheless, other authors have also reported amblyopia rates higher than those in the general population across other types of single-suture craniosynostosis (Vasco et al. 2008; Chieffo et al. 2020; Nguyen et al. 2014; Roider et al. 2021). The role of the paediatric ophthalmologist within the craniofacial team is, therefore, crucial for the early detection and treatment of the amblyogenic factors, in order to prevent the development of amblyopia.

In addition, optic neuropathy is a common cause of visual compromise, especially in patients with syndromic craniosynostosis. The optic nerve is susceptible to damage through several mechanisms, the most important being chronically elevated intracranial pressure (ICP), causing papilloedema and resultant optic nerve atrophy. The risk of elevated ICP varies depending on the type of craniosynostosis but is reported in approximately 30% of syndromic cases, especially in Crouzon/Pfeifer syndromes (Touze et al. 2019). Disrupted venous flow (venous hypertension) and severe obstructive apnoea related hypoxia, due to facial and respiratory disorders, may aggravate the elevation of ICP and optic neuropathy in syndromic craniosynostosis. Furthermore, compression of the optic nerves within the optic canal or orbit may contribute to optic atrophy as well (Touze et al. 2019).

In non-syndromic cases, elevated ICP has been reported sparsely and appears to be analogous to the number of sutures involved (Tamburrini et al. 2005). Furthermore, late-onset rise in ICP after surgery for sagittal craniosynostosis remains a controversial topic in the literature, with factors such as the type of the primary procedure, age at first operation and the presence of secondary coronal craniosynostosis contributing to the outcomes. (Thomas et al. 2015; Moore et al. 2021; Unander-Scharin et al. 2021).

Fundoscopy is a rapid, non-invasive and highly specific method for detecting papilloedema and optic nerve atrophy. However, its sensitivity in the younger age groups is low, at around 22% (Tuite et al. 1996). Lately, optical coherence tomography (OCT) has emerged as a useful tool for the quantification and documentation of optic disk changes, providing a more sensitive assessment of oedema or atrophy as signs of current or previously raised ICP. Nonetheless, the use of OCT is generally feasible only in cooperative children, typically those older than 4–5 years of age.

Image analysis in craniosynostosis

It is well established in the literature that bilateral orbital deformities and subsequent orbital asymmetry, both pre-operatively and after surgical correction, are the main determinants of the aesthetic and functional implications in UCS (Beckett et al. 2013; Yu et al. 2020; Lif et al. 2023; Lif et al. 2024). There is large variability in both the severity of the deformity and the associated functional deficits, including ophthalmological disorders. Therefore, an objective and reproducible method for evaluating the orbital shape changes in UCS would enhance the knowledge of the genesis of these disorders and help optimise the surgical treatment.

Previous research assessing morphological severity in UCS has mainly relied on craniofacial and orbital symmetry calculations based on CT images, or on geometric morphometrics that involve manual placement of numerous landmarks followed by statistical analyses (Alford et al. 2018; Liu et al. 2023; Rutland et al. 2021). While these methods have provided valuable insights, they are limited by issues of reproducibility, user dependency, and the lack of a three-dimensional perspective. More recently, principal component analysis (PCA), a statistical technique that reduces complex datasets into a smaller number of new variables, called principal components, has been utilised in geometric morphometric studies to quantify morphological variation (Touze et al. 2020; Bellaire et al. 2021; Rutland et al. 2021; Lif et al. 2023). PCA works by identifying the main patterns of variation in orbital shape, allowing researchers to summarise and visualise the most important differences within the data. The first principal component captures the most variance, the second captures the next most variance (while remaining uncorrelated with the first), and so forth. Each principal component represents a distinct morphological spectrum between positive and negative aspects, visualised as representative shapes, PC1-, PC1+, PC2-, PC2+, PC3-, PC3+ (Figure 5). This enables a more objective assessment of the correlation between morphological variation and clinical outcomes.

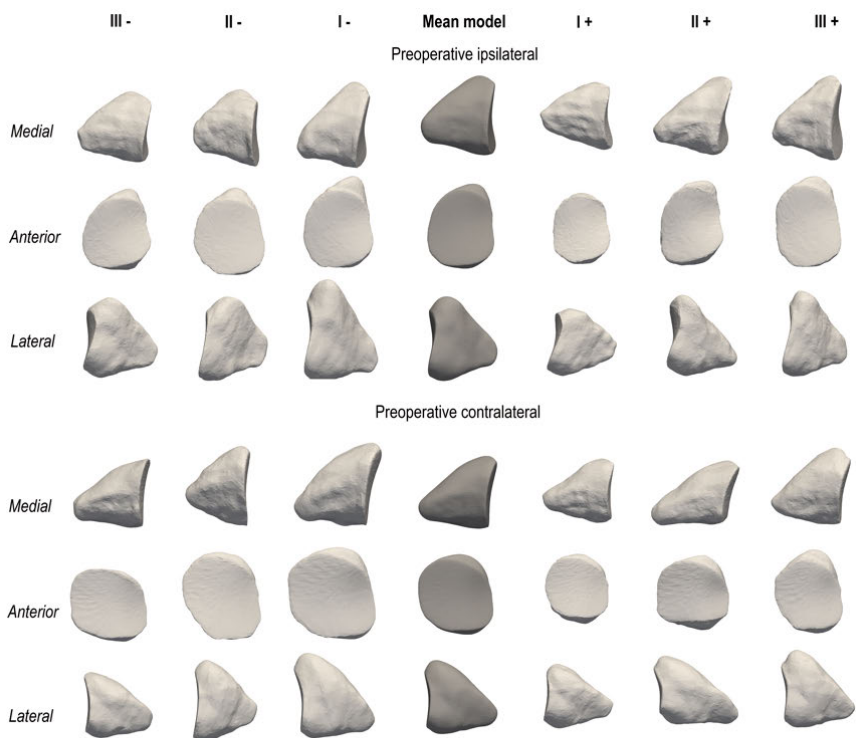


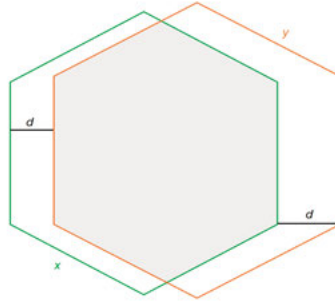
Figure 5. Principal component analysis. Visualisation of variations in orbital shape across both orbits. The mean model is shown in the middle (dark grey), with negative modes shown to the left and positive modes to the right. I+ = positive first principal mode, I- = negative first principal mode, II+ = positive second principal mode, II- = negative second principal mode, III+ = positive third principal mode, III- = negative third principal mode. (Lif-Ntoula et al. 2024)

Furthermore, statistical shape modelling approaches, such as the Dice similarity coefficient (Dice) for assessing symmetry at a voxel level (Figure 6), or objective shape parameters such as the mean absolute distance (global difference) and maximum distance (Hausdorff distance, local difference) measured between 3D surfaces (Figure 5), have been used in studies of syndromic craniosynostosis (Levasseur et al. 2018; Khonsari et al. 2019). However, their use in UCS research remains largely unexplored.

Recently, Lif et al. (2023), employed automated 3D bony evaluation of orbital shape in UCS and concluded that, despite surgical intervention, both global and local deviations in shape persist when compared with controls, and significant interindividual variation remains. Moving forward, studies that link detailed 3D morphological analyses with ophthalmological function and

long-term surgical outcomes will be crucial for improving patient care and refining surgical techniques.

A.



B.



Figure 6. Illustrations of quantitative comparison metrics. **A.** The green (X) and orange (Y) shapes represent slices of two superimposed anatomical structures. The grey area where the shapes overlap visualises the Dice similarity coefficient, which quantifies the degree of overlap between the two shapes, ranging from 0 (no overlap) to 100% (perfect overlap). The black lines (d) connect corresponding points between the shapes: the longest line represent the Hausdorff distance, a measure of the greatest local difference between the surfaces, while the average length of all lines (the other black line) represents the mean absolute difference, summarising the overall (global) difference between the shapes. Together, these metrics provide a comprehensive assessment of both local and global differences, with Dice focusing on voxel-wise overlap, and Hausdorff and mean absolute differences describing surface-based disparities. **B.** Example of the difference between two orbital shapes when calculating symmetry. The Dice similarity coefficient is illustrated as the beige area between the grey and blue shapes in the middle. Visualisation of the aligned and superimposed orbits to the left and right, illustrating the setup prior to 3D Dice calculation. (Illustrations courtesy of Dr. Hanna Lif)

Aims

The overall aim of the present PhD project, '*Ophthalmological findings in children operated for non-syndromic craniosynostosis*', is to contribute with valuable insights into the challenges that arise from an ophthalmological perspective, and to support the development of improved clinical care and ophthalmological follow-up for these children.

Specific aims

- To analyse ophthalmological findings, such as visual function, refractive errors, strabismus and fundus changes, in children with non-syndromic craniosynostosis, both preoperatively and post-operatively, and to document any effects of reconstructive surgery.
- To perform longitudinal follow-up at preschool age and evaluate changes in ophthalmological outcomes over time.
- To compare ophthalmological outcomes across different subtypes of non-syndromic craniosynostosis and identify subtype-specific risks and manifestations.
- To investigate the association between variations in orbital shape and volume and ophthalmological manifestations, with a focus on unilateral coronal craniosynostosis, the subtype most strongly associated with ophthalmological deficits.

Material and Methods

Material

The participants in the study were children with CT-confirmed types of non-syndromic craniosynostosis, referred to the Uppsala Craniofacial Centre, Uppsala University Hospital, Sweden, who underwent craniofacial surgery between September 2012 and April 2019. Pre-operative genetic screening was routinely performed in all cases of unicoronal craniosynostosis, multi-suture craniosynostosis; or when syndromic features or other malformations were suspected. Children with identified pathogenic mutations associated with craniosynostosis syndromes, such as Crouzon, Apert, Pfeiffer, and Saethre-Chotzen syndromes; complex craniosynostosis; or other rare genetic syndromes, were excluded. However, one child with Muenke syndrome was included in the study due to presentation with isolated unicoronal craniosynostosis and absence of additional craniofacial malformations.

A total of 122 children (93 boys) were included in the study. Demographic details are presented in Table 3. All children underwent surgery at the Uppsala Craniofacial Centre at a mean/median age of 7.7/6.0 months (range 3.2–42.6 months). Of the 84 children with sagittal synostosis, 71 (85%) were operated on before 6 months of age, with the so-called H-craniectomy, or Renier technique (extended strip craniectomy with parietal outfracture). The remaining 13 children (15%) underwent cranial vault remodelling at a later timepoint, because of delayed primary diagnosis and referral. Metopic craniosynostosis was addressed with fronto-orbital remodelling, and unicoronal craniosynostosis with bilateral asymmetric fronto-orbital advancement (FOAR).

Table 3. Number and proportion (%) of children included in the study, categorised by type of craniosynostosis, together with sex distribution, age at pre-operative examination, age at time of surgery and post-operative examination.

| <i>Pre-operative examination</i> | | | | <i>Post-operative examination</i> | | | |
|----------------------------------|------------------|---------|-------------------|-----------------------------------|------------------|---------|---------------------|
| | Patients (n=122) | Sex m:f | Age (months) | Age at surgery (months) | Patients (n=113) | Sex m:f | Age (months) |
| Sagittal | 84 (69%) | 70:14 | 4.3 (0.6–36.8) | 4.6 (3.2–36.9) | 78 (69%) | 62:16 | 13.7 (5.7–47.5) |
| Metopic | 22 (18%) | 17:5 | 4.5 (1.2–11.2) | 8.0 (6.1–11.2) | 20 (18%) | 16:4 | 15.8 (10.6–20.7) |
| Unicoronal | 16 (13%) | 6:10 | 8.0 (1.9–40.5) | 10.3 (7.8–42.6) | 15 (13%) | 6:9 | 21.0 (13.5–44.1) |

f = female, m= male

Median values and ranges are given for ages.

All children underwent pre-operative ophthalmological examinations conducted by experienced orthoptists and paediatric ophthalmologists within the craniofacial team. The mean/median ages at examination were 6.2/4.7 months (range 0.6–40.5 months). The age distribution of patients in the pre-operative craniosynostosis group is presented in Figure 7.

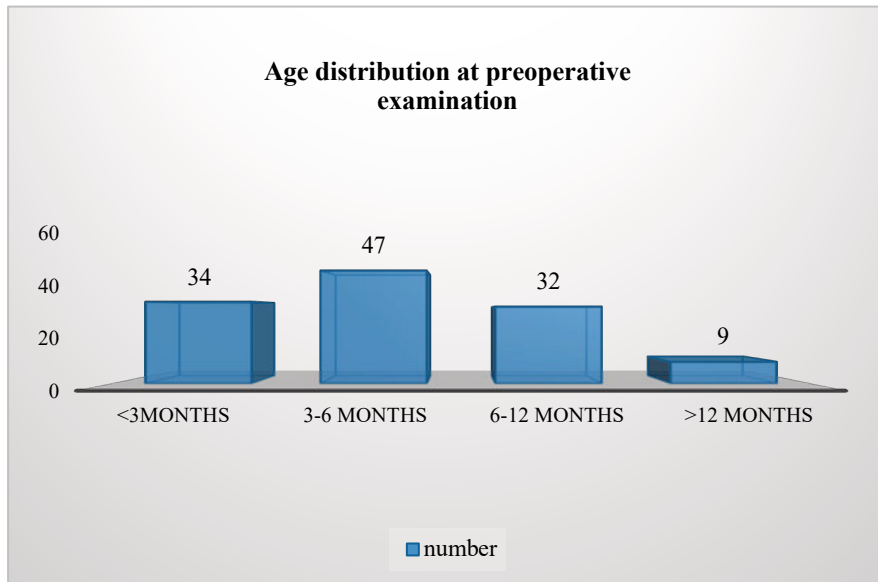


Figure 7. The age distribution of patients in the pre-operative craniosynostosis group.

Standardised ophthalmological follow-up assessments were scheduled at 6–12 months post-operatively and at 3 years of age. These were conducted at the referring hospitals by experienced orthoptists and paediatric ophthalmologists, in accordance with clinical praxis, and medical records were retrieved. Post-operative data (6–12 months after surgery) were available for 113 children (84 boys) from the initial cohort. The mean/median age at this first follow-up was 15.9/14.5 months (range 5.7–47.5 months). The demographics for this group are also presented in Table 3.

Comprehensive ophthalmological examinations were performed at 5 years of age at Uppsala University Hospital, as part of a protocolised multidisciplinary craniofacial assessment. These evaluations were conducted by the same orthoptists and paediatric ophthalmologists of the craniofacial team, between April 2017 and June 2022. A total of 89 children (63 boys) were included in the 5-year follow-up: 79 were examined at the Department of Ophthalmology, Uppsala University, while medical records from another 10 children who were unable to attend the follow-up appointment, were obtained from the local

hospitals. In total, 72 children had a complete longitudinal follow-up, consisting of a pre-operative examination, a post-operative examination 6–12 months after the surgery, and an assessment at 5 years of age. Thirteen were examined pre-operatively and at 5 years of age, and four children were examined post-operatively and at 5 years.

An age-matched control group of 32 healthy children was recruited through nursery schools or referrals to the Department of Ophthalmology of Uppsala University Hospital for other reasons. These children underwent ophthalmological examinations according to the same protocol, by the same team, between April 2018 and October 2022 (Paper II). The demographic characteristics of the total study group at the 5-year follow-up are presented in Table 4. The mean/median age at examination was 5.12/5.05 years (range 4.54–6.09 years) in the craniosynostosis group and 5.32/5.25 years (range 4.84–5.95 years) in the control group.

In 2023, another child was included in the control group; therefore, in Paper III, the control group consisted of 33 children: 16 girls and 17 boys.

Table 4. Number and proportion (%) of children included in the study group at the 5-year follow-up, categorised by type of craniosynostosis, together with controls, and age at surgery in the study group.

| | Number (%) | Sex f:m | Age at surgery (months) |
|----------------------|----------------------------------|-----------------|-------------------------|
| Sagittal | 58 (65.2%) | 12:46 | 4.9 (3.2–32.1) |
| Metopic | 15 (16.9%) | 4:11 | 8.2 (6.6–11.2) |
| Unicoronal | 14 (15.7%) | 9:5 | 10.5 (7.8–42.6) |
| Lambdoid | 2 (2.2%) | 1:1 | 26.0 (22.8–29.2) |
| Study group | 89 | 26:63 | 7.4 (3.2–42.6) |
| Control group | 32 (Paper II)/ 33 (Paper III) | 15:17/ 16:17 | – |

f=female, m= male

Median values and ranges are given for ages

At 3 years of age, a follow-up CT was also performed according to the multidisciplinary protocol. A focused subgroup analysis was conducted on 23 children with non-syndromic unicoronal synostosis, as this subtype is associated with most pronounced morphological and functional impairments. All patients in this subgroup had previously undergone FOAR. Data on the side of craniosynostosis, results of genetic panels, ophthalmological assessments, and age at surgery and examinations were collected from medical records. If complete ophthalmological examinations were performed at both 3 and 5 years of age, the latest was included in the study. For inclusion in the analysis, complete data and adequate pre- and postoperative CT imaging of both orbits were required. Lack of standardisation of CT examinations, performed at referring hospitals, was the main reason for exclusion. Eleven patients were excluded from the study: nine due to suboptimal pre- or postoperative CT imaging, one due to an identified mutation, and one who had not yet reached three years at the time of the analysis. For the included 12 patients (4 boys), data were categorised into four groups: pre-operative ipsilateral, pre-operative contralateral, follow-up ipsilateral, and follow-up contralateral. Nine patients had right-sided UCS and three had left-sided UCS. The ages at surgery, CT scans, and ophthalmological examinations are provided in Table 5.

Table 5. Ages at surgery, CT scans, and ophthalmological examinations.

| | | |
|---|----------------------------------|---------------------------------------|
| Mean age at surgery | 12 ± SD 5 (range 9–26) months | |
| | Pre-operative examination | Follow-up examination |
| Mean age at ophthalmological examination | 10 ± SD 3 (range 3–26) months | 4.2 ± SD 1 (range 3.1–5.4) years |
| Mean age at time of CT scan | 10 ± SD 5 (range 4–22) months | 3.1 ± SD 0.3 (range 2.7–3.7) years |

CT: Computed Tomography; SD: standard deviation

Methods

Paper I

In this paper, Visual acuity (VA), orthoptic status, refraction, stereoacuity, and the anterior and posterior segments were evaluated in children with non-syndromic craniosynostosis pre-operatively and at early post-operative follow-up (6–12 months after the craniofacial operation). Monocular and binocular VA were measured with the Preferential Looking tests (Teller Acuity Cards or Cardiff Cards) in younger children, and with logMAR single optotypes (LEA or HVOT) in older children. For children too young to cooperate, VA was assessed by observing the ability to fixate and follow a 5 cm target at a distance of 30 cm. Orthoptic assessment was conducted with the cover–uncover test, and in cases with poor compliance, by evaluation of the symmetry of corneal reflexes (Hirschberg test). Refraction was measured by retinoscopy under cycloplegia, after instillation of eye drops, including cyclopentolate 0.5% and phenylephrine 0.5% in children under 1 year of age, and cyclopentolate 1.5% and phenylephrine 0.85% in older children. The spherical component and astigmatism were noted. The spherical equivalent (SE) was calculated as the merging of the spherical and half cylindrical refractive error. Astigmatism and anisometropia were considered significant if ≥ 1.00 D. The anterior segment was examined, and funduscopy was performed through dilated pupils.

At 6–12 months post-operatively, medical records regarding visual outcome, refraction, funduscopy, and orthoptic measurements were collected from the children's local hospitals.

Paper II

This paper evaluated refractive outcomes and strabismus at pre-school age and analysed longitudinal changes in the refractive status and strabismic development over time. Ocular alignment was assessed with the cover–uncover test and the alternate cover test for both distance and near. Eye motility was also noted. The spherical component and astigmatism were measured in cycloplegia after instillation of cyclopentolate 1.5% and phenylephrine 0.85% eye drops. Hypermetropia was considered significant if ≥ 2.00 D, myopia ≥ 0.50 D, and astigmatism and anisometropia of spherical component or astigmatism if ≥ 1.00 D.

Paper III

At the 5-year follow-up, the visual outcomes were analysed to evaluate the long-term ophthalmological effects of the different subtypes of craniosynostosis. Visual acuity (VA) was assessed with Lea Hyvärinen charts (LEA). Values were noted in LogMar units (logarithm of minimal angle of resolution) and then converted to Snellen decimal equivalents. Best corrected distance VA was assessed monocularly and binocularly at 3m, using both LEA symbols linear test and LEA single optotype test, and a crowding ratio was estimated (see Background). A value >1.2 indicated crowding. Best corrected near VA was assessed binocularly, at 40 cm, with LEA symbols linear test. Subnormal VA was defined as >0.1 LogMar (<0.8 Snellen decimal) at both distance and near. Monocular amblyopia was defined as the difference of at least two logMar lines in VA between the eyes, and bilateral amblyopia as $VA > 0.3$ LogMar (<0.5 Snellen decimal) in both eyes. Amblyogenic factors were considered to be strabismus, anisometropia of astigmatism and/ or spherical component, and bilateral ametropia. Low contrast VA (LCVA) was measured monocularly and binocularly at 3 m, using LEA low contrast 2.5% linear symbols test and colour vision was assessed with HRR (Hardy Rand and Rittler) pseudoisochromatic plates. Stereoacuity (stereopsis) was tested at near (40cm) with the Lang 1 screening test. Fundoscopy was performed through dilated pupils.

Paper IV

Patient records were retrospectively reviewed to collect data on strabismus, refraction, and VA, pre-operatively and at ages 3 or 5, in a subgroup of children with non-syndromic unicoronal synostosis. Hypermetropia was considered significant if $SE \geq 2.0$ D, and astigmatism/ anisometropia if ≥ 1.0 D. The astigmatism axis was divided into three categories: with the rule (0° – 15° or 165° – 180°), against the rule (75° – 105°), and oblique (16° – 74° or 106° – 164°). The presence of manifest or intermittent strabismus, type and side of deviation, and eye motility were also documented.

For morphological analysis, pre-operative and follow-up CT images were processed using Vue Motion (Carestream), and the orbits were semi-automatically segmented in OrbSeg 0.9.3 (Nysjö J. 2016). All subsequent morphological analyses were conducted using the programming language Python. Two main assessments were carried out: orbital symmetry and shape variation. Orbital symmetry for each orbital pair, pre- and post-operatively, was quantified as the Dice similarity coefficient (Dice). Improvement in symmetry was defined as the difference in Dice between pre-operative and follow-up CT scans.

Additionally, surface differences between ipsilateral and contralateral orbits, were visualised as coloured distance maps, using Hausdorff distances, calculated in MeshLab 2022.02 (ISTI-CNR); see Figure 8.

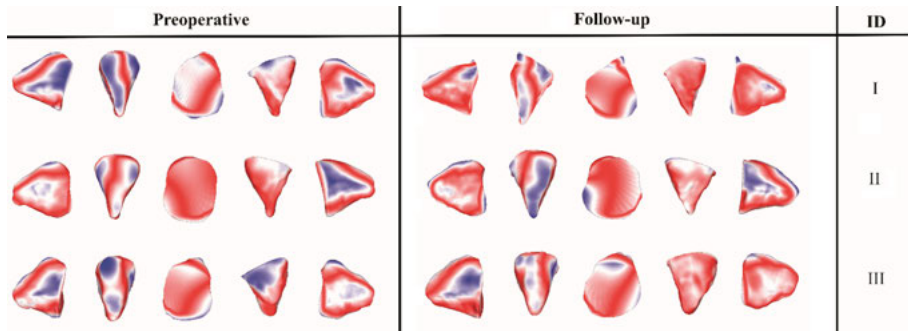


Figure 8. Distance maps comparing ipsi- and contra-lateral orbits pre- and post-operatively for three patients. The shapes of the ipsilateral orbits are visualised. Blue indicates areas where the contralateral orbit is locally smaller, red indicates where the contralateral orbit is locally bigger, and white indicates no local difference.

To assess shape variations, Principal component analysis (PCA) was performed for each of the four groups: pre-operative ipsilateral, pre-operative contralateral, follow-up ipsilateral, and follow-up contralateral. The first three principal components (PC1, PC2, and PC3), which explained most of the variation within each group, were used for further analysis. PCA coefficients were calculated to associate individual orbital shapes with specific morphological modes.

Globe segmentation was performed manually in ITK-SNAP (Yushkevich PA et al. 2006) and volumetric measurements were automatically generated by the software. The globe:orbit volume ratio was calculated by dividing the globe volume by the total orbital volume (globe + orbit).

Clinical correlations between morphological and ophthalmological outcomes were investigated using Python for data processing. The association between morphological symmetry (Dice) and anisometropia and strabismus was examined pre-operatively and at follow-up. Changes in Dice were further analysed in relation to changes in anisometropia and strabismus. Additionally, for each of the four groups, the relationship between the principal components and variables such as strabismus, astigmatism, SE, and subnormal vision was evaluated to determine whether specific morphological patterns correlated with particular clinical outcomes. Visualised shape differences, presented as coloured distance maps, further supported the interpretation of morphological changes over time.

Statistical Methods

Paper I

Descriptive statistics were performed with SPSS version 26 (IBM Corp). For further analyses, SAS software V.9.4 (SAS Institute) was used. For binary (yes/no) variables, exact logistic regression models were applied to assess the effect of the type of craniosynostosis on outcomes. For ordinal variables, proportional odds (ordinal) logistic regression models were used. All models were adjusted for age.

Paper II

Descriptive statistics were analysed using SPSS version 28 (IBM Corp., Armonk, NY, USA) and additional statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC). The study group and control group were compared with the independent T-test. Within the study group, the effect of craniosynostosis type on outcomes was assessed with proportional odds logistic regression for ordinal outcomes and exact logistic regression for binary outcomes, (yes/no). All models were adjusted for gender. McNemar's test was used to evaluate the agreement between pre-operative and post-operative results for binary outcomes.

Paper III

Descriptive statistics were calculated using SPSS version 28 (IBM Corp., Armonk, NY, USA), and further analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC). Proportional odds logistic regression models were used for ordinal outcomes, and exact logistic regression models for binary outcomes, to assess the effect of the type of craniosynostosis. The models were adjusted for gender, refractive error and strabismus.

Cases of lambdoid craniosynostosis was excluded from all the statistical analyses due to the small sample size (n=2). A p value < 0.05 was considered statistically significant. Due to the explanatory nature of the studies, no adjustments were made for multiplicity; therefore, all p-values should be interpreted as explanatory only.

Paper IV

Qualitative assessment and comparison of the data were conducted through visual inspection of individual orbits, mean orbits, and orbits derived from

principal component analysis (PCA), complemented by boxplots and summary tables to support interpretation and highlight relevant morphological patterns.

Ethical considerations

The study was approved by the Ethical Review Board of Uppsala, Sweden (Dnr 2017/452) and the Swedish Ethical Review Authority, Sweden (Dnr 2019-05851, 2021-04938, 2022-01851-02), and adhered to the Declaration of Helsinki.

The participants were children with craniosynostosis referred to the Uppsala Craniofacial Centre, Uppsala University Hospital and a control group of healthy children. Oral and written information about the study was provided to parents/legal guardians, and written consent was obtained prior to participation.

For the study group, data were collected as part of routine clinical care for craniosynostosis. A low-dose CT protocol was applied to minimise radiation exposure, and blood samples for genetic analysis were obtained under anaesthesia during surgery, to avoid additional discomfort. Ophthalmological assessments were performed in both the study group and the control group, using established clinical methods. The only potential adverse effects were mild, temporary itching during the instillation of cycloplegic drops, transient light sensitivity and reduced near vision for a few hours after the administration. Data were analysed at a group level without disclosure of individual identities. All participants received comprehensive ophthalmological examinations, and any conditions requiring follow-up were managed according to standard clinical care. The study procedures posed no risks to participants.

Results

Paper I

Sagittal craniosynostosis

Pre-operatively, 67/84 children cooperated to VA assessment with Preferential looking tests (PL), binocularly or monocularly, and VA was found normal for their age according to the test manuals. Twelve children could only be evaluated with fixation and following, and their visual behaviour was considered normal. Five children, all under 2 months of age, did not comply with any method of VA testing. Post-operative VA data were available for 59/78 children. Fifty-eight were examined with PL tests and maintained normal vision for their age. One child, with late diagnosed craniosynostosis at 3 years, was assessed with LEA optotypes and had normal vision in both eyes, both pre-operatively and 6-12 months post-operatively.

Refraction was assessed in 73/84 right eyes (REs) and 74/84 left eyes (LEs) pre-operatively and in 67/78 REs, and LEs at post-operative examination 6–12 months after surgery. Pre-operatively, the mean/median SE was +2.61/+2.50D (range 0.00 – +7.00D) in REs and +2.64/+2.50 D (range 0.00 – +6.50D) in LEs, while post-operatively, the mean/median SE was +1.74/+1.75D (range -1.25 – +4.75D) in the REs and +1.72/+1.5 D (range -1.87 – +4.25 D) in the LEs, respectively. The median values of spherical component, as well as prevalence of astigmatism ≥ 1 D and anisometropia of spherical component and astigmatism ≥ 1 D pre-operatively and post-operatively, are presented in Table 6.

Table 6. Refraction **(A)** pre-operatively and **(B)** 6–12 months post-operatively. Median values (range) of spherical component and prevalence rates of astigmatism ≥ 1 D and anisometropia of spherical component and astigmatism ≥ 1 D in 107 right eyes and 108 left eyes pre-operatively, and in 89 right and left eyes post-operatively.

A.

| <i>Pre-operative examination</i> | | | | |
|--|----------------------------|----------------------------|------------------------|------------------------|
| | Sagittal | Metopic | Unicoronal | Study group |
| Spherical refraction RE | +3.00 D (+1.00 – +7.00) | +3.00 D (+1.00 – +5.00) | +2.38 D (0 – +4.00) | +2.75 D (0 – +7.00) |
| Spherical Refraction LE | +3.00 D (+1.00 – +6.50) | +3.00 D (0 – +5.00) | +2.62 D (0 – +4.50) | +3.00 D (0 – +6.50) |
| Astigmatism ≥ 1 D RE | 29/73 (39.0%) | 9/20 (45.0 %) | 5/14 (35.7%) | 43/107 (40.0%) |
| Astigmatism ≥ 1 D LE | 34/74 (45.9%) | 7/20 (35.0%) | 6/14 (42.8%) | 47/108 (43.1%) |
| Anisometropia Spherical ≥ 1 D | 1/73 (1.4%) | 1/20 (5.0%) | 3/14 (21.4%) | 5/107 (4.7%) |
| Anisometropia Astigmatism ≥ 1 D | 2/73 (2.7%) | 1/20 (5.0%) | 5/14 (35.7%) | 8/107 (7.5%) |

B.

| <i>Post-operative examination</i> | | | | |
|--|----------------------------|----------------------------|----------------------------|----------------------------|
| | Sagittal | Metopic | Unicoronal | Study group |
| Spherical Refraction RE | +2.00 D (-0.75 – +5.50) | +2.00 D (+1.00 – +5.00) | +2.00 D (+1.00 – +4.25) | +2.00 D (-0.75 – +5.50) |
| Spherical refraction LE | +2.0 D (-1.25 – +5.00) | +1.50 D (+1.0 – +5.50) | +2.50 D (+1.00 – +5.25) | +2.00 D (-1.25 – +5.50) |
| Astigmatism ≥ 1 D RE | 16/67 (23.9%) | 2/13 (15.4 %) | 2/9 (22.2 %) | 20/89 (22.3%) |
| Astigmatism ≥ 1 D LE | 17/67 (25.4%) | 3/13 (23.1%) | 4/9 (44.4 %) | 24/89 (25.6%) |
| Anisometropia Spherical ≥ 1 D | 2/67 (2.9%) | 1/13 (7.7%) | 4/9 (44.4 %) | 7/89 (7.9%) |
| Anisometropia Astigmatism ≥ 1 D | 2/67 (3.0%) | 1/13 (7.7%) | 3/9 (33.3 %) | 6/89 (6.7%) |

D=diopeters, RE= right eye, LE= left eye

Strabismus (exodeviation) was present in three children, all under 3 months of age at the pre-operative examination; however, in all cases, it resolved after surgery. Five children, all under one and a half months of age at the pre-operative examination, did not cooperate with the orthoptic assessments. None of them were found to have strabismus at the post-operative examination, and no new cases of strabismus were found.

Metopic craniosynostosis

Pre-operatively, 18/22 children were evaluated with PL tests, and three only with fixation and following. In both cases, VA and visual behaviour, respectively, were considered normal for their age. One child, who was under 2 months of age, did not comply with any method of VA test. Post-operatively, all 20 children complied with the PL testing; one child had subnormal VA and was prescribed spectacles due to high hypermetropia.

Refraction was assessed in 20/22 REs and LEs pre-operatively and 13/20 REs and LEs post-operatively and is presented in Table 6. Pre-operatively, the mean/median SE was +2.20/+2.38D (range +0.50 – +5.00D) in the REs and +2.14/+2.38D (range -0.50 – +5.00D) in the LEs, while post-operatively, the mean/median SE was +1.83/+1.88 D (range +0.75 – +4.75D) in the REs and +1.92/+1.5D (range +0.63 – +5.25D) in the LEs, respectively.

No infants had strabismus pre-operatively; however, one was found to have esotropia post-operatively.

Unicoronal craniosynostosis

Pre-operatively, 14/16 children were assessed binocularly or monocularly with PL tests, and three were found to have subnormal vision for their age in one eye. One child, examined at 2 months of age, complied only with fixation and following testing and the visual behaviour was considered normal. One, 3-year-old child with late diagnosed craniosynostosis was assessed with LEA optotypes and had normal vision in both eyes pre-operatively and post-operatively ($VA \leq 0.2 \log \text{ Mar} / \geq 0.63 \text{ Snellen decimal}$). Post-operatively, 11/15 children cooperated to examination with PL tests, and two were found to have subnormal VA in one eye. Two children did not comply with any method of VA testing, while information about VA was not available for one child.

Refraction was assessed in 14/16 REs and LEs preoperatively and in 9/15 REs and LEs post-operatively, and is presented in Table 6. The mean/median SE was +1.90/+1.75D (range -0.25 – +4.00D) in the REs and +1.95/+2.25D (range -0.25 – +4.00D) in the LEs pre-operatively, and +1.63/+1.75D (range +0.50 – +2.50D) in the REs and +1.78/+2.00D (range -0.50 – +3.12D) in the LEs postoperatively.

Four children had strabismus pre-operatively, three had exotropia and one esotropia. In all four cases, the strabismus remained after surgery. Two new cases of strabismus were found post-operatively (Figure 9). Overaction of the inferior oblique muscle was noted in three children post-operatively.

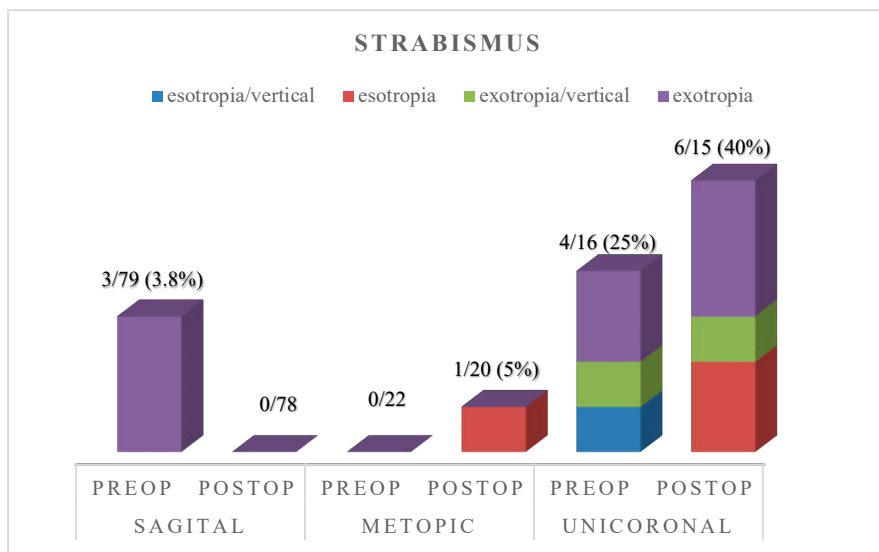


Figure 9. Prevalence of strabismus pre-operatively and 6-12 months postoperatively in children with sagittal, unicoronal, and metopic non-syndromic craniosynostosis.

Three children with unicoronal synostosis, all under 9 months of age, who presented with anisometropia, or a combination of anisometropia and strabismus, were prescribed occlusion therapy before surgery in order to prevent amblyopia. Post-operatively, anisometropia persisted, and they were prescribed spectacles. Additionally, three children who developed refractive errors and anisometropia post-operatively were also prescribed spectacles.

Overall, no differences were found between boys and girls, regarding strabismus and refraction. The anterior segment was evaluated and considered normal in all children across the various types of craniosynostosis. No disc oedema or pale disc was detected pre- or post-operatively.

Comparison of craniosynostosis

When comparing the different types of craniosynostosis, adjusted for age, significant differences were observed in spherical anisometropia of $\geq 1D$, both before surgery ($p = 0.05$) and after surgery ($p = 0.02$), as shown in Table 6. Similarly, there were significant differences in astigmatic anisometropia of $\geq 1D$ pre-operatively ($p = 0.01$) and post-operatively ($p = 0.03$) (see Table 6).

However, no statistically significant differences were found between the groups regarding the spherical component or astigmatism in the REs or LEs, either pre-operatively or post-operatively.

Regarding strabismus, a significant difference was noted among the different craniosynostosis types, both before surgery ($p = 0.02$) and after surgery ($p < 0.001$). Children with unicoronal synostosis had the highest prevalence of strabismus (see Figure 9).

Paper II

Sagittal craniosynostosis

At the 5-year follow-up, refraction was assessed in 58 REs and 57 LEs of 58 children. The mean/median SE was +1.44/+1.50D, (range -0.125 – +3.50D) in REs and +1.46/+1.50D (range -0.625 – +3.50D) in LEs. The refractive outcomes are presented in Tables 7 A and B.

Table 7 A. Refraction at 5 years of age. Mean/Median values (range) of spherical component and astigmatism in 88 right eyes and 87 left eyes, divided by craniosynostosis, subtype, and in 32 right and left eyes in the control group. **B.** Prevalence rates of spherical component $\geq 2D$ and astigmatism $\geq 1D$ at 5 years of age in 88 right eyes and 87 left eyes, divided by craniosynostosis subtype, and in 32 right and left eyes in the control group, as well as prevalence of anisometropia of spherical component and astigmatism $\geq 1D$ in the study group and control groups.

A.

| | Sagittal | Metopic | Unicoronal | Lambdoid | Study group | Control group |
|--------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------------------------|
| Spherical refraction RE | +1.50/+1.50D (0-+4.50) | +2.45/+2.25D (+1.00-+6.00) | +2.31/+2.00D (1-+4.50) | +1.86/+1.75D (0-+4.00) | +1.59/+1.50D (0-+4.50) | +1.52/+1.37 (+0.5-+4.25) |
| Spherical refraction LE | +1.62/+1.50D (-0.50-+4.50) | +2.43/+2.00D (+1.00-+6.25) | +2.94/+2.50D (+1.25-+6.00) | +2.75/+2.75D (+1.50-+4.00) | +1.99/+1.75D (-0.50-+6.25) | +1.63/+1.37 (+0.25-+4.5) |
| Astigmatism RE | -0.28/-0.25D (-2.75-0) | -0.48/-0.50D (-1.00-0) | -0.42/-0.50D (-1.25-0) | -0.25/-0.25D (-0.25-0.25) | -0.34/-0.25D (-2.75-0) | -0.33/-0.25 (-1.5-0) |
| Astigmatism LE | -0.33/-0.25D (-3.00-0) | -0.52/-0.50D (-2.75-0) | -1.23/-1.00D (-3.75-0) | -0.49/-0.25D (-3.75-0) | -0.49/-0.25D (-3.75-0) | -0.31/-0.25 (-1.5-0) |

B.

| | Sagittal | Metopic | Unicoronal | Lambdoid | Study group | Control group |
|---------------------------------------|------------------|-----------------|------------------|----------------|------------------|----------------|
| Spherical refraction ≥ 2D RE | 18/58 (31.0%) | 9/15 (60.0%) | 9/13 (69.2%) | 1/2 (50.0%) | 36/88 (40.9%) | 10/32 (45%) |
| Spherical refraction ≥ 2D LE | 17/57 (29.8%) | 9/15 (60.0%) | 10/13 (76.9%) | 1/2 (50.0%) | 36/87 (41.4%) | 12/32 (37%) |
| Astigmatism ≥ 1D RE | 3/58 (5.2%) | 3/15 (20%) | 1/13 (7.7%) | 0/2 | 7/88 (8.0%) | 2/32 (6.2%) |
| Astigmatism ≥ 1D LE | 4/57 (7%) | 2/15 (13.3%) | 7/13 (53.8%) | 0/2 | 13/87 (15.3%) | 1/32 (3.1%) |
| Anisometropia Spherical ≥ 1D | 0/57 | 1/15 (6.7%) | 3/13 (23.1%) | 0/2 | 4/87 (4.6%) | 1/32 (3.1%) |
| Anisometropia Astigmatism ≥ 1D | 2/57 (3.5%) | 1/15 (6.7%) | 6/13 (46.2%) | 0/2 | 8/87 (9.2%) | 1/32 (3.1%) |

D=diopters, RE= right eye, LE= left eye

In the sagittal craniosynostosis group, one child was found to have intermittent exotropia and inferior oblique overaction.

Metopic craniosynostosis

In this group, refraction was assessed in all 15 REs and LEs. The mean/median SE was +2.21/+1.88D (range +0.88–+5.50D) in the REs and +2.18/+2.00D (range +0.75–+5.75D) in the LEs. Refractive outcomes are presented in Tables 7A and B.

None of the 14 children were found to have strabismus.

Unicoronal craniosynostosis

Refraction was assessed in 13 REs and LEs of 14 children. The mean/median SE was +2.10/+1.75D (range +0.63 – +4.13D) in the REs and +1.73/+2.25D (range -0.25 – +5.50D) in the LEs. Data are presented in Tables 7A and B. In 6/13 children, anisometropia of astigmatism ≥ 1 D was found; in 5/6 children, the greater degree was detected in the contralateral eye to the fused suture.

Strabismus was present in 10/14 children (71%), including five new cases found at the 5-year follow-up. The main type of strabismus was exotropia with a vertical component (Figure 10). Overaction of the inferior oblique muscle in adduction with hypertropia consistent with a pseudo-superior oblique palsy, was noted in 6/14 (43%) cases, predominantly ipsilateral to the fused suture. In two cases, monocular elevation deficiency with hypotropia was noted; in one case, ipsilateral and in another, contralateral to the fused suture.

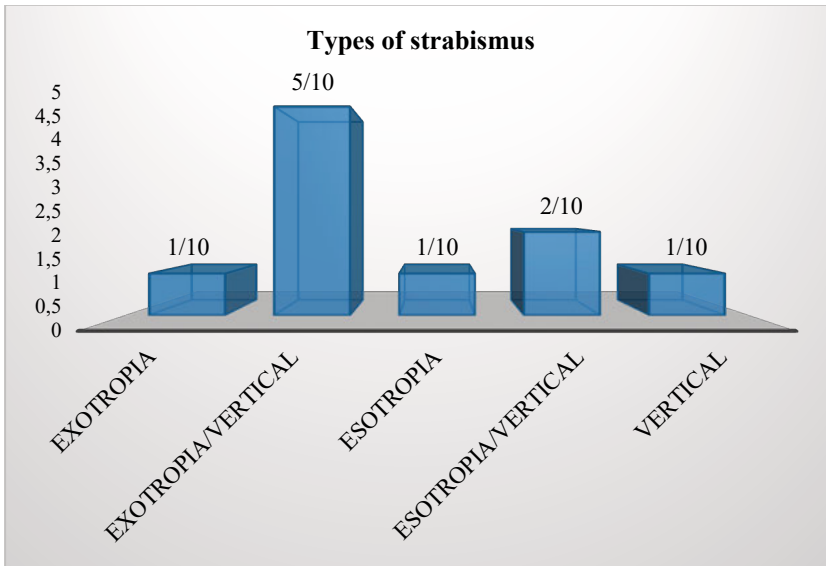


Figure 10. Prevalence of different types of strabismus in unicoronal craniosynostosis at 5-years follow-up.

Lambdoid craniosynostosis

Refraction and orthoptic examinations were conducted on both children in this group. Data are presented in Tables 7A and B. The mean/median SE was +2.13/+2.13D (range +1.38 – +2.86D) in the REs and +2.25/+2.25D (range +1.38 – +3.88D) in the LEs, respectively.

No cases of strabismus or motility disorders were found.

Control group

In the control group of 32 children, the mean/median SE was +1.36/+1.25D (range +0.25 – +4.00D) in the REs and +1.48/+1.25D (range +0.25 – +4.25D) in the LEs. Data are summarised in Tables 7A and B.

No strabismus or motility disorders were found in this group.

Comparison of different types of craniosynostosis at 5-years follow-up

Regarding refractive outcomes, significant difference was found in the spherical component in REs and LEs between the different types of craniosynostosis ($p=0.01$ and $p=0.005$, respectively); see Table 7A. Similarly, astigmatism differed between the groups in REs ($p=0.006$) and LEs ($p<0.001$). In the metopic craniosynostosis group, higher values of hypermetropia (≥ 2 D) were found in both REs and LEs. In the unicoronal group, high values of hypermetropia (≥ 2 D) and a higher degree of astigmatism (≥ 1 D), mainly contralateral to the synostotic suture (LEs) were observed (Tables 7A and B). A difference in anisometropia of spherical component ≥ 1 D ($p=0.02$) and anisometropia of astigmatism ≥ 1 D ($p=0.001$) was found due to the higher values in the unicoronal craniosynostosis group; see Table 7B. The prevalence of strabismus also differed among the craniosynostosis subtypes ($p<0.001$) and was higher in the unicoronal synostosis group (Table 8).

Table 8. Prevalence of strabismus over time in 5-year-old children, assessed on at least two out of three occasions (pre-operatively, 6–12 months post-operatively, and at 5 years of age), presented by craniosynostosis subtype. Data are presented as number and percentage (%).

| | Sagittal | Metopic | Unicoronal | Lamdoid | Study group |
|--|-----------------|----------------|------------------|---------|------------------|
| Strabismus pre-operatively | 1/52 (2.0%) | 0/15 | 3/14 (21.4%) | 0/1 | 4/82 (5.0%) |
| Strabismus 6–12 months post-operatively | 0/50 | 1/13 (8.0%) | 5/13 (38.5%) | 0/0 | 6/76 (8.0%) |
| Strabismus at 5 years follow-up | 1/58 (1.75%) | 0/14 | 10/14 (71.4%) | 0/2 | 11/88 (12.5%) |

Comparison between the control group and the study group

When comparing the control group with the study group, adjusted for gender, higher values of hypermetropia were observed in both the metopic and unicoronal groups ($p=0.003$ REs and $p<0.001$ LEs). Higher astigmatism in LEs ($p<0.001$), anisometropia of spherical component ($p=0.001$) and anisometropia of astigmatism ($p=0.008$) were also found in the unicoronal group. Children with sagittal craniosynostosis did not show a higher risk of refractive error compared with the children in the control group. See Tables 7 A and B.

Refractive development over time in different types of craniosynostosis

There was a statistically significant change over time in spherical component $\geq 2D$ in both eyes ($p=0.0008$ for REs and $p=0.0002$ for LEs) and in astigmatism $\geq 1D$ ($p=0.0002$ for REs and $p=0.006$ for LEs). However, anisometropia of spherical component $\geq 1D$ and anisometropia of astigmatism $\geq 1D$ did not change statistically over time.

Development of strabismus over time in craniosynostosis subtypes

The development of strabismus in children who had longitudinal follow-up, consisting of examinations on at least two occasions (pre-operatively, 6–12 months after the surgery and at 5 years of age), is presented in Table 8.

In the sagittal craniosynostosis group, three children, all under three months of age, exhibited exotropia pre-operatively. In all cases, the exotropia disappeared at the first post-operative examination. Two of these three children were lost to the follow-up at 5 years. One new case of strabismus (intermittent exotropia) was found at the 5-year follow-up.

In the metopic craniosynostosis group, no strabismus was noted pre-operatively, but one child developed esotropia at the first postoperative examination. This child failed to cooperate with proper orthoptic evaluation at the 5-year follow-up; therefore, strabismus could not be confirmed. No new cases of strabismus were found.

In the unicoronal craniosynostosis group, three children (two with exotropia, one with esotropia) had strabismus at all three examinations. Two new cases (one exotropia, one esotropia) were found at 6–12 months after surgery. The strabismus remained present at the 5-year follow-up, with the same children also developing vertical deviation. One child with intermittent exotropia pre-operatively and at 6 months post-operatively was lost to follow-up. Five new cases of combined horizontal and vertical deviation were found at 5 years of age (see Figure 8).

Paper III

Sagittal craniosynostosis

Best-corrected distance visual acuity (VA) was assessed in 56 of 58 children. In the REs, it was subnormal in seven cases, with two of these cases associated with hypermetropia. In the LEs, VA was subnormal in five cases, including one case with intermittent exotropia and one with hypermetropia. Two children cooperated only for assessment using isolated optotypes and had VA within the normal range for age. One child had VA > 0.3 LogMAR (< 0.5 Snellen decimal) in both structurally normal eyes, with no evidence of strabismus or refractive error. However, this child had a history of prematurity and global neurodevelopmental delay. No other cases of amblyopia were detected in this group; however, three children wore corrective spectacles due to high hypermetropia. Near VA was assessed in 53 children, with subnormal values identified in five cases. One of these also had intermittent exotropia and subnormal distance VA. The mean and median values of distance and near VA, are presented in Table 9A.

Crowding was evaluated in 45 children (Table 9C). A crowding ratio > 1.2 was observed in 30 REs and 32 LEs. No association was found with strabismus; however, hypermetropia was present in 6 REs and 7 LEs.

Low-contrast visual acuity (LCVA) data were available for 31 children. Nine were assessed only binocularly and one only in the RE. The mean and median LCVA values, as well as the prevalence of LCVA > 0.4 LogMAR (< 0.4 Snellen decimal), are presented in Table 9B and 9D respectively.

Table 9. A. Mean/Median values (range) of distance and near visual acuity in the study and control groups. **B.** Mean/Median values (range) of low contrast visual acuity in the study and control groups. **C.** Crowding ratio in the study and control groups. **D.** Prevalence rates of low contrast visual acuity > 0.4 LogMar (<0.4 Snellen decimal) in the study group and control groups.

A.

| | VA distance | | | | | | VA near | |
|----------------------|--------------------------------|-------------------------|--------------------------------|-------------------------|--------------------------------|-------------------------|--------------------------------|------------------------|
| | Binocular | | | Monocular | | | LogMar | Decimal |
| | LogMar | Decimal | LE | RE | LogMar | Decimal | | |
| Study group | 0.58/0.0 (-0.1-0.4) n=86 | 0.89/1.0 (0.4-1.25) | 0.8/0.1 (-0.1-0.6) n=85 | 0.85/0.8 (0.25-1.25) | 0.95/0.1 (-0.1-0.6) n=84 | 0.83/0.8 (0.25-1.25) | 0.84/0.1 (0.0-0.3) n=75 | 0.83/0.8 (0.5-1.0) |
| Sagittal | 0.48/0.0 (-0.1-0.4) n=56 | 0.92/1.0 (0.4-1.25) | 0.77/0.1 (-0.1-0.6) n=56 | 0.86-0.8 (0.25-1.25) | 0.75/0.1 (-0.1-0.6) n=56 | 0.86-0.8 (0.25-1.25) | 0.79/0.1 (0.0-0.3) n=53 | 0.84/0.8 (0.5-1.0) |
| Metopic | 0.71/0.1 (0.0-0.2) n=14 | 0.86/0.8 (0.63-1.0) | 0.86/0.1 (0.0-0.2) n=14 | 0.83/0.8 (0.63-1.0) | 0.86/0.1 (0.0-0.3) n=14 | 0.84/0.8 (0.5-1.0) | 0.77/0.1 (0.0-0.1) n=13 | 0.84/0.8 (0.8-1.0) |
| Unicoronal | 0.79/0.1 (0.0-0.2) n=14 | 0.85/0.8 (0.63-1.0) | 0.85/0.1 (0.0-0.2) n=13 | 0.84/0.8 (0.63-0.8) | 0.2/0.2 (0.0-0.5) n=13 | 0.68/0.63 (0.3-1.0) | 0.13/0.1 (0.0-0.2) n=8 | 0.76/0.8 (0.63-1.0) |
| Lambdaoid | 0.1/0.1 (0.0-0.2) n=2 | 0.82/0.82 (0.63-1.0) | 0.1/0.1 (0.0-0.2) n=2 | 0.82/0.82 (0.63-1.0) | 0.0/0.0 n=1 | 1.0/1.0 | 0.1/0.1 n=1 | 0.8/0.8 |
| Control group | 0.11/0.0 (0.0-1.6) n=33 | 0.92/1.0 (0.5-1.6) | 0.82/0.1 (-0.1-0.4) n=33 | 0.87/0.9 (0.4-1.3) | 0.79/0.1 (-0.1-0.3) n=33 | 0.87/0.9 (0.5-1.3) | 0.16/0.0 (-0.1-0.1) n=31 | 0.97/1.0 (0.8-1.25) |

B.

LCVA

| | Binocular | | | Monocular | | |
|----------------------|----------------------------------|--------------------------|----------------------------------|--------------------------|----------------------------------|--------------------------|
| | | | | LE | | |
| | LogMar | Decimal | LogMar | LogMar | Decimal | LogMar |
| Study group | 0.31/0.40 (0.10–0.60) n=57 | 0.43/0.40 (0.25–0.80) | 0.47/0.50 (0.20–0.70) n=46 | 0.36/0.32 (0.20–0.63) | 0.48/0.50 (0.20–0.70) n=45 | 0.35/0.32 (0.20–0.63) |
| Sagittal | 0.37/0.40 (0.10–0.50) n=41 | 0.38/0.32 (0.32–0.80) | 0.47/0.50 (0.20–0.70) n=32 | 0.36/0.32 (0.20–0.63) | 0.45/0.50 (0.20–0.70) n=31 | 0.38/0.32 (0.20–0.63) |
| Metopic | 0.39/0.40 (0.30–0.50) n=10 | 0.41/0.40 (0.32–0.50) | 0.47/0.50 (0.30–0.50) n=10 | 0.35/0.32 (0.32–0.50) | 0.49/0.50 (0.40–0.50) n=10 | 0.33/0.32 (0.32–0.40) |
| Unicoronal | 0.44/0.40 (0.40–0.50) n=5 | 0.37/0.40 (0.25–0.40) | 0.50/0.50 (0.40–0.60) n=4 | 0.32/0.32 (0.25–0.40) | 0.62/0.65 (0.50–0.70) n=4 | 0.24/0.23 (0.20–0.32) |
| Lambdoid | 0.60/0.60 n=1 | 0.25/0.25 | - | - | - | - |
| Control group | 0.36/0.40 (0.20–0.50) n=29 | 0.47/0.40 (0.32–0.63) | 0.42/0.40 (0.20–0.60) n=29 | 0.39/0.40 (0.26–0.63) | 0.43/0.40 (0.20–0.60) n=29 | 0.39/0.40 (0.25–0.63) |

C.

Crowding ratio

| | RE | LE |
|----------------------|--------------------------------------|-------------------------------------|
| Study group | 1.26/1.25 (0.79–2.52) <i>N=61</i> | 1.25/1.25 (1.0–2.52) <i>N=61</i> |
| Sagittal | 1.26/1.25 (1.0–2.52) <i>n=45</i> | 1.27/1.25 (1.0–2.52) <i>n=45</i> |
| Metopic | 1.30/1.25 (1.0–2.0) <i>n=11</i> | 1.26/1.25 (1.0–2.0) <i>n=11</i> |
| Unicoronal | 1.20/1.25 (1.0–1.27) <i>n=5</i> | 1.22/1.25 (1.0–1.6) <i>n=5</i> |
| Lambdoid | - | - |
| Control group | 1.13/1.11 (1.0–1.44) <i>n=29</i> | 1.09/1.11 (1.0–1.3) <i>n=29</i> |

D.

LCVA>0.4 LogMar

| | Binocular | Monocular | |
|----------------------|------------------|------------------|------------------|
| | | REs | LEs |
| Study group | 15/57 (26.3%) | 30/46 (65.2%) | 29/45 (64.4%) |
| Sagittal | 10/41 (24.4%) | 19/32 (59.4%) | 16/31 (51.6%) |
| Metopic | 2/10 (40%) | 8/10 (80%) | 9/10 (90%) |
| Unicoronal | 2/5 (40%) | 3/4 (75%) | 4/4 (100%) |
| Lambdoid | 1/1 | - | - |
| Control group | 3/29 (10.3%) | 11/29 (37.9%) | 12/29 (41.4%) |

LogMar: logarithm of minimal angle of resolution, VA: visual acuity, RE: right eye, LE: left eye, n: number, LCVA: low contrast visual acuity

Colour vision was assessed in 53 children, with one boy demonstrating red-green deficiency. Stereopsis was tested in all children and was positive. Fundoscopy was also normal in all children at the time of examination. However, three patients had a prior history of elevated ICP that necessitated a second craniofacial procedure. In two of these cases, secondary coronal synostosis was confirmed.

Metopic craniosynostosis

Distance VA was evaluated in 14 of 15 children (Table 9A). Subnormal VA was found in one RE with hypermetropia and in two LEs with combined hypermetropia and astigmatism; all three children were already using spectacles. Eight children with bilateral hypermetropia (as per study criteria) demonstrated normal VA for age. Two of these had hypermetropia of +4.00 D and +6.00 D, respectively, and were using corrective spectacles. No cases of amblyopia were identified. One child was assessed binocularly and showed normal VA. Near VA was measured in 13 children and was within the normal range in all cases (Table 9A).

Crowding was assessed in 11 children (Table 9C). A crowding ratio >1.2 was found in nine REs and seven LEs. Among these, hypermetropia was identified in one RE and four LEs. One child showed combined hypermetropia and astigmatism in both eyes.

LCVA data were available for 10 children (Tables 9B, 9D). Colour vision was normal in all 12/15 children who cooperated with testing. Stereopsis was positive in 14 of 15 children; one child did not cooperate. No fundus changes were found.

Unicoronal craniosynostosis

Distance VA was assessed in 13 of 14 children (Table 9A). Subnormal VA was found in two REs (including one case of hypermetropia) and in seven LEs, all associated with refractive error, strabismus, or both. One child had subnormal binocular VA. Amblyopia was identified in four LEs, related to strabismus and anisometropia (three astigmatic and one hypermetropic), despite spectacle correction. One child was assessed binocularly because of poor cooperation and had VA normal for the age. Near VA was measured in 11 children and was subnormal in three (Table 9A). All three children had bilateral refractive errors and used corrective glasses.

Crowding was assessed for five children, see Table 9C. A crowding ratio >1.2 was noted in four REs (two with hypermetropia) and in three LEs, of which one had strabismus with hypermetropic anisometropia and another had strabismus with astigmatic anisometropia.

LCVA data were available for four children (Tables 9B, 9D). One was assessed binocularly only. Colour vision was normal in all eight children. Stereopsis was negative in seven of 14 children, all of whom had strabismus.

Fundoscopy was normal in all 14 children.

Lambdoid craniosynostosis

Two children were assessed in this group. One had normal distance VA for age. The other did not cooperate for LE testing but showed subnormal VA in the RE and binocularly.

LCVA was assessed binocularly in only one child and was subnormal. Colour vision was assessed in one child and was normal. Both children demonstrated positive stereopsis and had normal fundoscopy.

The visual outcomes are presented in Table 9.

Control group

All 33 children in this group were evaluated for distance VA. One child had subnormal VA in both eyes, associated with bilateral hypermetropia. Near VA was assessed in 31 children and was normal in all (Table 9A).

Crowding was evaluated for 29 children, see Table 9C. A crowding ratio >1.2 LogMAR was observed in nine REs and five LEs. No child exhibited strabismus, and only one had a refractive error.

LCVA data were available for 29 children (Tables 9B, 9D). Colour vision was normal in 31 of the 33 children tested. Stereopsis was present in all. No fundus changes were found.

Comparison between craniosynostosis subtypes

After adjusting for gender, significant differences in distance VA and LCVA in the LEs were found between craniosynostosis subtypes ($p = 0.01$ and $p = 0.009$), primarily driven by lower values in the unicoronal group (Tables 9A and 9B). These differences were not statistically significant when further adjusted for strabismus and refractive error. No statistically significant differences were found in crowding or in the prevalence of a crowding ratio >1.25 across the craniosynostosis subtypes.

Comparison between the craniosynostosis and the control group

When adjusted for gender, both distance VA and LCVA in the LEs differed significantly ($p = 0.01$ and $p = 0.003$) due to lower values observed in the unilateral craniosynostosis group. The prevalence of subnormal VA and LCVA in the LEs was also significantly higher in the craniosynostosis group compared with controls ($p = 0.005$ and $p = 0.014$). These differences were not significant after adjusting for strabismus and refractive error. Near binocular

VA was significantly lower in children with craniosynostosis compared with controls ($p < 0.01$; Table 9A), across all subtypes. Crowding was more prevalent in the craniosynostosis group, with a statistically significant difference in the LEs between the sagittal group and controls ($p = 0.03$). The prevalence of a crowding ratio >1.25 differed significantly between craniosynostosis and control groups for both REs ($p = 0.002$) and LEs ($p = 0.0001$).

Paper IV

Detailed data on ophthalmological findings, orbital symmetry, and globe: orbit volume ratios for 12 children with unicoronal craniosynostosis are presented in Table 10.

Table 10. Ophthalmological status, symmetry, and globe:orbit volume ratio preoperatively and at follow-up in 12 children with unicoronal craniosynostosis.

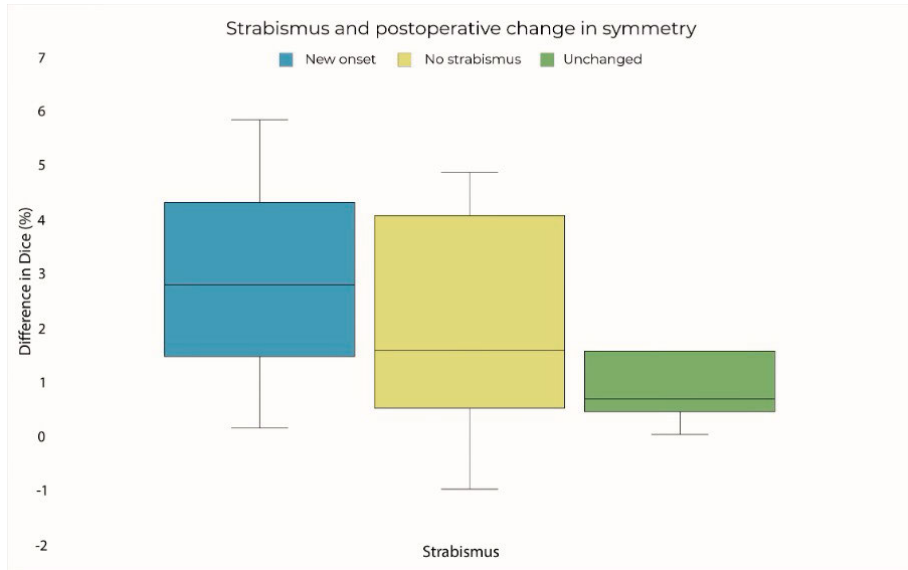
| | Pre-operative examination | Follow-up examination |
|--------------------------------------|--|--|
| Strabismus | Ipsilateral: 0/12 Contralateral: 3/12 Vertical: 1 Exotropia: 2 Esotropia: 1 | Ipsilateral: 4/12 Vertical: 4 Contralateral: 6/12 Vertical: 1 Exotropia: 4 Esotropia: 2 |
| SE ≥ 2D | Ipsilateral: 8/12 Contralateral: 8/12 | Ipsilateral: 6/12 Contralateral: 5/12 |
| Astigmatism ≥ 1D | Ipsilateral: 4/12 Oblique: 2 With the rule: 2 Contralateral: 3/12 Oblique: 1 With the rule: 2 | Ipsilateral: 0/12 Contralateral: 1/12 Oblique: 0 With the rule: 1 |
| Anisometropia of SE ≥ 1D | 2/12 | 2/12 New onset: 1 |
| Astigmatic anisometropia ≥ 1D | 3/12 | 1/12 |
| Subnormal vision | Ipsilateral: 0/12 Contralateral: 2/12 | Ipsilateral: 0/12 Contralateral: 4/12 New onset: 2 |
| Symmetry (%) | 84 ± SD 2 (range 80 – 88) | 86 ± SD 3 (range 81 – 90) |
| Globe:orbit volume ratio (%) | Ipsilateral: 38 ± SD 5 (range 31 – 50) Contralateral: 39 ± SD 6 (range 30 – 50) | Ipsilateral: 36 ± SD 5 (range 28 – 44) Contralateral: 35 ± SD 5 (range 28 – 43) |

SE= spherical equivalent; D=diopeters; SD= standard deviation

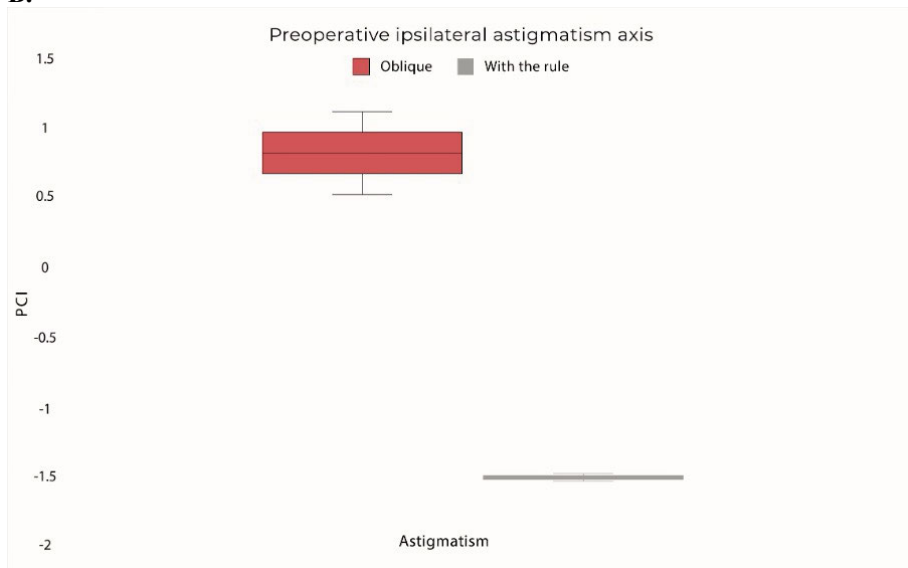
Post-operatively, 9/12 children showed improvement in orbital symmetry (range 1–6%), while two showed no change and one exhibited a 1% decrease in orbital symmetry. The mean improvement was 2%. Six children had a lower globe:orbit volume ratio on the ipsilateral side pre-operatively, and eight at follow-up. A decrease in the globe:orbit volume ratio was observed in 9/12 ipsilateral orbits (mean -2.2%; range -7.4 to +6.3%) and in 9/12 contralateral orbits (mean -3.3%; range -6.9 to +10.2%). In three patients, the ratio increased, in two bilaterally and one unilaterally.

Distinct orbital shapes variations were qualitatively associated with strabismus, refractive errors, and subnormal vision. Improvement in orbital symmetry at follow-up was related both to the development of new-onset strabismus and to a reduction in astigmatic anisometropia (Figure 11). Greater preoperative asymmetry was linked to higher levels of astigmatic anisometropia.

A.



B.



C.

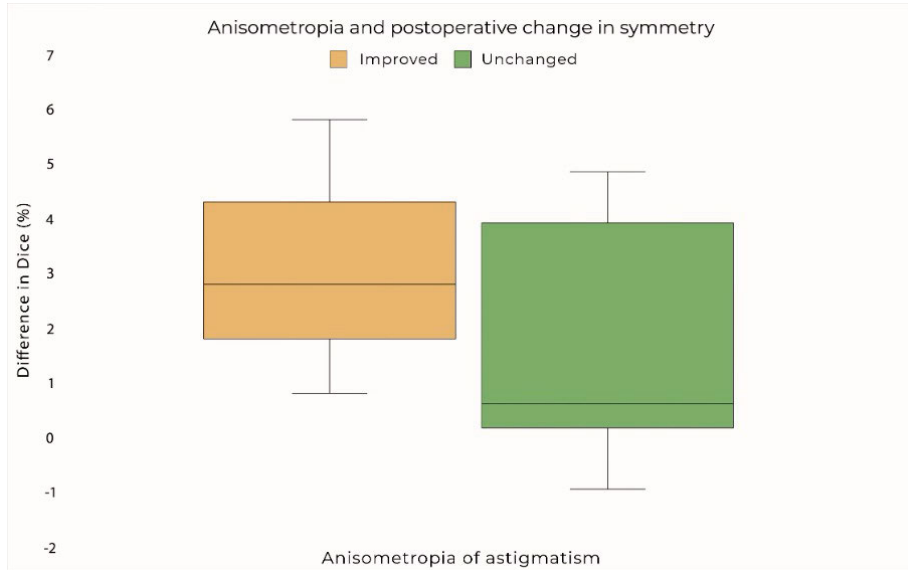


Figure 11. A. Post-operative change in orbital symmetry (measured as a % difference in Dice) in relation to strabismus status. Patients with new-onset strabismus are shown in light blue, those without strabismus at any time point in light green, and patients with persistent strabismus both preoperatively and at follow-up in dark green. **B.** Relationship between pre-operative axis of astigmatism and orbital shape variations on the ipsilateral side. Oblique astigmatism (dark red) was associated with the positive aspects of the first principal component (PC1+), while with-the-rule astigmatism (grey) was associated with the negative aspects (PC1-). **C.** Post-operative change in orbital symmetry (measured as a % difference in Dice) and its association with astigmatic anisometropia. Patients who showed improvement in anisometropia are depicted in orange, while those with unchanged anisometropia are shown in green. Dice = Dice similarity coefficient, PC1 = first principal component.

Strabismus

Pre-operative contralateral strabismus was associated with lower globe:orbit volume ratios and a large, diagonal shape (PC1-). At follow-up, contralateral strabismus was associated with higher globe:orbit volume ratios and orbits that were oval and vertically compressed (PC1-). Shapes associated with strabismus are visualised in Figure 12.

No consistent relationship between ipsilateral morphology or globe:orbit volume and strabismus was found at the post-operative examination.

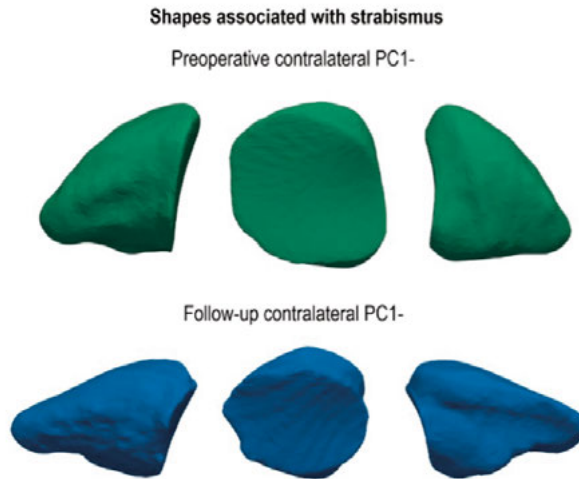


Figure 12. Shapes associated with strabismus. PC1- = negative first principal component. (Illustrations courtesy of Dr. Hanna Lif)

Refractive Errors

On the ipsilateral side, hypermetropia, both pre-operatively and at follow-up, was associated with variations of Harlequin orbital deformity (visualised as PC3- and PC3+). On the contralateral side, hypermetropia was linked to diagonal (PC2-) or small, rounded (PC2+) orbital configurations at follow-up. No clear relation was found between hypermetropia and globe:orbit volume ratio, nor between anisometropia of spherical equivalent and orbital symmetry or volume.

Astigmatism was associated with Harlequin deformity variants, characterised by vertically elongated/ horizontally compressed orbital shapes (PC1, PC2), on the ipsilateral side pre-operatively. Moreover, Harlequin deformity (PC1-) and small globe:orbit volume ratio were associated with with-the-rule astigmatism whereas vertically elongated, small, round orbital shapes (PC1+) and larger globe:orbit volume ratio was linked to oblique astigmatism. On the contralateral side, both large diagonal (PC1-) and small round orbits (PC1+) were associated with astigmatism pre-operatively. At follow-up, the single patient with significant astigmatism had it on the contralateral side, having also the highest globe:orbit volume ratio within the group.

Visual Acuity

Two children had subnormal vision on the contralateral side pre-operatively, which persisted at follow-up. One case was associated with astigmatic anisometropia and strabismus, and the other with strabismus alone. No correlations were found between orbital morphology or volume and subnormal vision. At follow-up, two additional cases of subnormal vision emerged—one related to new-onset strabismus, and the other to a combination of anisometropia and strabismus. Subnormal vision was associated with oval, vertically compressed orbital shapes (PC1-) and increased contralateral globe:orbit volume ratios.

Discussion

This thesis presents a comprehensive evaluation of ophthalmological outcomes, i.e. visual function, refraction, strabismus, and fundus changes, in children operated on for various types of non-syndromic craniosynostosis. Unlike previous studies, which primarily focused on selected subtypes, short-term outcomes, or relied on retrospective analyses, the present work is, to our knowledge, the first to systematically assess the full spectrum of non-syndromic craniosynostosis subtypes both pre-operatively and in the early post-operative period, with follow-up extending to 5 years of age. Importantly, quantitative volumetric orbital analysis based on CT imaging was incorporated to explore structural–functional correlations, offering novel insights into the relationship between craniofacial morphology and ophthalmological outcomes. The findings indicated that both the presence and severity of ophthalmic abnormalities vary by craniosynostosis subtype. Children with sagittal craniosynostosis exhibited a low prevalence of ophthalmic problems, while those with unicoronal craniosynostosis showed consistently higher rates of abnormalities throughout the study period.

In the first study, the timing of ophthalmological examinations varied among participants, reflecting differences in the timing of surgical treatment. At the Uppsala Craniofacial Centre, sagittal craniosynostosis is typically treated early, between 3 and 6 months of age, whereas metopic and unicoronal subtypes are usually operated between 6 and 18 months to reduce the risk of recurrence.

Refractive values were relatively similar across subtypes pre-operatively, with high rates of hypermetropia and astigmatism observed, as expected (see Background; Refractive development in the paediatric population), except for anisometropia, which was more frequently seen in the unicoronal group, in line with previous findings (Tarczy-Hornoch et al. 2008; MacIntosh et al. 2007; Levy et al. 2007; Gupta et al. 2003). At the first post-operative follow-up, anisometropia and astigmatism persisted in the unicoronal group but decreased in other subtypes. This contrasts with the findings of Vasco et al. (2008), who reported no significant changes in refractive error following surgery. By the 5-year follow-up, significant differences in refractive profiles were evident between craniosynostosis subtypes. In the metopic group,

hypermetropia was notably prevalent, consistent with MacIntosh et al. (2011). However, other studies have reported higher prevalence of astigmatism (Dennis et al. 1996; Nguyen et al. 2014) and, in our cohort, astigmatism was indeed more common in the metopic group compared with the sagittal group. These discrepancies may reflect differences in the age distribution between study populations. The unicoronal group continued to show high rates of hypermetropic anisometropia and astigmatism, predominantly affecting the eye contralateral to the fused suture. This pattern is consistent with previous literature (MacIntosh et al. 2007; Levy et al. 2007; Luo et al. 2020; Touze et al. 2022; Rostamzad et al. 2023) and is likely attributed to orbital deformation affecting corneal curvature. Furthermore, fronto-orbital advancement (FOAR), the standard surgical intervention for unicoronal synostosis, addresses cranial asymmetry, but does not fully correct orbital asymmetry (Lif et al. 2023), potentially explaining the persistence of refractive abnormalities (Tarczy-Hornoch et al. 2008; Song et al. 2016; Gencarelli et al. 2016; Elhusseiny et al. 2021).

Compared with the control group, children with non-syndromic craniosynostosis exhibited a higher prevalence and higher values of refractive errors at age 5, with the exception of the sagittal group, whose refractive values were comparable to those of the controls. Although the control group was relatively small, the refractive outcomes were consistent with normative data for age-matched children reported in other studies (Grönlund et al. 2006; Hellgren et al. 2016).

Strabismus was more prevalent in our cohort than in the general population (approximately 2%, Hashemi et al. 2019), both pre-operatively and at 6–12 months post-operatively. The observed rates remained higher at the 5-year follow-up, compared both with our control group and with findings from population studies of age-matched children (Grönlund et al. 2006). This was primarily driven by the higher prevalence of strabismus in children with unicoronal craniosynostosis. Pre-operatively, four out of 16 children with unicoronal craniosynostosis presented with strabismus, exotropia or mixed horizontal and vertical deviations. At the first post-operative examination, strabismus persisted in all affected children, although the vertical component resolved in one case. These findings are consistent with previous reports (Bennet KG et al. 2019; Gupta et al. 2003; Denis, Genitori, Bolufer, et al. 1994; Chieffo et al. 2020; MacIntosh et al. 2007; Rostamzad et al. 2023). Furthermore, two new cases of strabismus emerged shortly after FOAR surgery, and five additional cases developed between the first postoperative examination and the 5-year follow-up. Therefore, by 5 years of age, 10 out of 14 children had strabismus, most commonly exotropia with a vertical component. These findings align

with literature reporting iatrogenic strabismus following FOAR (Lee et al. 2008; Samra et al. 2015; Yu et al. 2020; Gencarelli et al. 2016).

The most frequent vertical deviation seen in our study was hypertropia of the eye ipsilateral to the fused suture, a pattern also observed in previous studies (Song et al. 2016; Luo et al. 2020; Rafique et al. 2022; Elhusseiny et al. 2021; Touze et al. 2022). This has been attributed to both orbital dysmorphology and to surgical factors. A systematic review by Gencarelli et al. (2016) concluded that FOAR does not significantly reduce strabismus rates and may, in fact, contribute to its development through periorbital remodelling. Alterations in the trochlea and oblique muscle positioning during surgery may induce motility abnormalities resembling trochlear nerve palsy. These findings support the need for surgical innovations aimed at minimising disruption of orbital structures. Earlier surgical intervention using less invasive techniques has been proposed as a potential strategy to reduce the risk of iatrogenic strabismus (Tahiri et al. 2015).

In contrast, no child with metopic craniosynostosis in our cohort had strabismus pre-operatively. One child developed strabismus by the first post-operative examination but failed to comply with orthoptic evaluation at the 5-year follow-up; therefore, strabismus could not be confirmed. Other studies have similarly reported low strabismus rates in this subgroup (Gupta et al. 2003; Denis, Genitori, Conrath et al. 1994; Chieffo et al. 2020), although higher rates have also been documented (Nguyen et al. 2014; MacIntosh et al. 2011), suggesting variability across cohorts. In our sagittal craniosynostosis group, three of 79 children, all of whom were under 3 months of age, showed exodeviation pre-operatively. These cases resolved by the time of the first post-operative assessment. Given the early age and known tendency for transient exodeviation in infancy (Archer et al. 1989), these findings likely reflect normal ocular development rather than surgical influence. At the 5-year follow-up, only one child exhibited intermittent exotropia. This is consistent with previous studies reporting a low strabismus prevalence in sagittal craniosynostosis (Gupta et al. 2023). Chieffo et al. (2020) reported three new cases of post-operative exotropia among 45 sagittal patients; however, the age at examination and type of surgery were not specified.

Visual acuity (VA) was generally within the normal range for age across the cohort in our first study, consistent with findings by Vasco et al. (2008). Nonetheless, previous research has highlighted an increased risk of amblyopia in children with unicoronal craniosynostosis (MacIntosh et al. 2007; Tarczy-Hornoch et al. 2008), primarily due to high refractive errors and strabismus. In our cohort, only children with unicoronal and metopic craniosynostosis required early treatment with occlusion therapy and corrective spectacles, while

no children with sagittal craniosynostosis required such interventions. At the 5-year follow-up, visual outcomes remained generally good, although distance VA was reduced in children with unicoronal synostosis, particularly in the eye contralateral to the fused suture. Statistical analyses confirmed that refractive errors and strabismus had a significant negative effect on VA, supporting the presence of amblyogenic mechanisms. Amblyopia associated with strabismus and/or anisometropia was identified in 31% (4/13) of cases, in line with previous findings (Touze et al. 2022; Levy et al. 2007). Interestingly, no amblyopia was observed in the metopic group, despite the high rates of hypermetropia, unlike previous studies (Nguyen et al. 2014; Roider et al. 2021). This discrepancy may be explained by differences in age distribution or by earlier correction with spectacles in our cohort, which likely helped prevent amblyopia.

By the age of 5, improved cooperation enabled a more comprehensive evaluation of visual function, including distance and near VA, low contrast visual acuity (LCVA), stereopsis, colour vision, and crowding. Binocular near VA was generally lower in the craniosynostosis group compared with controls. Notably, most children with reduced near VA did not have strabismus or refractive errors, suggesting a possible direct effect of craniosynostosis on near VA, or a role of reduced accommodation; although, this was not specifically assessed in the study. LCVA was largely preserved across the cohort; however, children with unicoronal craniosynostosis demonstrated both lower LCVA values and a higher prevalence of subnormal LCVA (>0.4 logMAR), primarily in the eye contralateral to the fused suture. Statistical associations between LCVA, refractive error, and strabismus pointed to amblyogenic factors rather than optic neuropathy or neuro-ophthalmological causes as the primary contributors. Stereopsis was significantly impaired or absent in a number of children with unicoronal synostosis, most likely due to associated strabismus, while colour vision remained unaffected across all subtypes.

Crowding is a developmental phenomenon in healthy young children and a characteristic of amblyopic eyes (see Background; Visual development and amblyopia), but it has also been linked to white matter lesions and dysfunction in the dorsal visual stream (Jakobson et al. 2002). In our study, a crowding ratio >1.2 was more frequently observed in the craniosynostosis group, despite the absence of amblyopia. Current understanding suggests that single-suture craniosynostosis may have a negative impact on visuospatial processing during the preschool years; however, differences among subtypes of craniosynostosis and the persistence of these effects into adulthood remain inadequately understood (Olsson et al. 2023).

Optic disc oedema or pale discs can be a sign of elevated intracranial pressure. In this cohort, no cases of optic disc oedema or pallor were identified on fundoscopy pre-operatively or within the first 6–12 months post-surgery. Similar findings have been reported by Bennet KG et al. (2019). In contrast, Chieffo et al. (2020) described pre-operative optic disc pallor in 51 out of 142 children with non-syndromic craniosynostosis, which persisted in only four cases post-operatively (two sagittal, two metopic), with no new cases reported. This variability may reflect the subjective nature of fundoscopy, which is influenced by examiner expertise and technique. At long-term follow-up, at 5 years, no optic nerve abnormalities were observed, although three children with sagittal craniosynostosis had required reoperation due to raised intracranial pressure (ICP), with papilloedema detected in only one case. In two of these cases, secondary closure of previously unaffected coronal sutures was confirmed on CT. These findings are consistent with the limited sensitivity of optic disc changes as indicators of raised ICP in young children. In a prospective study of 122 patients with craniofacial syndromes, by Tuite et al. (1996), reported that papilloedema was present in only 32% of patients with ICP >15 mmHg, with sensitivity increasing with age from 22% in younger children to 100% in those over 8 years. This may be due to greater cranial compliance in infants or reduced communication between the subarachnoid space and the optic nerve sheath. To summarise, these findings highlight the limitations of fundoscopy in detecting elevated ICP in early childhood and support the need for more objective and sensitive tools in routine follow-up.

In our final study, we investigated the relationship between ophthalmological outcomes (strabismus, refractive errors, anisometropia, and subnormal vision) and variations in orbital morphology and globe:orbit volume ratios in patients with unicoronal craniosynostosis undergoing FOAR. A key finding was the association between improved orbital symmetry post-operatively and the development of new-onset strabismus. This suggests that anatomical correction alone does not necessarily ensure functional ocular alignment, especially in cases requiring substantial orbital reshaping. Strabismus occurred both in cases with and without post-operative symmetry improvements, indicating multifactorial underlying mechanisms. Pre-operatively, contralateral strabismus was associated with a lower globe:orbit volume ratio and a diagonal orbital shape. Post-operatively, however, contralateral strabismus was more often linked to a higher globe:orbit ratio and vertically compressed orbital shapes. These contrasting associations imply that different mechanisms contribute to extraocular muscle imbalance before and after surgery. Together, these findings emphasize the complex nature of strabismus in UCS and

highlight the limitations of unilateral surgical approaches in achieving symmetrical and functional outcomes.

The study also supports the hypothesis that orbital morphology influences refractive errors, particularly hypermetropia and astigmatism. Vertically elongated orbits tended to associate with persistent ipsilateral hypermetropia, while contralateral hypermetropia post-operatively was more common in orbits with diagonal or small, rounded shapes. These changes likely reflect disturbances in normal ocular growth and axial length development, thereby interfering with the emmetropisation process. The characteristic ipsilateral Harlequin deformity appeared to contribute to with-the-rule astigmatism, possibly due to superolateral orbital elevation altering corneal curvature. However, astigmatism was also observed contralaterally despite relatively normal orbital morphology, suggesting differing mechanisms. A smaller globe:orbit volume ratio was associated with with-the-rule astigmatism, while oblique astigmatism was linked to larger ratios. Given that both orbits are generally smaller in UCS, these findings point to orbital size and shape as significant contributing factors. Astigmatic anisometropia was more common in patients with orbital asymmetry, particularly pre-operatively. Interestingly, while improved post-operative orbital symmetry corresponded with a reduction in anisometropia, it was also associated with an increased risk of developing strabismus, highlighting the complex interaction between anatomical and functional outcomes.

Finally, subnormal vision was observed more frequently on the contralateral side, particularly post-operatively, and was often associated with strabismus or a combination of strabismus and anisometropia. These visual deficits were linked to oval or vertically compressed orbits and higher globe:orbit ratios, features that were also associated with contralateral strabismus. Together, all the above findings suggest that specific orbital morphologies and volume ratios may predispose children with UCS to ophthalmological dysfunction.

Conclusions

- Children with non-syndromic craniosynostosis were at increased risk of ophthalmological disorders, with various craniosynostosis subtypes demonstrating different ophthalmological outcomes.
 - Unicoronal craniosynostosis (UCS) was most strongly associated with ophthalmological complications. Hypermetropia and astigmatism were more prevalent, especially in the eye contralateral to the fused suture. UCS also showed consistently higher rates of anisometropia (both spherical and astigmatic) and strabismus throughout the study period. Notably, some children developed strabismus after surgical intervention.
 - Metopic craniosynostosis was mainly linked to hypermetropia, but few other ophthalmological abnormalities were observed.
 - Sagittal craniosynostosis did not significantly increase the risk of refractive errors or strabismus.
- Regarding visual function, children with craniosynostosis, particularly those with UCS, had reduced distance Visual Acuity, Low Contrast Visual Acuity, and stereoacuity. These impairments were largely attributed to the increased prevalence of strabismus and refractive errors, especially in the eye opposite to the fused suture. In contrast, visual outcomes in children with sagittal craniosynostosis were comparable to those of controls, indicating a more favourable prognosis. Near binocular visual acuity differed between all craniosynostosis subtypes and the control group, with crowding being more common in the sagittal craniosynostosis.
- Analysis of orbital morphology in UCS revealed associations between orbital shape and strabismus (both pre- and post-operatively), as well as with ipsilateral and contralateral astigmatism. Improved orbital symmetry following surgery correlated with reduced, yet persistent astigmatic anisometropia, but also with new-onset strabismus.

- Fronto-orbital advancement and remodelling (FOAR), remains the most common surgical approach for UCS; however, it may not fully correct orbital deformity and appears to contribute to the development of post-operative strabismus.
- Optic disc oedema or pallor, as signs of elevated intracranial pressure, were rare in this cohort, both before and after surgery.

Reflections and methodological considerations

The present thesis provides valuable insights into the ophthalmological outcomes of children with non-syndromic craniosynostosis, an area with previously limited systematic data, through its prospective, longitudinal design and multidisciplinary approach at one of Sweden's national craniofacial centres. By assessing patients pre- and post-operatively and following them to pre-school age, the study offers a rare, systematic evaluation across all non-syndromic craniosynostosis subtypes. The inclusion of functional vision tests and CT-based orbital morphology analysis adds depth to the clinical findings and enables exploration of structure-function relationships. Comparisons with an age-matched control group further enhance the relevance of the results in the context of normal development.

Some limitations should be acknowledged, including the variable ages at pre-operative assessment, post-operative follow-ups conducted at multiple centres, a reduced cohort size at the 5-year follow-up, and a relatively small control group. These limitations, however, reflect the practical and ethical constraints inherent in conducting long-term paediatric research. Furthermore, the small sizes of certain subgroups within the study group reflect the natural prevalence of craniosynostosis types, where sagittal synostosis accounts for almost half of all cases. Despite these challenges, standardised protocols, expert examiners, and reference to population data helped to ensure the reliability of the findings.

Overall, this thesis highlights the critical relationship between craniosynostosis subtype and ophthalmological outcomes following surgical correction. Children with unicoronal craniosynostosis exhibited the highest prevalence of visual complications, while sagittal craniosynostosis was associated with minimal ophthalmic risk. Surgical techniques such as FOAR improved orbital symmetry but did not fully resolve functional deficits and, in some cases, contributed to new ocular imbalances. The findings emphasise the importance of subtype-specific screening and follow-up protocols. Early and tailored ophthalmological evaluation, particularly for children with unicoronal and metopic craniosynostosis, is essential for timely intervention and prevention of long-term visual impairment. Continued refinement of surgical

strategies, and ongoing longitudinal studies, will be the key to optimising both morphological and functional outcomes in this patient population.

Future perspectives

The early identification of elevated intracranial pressure (ICP) in children with craniosynostosis remains a clinical challenge, particularly given the limited sensitivity of fundoscopy in younger patients. Future analyses will investigate the potential of optical coherence tomography (OCT) as a non-invasive, objective tool for detecting ICP-related changes in the optic nerve and retina. Specifically, peripapillary retinal nerve fibre layer (RNFL) and macular thickness measurements obtained at the 5-year follow-up have already been collected and will be analysed in comparison with age-matched controls and normative paediatric data. Special attention will be given to children with sagittal synostosis who subsequently developed secondary fusion of previously unaffected coronal sutures, as this subgroup may provide further insights into progressive ICP-related changes.

In addition, long-term ophthalmological data, including visual function, refractive errors, strabismus, and OCT-derived structural parameters, have been collected at 8 years of age, when cranial growth is considered complete. At this age, visual function parameters can also be correlated with results of psychological assessments to better understand the neurodevelopmental impact of this condition.

These forthcoming analyses aim to enhance our understanding of the long-term visual impact of craniosynostosis and to guide the development of more refined, evidence-based follow-up protocols.

Populärvetenskaplig sammanfattning

Kraniosynostos, innebär att en eller flera av skallens tillväxtzoner (suturer) sluts för tidigt. Detta kan leda till förändringar i både skallens och ögonhålans form, vilket i sin tur kan påverka syn och ögonfunktion. Även om orsaken till stor del är okänd, kan tillståndet bero på genmutationer eller ingå som del i ett syndrom. Syndromformer är förknippade med störst risk för allvarliga komplikationer, men även de vanligare, isolerade formerna, så kallad icke-syndromal kraniosynostos, som vanligtvis involverar en enskild sutur utan samtidigt genetiskt syndrom eller ytterligare missbildningar, kan medföra risk för ögonproblem beroende på vilken sutur som är påverkad.

Denna avhandling omfattar barn med olika former av icke-syndromal kraniosynostos som opererats vid Uppsala kraniofaciala centrum, Akademiska sjukhuset, mellan 2012 och 2019. Syftet var att systematiskt utvärdera synfunktion, brytningsfel, skelning och förändringar i ögonbotten hos dessa barn, både före och efter operation, samt att följa utvecklingen upp till förskoleåldern och jämföra resultaten med en kontrollgrupp bestående av friska, åldersmatchade barn. Dessutom analyserades ögonhålornas form och volym med datortomografi för att undersöka samband mellan morfologi och ögonproblem, särskilt vid unikoronaria synostos, som är förknippad med högre risk för ögonbesvär.

Resultaten visade tydliga skillnader mellan de olika formerna av kraniosynostos:

- Sagittalis synostos, den vanligaste typen, var associerad med låg risk för synnedsättning, brytningsfel och skelning. Resultaten var jämförbara med dem hos friska barn.
- Metopika synostos var förknippad med en högre förekomst av över-synthet (hypermetropi).
- Unikoronaria synostos innebär störst risk för kvarstående astigmatism, skillnader mellan ögonen (anisometropi) och skelning, både före och efter operation. Nya fall av skelning kunde också uppstå efter kirurgi. Dessa barn hade även sämre synskärpa och stereoseende, framför allt på det öga som låg mot motsatt sida av den slutna suturen.

Analys av ögonhålornas form hos barn med unikoronaria synostos visade att olika orbitaformer var kopplade till skelning och astigmatism, både före och efter operation. Den vanligaste kirurgiska metoden (FOAR) korrigerade inte alltid dessa förändringar fullt ut och kunde i vissa fall leda till nya synproblem.

Dessutom, förändringar i ögonbotten såsom svullnad eller blekhet på synnerven var ovanliga mellan olika former av kraniosynostos, både före och efter operationen.

Resultaten tyder på att barn med sagittalis synostos inte behöver lika tät ögonuppföljning som man tidigare trott, medan barn med unikoronaria synostos behöver noggrannare och mer individanpassad kontroll. Fynden indikerar även att dagens kirurgiska metoder kan behöva utvecklas för att bättre korrigera ögonhålornas form och därmed minska risken för ögonproblem.

Sammanfattningsvis bidrar denna avhandling med ny kunskap om hur ögonens utveckling påverkas vid olika former av icke-syndromal kraniosynostos och visar att uppföljning och behandling bör anpassas utifrån vilken sutur som är påverkad. Detta kan leda till förbättrad vård och förbättrad synfunktion för barn med detta tillstånd.

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