SUMMARY

BIOMEDICAL ASPECTS OF CRANIAL SUTURES:

MICROSTRUCTURE, PHYSIOLOGICAL CLOSURE, METOPISM

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The aim of this work is to investigate the microstructure and physiological closure of the cranial sutures and to evaluate the peculiarities of cranial morphology in *metopism*.

Our observations on the structure of the cranial sutures at different stages of obliteration in dry skulls have confirmed that the open (functioning) suture is characterized by a relatively large gap between the compact bone edges of the adjacent cranial bones. During the process of closure, the suture undergoes reorganization of the microarchitecture, which eventually leads to its obliteration. The remodeled sutural area follows the 3-layered pattern of organization typical of the flat cranial bones. Generally, the sagittal suture closure progresses from the inner table through the diploe to the external table; however, the process is irregular and could be initiated at each of the three bone layers. Moreover, the closure of the sagittal suture begins and spreads simultaneously along the entire suture length, which indicates that there is no specific point or area of initiation.

Based on the observed changes in the suture microarchitecture during closure, we have developed an original descriptive scale for scoring the contact between the bone edges at the level of each of the bone layers. The scale allows us to precisely assess the degree of sagittal suture closure in cross-sectional tomograms. Thus, considering the closure of the sagittal suture in individuals with a known age at death, we have established that there is a positive, although weak, correlation between the closure of the suture and the individual's age. This finding confirms that suture closure is not solely a function of aging, and the factors initiating and managing this process are heterogeneous and complex. Nevertheless, we have developed regression models for age-at-death prediction based on the degree of sagittal suture closure using machine learning algorithms. We have found that the most accurate models are those learned from the dataset that describe the examples only by the degree of closure of the external table along the sagittal suture length. The addition of other attributes worsens the predictive ability of the learned models. These results clearly demonstrate that sagittal suture closure is not a reliable age-at-death indicator and should be used only as a supportive method in osteological expertise.

We have provided original evidence that the sagittal suture closure in the metopic crania is significantly delayed compared to that in the non-metopic ones. This suggests that the factors maintaining the metopic suture patency are not local but also affect the closure of the other calvarial sutures. Moreover, the elaborated linear regression models have demonstrated that the error in the age-at-death prediction for the metopic crania is almost two times bigger than that for the non-metopic ones. This clearly indicates that in individuals with *metopism*, there is no link between sagittal suture closure and aging.

We have performed comparative morphometric analyses between the metopic and non-metopic cranial series. Studies of the nasofrontal and orbital regions have demonstrated that they are significantly modified in *metopism*. We have found that the considerable differences in the nasofrontal region are mainly related to the nasal bones, which are shorter and wider in the metopic series. A comparative angular characteristic of this region has also shown that the metopic crania have significantly flattened glabella with shorter and less prominent nasal bones. There are no significant differences in the orbital dimensions or area between the series. The larger biorbital width in the metopic crania is related to a significantly greater interorbital distance, which in turn is a precondition for a wider nasal bridge.

In order to select the most distinctive features between the series, we have described the crania by quantitative (metric) and qualitative (anatomic variation) features (attributes) and have applied data mining algorithms to the collected data. The most accurate model for classifying a cranium as metopic or non-metopic turns out to be a decision tree based on four quantitative features of the frontal bone. This model reaches a classification accuracy of 83%. We have also applied geometric morphometric approaches to compare the size and shape of the metopic and non-metopic crania as independent components. Our results have demonstrated that there are significant size differences only in the neurocranium, but not considering it as a whole entity; rather, the differences are in the neurocranium segments, i.e., they are regional and reflect a size redistribution between the segments. Thus, in metopic crania, the size of the frontal part is significantly increased, but at the expense of the middle (parieto-temporal) and occipital parts, which are considerably reduced. At the same time, the total size of the neurocranium between the metopic and non-metopic crania does not differ significantly. Considering the shape, our results have shown that it differs significantly between the metopic and control series in all landmark configurations. The difference is greater in the parieto-temporal segment, while in the occipital one, the variation in shape is significantly influenced by size. In general, the shape modification in the metopic series reflects a mediolateral widening and an anteroposterior shortening, which contributes to a globular outline of the

neurocranium in *metopism*. Our results have demonstrated that despite the close interrelation between the development of the cranial vault and base, the metopic suture persistence, linked to a specific configuration of the vault, is not related to significant changes in the angulation of the base, measured by the cranial base angle.

Our original results have provided evidence that metopic suture persistence is associated with reduced pneumatization of the frontal sinus in the vertical part of the frontal bone. Bilateral aplasia of the frontal sinus is less common than unilateral aplasia, which in turn is predominantly right-sided. At the same time, our results have also demonstrated that the pneumatization of the frontal sinus is a spatially coordinated process that progresses proportionally in the vertical and horizontal parts of the frontal bone. Thus, the reduced pneumatization in the vertical part of the frontal bone in the metopic series is not compensated by a greater pneumatization in the horizontal part.

In our studies, we have observed that metopic skulls often demonstrate supernumerary calvarial bones, formed either by fragmentation of the normal ossification centers or by the emergence of additional ones in the cranial sutures and fontanelles. We have also found that the additional bones in the occipital region are not related to specific changes in the shape and size of the neurocranium. *Metopism*, in turn, has a significant impact on the overall morphology of the neurocranium, which is intensified by the presence of variations in the occipital region.

In summary, our results have provided considerable evidence that *metopism* is associated with a specific configuration of the cranial vault, delayed closure of the major sutures, the presence of supernumerary bones, and the underdevelopment of the frontal sinus. The combination of these features could be considered a sign of a generalized disturbance in the intramembranous ossification, which is overexpressed in some types of skeletal dysplasia. Consequently, it is important to consider *metopism* as a manifestation of an ossification disturbance, which could vary from a combination of "innocuous" variations to skeletal dysplasia. A further use of experimental models and data from clinical practice could contribute to understanding the etiology of *metopism*, including the boundaries between "innocuous" variations and pathology. The use of high-resolution 3D imaging, artificial intelligence, and mathematical modeling contributes significantly to data collection, analysis, interpretation, and elaboration of models, which are important steps in understanding cranial suture biology.