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Review

Jelena Krmpotić-Nemanić (1921–2008): Contributions to Human Neuroanatomy

Miloš Judaš[1], Zdravko Petanjek[1,2] and Ivica Kostović[1]

[1] University of Zagreb, Croatian Institute for Brain Research, Zagreb, Croatia
[2] University of Zagreb, School of Medicine, Department of Anatomy, Zagreb, Croatia

A B S T R A C T

Jelena Krmpotić-Nemanić (1921–2008) was a world-famous anatomist, internationally distinguished otolaryngologist, a member of the Croatian Academy of Sciences & Arts and appreciated professor at the School of Medicine University of Zagreb. The founding influence in her scientific career came from her mentor Drago Perović who was a student of Ferdinand Hochstetter, the leading authority in the field of human developmental neuroanatomy and embryology. Such an influence was obviously important in early shaping of the research agenda of Jelena Krmpotić-Nemanić, and it remains important in a long series of studies on developing human telencephalon initiated by Ivica Kostović and his collaborators – with an always present and active support of Jelena Krmpotić-Nemanić. The aim of this mini review is to briefly describe her numerous contributions to the anatomy of the human peripheral and central nervous system.

Key words: *Ferdinand Hochsteter, Drago Perović, developmental neurobiology, neuroscience, embryology, telencephalon, human, otolaryngology, anatomy, neurocranium*

Introduction

Jelena Krmpotić-Nemanić (1921–2008) was a world-famous anatomist, internationally distinguished otolaryngologist, a member of the Croatian Academy of Sciences & Arts, perhaps the best known and appreciated professor for generations of students at the University of Zagreb, and our teacher, supervisor and friend. Through the founding influence of her mentor Drago Perović, as well as her own efforts and research and teaching endeavours, we are all descendants and inheritors of the long and noble tradition of the Austrian-German anatomy, represented by many famous anatomists such as Joseph Hyrtl, Carl Toldt and Ferdinand Hochstetter. In fact, Drago Perović was a student of Ferdinand Hochstetter[1,2] (the leading authority in the field of human developmental neuroanatomy and embryology – see Hochstetter[3–7]), and Hochstetter's beautiful models of embryonic human brain are still availabe to students in our Department of Anatomy's museum. This tradition has been underlined by the fact that Jelena Krmpotić-Nemanić had the honour to edit 26th and 27th edition of the famous Toldt-Hochstetter Anatomical atlas[8,9] and its translation in Croatian[10] as well as to publish a highly esteemed textbook of surgical anatomy of the head and neck[11] which was soon translated in English[12] and Italian[13].

Such an influence was obviously important in early shaping of the research agenda of Jelena Krmpotić-Nemanić, and it remains important in a long series of studies on developing human telencephalon initiated by Ivica Kostović and his collaborators – with an always present and active support of Jelena Krmpotić-Nemanić (Figure 1). The aim of this paper is to briefly describe her numerous contributions to the anatomy of the human peripheral and central nervous system.

Contributions to Clinically and Surgically Relevant Anatomy of the Human Peripheral Nervous System

Jelena Krmpotić-Nemanić was not only an anatomist, but also a practicing clinician – otolaryngologist. Thus, all aspects of her anatomical studies were always conducted with an eye for practical (clinical and teaching) application of newly acquired knowledge. In fact, her

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Fig. 1. Members of the Laboratory for neuroanatomy at the Department of Anatomy, School of Medicine, University of Zagreb in year 1984. Standing (from left to right): Ivica Kraćun, Nenad Bogdanović, Zdenka Cmuk, Ladislav Mrzljak, Danica Budinšćak August Mijić. Sitting: Zlatko Kelović, Jelena Krmpotić-Nemanić, Ivica Kostović.

early anatomical studies related to certain aspects of otolaryngological practice won her a quick and enduring international reputation.

The first line of research may serve as a clear example of her originality and creative approach to classical anatomical studies. These are studies on the neuromuscular chronometric index, which she was first to describe and put to practical use. The neuromuscular chronometric index is a numerical value indicating the moment of the arrival of action potential at the innervated muscle, derived from the relationship between the length of the nerve and the average caliber of its axons. Thus, the determination of this index in a given neuromuscular system (e.g. innervation of laryngeal, pharyngeal, buccal and intercostal muscles important for phonation) can provide the insight into the sequence of activation of individual muscles[14–28] and can be usefully applied in diagnosis of speech disorders such as stottering[29–31].

The second, and equally important, line of research was developed in collaboration with professor Ante Šercer and focused on clinically important features of the cranial basis[32], development of the labyrinthine capsule[33], the pathogenesis of otosclerosis[34,35] and presbyacusis[36–39]. With her characteristic wit and creativity, Jelena Krmpotić soon generalized these findings to explain the pathogenesis of presbyostasis and presbyosmia[40,41] and the appearance of presbyacusis in Down's syndrome[42,43]. She proposed a new concept – that the progressive ossification of bone openings (leading to a compression of auditory nerve fibers) represents the cause of presbyacusis, and that similar changes may be involved in the pathogenesis of presbyostasis and presbyosmia. This line of research was continued in a number of publications with her colleagues and associates at the Department of Anatomy[44–48] including the tomographical and densitometric studies of the labyrinthine capsule[49–54] and the development of the inner ear labyrinth[55,56]. She also continued to publish important studies on the clinically important variability of the cranial base[57] and the junctional regions between the eye and the brain[58] and the nose and brain[59–62].

As she realized that gradual compression of cranial nerves (caused by ossification of their bone passages) can lead to neurological symptoms, she also realized that other types of nerve compression may have a similar pathogenetic role, too. Thus, she found that the presence of a lymph node in the facial canal can cause facial cramps[63], that anatomical variations can cause mandibular neuralgia[64], and she conducted several pioneering studies on the application of conduction anaesthesia in the treatment of facial cramps and Bell's palsy[65–69], or the treatment of Morton's metatarsalgy[70]. This work culminated in the publication of an internationally important monograph on peripheral nerves compression syndromes, in collaboration with her former student and presently professor of orthopaedic surgery and the member of the Croatian Academy of Sciences & Arts, professor Marko Pećina[71–73]. Finally, she published several studies relevant for neurosurgical approaches to nerve of Vidius[74,75], to the nervus petrosus superficialis major[76], to the hypophysis[77], to radiological imaging of the brain and its ciŠternal spaces[78–80], and to the role of vegatative nervous system in the pathogenesis of headaches[81,82].

For all these important contributions, Jelena Krmpotić-Nemanić received many prestigious international awards, such as: Jansen Award and the title of Laureate of the National Medical Academy in Paris (1957) – for the discovery of neuromuscular chronometric index; Ruđer Bošković Award (1977) – for her studies of otosclerosis and presbyacusis; Ludwig Hayman Award (1979) – for her studies of head and neck angiology; and »Oesterreichisches Ehrenkreuz für Wissenschaft und Kunst I. Klasse« (1979) – for her completely revised edition of the Toldt-Hochstetter Anatomical Atlas.

Contributions to the Anatomy and Development of the Human Central Nervous System

As already mentioned, being deeply involved in the Hochstetter-like approach to human anatomy, Jelena Krmpotić-Nemanić in fact started her research career by investigating certain features of the human brain and skull. This also illustrates how an excellent education coupled with a keen eye and meticulous hard work could lead to discovery of hitherto unnoticed macroscopical features of the human brain even in the middle of the twentieth century. In these studies, Jelena Krmpotić-Nemanić started from the initial discovery that a defined bone crest, which she named *Jugum cerebellare intersemilunare* (and later described in the leading anatomical journal of that period)[83], exactly corresponds to the position of the horizontal cerebellar fissure and thus marks the border between the superior and inferior cerebellar semilunar lobules. Thus, she immediately became inter-

ested in the old and still unresolved problem in the human neuroanatomy – why some cortical gyri leave impressions on the developing skull? This led to a thorough investigation of a large series of developing and adult human skulls[84,85]. She analyzed a total of 1316 human skulls (124 fetal, 157 aged 1 to 18 postnatal months, 37 aged 18 months to 10 years, and 1122 older than 10 years). The important finding was that about 50% (16 out of 37) of human occipital bones display characteristic *Impressiones gyrorum cerebelli* – but, this phenomenon is transient and occurs only in children aged 1.5 to 10 years[84,85]. In the subsequent study[86,87], she discovered a new kind of cerebellar lobuli (*Lobuli spirales cerebelli*) which were hidden in the depth of horizontal and some other fissures. For that study, she analyzed macroscopically 252 cerebellar hemispheres, as well as 3 celloidin-embedded, serially sectioned and borax-carmine-stained cerebella of the fetuses from the last trimester. Finally, she used two gelatine-embedded, serially sectioned and borax-carmine stained cerebellar hemispheres to make detailed models by using a well-known Born's reconstruction method by means of wax plates. Important finding was that spiral lobulles occur only in the neocerebellar (lateral) part of cerebellar hemispheres, which is connected with pons and neocortex and is the last part of cerebellum to develop gyri, to myelinate and to attain the morphological maturation of its cells[86]. These observations concerning the spiral lobules of the human cerebellum were presented at the International Anatomical Congress in Oxford in July 1950.

After these initial studies, Jelena Krmpotić turned to the most important and unresolved problem: how and why gyri and sulci develop in their characteristic form and arrangement in both the cerebellum and the cerebrum? As described in a recent review[88], more than a century-old discussions of developmental determinants of convoluted cortex have centered around four general subject areas: normal development, the role of nonneural tissues in development (e.g. skull, blood vessels), experimental alterations of development, and developmental pathology. Historically, two contrasting views have been proposed to account for the folding and fissuring of cortex[88]. In one view, the structural differences between cortex of gyral crowns, sulcal walls, and fundi are seen as secondary to mechanical folding, and therefore functionally insignificant. In the other view, these differences are conceived as being structurally, connectionally, and functionally significant. Jelena Krmpotić was one of the earliest representatives of the second view. She first made an extensive review of all previously published studies – and that was a feat characteristic for her erudite mind from the onset of career, because these studies were published during the past three centuries in various languages (Latin, German, French, Italian, Spanish) which she had all at her command. In trying to find a solution to this problem, Jelena Krmpotić spent almost 10 years of intense research. Previous studies on cerebellum[83–87] were finally summarized in an important contribution to the leading international journal – »Zeitschrift für Anatomie und Entwicklungsgeschichte«[25]. There she developed a concept of cerebellar endoplasty (Endoplastik des Kleinhirns), firmly arguing that the external morphology of the cerebellum reflects its internal structure and its development. In other words, she proposed that histogenetic processes represent »intrinsic determinants« of gyrus building. This concept of the endoplasty of the cerebellum was also presented and highly acclaimed at the International Anatomical Congress in Paris in July 1955. Finally, the concept of the endoplasty was also successfully applied to the Rolandic (sensory-motor) region of the human cerebral cortex[89–91]. In fact, this work represented the topic of her doctoral degree dissertation at the University of Zagreb, School of Medicine[90] and was later printed in the Proceedings of the Croatian Academy of Sciences & Arts[91] and in the Proceedings of the German Anatomical Society[89]. In a subsequent study, she also described the endoplasty of the human hippocampal formation[92].

Turning to the prenatal development of the human telencephalon, it should be noted that this series of publications may serve as the best illustration of two key features characterizing Jelena Krmpotić-Nemanić's approach to scientific research and academic life: (1) her life-long passion for studying the human brain, and (2) her firm and consistent role in stimulating and enhancing independent research careers of her younger collaborators. Thus, as soon as she realized that Ivica Kostović has nurtured a particular fondness for the developing brain, she arranged that Kostović went to additional training in Hungary, in the laboratory of Jánosz Szentágothai (one of the leading neuroanatomists of the twentieth century)[93,94] and soon afterward to receive a postdoctoral training at The Johns Hopkins University in Baltimore (in the laboratory of Drs. Mark E. Molliver and Hendrik Van der Loos). When Ivica Kostović returned from the U.S.A. in 1975, Jelena Krmpotić-Nemanić, as the head of the Department of Anatomy, whole-heartedly embraced the opportunity to introduce and develop an entirely new field of research – human developmental neurobiology. In fact, she was instrumental in bringing to official recognition the Laboratory of Neuroanatomy which served as a core facility for the future development of the Croatian Institute for Brain Research.

As a practicing otolaryngologist, she was naturally interested to collaborate in studies on the prenatal development of the human auditory system. This led to a series of publications, describing the development of medial geniculate body[95], cytoarchitectonic development of the auditory cortex[96–98], its afferent innervation[99–102], and its Cajal-Retzius cells[103].

However, she also participated in numerous other studies on the developing human brain: the development of acetylcholinesterase (AChE)-reactivity in the human hippocampus[104] and other limbic structures[105–107], in the human somatosensory cortex[108], other cortical areas[109], and in the cerebellar cortex[110]. Finally, she co-authored studies on the early development of radial glia[111], the initial formation of the cortical plate[112], early prenatal synaptogenesis and connectivity development in the hu-

man cingulate cortex[113,114] and the synaptogenesis in the human fetal hippocampus[115].

As the Editor-in-Chief of the »Collegium antropologicum« is professor Pavao Rudan, also a member of the Croatian Academy of Sciences & Arts and a former student of Jelena Krmpotić-Nemanić, it seems appropriate to conclude this review by pointing out that some of the last publications of our common mentor and friend were not only published in this journal, but also symbolically represent her final return to studying the human brain. The first of these studies was devoted to the fate of the arachnoid villi in humans[116] and the second one described the sequence in appearance and disappearance of her »Lieblingsstück« in human brain anatomy – *impressiones gyrorum cerebri et cerebelli*[117].

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I. Kostović

University of Zagreb, Croatian Institute for Brain Research, Department of Anatomy, 10000 Zagreb, Croatia
e-mail: ikostov@hiim.hr

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JELENA KRMPOTIĆ-NEMANIĆ (1921–2008): DOPRINOS NEUROANATOMIJI ČOVJEKA

S A Ž E T A K

Jelena Krmpotić-Nemanić (1921–2008) bila je svjetski poznati anatom, međunarodno istaknuti otolaringolog, član Hrvatske akademije znanosti i umjetnosti i cijenjeni profesor Medicinskog fakulteta Sveučilišta u Zagrebu. Temeljni utjecaj na njezinu znanstvenu karijeru imao je njezin mentor Drago Perović koji je bio student Ferdinanda Hochstettera, vodećeg autoriteta u polju razvojne neuroanatomije i embriologije čovjeka. Ovaj utjecaj očito je bio ključan za smjer znanstvenih istraživanja Jelene Krmpotić-Nemanić tijekom početnog razdoblja, te je ostavio trag i u velikom broju studija o razvoju ljudskog telencefalona, a koje su bile potaknute od Ivice Kostovića i njegovih suradnika, ali uz uvijek prisutnu i aktivnu podršku Jelene Krmpotić-Nemanić. Cilj ovog preglednog članka je u kratkim crtama prikazati njen veliki doprinos istraživanjima anatomije perifernog i središnjeg živčanog sustava u čovjeka.