Volume 2 • Issue 3

Topics in Biomedical Research and Education

Official Journal
Research and Education Institute in Biomedical Sciences

ISNN: 2945 -0675

2024

Topics in Biomedical Research and Education

Quarterly Scientific Publication of REIBS
Research and Education Institute in Biomedical Sciences

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Publisher/Owner
RESEARCH AND EDUCATION INSTITUTE IN BIOMEDICAL SCIENCES
92-94 Kolokotroni str.
GR-185-35 Pireaus, Attika, Greece
Tel: +30.6986564295
E-mail: irebiomeds@gmail.com

Open Access Journal
ISSN: 2945-0675

July-September 2024 | Volume 2, Issue 3

CONTENTS

Editorial

The Future of Personalized Medicine: How Genomic Data Is Shaping Individualized Treatment Plans

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The beginning of the 21st century has brought about a profound change in medical approaches, transitioning from broad treatment guidelines to more personalized therapeutic methods. This evolution, largely fuelled by progress in genomic technologies, has led to the rise of personalized medicine—where therapies and preventive measures are tailored to an individual's genetic profile. As we explore the genomic age further, it's crucial to comprehend how this information is transforming healthcare and what prospects lie ahead for customized treatment strategies.

The Genomic Revolution. The Human Genome Project's completion in 2003 represented a pivotal achievement, unveiling the genetic foundation of human existence. This landmark event spurred a vast number of research endeavours focused on exploring the complex connections among genes, diseases, and potential therapies. Following this, reductions in genome sequencing expenses and advancements in high-throughput sequencing methods have broadened access to genomic information, establishing it as a fundamental element of contemporary medical research.

Pharmacogenomics: Tailoring Drug Therapies. Pharmacogenomics is an emerging field that merges pharmacology with genomics, concentrating on how a person's genetic profile affects their drug responses. This area of study aims to unravel the genetic elements that cause differences in drug effectiveness and adverse reactions, with the primary objective of enhancing and individualizing medical therapy. As our understanding of the human genome deepens, pharmacogenomics is revolutionizing drug treatment methodologies, providing more tailored and effective therapeutic options.

Historically, medication prescriptions have adhered to a "one-size-fits-all" model, where individuals with identical conditions receive the same treatment irrespective of their genetic variations. Nonetheless, this approach frequently results in considerable inconsistencies in drug response, with some patients attaining ideal therapeutic outcomes while others may experience minimal benefits or even detrimental side effects. This variability is often rooted in genetic differences that affect drug metabolism, transport, and targets within the body.

A prominent illustration of pharmacogenomics in practice is the application of genetic testing to optimize warfarin dosing. Warfarin, an anticoagulant frequently prescribed to avert blood clots, has a narrow therapeutic range, and incorrect dosages can result in serious issues like bleeding or thrombosis. Genetic variations in the CYP2C9 and VKORC1 genes have a considerable impact on a patient's ability to process warfarin. CYP2C9 determines how quickly warfarin is metabolized in the liver, while VKORC1 affects the drug's primary target, vitamin K epoxide reductase. By performing genotyping for these genes, healthcare providers can anticipate warfarin metabolism in patients and adjust dosages accordingly, thereby lowering the risk of negative side effects.

An essential use of pharmacogenomics lies in cancer treatment, especially with targeted therapies. Tumour genomic profiling has become routine in oncology, enabling the detection of specific genetic alterations that promote cancer progression. A notable example is trastuzumab (Herceptin), utilized for breast cancer patients whose tumours overproduce the HER2 protein, a situation linked to the amplification of the ERBB2 gene. Patients possessing this genetic marker tend to experience greater benefits from trastuzumab, highlighting its role as a targeted therapy. This precision medicine strategy enhances treatment success while reducing exposure to the adverse effects of non-effective medications.

Pharmacogenomics is crucial in the treatment of psychiatric disorders, where individual responses to

medications can vary widely. For instance, genetic differences in the CYP2D6 and CYP2C19 genes influence the breakdown of multiple antidepressants, including selective serotonin reuptake inhibitors (SSRIs). Patients identified as poor metabolizers due to these genetic variations may have elevated drug levels and a higher likelihood of experiencing adverse effects, while those who are ultra-rapid metabolizers might need increased dosages for optimal effectiveness. By incorporating genetic testing into psychiatric practice, healthcare providers can more accurately align patients with appropriate medications, minimizing the often tedious trial-and-error process in psychiatric pharmacotherapy.

While pharmacogenomics holds great potential, its widespread implementation encounters several obstacles. These challenges include the prohibitive costs associated with genetic testing, restricted access to testing in certain areas, and the necessity for more comprehensive clinical evidence to support the efficacy of pharmacogenomic-based therapies. Furthermore, the incorporation of pharmacogenomic information into electronic health records and the training of healthcare providers to accurately interpret and utilize this data remain significant hurdles.

In conclusion, pharmacogenomics has the capacity to transform drug therapies by customizing treatments based on individual genetic profiles. As research progresses and technology improves, this personalized medicine approach is expected to become increasingly available and pervasive, resulting in enhanced and safer treatment options for various health issues.

Predictive Genomics Anticipating Disease Risks. In addition to customizing treatments, genomic information provides valuable insights into an individual's risk for various diseases. Predictive genomics, an advancing area within genetics, is transforming our comprehension and management of health by allowing predictions about a person's likelihood of developing certain conditions based on their genetic profile. With the declining costs of genome sequencing and enhanced knowledge of the human genome, predictive genomics is gaining importance in preventive healthcare. By pinpointing genetic vulnerabilities to diseases, medical professionals can implement personalized prevention strategies, early detection methods, and interventions, thus prioritizing prevention over treatment.

A significant application of predictive genomics is its role in identifying individuals at elevated risk for hereditary cancers. For example, mutations in the BRCA1 and BRCA2 genes are renowned for greatly increasing the likelihood of breast and ovarian cancers. Women who inherit these mutations have a lifetime risk of up to 80% for breast cancer and around 45% for ovarian cancer, compared to much lower rates in the general populace. Understanding their BRCA status empowers these women to take proactive steps, such as undergoing enhanced screenings with regular mammograms and MRIs, making lifestyle changes, and considering preventive surgeries like mastectomy or oophorectomy to mitigate their cancer risk.

Predictive genomics is also greatly influencing cardiovascular health. Genetic variations in LDLR, APOB, and PCSK9 are linked to familial hypercholesterolemia, a disorder that results in dangerously high cholesterol and a higher likelihood of early heart disease. People with these genetic markers may gain from prompt interventions, including lifestyle modifications, statin treatment, or advanced cholesterol-lowering drugs like PCSK9 inhibitors, which can aid in avoiding coronary artery disease and additional cardiovascular issues.

Alzheimer's disease exemplifies a condition where predictive genomics is vital. The APOE gene, specifically the APOE ε4 allele, is linked to a greater likelihood of developing late-onset Alzheimer's. Those who possess one or two copies of this allele face a markedly elevated risk in comparison to individuals without it. Although effective prevention strategies for Alzheimer’s are not yet available, being aware of one’s APOE status can enhance vigilance in monitoring cognitive health, facilitate involvement in clinical trials for potential preventive therapies, and encourage lifestyle modifications that are believed to lower Alzheimer’s risk, such as engaging in regular exercise, maintaining a

nutritious diet, and participating in mentally stimulating activities.

While predictive genomics holds great potential, it also presents numerous ethical, legal, and social issues. The risk of genetic discrimination by insurers or employers remains a major worry, even with safeguards like the Genetic Information Non-discrimination Act (GINA) in the U.S. Furthermore, the emotional effects of being aware of one's genetic susceptibility to severe illnesses can be significant, potentially causing anxiety or prompting life choices driven by likelihoods instead of certainties. Consequently, genetic counselling is frequently suggested to aid individuals in comprehending their risks and making informed choices.

Additionally, predictive genomics is not fool proof; it frequently addresses probabilities instead of certainties. While possessing a genetic predisposition to a condition heightens the risk, it does not ensure that the condition will occur. Various factors, including lifestyle and environmental influences, significantly impact the actual development of numerous diseases. Therefore, predictive genomics should be utilized as part of a broader, holistic approach to healthcare.

Predictive genomics is a formidable instrument that revolutionizes our methods of disease prevention and health management. By detecting genetic risks early on, it facilitates tailored preventive measures, which may lower the occurrence and severity of many illnesses. As this field progresses, it promises a future where proactive healthcare becomes standard practice, ultimately fostering longer and healthier lives.

Ethical, Legal, and Social Implications. Incorporating genomic data into healthcare brings several challenges. Key issues include genetic privacy, data protection, and the risk of discrimination. Personalized medicine, fuelled by progress in genomics and biotechnology, holds the potential to transform healthcare by customizing treatments based on individual genetic makeup. Although this strategy offers considerable advantages, it also presents numerous ethical, legal, and social implications (ELSI) that require thorough examination. As personalized medicine becomes increasingly prevalent in conventional healthcare, tackling these challenges is vital to guarantee that its adoption is both fair and ethically responsible.

A major ethical issue is the matter of genetic privacy. Personalized medicine fundamentally depends on the gathering and examination of genetic data, which is highly personal and can expose delicate aspects of a person's health, lineage, and even possible future illnesses. The risk of this information being exploited by entities such as employers or insurance firms leads to worries about genetic discrimination. While legislation like the Genetic Information Non-discrimination Act (GINA) in the U.S. offers some level of protection, it might not address every possible situation, leaving the potential for genetic data misuse as a serious concern. This prompts the ethical dilemma of how to reconcile the advantages of personalized medicine with the imperative to safeguard individual privacy and avert discrimination.

Another significant ethical concern revolves around the notion of informed consent. In the realm of personalized medicine, patients frequently need to consent to genetic testing, the retention of their genetic data, and its application in research. However, the intricate nature of genetic information and the ambiguity surrounding its consequences pose challenges for patients to fully grasp what they are agreeing to. This issue is further complicated by the likelihood of incidental findings—genetic data that might indicate susceptibility to diseases unrelated to the primary condition being examined or treated. Such incidental findings can lead to ethical dilemmas regarding whether, how, and when to disclose risks that patients may not have foreseen or wished to uncover. To ensure patients can provide genuinely informed consent, it is essential to foster clear communication, comprehensive education, and ongoing discussions between patients and healthcare providers.

The legal ramifications of personalized medicine are significant, especially regarding the ownership and management of genetic data. With the increasing prevalence of genetic testing, questions emerge about who possesses the genetic information: is it the individual, the healthcare

provider, or the testing company? This uncertainty can result in conflicts over the application and dissemination of genetic data, particularly within research and commercial environments. Additionally, the international scope of genetic research, which frequently entails cross-border data sharing, introduces further complexities due to varying legal systems and regulations that oversee genetic information.

The social implications of personalized medicine, particularly regarding its potential to worsen health disparities, raise important concerns. This approach could lead to a divide between individuals with access to sophisticated genetic testing and customized treatments and those without such access. Socioeconomic factors, including the high costs of genetic tests and therapies, as well as uneven healthcare infrastructure, often limit access to personalized medicine. Consequently, only affluent individuals or those in developed nations may fully benefit from advancements in this field, leaving others at a disadvantage. It is essential to tackle these disparities to prevent personalized medicine from increasing health outcome inequalities among various population groups.

All this evidence indicates there is a challenge in incorporating personalized medicine into current healthcare frameworks. This not only includes technical tasks like integrating genetic information into electronic health records but also necessitates educating healthcare professionals on how to interpret and utilize this data effectively in clinical settings. The swift evolution of genomics can make it challenging for healthcare systems to adapt, which may result in disparities in the quality and accessibility of personalized treatments.

Although personalized medicine offers considerable potential to enhance healthcare, it also introduces substantial ethical, legal, and social dilemmas. Tackling these concerns calls for a collaborative effort from policymakers, healthcare professionals, ethicists, and the broader community to ensure that the advantages of personalized medicine are achieved in a manner that is just, equitable, and ethically responsible. The potential of personalized medicine is vast, yet there are significant challenges to overcome.

Data Interpretation. The enormous amount of genomic information necessitates advanced bioinformatics tools and expertise to derive valuable insights.

Cost and Accessibility. Even though prices are declining, extensive genomic testing is still inaccessible for many individuals, highlighting issues of health inequity.

Integration into Clinical Practice. It is crucial to educate healthcare professionals in understanding and utilizing genomic data. Furthermore, incorporating this genomic information into electronic health records presents technical obstacles.

The combination of genomic data with artificial intelligence (AI) and machine learning (ML) could further transform personalized medicine. AI-powered systems are capable of analysing large genomic datasets, revealing patterns and relationships that might be missed by human scrutiny. In addition, advancements in gene-editing technologies like CRISPR-Cas9 promise new possibilities for rectifying genetic issues at their origin.

Preventive Medicine Dominates: Early Detection of Genetic Risks. A significant transformation in healthcare spurred by genomic progress is the shift from reactive treatment methods to proactive prevention strategies. Historically, the focus of medicine has been on addressing illnesses only after they occur, often resulting in considerable morbidity and mortality rates. However, advancements now allow for early detection of genetic vulnerabilities, placing preventive medicine at the forefront and empowering patients and healthcare providers to intervene before the onset of diseases.

While the notion of preventive medicine is not entirely new, genomics equips us with the means to enhance its accuracy and efficacy. By examining a person's genetic profile, we can uncover susceptibilities to a broad spectrum of conditions, ranging from prevalent illnesses like heart disease and diabetes to rarer genetic disorders. For instance, individuals with alterations in the BRCA1

or BRCA2 genes face a markedly elevated likelihood of developing breast and ovarian cancers. Identifying these mutations early facilitates focused monitoring, lifestyle modifications, and potentially prophylactic surgeries, greatly minimizing the chances of developing cancer. In a similar vein, genetic assessment for disorders such as familial hypercholesterolemia can pinpoint those at elevated risk for early cardiovascular issues. Those identified can be regularly tracked and managed with statins or other cholesterol-lowering treatments, which can meaningfully decrease their susceptibility to heart attacks and strokes. Moreover, within a broader context, predictive genomics can guide public health initiatives, allowing for tailored actions in high-risk groups, thereby lessening the overall disease burden. Preventive genomics encompasses common chronic illnesses, as lifestyle changes can significantly impact outcomes. For instance, being aware of carrying the APOE ε4 allele, linked to a higher likelihood of developing Alzheimer's disease, may inspire individuals to pursue a brain-healthy lifestyle that prioritizes nutrition, physical activity, and cognitive engagement. Such proactive strategies, based on genetic predispositions, could potentially postpone or even avert the progression of the disease.

Dynamic Treatment Plans: Real-Time Genomic Monitoring. As personalized medicine evolves, the idea of dynamic treatment plans is becoming more prominent. Conventional treatment approaches typically follow rigid protocols that may overlook individual differences in disease progression or therapeutic response. However, through real-time genomic monitoring, healthcare professionals can adapt treatment strategies, improving their effectiveness and reducing negative side effects.

Dynamic treatment plans hold great potential in oncology, where tumor genomics can swiftly evolve with treatment. For instance, a patient with metastatic cancer may initially benefit from targeted therapy, but over time, cancer cells might acquire resistance via new mutations. By employing real-time genomic monitoring, these alterations can be identified promptly, facilitating a timely transition to alternative therapies that address the emerging mutations. This method not only extends the treatment's effectiveness but also minimizes the risk of unchecked cancer progression.

Real-time genomic surveillance extends beyond cancer. In the realm of infectious diseases, tracking the genetic changes in pathogens can guide treatment strategies, particularly when resistance to standard medications emerges. For instance, swiftly sequencing the genome of a bacterial infection in a patient can identify antibiotic resistance traits, enabling healthcare providers to modify the treatment protocol as needed. This timely method guarantees that patients access the most suitable therapy, minimizing complications and enhancing overall outcomes.

Dynamic treatment plans also demonstrate potential in managing chronic illnesses. Diseases such as diabetes, hypertension, and autoimmune disorders typically necessitate ongoing treatment with medications that may require modifications over time. Genomic monitoring can assist in recognizing when a patient's reaction to a medication is diminishing or when adverse effects arise, signalling the need for a therapy adjustment. By persistently customizing treatment according to the patient's changing requirements, healthcare professionals can enhance disease management and boost the patient's overall quality of life.

Global Collaborations Flourish: Accelerating Discoveries and Improving Patient Outcomes. The internationalization of genomic research and the sharing of data represent a significant trend influencing the future of healthcare. Collaborative efforts across countries and the establishment of global genomic databases are speeding up discoveries, facilitating more in-depth studies and the formulation of more effective therapies.

A major advantage of these worldwide collaborations is the opportunity to gather data from varied populations. Traditionally, genomic research has focused primarily on populations of European descent, resulting in knowledge gaps regarding the genetic underpinnings of diseases in other groups. By working together globally, researchers can compile and examine data from a wider array of genetic backgrounds, yielding findings that are more inclusive and relevant. This

improved approach leads to the creation of treatments that are effective for diverse populations, helping to diminish health inequities.

Worldwide genomic databases are essential for pinpointing uncommon genetic variants linked to diseases. A single research facility may lack sufficient cases to thoroughly investigate these variants, but global partnerships can achieve the larger scale needed. For instance, major consortia such as the Global Alliance for Genomics and Health (GA4GH) unite researchers, healthcare professionals, and policymakers globally to exchange data and resources. These collaborations have resulted in the identification of new genes responsible for diseases, the creation of innovative treatments, and the discovery of potential drug targets.

In addition, international partnerships are crucial for addressing public health issues that cross national boundaries. The COVID-19 pandemic underscored the necessity of global collaboration in genomic monitoring, as scientists globally sequenced the virus's genome to trace its transmission and detect variants of concern. This collective endeavour facilitated the swift creation of vaccines and guided public health strategies, illustrating the effectiveness of global genomics in responding to pressing health emergencies.

In personalized medicine, international partnerships promote the creation of extensive clinical trials essential for validating innovative therapies and diagnostic methods. These trials can recruit varied populations, ensuring that results are applicable across different groups and that the advantages of personalized medicine reach a broad audience. Furthermore, unified global standards for data gathering, storage, and analysis contribute to maintaining the quality and consistency of genomic studies, thereby speeding up advancements in the field.

The Integrated Future of Healthcare. The future of healthcare, propelled by advancements in genomics, is expected to embrace a model that emphasizes preventive medicine, flexible treatment strategies, and international partnerships. As these elements come together, they will shape a healthcare landscape that is more anticipatory, responsive, and just.

Preventive medicine, supported by the early identification of genetic predispositions, will enhance disease prevention efforts, alleviating pressure on healthcare systems and fostering better health outcomes for populations. Flexible treatment strategies will guarantee that patients receive optimal care, customized to their specific genetic makeup and shifting health requirements. At the same time, global partnerships will continue to fuel innovation, expanding the reach of personalized medicine to diverse communities worldwide.

Nonetheless, achieving this vision will necessitate tackling a variety of challenges. Ethical, legal, and social concerns, including data privacy, equitable access, and informed consent, must be meticulously handled to guarantee that the advantages of personalized medicine are distributed justly. Furthermore, healthcare professionals will require continuous education to accurately interpret and utilize genomic data, and healthcare systems must evolve to accommodate these emerging technologies.

The evolution of healthcare is set to be revolutionized by the integration of preventive medicine, adaptive treatment strategies, and international partnerships. Fuelled by advancements in genomics, these trends aim to boost healthcare effectiveness, elevate patient outcomes, and minimize inequalities. As we further utilize genomic data, the emphasis will progressively move from managing illness to preventing it, from rigid guidelines to flexible adaptations, and from local initiatives to worldwide collaboration. This cohesive strategy has the power to lead us into a ground-breaking age of health and wellness for everyone.

Genomic information is leading a transformation in healthcare, guiding us toward a future where treatments are tailored not only to diseases but also to individual patients. Despite on-going challenges, the teamwork of researchers, healthcare providers, policymakers, and ethicists is creating a pathway to a more precise, effective, and empathetic healthcare system. As we delve deeper

into the intricacies of the human genome, personalized medicine heralds a new age where healthcare is custom-fitted to the unique needs of each person it caters to.

Letter to the Editor

Sheep in Greece, from antiquity to modern livestock and the Dementia in Sarakatsani herds

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In Hellenic antiquity sheep were used as a livestock, in sacrifices rituals, as gifts to an important person or a god, in magic, in symposia and in daily nutrition. The idea of someone to torture, mutilate and kill a live animal may seem as a rather strange and brutal concept in the mind of an ordinary people, but it is ritually documented in ancient Greece. Sheep as an anima kind is surround it by a wide variety of traditional uses. You may take an oath by killing a sheep, and pray that you shall be treated like one if you violate the oath. You may sacrifice a sheep to cast an erotic spell or put a curse upon a person [1]. To offer sheep to be sacrificed in an altar to please gods and then participate in a symposium was a most usual form of gratitude for having a plentiful livestock and you donate some the gods and the people participating in prayers [2]. Reports exist for sacrificing sheep to Apollo, the god of light, epidemics and medicine. Although infrequently, sheep were offered to the patron god of medicine Asclepius, as an offering to be sacrificed in an altar, or as a gift to the priests serving the god [*Figure 1*] [2-3].

Shepherds and sheep is a famous folklore image since the bronze era in ancient Greece. Inside the first written Hellenic documents, in the Homeric epic poem of Odyssey, we encounter the savage Cyclopes tribe which breeds sheep. Despite the emphasis given on the Polyphemus Cyclops' cruelty and barbarism, the bond between shepherd and sheep is evident, in a greater passion that among Greeks, whose only impulse was to slaughter and eat them. The poet emphasizes on the fact that sheep have much more to offer to their owners [14].

Figure 1. Stone votive relief stele, family visiting Asclepius and sacred Snake (dual nature of the god). Family offers sacrificial lamb, 5th-4th century BC, Berlin Museum of the History of Medicine.

Such a Mediterranean people who care about the sheep is the pastoral communities of Sarakatsani in continental Greece. Among Sarakatsani, sheep are being tended by men, while women only milk goats. Sheep for Sarakatsani provide everything, from wool, meat, milk and income. Sheep are sacred and as shepherds pass most of their time next to them in the mountainous countryside, avoiding long visits in towns [5]. There are reports since 1960's for an alien behavior of mountainous sheep of the kind Ovis aries. The intense observation of Sarakatsani, demonstrated by the fact that those sheep are considered to belong in a generation above the 5th by measuring the sheep being born. A recessive gene may alter the white sheep color and in some case a black sheep, named laia, or laios (meaning black) is born. Sarakatsani believe that those sheep do not demonstrate such a

deviated behavioral pattern, which on the other hand was demonstrated by white sheep in old age. Two forms of symptomatology had been observed. The first, is the sluggish (hypotonic), with the sheep called "dumusarika" (nonchalant, indifferent), which they stay behind and do not follow the rest of the herd especially in spring and summer (free grazing in the mountains), while staying aside in winter due to their confinement in stables. They stop grazing, lose weight, most probably don't see or hear, their bodies shrank and they lay down for hours and despite human efforts, they ultimately die. The second is the hypertonic with sheep being called in the language of the herdsmen, "seritka" (slow heavy movements, excitable). This form appears at a younger age, with sheep being nervous and anxious, keeping their heads up, going back and forth, moving away from the herd, usually to fall off the cliffs or be eaten by the wolves. Sarakatsani shepherds [Figure 2] having encounter dementia syndromes among them, as they lived almost isolated, succeeding long age and having limited cognitive reserve, connected this peculiar behavior with dementia. By connecting these sheep with a degenerative brain disease, they have been avoiding eating the ill livestock.

Figure 2. Sarakatsani shepherd Christos E. Voulgaris and his flock, Keleria area, 1965.

Science today, demonstrated through various studies the AD-associated neurofibrillary accumulation (tau pathology) in normal aged sheep. The presence of neurofibrillary tangles in aged sheep brain has been established, while the Alzheimer's disease itself has been recognized. Sheep have a face recognition system, live in communities, are trained in behavior and have a brain in volume and complexity similar to human, thus constituting a perfect candidate for dementia syndromes observation, or for clinical trials and possible gene manipulation to confront mental diseases [6]. Dementia which have been for decades been observed by Sarakatsani, do exist in sheep and may in the near future by their study to present promising results for the confrontation of dementia syndromes.

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Case Report

Pancreatic Head Adenocarcinoma: a case report

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Abstract

Pancreatic adenocarcinoma is a very common type of pancreatic cancer that refers to the exocrine part of the organ. Such disease is connected with low prognosis and especially low survival rates in patients presenting with metastatic sites. In this report, we present a case, where a male patient was diagnosed with pancreatic head adenocarcinoma, with also presenting metastatic sites later on. Following a pancreaticoduodenectomy, provision of FOLFIRINOX and TIPS placement, the patients remained stable. Optimal method of treatment is still not decided, despite recent studies experimenting with chemotherapy and surgery.

Key words: Adenocarcinoma, Metastasis, pancreatic head adenocarcinoma

Introduction

In general, pancreatic adenocarcinoma is classified under the broad category of exocrine pancreatic cancer (1). Pancreatic cancer is responsible for roughly 4% of all total deaths, while also being the seventh leading cause of cancer deaths (2).

Pancreatic head adenocarcinoma is considered to be a very aggressive malignancy, with a relatively low survival rate. This type of cancer presents a variety of difficulties, including possible lymph metastases and vascular involvement. (3). Unfortunately, the majority of patients does not present symptoms in the early stages of the disease, which delays the process of diagnosis. Surgery is considered to be the only option for long-term survival. Despite this, prognosis still remains poor, with a five-year survival rate after resection at approximately 30% (4). While pancreatic metastatic cancer has an even lower survival rate of just 5%.

Case presentation

A 38-years old Caucasian male was diagnosed with jaundice and a pancreatic head Adenocarcinoma. Following the pancreaticoduodenectomy, classic Whipple, pathology revealed a T2N1M0, moderately differentiated adenocarcinoma. Thus, he patient was treated with 8 cycles of FOLFIRINOX.

2 years after the initial treatment, the patient was diagnosed with 2 liver metastases, which responded to chemotherapy. The increase of liver enzymes led to the modification of chemotherapy regiment and the provision of abraxam/hemcar.

One month later, the patient was diagnosed with moderate ascites and Gastrointestinal (GI) bleeding. A thorough workup of upper and lower endoscopy, Computed Tomography (CT) angiography and radiolabeled erythrocytes was executed. These tests revealed jejunal pooling of erythrocytes without contrast extravasation. Moreover, portal stenosis with thrombosis of the Superior Mesenteric Vein (MSV) at the splenoportal junction was documented. Therefore, a Transjugular Intrahepatic Portosystemic Shunt (TIPS) was placed *(Figure 1, Figure 2, Figure 3).* Following this, the patient tolerated the procedure well and remained stable with bleeding and ascites under control.

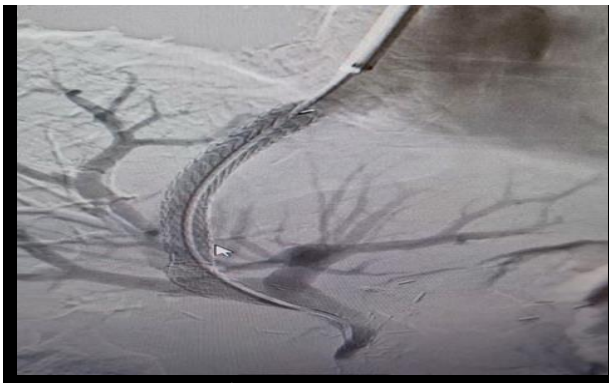

Figure 1: TIPS Placement

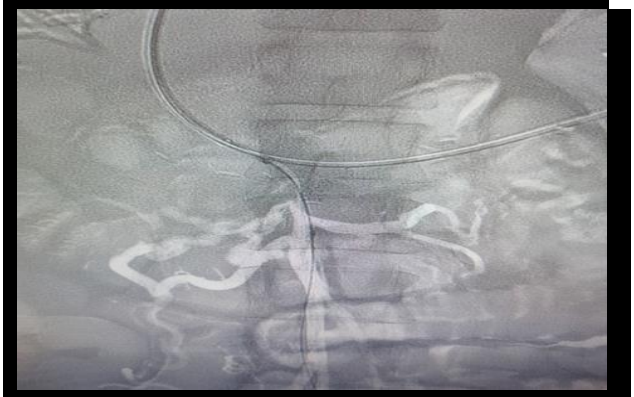

Figure 2: TIPS Placement

Discussion

Pancreatic head adenocarcinoma makes up the majority of all pancreatic neoplasms. It still remains a very dangerous disease with high morbidity and poor prognosis. Risk factors include cigarette smoking, chronic pancreatitis, diabetes mellitus and obesity among others (5). Unfortunately, this type of cancer has a high metastatic potential, while metastatic pancreatic adenocarcinoma has a significantly small five-year survival rate of 3% (6).

Process of diagnosis can be proved to be challenging. Lab tests are, in most cases, no-specific, though increased liver tests suggest biliary obstruction. Cancer-associated antigen is considered to be the most useful in diagnosis, as well as the monitoring of response to treatment (4).

It is important to note that in the case of pancreatic adenocarcinoma metastasis to the liver, the primary tumor is highly similar to the liver metastasis. Genomic analysis has also proved that the mutation spectrum between these two tumors are also similar, impacting almost identical genes (KRAS, TP53). Patients who have presented liver metastasis have worse prognosis compared to other metastatic sites. After the onset of metastasis, surgical resection is not applied, while chemotherapy, like FOLFIRINOX, and other treatments are used (7). Recent studies are exploring the efficacy of perioperative or preoperative chemotherapy for pancreatic adenocarcinoma liver metastases (8).

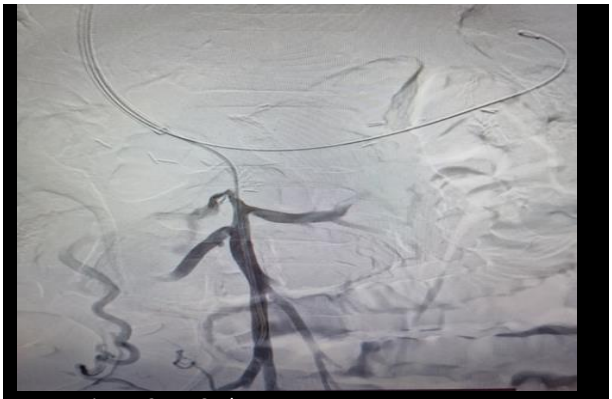

Figure 3: TIPS Placement

Conclusion

Pancreatic adenocarcinoma is a common gastrointestinal malignancy, related to a poor prognosis. This challenging disease becomes even more demanding after the presentation of metastatic sites. There is still a lot to learn about the ideal treatment for these cases that will ensure the best results for the patient.

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Historical Vignette

Parnitha Sanatorium a place of hope in the past, nowadays in "haunted" ruins

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Dear Editor,

The former Parnitha Sanatorium, now in ruins, was located on Mount Parnitha in the Municipality of Acharnon in the outskirts of the city of Athens. It was in 1914 when the Monastery of Petraki donated a piece of land to the "Evangelismos Hospital" of Athens to establish a sanatorium for the care of tuberculosis patients, as the disease was rampant at that time, causing numerous deaths [1]. The favorable climate of the Parnitha mountain due to its altitude was considered ideal for the treatment of patients. Clean air, forest environment and modern facilities rendered sanatorium to a place of hope [2]. It was established after the early death of Konstantinos Foug, who succumbed to tuberculosis, as he honored the wishes of his late mother, Fainareti Ervert, and the memory of his father, Georgios Foug, after the tragedy that was faced by the Foug family. Fainareti Ervert was the niece of the founder of the National Bank of Greece Georgios Stavrou. After Fainareti lost both her husband and her eldest son, she stated in her will that, should her surviving son die without heirs, the entirety of their estate would be used for the establishment of a sanatorium for tuberculosis patients, under the name "Georgios Stavrou and Georgios Foug" [3] Among the many inmates, the famous poet Yiannis Ritsos was admitted to the sanatorium. Ritsos was infected with tuberculosis and suffered from hemoptysis since 1926, while he had been hospitalized in Parnitha Sanatoriun between 1937 and 1938. There, Ritsos wrote his poem "Spring Symphony" [4-5]. Parnitha Sanatorium consisted of five floors and an elevated basement, a design by the architect Ioannis Antoniadis (1890-1977), starting its operations in August 1936 [Figure 1]. However, its first inauguration during August 1914 marked the beginning of the efforts of the families of Georgiou Staurou and Georgiou Fougk, who left their fortunes to establish a tuberculosis sanatorium.

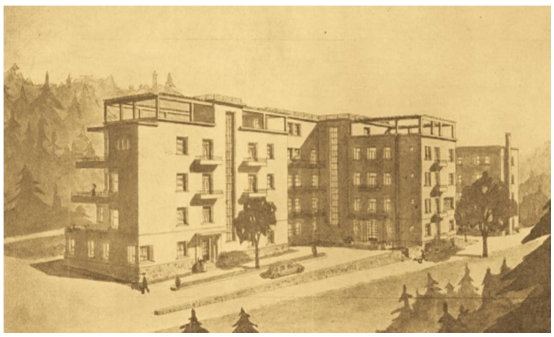

Figure 1. Parnitha Sanatorium, a design by the architect Ioannis Antoniadis, 1936.

The original hospital of 1914 was simply a wooden pavilion. The 1936 Parnitha Sanatorium used all modern techniques of the era, such as the iron lungs to treat the more than 100.000 ill all around Greece [6]. With the discovery of penicillin in 1943 and the gradual abandonment of sanatoriums, Parnitha Sanatorium closed in 1960. A few years later, it was converted into a hotel named "Xenia" and was also used as a school for tourism professions, until 1984, when its final abandonment was announced [Figure 2].

Figure 2. The renovated entrance of the Xenia Hotel with the stairs added to create a lobby.

In 1999, after an earthquake centered in Parnitha, the building was deemed unsuitable for visitation. However, not only did visitors continue arriving, but there were also numerous looting incidents of

its equipment and records. Finally, in July 2022, it was declared a “preserved” building by the Hellenic Ministry of Environment and Energy [7]. The abandoned appearance of the building, combined with the care of tuberculosis patients and the numerous deaths that occurred while it operated as a sanatorium, have led to the creation of urban legends around it. Many people believe it is haunted, claiming to have felt supernatural entities and heard eerie screams. As a result, it continues to attract crowds wishing to verify these claims. Meanwhile, a few meters away is located the “Park of Souls”, an outdoor museum created in 2012 by sculptor Spyridon Dassiotis, consisting of exhibits that represent human figures made from tree trunks, evoking awe in visitors [Figure 3] [8].

Figure 3. The Park of Souls in Parnitha near sanatorium.

The building may have been vandalized and exhibits a strong image of abandonment, yet, as experts from the Ministry of Environment and Energy emphasize, it is one of the few large-scale sanatorium examples in Greece, retaining many elements of its original form, and serves as a central piece in the history of Greek sanatoriums. Parnitha Sanatorium of a bygone era is decaying day by day. Sadly, societal neglect has played a significant role to the symbolic building, and everything it represents from the tuberculosis era is being forgotten as history of medicine tries to retains its memory.

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Review Article

The Effect of Medical Cannabis on Neurological Disorders

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Abstract

Introduction: Over the centuries, cannabis has been used for recreational purposes, to produce euphoric effects. However, several studies indicate the potential of cannabis, used as a therapeutic drug. D9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two phytocannabinoids, the basic components of cannabis, that activate receptors of the endocannabinoid system and can be used as a drug for its activation. Endocannabinoid receptors are mainly expressed on central nerve system (CNS).

Materials and Methods: Detailed research was performed via the PubMed database, using the following keywords: THC, CBD, neurological disorders, psychotropic plant, medical cannabis.

Results: The aim of this review is to highlight the effect that THC and CBD has on neurodegenerative disorders and in particular, in Parkinson Disease (PD), Alzheimer Disease (AD) and amyotrophic lateral sclerosis (ALS).

Conclusion: The clinical significance of medical cannabis is great, as it may offer anti-inflammatory, anxiolytic, anti-psychotic effects and act as neuroprotective for neurodegenerative disorders.

Keywords: THC, CBD, neurological disorders, psychotropic plant, medical cannabis

Introduction

Over the last few decades, cannabis products have become popular among young adults for recreational purposes, to produce euphoric effects. However, over the decades, several studies have investigated the wide use of cannabis in medicine [1]. Cannabis Sativa, commonly known as cannabis, has been used for thousands of years as medical plant for recreational and therapeutic or medicinal purposes.

According to various targeted commercial purposes, cannabis plants have been under hybridization into hundreds of strains. They are classified under various classification methods depending on their botanical morphology, subjective effects, chemotoxins and other factors. Cannabis plant contains more than 550 phytochemicals, including 120 identified phytocannabinoids [2]. The primary psychoactive cannabinoid in the cannabis plant is D9-tetrahydrocannabinol (THC), which is mainly produced in the leaves and flower buds of cannabis plant [3]. Additional cannabinoids, such as cannabinol and Δ8-tetrahydrocannabinol, are also present in Cannabis Sativa, but in a smaller amount than THC. Moreover, some other basic, but non-psychoactive phytocannabinoids are cannabidiol (CBD), cannabichromene (CBC) and cannabigerol (CBG). Cannabis plants have different concentration of each of these phytochemicals in each of their part. CBD is about 10% active ingredient, whereas THC about 90% and thus CBD is considered to be non-psychoactive. However, it's non-psychotropic effect can alter when the ratio of THC and CBD is above 1:1. Recent studies have shown that CBD has anxiolytic, anti-inflammatory and antipsychotic action [1,4].

The role of these phytocannabinoids is to bind to the cannabinoid receptors (CB1 and CB2), as well as to other receptor systems, via a mechanism that will be discussed below. The CB1 receptor is the most common receptor of the central nervous system and

is highly expressed in hippocampus, ganglia and cerebellum. Also, CB2 receptor is expressed in high levels in the periphery, spleen and thymus. Therefore, phytocannabinoids regulate many procedures in neurogenesis and central and peripheric nervous system [3,5].

This review aims to examine the use of the medical cannabis in the neurodegenerative disorders.

Materials and Methods

Detailed research was conducted through the published bibliography via PubMed database. The keywords used for the search were THC, CBD, neurological disorders, psychotropic plant, medical cannabis. To ensure accuracy and adequacy, information was gathered through a common data extraction form designed for the aforementioned keywords. The research study adhered to the guidelines of PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews), a comprehensive approach for conducting scoping reviews. Specifically, as regards the PRISMA, the records that were initially identified through PubMed search were 35. Additionally, 6 relevant records were obtained through a thorough review of similar articles that accompanied each of the initials records. The final number of screened records was 41. A total of 16 full-text articles were assessed for eligibility, resulting in the exclusion of 25 articles, titles, and abstracts that were not relevant with the conducted research. Hence, the specific article is based on the information retrieved from 16 reliable references (Figure 1).

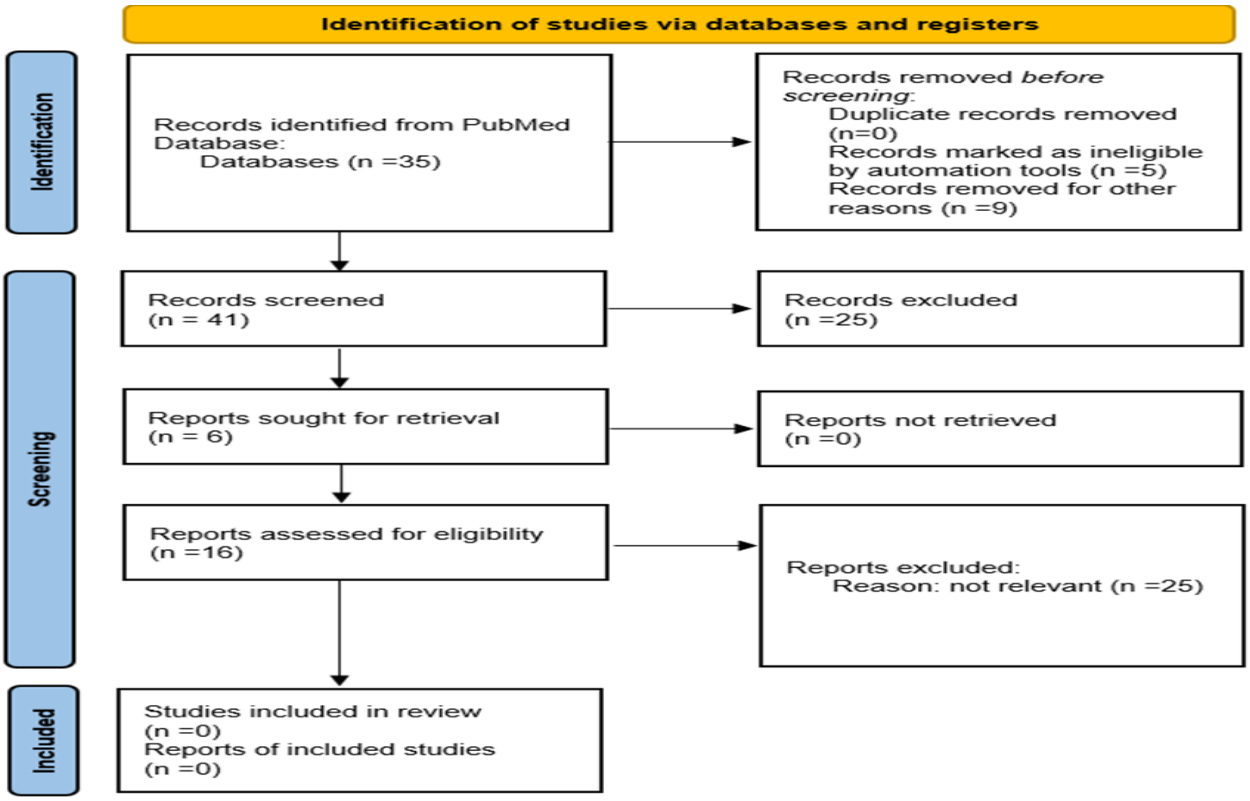

Figure 1: The Effect of Medical Cannabis on Neurodegenerative Disorders, Prisma

Results

Cannabinoids and the endocannabinoid system: Cannabinoids, that are produced endogenously, endocannabinoid receptors and their metabolite enzymes consist the endocannabinoid system (ECS) which regulates many procedures such as hunger, memory, pain, neurogenesis and the central

nervous system (CNS). CB1 receptor is a G-protein coupled receptor (GPCR), mostly expressed in the brain, as we mentioned above. CB2 receptor is also a GPCR that is highly expressed in periphery and in spleen and thymus and therefore, has a significant role in the immune system. The lipids anandamide (the ethanolamide of arachidonic acid) and 2-arachidonoylglycerol (2-AG), are the two known endocannabinoids that activate GPCRs, several ion channels and nuclear receptors. Hydrolases and lipases are the metabolite enzymes that are involved in biosynthesis and inactivation of endocannabinoids [6-8].

As we mentioned above, CB1 receptor have been detected in high levels in hippocampus, basal ganglia, prefrontal cortex and cerebellum. The location of CB1 receptor in these tissues proves the significant role of cannabinoid system in the motor and cognitional function. On the contrary, CB2 receptors have a more restricted distribution and have been found in the periphery, thymus and spleen, in cerebellum and in few brain neurons, as well. However, CB2 receptors are found in low levels in healthy brain, as they are increased in inflammation [1,9].

The expression and localization of these two receptors in CNS identify the implication of cannabinoid system in many pathophysiological procedures of the neurons and in neurodegenerative disorders. Phytocannabinoids in C. Sativa, including THC and CBD, are used for many therapeutic effects. Recent studies have proven that although, THC activates CB1 and CB2 receptors, CBD modulates the activity of both these receptors and metabolite enzymes of endocannabinoids. Also, it can modulate THC's effects on CB1 receptor. Therefore, CBD can have either a negative allosteric modulation or an adaptogen, depending on the location that it acts [6,9,10].

CBD has shown great efficacy as an antipsychotic, anti-seizure, anti-inflammatory and anxiolytic, as it activates endocannabinoid receptors and reduces OS and inflammation. CBD is significantly used as neuroprotective of neurodegenerative diseases and in particular, Parkinson disease (PD) and Alzheimer disease (AD) [11].

Neurodegenerative diseases: Neurodegenerative disorders consist one of the most recent causes of death worldwide. The pathophysiology of neurodegenerative diseases is the oxidative stress (OS) and the inflammation that cells undergo [12]. In these diseases and in particular in PD and AD, pathological genes express altered proteins which undergo a procedure of unfolding and form β-structures. Amyotrophic lateral sclerosis (ALS) is also one of the common neurodegenerative disorders. These structures self-aggregate and represent a-synuclein in PD and tau proteins (TAU) in AD. Thus, neuroinflammation and nerve cell loss are the following procedures that effect negatively motor function and cognition. Cells are protected from OS by producing cytoprotective enzymes, regulated by Nrf2 (nuclear factor erythroid 2-related factor 2). Nrf2 has an anti-inflammatory action and regulates hemostasis, in several pathological mechanisms of neurological diseases and thus, it consists a novel therapeutic product [5].

Recent studies have shown that CBD increases the expression of Nrf2 activators and thus, Nrf2 activity. Therefore, CBD's anti-inflammatory, antioxidant and anxiolytic actions are manifested through Nrf2 activation [3,13].

Medical cannabis and Parkinson Disease: PD is a major neurodegenerative disorder that affects mostly the elderly and is characterized by the dysfunction and degeneration of the extrapyramidal system. In specific, the primary locus of the disease is the loss of dopaminergic neurons in the substantia nigra. The loss of dopamine levels has as a result the initiation of motor symptoms. Moreover, patients with PD present bradykinesia, stiffness and slow rhythmic tremors. As regards the nonmotor symptoms, patients exhibit depression, psychosis and difficulties in cognition. As we mentioned above, nerve cells undergo inflammation and OS [14].

In addition, recent studies have proven the dysfunction of endocannabinoid system in PD. Therefore, drugs that target endocannabinoid system have been shown to reduce PD's symptoms. According to studies, THC relieves partially, patients

from motor difficulties, as it enhances physical activity and hand-eye coordination and also, reduces motor symptoms such as tremors, rigidity and bradykinesia [15,16].

In clinical studies, CBD treatment diminished rapid eye-movement and improved patients' sleep behavior. In particular, optic nerve and impulse are synchronized with the optic stimulus and the eyes' tremor is reduced. CBD reduces the fourth stage of sleep and the brain activity and patients present diminished dream occurrences [9,14].

Medical Cannabis and Alzheimer Disease: Alzheimer disease is a chronic neurodegenerative disorder that affects central nerve system and is characterized by memory weakening, declining subsequently cognitive functions of the patient. In particular, the cause of AD is a combination of many pathological procedures, depending on both genetic and environmental factors. The main causes of AD are the aggregation of β-amyloid plaques (Aβ), leading to loss of synapses and lesions. These lesions are characterized by many inflammatory mediators, produced by brain cells and neurons, which undergo neuroinflammation and OS. Recent studies have proven that CB1 and CB2 cannabinoid receptors are expressed in senile plaques of AD patients. However, in brain areas of microglia activation CB1 and CB2 receptors are significantly reduced, with the CB2 to become highly dysregulated. Therefore, cannabinoids, THC and CBD, act positively on AD brain, preventing brain's neurodegeneration [1,3,16].

In particular, a mix of THC-CBD drugs has been indicated to decrease the accumulation of amyloid-beta plaques and thus, to impair AD symptoms. However, this has primarily been observed in animal models. CBD acts as neuroprotective, anti-oxidative and anti-apoptotic suppressing Aβ peptide toxicity. However, THC can cause confusion, dizziness, and worsening cognitive impairment in elderly patients, which may limit its use in AD [2,9].

Medical Cannabis and Amyotrophic Lateral Sclerosis: Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, is a progressive neurodegenerative disorder that affects nerve cells in the brain and spinal cord, leading to loss of muscle control. The exact causes of ALS have not yet been cleared. Recent studies have proven that neuroinflammation, OS, glutamate-induced excitotoxicity and cytotoxicity are responsible for the disease. Medical cannabis can pharmacological potentials for symptom relief in ALS patients. Some research suggests that cannabinoids might reduce glutamate toxicity, potentially offering neuroprotective benefits [2,16].

ALS patients often experience significant pain due to muscle spasticity, cramps, and joint discomfort. Cannabis, particularly THC, is known for its analgesic properties and can help alleviate chronic pain. Moreover, cannabinoids may reduce muscle stiffness and spasms, Sleep disturbances and anorexia [3,9].

Conclusion

Cannabis has been used for decades for recreational purposes, to produce euphoric effects. However, hundreds of studies and experiments through the years, have indicated the medical aspect of cannabis and it's use for therapeutic option in neurodegenerative disorders, such as ALS, PD and AD. In particular, these diseases are characterized by the abnormal accumulation of mutant or damaged proteins, forming plaques that lead to brain dysfunction.

Endocannabinoid system has a significant role in many procedures and regulates many pathways such as neurogenesis, CNS, hunger, pain, sleep and memory, through CB1 and CB2 receptors that are mainly expressed in nerve cells. Medical cannabis, THC and CBD, can imitate endocannabinoids and act as neuroprotective, antipsychotic, anxiolytic and anti- inflammatory, consisting therefore, a powerful therapeutic drug slowing the progression of these neurodegenerative diseases. In particular, THC has shown potentials for cognitive improvement, while CBD for diminishing spasticity, rigidity and sleep disturbances.

However, clinical and animal studies over the years, indicate have brought to light some concerns and adverse effects of cannabis use, such as addiction, legacy issues, drug interaction or impairment of the disease. To conclude, data insufficiency, access issues and small-scale clinical

trials should make cannabis be used cautiously until more evidence and clinical studies be confirmed.

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Review Article

Physicians in Christian Orthodox History: Healers of Body and Soul

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Key words: Adenocarcinoma, Metastasis, pancreatic head adenocarcinoma

Introduction

Introduction. In the history of Christianity, there have been many saints with the status of physician, of various specialties. The Orthodox Christian teaching and church applaud the progress of science and especially medicine. Medicine is a work of blessing since it ensures the eudoxification of health. The Orthodox Church rejoices in scientific progress, discoveries, new medicines and modern achievements of medical practice. This synergy is confirmed both by the sacred texts of the Holy Bible and by the very act of the Church over the centuries.

Luke the Evangelist. Luke was a physician from the Hellenistic city of Antioch in Ancient Syria (*Figure 1*). It is not certain whether he was Greek or a Hellenic Jew. Regardless of his ethnicity, Luke is recognized for his high level of education, demonstrated by his proficient Greek and references to classical Greek authors. This education likely stemmed from the Hellenistic curriculum of his youth. Luke is traditionally identified as the author of the Gospel of Luke and the Acts of the Apostles. Luke's Gospel includes several detailed accounts of healings, such as the healing of the hemorrhaging woman (Luke 8:43-48) and the man with dropsy (Luke 14:1-6). These accounts often use precise medical terminology, which may reflect Luke's medical training. His attention to detail and structured narrative style in both the Gospel and Acts indicate a methodical and analytical approach, consistent with someone trained in the medical sciences. Luke was present with Paul in Rome and is also thought to have contributed to the Epistle to the Hebrews. He died at age 84 in Boeotia (1).

Figure 1: St. Luke, Evangelist and Physician.

Zenaida and Philonella. Zenaida and Philonella were sisters born in a rich Jewish family in the city of Tarsus (*Figure 2*). They were instructed and baptized into the Christian faith by their brother Jason, who was bishop of Tarsus. They studied medicine and practiced their profession unprofitably while at the same time preaching the Gospel. The result of their work was the conversion of many people to Christianity. They relocated to the mountainous region around Pelion near Demetriada in Thessaly, an area famous for its healing springs and shrines to Asclepius. The local physicians served wealthy clients, charging high fees and increasing their income by selling magical amulets and charms. The sisters, however, opposed this common practice. They found a cave with a

mineral spring, where they set up a chapel and living quarters, and opened a clinic to treat all patients regardless of their financial means. Philonella focused on experimental medicine, using methods similar to modern scientific practices, and worked diligently to separate effective treatments from superstitions. Zenaida was especially interested in pediatrics and later dedicated herself to the treatment of psychiatric disorders, such as clinical depression. Both sisters committed themselves to prayer when not working in their clinic. Their death was either peaceful or a result of an attack by pagans (2).

Figure 2: Saints Zenaida and Philonella by Symeon van Donkelaar

Antipas of Pergamum. Antipas of Pergamum lived during the 1st century A.D. He studied at the famous medical school of Pergamum and practiced medical science uncharitably, specializing in treating pain and dental diseases. According to Christian tradition, John the Apostle ordained Antipas as bishop of the Church of Pergamon during the reign of the Roman emperor Nero. During his time, Pergamum was a pagan city with a famous Asklepion. The Christian population was just a minority in the city and persecutions against Christians were the common practice. In one of those, Antipas was arrested and led to the local ruler. After rejecting the offer to spare his life and staying loyal to his Christian faith he was sentenced to death and martyred in the Brazen Bull. In this, the condemned were locked inside the device (with their head aligned within the bull's head), and a fire was set beneath it, heating the metal to the extent that the person within was slowly roasted to death. His fame made him the patron saint of the dentists and contributed to the construction of the Byzantine church of Saint Antipas in the precinct of the Dental School of Athens in Goudi which was inaugurated on May 25, 1975 (3).

Hermione of Ephesus. Hermione came from Caesarea of Palestine and studied medicine and philosophy. She was one of the four daughters of Saint Philip the Evangelist, practiced medicine uncharitably, and was a deeply faithful Christian. Hermione and her sister Eukhilda traveled to Ephesus to meet John the Evangelist in order to help him with his missionary work. Despite not finding him due to his death they decided to stay in Ephesus. Hermione founded there the first Christian hospital in Ephesus where she treated all people in need of medical care. The sisters were arrested and tortured by order of the emperor Trajan but were eventually set free. However, when Hadrian ascended the throne of emperor, Hermione was captured, tortured, and finally beheaded, becoming a martyr of the Christian faith (4).

Diomedes of Tarsus. Diomedes was born in Tarsus during the 3rd century A.D. and studied medicine. He traveled across the world and practiced medicine uncharitably while preaching the Gospel to the sick, converting many of them to Christianity. During the Great prosecution of Diocletian, Diomedes arrived at Nicaea to help the sick and preach. There the emperor ordered his arrest sentencing him to death. However, he died before his arrest. Despite his death he was beheaded by Roman soldiers (5).

Blaise of Sebastea. Blaise of Sebastea (Saint Blaise) was born in the early 4th century A.D. in the city of Sebastea in Armenia. After studying philosophy and medicine he returned to his city of birth to practice medicine. At the same time, Blaise preached the Christian faith and converted thousands of pagans to Christianity. When the bishop of the city died, he was chosen to succeed him thus becoming bishop of the Church of Sebastea. After some time, he retired to Mount Erciyes where he remained as a prayer. There, he

gathered herbs and minerals from which he prepared medicines that he distributed free of charge to anyone in need. In 316, Agricola, the governor of Cappadocia and of Lesser Armenia, arrived in Sebastia at the order of the emperor Licinius to persecute Christians. Blaise was arrested and after denying to denounce his faith he was tortured and beheaded. References of Blaise can be traced in the writings of Aetius Amidinus where his practice of treating patients with throat infections is presented. He is considered the patron of otorhinolaryngology (6).

Thalalaios the physician from Lebanon. Thalalaios a diligent, and faithful Christian, he had studied at many schools, but finally devoted himself to medical science. Being a physician, fe did not receive any remuneration from the people he healed. The Orthodox Church calls him an Unmercenary Physician. He was beheaded during his martyrdom at Aegea, in the autumn of the year 284 (or 289) (7).

Pantaleon. Pantaleon lived during the 3rd century A.D and came from the city of Nicomedia in Anatolia (*Figure 3*). He received his medical training from the esteemed physician Euphrosinos. With Euphrosinos's support, he was subsequently appointed Emperor Maximian's physician. At the same time, he treated poor sick people without any charge for his medical services. During the Diocletian prosecution, Pantaleon was arrested. After refusing to denounce his faith Pantaleon was condemned to death and beheaded becoming a martyr of Christianity (8).

Cosmas and Damian. There are three pairs of saints named Cosmas and Damian. The first were brothers, who lived in the time when Carus was emperor of the Romans, they were physicians by profession and provided healing to all who were in need. In return, they did not take money but asked the patient to believe in Christ. They even cured emperor Carus himself of a wry neck, which resulted in enormous glory and fame for the brothers.

Figure 3: Hand-painted icon of St Panteleimon by Joan Burkitt-Gray.

Eventually, that fame led to their end as their former teacher was so jealous that he caused them to be stoned to death. The second pair named Cosmas and Damian (*Figure 4*), were twin brothers living in the Aegea of Cilicia. They studied medicine and surgery and became two of the most famous physicians in the known world. However, they refused all payment and practiced their work uncharitably. During Diocletian's persecution, they were denounced for their Christian faith and arrested by Lycias of Arabia. After much torture, they suffered death by beheading. The third pair were famous doctors and veterinary surgeons. Their mother was Saint Theodoti, who nurtured them in Christian values and principles. They studied the Gospel and never accepted payment for their services. They died peacefully in their hometown (9)(10).

Figure 4: Cosmas and Damian the Saint Anargyroi.

Saint Basil the Great. Saint Basil the Great (Basil

of Caesarea) was born to a wealthy family around 330 A.D. in Cappadocia. His studies began in Caesarea, continued in Constantinople, and lastly in Athens where he stayed for four years to excel at philosophy, rhetoric, grammar, astronomy, and medicine. For approximately a year, he practiced law and taught rhetoric in Caesarea. Basil's life underwent a profound transformation after meeting Eustathius of Sebaste, a charismatic bishop and ascetic. Renouncing his legal and teaching career, Basil dedicated his life to God. He traveled to Egypt, Palestine, Syria, and Mesopotamia to be taught about ascetic life and stayed as a monk in a monastery of Pontos for 5 years (357 – 362). In 370 A.D. he succeeded bishop Eusebius and was ordained as archbishop of Caesarea. Basil took the lead in the struggle against the heresy of Arianism and courageously defended the Orthodox Christian faith. His literary work is vast and important, consisting of many discourses, six ascetic writings, two doctrinal writings, and 365 letters. Furthermore, he constructed an extensive complex just outside Caesarea, known as the Basiliad, which comprised a poorhouse, hospice, 300-bed hospital, wards for travelers who were sick, and a unit for people with leprosy which became a lasting monument of Basil's episcopal care for the sick and the poor. Basiliad was the inaugural hospital established by the Christian church, marking the beginning of numerous such institutions constructed worldwide, both in ancient and modern eras. At the age of fifty, Basil the Great, dies due to an illness (some sources say from severe liver or kidney disease), on January 1, 378 AD. or according to others in 379 to 380 A.D., bequeathing to humanity a huge spiritual work and an outstanding paradigm (11) (12).

Gregory of Nyssa. Gregory was born in Neocaesarea of Pontus in 332 A.D. and he was the brother of Basil the Great. Little is known of what further education he received. Some say that he accompanied his brother, Basil, in Athens while others argue that he studied classical literature, philosophy, and perhaps medicine in Caesarea. Gregory became bishop of Nyssa and had a major role in the First Council of Constantinople. He is known for his theological and philosophical work rather than his work as a physician. However, his works occasionally touch on themes related to health, the human body, and healing, reflecting the broader context of early Christian engagement with medicine. In On the “Making of Man”, Gregory reflects on the creation and nature of the human body. While this is a theological work, it demonstrates an understanding of human anatomy and physiology, influenced by the medical knowledge of his time. Gregory discusses the harmony and functionality of the body, seeing it as a reflection of divine wisdom. Gregory draws on both earlier sources such as Galen and contemporary sources. He produced detailed descriptions of the human body's functions and acknowledged the ability of humans to learn from sensory experience. According to Gregory, the human body consists of three groups of organs: i. The vital organs that are necessary for life to exist i.e. brain, heart, liver, ii. The sensory organs and iii. The reproductive organs. Other organs such as the stomach and lungs only serve to support the three systems mentioned above. Furthermore, he explains how the elements of the material world interact and are used by the body. He describes the body as a perfect balance of heat and cold, as well as moisture and dryness. He accurately describes the role of the heart, the lungs, the liver, and the stomach in the function of the human organism. Regarding the brain, Gregory acknowledges its importance, characterizing it as the seat of the mind. He observed the proximity of the eyes, ears, nose, and mouth to the brain to directly transmit information from the senses to the brain while also observing that the nerves connect to the brain via the spinal cord, enabling sensory input from the extremities to reach the brain. Additionally, the immediate onset of death following a brain injury provides further evidence that the brain is the seat of the mind. He died around the year 395 A.D. (13).

Sampson the Hospitable. Sampson was born and raised in Rome to a rich family thus studying philosophy and medicine. As a physician, Sampson never sought the pecuniary benefits and treated all patients lovingly and without discrimination. When

his parents died, he gave away his inherited fortune and moved to Constantinople. There, he visited all the monasteries where he found peace and studied the Gospel. He turned his house into a free clinic where patients were provided all the necessary medical care and food. He even treated Justinian, the Byzantine Emperor, when he fell ill. For Justinian to express his appreciation and gratitude to Sampson, Justinian built a hospital in Constantinople that quickly became a great charitable institution where the needy and the weak took refuge to be healed and find comfort and support for 600 years. Sampson died circa 530 A.D. (14).

Zenobius, the wealthy physician from Cilicia. Saint Zenovius Bishop of Cilicia, studied medicine, healed and worked miracles in his area. He was the heir to a large fortune, but this did not prevent him from distributing it to the poor. The holy physician healed without money. He was beheaded together with his sister Zenobia by the prefect Lysias (15).

Agapetus of the Kiev Caves. Agapetus was born during the 11th century A.D. in Kiev. He lived as a monk in the Kiev Monastery of Caves where he practiced medicine. There, he treated not only his monastic brethren but also many laymen who asked for his help. He used to collect herbs which he later boiled and administered to his patients as a drug to recover from their disease. Those oiled herbs were once used to treat Prince Vladimir Monomakh of Chernigov, the future Great Prince of Kiev himself. Saint Agapetus died in 1095 due to sickness (16).

Luke of Simferopol. Luke (Valentine Felixovich Voino Yassenetski) (*Figure 5*) was born in Kertz, on April 27th, 1877. He studied Medicine at the Great Prince St. Vladimir Medical School at the University of Kiev between 1898-1903. After graduating Luke specialized in surgery and ophthalmology at the University of Kiev. During the Russian-Japanese War he served at the Red Cross Hospital in Chita, where he gained significant surgical experience, particularly in major skeletal and cranial surgeries. Concurrently, he focused on treating pyogenic infections, a major issue in daily medical and surgical practice. For thirteen years, he worked extensively in this area as a provincial doctor in Siberia and other regions (Simbirsk, Kursk, Saratov). Luke has also been extensively involved in research in the field of regional anesthesia making the first recorded attempt to treat trigeminal neuralgia. In 1917 he was appointed as the head surgeon of the Tashkent Municipal Hospital, while in 1921 he was appointed professor of Topographic Anatomy and Surgery at Tashkent's University. At the same year, he was ordained priest by Bishop Innokenty of Tashkent. In 1923 an era of intense persecution of Orthodox Christians in Russia began, which saw the execution of numerous clergy and monks. Bishop Innokenty of Tashkent was sent into exile, thus Luke was appointed as his successor in May 1923. In December 1923, Bishop Luke himself was exiled for the first of three times, enduring a total of 11 years in exile without formal charges. His initial exile took him to Omsk, followed by Novosibirsk and Krasnoyarsk in central Siberia, before being relocated 430 kilometers north to Yeniseisk. During his exile, Bishop Luke transformed his prison into a chapel and outpatient clinic. In 1924, he achieved a medical milestone by performing the world's first successful kidney transplantation from an animal to a human. He also conducted various surgeries, including ophthalmological, gynecological, pediatric, and neurosurgical operations. Bishop Luke continuously treated outpatients both in the hospital and at his prison, and taught new surgical techniques to his peers and young doctors, who respected and admired him greatly. Later, he was moved to the remote village of Khaya on the Chunya River, where he continued to practice surgery despite minimal equipment. In the summer, he returned to Yeniseisk to operate at the hospital and serve in an old monastery. Due to his ecclesiastical activities, he was transferred to Turukhansk under harsh conditions. There, he performed surgeries with only a pocketknife. Bishop Luke's preaching and spiritual support led to public outcry, prompting his return to Turukhansk, where he continued his medical work with dedication. Eventually, he was permitted to settle in Krasnoyarsk, where he immediately resumed his surgical practice. He performed a range of

procedures, including iridectomies, lacrimal sac removals, upper jaw resections, large laparotomies, and gynecological operations, continuing to treat diverse medical conditions and injuries. In April 1930, he was arrested on charges of incitement to murder and underwent intense interrogation. He was transferred between several locations, including Samara, Moscow, Kotlas, and eventually Archangel, where he lived in near-homelessness but continued performing surgeries, including radical operations on breast cancer. Due to the harsh conditions of exile, Bishop Luke developed severe health issues. In late 1933 he was released but in 1937, he was arrested again during a severe persecution of the Orthodox Church and subjected to brutal treatment. Despite severe torture and a hunger strike, he maintained his faith and continued to help others. During World War II, after the German invasion in 1941, Bishop Luke served as a chief surgeon in Krasnoyarsk saving many soldiers' lives. Post-war, Bishop Luke was appointed Archbishop of Tambov and Michurinsk in 1944 and, later, Archbishop of Simferopol and Crimea in 1946. He continued his medical practice, even after losing his sight in 1956, and contributed significantly to medical literature and education. Despite facing persecution, he remained steadfast in his faith and medical duties until his death on June 11, 1961. He was canonized as Saint Luke by the Russian Orthodox Church on May 25, 1996.

Figure 5: St Luke the surgeon of Simferopol by Aidan Hart.

Luke's contributions to the field of medicine are extensive, with numerous papers to his name spanning all over his medical career from 1908 to 1956. Those papers concerned many fields of medical science, especially surgery e.g. new surgical methods, surgical treatment of spinal cord injuries and CNS tumors, treatment of pyogenic infections, treatment of osteomyelitis, etc. He even published a book, the "Textbook on Pyogenic Infections" where he precisely describes the surgical treatment of pyogenic infections. This innovative method could assist patients with pus-filled abscesses, localized infections, and infected wounds in surviving in a time when antibiotics were rare and too expensive. In 1946 he was awarded Stalin's prize for his book. He also has rich writing work in the field of theology with books such as "The Spirit, the Soul and the Body'', and "Science and Religion" being some of his most significant contributions (17).

Conclusions

In general, the Orthodox Church honors many physicians as saints, calling them the Unmercenary (Anargyroi) saints, i.e., doctors who treated their patients without silver (money). Besides the ones mentioned above, other such saints are Cyrus and John, Ermolaos (teacher of Pantaleon), Mocius, Photius and Anicetus of Nicomedia, Sophia the Physician, Papylos, Alexander of Lugdunum (Lyon), Loukianos, Aimilianos, Episcope Vlasios, Pausikakos, Karpos, Antiochos of Sevasteia, Orestis of Tyana, Aggelis of Chios, Nikostrate the Physician, and more (18).

The Orthodox Church founded by Jesus Christ never rejected medical science. After all, such a thing would be absurd, since the Holy Bible itself, which was studied by the first Christians (the Old Testament), in the book Sophia Sirach, ch. 38, 1-15, orders: "Honor physicians for their services, as the Lord created them and bestowed upon them the gift of healing, which comes from the Most High and is rewarded by the king. The skill of physicians sets them apart, earning them admiration in the presence of the great. Medicines, created by the Lord from the earth, are not to be despised by the wise. Just as water was sweetened by a tree to reveal its power, God granted skill to humans to

glorify His marvelous works. Physicians heal and alleviate pain, while pharmacists create mixtures from these remedies. God's works are boundless, and from Him, health spreads across the earth. When ill, one should pray to the Lord for healing, rectify one's faults, and cleanse the heart from sin. Offer a sweet-smelling sacrifice and a portion of choice flour, and give physicians their due respect, as they are created by the Lord. Their role may be crucial for recovery, and they pray for success in their work to preserve life. Those who defy their Maker will also defy the physician.''

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Review Article (Erratum)

Anatomical variations of the dorsal motor nucleus of the vagus (DMN)

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Abstract

The aim of our review is the description of possible anatomical variations of the dorsal motor nucleus of the vagus nerve (DMN). However, due to the insufficient literature, only a short summary of these sources was achieved. The topic of our project focuses on the anatomical variations of the dorsal motor nucleus of the vagus nerve. Data base Pub Med was the source of our search. We inserted in advanced search of Pub Med the block chain; "anatom*" AND ("variat*" OR "categor*" OR "type*" OR "difference*" OR "version*") AND ("human*" OR "man*") AND ("dorsal motor nucleus" OR "DMN" OR "DMNX"[MeSH]) AND ("vagus" OR "X"). Initially, 19 articles arose. From 19, 7 of them were related to the topic of our paper and 1 article was not accessible. Consequently, for the composition of our paper 6 articles were utilized.Hence, the DMN exhibits distinct differences between infants and adults, with a potential pathogenic mechanism for Sudden Infant Death Syndrome (SIDS) involving abnormal or delayed neurogenesis in the DMN nucleus. Additionally, the distribution of substance-P neurons and tyrosine hydroxylase neurons is unique in the DMN. The overall variations in the dorsal motor nucleus of the vagus nerve are minimal, and the significance of this study lies in its potential for informing future research.

KeyWords: DMN, SIDS, Substance-P, Tyrosine Hydroxylase, variations

Introduction

The DMN, the largest parasympathetic nucleus in the brainstem, is a diverse collection of approximately 16,826 neurons on each side of the brain. These neurons can be classified into two groups: vagal motor neurons and interneurons. There are five types of vagal motor neurons, with Type I being the largest and Type IV being the smallest. Type V neurons are pigmented. Type I neurons have a mean diameter of 31 µm and are the largest in the DMN, while Type II neurons are medium-sized with differences in soma size. The percentage of Type II neurons is estimated approximately in 27%. Additionally, Type III neurons in the DMN are characterized by a fusiform shape and medium size in transverse sections, with an estimated total number of 1.643, making up 13% of the motoneuronal population.[(1)] On the other hand, Type IV neurons are small and ovoid, with a total estimated count of 3.653, comprising 29% of the motoneuronal population. Type V neurons, which contain black pigment, are described as ovoid and medium-sized, with a total estimated count of 1.392 pigmented neurons. In contrast, the presumed interneurons are significantly smaller, measuring three to five times smaller than the average size of the other neuron types in the X. The interneurons in the nucleus are observed to have various shapes, including oval, fusiform, or round, with an estimated total of 3,024. These neurons are not evenly distributed throughout the nucleus. The DMN is subdivided into three major subnuclei: the rostral, intermediate, and caudal.[(2)]

The DMN functions by projecting parasympathetic preganglionic cholinergic efferent fibers to the viscera. It is commonly observed that the rostral part of the DMN represents abdominal organs, while the cardiac representation is located in an intermediate region between the rostral and caudal parts. However, most organs are not exclusively represented in only one division of the nucleus.

Additionally, the DMN communicates with the NTS, which sends vagal information to the DMNV and integrates sensory vagal afferent stimuli.

Our work aims to explore anatomical variations in the DMN in humans. Limited literature and a lack of studies on this topic have restricted our ability to provide in-depth analysis, but we can discuss certain anatomical features based on immunoreactivity and histological observation.

Materials and Methods

The topic of our project focuses on the anatomical variations of the dorsal motor nucleus of the vagus (DMN). Data base Pub Med was the source of our search. We inserted in advanced search of Pub Med the block chain; "anatom*" AND ("variat*" OR "categor*" OR "type*" OR "difference*" OR "version*") AND ("human*" OR "man*") AND ("dorsal motor nucleus" OR "DMN" OR "DMNX"[MeSH]) AND ("vagus" OR "X"). Initially, 19 articles arose. From 19, 7 of them were related to the topic of our paper and 1 article was not accessible. Consequently, for the composition of our paper 6 articles were utilized.

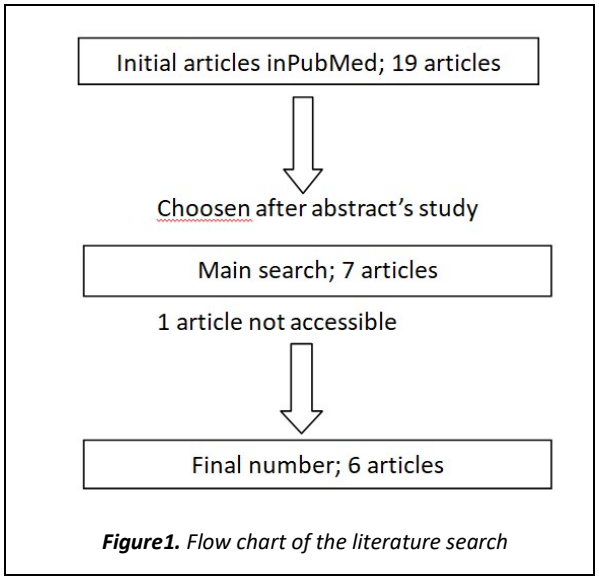

Figure1. *Flow chart of the literature search*

Discussion

The comparison of the DMN in adults and infants reveals interesting things. Although the number of neurons in the DMN remains consistent between adults and infants, adults have a higher nuclear volume and lower neuronal density in this medullary nucleus compared to infants.[3,4] Additionally, apoptosis levels in DMN neurons are higher in adults than in infants, with no significant statistical difference in glial cells. The differences in neuronal volume and density between adults and infants may be due to variations in microvascularization and distribution of neuropil. Microvascularization also plays a role in the progression of apoptosis.[5]

The DMN seems to possess and important role in Sudden Infant Death Syndrome (SIDS). Sudden Infant Death Syndrome (SIDS) is the leading cause of death in infants between the ages of one month and one year.[6] It is believed that abnormal or delayed neurogenesis in the DMN may be linked to SIDS.

In control infants, neurogenesis in the DMN nucleus is complete at birth, with exponential postnatal growth as infants develop. However, in SIDS victims, there is a lack of development and dendritic arborization, leading to a deficiency in neuron size in the DMN. Differences have been observed in the growth of DMN neurons in SIDS infants compared to age-matched infants, with a delay in the expected loss of dendritic spines.6 Reduced neuronal density has also been observed in SIDS infants compared to normal infants.4

Immunoreactivity of the DMN. Some neurons in the DMN contain special substances such as substance-P, an undecapeptide, and tyrosine hydroxylase, a cell enzyme. Substance-P is found in both somata and fibers of approximately 16% of the total number of neurons in the DMN, totaling around 2040 neurons. The distribution of substance P positive neurons is higher in the intermediate division compared to the caudal division, with a lower presence in the rostral division. These Substance-P neurons in the DMN can appear either round or fusiform.[2] Regarding tyrosine hydroxylase; neurons that are positive for this enzyme can be round, oval, or fusiform in shape. The distribution of tyrosine hydroxylase is higher in the intermediate subdivision, while in the caudal subdivision, these neurons are only located ventrally and in the rostral subdivision, they are found medially. Notably, substance P positive neurons are primarily located in the

center of the DMN, whereas tyrosine hydroxylase positive neurons are more commonly found in the periphery. Additionally, there is a difference observed in Parkinson's disease, where substance P positive neurons are decreased in the DMN compared to non-Parkinson individuals.[(2)]

Conclusion

The DMN, the brainstem's largest nucleus, is divided into sub nuclei based on functional and anatomical specialization. Despite its significance, there have been limited studies on the anatomical variations of the DMN. However, we emphasize specific anatomical differences between adults and infants, the growth pattern of neurons in SIDS infants, and the distribution of specific neuron types in the DMN sub regions. Therefore, understanding the cyto-architecture of the DMN could be essential for explaining clinical conditions and guiding future research.

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