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Craniosynostosis: State of the Art 2019

# What remains of non-syndromic bicoronal synostosis?

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ABSTRACT

More and more genetic syndromes are associated with bicoronal synostosis (BCS), making non-syndromic BCS (NSBCS) a shrinking entity. However, the numerical importance and clinical impact of syndromic BCS (SBCS) versus NSBCS have not been much studied. We retrospectively reviewed our experience with BCS over the last four decades in order to compare prevalence trends in SBCS and NSBCS. 195 patients were treated for BCS during the period 1978–2017: 104 (53.3%) were syndromic, 24 (12.3%) showed clinical and/or familial features suggesting a syndrome, although without final diagnostic confirmation, and 7 (3.5%) had associated extra-cranial malformations suggesting a syndromic context without identified genetic mutation; the remaining 61 (31.3%) were purely NSBCS. Surgery was required earlier in SBCS (21.7 months, 95%CI 18.4–25.1) than in NSBCS (29.5 months 95%CI 26.4–32.7). Prevalence of hydrocephalus and tonsillar herniation was significantly lower in NSBCS, and mortality concerned only SBCS. Prevalence of NSBC decreased significantly over the study period, likely because of more accurate testing, and decreased slightly over the last decade, possibly because of prenatal testing and abortion. NSBCS is now much less common than SBCS, and has a less aggressive clinical course, with lower rates of hydrocephalus, tonsillar herniation and mortality. This subgroup also deserves attention because it is likely that new discoveries are still to be made.



## 1. Introduction

Unlike synostosis involving the sagittal system, synostosis of the coronal suture, especially bicoronal synostosis (BCS), is often syndromic. Since the pioneering work by Apert and Crouzon, BCS has been associated to a variety of malformation syndromes, and new mutations are reported every year. Historically, syndromic BCS was mostly associated with faciostenosis, as in Crouzon, Pfeiffer, Apert and Saethre-Chötzen syndromes; in recent decades, however, syndromic BCS without faciostenosis was described, as in the FGFR3 p250 mutation described by Lajeunie and Muenke [1]. In addition, BCS is often a late feature in other synostoses, in particular sagittal synostosis [2], or can be associated with other malformations, which suggests that the list of syndromes associated with BCS in not closed.

With this ever-increasing knowledge, and progress toward increased exhaustiveness of genetic testing, the question arises as to whether non-syndromic BCS (NSBCS) will exist any an entity in the future.

On the other hand, increased awareness of malformation associations, often associated with poor developmental outcome, has led to heightened concern for cases diagnosed in utero, with abortion in countries where the law allows. As a result, in many centers, the prevalence of live births with syndromic BCS appears to be decreasing, although data are lacking. In order to evaluate the remaining importance of NSBCS, we reviewed our clinical experience.

## 2. Material and methods

We retrospectively reviewed our registry of craniofacial malformations followed by our multidisciplinary team since 1978 and logged prospectively, in order to identify pediatric patients followed for BCS. BCS, defined by radiological closure of both coronal sutures, was classified as isolated throughout follow-up, or associated with closure of other sutures, either at initial diagnosis or during follow-up for other synostoses (for example, sagittal synostosis progressing toward oxycephaly). Patients were identified as syndromic when they presented characteristic morphology, associated lesions, familial background and/or genetic test results. Because the series spanned 4 decades and criteria greatly progressed over time, in many cases diagnosis was corrected later during follow-up in a patient initially diagnosed with non-syndromic BCS.

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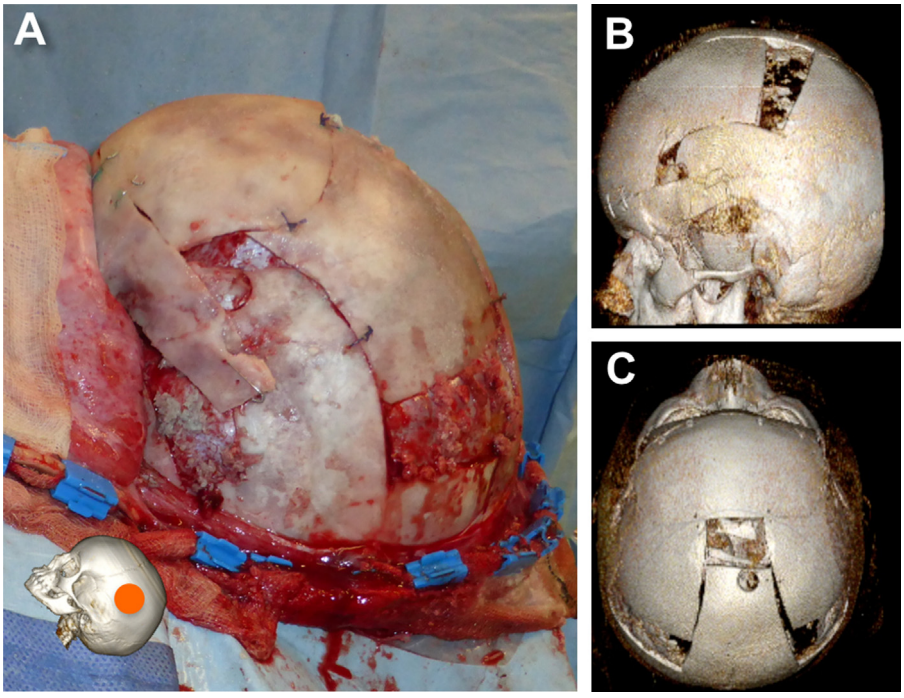


**Fig. 1.** surgical technique of fronto-orbital advancement with fan-shaped parietal flaps. A. intraoperative view, left lateral aspect. B, C. postoperative 3D CT-scan showing advancement of the fronto-orbital bandeau and parietal flaps. Technique chirurgicale de l'avancement fronto-orbitaire avec volets pariétaux en éventail. A. vue opératoire latérale gauche. B, C. scanner 3D post-opératoire montrant l'avancée du bandeau fronto-orbitaire et des volets pariétaux.

We thus defined patient groups:

- with established diagnosis of syndromic BCS (based on clinical and/or genetic testing);
- with clinical or familial elements in favor of a syndrome but awaiting confirmation or with negative testing;
- without syndromic diagnosis but with associated extra-cranial malformations;
- with pure (isolated), non-familial BCS.

We then compared patients with established SBCS (group A) versus NSBCS (group D) regarding associated disorders such as hydrocephalus or chronic tonsillar herniation (CTH), mortality, and school achievement.

In order to study chronological trends over the years 1978 to 2017, the series was divided according to 4 decades: 1978–87, 1988–97, 1998–2007 and 2008–17.

### 2.1. Surgical management

Surgery was decided on in a multidisciplinary team meeting in our craniofacial unit. The aims of surgery for BCS were: craniocerebral decompression to avoid optic atrophy, developmental retardation and CTH; functional improvement of breathing and feeding in case of associated faciostenosis; and morphological correction. The morphological elements to be corrected were tall, broad, flat forehead and hypertelorism. In addition, facial structures are displaced upward because of the BCS, and surgery aims to lower these whenever possible. Ideally, according to our management strategy, surgery is performed after the age of 9 months, because the calvaria is more easily remodeled and the child is better able to withstand heavy surgery. Surgery can also be performed in older children, especially in oxycephaly, which is often diagnosed late; conversely, early intracranial hypertension can require surgery in small infants and even neonates, in which case only perifrontal craniectomy (floating forehead) or posterior perioccipital craniectomy is performed [3]. Cranioplasty for BCS, performed after 9 months, consists in fronto-orbital advancement (FOA), as previously described [4]. Fronto-orbital advancement with kyphosis of the bandeau and fan-shaped parietal flaps provides satisfactory calvaria expansion and morphological correction along a curvilinear vector in accordance with the natural growth pattern (Fig. 1). In order to correct hypertelorism, the frontal bone flap and fronto-orbital bandeau can be split along the metopic suture and repositioned with midline overlap, to narrow and increase the curvature of the forehead. In order to correct the turricephalic aspect, the frontal bone flap can be overturned by 180°, to create a more harmonious convexity of the forehead. In turricephalic cases with severely broadened forehead, the fan-shaped parietal flap can be made smaller in the back, so that advancement correlates with reduction of transverse diameter. Conversely, in the oxycephalic form, transverse diameter can be increased by advancing a parietal flap that is smaller in front (like a wedge splitting the midline crest and temporal region). Early fronto-orbital curvilinear advancement also untethers the facial growth and allows the midface to be lowered (Fig. 2). When indicated, in cases with facial stenosis, mid-face distraction can be performed in the same step, as previously described [5]. Overall, the majority of patients require only one surgery. After the initial postoperative period, patients undergo clinical controls with plain X-rays every 3 years until adulthood, to evaluate morphology, development and school achievement.

## 3. Results

We reviewed 195 consecutive patients treated for BCS during the period 1978–2017; 87 were male and 108 female (M/F ratio 0.81). One hundred and four (53.3%) were identified as syndromic. In the other 91 cases (46.7%), familial features suggestive of a syndrome were found in 24 (12.3%), suggesting Saethre-Chötzen syndrome in 9, TCF12 mutation in 2, FNB2 mutation in 1 and Bent-bones disease in 1, although genetic confirmation was

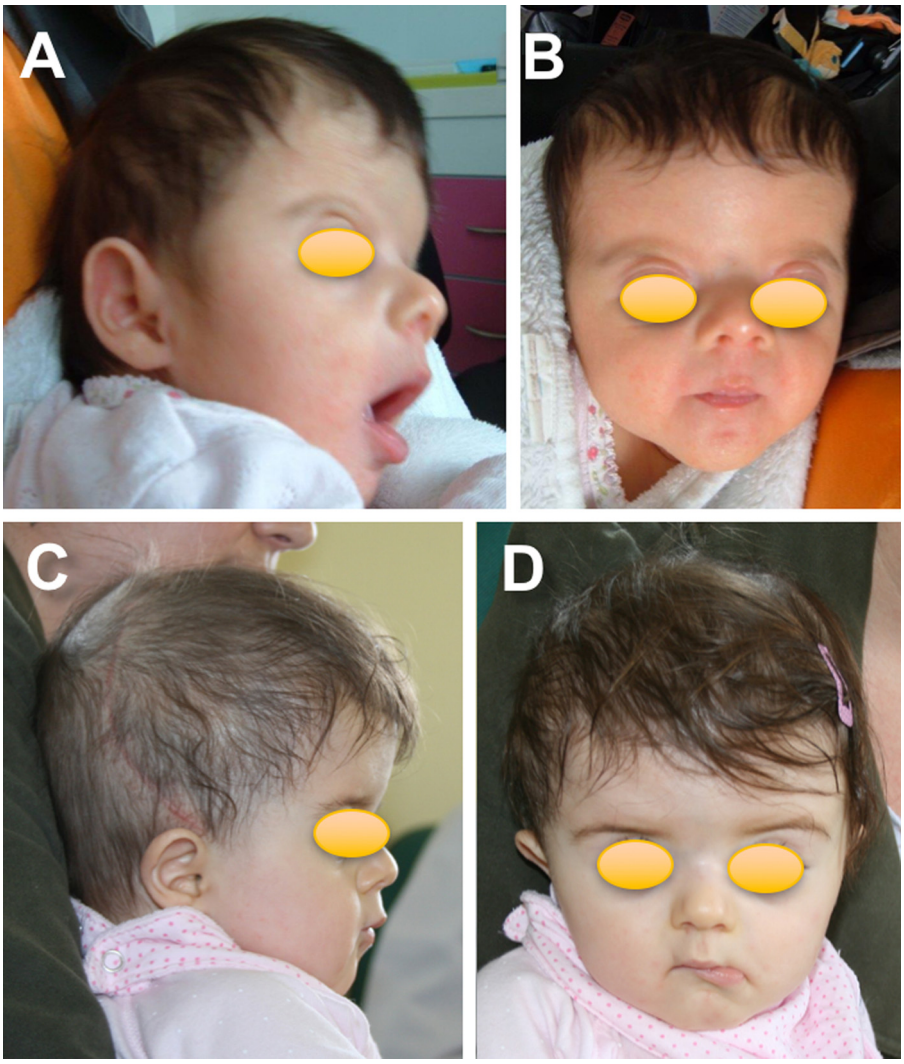


**Fig. 2.** Patient operated on by fronto-orbital advancement and frontal vault reshaping. A, B. preoperative view. C, D. postoperative view. Note improved frontal convexity and spontaneous correction of the mid-facial features after surgery. Patiente opérée par avancée fronto-orbitaire et remodelage frontal. A et B. aspect pré-opératoire. C et D. aspect post-opératoire; noter l'amélioration de la convexité frontale et la correction spontanée des déformations médio-faciales après chirurgie.

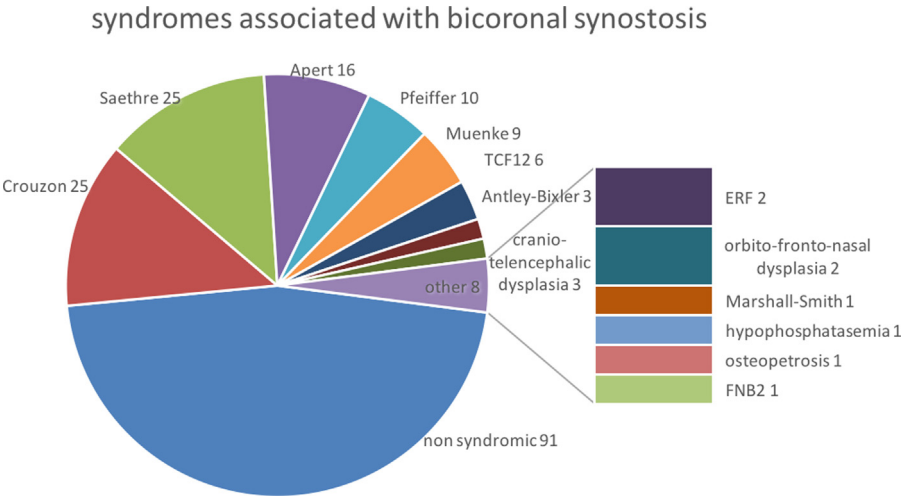


**Fig. 3.** Pie-chart showing the various syndromic diagnoses in our series. Camembert montrant les différents diagnostics syndromiques dans notre série.

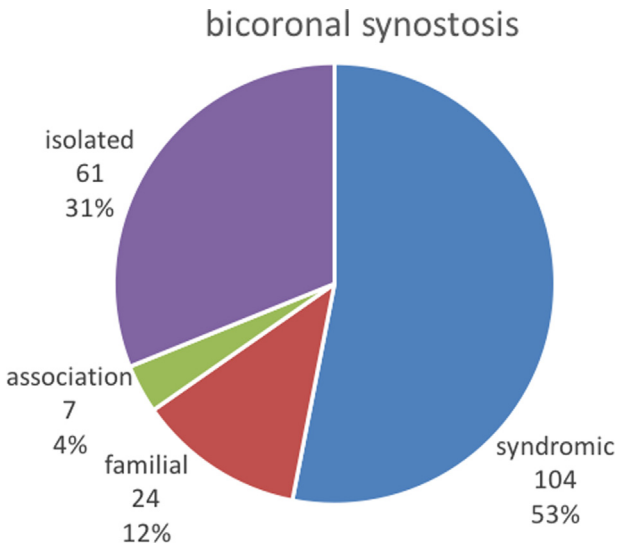


**Fig. 4.** Pie-chart showing the proportion of syndromic non-syndromic non-familial isolated bicoronal synostosis. Camembert montrant la proportion de cas de sténose bicoronale isolée, non-syndromique, non familiale dans notre série.

lacking. The various syndromes are detailed in Fig. 3. In addition, 7 patients (3.6%) presented other malformation conditions: dysraphism (Currarino, VACTREL syndrome), heart malformation, thyroid dysfunction, cataract, or ear malformation. As a result, the number of cases of pure NSBCS (isolated, non-syndromic, non-familial) was reduced to 61 (31.3% of the whole series). Diagnosis of syndromic or non-syndromic BCS is detailed in Fig. 4.

### 3.1. Complications of bicoronal synostosis

Hydrocephalus or other CSF-related problems requiring surgery were found in 2/61 cases of pure BCS (3.3%), compared with 17/104 of syndromic BCS (16.3%); the difference was statistically significant ($P = 0.01$). CTH, whether requiring decompressive surgery or not, was found in 2/61 cases of pure BCS (3.3%), versus 18/104 of syndromic BCS (17.3%); this difference was also statistically significant ($P = 0.008$). Median age at surgery was younger in the syndromic group (21.7 months, 95%CI 18.4–25.1) than in the non-syndromic group (29.5 months, 95%CI 26.4–32.7).

### 3.2. Outcome

Mean age at last control was 12.3 years. During follow-up, 8 children died, all in relation with syndromic BCS: 4 with Pfeiffer, 2 with Apert, 1 with Crouzon syndrome, and the child with putative diagnosis of bent bone dysplasia. In the 142 children alive and of school age, schooling was normal in 92 (65%), required help in 33 (23%), was retarded in 9 (6.3%), and required a special institution in 8 (5.6%); school achievement appeared overall better in pure NSBCS than in syndromic BCS, although the difference was not significant (Fig. 5).

### 3.3. Trend

The proportion of syndromic cases increased significantly ($P = 0.01$) during the first 3 decades of the study (1978–2007), and decreased during the last decade (2008–2017), although the latter difference was not significant (Fig. 6).

## 4. Discussion

### 4.1. Pathophysiology and surgery

The coronal suture is of major importance in calvaria growth. Coronal growth follows a curvilinear vector, reminiscent of conch shells [4]. The result is not just to increase calvaria volume and advance the forehead, but also to lower the face. Thus, the role of the coronal suture is both quantitative enlargement and morphological maturation. Conversely, in patients with BCS, the calvaria is shorter and smaller, the forehead is tall, broad and flat, and the midface is held upward. Insufficient calvaria expansion leads to intracranial hypertension with risk of visual impairment and retarded developmental. Impaired facial growth results in short nose with anteverted nares, and hyperteloric down-slanted eyes. In small infants with BCS, compensation in the metopic and pterional fontanels causes hypertelorism, bulging temples and bregma, in a typical cloverleaf aspect. In contrast, oxycephalic children, developing BCS later in life after closure of the metopic suture and fontanels, are deceptively harmonious, which can lead to diagnosis being delayed until visual impairment sets in. The aims of surgery are to decompress the brain and allow normal craniofacial development; by untethering the facial skeleton early, fronto-orbital advancement also allows restoration of normal facial growth dynamics (Fig. 2).

### 4.2. Syndromic versus non-syndromic BCS

The range of syndromic associations with BCS is constantly increasing, making non-syndromic BCS a provisional diagnosis. Classical mutations of the FGFR gene group and Twist are the most readily identified, because of tell-tale anomalies in face, ears and limbs. In addition, new mutations, such as TCF12 and ERF mutations, in FGFR-normal Crouzon-like or Twist-negative Saethre-Chötzen-like syndromes, have broadened the range and the variety of phenotypes, since these genes often result in closure of the lambdoid and/or sagittal sutures as well. Other rare bone diseases, such as osteopetrosis [6], pseudo-hypophosphatasemia or Marshall-Smith syndrome, have been identified as causing, among other problems, intracranial hypertension in relation with BCS. Overall, these new mutations often escape classification and challenge our understanding of the geno/pheno-type correlation. The result is that genetic evaluation of BCS is now mandatory, although complicated by the multiplicity of genes involved. At the same time, interpretation becomes even more delicate, because new variants of potentially deleterious genes are regularly being discovered, the pathogenicity of which often has to await confirmation. As a result, in many cases, patients are provisionally considered NSBCS, awaiting a genetic confirmation that can take years.

The present study found that non-syndromic BCS was not only a minority but also had shrunk over time. This trend is the result of new genetic syndromes being discovered at an accelerated rate, but also of the emergence of new features during follow-up, (mostly faciostenosis or new calvaria suture closure), or new family members involved, indicating syndromic BCS. Another contingent of children with BCS is formed by patients with sagittal synostosis, presenting secondary closure of the coronal and/or lambdoid sutures, often in association with a genetic context [2]. These findings confirm that children operated on for craniosynostoses should be followed until adulthood.

On the other hand, although the percentage of syndromic BCS increased significantly between 1978 and 2007, there was a decrease during the last decade. This trend, which remains to be confirmed, may simply be due to patients still awaiting diagnosis, or else may be a true decrease in live births, due to prenatal

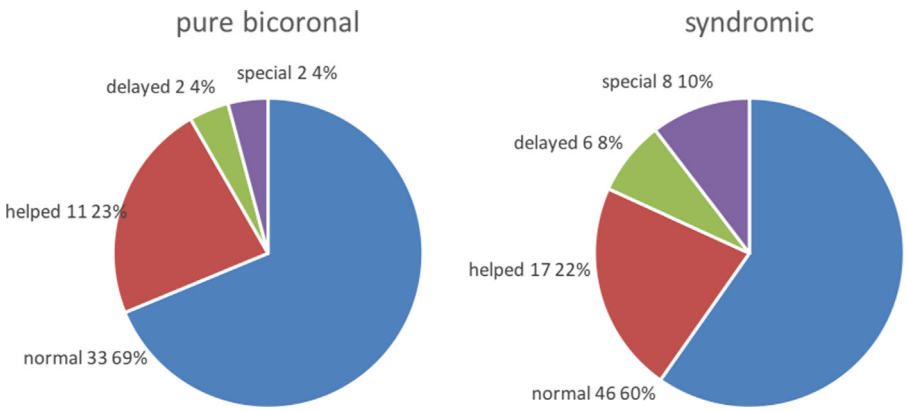


**Fig. 5.** Pie-chart detailing school achievement in patients of school age in the syndromic and purely non-syndromic groups. Camembert montrant les résultats scolaires chez les enfants ayant atteint l'âge scolaire dans les groupes syndromique et non-syndromique pur.

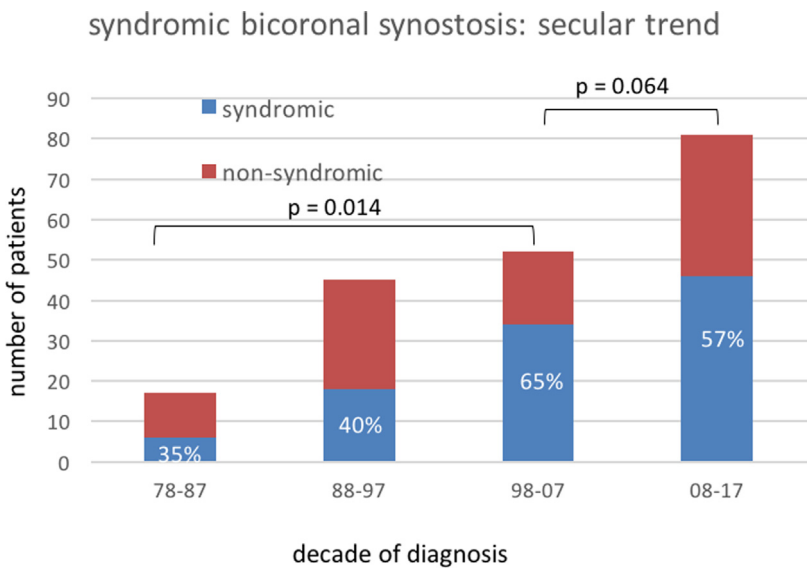


**Fig. 6.** Number of new cases of BCS during the last 4 decades, and the proportion of syndromic to non-syndromic cases. Nombre de nouveaux cas de SBC diagnostiqués au cours des quatre dernières décennies et la proportion de cas syndromiques VS non syndromiques.

diagnosis and abortion. This trend, if confirmed, will make these rare diseases even more rare.

The phenotype is more benign in non-syndromic than syndromic BCS [7], because of the absence of respiratory and feeding problems associated with faciostenosis, or deafness associated with Muenke syndrome. We also found that mortality, hydrocephalus and CTH were markedly less common in NSBCS. The more severe clinical presentation, as well as associated malformations and complications in the syndromic group, account for the younger age at surgery.

## 5. Conclusion

Unlike synostoses of the sagittal sutural system, which are often attributed to environmental factors and show markedly male predominance, BCS is mainly associated with genetic mutations and an even sex-ratio. Diagnosis of syndromic BCS is often easy, whereas non-syndromic BCS is often a default, provisional diagnosis, with many cases in a gray zone awaiting confirmation or further testing. As a result, NSBCS is likely to shrink in the future, although this real decline can be masked by a decrease in live births with openly syndromic BCS. The particular subgroup of BCS associated with other malformation syndromes is temptingly similar to metopic synostosis, which is classically attributed to environmental rather than genetic factors, and is associated with malformations in other organs in up to a third of cases (unpublished data). Although at present, no conclusion can be drawn regarding the possible effect of environmental agents on the coronal suture, we should keep an open mind about this possibility. Thus, the shrinking entity of non-syndromic BCS is a terrain for new discoveries, in the genetic and non-genetic fields.

## Disclosure of interest

The author declares that he has no competing interest.

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