doi: 10.53446/actamednicomedia.1644183

Acta Medica Nicomedia

Cilt: 8 Sayı: 2 Haziran 2025 / Vol: 8 Issue: 2 June2025
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

HYPEROSTOSIS FRONTALIS INTERNA AND ITS CLINICAL SIGNIFICANCE

HIPEROSTOZIS FRONTALIS INTERNA VE KLİNİK ÖNEMİ

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ABSTRACT

Objective: The metabolic, endocrinological, neurological, and psychological causes of heterotopic ossification in the frontal bone have become increasingly important. Overgrowth of the frontal bone, called hyperostosis frontalis interna (HFI), can cause headaches and, rarely, seizures. HFI is nine times more common in women and is called Morgagni-Stewart-Morel syndrome when it occurs with virilization, obesity, and neuropsychiatric problems. Long-term estrogen exposure, advanced age, female gender, testosterone suppression removal, male-type hypogonadism, genetics, environmental factors, obesity, diet, Diabetes mellitus, some metabolic diseases, autoimmunity (ANA+), endocrine imbalance, and LEPTIN cause HFI. About 20% of HFI patients experience headaches, obesity, vertigo/dizziness, cognitive decline, and depression.

Methods: Our study was conducted over four years, from 2016 to 2019, at the Anatomy Department of Albert Einstein College of Medicine, New York, USA. We utilized formalin- fixed course cadavers from the department to assess heterotopic ossification. The cadavers exhibiting HFI+ were particularly recognized. The gender and age of the cases were considered. 74 donors, ranging in age from 42 to 103, were assessed.

Results: The study indicates that the frequency of HFI is 41.89%, with a prevalence of 9.45% among men in the population. This represents 22.58% of all HFI cases. The incidence among women is recorded at 32.43% within the population, representing 77.42% of total HFI cases.

Conclusion: Our study sample had 9.45% male HFI, which is remarkable. Although estrogen has been the main driver in HFI etiopathogenesis, the reported rate in males will illuminate fresh research and conclusions, allowing a full study of alternative variables.

Keywords: Hyperostosis frontalis interna, acromegaly, postmenopausal women, calvarial growth, heterotopic ossification

ÖZ

Amaç: Frontal kemikteki heterotopik ossifikasyonun metabolik, endokrinolojik, nörolojik ve psikolojik nedenleri giderek önem kazanmaktadır. Hiperostozis frontalis interna (HFI) adı verilen ön kemiğin aşırı büyümesi baş ağrısına ve nadiren nöbetlere neden olabilir. HFI kadınlarda dokuz kat daha sık görülür ve virilizasyon, obezite ve nöropsikiyatrik problemlerle ortaya çıktığında Morgagni-Stewart-Morel sendromu olarak adlandırılır. Uzun süreli östrojen maruziyeti, ileri yaş, kadın cinsiyet, testosteron baskılanmasının ortadan kalkması, erkek tipi hipogonadizm, genetik, çevresel faktörler, obezite, diyet, Diabetes Mellitus, bazı metabolik hastalıklar, otoimmünite (ANA+), endokrin dengesizliği ve LEPTIN HFI'ye neden olur. HFI hastalarının yaklaşık %20'sinde baş ağrısı, obezite, vertigo/baş dönmesi, bilişsel gerileme ve depresyon görülür.

Yöntem: Çalışmamız ABD'nin New-York Albert Einstein College of Medicine'de, Anatomi Laboratuvarında 2016-2019 yılları arasında dört yıl boyunca gerçekleştirildi. Heterotopik ossifikasyonu değerlendirmek için bölümden alınan formalinle sabitlenmiş kadavralardan yararlandık. HFI+ sergileyen kadavralar özellikle tanındı. Olguların cinsiyeti ve yaşı dikkate alındı. Yaşları 42 ila 103 arasında değişen 74 donör değerlendirildi.

Bulgular: Çalışma, HFI sıklığının %41,89 olduğunu, toplumdaki erkeklerde görülme sıklığının ise %9,45 olduğunu göstermektedir. Bu, tüm HFI vakalarının %22,58'ini temsil etmektedir. Kadınlar arasındaki insidans, popülasyonda %32,43 olarak kaydedilmiş olup, toplam HFI vakalarının %77,42'sini temsil etmektedir.

Sonuç: Bulgular, HFI araştırması ve etiyolojisinde östrojen maruziyetinin diğer faktörlerle birlikte dikkate alınması gerektiğini göstermektedir. Genetik veya epigenetik faktörler bazı kliniklerde daha sık görülen HFI'yi tetikleyebilir. Bu korelasyonu doğrulamak için daha büyük bir popülasyon çalışmasına ihtiyaç vardır.

Anahtar Kelimeler: Hiperostozis frontalis interna, akromegali, postmenopozal kadın, calvarial büyüme, heterotopik ossifikasyon

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Submitted/Başvuru: 25.02.2025 • **Accepted/Kabul:** 18.06.2025 • **Published Online/Online Yayın:** 30.06.2025

Introduction

Heterotopic ossification in the calvaria, while present in other cranial bones, is particularly prevalent in the frontal bone and has garnered significance in recent years regarding its metabolic, endocrinological, neurological, and psychiatric etiopathogenesis. Hyperostosis Frontalis Interna (HFI) refers to anomalies in the inner surface of the calvaria, characterized by widespread, nodular development and thickening of the bone tissue from the lamina interna of the frontal bone to the cranial cavity. This action transpires within the spongy bone tissue. The frontal bone is intact in the midline and is distinctly bounded by the middle meningeal artery. In radiological imaging, "butterfly-like density" is characteristic. Initially delineated by Morgagni in 1719[1], HFI was thoroughly analyzed and categorized by Moore in 1955[2], and further subtyped in 1999 by Herskovitz et al.[3] For classification, it is essential to ascertain whether it pertains to morphology, distribution, localization, size, or adjacent structures of the frontal bone. Estrogen, parathormone, calcium ATPase, and neuropeptides contribute to the pathophysiology of HFI. The majority of instances involve postmenopausal women. Chronic exposure to estrogen, advanced age, female sex, cessation of testosterone's suppressive effects, male-type hypogonadism, genetic predisposition, environmental influences, obesity, dietary factors, diabetes mellitus, certain metabolic disorders, autoimmunity (ANA+), endocrine dysregulation, and leptin are implicated in the etiology. Klippel-Trenaunay-Weber Syndrome, Frolich Syndrome, Morgagni Syndrome, Stewart-Moral Syndrome, Troell-Junet Syndrome, and Morgagni-Stewart-Morel Syndrome have all been linked to HFI. Frontal pain, psychoneuroses, obesity, Parkinsonism, depression, frontal cortex managerial dysfunctions, epilepsy, and hypertrichosis may accompany HFI. Using osteoarchaeological evidence and unintentional cadaver autopsy images, HFI can be diagnosed. In the differential diagnosis, it is crucial to consider localized malignancies (endosteal osteoma, osteosarcoma), Paget's Disease, fibrous dysplasia, Leontiasis ossea, pregnancy osteophytes, and metabolic craniopathy.

Moore comprehensively analyzed roentgenograms to identify four distinct forms of hyperostosis cranii.[4-6] HFI was utilized solely for description. Instances where only the frontal bone is involved; nebula frontalis (NF) refers to a consistent, uniform thickening of the frontal bone; hyperostosis calvaria diffusa (HCD) denotes a condition affecting all flat bones of the calvaria. Perou expanded the existing terminology to incorporate hyperostosis cranii interna (HCI) for cases of HFI where remodeling extends beyond the frontal bone to include the parietal, temporal, or sphenoid bones (Perou, 1964)[7]. Therefore, the term HCI encompasses all instances of endostosis, irrespective of their location and extent.

A further classification has been developed by Herskovitz et al.[3] Observation or extension of hyperostosis in bones other than the frontal bone, classification based on; morphology, form, type of border, location of lesion;

*Type A: Singular or multiple isolated osseous elevations of less than 10 mm in diameter situated on the endocranial surface of the frontal bone.

*Type B: Nodular osseous formations that comprise less than 25% of the frontal bone.

*Type C: Nodular osseous formations include up to 50% of the frontal bone.

*Type D: Nodular osseous formations situated on the endocranial surface of the frontal bone, exceeding 50% and exhibiting continuity.

*Type E: Severe hyperostosis frontalis interna characterized by soft tissue proliferation and expansion.

Hyperostosis frontalis interna (HFI) develops when the frontal bone grows abnormally behind its internal table. According to She et al., 5%-12% of people could develop HFI.[8] Clinicians consider the pathology benign mostly because a significant number of patients are asymptomatic. When compared to the general population of the same age, those with HFI who do experience symptoms most often report headaches and depression.[9]

This condition should be seen as a metabolic bone disease because it is associated with HFI, diabetes, hirsutism, and acromegaly. Dementia and seizures are two other disorders that are not as strongly linked to HFI. Hormones seem to be the likely culprit, according to the research. For example, according to Murphy et al. (2018), the primary population of HFI consists of elderly, obese, diabetic, hyperandrogenic, or nulliparous postmenopausal women.[9] According to Morita et al. (2021), one theory is that estrogen dysregulation can promote bone formation by stabilizing the networks of meningeal microvasculature.[10] Despite Hershkovitz's first classification scheme for HFI in cadavers, neither the living population nor cadaveric case reports consistently use it. [11] Patients coping with HFI do not have access to a similarly reliable classification scheme. Furthermore, historical records show that HFI has been a problem for humans for a long time.[12]

The pathogenesis of HFI remains little elucidated. The 'global model' of HFI, presented by Hershkovitz et al., identifies vascularization from the dura as a crucial element in the pathophysiology of HFI.[3] Talarico et al. found that in the woman with HFI, the inner table displayed significant remodeling, comprised predominantly of big sinuses, and extended to the external periosteal layer of the dura.[1]

Larger pores may arise from the infiltration of blood vessels from the dura, ultimately resulting in the diploidization of the inner table.[13]

Estrogen receptors are predominantly situated on the vascular tissue of the dura, and estrogen is recognized for its significant influence on meningeal vascularity.[14] Angiogenesis stimulated by estrogen has been extensively studied.[15,16] Estrogen is proposed to trigger the hypoxia-inducible factor-a (HIFa) signaling pathway, resulting in the activation of proangiogenic genes, chiefly vascular endothelial growth factor (VEGF).[15,17] Estrogen can thereby promote angiogenesis. Numerous studies

indicate that bone turnover is associated with bone vasculature.[18,19,20]

Methods

Our study was conducted for 4 years between the years of 2016 to 2019 at Albert Einstein College of Medicine, Anatomy Department, New York – U.S.A., utilizing cadavers of the department, which were examined and evaluated for heterotopic ossification. This study examined heterotopic ossifications in the calvaria of 74 formalin-embalmed cadavers (44 males, 30 females, aged 42-103) donated to the Department of Anatomy at Albert Einstein College of Medicine (AECOM). All donors permitted for donation and utilization in clinical trials were accepted in accordance with New York's Anatomical Gift Law. This study does not require ethical approval as it utilizes course cadavers from the Albert Einstein College of Medicine C&DA Department, in accordance with the exemption categories outlined in Einstein-IRB-citation104(d).

Excision of Calvaria and Cerebrum

The scalp was retracted from the cranium while in the supine posture. The temporalis fascia was severed. The temporalis muscle was reflected inferiorly, and the bones were meticulously cleaned. The external lamina and diploë were circumferentially incised with a Stryker saw along a line commencing 1.5 cm above the supraorbital edge and extending to 2 cm superior to the external occipital protuberance. Meticulous precautions were implemented to avoid harming the underlying dura mater and brain. A Verchow Skull Breaker and a chisel were employed to penetrate the endocranium. The calvaria was excised by carefully separating it from the dura mater through blunt dissection. The cadaver was thereafter positioned prone, and the tentorium cerebelli was incised bilaterally, extending the incision posteriorly to the superior border of the petrous bone. The spinal cord, along with the vertebral arteries and cranial nerves IV, V, VII to XI, as well as the hypoglossal nerve bundle, were severed. Subsequently, while in the supine posture, gentle pressure was exerted on the frontal poles of the cerebral hemispheres, the falx cerebri was incised near the crista galli, and the brain was retracted superiorly and posteriorly, displacing the olfactory bulbs and tracts from the cribriform plates. The brain was elevated, and the infundibulum, internal carotid arteries, and other cranial nerves were transected.

The brain was carefully retracted posteriorly, extracted from the cerebral cavity, and immersed in 10% neutral buffered formalin.

Comprehensive Assessment of the Calvaria and Cerebrum

The calvaria was examined, and images were captured using a Canon PowerShot SD1100 IS Digital ELPH 8.0-megapixel camera, which was utilized to document the extent and borders of hyperostosis, as well as the dimensions of hyperostotic nodules. The brain, with intact meninges, was analyzed and photographed.

The meninges were meticulously dissected to prevent injury to the underlying tissue, and the brain was thoroughly examined and photographed for potential indications of topographical anomalies resulting from hyperostotic bone or bony nodules.

Results

HFI+ was detected in 31 cases in total among 74 donors. In contrast to the expected number of HFI cases, 7 of the 31 cases were observed in the male gender. In addition, another important feature of this study is its evaluation in terms of HFI in the American population observed during these 4 years. Our study reveals that the frequency of HFI stands at 41.89%, with a prevalence of 9.45% among men in the population. This accounts for 22.58% of all HFI cases. In contrast, the incidence in women is observed at a rate of 32.43% within the society, constituting 77.42% of total HFI cases.

In the male cases of HFI, one case was identified in the 54-year age range, four cases were identified in the 70-80 year age range, and two cases were identified in the 80-90 year age range. Among female cases of HFI, 91.6% were aged over 60 years.

Figure 1, visually illustrates the incidence of HFI cases detected in males and females separately, as well as the overall cases.

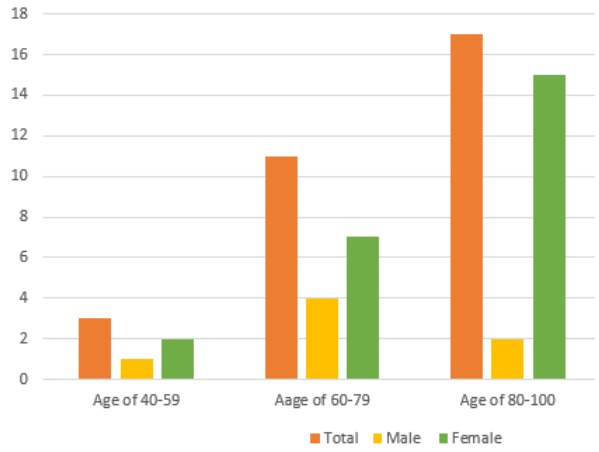

Figure 1. Displays graphically the overall case count, the number of cases found in males and females individually, and the incidence of HFI.

Macroscopic Analysis of the Frontal Lobe and the Calvaria

In Figure 2a, in a 78-year-old male case, a butterfly-shaped location in the Os frontale, bilaterally on the right and left, not exceeding the distribution area of the a.meningea media, is observed, which is the typical definition of HFI.

In Figure 2b, illustrates the impressions created by protrusions from heterotopic ossifications on both the right and left brain lobes, corresponding to the regions where impressions from hyperostosis frontalis interna are observed, as indicated by the areas encircled in red.

In Figure 3a, regarding the 64-year-old female instance, the os frontale is more prominent on the right, encompassing 50% of the frontal bone area up to the bifurcation of the a. meningea media on the left. On the left, it is less prominent than on the right, heterotopic ossifications are noted reaching to the branches of the a. meningea media.
In Figure 3b, HFI, observable in the right os frontale region, also significantly impacted the corresponding brain lobe due to compression.
In instances where HFI was identified, the dimensions of the osseous protrusions in the frontal bone correlated with observable compression-induced impressions in the neighboring dura mater and frontal cerebral lobes. The primary feature that captures our attention is heterotopic ossifications, located in the frontal bone and adjacent to the parietal bone, attributable to their morphological characteristics. It did not extend to the bifurcation of the meningea media and did not occupy the midline. In other words, the midline exhibited no involvement of HFI.

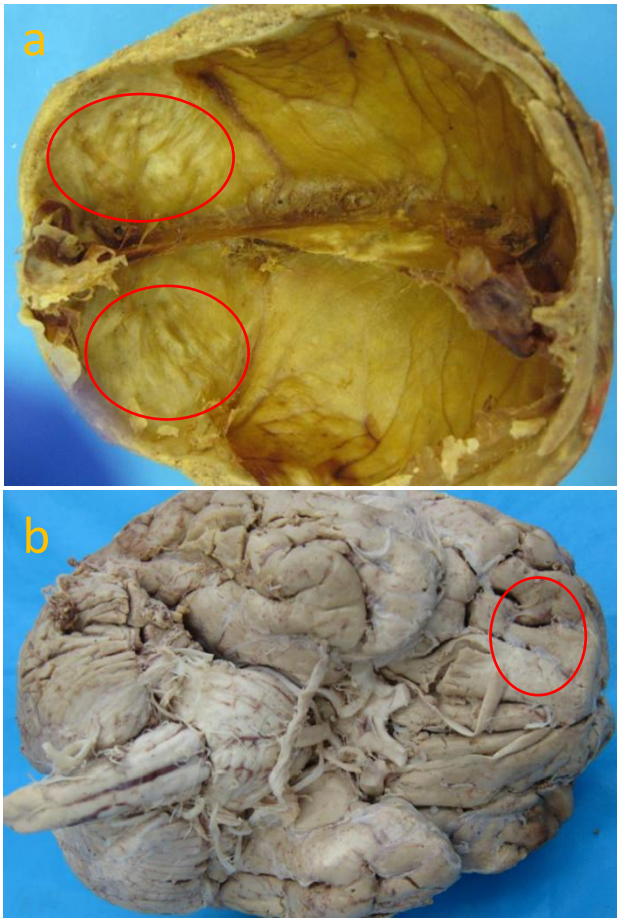

Figure 2a-2b. A typical definition of HFI is noted in a 78-year-old male case: a butterfly-shaped position in the Os frontale, bilaterally on the right and left, not surpassing the distribution area of the a.meningea media.

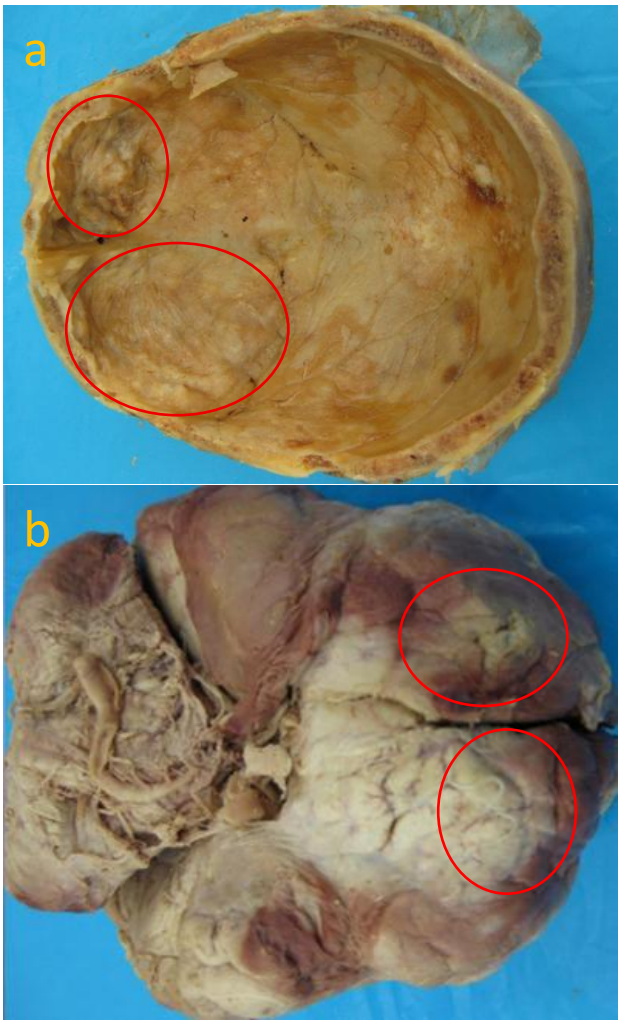

Figure 3a-3b. In the case of the 64-year-old female, the os frontale exhibits greater prominence on the right side, covering 50% of the frontal bone area up to the bifurcation of the a. meningea media on the left. Heterotopic ossifications are observed on the left, where they are less prominent compared to the right, extending to the branches of the a. meningea media. **3b.** HFI, which is visible in the right os frontale area, compressed the corresponding brain lobe and had a substantial impact on it.

Discussion

Our work was significant in identifying HFI in males through the examination of 74 cases. Nevertheless, no documentation existed concerning the backgrounds of the cases. The existing research indicates that the replacement of estrogen effects by testosterone dominance plays a crucial role in the pathogenesis of HFI; notably, we observed considerable cases of HFI in males. Nonetheless, it is recognized that HFI induces not only morphological alterations in bone. Simultaneously, it may coexist with other metabolic, neuroendocrine, genetic, and psychiatric disorders.
Symptoms occurring in over 20% of HFI patients included headaches, obesity, vertigo/dizziness, cognitive decline, and depression. Symptoms of moderate frequency observed in 5% to 20% of HFI patients included unspecified psychological diagnoses, extremity weakness

or gait abnormalities, giddiness, vision dysfunctions, diabetes, and hypertension.

Symptoms occurring at low frequency in fewer than 5% of HFI patients included a history of head trauma, energy decrease or fatigue, frontal lobe compression, cerebral atrophy, epilepsy, cystic ovaries, endocrine dysfunctions (excluding diabetes), speech dysfunctions, and increased intracranial pressure.[42]

Roybal et.al. suggested that Msx genes play a dual role in calvarial development by facilitating the differentiation and proliferation of osteogenic cells in rudiments, while also inhibiting an osteogenic program in the surrounding cell layer where the rudiments develop. The inactivation of this repressive activity may contribute to the formation of Wormian bones, which are ectopic bones associated with various pathological conditions that compromise calvarial bone development.[43]

The absence of Fgfr1 in neural crest cells results in heterotopic chondrogenesis and osteogenesis during the development of the frontal bone.[44]

Klippel-Trenaunay-Weber Syndrome, Frolich Syndrome, Morgagni Syndrome, Stewart-Moral Syndrome, Troell-Junet Syndrome, and Morgagn-iStewart-Morel Syndrome have all been linked to HFI. Frontal pain, psychoneuroses, obesity, parkinsonism, depression, frontal cortex managerial dysfunctions, epilepsy, and hypertrichosis may accompany HFI. In the differential diagnosis, it is crucial to consider localized malignancies (endosteal osteoma, osteosarcoma), Paget's Disease, fibrous dysplasia, Leontiasis ossea, pregnancy osteophytes, and metabolic craniopathy.[1]

Klippel-Trenaunay-Weber Syndrome is associated with varicose veins, port wine stains, and bone and soft tissue enlargement.

Troell-Junet Syndrome, accompanied by acromegaly, toxic goiter, diabetes mellitus.

Frolich Syndrome is associated with, pituitary anterior lobe atrophy-pituitary hypocrinism, obesity, growth retardation, port wine stain, and pituitary gonadotropic hormone deficiency.

The coexistence of metabolic, endocrine, and neuropsychiatric disorders with HFI is referred to as Morgagni-Stewart-Morel (MSM) syndrome. This instance was first recorded in 1719 by Giovanni Battista Morgagni, who noted a relationship between hirsutism and obesity, along with a thickening of the frontal bone.[38] Surprisingly, very little is known about this disease, even after three centuries of research. Stewart and Morel documented chronic headaches and neuropsychiatric symptoms in the early 1930s. [39,40] Recent studies have established a connection between MSM syndrome and neuropsychiatric disorders, metabolic and hormonal problems (including hirsutism, diabetes, and obesity), and other health issues. The reported clinical pattern is rarely consistent because the illness can have a wide array of symptoms and varied degrees of severity. Many medical professionals dispute the syndrome's validity because its related diseases can appear in older women on their own.[8,3] Although the exact cause of HFI and MSM syndrome is still a mystery, prominent hypotheses point to malfunctions in estrogen, obesity, and leptin, in addition to genetic components.[33]

Conditions and cases associated with HFI encompass frontal headache, intracranial hypertension, cognitive impairment, behavioral disorders, psychoneuroses, obesity, Alzheimer's disease, Parkinsonism, depression, executive dysfunction of the frontal lobe, epilepsy, and hypertrichosis.

Frontal lobe compression due to significant HFI may lead to psychiatric illnesses and cognitive deficits, especially impacting executive processes. In instances of concurrent degenerative dementia, the existence of HFI may signify a negative prognosis for the swift advancement of cognitive deterioration.[41]

A case presented by Brodoehl et al. illustrates transcortical motor aphasia, marked by reduced spontaneous speech, naming, and writing capabilities, whereas repetition and comprehension are preserved. The patient presents with moderate dementia and right-sided parkinsonism, characterized by increased muscle tone, a slight hand tremor, and supranuclear vertical gaze palsy. Neuroimaging demonstrated notable bifrontal hyperostosis. Hyperostosis frontalis interna (HFI) is characterized by a continuous proliferation of the frontal bone, commonly linked to chronic headaches and, less frequently, to seizures. HFI is observed to occur nine times more frequently in women and, when associated with virilisation, obesity, and neuropsychiatric issues, is classified as Morgagni-Stewart-Morel syndrome.[45]

HFI is associated with increased thickness of all calvarial bones and a reduction in intracranial volume.[46]

A considerable proportion of female specimens displaying heightened severity of HFI demonstrated a range of neuropsychiatric abnormalities, such as dementia, depression, Parkinson’s disease, and Alzheimer’s disease. Alzheimer's disease correlates with bone density. The severity of Alzheimer's disease in a patient may increase the risk of low bone mineral density.[47] This indicates that the body's reaction to the reduction of brain matter and the increase in skull volume is to promote bone deposition, which serves to reduce brain movement and stabilize it within the cranial cavity.[48]

Postmenopausal women, people with long-term estrogen exposure, overweight people, diabetics, and the elderly are at increased risk for HFI.

Hershkovitz indicates that the least severe variant of HFI manifests in females as early as 21 years of age, while advanced HFI does not emerge prior to 40 years of age. The initial psychological symptoms linked to HFI generally manifest after the age of 35.[49]

HFI occurs more frequently in females, particularly in postmenopausal women (40-60%).

Patients are typically asymptomatic or exhibit non-specific symptoms, including headache, neurological, or mental issues. The characteristic observation on [99mTc] HDP-bone scintigraphy and [18F] FDG-PET/CT is symmetrical and bilateral uptake in the frontal bones, resembling a butterfly pattern. [99mTc] HMPAO-labeled white blood cell scintigraphy demonstrates elevated

uptake, as the thickening results from higher bone marrow activity.[50]

This work is significant for elucidating clinically linked disorders by analyzing the incidence of HFI cases across both genders in American cadavers during a four-year period, as well as referencing reported instances in the literature. In Clinical Anatomy, it is crucial to recognize that HFI is not merely a physical structure seen in the calvaria, but is linked to various clinical fields, particularly neuroendocrinology, genetics, and neuropsychiatry.

Conclusion

The prevalence of male individuals with Hyperostosis Frontalis Interna in our study sample was 9.45%, which is noteworthy. Although the influence of estrogen has been the predominant factor in the etiopathogenesis of HFI thus far, the observed rate in males will illuminate new research and findings, facilitating a comprehensive exploration of the factors potentially involved in etiopathogenesis.

Given the unclear etiology, pathogenesis, and clinical presentation of HFI, it may be advantageous for clinicians to explore a potential relationship between HFI and the reported high to moderate symptoms. Furthermore, further research is necessary to accurately represent the current population of HFI patients and their associated symptoms. In extensive case groups, both cadaveric and forensic science cases, as well as living HFI instances, will be identified through radiological imaging, particularly in endocrine, neurology, and psychiatry clinics. This will facilitate multidisciplinary research, early diagnosis of HFI, and the development of novel treatment modalities in the relevant clinics.

Description

This article contains a portion of the research that was delivered as an oral presentation at the 2nd International Congress on Sports, Anthropology, Nutrition, Anatomy, and Radiology (SANAR), which took place from the 20th to the 23rd of July, 2020. The summary text was published in the booklet that contained the proceedings of the congress, namely on pages 100-105.

Compliance with Ethical Standards

This project is exempt from ethical approval as it employs course cadavers from the Albert Einstein College of Medicine C&DA Department, consistent with the exemption categories specified in Einstein-IRB-citation104(d).

Conflict of Interest

The author have no conflicts of interest relevant to this article.

Author Contributions

HC: The hypothesis of the study; HC: The Study desing; HC: Project development; HC: Literature search; HC: Analysis; HC: Manuscript writing; HC: Critical review.

Financial Disclosure

The author declare that this study has received no financial support.

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