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FOCUS SESSION

The growth of the neurocranium: literature review and implications in cranial repair

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Abstract
Background Postnatal growth of neurocranium is prevalently completed in the first years of life, thus deeply affecting the clinical presentation and surgical management of pediatric neurosurgical conditions involving the skull. This paper aims to review the pertinent literature on the normal growth of neurocranium and critically discuss the surgical implications of this factor in cranial repair.
Methods A search of the electronic database of Pubmed was performed, using the key word "neurocranium growth", thus obtaining 217 results. Forty-six papers dealing with this topic in humans, limited to the English language, were selected. After excluding a few papers dealing with viscerocranium growth or pathological conditions not related to normal neurocranium growth 18 papers were finally included into the present review.
Results and conclusions The skull growth is very rapid in the first 2 years of life and approximates the adult volume by 7 years of age, with minimal further growth later on, which is warranted by the remodeling of the cranial bones. This factor affects the outcome of cranioplasty. Thus, it is essential to consider age in the planning phase of cranial repair, choice of the material, and critical comparison of results of different cranioplasty solutions.

Keywords Cranial growth · Cranial repair · Cranioplasty · Neurocranium · Precision medicine · Skull growth

Introduction

The knowledge of the postnatal growth mechanisms of neurocranium started with anatomical studies and significantly evolved with the readiness of radiological imaging modalities. Although the prevalent growth of the skull in the first years of life is obviously understood and is confirmed by ex vivo and in vivo radiological data, the clinical and surgical implications are frequently under-recognized or completely disregarded.

The aim of this paper is to thoroughly review the pertinent literature on the physiological volumetric growth of neurocranium and critically discuss the surgical implications of this factor in cranial repair. On these grounds, the biochemical mechanisms involved in cranial growth go beyond the purpose of this review and would be not discussed.

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Literature review

Methods

A search of the electronic database of PubMed using the key word "neurocranium growth" was performed, thus obtaining 217 results. We then applied a series of filters (human, English, and childbirth to 18 years) to refine the aforementioned research, thus selecting 46 papers. Papers dealing with viscerocranium growth or pathological conditions not related to normal neurocranium growth were excluded. Finally, 18 papers were included in the present review.

Cranial growth

The neurocranium can be divided into the cranial base, also known as the chondrocranium, which refers to the cranial base bones that originate from the paraxial mesoderm and undergo endochondral ossification, and the cranial vault, which is also known as the membranous cranium or calvaria [28].

The calvarial bones are connected together around their periphery by sutures that are bands of fibrous connective tissue that prevent premature bone fusion and are important new bone deposition sites that allow for uniform growth of the cranium during brain development.

As the cerebral and cerebellar hemispheres grow, the calvarial bones are displaced outward, by expanding intracranial structures. In fact, each flat bone is suspended, with the existent traction forces, within a widespread sling of the collagenous fibers of the enlarging inner (meningeal) and outer (cutaneous) periosteal layers. As these membranes grow in an ectocranial direction ahead of the expanding brain, the bones are carried with them and thus displaced (Fig. 1).

It is widely accepted that various genetic and epigenetic factors regulate bone formation at the sutures, with one of the key driving factors for skull growth being provided by the rapidly expanding brain, through the mechanical tension exerted on the immature dura mater. Indeed, the dura mater is considered the main regulator of osteogenesis, by producing signaling and growing factors [9].

These signals stimulate osteoclasts to break down the interior of the cranial element in order to provide more room for the growing brain. As a direct reaction to the destruction of the inner surface of the bone, osteoblasts on the ectocranial surface activate and begin laying down new bone on the exterior surface of the element. This corresponding action of destruction and construction upon the cranial elements, due to the pressure exerted by the brain, causes a direct correlation between the size and shape of the brain to the size and shape of the cranial vault, as the skull is essentially formed and molded by the increase of brain tissue. With the human brain having such a close developmental correlation to the cranial vault, it has been shown that the inverse relationship between the cranial vault and the brain is comparable. This parallel growth allows for the possibility to measure the external dimensions of the cranium and extrapolate the interior volume of the brain in physiological conditions.

During the early years of life, human brain volume increases rapidly and the cranium undergoes rapid morphological changes in both size and shape, with the neurocranium in particular required to expand to provide protection for the brain.

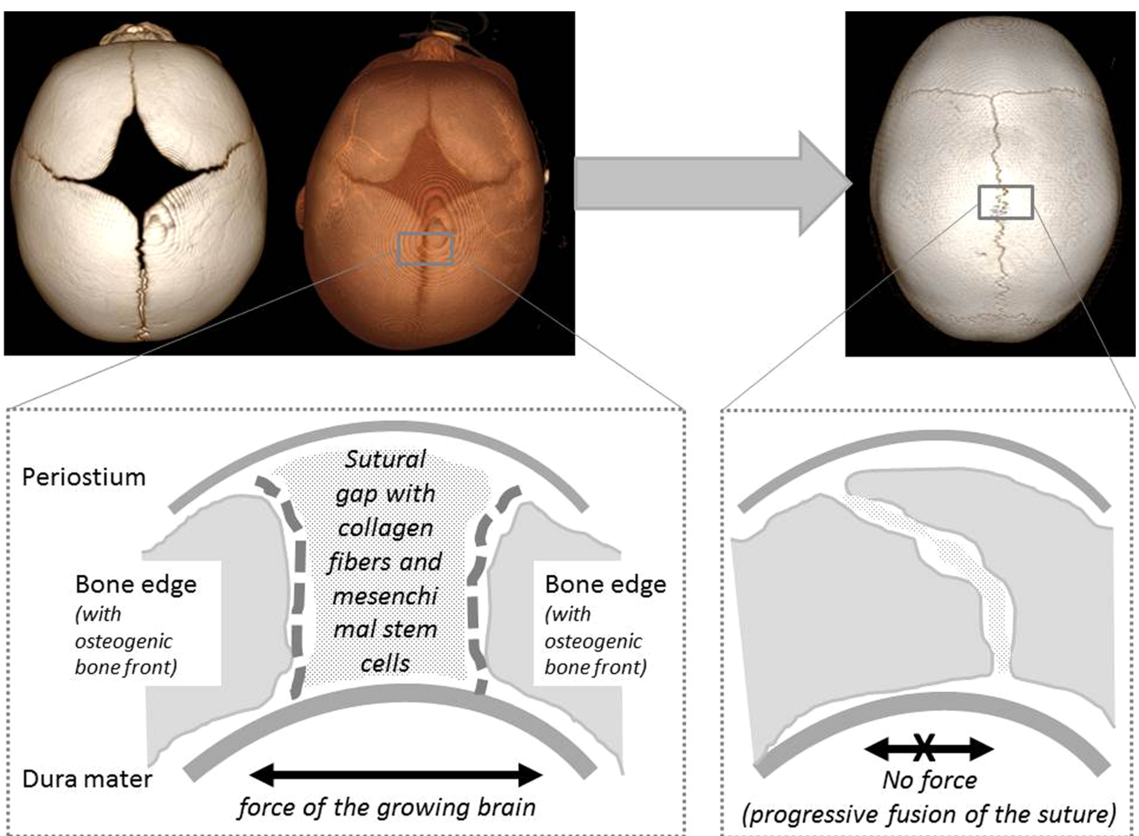

Fig. 1 The complex osteodural structure of the neurocranium with large and patent sutures and fontanelles in the first months of life (left), accounting for growth of the calvarium with outward displacement of the cranial bones and progressive bone deposition at the suture site. When brain growth is completed, the tension on the dura mater stops, thus resulting in closure of the fontanelles and sutures (right). See text for further details

Indeed, the neurocranium is normally estimated to be 25% of its adult size by birth, 50% by 6 months, 65% by 1 year, and 90% by 7 years, with minimal further growth after 10 years [15]. Variability of volume estimation at birth, ranging from 23 to 40%, has been reported through the literature. This may be partly due to the deformation and compression of the head related to the delivery, though this picture is estimated to solve spontaneously within a few days after birth. Indeed, overriding of cranial sutures after delivery is a common finding in daily clinical practice as well as the possibility of significant difference in head circumference between the measurement at birth and at discharge, due to the rapid resolution of this picture.

On the other side, variability at elder age may be observed through the literature studies according to the different methods used to estimate the volume (anthropometric or cephalometric versus more modern cross-sectional radiological methods). However, the trend of growth observed by different studies seems constant. The postnatal growth of the calvarium proceeds very rapidly during the first 2 years, particularly in the first year of age, and is followed by a much slower growth rate until approximately the seventh year when the skull approaches adult size.

The rapid cranial growth in the first years of life is well represented by the Center for Disease Control and Prevention (CDC) growth charts [27]. Indeed, the growth of occipito-frontal circumference (OFC) parallels the growth of the calvarium. In fact, in a postmortem study on 128 infants (age < 1 year), the thicknesses of the calvarium and dura increase with increasing OFC. On the other side, the vascular density within the dura decreases with increasing OFC, suggesting the loss of "activity" of the dura during its maturation and the concomitant skull growth [3].

Later on, the structure of calvarial bones maturates, by changing from unilaminar to trilaminar when the diploe appears in approximately the fourth year of life [29].

During the growth and maturation of the skull, the sutures and fontanelles close at different times. Mature suture closure occurs by 12 years of age, but completion continues into the third decade of life and beyond [15].

Methods to estimate skull growth

Initial studies estimate the growth of the skull by directly measuring the skull volume by water filling on a postmortem dry skull. Although this is considered the definitive standard for skull volume, a true normative database of volumes calculated using this direct method does not exist.

In vivo, the growth of the head has been studied by evaluating the main linear craniometric parameters on the subject or on the radiography of the skull (anthropometric and cephalometric method, respectively) and eventually calculating the intracranial volume with mathematical formulas, such as the ellipsoid formula or the one devised for dried skulls.

Technological evolution has allowed assessing these parameters more easily and accurately by means of sophisticated measurement instruments, such as optical scanners and stereophotography.

On the other hand, the introduction of CT scan and MRI offered the possibility to evaluate in vivo the intracranial compartment and calculate the intracranial volume by cross-sectional methods, such as the less accurate point-counting method and the more evolved planimetry method [19, 24].

Craniometric data

In one of the first craniometric studies, assessing the growth of the skull in the pediatric age, Lichtenberg measured widths, lengths, and heights from plain radiographs of the head of 226 French children aged up to 8 years. He used MacKinnon's formula to calculate the intracranial volume. Mean intracranial volume stops its growth by the seventh year of age [1].

Another study assessed skull growth beyond pediatric age, including 1058 Caucasian subjects, 555 males and 503 females in 20 consecutive age groups from 7 days to 20 years of age. They were evaluated by measuring linear craniometric parameters using manual instrumentation (the measuring instruments consisted of a metric linen spring tape graduated in millimeters, the spreading and sliding calipers of Hrdlitka, and a Western Reserve scepter) and calculating the cranial volume using the mathematical formula devised for dried skull.

The results show that at 1 year of age, the cranial volume has increased by a factor of 2.3 and the head circumference, cranial breadth, length, and height by a factor of 1.4 over that at birth. Subsequently, the pace of growth slows; at 5 years of age, cranial volume has increased up to a total factor of about 3 while head circumference and the other three cranial measurements have expanded by a factor of about 1.5 over the dimensions at birth. By 20 years of age, the cranial volume is about 3.8 times that at birth, and the head circumference and the three principal cranial dimensions have increased by a total factor of about 1.6. Moreover, the mean intracranial volume by 7–8 years of age approximates 90% of adult volume [5].

Interestingly, the growth of linear parameters is not uniform during the first years of life, since the horizontal length of the cranium is about 90% complete by 5 years, and the width has been largely established by about the second year [7].

Later on, further studies confirmed that by 5 years of age, the developmental level of all measurement in head width, head length, and circumference closely approach the maturation, although maturation slowly continues until elder age. Indeed, head length reached full maturation at 10 years in female and at 14 years in males. In females, head width showed the most advanced maturation at 14 years. In males, most head measurements matured at 15 years. Adult head height approached maturation at 13 in both sex. Head circumference reaches the greatest level of development in the first year (87.5%), at 5 years (93.9%), remaining growth till 18 years old [8].

These data pushed the following studies to focus on pediatric age, since the growth of the skull is very rapid in the first 2 years of life, particularly in the first year, and is almost completed by the age of 5 years.

More recently, the growth of the craniometric parameters has been assessed in infants at 6 and 12 months (T1 and T2, respectively) using an optical scanner combined with a stereophotogrammetric method. The highest increment of growth was observed in the total volume of the cranium, with an increase of 18.76%.

In contrast, the cephalic index, which is a measure of the width-to-length ratio, exhibited a significant decrease over the observation period [22]. This confirms the prevalent postnatal growth of the head length that was already observed by previous authors [7].

Sex-specific analysis showed a significantly higher circumference and length in male infants at 6 and 12 months of age, with no sex-related differences in the growth increment between T1 and T2 with respect to the circumference or any other two-dimensional parameter [22].

Radiological data

In vivo measurement of intracranial volume was not possible until the advent of modern-day sectional imaging technologies. Previously, intracranial volume was solely a mathematical approximation, using an ellipsoid formula or Mackinnon's formula. Numerous "normative" databases exist that are based solely on these estimated intracranial volumes. The accuracy of these techniques has been criticized, as the results obtained by these techniques were found to be statistically different from the actual volumes of skulls obtained by a water-filling method [24]. On the other hand, despite some differences in the absolute values related to the techniques, the trend of growth that was already observed by previous studies was confirmed.

Furthermore, the constant evolution of modern radiological exams and software tools for analysis is overcoming the limits of cephalometric studies. Thus, nowadays, computed tomography (CT) and magnetic resonance imaging (MRI) seem to offer accurate measure of the intracranial volume.

Initial studies based upon CT scan evaluated the intracranial area on a single slice (usually the midventricular) that was considered representative of the intracranial volume and subsequently of skull growth. This type of studies has several obvious limitations, but may provide some qualitative hints concerning the differential growth of the different portions of the head. In fact, the volume of the forehead area enlarged until the age of 2 years, and there were no significant changes thereafter. The volume of the occipital region increased with age under 10 years [14].

Subsequent studies based upon radiological examination and exploiting the refined and more reliable segmentation process offered the possibility to evaluate the whole exam rather than a single slice. CT data using the Cavalieri estimator method indicate that 95% of the final intracranial volume has been attained by 42 months for girls and 46 months for boys in a study involving 157 unaffected individuals, 82 females and 75 males, aged from 0 to 18 years [1]. The shape and rate of growth of male and female intracranial volume are similar, though the final mean intracranial volume is approximately 1.3 standard deviation larger in males.

The curves obtained in this study were compared with historical models obtained by direct method and craniometric method with volume estimation [5, 18], discussing the limits and bias of these previous studies to explain the differences observed.

Another study based upon CT scan included 123 children, 56 females and 67 males, with age ranging from 8 days to 6 years. In this study, the indirect CT imaging method based upon a segmentation software was validated with comparison to volume-filling method. A mean difference of 0.66% was obtained between the two techniques. The curve of growth provided by this study shows a doubling of the intracranial volume from birth to 9 months of age and a tripling of the intracranial volume by 6 years of age [16].

A similar study created the intracranial volume growth curve for Asian children, thus revealing that it parallels curves previously reported for other races, while trending slightly higher in values [17]. The shapes are consistent, even if overall brain volume in Asians was reported to differ slightly with respect to white and black races. Patients that Kamdar et al. and Sgouros et al. have analyzed were racially mixed [16, 25], so the authors conclude that the slight deviation mentioned above is not untoward [17].

Similar findings were provided by MRI. A first study included 24 children during the first 3 years of life. A series of intracranial volumes obtained from MRI data and showed intracranial volume in the first few months of life is on average 900 cm^3 in boys and 600 cm^3 in girls, increasing to 1300 to 1500 cm^3 by 15 years. By the age of 2 years, intracranial volume has reached 77% (1150 cm^3 in boys and 1000 cm^3 in girls) and, by 5 years, 90% (1350 cm^3 in boys and 1200 cm^3 in girls) of the volume observed at age 15 years. It is notable that, although the change in intracranial volume that accompanies age is not linear, there seems to be a segmental pattern. Three main periods can be distinguished, each lasting approximately 5 years (0–5, 5–10, and 10–15 years), during which the growth of intracranial volume is linear, although the rate of growth differs between those periods. The overall growth trend demonstrated in this series corresponds well with established trends for other parameters of the human head from anthropometric and 2D radiographic measurements [25].

Nowadays, the evolution of software allows to significantly fastening the methodological process used in these studies to obtain normative database of intracranial and brain volume growth. A recent study exploiting synthetic MR segmentation included 122 subjects, with age ranging 0.1–21.5 years. The intracranial volume increased rapidly from 0 to 18 months, with progressive slowing, reaching a plateau in early adolescence with an intracranial volume of approximately 1400 mL. In spite of this sentence, the curve included in the paper clearly shows that the plateau is reached already by 7 years of age [21].

Discussion

Clinical, anthropometric, and radiological data clearly show that the skull growth is very rapid in the first 2 years of life and approximates the adult volume by 7 years of age, with minimal further growth later on, which is warranted by the remodeling of the cranial bones. Obviously, this has clinical and surgical implications in the management of pediatric neurosurgical conditions. Craniosynostosis surgery represents a good example of how the surgical treatment options and timing may be tailored according to this factor [6]. On the other hand, this factor has been poorly considered in cranial repair so far.

Indeed, cranial repair in children is burdened by significantly higher rate of complications compared with adult counterpart [4]. In particular, the risk of autologous bone resorption seems to linearly decrease with age in the pediatric population [2, 11, 13, 20], as initially hypothesized by our group [11] and recently confirmed by a large multicenter retrospective study [23]. The failure of autologous bone cranioplasty has been partly explained by general problems that are shared with the adult counterpart, as the method of storage, and peculiar issues that are related to the age of the patient, as the minor bony reserve in children. However, the impact of the growing brain with its pushing force on the stability, and consequently on the outcome, of cranioplasty has been underestimated so far. Once the skull and dura are open, the growth of the skull is somehow impaired. Thus, the residual potential of growth of the skull should be not underlooked in cranial repair, though it would be better to consider the growing potential of the brain, since the growth of the skull is directly related to the growth of the brain. When we deal with cranial repair, we should carefully consider if a brain injury coexists and the entity of parenchymal atrophy that would eventually affect the potential of growth of the skull. In other words, cranial repair of hemispheric defect in an infant would be not problematic if a concomitant severe injury of the brain is present. On the other side, cranial decompression for subdural hematoma in the first years of life represents the most challenging picture for cranial repair, since the brain parenchyma is frequently preserved resulting in the highest risk of craniocerebral disproportion (see the following paper in the focus session for further details).

The impact of age-related factors may be also noticed analyzing the failure rate of alloplastic material. The results of CustomBone (CBS), that is a custom-made device made of porous hydroxyapatite with biomimetic and osteoconductive properties, seem highly significant. Post-marketing surveillance studies in pediatric population [10, 11], compared with data pulled from large clinical studies in adults, showed that the failure rate in children under 7 years of age is significantly higher (20%) than reported in patients aged 7–13 years old that on the other hand is roughly comparable with adults (6.6% versus 8%).

Thus, the growing neurocranium represents a challenge for cranial reconstruction as autologous bone flap is burdened by high risk of resorption and custom-made prosthesis has significant complications that may be partly related to defective osteointegration.

This figure is less clear for other alloplastic material since age stratification in the pediatric population is completely lacking through the current literature.

However, the lack of osteointegration and the impossibility to “grow” of alloplastic materials have been largely recognized [12]. The evidences that poly-methyl-methacrylate (PMMA) should be avoided in children younger than 5 years old may be related to the prevalent growth of the skull in this period.

Similarly, this argument may be used to critically analyze the results of some papers reporting good results with material, such as the titanium, usually considered to be avoided in children. Indeed, Williams et al. [26] suggest that in children, results are comparable with those of the adult population. However, all the subjects included in the study were older than 7 years of age. On the other hand, in younger children, the use of titanium has been complicated by skin breakdown, decubitus, or “sinking into the bone.”

Finally, another argument indirectly sustaining this comes from the use of the exchange cranioplasty, at least in infants and toddlers. Although the main advantage of this procedure is considered the possibility to exploit a full-thickness calvarial graft, its effectiveness may be partly explained by the impact on cranial growth. Indeed, cranial decompression may impair the physiological cranial growth and the delay between decompression and cranioplasty may make irreversible this process, thus affecting the outcome of cranioplasty. The exchange cranioplasty is a reconstructive solution based on the displacement of the normal calvarial bone over the cranial defect that may involve the contralateral intact hemicranium. Bony decompression of the unaffected site may partly buffer the expanding forces of the growing brain, which are driven away from the affected side and thus from the cranioplasty [10].

Table 1 Age stratification with related features of skull growth and hints for cranial repair

Age group	% skull growth	Residual potential of growth	Resorption risk of autologous bone	KO rate of CBS	Options for cranial repair	Alternative options
0–1 year	25➔~60	High	~100%	n.s.	• Autologous-bone assisted cranioplasty • Exchange cranioplasty	Decompressive craniotomy
1–7	~60➔~90	Medium	~80%	~20%	• Autologous-bone assisted cranioplasty • Other materials -when autologous bone is not available -osteointegrative solutions are preferred	Solutions to manage the residual potential of growth of the skull?*
7–18	~90➔100%	Low	~20–50%	6–8%	• Autologous-bone assisted cranioplasty • Other materials -when autologous bone is not available -osteointegrative solutions are preferred	Similar to adults

KO, complications; CBS, CustomBone Service (custom-made macroporous hydroxyapatite)

*See the following paper in the focus session for further details

In conclusion, age stratification seems essential to personalize the approach to cranial repair in children. On these grounds, age under 7 years represents a negative prognostic factor and the impact of age further increases in the first 2 years of life, due to the rapid growth of the skull.

Therefore, a proposal for stratification by age would be (i) under 1 year of age, when the skull growth is extremely rapid, (ii) in 1–7 years of age, when the skull growth is slower but still significant, and (iii) over 7 years of age, when the skull could be assimilated to the "inert" adult skull.

The impact of age-related factors would be the highest in the first group, with a rate of resorption of almost 100%. This would require different solutions for cranial repair, as the exchange cranioplasty, and eventually different solutions for relieving the intracranial hypertension, as decompressive craniotomy rather than craniectomy (see the dedicated paper in the focus session for further details). On the other hand, the role of these factors significantly decreases in the last group of patients and solutions adopted for cranial repair in adults warrants the same results. In the intermediate group, the role of these factors would be variable and surgical variants would be eventually required for proper cranial repair, as expansion osteotomies in less severe cases and either augmented cranioplasty or contralateral cranial expansion in most severe cases (Table 1).

Compliance with ethical standards

Conflict of interest The authors have no funding or conflict of interest to disclose.

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