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Craniosynostosis: State of the Art 2019

Ophthalmological management in craniosynostosis

R. Touzé [a,*], D. Bremond-Gignac [a], M.P. Robert [a,b]

[a] Ophthalmology Department, Necker Enfants Malades University Hospital, AP–HP, 149 Rue de Sèvres, 75015 Paris, France
[b] COGNAC-G, UMR 8257, CNRS - SSA–Université de Paris, Paris 75006, France

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ABSTRACT

Introduction. – In published series, a large proportion of patients with craniosynostosis show impaired vision.
Materials and methods. – A literature review was performed, using the PubMed and Google Scholar databases, to identify original and review articles on the consequences of craniosynostosis on the eyes and visual pathways, and on the ophthalmological management of craniosynostosis.
Results and discussion. – Many ophthalmic, potentially sight-threatening, complications, can occur in patients with craniosynostosis, especially when syndromic. Optic neuropathy, mostly resulting from the papilledema-optic atrophy sequence, secondary to raised intracranial pressure (ICP), should be diagnosed early, in order to promptly lower the ICP. Cyclovertical and horizontal strabismus and refractive errors are frequent in unicoronal synostosis (anterior plagiocephaly) and syndromic craniosynostosis. Exorbitism, encountered in some cases of syndromic craniofacial synostosis, leads to exposure keratopathy, which requires aggressive management to avoid severe irremediable corneal complications. Amblyopia can result from optic neuropathy, corneal opacities, strabismus, or refractive errors. If undiagnosed and untreated at a young age, it results in permanent visual impairment.
Conclusion. – Children with craniosynostosis require a multidisciplinary care network including a pediatric ophthalmologist. Systematic ophthalmological follow-up enables papilledema to be diagnosed and amblyopia to be diagnosed and treated, in order to avoid visual impairment.

1. Introduction

Children with craniosynostosis require a multidisciplinary care network including many specialists and paramedics. Ocular complications are very frequent in children with craniosynostosis, optic neuropathy, strabismus, refractive disorders, corneal injury and amblyopia being the most frequent. The ophthalmologist has to follow these patients:

- firstly, to help diagnose intracranial pressure elevation;
- secondly, to prevent, diagnose and treat amblyopia, as treatment is possible only during childhood – and the earlier the better;
- finally, to manage the specific ocular complications of craniosynostosis.

This review presents the most common ophthalmological complications encountered by these children and the investigations that are needed in their management.

2. Methods

A PubMed and Google Scholar literature review was carried out, selecting all relevant articles in English or French focusing on ophthalmological involvement in craniosynostosis, using the search-terms: “ocular”, or “ophthalmological”, or “papilledema”, or “strabismus”, and “craniostenosis” or “craniosynostosis” or “anterior plagiocephaly”.

3. Results and discussion

3.1. Complications of craniosynostosis in the eyes and visual pathways

3.1.1. Optic neuropathy

Around 65% of children with syndromic craniosynostosis have at least one eye with visual acuity equal to, or less than 20/40, including 40% in the better eye [1]. Optic neuropathy is the most

* Corresponding author.
E-mail addresses: r.touze.rt@gmail.com (R. Touzé), dominique.bremond@aphp.fr (D. Bremond-Gignac), matthieu.robert@aphp.fr (M.P. Robert).

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common ophthalmologic complication, after amblyopia, in children with craniosynostosis [2]. However, complications very much depend on the type of craniosynostosis and are much more severe and frequent in cases of syndromic craniosynostosis.

Several mechanisms can lead to optic neuropathy in these patients. Above all, chronic elevated intracranial pressure (ICP) will cause papilledema, which can result in optic nerve atrophy. Although the risk of elevated ICP depends on type of craniosynostosis and is highest in Crouzon syndrome, oxycephaly and Apert syndrome [3], it is present in all cases, and around 30% in syndromic craniosynostosis [4]. Compression or even chronic elongation of the optic nerves within the orbit or optic canal may also contribute to optic atrophy. The name "papilledema" is actually not appropriate to designate the ongoing phenomenon: there is no true edema, but rather a swelling of the axons of the ganglion fibers in the optic disk: i.e., the most anterior, intraocular portion of the optic nerve, also called the prelaminar region because it is located anteriorly to the lamina cribrosa, a sheet of collagen pierced by numerous orifices allowing the retinal axons and retinal vessels to pass through [5]. The role of the lamina cribrosa is to protect nerve structures from pressure gradients between the intra- and extra-ocular compartments of the optic nerve. Prelaminar axonal lesions, whatever the mechanism, can lead to a slow down of cytoplasmic transport, resulting in accumulation of toxic substances responsible for the axonal swelling [5]. In papilledema, elevated ICP is reflectedwithin the sheath of the optic nerve, leading to dilation and tortuosity of these sheaths (a good sign of elevated ICP on MRI). An imbalance is created between intra- and extra-ocular pressure (also called the translaminar pressure gradient), resulting in the prelaminar axonal injuries that lead to papilledema [6].

Any papilledema should be graded according to two classifications: the quantitative Frisén staging, (Table 1 [7]), and the Hoyt & Beesten progression staging (early, fully developed, chronic, atrophic). As soon as feasible, the papilledema should also be documented by pictures and quantified using optical coherence tomography (OCT) (see below). In papilledema, the risk of atrophy depends on two criteria: papilledema stage and duration. A minimal, Frisén stage 1 or 2 papilledema, can be tolerated with no functional consequences for several months or even years. Conversely, an untreated, Frisén stage 5 papilledema, can result in irreversible destruction of the optic nerve fibers within a few days; lowering ICP is then a true emergency. For papilledema of intermediate severity, prognosis mostly depends on duration (Fig. 1A & B).

In case of optic atrophy, absence of papilledema is much less contributive than usual in ruling out elevated ICP: destroyed ganglion fibers can no longer swell; the papilledema may then be minimal or absent, and therefore difficult or impossible to diagnose clinically or even with the help of OCT.

Table 1
Papilledema Grading System (Frisen Scale) [7].

Stage 0 - Normal Optic Disc. Blurring of nasal, superior and inferior poles in inverse proportion to disc diameter. Radial nerve fiber layer (NFL) without NFL tortuosity. Rare obscuration of a major blood vessel, usually on the upper pole
Stage 1 - Very Early Papilledema. Obscuration of the nasal border of the disc. No elevation of the disc borders. Disruption of the normal radial NFL arrangement with grayish opacity accentuating nerve fiber layer bundles. Normal temporal disc margin. Subtle grayish halo with temporal gap (best seen with indirect ophthalmoscopy). Concentric or radial retrochoroidal folds
Stage 2 - Early Papilledema. Obscuration of all borders. Elevation of the nasal border. Complete peripapillary halo
Stage 3 - Moderate Papilledema. Obscurations of all borders. Increased diameter of optic nerve head. Obscuration of one or more segments of major blood vessels leaving the disc. Peripapillary halo-irregular outer fringe with finger-like extensions
Stage 4 - Marked Papilledema. Elevation of the entire nerve head. Obscuration of all borders. Peripapillary halo. A combination with obliteration of the optic cup, or compression of the cup to a slit, or total obscuration of a segment of the major blood vessel.
Stage 5 - Severe Papilledema. Dome-shaped protrusions representing anterior expansion of the optic nerve head. Peripapillary halo is narrow and smoothly demarcated. Total obscuration of a segment of a major blood vessel may or may not be present. Obliteration of the optic cup

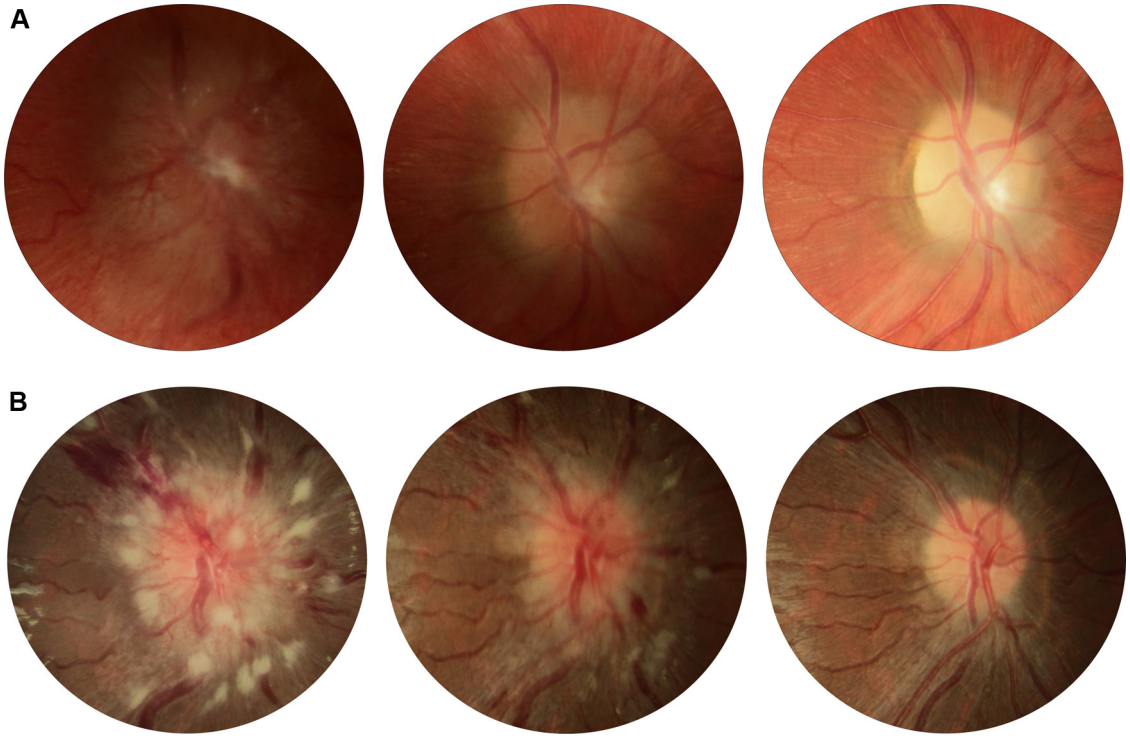


Fig. 1. A. Natural history of a chronic and severe papilledema: day-0 (Hoyt Stage 3, Frisén stage 4); 3 weeks later: major decrease of the papilledema; 2 months later: residual optic atrophy (pale optic disk). B. Natural history of an acute and severe papilledema: day-0 (Hoyt stage 2, Frisén stage 4); 2 weeks later: major decrease of the papilledema; 4 weeks later: resolution, without residual optic atrophy (pink healthy optic disk).

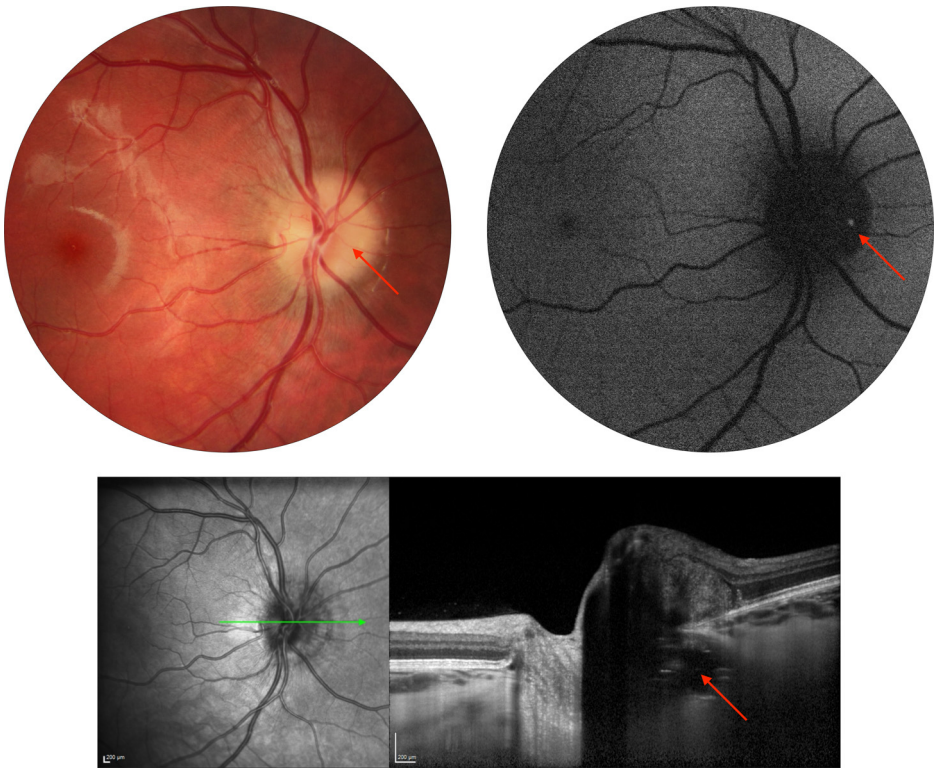


Fig. 2. Typical case of pseudo-papilledema secondary to optic nerve drusen in a 7 year-old child: top left: fundus picture; top right: fundus autofluorescence (FAF) showing small spontaneous hyperautofluorescence; bottom: OCT showing a hyporeflective round lesion – the buried drusen. This is a typical, illustrative case of lage drusen in a child. In a younger child, differential diagnosis with true papilledema is often more difficult.

Box 1: Diagnosis of papilledema

It is difficult to distinguish between optic disk swelling due to raised ICP (called papilledema) and swollen or elevated optic disk due to other causes, often called pseudo-papilledema, most often related to the presence of optic disk drusen, or druses (Fig. 2). Optic disk drusen consist in a very slowly progressive accumulation of cytoplasmic material that is associated with peculiar constitutional features of the optic disk. They increase very gradually in size and are slowly superficialized with age, becoming easy to diagnose in adulthood. In children, optic disk drusen are frequently buried; it is not possible to visualize them ophthalmoscopically and additional investigations do not always formally distinguish between optic disk drusen and papilledema. Diagnosis is based on a set of arguments summarized in Table 2. It is usually not necessary to perform all of the examinations listed in Table 2 to make the diagnosis.

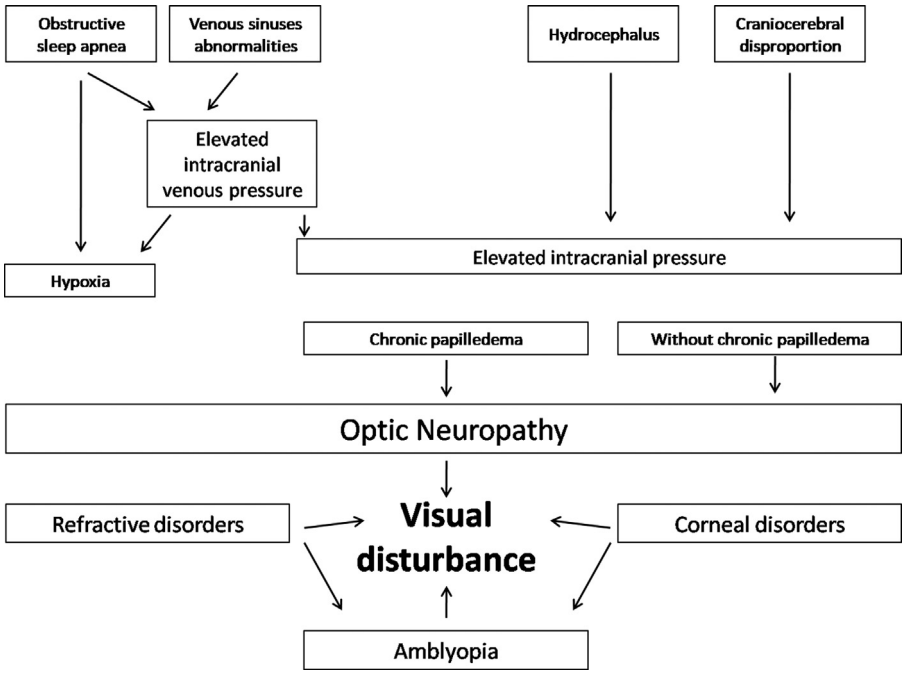
Table 2
Multimodal imaging helping diagnosis between papilledema and pseudo-papilledema.

Examinations	Results for diagnosis of papilledema	Results for diagnosis of pseudopapilledema
Fundoscopy/ retinophotography	Swelling of the peripapillary nerve fiber layer causes an obscured view of underlying retinal vessels Disappearance of the spontaneous venous pulsation	Vessels in the peripapillary nerve fiber layer remain visible
Fundus autofluorescence	Spontaneous autofluorescence	Focal hyperautofluorescence from drusen
B-scan	Superficial hyperechoic signal	Deep hyperechoic signal
Fluorescein angiography	Capillary leakage	No capillary leakage

The question of the sensitivity of papilledema in the diagnosis of raised ICP is complex and hotly debated. Papilledema is, by definition, specific to raised ICP: once the differential diagnoses of optic disk swelling have been eliminated (which is easy in case of severe papilledema or recent papilledema with previously documented normal disks, but often difficult in case of moderate edema; see Box 1), its presence indicates elevated ICP. However, papilledema does not seem to be a good way of detecting elevated ICP, particularly in patients with syndromic craniosynostosis, as some studies reported sensitivity no greater than 17–40% [8,9]. Absence of papilledema therefore does not formally exclude elevated ICP [10,11]. FGFR2 mutations are involved in syndromic craniosynostosis. As FGFR2 is expressed during the development of the fetal orbit within the muscular and cartilaginous structures and in the optic nerve sheaths [12], FGFR2 mutation may lead to structural abnormalities of the lamina cribrosa, which could alter the relation between translaminar pressure gradient and papilledema [10].

Although the presence of papilledema is not a very sensitive sign of elevated ICP, particularly in syndromic craniosynostosis, it is nonetheless a key element in follow-up: papilledema is the main provider of optic neuropathy, and therefore a main cause of low vision visual impairment, in these children. Moreover, papilledema may not be associated with other clinical signs of raised ICP in these children [13]. Therefore, papilledema is, per se, one of the most important factors in the decision to treat.

Respiratory disorders are also involved in the pathogenesis of optic neuropathy in patients with syndromic craniosynostosis. Facial and respiratory malformations can lead to severe obstructive apnea, aggravating elevated ICP and optic neuropathy.



Summary of visual disorders in craniosynostosis. From Nischal K., 2014.

3.1.2. Oculomotor disorders

Oculomotor disorders are very common in these patients, and vary according to the type of craniosynostosis [14,15]. They are frequent in unicoronal synostosis and in syndromic craniosynostosis, where prevalence of strabismus is estimated between 40 to 70% [1,2].

Typically, strabismus in craniosynostosis is primarily characterized by a vertico-torsional component, and a variable horizontal component. The vertico-torsional component is often very visible; it constitutes a particular oculomotor syndrome, which could be referred to as "excyclotorsional syndrome": it associates excyclotorsion of the eyeball (which all other signs result from), best seen on fundus image (Fig. 3), ocular elevation in adduction movements, ocular lowering in abduction movements, and a V-pattern (eyes are further apart upward than downward) (Figs. 4–6). The inconstant horizontal component, either associated with the excyclotorsional syndrome or isolated, most frequently consists in exotropia (divergent strabismus) [2,16]. This syndrome is usually unilateral, on the side of the synostosis, associated with head tilt toward the contralateral shoulder, in unicoronal synostosis [17], and bilateral, and often spectacular, in syndromic craniosynostosis [18]. In unicoronal synostosis, it may be present either before or only after conventional fronto-orbital advancement [19].

The mechanisms are complex and mostly depend on the orbital involvement of the craniosynostosis. In unicoronal synostosis, strabismus is induced by excyclorotation of the oculomotor recti muscles and an abnormal position of the trochlea of the superior oblique within the orbit [20,21]. The shape of the orbit is determinant for extra-ocular muscle (EOM) functioning. In addition, fibrosis or absence of the EOMs can be encountered in syndromic craniosynostosis [22,23]. This strabismus has two major consequences: esthetic blemish, and amblyopia (see below).

3.1.3. Refractive disorders

Refractive disorders are more frequent in children with craniosynostosis than in the normal age-matched population. A large series of 141 children with syndromic craniosynostosis found 40% with more than 1 diopter astigmatism in at least one eye.

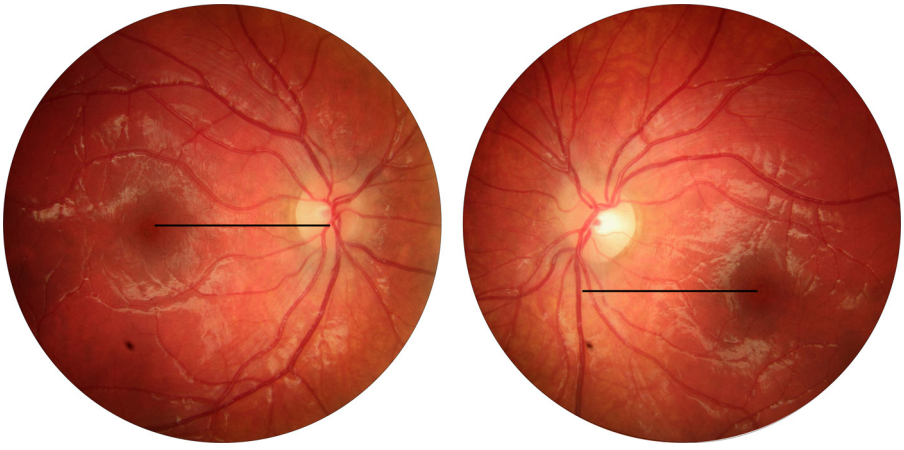


Fig. 3. Fundus appearance in a left excyclotorsional syndrome: the horizontal line from the fovea should normally intersect the inferior third of the optic disk, as in the right eye depicted in the left panel. In the left eye (right panel), this line is far below the optic disk.

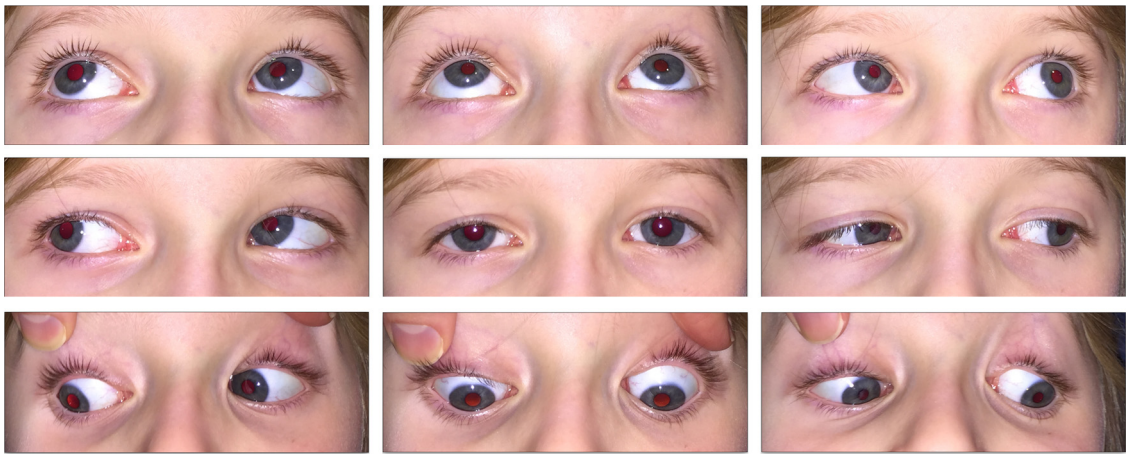


Fig. 4. Typical example of a unilateral excyclotorsional syndrome in a child with left unicoronal synostosis: ocular elevation in adduction of the left eye (in rightward gaze); as the left eye is displaced upward, the corneal light reflex is displaced downward. There is a moderate V-pattern: the eyes go further apart in upgaze (as the left eye moves laterally, the corneal light reflex is moved medially).

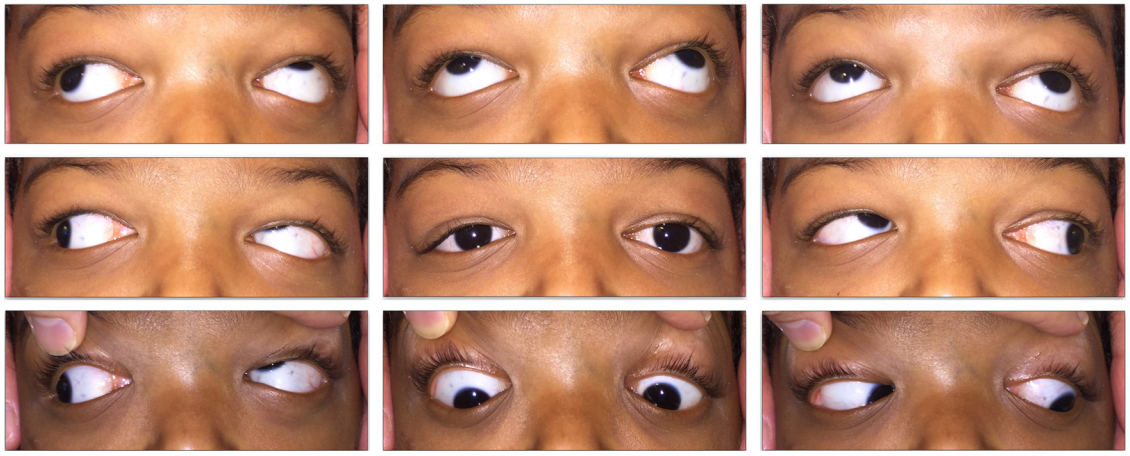


Fig. 5. Typical example of a severe bilateral excyclotorsional syndrome in a syndromic craniosynostosis: bilateral ocular elevation in adduction: the right eye is displaced upward in leftward gaze; the left eye is displaced upward in rightward gaze. There is a severe V-pattern.

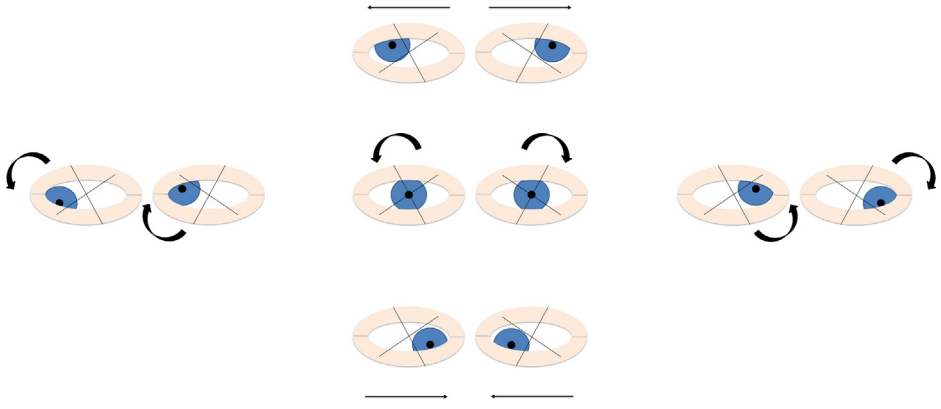


Fig. 6. Schematic drawing of eye-ball excyclotorsion and its consequences in eye versions, constituting the "excyclotorsional syndrome".

Anisometropia (difference in refraction between the two eyes) was found in 18% of patients, versus 3.5% in the normal population [1].

Patients with unicoronal synostosis have a high risk of amblyopia, usually in the eye contralateral to the synostosis, due to a high prevalence of astigmatism, secondary to the deformation of the orbit contralateral to the synostosis [24]. Anisometropia is highly amblyogenic and should be screened for by systematic refraction examination every 6 months in young children, and then every year until 9 years of age.

3.1.4. Corneal disorders

Exposure keratopathy is a severe complication that needs to be avoided. Without regular blinks to spread tears, the corneal surface quickly suffers. The first signs are redness, ocular pain and photophobia. If left untreated, exposure keratopathy leads from

superficial punctate keratopathy to corneal ulcer, which carries a risk of white corneal scar, corneal abscess and, more rarely, eye-ball perforation and infection (endophthalmitis). It is the main cause of corneal injury related to craniosynostosis [25]. It occurs preferentially in case of exorbitism, more frequently found in syndromic craniosynostosis. Craniofacial surgery is an at-risk time for the cornea because of the increased exophthalmos associated with postoperative edema. Spontaneous dislocation of the eye-ball is an extreme situation, mainly encountered in Crouzon syndrome: the eye-ball spontaneously shifts in front of the plane of the eyelids, when the infant cries for example; it may then either remain dislocated or return to positon. This situation is a medical and surgical emergency: the cornea suffers and the optic nerve is distended.

In children with syndromic craniosynostosis, lagophthalmos (incomplete palpebral closure), including during the night, should be looked for. Prevention of exposure keratopathy (and treatment in cases of little severity) is based on long-course lubricant eye drops (artificial tears) regularly instilled during the day and eye ointment with vitamin A at bedtime. In selected cases (especially in postoperative follow-up or in case of eye-ball dislocation), lateral tarsorrhaphy (suture of the lateral lower and upper eyelids to decrease the width of the palpebral fissure) is indicated urgently, in order to reduce exophthalmos. Vitamin A ointment in large amounts is then necessary, awaiting tarsorrhaphy. In case of dislocation with no spontaneous resolution, the eye-ball should be immediately put back in place by pressing with two fingers on each side of the cornea covered with vitamin A ointment, without touching the cornea, awaiting the ophthalmologist's intervention.

3.1.5. Amblyopia

Before 8 years of age, cortical development of vision requires equal stimulation from both eyes. If one eye is either deprived of vision (due to a corneal scar, for instance) or constantly deviated (in the case of strabismus), or even if the vision in one eye is just blurred (in the case of asymmetric refractive error), the corresponding cortical neurons are not stimulated and vision in this eye is impaired; the resulting low vision is called amblyopia. If the cause is treated too late, vision can never be restored. Amblyopia is the most common cause of decreased visual acuity in children with craniosynostosis. It must therefore be prevented and treated by systematically screening for risk factors.

Once a central corneal opacity is formed in an infant, amblyopia is usually inevitable, hence the crucial role of prevention. In case of strabismus (which may not be visible to the naked eye, as is the case with microstrabismus), it has to be established whether one eye is constantly (or predominantly) fixating. In case of refractive error, full optical correction with spectacles should be prescribed. Many methods can then be used in order to improve vision in the deviated ("lazy") eye, the most effective and widely used being masking the other eye (dominant eye) a given number of hours per day using a patch on the skin. Amblyopia must be treated early, because the older the child, the more difficult the treatment; after the age 10, it is irremediable and the amblyopic eye is definitively visually impaired.

3.2. Expression of ophthalmological complications according to type of craniosynostosis

Ophthalmological complications can be encountered in all craniosynostoses. However, prevalence varies according to the type of craniosynostosis. Table 3 presents the clinical expression of syndromic craniosynostoses [2,3,23,25].

Table 3
Clinical expression of syndromic craniosynostoses [2,3,23,25].

Type of syndromic craniosynostosis	Ophthalmological findings
Crouzon	Exorbitism (luxation of eyeballs is possible)
	Hypertelorism
	Exotropia + excyclotorsional syndrome
	Corneal disorders
	Optic neuropathy
Apert	Exorbitism
	Hypertelorism
	Esotropia + excyclotorsional syndrome
	Down-slanting palpebral fissures
	Corneal disorders
	Congenital glaucoma
	Optic neuropathy
Saethre-Chotzen	Ptosis
	Hypertelorism
	Vertical strabismus
	Optic neuropathy
Pfeiffer	Exorbitism
	Corneal disorders
	Optic neuropathy
Muenke	Variability
	Strabismus
	Exorbitism
	Optic neuropathy

3.3. Ophthalmological investigations and management in children with craniosynostoses

3.3.1. Optic nerve management in craniosynostoses

In recent years, technological advances have transformed ophthalmic imaging. As a result, the optic nerve can be studied by various techniques, which should ideally be combined, to detect and monitor brain damage and optic neuropathy. As soon as the age of the child allows, it is advisable to perform fundus imaging centered on the optic nerves (usually possible from 3 years of age) and OCT in RNFL (retinal nerve fiber layer) mode to detect early papilledema or optic atrophy (Fig. 7) [26,27]. RNFL OCT can more accurately detect early papilledema and optic atrophy [28], which is especially useful in situations, such as some syndromic craniosynostoses [11], where constitutional abnormalities of the optic nerves can alter the relationship between ICP and optic nerve appearance [26]. OCT, however, cannot be isolated from a specialized clinical ophthalmic examination: interpretation of RNFL thicknesses without a careful examination of the optic nerve could result in serious interpretation errors. Indeed, in case of papilledema, RNFL thicknesses increase. A decrease may result either from a decrease of the papilledema (favorable), or from optic atrophy (unfavorable); only the clinical aspect, including the color of the optic nerve, can distinguish between these two opposite phenomena, the expression of which is exactly the same on OCT.

Electrophysiological assessment, including visual-evoked potentials (VEP), can be used in case of uncertain diagnosis of optic neuropathy; it is used by some teams to monitor ICP [29].

Finally, craniofacial imaging by CT and MRI is useful, either in cases where the mechanisms of optic neuropathy or visual loss are not clear, or in order to analyze the orbit and its contents, including the EOMs, in complex strabismus.

3.3.2. Strabismus management in craniosynostosis

The management of strabismus in children with syndromic craniosynostosis remains a therapeutic challenge. The strabismus is often multifactorial: orbital deformity, positional abnormalities of the EOMs, and sometimes absence of some EOMs. Orbital imaging, on MRI if possible, is useful to optimize surgery, especially when EOMs are missing [22,30]. Surgery is most often scheduled after the age of 5. It consists in oblique muscle recession or resections, and/or

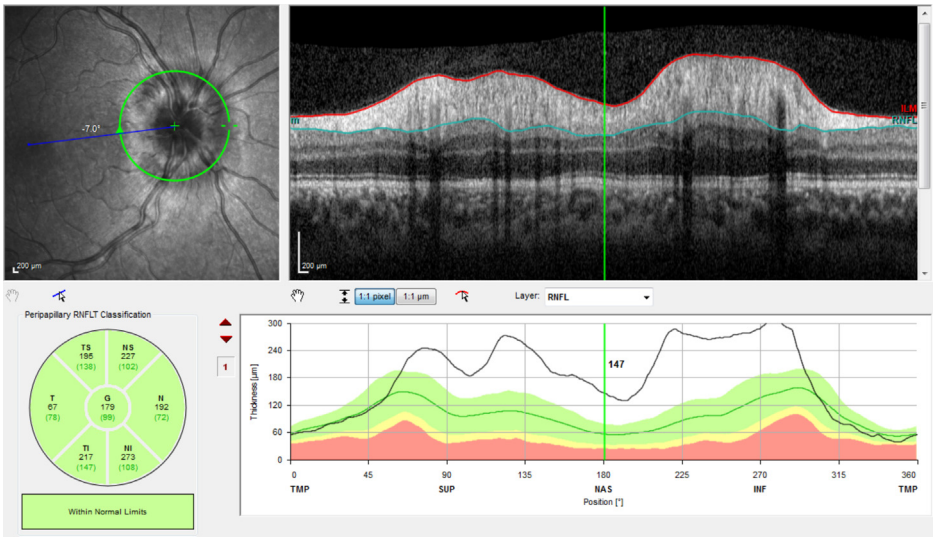


Fig. 7. Example of the retinal nerve fiber layer mode of optical coherence tomography (RNFL OCT) in the case of early right eye papilledema (Frisén stage 2). Top left: infrared image of the disk; the green circle is placed around the disk and defines the location of the considered retinal section. Top right: OCT slice of the retina along the depicted section, represented clockwise from the temporal side (arrow in the top left infrared image). The RNFL lies between the green and the red line. Top right: the black line represents the RNFL thickness of the present case. The green area represents normal thicknesses. Here the thickness is increased on the whole section, except for the temporal part (Frisén stage 2). Bottom left: mean thickness of each quadrant. The mode used here (basic RNFL) was primarily designed for glaucoma patients; hence only reduced thicknesses appear "abnormal"; increased thicknesses, which are highly abnormal, falsely appear as "within normal limits" on this diagram. This examination allows diagnosis of early and very early infraclinical papilledema, and also serial analyses, useful in monitoring an existing papilledema.

transpositions of the vertical recti muscles, in order to minimize the excyclotorsional syndrome, without jeopardizing stereoscopic vision if present. More than one operation is usually indicated; the aim is to reduce the often extreme V-pattern; it is, however, rarely possible to eliminate it completely.

3.3.3. *Ophthalmological follow-up in craniosynostosis*

Ophthalmological examination is mandatory in all cases at diagnosis. The follow-up agenda then depends on the kind of craniosynostosis and the presence of either ophthalmological or neurological abnormalities prompting examinations. American guidelines were published in 2012 [31]. Until the age of 9, in absence of any specific indication for further examination, children with syndromic craniosynostosis should undergo ophthalmological examination twice yearly, and children with non-syndromic craniosynostosis once yearly. From the age of 9 to adolescence, examinations should be performed at least once a year in children with syndromic craniosynostosis, and as needed in children with non-syndromic craniosynostosis [10]. Examination should comprise orthoptic evaluation, to diagnose and quantify strabismus, refraction (which requires a cycloplegia in children), evaluation of eyelid function and the ocular surface, and a fundus examination screening for ophthalmological signs of elevated ICP.

4. Conclusion

Ophthalmological involvement depends on the type of craniosynostosis. Ophthalmologic complications, sometimes severe, affect more than 40% of children with syndromic craniosynostosis and may greatly impair quality of life. The role of the pediatric ophthalmologist is therefore crucial, at diagnosis and during follow-up. Visual impairment by exposure keratopathy, papilledema and amblyopia can and should be avoided in these children.

Disclosure of interest

The authors declare that they have no competing interest.

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None.

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