

Sellar Region Surgery in Croatia in the First Half of 20th Century

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Although the pituitary gland was first described in ancient times, its function remained unknown for centuries afterwards. Some diseases caused by pituitary dysfunction were also recognized long time ago, but were not linked to the gland. In 1886, Pierre Marie (1853-1940) published the first de-

We reconstructed the historical development of surgical approaches to the pituitary gland, which were used in Croatia in the first half of the 20th century, on the basis of earliest clinical case reports and descriptions of initial surgical attempts. The first published case report on surgical treatment of acromegaly was described, as well as the review of 11 patients with pituitary disease admitted to the Ophthalmology Clinic in Zagreb in the period 1925-1927. The earliest 5 reports on pituitary surgery dating from 1925 were analyzed to reveal the circumstances that led to the development of transsphenoidal approach as a method of choice in Croatia, when this technique was becoming obsolete in other parts of the world. Frequent modifications of surgical approaches to sellar region have been shown a suitable historical-medical model for analysis of changes in surgical trends.

scription of acromegaly, the disease characterized by overgrowth of the jaws and facial bones, hands, and feet and the curvature of the spine (1). Oscar Minkowski (1855-1931) noted that the pituitary gland was enlarged in fatal cases of acromegaly. Deducing from this, Woods Hutchinson (1862-

1930) noted that the pituitary gland was likely responsible for the growth of the body, while Benda proved that acromegaly was always associated with the presence of eosinophilic pituitary adenoma (1,2). By recognizing the brain as the control center for the complex chemical functions of the body, scientists created the fields of neurology and endocrinology, ushering in the discipline of neuroendocrinology. Surgery soon became part of this newly established medical field, particularly by exploring and developing different techniques and previously unthinkable approaches to some brain areas. After the pioneering work of Victor Horsley (1857-1916) and Harvey Cushing (1869-1939) in the field of neurosurgery, technical aspects of surgical approach to the pituitary gland quickly developed and were modified in many ways. After the transcranial approach, transsphenoidal pituitary surgery was developed independently by different groups of physicians worldwide (3-5).

Several authors reported that the first transsphenoidal pituitary surgery in Croatia was performed in 1922 by Aleksandar Blašković (1882-1953), a surgeon working in the Sisters of Mercy Hospital in Zagreb (6,7). Although there are no written documents containing clinical details of these earliest operations or operative techniques, clinical parameters and operative methods used in the treatment of pituitary tumors during the first half of the 20th century can be reconstructed on the basis of reports and review papers published by Croatian clinicians.

Oldest Croatian case report on acromegaly from 1896

The first specialized hospital departments in Croatia were established at the end of the 19th century. The departments consisted of different units. For example, in 1894, the Sisters of Mercy Hospital in Zagreb established the Third Department for patients with diseases of the skin, genitalia, eyes, throat, and nose. The first

head of the Department was Dragutin Mašek (1866-1956), otorhinolaryngologist, who was succeeded by Aleksandar Blašković, the founder of Croatian urology (8). The group of surgeons working in the Sisters of Mercy Hospital was important for organizing the basic institutional level of health care in Croatia, and subsequent establishment of many university clinics that we have today (9). Their efforts culminated with the foundation of the Zagreb School of Medicine in 1917.

The institutionalization of health care marked the beginning of organized and systematic clinical research in Croatia. However, even before, there had been an evident interest in obtaining, producing, and promoting medical knowledge, which can be traced back to the early pages of *Liječnički vjesnik*, the oldest Croatian medical journal launched in 1877. Before the foundation of the Zagreb University School of Medicine, *Liječnički vjesnik* had served as the leading professional communication and education medium. Therefore, it is a valuable source of earliest scientific achievements, clinical case reports, and descriptions of operational techniques performed in Croatia at the time. It brought the earliest description of acromegaly in Croatia from 1896 (10,11), written by a specialist in internal medicine Pavao Čulumović (1868-1963). This paper was published exactly 10 years after Pierre Marie had published his description of acromegaly in *Revue de Médecine* (12) and is the oldest Croatian article published in the field of neuroendocrinology. Čulumović described clinical characteristics of a 30-year-old patient who was admitted to the hospital in Osijek because of the enlargement of extremities and pain in both legs. He was twice unsuccessfully operated for sarcoma. On the right side of his face, there was an egg-size tumor close to the ear and another one located more centrally. A variety of different size nodules were spread all over his body. Čulumović also provided detailed measures of the patient's head, nose, tongue, neck, extremi-

ties, fingers, and nails (10). He further updated the readership on the most recent information on acromegaly, referring particularly to the Pierre Marie's article, and concluded that around 90 cases of acromegaly had been described worldwide thus far.

All reported cases of acromegaly brought a similar description of the symptoms, because the disease is recognizable rather early. However, the etiology of the disease remained unknown. In his report, Ćulumović also mentioned Marie's presumption that acromegaly was caused by pituitary tumor or dysfunction and laid out Marie's theory based on an analogy with the thyroid gland. At the time, Marie probably believed that the pituitary gland produced unknown factors influencing the nervous system through circulation. Ćulumović reflected on his patient's symptoms and, since hemianopsia was not found, he speculated that thymus rather than pituitary tumor was the cause of symptoms in that particular case and considered its association with sarcomatosis. He finally concluded that "we could speculate about all possible hypotheses, but let us end only with a simple claim that our case of acromegaly that developed with sarcomatosis could be added to the already existing list of published cases" (11). The patient Ćulumović described left the hospital without any hope of improvement. Had he developed the symptoms only a decade later, he would have had some chance for surgery.

After 1886, when Pierre Marie first described acromegaly (11), the interest of medical community in this condition started to increase. Social reaction to patients with acromegaly was not indifferent either. Perhaps the most impressive example of public fascination by these patients was the article *Uglies*, published in *Time* magazine in 1927 (13). It brought the picture of a woman with a typical case of acromegaly and pronounced her the ugliest woman in the world (13). This article provoked Harvey Cushing (1869-1939), who was engaged in pituitary gland investigations

for most of his professional life, to send a detailed explanation of the disease to *Time* magazine (13): "She, previously vigorous and good-looking woman, has become the victim of a disease known as acromegaly. This cruel and deforming malady not only completely transforms the outward appearance of those whom it afflicts, but is attended with great suffering and often with loss of vision. One of Mr. Ringling's agents prevailed upon her to travel with the circus and to pose as the "ugliest women in the world" as a means of livelihood. Mr. Ringling is kind to his people and she is well cared for. But she suffers from intolerable headaches, has become nearly blind, and permits herself to be laughed at and heckled by unfeeling people in order to provide the wherewithal to educate her four children. Beauty is but skin deep. Being a physician, I do not like to feel that TIME can be frivolous over the tragedies of disease."

Published reports on pituitary tumors – clinical and surgical case studies

Even though the earliest description of the clinical presentation of pituitary tumor in Croatia was published by a specialist in internal medicine, the interest for this subject spread to other medical specialties as well. The First Meeting of the Yugoslavian Otolological-neurological-ophthalmological Society in Zagreb in 1927 brought together ophthalmologists, otorhinolaryngologists, psychiatrists, and neurologists who presented their own experiences, findings, and procedures for the treatment of pituitary tumors (14). The earliest results of surgical procedures for pituitary tumor treatment in Croatia were published in a Czech journal in 1927 by Ante Šercer (15). Of 10 cases of pituitary adenoma presented by Šercer, the first two were admitted to the Otorhinological Clinic in Zagreb in October 1924, but were not operated on. However, 6 patients admitted during the period 1925-1926 were surgically treated by the trans-

septal-endonasal method modified according to Hirsch-Segura.

The next paper on the subject was a detailed review, "Addition to the Clinic for pituitary tumors with special attention to dysfunctions of a sight organ," published in 1928 by Mira Mašek-Breitenfeld, from the Ophthalmological Clinic of Albert Botteri in Zagreb (16). In this thorough review, the author described 11 patients admitted to the Ophthalmology clinic between 1925 and 1927, mostly for visual disturbances. Seven of them underwent surgery at the Clinic of Dr Hirsch in Vienna, and the rest were treated at the Clinic for Otorhinolaryngology in Zagreb. Four of these patients had been previously described by Šercer in his article (15). All patients underwent transseptal endonasal surgery. There were 6 women and 5 men patients; the oldest was 48 and the youngest 14 years old. The age and sex distribution of the disease at the time did not significantly differ from that today (17). The first patient from the series was operated in Dr Hirsch's Clinic in Vienna. Removal of the frontal sphenoidal sinus wall allowed for irradiation treatment of the pituitary gland with radium. This combination of surgical and radio-therapy significantly improved the outcome and seems to represent the very beginning of brachitherapy as such, since radiotherapy in the pituitary region was already in use in 1909 (18).

In the second patient, who was not operated on, a cocainization of the nasal mucosa was done with the purpose of exploring paranasal sinuses. The author wondered whether cocainization improved the patient's condition, considering that applied cocaine narrowed the blood vessels in the edematous mucosa of the sphenoid sinus and the tissue surrounding pituitary tumor, consequently decreasing the pressure of the tissue and improving vision. Today, it is clear that such an effect of cocaine was possible but temporary, and would have eventually ceased with the breakdown and elimination of cocaine from the body. It could be presumed that this patient had a sphenoid sinus

abscess or a mucocoele, which could have been pressing against the perisellar structures, including the optic nerves. By cocainization, sphenoid sinus could have become open and the puss or mucus could have leaked out, decompressing the optic nerves. At the same time, if it was a matter of pituitary adenoma with preceding "apoplexy" or hemorrhagic necrosis, its liquid content could have perforated the mucosa and leaked out after the cocainization of mucosa.

In the third patient, the symptoms worsened 6 months after the surgery. According to the data from the patient's physician from the island of Brač, the disease had a fatal end. Even though the histological finding was *hyperplasia hypophyseos*, it was likely a pituitary adenoma that showed expansive growth after the surgery.

Postoperative diagnosis in the fourth patient was *hydrocephalus internus et externus* with *dystrophia adiposo-genitalis*. The author concluded as follows: "This case, although misdiagnosed, is very educational, since it shows that hydrocephalus can indeed have the same clinical, ophthalmologic, and radiological presentation as pituitary adenoma. In our case, it wasn't possible to radiologically conclude on the increase of intracranial pressure or increased pressure of the structures. The only diagnostic method that would have led us to the right path in this case is encephalography, since that would have been the only way of seeing the enlargement of cerebral ventricles due to hydrocephalus. (Nevertheless, in that time, in our region such method was not in diagnostic use.) Therefore, I believe that every case of pituitary tumor, especially with unclear etiology, should be diagnosed with encephalography, thus avoiding the possibility of incorrect diagnosis."

This case is interesting for its diagnostic procedure of pituitary tumor, obviously still in the developmental phase. The author's awareness of the importance of diagnostics is impressive; hence she suggests the introduction of encephalography. The self-criticism is also meritorious.

The fifth patient was not operated on, but treated with Ricord's oral solution (iodine and mercury). In this case, the final diagnosis was not confirmed. Histological analysis in the sixth patient confirmed sarcoma. The seventh case was of special interest since the patient was operated on 11 times over 7 years at Dr Hirsch's Clinic in Vienna. According to the author, it was a cyst (current diagnosis would probably be calcified craniopharyngeoma), which resulted in permanent improvement only after the last surgery when a large portion of cystic wall was excised.

The eighth case was conservatively treated, and in the ninth, additional radio-therapy was performed 6 months after the surgery. In the tenth case, a pituitary tumor was operated, the symptoms disappeared thereafter and the width of visual field doubled. In the last, eleventh case, the patient did not undergo surgery.

These articles by Ante Šercer and Mira Mašek-Breitenfeld are good examples of the doctrine and surgical practice at the time, with respect to understanding of etiology, diagnostic approach, and therapy of pituitary tumors. They show the level of knowledge of Croatian medical practitioners, their attitudes, doubts, and uncertainties about pituitary disorders, as well as their firm opinion on specific surgical procedure. The importance of early diagnostics was pointed out, as well as the role of the ophthalmologist. The necessity for interdisciplinary diagnostic and therapeutic approach to this complex area was obvious. The cooperation among ophthalmologists, radiologists, and otorhinolaryngologists and involvement of other medical specialties eventually led to the development of new subspecialties, such as neurosurgery, neuroradiology, or neuroendocrinology. The standards in diagnostic and other procedures, especially in operative techniques, slowly crystallized. All patients with pituitary diseases at the Clinic for Otorhinolaryngology in Zagreb were operated by transsphenoidal approach, obviously the initial approach and the method of choice from the very beginning. On

the one hand, it is understandable considering the fact that such surgeries were done by Ante Šercer, an otorhinolaryngologist, to whom surgical approach to nose and sinuses was a daily routine. In his 1926-1927 article, Šercer clearly defined his position on the indication for pituitary tumors surgery by saying that "absolute indication for pituitary surgery exists only in presence of ocular disturbances with signs of increased intracranial pressure. In all other cases, indications for surgical therapy are relative" (6).

Communication network on pituitary surgery techniques

The pituitary gland was a strong research challenge from the standpoint of anatomy, pathological anatomy, pathophysiology and surgery since the end of 19th century, when significant improvement was achieved by an Italian doctor David Giordano (19). He intensively studied the problem of approaching the pituitary gland and performed a series of anatomical studies on corpses between 1890 and 1896. After 1897, in further anatomical studies, he applied transglabellar transnasal approach to pituitary gland (19). After Victor Horsley performed the first pituitary tumor surgery using transcranial approach in London in 1904, numerous surgeons accepted this method (20). Austrian surgeon Schloffer takes the credit for showing a great practical value of the sinus of the sphenoid bone through which pituitary gland is easily reachable. He published his studies in 1906 in Prague (21). Only a year later, in 1907 in Innsbruck, he had a brilliant idea to use natural cavities of the nose and the sphenoid bone, and for the first time, successfully operated a pituitary tumor in local anesthesia with cocaine (22). Following this initial success, a large number of surgeons and otorhinolaryngologist have accepted this method with some modifications depending on available resources, equipment, and personal talents. Šercer expressed his especially positive opinion

on Hirsh's and Segura's methods of endonasal approach, providing the following arguments (6): "If we have to use substantial energy to master *lege artis* the resection of the septum, then for aseptic reasons, we could request this surgery be done through the nose rather than the mouth. Surgeons have a wrong attitude anyway, thinking that the septum resection is easier through the mouth rather than the nose. The orientation is more difficult through the mouth and everyone who had a chance to operate the septum through the nose as well as the mouth could confirm that. So I stay with my principles and support the endonasal transseptal method with several modifications." Šercer used Segura's modification of Hirsch's method, specifying that only one of 6 patients operated by this approach died of post-operative consequences, and that he considered this approach to be the most acceptable in surgery of pituitary tumors.

While Croatian surgeons were perfecting this widely accepted surgical approach to the pituitary gland, an amazing change happened on the international level. Cushing, the famous authority in this area who had published the results of transnasal surgeries of pituitary tumors in 231 patients with mortality rate of only 5.6%, slowly abandoned this method and shifted to transcranial approach, with a belief that optic nerves and the chiasm were immediately decompressed after transcranial approach. Due to his great reputation and influence, the transnasal approach in most neurosurgical societies became abandoned too (4,23,24).

By the beginning of the 1940s, this method was almost forgotten. Norman Dott, a Scottish neurosurgeon from Edinburgh, had learned the transsphenoidal approach from Cushing himself and applied it in indicated cases by using all of its comparative advantages. It was believed that he was the only neurosurgeon for a while still using the transsphenoidal approach in the treatment of pituitary tumors. This is why he is given a special credit for the preservation of this exception-

ally valuable surgical method (25,26). A Parisian neurosurgeon Gerard Guiot learned this method from Dott in 1956, and a year later returned it to Europe, where it was almost completely forgotten (27-29).

Canadian neurosurgeon Jules Hardy moved in 1962 from Paris, France, to Montreal, Canada, and "returned" the transsphenoidal approach to pituitary tumors that he learned from Guiot to North America (30). He is responsible for modern standardization of this method, introduction of intraoperative radiological control of instrument positioning, and for the introduction of microsurgical operative technique. Hardy published initial results on the possibility of selective therapy of pituitary microadenoma by protecting the healthy pituitary tissue (30) and this method became accepted widely in the world as a predominant method in the therapy of sellar region pituitary tumors.

From the previous recount, we have seen how standardized operation has been continuously modified with numerous technological advances, but its basic idea and strategy remained unchanged for almost a century. Usage of natural skull cavities, the nasal cavity and sphenoid sinus, as a way to reach the center of the skull base, sella turcica, and further into wider perisellar region, with minimal operative trauma, gave this operation attributes of a forerunner in the concept of currently dominating minimally invasive surgery. This was also the basis for development of a "keyhole concept" in surgery. This is how a circle of adopting, rejecting, and re-adopting the same method over the decades closed. In our region, this method was initially adopted and used without any modifications. Furthermore, in 1952, transsphenoidal surgery was enlisted in the register of otorhinolaryngological surgeries (31). It became a lasting challenge and a subject of numerous studies and debates among Šercer's pupils and coworkers who tried to study the anatomical relations of nasal septum and the sphenoid, as well as the relation of the sphenoid to

the hypothalamic-pituitary area, to use them in new trends of pituitary surgery and radiosurgery. These anatomical relations were extensively studied by Drago Perović, Jelena Krmpotić Nemanić, Đorđe Nemanić, Mihovil Novoselec, Marko Pećina, and Ivo Padovan (31-35). Padovan developed his modification of the surgery, the so-called transthemoidal approach (Table 1).

Table 1. Modifications of extracranial surgical approach to pituitary gland (ref. 32)

| Year | Method | Surgeon |
|-----------|---|-------------------|
| 1906-1907 | transnasosphenoidal approach | Schloffer |
| 1909 | transnasal-transseptosphenoidal approach | Kanavel |
| 1900 | sublabial transseptosphenoidal approach | Kocher |
| 1909 | | Proust and Lecőne |
| 1910 | | Halsted |
| 1910 | | Cushing |
| 1911 | transthemoidal-sphenoidal approach | Chiari |
| 1910 | endonasal-transseptosphenoidal approach | Hirsch |
| 1925 | modification of Hirsch method | Segura |
| 1925 | transseptoendonasal method, modification by Hirsch-Segura | Šerčer |
| 1933 | transseptosphenoidal approach | Nager |
| 1936 | | Montmollin |
| 1957 | | Escher |
| 1957 | | Padovan |
| 1960 | | Bateman and James |

Despite the intensive development of neurosurgery in the early 1930s, pituitary surgeries in Croatia were done exclusively within the field of otorhinolaryngology. The process of transferring pituitary surgery into the domain of neurosurgery gradually began in the second half of the 20th century.

In Zagreb medical circles, the interest for transsphenoidal approach to pituitary tumors neither diminished nor was lost but was rather nourished, developed, and further modified. Norman Dott was doubtlessly accountable for sustaining and reaffirming transsphenoidal pituitary surgery by returning it in a big fashion to respectable hospitals across Europe and North America (25,26). Nevertheless, in our region, Ante Šerčer was just as important. Due to him, this method was never abandoned, and his students have improved and popularized it.

Even though indications for transsphenoidal surgeries from Šerčer's period (6) were significantly different in comparison with the current ones, the concept of minimal invasiveness remained the main link, making it the method of choice. Today, almost a whole century after its introduction, it is used in almost 95% of sellar region tumors operations (35).

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