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Craniosynostosis: State of the Art 2019

Recent advances in trigonocephaly

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ABSTRACT

Introduction. – The aim of this review was to report on recent advances in trigonocephaly since the last report on craniosynostosis published in 2006.
Material and methods. – The review was conducted in accordance with the PRISMA guidelines. Research focused on four main topics: epidemiology, neurodevelopmental disorders, genetics and surgical techniques.
Results. – Forty reports were included. The prevalence of trigonocephaly increased during the last two decades both in Europe and in the United States, but no clear contributing factors have yet been identified. Neurodevelopmental disorders are frequent in syndromic trigonocephaly and not particularly rare in non-syndromic cases (up to 34%). Developmental retardation (speech, motor or global) was almost always present in children exposed to valproic acid. Chromosomal abnormalities described in metopic synostosis comprised deletion of chromosome 11q24, deletion or trisomy of 9p and deletion of 7p, deletions of 3q, 13q, 12pter, 22q11, and duplication of 15q25. SMAD6 mutations should be systematically screened for in familial cases. Recent advances in surgical techniques have mainly concerned endoscopic-assisted procedures, as they significantly reduce perioperative morbidity.
Conclusions. – Neurosurgeons, maxillofacial and plastic surgeons will be increasingly concerned with trigonocephaly because of the increase in prevalence observed over the last two decades. Cytogenetic alterations are probably underestimated in this craniosynostosis, considering the high rate of neurodevelopmental retardation compared to other single-suture synostoses. Genetic counselling is therefore more and more effective in this pathology. An objective method to evaluate the cosmetic results of both endoscopic and open surgeries is necessary, as some under-corrections have been reported with minimally invasive surgery.

1. Introduction

Premature fusion of the metopic suture may result in trigonocephaly [1]. While it is a rare condition, recent studies reported an increase in prevalence [2–6]. Consequently, neurosurgeons, maxillofacial and plastic surgeons will be increasingly involved with these patients.

The objective of this report was to review significant advances reported in scientific literature on trigonocephaly since the last report in 2006 [7]. The review focused on four main topics: epidemiology, neurodevelopmental prognosis, genetic advances and surgical techniques.

2. Material and methods

We conducted a review in accordance with the PRISMA guidelines. Ethics committee approval was not required for our research protocol. We used the databases PubMed and Medline, with "trigonocephaly" or "metopic" and "craniosynostosis" as keywords. Our research was limited to reports published in English between January 2006 and March 2019, and focused on four main topics: epidemiology, neurodevelopmental disorders, genetics and surgical techniques. The references from the reports included were also manually searched to find further references and reported studies not identified using our initial search strategy. Case reports were

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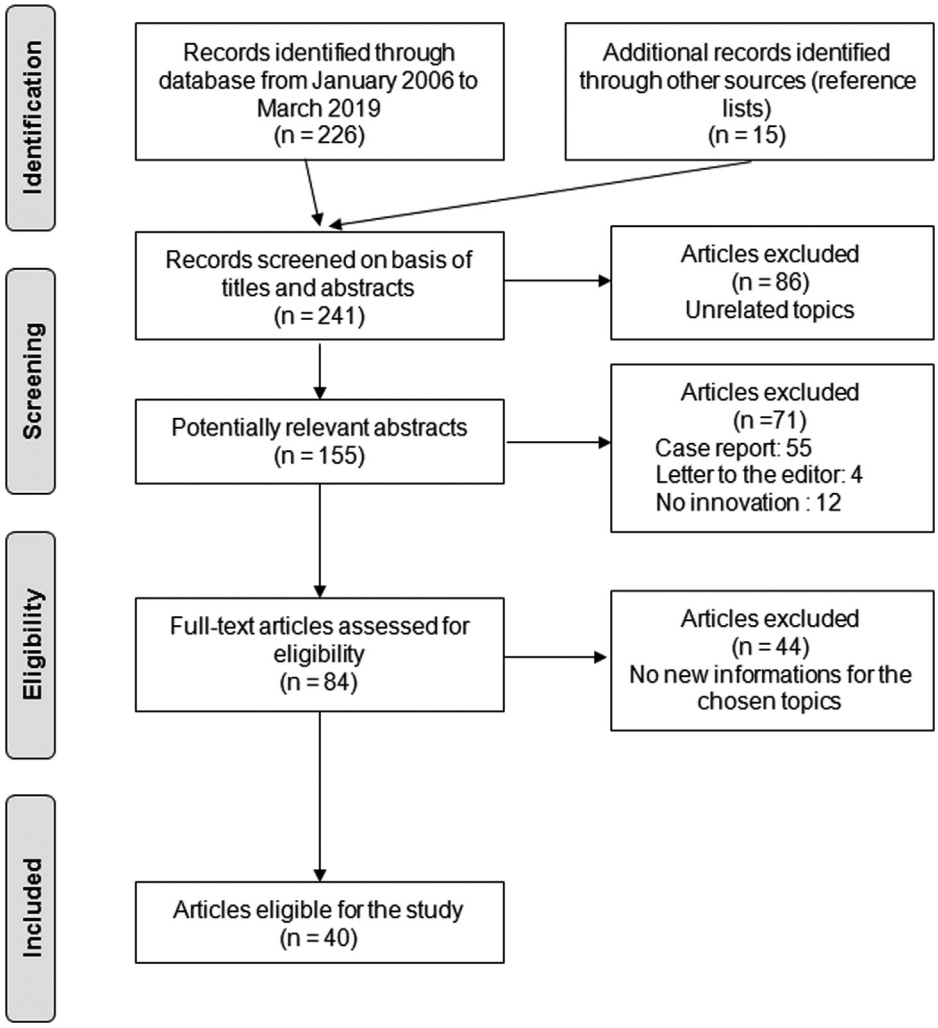

Fig. 1. Literature analysis flowchart.

excluded except for two publications [8,9], which we considered important for the genetics section.

3. Results

Our search initially identified 241 reports. Of these, 40 were eligible for our study. The flow chart is shown in Fig. 1.

3.1. Epidemiology

3.1.1. Epidemiologic data

Metopic synostosis is the second most common craniosynostosis, after scaphocephaly, with an estimated prevalence of 1/5000 live births in 2013 [2]. This prevalence has grown over the past two decades in Europe and the US [2–6]. According to these studies, the absolute number of craniosynostoses increased significantly, as did the proportion of metopic synostoses. For example, the incidence of trigonocephaly increased 4-fold and its proportion of non-syndromic cases increased by 25% in the Necker-Enfants Malades Hospital between 1988 and 2007 [4]. Simultaneously, scaphocephaly also increased, but not significantly. It remains unclear whether diagnosis of craniosynostosis has simply become more effective or whether the rate really grew during the last few years. In the Netherlands, the prevalence of trigonocephaly increased over a long period and no sudden change was seen in 2011, when guidelines for craniosynostosis care were published [2]; the authors posed the question of "what factors are at work in the background", but did not suggest an answer.

3.1.2. Risk factors

Some factors may have been identified to explain the increase in prevalence of metopic synostosis. One could be folic acid intake before pregnancy: deficit is known to play a role in several midline defects such as cleft lip or neural-tube defects. Periconceptual supplementation with folic acid (from 4 weeks before until 8 weeks after conception) has been advocated in the Netherlands for all women since 1998, but not in France according to some authors [5]. Thus, considering metopic synostosis as a midline defect, the two different guidelines in these two countries should logically have induced a difference in the prevalence of metopic synostosis cases over a period of years, but the same increase was in fact observed in both countries [5]. This is quite surprising, as folic acid supplementation has been formerly advocated in France since 2000. We presume that these authors considered that this prevention was probably underused in France.

Another suspected factor is exposure to valproic acid during the first trimester of pregnancy. A case-control study published in the *New England Journal of Medicine* [10] identified 14 malformations, which were significantly more common among women who received valproic acid during the first trimester. Compared to non-exposure, use of valproic acid monotherapy was associated with significantly increased risk for 6 of the 14 malformations: spina

bifida, atrial septal defect, cleft palate, hypospadias, polydactyly and craniosynostosis. The adjusted odd ratios were 6.8 (95% CI: 1.8 to 18.8) for craniosynostosis. In this study, exposure to valproic acid monotherapy during the first trimester was compared with absence of exposure to antiepileptic drugs and with exposure to an antiepileptic drug monotherapy other than valproic acid. Significant associations were noted for 5 of the 6 malformations above but not for craniosynostosis: the risk of craniosynostosis was not significantly different between valproic acid and other antiepileptic drugs in monotherapy.

Several observations suggested that trigonocephaly is typically part of the fetal valproate syndrome [11]. All children born to mothers who had received valproate monotherapy throughout pregnancy had trigonocephaly in Lajeunie et al.'s series [12]. Metopic synostosis was associated with fusion of another suture in 12% of cases in this series. The manifestation of this cranial malformation is probably dose-dependent, like other congenital malformations in this syndrome, and dose was > 1000 mg a day in all cases [12].

Other suspected risk factors include environmental factors such as external pressure on the fetal skull, birth presentation, birth weight, gestational age and mode of delivery [13].

3.2. Behavioral and neurodevelopmental disorders

Patients presented a typical frontal ridge, hypotelorism and distortion of the orbital roofs. The total skull volume was usually unrestricted, but the anterior cranial fossa was reduced [5]. Recently, Cornelissen et al. [14] studied funduscopy and occipitofrontal head circumference in 262 trigonocephalic patients to quantify more accurately the prevalence of preoperative and postoperative intracranial pressure elevation. Intracranial pressure elevation was present in only 1.9% preoperatively and in 1.5% postoperatively.

Kelleher et al. [15] reported a high frequency of developmental, educational and behavioral problems in children with non-syndromic trigonocephaly: speech or language retardation in 34%, need for an educational psychologist in 33%, remedial or resource hours within the school system in 47%, and requirement for a classroom assistant in 20%. Results did not differ between children treated surgically and those with mild deformity treated conservatively. Another report used the Bayley Developmental Scales in a series of 110 children with trigonocephaly [16]. A total of 19% of children had developmental retardation in the non-syndromic group and 29% in the syndromic group. Similarly 18% of children with non-syndromic trigonocephaly had a speech delay. This suggests that neurodevelopmental prognosis is much better in non-syndromic trigonocephaly. Developmental retardation (speech, motor or global) was almost always present (90%) in the group exposed to valproic acid.

3.3. Genetics

Syndromic craniosynostosis (patients with associated malformations) represents 15–20% of all craniosynostoses [13]. These patients usually have a monogenic etiology; the main genes known to be involved with syndromic craniosynostosis are FGFR1-3 and TWIST1, more frequently responsible for coronal synostosis [17].

The genetic causes of non-syndromic craniosynostosis are largely unknown and mutations in the genes causing syndromes are not a common cause of non-syndromic craniosynostosis [18]. Recent studies demonstrated that animal models and some patients with presumably non-syndromic craniosynostosis had mutations in specific genes: *TCF12*, *EFBN1*, *ALX4*, *POR*, *FGF10* and, most notably for metopic synostosis, FREM1 and SMAD6 [19–21]. Neurodevelopmental problems are not particularly rare and cannot be completely attributed to the skull phenotype or surgical trauma. For these reasons, genetic counseling remains more and more effective in such pathology.

3.3.1. Metopic synostosis

While specific gene mutations for metopic craniosynostosis are rare, at least 6% of these patients have cytogenetic abnormalities, including deletion of chromosome 11q24, deletion or trisomy of 9p [22] and deletion of 7p [16,23]. Patients with these syndromic trigonocephaly have characteristic facial dysmorphisms and psychomotor retardation [18,22]. Other rare chromosomal abnormalities have been described in metopic synostosis: deletions of 3q, 13q, 12pter, 22q11, duplication of 15q25 [16] , and mosaic trisomy 13 [9].

Non-syndromic trigonocephaly seems to have a stronger genetic component than sagittal synostosis: family recurrence is reported in up to 10% of patients, and the incidence of the phenotype observed in first-degree relatives is 6.4%, which is higher than in any other craniosynostosis [24]. Recently, Magge et al. [8] reported the case of genetically confirmed identical twins discordant for metopic craniosynostosis. They therefore hypothesized that epigenetic and environmental influences play a role in the development of metopic fusion.

3.3.2. Genetic counseling

Analysis of family histories of 660 mutation-negative non-syndromic patients showed the highest incidence rate of craniosynostosis for first-degree relatives of probands in metopic craniosynostosis (6.4%), followed by complex, sagittal, lambdoid and coronal craniosynostosis [24]. Suture category did not differ significantly in the patient and in the affected relative: 67% of metopic craniosynostosis patients had the same suture synostosis as their relative. This finding supports the hypothesis that each suture synostosis has suture-specific genetic/environmental factors.

Timberlake et al. [19] suggested that all non-syndromic cases of sagittal or metopic craniosynostosis should be screened for *SMAD6* mutations, because they are the most frequent cause of non-syndromic craniosynostosis identified to date, incurring a greater risk of recurrence in families harboring mutations. The authors also recommended specific screening for familial cases of midline non-syndromic craniosynostosis: extremely rare mutations in *SMAD6* and, if negative, *TWIST1*, *TCF12*, *MSX2* and *ERF*. A recent study similarly demonstrated that pathogenic or likely pathogenic variants can be identified in about 15% of patients with craniosynostosis without prior molecular diagnosis, most commonly in the TCF12 and EFNB1 genes [20]. This indicates that patients thought to have craniosynostosis without genetic molecular support may in fact have a mutation. According to Johnson and Wilkie [25], when the family history is negative for craniosynostosis and no genetic or cytogenetic alterations are found, the recurrence risk for offspring is around 5% and the risk for sibling recurrence is around 2% in the case of non-syndromic metopic suture.

Lattanzi et al. [18] advocated chromosomal microarray screening for patients with metopic craniosynostosis associated with developmental retardation or additional anomalies and for those with affected relatives, since cytogenetic abnormalities are not particularly rare and can be subtle.

Finally, Wilkie et al. [26], in a large cohort of 326 children reported that single gene disorders which disrupt physiological signaling in the cranial sutures often required reoperation, whereas chromosome abnormalities followed a more indolent course, thus suggesting a different, secondary origin of the associated craniosynostosis.

3.4. Surgical techniques

3.4.1. Endoscopic and microscopic minimally invasive approaches

The first description of endoscopically assisted surgery for craniosynostosis dates back to 1998 when Jimenez and Barone performed strip craniectomy on 4 patients with scaphocephaly, with good outcome [27]. The primary principle for endoscopy-assisted techniques was to perform surgery at an early age (preferably around 3 months) in order to take advantage of the very rapid brain growth during the 1st year of life [28]. Operations in children older than 9 months were reserved for patients with mild deformity. In a recent report by Jimenez et al. [28], the authors reported their 2 decades' experience of endoscopy-assisted surgery. They compared their own results and those from an extensive literature review using minimal invasive surgery (MIS) to results from traditional open surgery. They concluded that MIS reduces perioperative morbidity, with equivalent long-term functional and cosmetic results. The first important point is that mean age at surgery was much lower in MIS (3.8 months versus 11.5 months for traditional open surgery), which presumes accurate early diagnosis. Other parameters were very different between the 2 groups. Hospital stay was significantly lower: 1.7 days for MIS versus 3.7 days for open surgery, reducing the overall cost. Operative time was significantly lower in MIS than open surgery, being 3 to 4 times shorter (67 min versus 224 min), with consequently less blood loss (55 mL versus 224 mL) and fewer transfusions (0.22 versus 0.77). Finally, the authors highlighted other advantages, such as conserved development of the frontal sinuses compared to fronto-orbital advancement, and long-lasting cosmetic results. From a technical standpoint, the main problem of the endoscopic technique is the learning curve: these experienced authors concluded that trigonocephaly is the most difficult endoscopic procedure they had to perform. Challenges comprised: the small scalp incision, long distance from incision to nasofrontal suture, presence of venous perforators from the sagittal sinus, and the narrow osteotomy corridor (5 mm). Most authors shared these observations and point of view concerning early cosmetic results [29–35]. Others analyzed their long-term results using a microscopic minimally invasive approach and concluded that it was not appropriate for trigonocephaly, and therefore stopped using this technique in these patients [31]. The reason was a high reoperation rate (25%) because of inadequate correction of the deformity, and not the suture refusion: patients then needed an additional open bifrontal cranioplasty with frontal bar reconstruction. Under-correction was sometimes reported, but without requiring reoperation, and some families accepted suboptimal esthetic correction because of a desire to avoid an open procedure [29]. Finally, a real challenge remains: finding an objective method to evaluate cosmetic results in both MIS and open surgeries.

A major limitation of MIS is the need for helmet. Jimenez et al. [28] also insisted on the use of a custom-made postoperative cranial orthosis 23 h per day to obtain good results. Delye et al. [35] evaluated the burden of 10 months' helmet therapy on an online questionnaire covering social impact and general satisfaction: the social inconveniences due to helmet therapy led to little dissatisfaction, proving that this treatment is well tolerated by both parents and children. A total of 74% of patients showed compliance, interrupting helmet therapy for a maximum 1 day per month (due to high temperature in summer or to fever). Skin irritation was infrequent, and inconvenience was mostly reported during physical contact with the child, such as cuddles.

Another limitation of the technique is how to manage the bleeding from bridging veins that extend from the sagittal sinus and dura to the stenosed suture and frontal lobe [28]. Bipolar coagulation with the endoscope may not be sufficient, and manoeuvres (table lowered and head elevated) are probably necessary, but should be implemented with caution to avoid venous air emboli. Hemostatic agents are also used, as well as bone wax.

The third limitation of the endoscopic technique is the necessarily early age of patients for surgery. After 6 months of age, open surgery is preferentially recommended by most authors as achieving significantly better results, because of bone thickness and difficulties in remodeling and reshaping. Moreover, some authors advocate very early endoscopic procedures, around 3–4 months of age, to avoid the use of helmets [36].

3.4.2. New techniques

If an open approach is chosen, the surgery is usually performed before the age of 1 year (9 to 12 months) [37]. For example, Lille's technique consists in constructing a large frontal panel stabilized with absorbable plates after resection of the metopic suture. Fronto-orbital advancement is performed, with parietal craniectomies and pterional resection to optimize cranial expansion and allow future cranial growth [38]. Other authors tailored a neoforehead to match the remodeled supraorbital bar, then stabilized it by wires and internal bone graft [39]: the advantages of wires are their significantly lower cost compared to absorbable plates, and their malleability. However, they can loosen over time and may become palpable through the skin, requiring subsequent removal in 8.4% of cases.

To reduce blood loss, Di Rocco et al. [40] reported a variant technique to control bleeding over the region of the glabella and ophryon. It consisted in changing the design of the frontal craniotomy and conserving a triangle of bone based above the glabella at the site of the osteotomy of the bandeau. The technique allowed a better control under direct visualization of the emissary metopic veins and the superior sagittal sinus from the surrounding bone structures, and consequently better hemostasis before removing the last piece of frontal bone.

To achieve a better cosmetic result and to decrease relapse and the need for subsequent revision surgery, Bennett et al. [41] proposed a method of "hypercorrection". The technique consisted in 2.5 to 3.5 cm fronto-orbital advancement and concomitant hyperexpansion of the bitemporal projection. However, some patients needed additional operations because of relapse or cranial bone defects which required camouflage procedures. Despite hypercorrection, mild lateral orbital recession was reported in 14% of cases and mild bitemporal constriction in 9%.

3.4.3. Secondary corrections

One of the common late consequences of fronto-orbital advancement with frontal remodelling of trigonocephaly is contour irregularities in the frontal region and temporal hollowing. These irregularities can vary in extent but are invariably palpable and often visible [42]. Because facial asymmetry causes psychological issues which may affect academic performance and the development of the child's personality, lipoinjection has been proposed to further refine the results obtained after the primary procedure [42,43]. This technique is a low-risk, minimally invasive, reproducible and inexpensive procedure. To improve the volumetric results of lipoinjection, some authors propose adipose stem cells to enrich autologous fat grafts for mild to moderate depressions [43].

Others propose a recontouring procedure using hydroxyapatite onlay after the age of 14 to 16 years [39]. For patients with long-term persistent sequelae of trigonocephaly and anterior plagiocephaly surgery, Queiros et al. [44] used cutting guides to facilitate scheduled complex reconstruction with autologous bone; in their series, sequelae were due to a frontal ossification defect on the midline at the suturectomy level, with visualization

and palpation of the brain beats. Excellent aesthetic results were reported with this technique.

4. Conclusions

Prevalence of trigonocephaly has increased during the last two decades, with no clear contributing factors identified. As a result, practitioners increasingly have to deal with these patients. Neurodevelopmental disorders are frequent in syndromic trigonocephaly and not particularly rare in non-syndromic cases. Cytogenetic alterations are probably underestimated because chromosomal screening is not systematic in routine practice. For these reasons, genetic counseling is more and more effective in this pathology. Recent advances in surgery have mainly concerned endoscopically assisted techniques, but long-term cosmetic results need to be better refined because of potential under-correction by minimally invasive surgery.

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Disclosure of interest

The authors declare that they have no competing interest.

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