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Editorial

Unlocking Hope: Rare Diseases and the Promise of Orphan Drugs

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Rare diseases, also known as orphan diseases, may have a limited impact on individuals, but their collective effect is felt by millions worldwide. These diseases are considered rare as they afflict less than 1 in 2000 people. Although each specific rare disease has a low prevalence, the overall burden is significant. Thankfully, advancements in medical research and the development of orphan drugs offer hope for those living with these conditions. This article will explore rare diseases, the challenges they present, and the incredible potential of orphan drugs to improve lives. Rare diseases encompass a wide range of conditions, such as genetic disorders, autoimmune diseases, and infectious diseases. Their rarity often leads to underdiagnosis or misdiagnosis, causing delays in treatment and increased suffering for patients. Examples of well-known rare diseases include Huntington's disease, cystic fibrosis, and ALS (Amyotrophic Lateral Sclerosis).

Rare disease patients face significant challenges in their journey, including delayed diagnosis, limited treatment options, high costs, and feelings of isolation. One of the main hurdles they encounter is delayed diagnosis, as a result of healthcare professionals' lack of awareness and the limited availability of diagnostic tests. Moreover, the limited treatment options for rare diseases pose another challenge, as pharmaceutical companies find it financially challenging to develop drugs for small patient populations, leaving many rare diseases without approved treatments or therapies. Additionally, even when treatments do exist, they are often exorbitantly expensive, placing an immense financial burden on patients and their families. Lastly, patients with rare diseases may feel isolated due to the absence of support groups or communities where they can connect with others who share their condition. These challenges collectively impact the lives of rare disease patients significantly.

As previously mentioned, orphan drugs are medications specifically created for the treatment of rare diseases. They bring a sense of hope to individuals and families who are facing these often life-threatening conditions. They offer numerous benefits that make a significant difference in the lives of patients.

One of the main advantages of orphan drugs is that they are targeted therapies. Instead of merely managing symptoms, these drugs are designed to address the underlying causes of rare diseases. This can result in more effective treatments and an improved quality of life for patients. Furthermore, orphan drugs serve as incentives for development. Governments worldwide have recognized the importance of these medications and provide various incentives to encourage their creation. These incentives include tax breaks, extended patent exclusivity, and expedited approval processes. This support facilitates the development of orphan drugs and ensures that these treatments reach the individuals

who need them. In the pharmaceutical landscape, the role of patient advocacy associations and groups is crucial. These organizations play a vital role in raising awareness about rare diseases and advocating for further research and funding. By working alongside these groups, the development and accessibility of orphan drugs can be enhanced, ultimately benefiting those with rare diseases.

Their contributions have played a crucial role in promoting the progress of developing drugs for orphan diseases. Moreover, collaborative efforts between academia, pharmaceutical companies, and government agencies are often necessary in conducting research on rare diseases. This interdisciplinary approach helps speed up the process of making new findings. Although each individual rare disease may be infrequent, their overall impact is significant. The emergence of orphan drugs offers a glimmer of hope for those affected by these conditions. With ongoing research and advocacy, more advancement in treating rare diseases is anticipated. The collaboration among scientists, pharmaceutical companies, and patient advocates serves as an outstanding example of the strength of working together to bring hope to individuals with rare diseases.

The development of orphan drugs, which are pharmaceuticals specifically designed to treat rare diseases, is a crucial and noble undertaking. These drugs serve as a lifeline for individuals who often have no other treatment options. However, the process of creating and making these drugs available presents unique challenges that require innovative solutions and unwavering dedication. In this article, we will delve into the difficulties of developing orphan drugs and explore the reasons underlying these challenges.

Orphan drug development is closely intertwined with innovation in the pharmaceutical industry and healthcare systems. Most experts agree that innovation is the future of patient treatment and holds great promise for the research and development of the pharmaceutical industry. However, there are numerous limitations and problems that need to be resolved in order to facilitate the production and access to orphan drugs, making them widely and easily available to patients worldwide.

Limited Patient Populations. The limited number of patients impacted by each rare disease presents a major obstacle in the development of orphan drugs. Due to the rarity of these conditions, clinical trials face the challenge of recruiting participants from a geographically dispersed and limited pool. This scarcity of individuals hampers the collection of statistically significant data, thereby impeding the progress of drug development.

High Development Costs. Developing a new pharmaceutical is a costly and time-consuming endeavor, and the economics become even more challenging for orphan drugs. The smaller patient population means that pharmaceutical companies cannot rely on high sales volumes to recoup their investments. Consequently, development costs per patient can be exceptionally high.

Lack of Investment. Both investors and pharmaceutical companies need to carefully evaluate the possible return on investment. Orphan drugs, which cater to a small market, may seem less financially appealing compared to drugs focused on more common diseases. Consequently, obtaining financial support for research and

development of orphan drugs can be a challenging endeavor.

Complex Regulatory Pathways. The approval process for orphan drugs is challenging and involves navigating intricate regulatory pathways. These pathways are different from those for drugs intended to treat common diseases, and they often necessitate the submission of extra documentation and evidence of safety and effectiveness. As a result, this can cause delays and escalate the costs of development.

Difficulty in Proving Efficacy. The lack of comprehensive knowledge about the natural progression of rare diseases poses a significant challenge in developing effective measures of treatment success. Consequently, the design and execution of clinical trials that adhere to regulatory standards become increasingly problematic.

Limited Disease Understanding. The limited understanding of the molecular and genetic aspects of rare diseases impedes drug development, as an in-depth comprehension of the underlying mechanisms is essential for creating successful treatment options.

Access to Clinical Expertise. It can be difficult to locate clinicians and researchers who specialize in rare diseases. Establishing collaboration among experts, pharmaceutical companies, and patient advocacy groups is necessary but can be logistically challenging.

Market Access and Reimbursement. Even after gaining regulatory approval, orphan drugs face challenges in accessing the market. Negotiating reimbursement with healthcare payers can be difficult due to pricing concerns and limited budgets.

While developing orphan drugs presents clear and daunting obstacles, they are not insurmountable. The pressing need to offer hope and treatment options to individuals affected by rare diseases motivates researchers, clinicians, patient advocates, and pharmaceutical companies to persevere in their endeavors. Progress has been made in tackling these challenges through collaborative approaches like public-private partnerships and government incentives. As our knowledge of rare diseases improves and drug development strategies evolve, the future looks promising. Cutting-edge technologies like gene therapies and precision medicine are opening up new possibilities for treatment. With the dedication of all stakeholders, ongoing support, and advocacy, orphan drugs will continue to emerge, transforming the lives of those who need them the most.

Examining the multifaceted impact of orphan drugs on health systems is crucial, as they provide much-needed treatment options for patients suffering from rare and life-threatening conditions. These drugs offer immense hope to individuals who would otherwise be left without adequate medical care.

The economic impact of orphan drugs can be significant, placing a burden on health systems. These drugs often come with a hefty price tag due to the small patient populations they serve. Combined with the high costs of development, this can strain healthcare budgets. As a result, health systems must carefully allocate resources to ensure that these treatments remain accessible while also maintaining financial sustainability. Budgetary constraints pose a challenge in incorporating orphan drugs into healthcare budgets, particularly for health systems with limited resources. These drugs can consume a large portion of the budget, potentially leaving less funding available for other essential services and treatments.

Policymakers must continuously strive to strike a balance between providing access to orphan drugs and ensuring the overall sustainability of healthcare. Negotiating fair prices and reimbursement for orphan drugs proves to be a complex task. Health systems and payers struggle to evaluate the value of these drugs due to the limited number of patients they cater to. As a result, negotiations become lengthy and uncertainty arises regarding the appropriate payment for these treatments.

The cost of orphan drugs indirectly affects insurance premiums. Health insurers, faced with high expenses for covering these drugs, may transfer some of the costs to policyholders through increased premiums. This situation presents affordability challenges for individuals and families seeking comprehensive healthcare coverage. Equity and Accessibility are main priorities in the treatment of patients with rare diseases. It is crucial for health systems to prioritize fair and equal access to orphan drugs. Patients suffering from rare diseases should have equal opportunities to receive life-saving treatments, just like those with more common conditions. However, inequalities in access can arise due to factors such as location, socioeconomic status, and insurance coverage. Health systems must proactively address and eliminate these disparities.

Introduction of orphan drugs often requires healthcare providers to possess specialized clinical expertise and infrastructure. Proper training is necessary for healthcare professionals to accurately diagnose and effectively treat rare diseases. Additionally, health systems may need to invest in specialized laboratories, equipment, and support services in order to deliver these treatments. The demand for expert knowledge in rare diseases can also lead to disparities in geographical access to care. Orphan drugs are frequently utilized for persistent and lifelong ailments, necessitating health systems to contemplate their long-term viability. The expenses associated with orphan drugs can amass over time, potentially placing strain on healthcare budgets and resources down the line. Although orphan drugs pose challenges for health systems, they are also essential in motivating pharmaceutical companies to invest in research and development for rare diseases. Government incentives, like granting extended patent exclusivity and providing research grants, encourage innovation in this vital realm of medicine.

Orphan drugs exemplify the move towards prioritizing patients' needs and preferences. By offering hope and treatment options to individuals with rare diseases, these drugs empower patients in ways that were previously non-existent. In light of this evolving healthcare landscape, healthcare systems must adjust their practices to prioritize personalized medicine and patient advocacy. The creation of orphan drugs often heralds progress in science and technology. Research into rare diseases can unearth precious knowledge that can be beneficial to various medical fields. Ultimately, these innovations can enhance the overall quality of care delivered by healthcare systems.

In conclusion, orphan drugs greatly influence health systems and give rise to important concerns regarding affordability, fairness, and long-term viability. Although these drugs come with financial and logistical hurdles, they are crucial in fulfilling the objective of healthcare: offering life-saving treatments and enhancing patients' well-being. Health systems need to adjust to the ever-changing medical field by

acknowledging the value of individualized care and patient support. To ensure both access to orphan drugs and the sustainability of health systems, collaboration between governments, pharmaceutical companies, healthcare providers, and patient advocacy groups is crucial. The significance of orphan drugs goes beyond their expenses. They represent our determination to ensure that nobody is left behind in the pursuit of improved health and relief from human suffering. While dealing with the difficulties associated with orphan drugs, we should also acknowledge the incredible advancements they bring to the lives of individuals with rare diseases, giving them hope in place of hopelessness.

Review Article

Covid-19 outbreak reminds of personal accounts providing a story of pandemic flu 1918 individual suffering

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Running Title: Flu 1918, Individual Suffering Stories

Abstract

Aims: This review aims at investigating personal stories of ordinary people who faced the deadly flu 1918, dealing with the loss of loved ones, with little knowledge of how to fight the invisible enemy of this frightening illness.

Methods: An extended literature search in English using databases as Pubmed, Google Scholar and other sources was conducted , using the terms: "pandemic, flu virus, humanitarian crisis". A total of 47 relevant records were studied. Out of them 11were excluded and the remaining 36 were included in the study.

Results: Reports from one country reflect what happened worldwide. Eskimo settlements, who provided Dr Hultin the flu victims' tissues, from permafrost massive graves, for his virus hunting, lost 70% of inhabitants. The Greek Aegean island Skyros lost two thirds of its population. Soldiers having arrived back home from the front alive, glad to see their loved ones, died 1-2 days after. There is an enormous number of family tragedies, millions of young victims of the pandemic, leaving orphans in poverty and pain. Two famous personalities the Canadian doctor Sir William Osler and the American president Thomas Woodrow Wilson fell ill with the Spanish Flu. The first died on December 1919, despite long, intensive treatment. The latter, following his illness, became forgetful, concentrated with difficulty during signing of peace treaty between the Allies and the defeated Central Powers in Paris 1919 and his personality and conduct had somehow changed.

Conclusions: Flu 1918 was a major humanitarian crisis with lots of individual suffering, which counts more than mass casualty estimations. We should never forget the devastating impact of pandemics on each single, unrepeatable human life and strive by all means to prevent any similar future mass tragedy.

Keywords: pandemic, flu virus, humanitarian crisis

Introduction

With all the heartache the COVID-19 pandemic has caused, with our lives truly threatened, this crisis is helping us gain a greater appreciation for life and remind us of all the people, who suffered recently and in the past in similar pandemic outbreaks, as flu pandemic of 1918, who killed more than 50 million people across the planet. [1].

Dealing with the loss of a loved one is probably one of the most traumatic and difficult things in life, and sometimes, we never fully heal from losing someone dear to us. All personal accounts regarding the COVID-19 pandemic may not have yet been recorded systematically, as those of flu 1918 pandemic, but focusing on them, great parallelisms between these two global pandemics are unrevealed.

Flu 1918 pandemic was not only a public health care phenomenon; rather it was a global humanitarian crisis. Individual stories count more than mass casualty estimation and relevant reports from pandemics outbreak in a country reflects what happened worldwide. The statistics associated with pandemics, sometimes makes it difficult to remember, that each number represents a single, unrepeatable human life.

First World War logic priorities brought flu by USA troops to Europe, as a war secret. Neutral Spain's uncensored press announced so many victims, that Barcelona mayor called military services for burial of the dead, so the flu was named Spanish. The first 4–5 pages of the Spanish papers consisted of obituaries, during the peak of the pandemic [2]

War propaganda interests led Philadelphia city authorities to organize a Liberty Loan Parade on September 28, 1918, although doctors tried to prevent it. After just three days, every patient hospital bed was occupied.[3] Following the epidemic explosion in Philadelphia, with every hospital in the city overcrowded, nurses were in high demand.[4]

Hundreds died daily and corpses stayed in homes due to paralysis of the mortuary services.[5]

In other communities people took ceiling boards out of their own houses to make coffins for the dead. It is an example of people helping each other, but it is chilling to think of the circumstances that would require people to do that.[6]

Physician N. Roy Grist described the devastation to his friend Burt in a September 29 letter sent from Devens' military camp, near Boston USA, hardly hit by the 1918 influenza, with 10,500 cases out of some 45,000 soldiers stationed at the fort, waiting to be deployed to France. Grist's letter is "a remarkably distinct and accurate description of what it was like to be": „These men start with what appears to be an ordinary attack of Influenza, and very rapidly develop the most vicious type of Pneumonia that has ever been seen, the Mahogany spots over the cheek bones and the Cyanosis extending from their ears and spreading all over the face. It is only a matter of a few hours then until death comes... It is horrible." The body would not get enough oxygen through lungs… how it was possible for lungs to become useless in such a short time… the young, strong people, the very ones who had had perfect health until then, developed an extremely intensive inflammatory response to the antigenically new influenza virus… in lung tissues, the main obstacle to their normal functioning, it is simply a struggle for air until they suffocate. It is horrible…. these young people had actually suffocated in their own blood… in the products of an intensive inflammatory reaction, which is called „cytokine storm".

The diseased, mostly young and strong people, the ones who were believed to be the most resistant ones, would die quickly, after two to three days from the manifestation of the first symptoms, and the deadly outcome followed terrible suffering of the diseased. The manner of dying was extremely striking for the people in the vicinity of the diseased. [7]

The1918 pandemic flu, at that time, was thought to be caused by bacteria. Viruses were not well known and antibiotics still not invented. The very important discovery of flu viral cause was made in USA by the Swedish microbiologist John Hultin after his 2 attempts, some 50 years apart. First, as an Iowa student in 1951 he travelled to Alaska Brevig Mission village and from permafrost massive graves of flu 1918 victims, he obtained lung tissues hoping to find traces of the 1918 virus and revive it, but he failed and resigned. In 1997, then72 living in San Francisco, Hultin, was informed that virologist Jeffery Taubenberger, with RNA from a preserved lung tissue of a 21-year-old male U.S. service member having died 1918 with influenza, was able to sequence 9 fragments of viral RNA from 4 of the virus' 8 gene segments. But it was not the complete sequence of the entire 1918 virus' genome.[8]

Hultin inspired to attempt again to recover the 1918 virus, departed for Brevig Mission at a personal cost of about $3,200 and after a 5 days excavation, found a young mid-20s obese woman's lungs well preserved, since the body's excess fatty tissue had insulated and protected them from decay, shipped them, in preserving fluid, to Taubenberger. He confirmed an A H1N1 virus subtype as the flu cause, reconstructed the virus and in 2005 the vaccine, to prevent such a future pandemic, was developed.[9]

Hultin, in a 1998 interview over the phone from San Francisco, attributed his success to the village's elders, who gave him the opportunity to do something good- not just for themselves but for the whole world." [10]

The touching details of Hultin missions is the particularly cruel facts in isolated human communities, as Eskimo settlements, for whom the virus was absolutely new in antigenic respect. Some were almost completely devastated as Brevig Mission village, where out of 80 people 72 died. *Out of 300 people 176 died in another Eskimo settlement.* When Hultin first opened the permafrost grave, he came across the body of a little girl, still preserved wearing a blue dress, her hair adorned with red ribbons. Hultin's consideration for the burial site made him replace the two Crosses previously marking it and now swept away, by building himself, within the woodshop of a local school, two new large Crosses to respect the grave. [11]

Materials and Methods

The literature search, for this narrative review, was conducted using the keywords "*pandemic* ", "

flu virus ", "*humanitarian crisis*, and the PubMed, Google Scholar databases' published bibliography as well as other sources , in English language.

Out of the 47 records identified initially, 11 were excluded due to similarities or not availability of full text.

A total of 36 records were included, *with References' list numbers* respectively as follows:

(a) *Pubmed, n=13: 2, 4, 7, 12, 14, 20, 23, 25, 27, 28, 30, 31, 36; (b)*Google scholar n= 8*:* 13, 15, 16, 26, 29, 32, 33, 34; (c) *Websites: n*= 10 https:// www.history.com/news/spanish-flu-pandemic-dead: *3, science.org:* 8 *sfgate.com: 9* https:// www *nytimes.com : 10, 35;* https://www.cdc.gov : *11*, https://www.researchgate: *17,* https://bic-pk.ceon.rs/CEON/CEES: 18, 22, https://www.cdc.gov.storybook: *19; (d) Books: n=2: 5, 21; (e) Newspaper: n= 1, 24, and (f) Other sources n = 2 : 1,6.*

Database search	**Other sources**	**Records excluded**	**Records included**
Pubmed n=13	*Websites* n=17	*Websites* n=7	23
Google scholar n=8	Books Press etc n=9	Books Press etc n=4	13
Total 21	**Total 26**	**11**	**36**

Table 1. *Summary of literature searce: Flu 1918, Individual Suffering Stories*

Results-Discussion

Flu pandemic 1918 took five times as many lives as the War and preferably healthy young people, who died in 1-4 days after the first symptoms. [12]

When hospitals were filled to capacity, temporary emergency hospitals in schools, warehouses, and churches were set up [13]**.**

The experience of one student nurse, who worked 12-hour shifts in a flu ward, in New York City hospitals, was typical: *Almost overnight the hospital was inundated.… Wards were emptied hastily of patients convalescing from other ailments … and only emergency operations were performed. Vacations all cancelled … classes disrupted. … Care was mainly supportive: we gave heart and respiratory stimulants, or sedation as the condition dictated. A variety of cough medicines … were ordered. Camphor in oil and caffeine by hypo [hypodermic injection] were in constant use, and we were forever balancing the advantages of forcing fluids against the disadvantages of edema, as kidneys or heart became overtaxed and the lungs showed congestion. … Victims came on stretchers…their faces and nails as blue as huckleberries."* [14]

In many families, more than one member was ill and, when both parents succumbed to the flu, the nurses not only had to care for the sick, but also for the entire family. In one account, a nurse found four out of seven in the family, including both parents, a baby, and two small children, ill:

In a crib beside the mother's bed was a six-week-old baby who had not been bathed for four days and was wet and cold. Though the father … running a temperature of 103 degrees, had to get out of bed … to care for his wife and children. … The family had no coal, and the three well children were shivering and hungry. The nurse gave care to the sick and bathed and fed the baby. She made a wood fire in the stove and prepared food for the other children. She then found a kind neighbor to continue to look after the children.…[15]

Euphemia Davis and Bessie B. Hawse, African American nurses, recalled similar situations during the influenza noting:

… a family of ten were in bed and dying No one would come near. I was asked by the health officer if I would go. As I entered the little country cabin I found the mother dead in bed. Three children buried the week before. The father and remainder of the family running a temperature of 102–104. Some had influenza, others had pneumonia.… I rolled up my sleeves and began to cook,.. I milked the cow, gave medicine … I only thought of saving lives. I didn't realize how tired I was until I got home." [16]

There is an enormous number of family tragedies, millions of young victims of the pandemic, leaving orphans, bringing pain to elderly people and their dearest ones, who survived, left with suffering for life. Public funerals and even the

opening of caskets were prohibited. Exceptions were made only for parents or wives identifying soldiers before burial – and even then, covered their mouths and noses with masks and refrained from touching the body.[7]

On July 1918 (1st flu wave) at the Greek port town of Patras, a tobacco factory's Director and a worker died 4 days after opening 5 boxes arrived from Thessaloniki, then war front, while most workers became ill by the flu. [17]

The 2nd wave (autumn 1918) marked the beginning of mass deaths throughout the world. Reliable statistical data can rarely be found. It is possible to conclude from incomplete data, memories, newspaper articles and graves.[7]

The first cases of 1918 flu pandemic in the United States were reported from Fort Riley, Kansas on March when an Army private became ill; complaining of fever, sore throat, and headache. Military personnel were greatly impacted by the virus and many young recruits were dead from the flu before they ever saw combat. [18]

Dr. Otto Wernecke 39 , a dentist in Wisconsin, father of 5 children (having lost a 2–year–old daughter from scarlet fever in 1910) died from the flu epidemic in1918, leaving them in devastation and poverty.[19]

Dr James H. Wallace was on duty at Great Lakes Navy base in Chicago September 1918, when he was assigned to a ward of "flu" patients responsible for about 100 patients, most with violent broncho–pneumonia with no sulfa, no penicillin, not much but aspirin and death rate of over 100 a day. [19]

Carlandrea Didio, immigrated from Italy to the United States in 1889 with his young wife Louisa. He was one of the many victims of the 1918 influenza pandemic, at the age of 47. Left to mourn his death was his wife Louisa and three children, ages 13, 11 and 7. When Didio's grandson obtained a copy of his grandfather's death certificate, he cried wondering how different his dads' life would have been, if his father had lived. [19]

The Colorado eight Phye family members (parents, a daughter and five sons) were admitted to the emergency hospital having been set–up by the Red Cross in a banquet hall, as the general hospital was full, and between October 30 and November 9, 1918, all eight died from the flu. Charlie, age 45 (died Nov. 2); Jessie, age 40 (died Oct. 30); Florence, age 19 (died Nov. 1); Tommy, age 16 (died Nov. 7); Harry, age 10 (died Nov. 5); Bobbie, age 8 (died Nov. 4); Davie, age 6 (died Nov. 9); and Willie, age 4 (died Nov. 5). [19]

A polish couple, Joseph and Tekla with four kids, were living in Minneapolis, MN. In October 1918, Joseph contracted the flu, was seen by a doctor, was told to stay in bed. However being the breadwinner supporting his family with a new baby born a month before, he went back to work outside in a junkyard under cold and rainy weather, developed pneumonia and died 5 days later. His widow in such tough time with a family to support saw an advertisement in the newspaper and married a man whose first wife and a child died of the flu, and had three more children. [19]

Following the penetration of the Thessaloniki front, Dr Aleksandar Radosavljeviü noted a sudden disease among soldiers and disturbing French and Serbian medical corps units. A suspicion spread wide, that the enemy had poisoned the wells and the food while retreating, and that this was the cause of the disease. Only upon arrival in Raška, he found the local hospital full of diseased citizens and soldiers. Tiüa an active joyful lieutenant, born in Kraljevo, having arrived back from the front alive, glad to see his mother, died two days later.[20]

The Croatian paper Ozbor reported on October 19, 1918 that the state railway was forced, due to the illness of the employees, to reduce the number of train lines. Zagreb horse cab drivers refused to transport Zagreb doctors, for fear of the disease, which was the cause for the intervention of the municipal administration. Ozbor"dated November 9, reported that entire houses were left empty in Bosnia.[21,22]

The hospital staff in just liberated Vranje consisted mainly of women doctors and medical nurses from Australia and New Zealand. These brave women represented the personnel of the third field surgical hospital, which was the only one which managed to follow the liberation army. Many Serbian soldiers from this region came home to tragic scenes, their dearest ones had died just a

day or two before their return. Cries and laments were heard instead of laughter and joy. [23]

As the pandemic second deadly autumn wave made its way through Greece, the mortality rates were extremely high. [24,25]

Konstantinos Faltaits (1891-1921), a 27-year-old author and journalist in his unique 1919 book, written in Greek , describes with touching details the disease hitting '*like a thunderbolt*' his native Aegean Sea Greek island Skyros "with a ferocity akin only to the plagues of the Middle Ages''. At night, people would fall asleep healthy but never woke in the morning. They came from the countryside to buy food, but died in the street. Angelos Kanas 8 years old, got sick, survived, but his brother Anestis 12 died within 3 days. He narrated on camera about no space in the cemetery, the burials out of churches on hills on the edge of the village with the rain drifting the soil and bringing to light his brother's body, an image not escaping from Angelos mind for nine decades. The island suffered without medicines and hospitals, with 4 doctors, refusing to visit the sick and giving advice from the balcony- good food and wine - resulting in enriching the merchandise that ruthlessly raised the prices in the crisis. Skyros had a population of 3,200 at the time; two-thirds did not make it through the pandemic. Those who managed to survive ' *the Biblical Cataclysm',* being enemies or hating each other '*from generation to generation wanted to hug each other and everybody, who had lost many or even only a few of their parents, their children, their brothers and sisters, women, men were comforting each other*' .[26, 27,28,29,30]

Faltait's unique report is similar to Hippocrates's analysis of Perynthos influenza – like outbreak 2400 years ago.[31]

Similar family cases have been reported in the nearby Greek islands of Euboea and Andros. [32, 33, 34].

The 3rd pandemic wave, at the beginning of 1919, took thousands of lives in Australia, not however possible to talk about a 3rd wave in this case, as 2nd wave was not present at all on this continent, due to the strict quarantines. [6]

The disease appeared sporadically also after the first half of 1919. The renowned Canadian doctor, Sir William Osler, (1849–1919) fell ill with the Spanish Flu on September 29, 1919, working at the Oxford University in England at that time. Following a short recovery, he got pneumonia, of which he died on December 29, 1919, despite long, intensive treatment.[6]

Many authors indicate 1920 instead of 1919, as the final year of the Flu pandemic. There is an indication of numerous death cases caused by influenza and its consequences in New York and Chicago at the beginning of 1920 [5] Many having recovered from the Spanish Flu, presented neurological and psychiatric complications. The American president Thomas Woodrow Wilson, (1856–1924), fell severely ill on April 3, 1919 in Paris during signing of peace treaty between the Allies and the defeated Central Powers. After his recovery he became forgetful, he concentrated with difficulty and his personality and conduct had somehow changed. This was manifested in his refraining from the political principles, he had advocated before his disease, insisting on the peace treaty being acceptable for both sides and if not, threatening the French prime minister, Georges Benjamin Clemenceau, (1841–1929) to abort negotiations. So he accepted easily the latter's requests, entailing extremely humiliating terms for the defeated Germany, to which he before flu strongly opposed. [6]

Conclusions

COVID-19 outbreak has driven a great interest toward the influenza pandemic of 1918.. When infectious diseases are intruding in everyday life, humans are forced to rapidly reassess their attitudes in all aspects and mainly in social behaviors.

Lessons we should learn from the pandemic flu 1918 and the coronavirus recent pandemic is that, whenever our lives are truly threatened, it forces us to think about our own mortality, and of those we love.

The mayor of Cologne of that time, Konrad Hermann Joseph Adenauer, (1876–1967), the future chancellor of the Federal Republic of Germany, said that the Spanish Flu was exhausting so much thousands of sick people, that it made them incapable of hatred [5]

We should also not allow these disasters and each personal suffering, to be forgotten. The millions of those, whose unrepeatable lives the Spanish Flu and Covid- 19 claimed, oblige us to remember them and to strive by all means to prevent any similar future mass tragedy.

Scientists and governments worry about a repeat of a devastating epidemic. **[**35**]**

We should learn from examples, as Australia and 23 American towns, where early public health measures significantly reduced the number of deaths. [36]

No conflicts of interest

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Case Series

Injection of fentanyl patches – a deadly route

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Abstract

Transdermal fentanyl therapeutic system was developed to provide continuous, controlled, systemic release of fentanyl. Modifying the route of administration of the drug by violating the appropriate, proposed medical method for the treatment regimen can be fatal. We present four (4) fatal cases of intravenous abuse of fentanyl transdermal patches, which took place in the wider region of Northern Greece in a short time period. We review the reported cases worldwide and emphasize the importance of public awareness for the prevention of fatalities.

Key words: fentanyl-related death, intravenous drug abuse, transdermal fentanyl patches

Introduction

Fentanyl is an extremely potent analgesic and anesthetic synthetic opioid, whose chemical properties enable different routes of administration. This novel drug was synthesized in the 60's and is widely used since. The development of multiple pharmaceutical dosage forms increased its market dissemination and availability. One of these formulations was the transdermal therapeutic system (TTS) which provides continuous, controlled, systemic release of fentanyl [1].

Opioids constitute a significant part of the drug abuse problem, including fentanyl abuse, which rapidly increased with the introduction of transdermal patches [2].

The increase in fentanyl-related mortality, both through prescription medication and through illicit use, was attributed to the toxicity of fentanyl, either as a single administration or in combination with other drugs, to the extent that it was characterized in developed countries, such as the United States of America and Canada, as "fentanyl epidemic" [3], [4].

The drug's potency and the lack of awareness for the great importance of its proper use intensified the problem in the years following the introduction of fentanyl into the pharmaceutical market [5].

The high toxicity of fentanyl, combined with its addictiveness, as it produces 50 to 2000 times greater than heroin euphoric symptoms, if IV applicated, has signaled an alert for the ease with which it can be spread to drug addicts' circles [6]. To quickly achieve the euphoric level, drug users modify the delivery route of the transdermal patch, in violation of the drug's instructions [2]. It should be noted that high toxicity is not the only factor contributing to the increased risk of fentanyl abuse with respect to other opioids; fentanyl transdermal patch (the 72h regimen) contains a fatal amount of opioid when it is intravenously administrated [7]. The first case of intravenous abuse of a transdermal fentanyl patch was reported by DeSio and his colleagues [7] in 1993.

We present four (4) fatal cases of intravenous abuse of fentanyl TTS originating from the wider region of Central and Eastern Macedonia and

Thrace. Three of these were processed at the Laboratory of Forensic Medicine and Toxicology of Democritus University of Thrace and the fourth at the corresponding Laboratory of Aristotle University of Thessaloniki. All cases occurred within three years' time.

In the light that the reported number of deaths from intravenous fentanyl patches abuse is only 12 worldwide; our report reflects the rare phenomenon of the accumulation of four fatalities in a short period in a small Greek territory.

Case Presentations

In all cases, the death scene was examined to exclude the possibility of a criminal act, including the position of the deceased. Medical history and clinical records of the victims and additional information from the deceased's relatives or friendly environment and police investigating authorities was obtained. Later, autopsy was performed to clarify the cause of death and collect biological samples for toxicological analysis. External examination of the body included recording body weight and height and identifying and photographing skin features, such as tattoos, venipunctures, recent or old scars, etc. Thorough internal examination of the deceased was performed, during which biological material (blood, urine, bile) and visceral tissue biopsies were obtained and forwarded, for laboratory documentation of the use of addictive substances. All biological samples were screened for ethanol and drugs of abuse. For presumptive positive screening tests, confirmatory analysis was performed by Gas Chromatography/Mass Spectrometry (GC-MS).

Case 1

A 46-year-old female of 57 kg weight and 1.66 m height, with a known long history of heroin and ethanol abuse, was found dead at home. Externally, the decedent had a recent venipuncture on her left arm. An empty Durogesic 12 μg/h package was found in the trash, but no sign of a patch was spotted on her skin and no syringe or other drug IV equipment was discovered. Presumably, paraphernalia were removed from the scene by co-users, friends, or relatives. During forensic autopsy, the brain was markedly edematous and in the thoracic region there was pulmonary congestion and edema. From the presumptive screening tests of biological fluids (blood and urine), performed at the Laboratory of Pharmacology of the General University Hospital of Alexandroupolis, resulted negativity for ethanol, cannabinoids and opiates and positivity for benzodiazepines. After these results, additional confirmatory toxicological analysis was carried out at the Laboratory of Forensic Medicine and Toxicology of the National and Kapodistrian University of Athens and concluded positivity for fentanyl at a concentration of 8 ng/mL in blood sample.

Case 2

A 24-year-old man of 81 kg weight and 1.73 m height, with a history of alcoholism and continuous intravenous heroin use over the last four years, was found dead after a day's search, at a building under construction. During examination of the scene, we found equipment for intravenous drug use and a used Durogesic 12 μg/h package. An insulin syringe full of yellowish liquid was observed on his left arm and a tourniquet above it. Additionally, there was evidence of contusions on his left facial, frontal and nasal area, which were not responsible for his death and attributed to falling on the building materials, where he was found. During autopsy, we observed marked brain edema and severe congestion of the lungs.

	Author	Year	Cases	Gender		Drug Inter-actions	Deaths
				Male	Female		
1	DeSio et al. [7]	1993	1	-	1	-	-
2	Reeves & Ginifer [8]	2002	2	1	1	-	1
3	Kuhlman et al. [9]	2003	5*	3	2	2	5
4	Tharp et al. [10]	2004	4	4	-	3	4
5	Lilleng et al. [11]	2004	2	2	-	2	2
6	Jost et al. [22]	2004	1	1	-	-	-
7	Martin et. al. [23]	2006	10*	10	-	1	10
8	Magdalan [24]	2009	1	1	-	-	-
9	Schauer et al. [25]	2015	1	-	1	-	-
10	Sinicina et al. [15]	2017	72*	Not reported	Not reported	Not reported	72
	Total		99	22	5	8	94

Table 1. *Review of reported cases of abuse of fentanyl transdermal system with intravenous administration (* 5 out of 23 / 10 out of 112 and 72 out of 242 fatal cases.)*

Blood and urine samples were sent for toxicological analysis to the Laboratory of Pharmacology of the General University Hospital of Alexandroupolis, as well as to the Laboratory of Forensic Medicine and Toxicology of the National and Kapodistrian University of Athens. The presumptive screening tests were positive for benzodiazepines and cannabinoids and negative for opiates. Biological materials processed by the Laboratory of Forensic Medicine and Toxicology of the National and Kapodistrian University of Athens, were negative for ethanol and positive for bromazepam, cannabinoids and fentanyl, that was detected and quantified in the blood sample at the concentration of 98 ng/mL. Fentanyl was also identified in the remnants from the syringe.

Case 3

A 37-year-old man, of 86 kg weight and 1.81 m height, was found dead in his home by his father two days after he had last been known to be alive. The deceased had a history of hepatic cirrhosis, due to chronic alcoholism and use of addictive substances (opioids, cannabis and benzodiazepines). Tools for intravenous drug use were found at the death scene, as well as a coffee pot containing a molten plastic residue from a Durogesic transdermal patch. At external examination, we observed a tourniquet in his right upper limb and a recent venipuncture under it, while old needle marks were seen to both his upper limbs. During forensic autopsy, severe cerebral edema was found, while the lungs were edematous. The toxicological analysis by the Laboratory of Toxicology of Aristotle University of Thessaloniki was positive for benzodiazepines and positive for fentanyl in blood sample. Although the fentanyl concentration in the blood was “very high”, quantification was not possible.

Case 4

A 34-year-old man, of 83 kg weight and 1.77 m height, chronic user of addictive substances (heroin, benzodiazepines, cannabis) for at least five years, was found dead in a building under construction. External examination revealed old needle puncture sites in his upper and lower extremities and a recent venipuncture on his left arm. During forensic autopsy, acute pulmonary and cerebral edema was found. The results of the toxicological analysis by the Laboratory of Toxicology of Aristotle University of Thessaloniki were positive for diazepam, nordiazepam, oxazepam, bromazepam, temazepam, 7-amino flunitrazepam and fentanyl in blood sample. In this case fentanyl was primarily detected, but again quantification was not possible.

Discussion

Fentanyl abuse and related deaths has a young to middle aged male predilection [26].

Accordingly, our cases comprised 3 males and 1 female with ages ranging from 24 to 46 years.

***Figure 1**. Isolation by heating of the active substance from fentanyl transdermal patch (Case 3).*

***Figure 2.** Intravenous injection of fentanyl (Case 2).*

All cases had a known prior history of drug abuse. Information gathered from co-consumers and / or relatives revealed that the supply of fentanyl transdermal patches was through legal prescription to patients, who were relatives of the deceased. The latter, after illegally obtaining the pharmaceutical preparations, isolated fentanyl by heating the patch and injected it in their body *(Fig. 1, Fig. 2).*

In most fentanyl abuse cases reported in the international literature, death comes due to interaction with other toxic substances, mainly ethanol, amphetamine, cocaine, codeine, benzodiazepines and others [9], [10], [12], [13], [14], [15].

The toxicological analysis of all four cases detected the presence of other addictive substances in addition to fentanyl including cannabinoids and benzodiazepines and so the intoxication could not be attributed to fentanyl alone. In view of the low concentrations of the accompanying drugs compared to the fentanyl concentration, fentanyl was considered as the leading substance.

Despite extensive international research efforts, as in Andresen et al. [16] review, it is not possible to determine a marginal level between toxic and non-toxic concentrations of fentanyl. The determination of the precise antemortem dose of fentanyl with the use of its postmortem concentrations is impossible in cases of abuse [17], and even in cases of prescriptive therapeutic use [18].

In fact, many factors may play a role in each case: the degree of opioid tolerance is the most important, as it can explain why new users show extremely high concentrations of the substance and run the risk of a single application of the transdermal patch being fatal [13].

The diversity of postmortem fentanyl concentration levels involves the time elapsed from fentanyl use to the time of death and the possibility of multiple, simultaneous routes of administration [14] [15] [26]. Postmortem redistribution of fentanyl should also be considered, since completely different pharmacokinetics of the substance is observed in new users [17]. Other idiosyncratic factors may also play a role, such as obesity [16]. As observed from body mass indexes (BMI) none of the decedents in our cases were obese; they were in weight normal range.

The reported levels of fentanyl (8 and 98 ng/mL for cases 1 and 2 respectively) were consistent with the Anderson and Muto [19] suggestion that "Postmortem blood fentanyl levels following therapeutic administration can range to 7 µg/L." Furthermore, the post-mortem fentanyl redistribution phenomenon seems to be enhanced as the drug levels increase [19]. Fentanyl related death occurs from acute respiratory failure, accompanied by severe cerebral and pulmonary edema, as has been observed in all our cases, in accordance with international literature.

It is also noteworthy that in the death reports associated with fentanyl's abuse, there is a period of accumulation of fatal incidents, ranging from 2 to 55 months [10], [12], [20]. The same plateau was also observed in our cases, considering that three out of four (in the Thrace district) took place in just a three-month period. This observation demonstrates that probably the information about fentanyl isolation and abuse methods is rapidly spread among drug addicts' circles.

Another important factor is that transdermal fentanyl patches are relatively easy to obtain. Users can secretly or violently detach them from their chronically ill relatives [13] or they can obtain them by misleading doctors to multiple prescribing [7], or even remove them from the dead body of cancer patients [21].

In several reported cases of transdermal fentanyl-related deaths, it is not entirely possible to document the precise way of use of the patch. Its intravenous abuse is deduced from the presence of needle puncture sites on the cadaver, either from testimonies of relatives or friends and "co-users" of the deceased, or when it is the most likely cause of death, with the method of exclusion [15].

In our literature search, we unearthed 10 reports, with 99 cases of intravenous abuse of fentanyl patches, 94 of which fatal (Table 1). The large study of fentanyl-related deaths in Germany by Sinicina et al (2017) considerably raises the number of the reported abuse cases, but no further information is available regarding gender and mixed intoxication of the cases.

There is a remarkable proposal, introduced by Reeves & Ginifer [8], highlighting the importance of proper use of transdermal patches after legal prescribing and safe storage, to avoid the possibility of them being stolen. They also suggested that accounting of the transdermal patches should be legislated, accompanied by the obligation to return the used patches to make it possible for new ones to be prescribed. The latter method does not find us in agreement, as there is no way to ensure that the transdermal patches have been appropriately used.

Conclusion

Public warning about the danger of fentanyl, targeted on both health care professionals and drug addicts, is crucial to fatalities prevention. In our point of view, more than monitoring its prescription, bringing the lethal potential of fentanyl abuse to public attention is the most important factor for eliminating its further illegal and uncontrolled use.

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Case Report

Thyroidea-Ima Artery: A case report

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Abstract

Thyroidea ima artery is a rare anatomical entity that may present in 3-10% of the general population as an embryonic remaining. It is an accessory vesicle for the blood supply thyroid's gland isthmus and lower lobe. The artery may also supply the trachea and the parathyroid gland. The artery may origin from the brachiocephalic trunk, the arch of aorta or even from the left common carotid artery. The knowledge of this vascular anatomic anomaly is important for tracheal, thyroid and parathyroid surgeries. We present a rare case of a thyroidea-ima artery (TIA) that was discovered during thyroid surgery.

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Introduction

An extend part of the thyroid gland (TG), the inferior part and the isthmus, is supplied from the inferior thyroid artery (ITA). The upper part (36%) of the gland is supplied from the superior thyroid artery (STA). Occasionally, a small auxiliary artery is present and provides with blood the thymus gland, the thyroid gland and the parathyroid glands. This artery is called as Thyroid IMA Artery (TIA), or lowest thyroid artery. The artery first described from Neubauer in 1772 as an artery that marches along the anterior surface of trachea and can also been found as Neubauer artery. The origin of TIA varies from the brachiocephalic artery 74%, the aortic arch 7.7%, the left common carotid artery 1.9%, the left internal thoracic artery 1.9%, the right common carotid artery 9.6%, the right internal thoracic artery 4.8%, the subclavian artery and the vertebral artery. TIA provides with blood the isthmus and the inferior poles of the thyroid gland and may follow various courses. It is also usual for TIA to coexist with a brachiocephalic-carotid trunk, a devious right subclavian artery of retroesophageal course, a variable march of the inferior laryngeal nerve (non-recurrent and recurrent) and the bilateral absence of the inferior thyroid artery. It is high yield for surgeons to have awareness of the IMA and its variabilities in order to avoid massive intraoperative hemorrhages during tracheotomy and cricothyroidotomy.

We present a rare case of thyroid IMA artery that was identified during a thyroidectomy performed to a male patient.

Case report

A 59-year-old Caucasian male underwent total thyroidectomy for thyroid cancer. He had not undergone any other previous surgeries in the thyroid gland.During the operation, the TIA was found arising from left common carotid artery (Figure 1). The superior and inferior thyroid artery and vein recognized, ligated and dissected. During the dissection of the tissues above trachea we found thyroid IMA over the trachea entering the

inferior surface of the gland in the region of isthmus. This is carefully separated from the trachea with a blunt- nosed hemostat and ligated in the usual fashion.

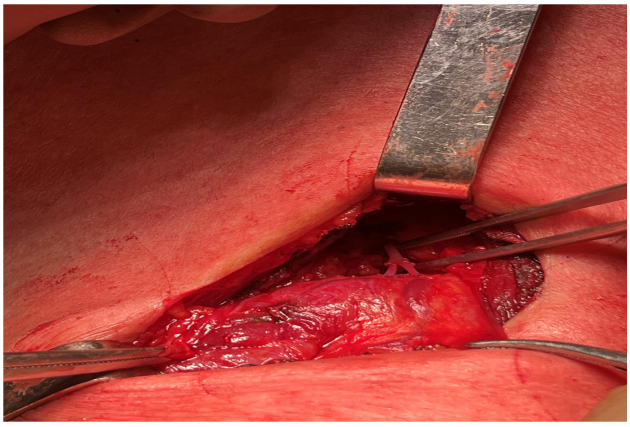

***Figure 1**: The thyroidea-ima artery, during thyroidectomy.*

We routinely dissect and expose the common carotid artery before mobilizing the thyroid gland (lateral to medial approach). By this approach, a good vascular control is achieved and inadvertent injury to blood vessels is avoided even if the thyroid gland is large and extending retrosternal. The three structures of significance between common carotid and trachea are the recurrent laryngeal nerve, inferior thyroid artery and middle thyroid vein. Any anomalous vessel in this location can be easily identified and dissected to its origin thereby avoiding injury.

In the present case TIA was found arising from the left common carotid artery and it was dissected and ligated carefully, without injuring it and avowing any possible bleeding.

Discussion

Embryologically, the thyroid gland has a rich vascular supply, as it consists one of the most important endocrine glands in the human body. The main arteries that supply blood to the thyroid gland are the superior thyroid artery, inferior thyroid artery, and sometimes the thyroid Ima artery (1). Specifically, superior thyroid artery is typically the first branch of the external carotid artery (2). It supplies blood to the upper part of the thyroid gland and gives off branches that provide blood to surrounding muscles and structures in the neck. As regards the inferior thyroid artery arises from the thyrocervical trunk, which is a branch of the subclavian artery. This artery supplies blood to the lower part of the thyroid gland. It usually has two branches: a superior branch and an inferior branch, both of which contribute to the blood supply of the thyroid gland. The TIA is not present in everyone, and when it is present, it can be a variation in the blood supply of the thyroid gland. This artery is relatively small and inconsistent in its occurrence (3,4).

Developmental anatomy of IMA. The aortic arch and the thyroid gland format during the 3rd and 7rd gestational week. The thyroid gland has an extensive arterial supply, and most of the arteries regress. The remaining arteries that supply the thyroid gland after the birth are the superior and the inferior thyroid arteries. The excessive vascularization of the arteries may lead to the morphogenesis of the thyroid gland. Thyroid defects, cardiovascular variants and also the TIA variation occur from disruptions between thyroid gland morphogenesis and angiogenesis (5).

The thyroid-IMA artery or Arteria thyroid-ima or thyroid artery of Neubauer, firstly described by the German Neubauer in 1772, is an anatomical anomaly that commonly functions as an accessory blood supply for the isthmus and inferior aspect for the thyroid (6). The artery also supplies the trachea, the parathyroid gland and the thymus gland in rare

cases. The IMA artery occurs in 3-10% of the population as a persistent embryonic remaining (3).

Although thyroid-IMA arises mainly from the brachiocephalic trunk, it may also originate from the aortic arch, the right common carotid artery, the subclavian artery, the cardio phrenic artery, the thyrocervical trunk or the internal mammary artery (7,8). The thyroid-IMA is located on the right side, crosses the trachea to the bottom of thyroid gland and its size varies in 3-5mm in diameter (2). Some studies suggest that ethnic and anthropological factors may affect the incidence of the thyroid-IMA artery concerning people of Asia (10%), compered to the Europeans (6%) (2,8-10). A branch of the superior thyroid arteries or the inferior artery replaces the opposite inferior thyroid artery, when it is absent (1).

Clinical significance. Due to its small size and its scarce presence, thyroidea-ima artery can easily be injured during surgical operations. Therefore, an accurate knowledge of the vessels of the thyroid gland, of the parathyroid gland and more specific of the variations and the anomalies of their vessels, is important in order to avoid injury or fatal hemorrhage during thyroid, parathyroid, tracheal, mediastinal surgeries and tracheostomy. However, to our knowledge, there is no specific method for surgeons in order to exclude this possible bleeding, except for their aware of arteries variations and their careful and fine movements (6,7).

Tracheostomy is required in emerge situations where the airway is not open. It can be done either percutaneously or surgically. In the percutaneous tracheostomy, the preferred site of entry is between the first and second or second and third tracheal rings. It is of high importance that surgeons identify the anatomical landmarks of the cricoid cartilage and the sternal notch. The surgical tracheostomy can be done in the area between the second and third or third and forth tracheal rings. Thyroid-IMA artery mostly originates from the right side and therefore, the endotracheal tube should be inserted on the left side of the midline. In both cases the thyroid-IMA artery can easily be injured and cause fatal hemorrhage and only the urgent sternotomy can finally control the bleeding and save the patient's life (7).

Therefore, on scheduled surgeries, thyroid-IMA artery is important to have been detected under ultra sound sonography. In all cases, thyroid vessels must be preserved during surgeries, as they supply the endocrine gland (5).

Conclusion

Thyroid-IMA artery may be present with numerous variants. The ignorance of this anatomical variation may lead to massive hemorrhages during surgeries in the trachea, the thyroid and the parathyroid glands. It is of great importance for surgeons to have an adequate knowledge of the regional anatomy and the vascular variabilities so as to avoid fatal complications. It is also of great significance for surgeons to be prepared for the upcoming surgery with multiple scans in order to have a good awareness of the vascular anatomy of the specific incident.

Conflicts of interest

All authors have no conflicts of interest to disclose.

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Ethical approval

This is a a case report for which the patient provided written informed consent. Ethical approval has also been provided by the ethical committee of the General & Anticancer Hospital of Kifissia.

Consent Form

Written consent for the publication of this case report and accompanying images was obtained from the patient. The consent can be provided to the Editor if he asks so. The written approval of the Ethical Committee of our Institution is also available on request.

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Short Review – Historical Article

Hernia management through the ages: an evolutionary journey from ancient times to modern innovations

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The history of hernia surgery spans across ancient civilizations and evolves through various historical periods, reflecting advancements in medical knowledge and surgical techniques. This article explores the evolution of hernia surgery practices, ranging from ancient Egypt to modern times, highlighting key developments and prominent surgeons who contributed to the field.

Hernia surgery in ancient Egypt. There is limited information on hernia surgery in ancient Egypt, as the surgical repertoire was limited, and bone abnormalities were more common than soft tissue injuries. However, the ancient Egyptians practiced medicine with highly professional methods and had advanced knowledge of anatomy and surgery, leaving us with some of the earliest evidence of surgical techniques, tools, and reasoning. Nevertheless, their surgeries were performed with crude tools and techniques that physicians had to refine over time. The first treatise on surgery was written by Imhotep, the vizier of Pharaoh Djoser, priest, astronomer, physician, and architect, during the first monarchic age around 2700 BCE. The inguinal hernia was described in an ancient Egyptian papyrus dating back to 1500 BC, The Ebers Papyrus. This was an ancient Egyptian medical text, that described the reduction of hernias. Furthermore, physicians in ancient Alexandria used tightly fitting bandages to treat inguinal hernias in 900 BC, as depicted in a Phoenician statue. There is no specific information on hernia surgery and therefore, it is unclear if hernia surgery was performed in ancient Egypt.

Hernia surgery in ancient Greece. Hernia surgery was performed by ancient Greek doctors, as hernias were a common problem among other surgical entities. The term "hernia" comes from the Greek word "hernios," meaning "bud" or "offshoot". Although there is no clear evidence of hernia surgeries being performed in ancient Greece, surgical intervention is described in ancient scripture as well as demonstrated in sculpture and other forms of record. There are two known examples of hernias depicted in ancient Greek sculpture. However, most ancient Greek sculptures depict idealized human forms, often of Greek gods and goddesses, and are not intended to be realistic portrayals of physical ailments. [1]

Inguinal hernia in Roman Empire. Reports of inguinal hernia can be traced in the books of the Greek nobleman Celsus who gave a detailed view of the anatomy of hernia, as well as Heliodorus, the first doctor to ever describe incarcerated hernia. Furthermore, they both presented methods for its treatment, with the first proposing removal of the testicle and the latter proposing amputation of the hernia sac. Galen, the most famous physician of Roman time, whose work influenced and dominated Western medicine for ages, also dealt with hernia, proposing a concept for the pathogenesis of it, coming from a rupture of the peritoneum. Ileus was first related to incarcerated hernia by Aretaios of Cappadocia who lived approximately 100 A.D.. [2,3]

Inguinal hernia in the Byzantine Empire. Aetius of Amida (502-575 A.D.) was the first Byzantine physician to deal with inguinal hernia. In his medical compendium, Tetrabiblos, he observes

that inguinal hernia is more often in women and proposes conservative treatment with bandages and drugs before proceeding to surgery if necessary. The surgery technique he applied is described in his books. Paul of Aegina, a physician who lived approximately a century later, also described inguinal hernia treatment in his work Epitome. There, he proposes two methods, one surgical and one involving cauterization of a triangle area around the hernia with its base towards the groin. The latter was preferred among physicians at the time as it had a lower recurrence rate, despite leaving an ugly scar. Two of the greatest physicians of the Byzantine Era, Theophanes Chryssobalantes (10th century A.D.) and Ioannes Actuarius (14th century A.D), in their works, describe conservative, pharmaceutical methods to treat hernias rather than surgery. However, surgical treatment of hernias was very common especially in the later years, as there was a special category of surgeons called celotomes that performed exclusively that kind of operation in the hospitals called 'Xenones'. Famous Arab physicians, Rhazes, Haly Abbas, Avicenna, and, Abulcasis adopted the surgical methods for hernia treatment applied by their Byzantine colleagues. [4]

Inguinal hernia in Dark Ages. Although science didn't progress extensively during the Dark Ages, certain breakthroughs still appeared in hernia management. Celsus and Galen were disputed with William of Salicet (1210-1277) disagreeing with the testicle removal during hernia surgery and Guy de Chauliac proposing a different method for hernia pathogenesis and being able to recognize the difference between inguinal and femoral hernia. However, the latter applied a rather unorthodox method for the treatment of hernia including modifications in the patient's diet, use of laxatives, and bloodletting. Then a manual reduction of the hernia was performed, and a plaster was applied to hold it in its position. Mondino de Luzzi, a surgeon from Bologna, described a radical method for the cure of hernia in his book published in 1487, Anothomia.[5,6]

Inguinal hernia in the Renaissance. The Renaissance (15th and 16th centuries) is a period in human history marked by great developments in science, art, architecture, politics, and medicine. Of course, the study of hernia and its treatment also made remarkable progress. Numerous surgeons and doctors performed herniotomies which became a common practice. Among them, Antonio Benivieni (1440-1502), Horace of Norsini, and, Caspar Stromyar performed numerous herniotomies which they later described in books they published. Pierre Franco (1505-1578) was the writer of a book called Traite´ des Hernies that included surgery methods for the various forms of hernia including patients that suffered from monorchism, incarnated hernias, and hydrocele. Hydrocele treatment was also the subject of study by Marcel Cumanus and Zaeutus Lusitanus (1575–1642), doctors who proposed their own treatment methods for the disease, orchiectomy and drainage of its fluid after puncture with needles each respectively. The famous doctor Ambroise Pare´ (1510-1590) performed surgery only for strangulated hernia preferring trusses for all other instances. The anatomy of the inguinal canal was first described by Gabriello Fallopius. [7]

Anatomic Description of the Area. Study of hernia anatomy was extensive in the centuries that followed. Anatomists such as Antonio Scarpa (1747-1832), Pieter Camper (1722-1789), Franz Hesselbach (1759-1816), Antonio de Gimbernat (1734-1817), August Ricter (1742-1812), Sir Astley Paston Cooper (1768-1841) described various anatomical structures, significant for hernia anatomy and formation, some of whom were later named after them. It was the same era when the theory of the hernia formation by peritoneum rupture was disproved (F. Ruysch) and direct inguinal hernia (L. Heister), congenital hernias (A. Haller) the ileopubic tract (J. Cloquet), and the femoral sheath and canal (J. Gay) were firstly described. Eventually, a very detailed description of the inguinal canal and other anatomical structures related to inguinal hernias was formed. The invention and proposal of new methods for hernia treatment also continued. Jacques Beaulieu (1651-1719) was a doctor who performed over 2000 hernia operations during his travels from

Amsterdam to Rome, which was enough for his name to stay in history. [8,9]

Inguinal hernia repair

Bassini's method. Edoardo Bassini (1844-1924) was born and raised in Pavia, Italy where he also studied medicine to become a surgeon. After his graduation, he enlisted in the army and participated in 2 battles not as a doctor but as a soldier. In one of his battles, in 1867, he was severely wounded in the right groin by a bayonet. He later developed an infection in the wound and a fecal fistula which were successfully treated by Luigi Porta, chief of the surgical clinic of Pavia, when he returned home. In the years that followed he served as the assistant of Porta and worked with famous doctors such as T. Bilroth, B. Langenbeck, J. Nussbaum, J. Lister, and T. Spencer-Wells. During the 1880s he worked in the University of Padua. There he had unlimited access to human cadavers which he used to understand the anatomy of inguinal hernias and create a method for its treatment. After years of research, Bassini finally achieved the first ever successful inguinal hernia repair on December 23, 1844. His technique included cutting the transversalis fascia from the internal inguinal ring to the pubic tubercle, after dividing the cremasteric muscle, and ligating the hernia sac eventually reconstructing the inguinal canal. He continued to apply his method, Bassini's method, leading to 262 herniorrhaphies in 216 patients with no reported deaths and only a 2,7% recurrence, a success rate of 97 percent. His work was recognized in the medical community as it had the best results in comparison to any other method proposed until then. [10,11,12]

Halsted's method. William S. Halsted (1852-1922) proposed a method similar to Bassini's at Johns Hopkins Hospital Bulletin in 1890. His technique includes the removal of the majority of veins in the spermatic cord, relocating the vas deferens beneath the skin, and sealing the components of the abdominal wall (except peritoneum and skin) with single-layer interrupted mattress stitches. In 1903 he presented a new method, Halsted II, very similar to the one Ferguson published three years earlier. His new method involved repositioning the hernia sac's neck, precise removal of any dilated veins in the spermatic cord, incorporating the cremaster muscle and transversalis fascia, and employing three sets of interrupted silk sutures along with a row of catgut, creating an overlapping layer repair for the affected area. [13,14]

McVay's method. American surgeon Chester McVay (1911-1987) tried to design his hernia repair technique as Bassini and Halsted's methods often failed. He theorized that this happened due to the suture of the conjoined tendon to the weak inguinal ligament. His method included separating the hernia sac from cord structures, followed by suturing the weakened abdominal wall. The Cooper's ligament is utilized to anchor the repair. This method reinforces the area and prevents hernia recurrence through strategic tissue manipulation and ligament fixation. [15]

Modern techniques

Shouldice's method. Shouldice inguinal hernia repair, designed by Dr. Edward Shouldice in 1945, is considered the best non-mesh technique. It involves a tension-free approach, utilizing four layers of sutures to sew distinct anatomical structures in for layers and therefore, reinforce the abdominal wall. This way, a low recurrence rate of about 1% is achieved. It is performed under local anesthesia. [16]

Lichtenstein's method. Lichtenstein inguinal hernia repair, pioneered by the Lichtenstein Hernia Institute in 1984, is a tension-free mesh repair. The hernia is separated from the cord structures and reinserted into the abdominal cavity. The wall opening is then sutured, and a mesh patch is positioned in the inguinal canal to reinforce the abdominal wall, preventing herniated tissue protrusion. The mesh helps achieve a low recurrence rate and reduces postoperative pain. The operation is performed under local anesthesia. [17]

Laparoscopic methods. Laparoscopic inguinal hernia treatment includes two methods, the

Transabdominal Preperitoneal (TAPP) approach and the Totally Extraperitoneal (TEP) approach. The difference between the two techniques lies in the port placements site and in the fact that in the TAPP approach, the peritoneum is incised. In general, both methods involve making small incisions near the hernia site. A camera and specialized instruments are inserted, allowing the surgeon to view and repair the hernia from within. The hernia is usually reinforced with a mesh, reducing recurrence risk, and the small incisions lead to quicker recovery and less postoperative discomfort. [18,19]

Conclusion

Inguinal hernia is a medical entity known since antiquity. The journey through the annals of history reveals a fascinating evolution in hernia surgery techniques, from the enigmatic practices of ancient Egypt to the introduction of laparoscopic methods that added a layer of innovation, allowing for minimally invasive surgeries and accelerated recoveries. As we reflect on this historical tapestry, it becomes evident that the progress of hernia surgery mirrors the broader human journey of advancement. From ancient mysteries to contemporary precision, each epoch contributed to a cumulative pool of knowledge that has transformed hernia surgery into a refined and sophisticated discipline. This historical voyage underscores the resilience of the medical profession in its pursuit of improved patient care and the unwavering commitment to alleviating human suffering across the ages.

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