

Review

by Prof. Lazar Jelev Slavov, MD, PhD

Department of Anatomy, Histology and Embryology, Medical University - Sofia,

Member of the scientific jury according to the Order No. RD-09-37 of 27.07.2023 of the Director of
IEMPAM-BAS

of the Dissertation for the award of the scientific degree "Doctor of Sciences",

Field 4. Natural Sciences, Mathematics and Informatics, Professional field 4.3. Biological sciences,
Scientific specialty "Anthropology"

Title: Medico-biological aspects of cranial sutures: microstructure, physiological closure, metopism

Author: Assco. Prof. Sylvia Yanakieva Nikolova, IEMPAM-BAS

The review was prepared in accordance with the Law on the Development of Academic Staff in the Republic of Bulgaria (LADRB), the Regulations for the Implementation of the LADRB and the Regulations for the Conditions and Procedures for the Acquisition of Scientific Degrees and the Holding of Academic Positions at IEMPAM-BAS.

Biographical data and career development

Assoc. Prof. Sylvia Yanakieva Nikolova holds a Master's degree in General Anthropology, majoring in Biology from Sofia University "St. Kliment Ohridski" in 2005. In 2009 she was appointed as a Biologist-Specialist at the Institute of Experimental Morphology, Pathology and Anthropology with Museum of BAS (IEMPAM-BAS). In 2011 Silvia Nikolova obtained the educational and scientific degree "Doctor" in the scientific specialty "Anthropology" after a successfully defended dissertation entitled "Anatomical variations of the skull - anthropological characterization and assessment of intersex and bilateral differences". In 2011, Dr. Nikolova was appointed to the position of Assistant Professor at IEMPAM - BAS, and in 2012, after a competitive examination, she took the position of Senior Assistant Professor at the same institution. In February 2023, she became an Associate Professor.

Assoc. Prof. Silvia Nikolova is a member of the Bulgarian Anatomical Society, the European Anthropological Association, the Working Group on Anthropology of the Federative International Programme for Anatomical Terminology (FIRAT).

Assoc. Prof. Nikolova has completed an intensive course on digitization and creation of replicas of cultural heritage objects and on the use of new technologies and mobile applications for museums in 2015 at UASG under the European project of the 7th Framework Programme.

Project and expert activities

Assoc. Prof. Sylvia Nikolova has presented a list of participation in 6 scientific projects - 4 at the National Research Fund of the Ministry of Education and Science, 1 project at the Bulgarian Academy of Sciences and 1 project under the Human Resources Development Operational Programme. In 3 of the projects Assoc. Prof. Nikolova is a supervisor, including young scientist - supervisor.

The expert activity of Sylvia Nikolova comprises numerous reviews for journals such as Anatomy Research International, Journal of Oral and Maxillofacial Radiology, Surgical and Radiologic Anatomy, Argentine Journal of Clinical Anatomy, International Journal of Osteoarchaeology, European Journal of Forensic Science, Morphologie, Oral Diseases, International Medical Case Reports Journal, Journal of Applied Oral Science, Archaeological and Anthropological Sciences.

Relevance of the dissertation topic for the award of Doctor of Sciences

The subject of the presented dissertation is a detailed study of the microstructure, age dynamics and the process of physiological closure of the cranial sutures as well as a comparison of the anthroposcopic and anthropometric characteristics of skulls with adherent sutura frontalis in comparison with those with persistent sutura frontalis - sutura metopica (metopism) in a large amount of bone material.

From the literature review presented, it can be concluded that the underlying mechanisms that regulate the formation, functioning and closure of cranial sutures are not yet fully understood and remain the subject of active research. The clinical significance of the process of cranial suture closure is mainly associated with the process of premature suture closure (craniosynostosis), which necessitates surgical remodeling of the cranial cavity. The opposite process, delayed closure of the cranial sutures, specifically metopism, remains a poorly studied condition as it is considered a harmless anatomical variation rarely associated with clinical symptomatology. All this clearly highlights the need to plan and conduct comparative studies in homogeneous and statistically representative cranial series, and to analyze and interpret the collected data using modern and interdisciplinary approaches.

Methodology of the study

For the purposes of the dissertation, medieval male and female skull series from the osteological collection of the IEMPAM-BAS were examined, including a total of 318 skulls of adult individuals, of which 159 were identified as male and 159 as female, as well as a modern series of skulls of adult males, which are stored in the Military Mausoleum - Ossuary at the National Museum of

Military History, Sofia. For the comparative analysis performed entirely on the modern skull series, the skulls were grouped into two series - a metopic series (with fully preserved metopic suture) and a control series (with no traces of metopic suture).

Morphometric analyses were performed entirely in virtual space after generating two- and three-dimensional images of the skulls under study using a Nikon XT H 225 industrial microcomputed tomography (μ CT) system (Nikon Metrology). To generate polygonal three-dimensional models, the skulls were scanned with a Creaform VIUscan handheld laser scanner (Creaform Inc., Quebec, Canada). A program of craniometric points was prepared for each individual study. The three-dimensional coordinates of the points were taken using the computer program MeshLab version 2016.12.

Characteristics and evaluation of the doctoral thesis

The dissertation is presented on 251 pages and contains in sufficient volume all the necessary parts: Introduction - 1 page, Literature review - 38 pages, Aim and objectives - 1 page, Material and methods - 21 pages, Results and discussion - 129 pages, Summary - 4 pages, Conclusions - 1 page, Scientific contributions - 2 pages. The structure and the content of the dissertation are meaningfully well linked and balanced in terms of the volume of information.

The literature review is distinguished by its detail and presents in an extended form a comprehensive analysis of the process of morphogenesis of the bones of the cranial vault - embryonic development and ossification of the bones, formation of the bony sutures and the process of physiological closure of the cranial sutures, as well as the use of these data to determine age by bony remains. The molecular and cellular mechanisms governing cranial suture morphogenesis and determining pathological biology are discussed in detail. The main focus of the review is on presenting the known literature on metopic suture and its persistence status - metopism with its frequency of occurrence, skull configuration, degree of frontal sinus pneumatization, and association with anatomical variations and pathological conditions. In the concluding part, the annotation of the research, the dissertation summarizes the known data and makes a reference to the stated aim and objectives.

The methodological part of the study includes a detailed description of the bone material used and the digitization process with subsequent data processing and analysis.

The results of the researcher's own study are reported in sufficient detail and discussed with references to published data in the world scientific literature. Firstly, detailed results of a study of the microstructure of cranial sutures using microcomputed tomography are presented. This is followed by an analysis of the dynamics in the process of physiological closure in sagittal and squamous sutures. The closure processes of frontal-nasal, internasal and sagittal sutures in cases of

metopism are analyzed. Data from a study on the configuration of the skull in the orbital and nasal-frontal regions as well as the angle of the skull base in methopism are presented. Of interest are studies on the degree of pneumatization of the frontal sinus in metopic skulls, as well as the association of metopism with anatomical variations (excessive number of ossicles, ossification of the atlas) and some pathological conditions in the cranial bones.

The results are illustrated with 71 figures and contain 28 tables with analysed data.

In summary, the dissertation points out that the results of the study provide concrete evidence for the association of metopism with a specific configuration of the cranial vault and delayed suture closure, the presence of accessory bones, and also with underdevelopment of the frontal sinus. The combination of all these features can be considered as an expression of a generalized disturbance in intramembranous ossification. In the author's opinion, similar to craniosynostosis, metopism should be considered as a complex disturbance in cranial development.

The conclusions drawn are logical and consistent.

The bibliography contains 378 references. A significant number of the cited sources were published after 2000.

Contributions and significance of the dissertation for science and practice

In the presented dissertation, Assoc. Prof. Sylvia Nikolova defines six original contributions of theoretical value: 1/ The detailed structure of the open cranial sutures and the changes in the process of closure and reorganization to the three-layer structure characteristic of the bones of the cranial vault have been established. 2/ It has been shown that the physiological closure of the main cranial sutures correlates positively but weakly with the age of the individual, which makes models for age prediction by the degree of suture closure unreliable. 3/ Methopism has been shown to be associated with a generalized delay in cranial vault suture closure, confirming the presence of common factors. 4/ It has been demonstrated that metopic skulls are characterized by specific and significant modifications in the cranial vault, orbital and frontal-nasal regions, but not the cranial base. 5/ It has been shown that pneumatization of the frontal bone is a spatially coordinated process and the development of the frontal sinus is significantly less pronounced in metopism. 6/ It has been hypothesized that methopism-specific features can be viewed as a disturbance in intramembranous ossification that is overexpressed in some types of skeletal dysplasias; therefore, methopism should be considered as a complex condition associated with developmental disturbance.

Six contributions of scientific and applied value are also mentioned in the thesis: 1/ Protocols have been developed for the generation of three-dimensional images of dry skulls by laser scanning and micro-computed tomography at optimal parameters to allow the acquisition of reliable morphometric data and statistical analyses. 2/ An innovative method has been developed and a

protocol for scanning objects larger than the detector area of the μ CT system (Nikon XT H 225) has been validated. 3/ A virtual collection of high-resolution three-dimensional images (polygonal and volumetric) of homogeneous metopic and control series of skulls of adult males from the modern Bulgarian population was created. 4/ An original 4-level scale for reporting the degree of sagittal suture closure in cross-section was developed. 5/ Configurations of points describing the morphology of the whole skull as well as of its parts have been constructed, and approaches from the field of geometric morphometry have been applied to comparative analyses of size and shape in metopic and control skull series. 6/ Methods from the field of artificial intelligence have been adapted and applied to qualitative and quantitative skull characteristics to extract the features that most clearly distinguish metopic from control skulls and data on the degree of closure of the cranial sutures to create models for predicting age at death of an individual.

Assessment of the publications related to dissertation

Assoc. Prof. Sylvia Nikolova has attached a list and copies of 32 full-text publications and a list of 35 scientific presentations at national international and foreign scientific forums related to her dissertation work. Most of the submitted articles have been published in national and international refereed journals with IF and SJR (n=18). A list of 118 publications citations is presented. The citation index (h-index) of Assoc. Prof. Sylvia Nikolova is 7.

Abstract

The abstract of the thesis is written as required and reflects in sufficient detail the main parts, including the results achieved in the thesis.

CONCLUSION

The dissertation of Assoc. Prof. Sylvia Yanakieva Nikolova, entitled "Medical and biological aspects of cranial sutures: microstructure, physiological closure, metopism" contains valuable scientific and applied results that represent an original contribution to science.


The analysis of the documents shows that Assoc. Prof. Sylvia Nikolova meets the obligatory conditions for the award of the scientific degree "Doctor of Sciences" under the Law on the Development of Academic Staff in the Republic of Bulgaria (LADASB), the Regulations for the Implementation of the LADASB and the Regulations on the Conditions and Procedure for the Acquisition of Scientific Degrees and the Occupation of Academic Positions at the IEMPAM-BAS.

Group of indicators	Content	Assoc. Prof. IEMPAM-BAS	Assoc. Prof. Sylvia Nikolova
A	Indicator 1	50	50
B	Indicator 2	100	100
C	Indicator 3 or 4	-	-
D	Sum of indicators 5-10	100	120
E	Sum of points in indicator 11	100	104
F	Sum of indicators 12-20	-	-
Min. total score		350	374

On the basis of the above, I confidently give my **positive assessment** of the dissertation and propose the members of the scientific jury to **award** the degree of Doctor of Sciences to Assoc. Prof. Sylvia Yanakieva Nikolova.

12.10.2023

Sofia


Prof. Lazar Jelev Slavov, MD, PhD