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Development of medical knowledge for understanding, treating, and counteracting orphan diseases

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Abstract

COVID-19 made it clear to us that not knowing the pathogens and risks associated with so-called orphan or rare diseases can cost us thousands of lives, including those of young and healthy individuals, who represent our human capital. This literature review analyzes the promotion of existing medical knowledge in medical students to understand, treat, and counteract orphan diseases. This analysis has been presented by many authors and researchers who recognize that medicine still has a lot to do and that it is in university classrooms where the mission of building knowledge that helps manage what ails human life must begin. Authors such as Klein & Nori, et al. [1,2] state that "around 7,000 identified rare diseases affect approximately 350 million people worldwide". The lack of knowledge of the new generations of doctors about orphan diseases makes it difficult to diagnose and treat patients who suffer from them in various parts of the world. According to Jacewicz [3], rare diseases affect approximately 400 million people worldwide. It is predicted that one in twenty people will be affected by a rare disease at some point in their lives. These statistics make it clear that academic medical institutions must promote the necessary knowledge to establish research on these conditions, thereby reinforcing the scientific skills of their students and advancing medicine for social welfare and the prevention of human resource loss in the productive stage.

Introduction

Young human capital is that entity capable of moving the economic system with its good physical, mental, and psychological health. Their participation is irreplaceable for the future of the economy and nations. But "Around the world, COVID-19 has had a huge impact on health, economies, and daily life [37]." Therefore, following this premise, it is pertinent to mention that the relevance of promoting medical knowledge is crucial in the medical training of medical students to understand, treat, and counteract orphan diseases. The academic medical environment should have no limits for the dissemination of knowledge and research, which should be used to assertively prepare future doctors who will have the individual and societal responsibility to protect the health of their patients and human capital. Currently, the National Organization for Rare Disorders [28] provides information services on rare diseases, committed to identifying, treating, and curing these diseases through education, research, public policy, and community engagement.

The agency also aids programs to patients, caregivers, and supports research through grants. However, despite these efforts, there is still a lack of knowledge worldwide about the early diagnosis and treatment of orphan diseases, which results in a discouraging outlook for patients with these diseases.

According to Rare Diseases International [32], the low number of cases per disease makes it challenging for health systems to develop local knowledge and, in turn, to make accurate and timely diagnoses. Regarding the number of orphan diseases globally, Haendel et al. [18] explain that "scientific regulators, doctors, and patient advocacy groups often cite 7,000 as the number of rare diseases, or between 5,000 and 8,000 depending on the source" (p.3). It should be noted that within the group of diseases identified as the rarest in the world is ribose-5-P isomerase deficiency, considered, according to Keskin & Keskin [23], the rarest disease in the world, with only one reported case. Certainly, the rarity of these diseases should be studied in the scientific community of doctors in training. It should also represent a priority in public health at the global level. According to Chung et al. [9], the challenges arising from the nature of rare diseases make them a global public health priority. For these authors, research on rare diseases is crucial

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for raising awareness, improving understanding, advancing diagnosis, and enhancing the treatment of these diseases.

Definition of orphan diseases

Knowing broadly and assertively what has been called an orphan disease is the key to effectively understanding what the teacher faces during his or her research management in academia. Regarding the contribution received internationally to define orphan diseases, Wainstock & Katz argue that,

Despite international support for defining rare diseases, each country has adopted its own. In Latin America, there is a wide range of classifications. In Brazil, it is considered a rare disease when it affects fewer than 65 inhabitants per 100,000. In Colombia, the range for classifying a rare disease is 2 per 10,000 people. In the case of Argentina, Chile, Mexico, and Uruguay classify a rare disease is classified when it affects 5 out of every 10,000 people. These authors argue that standardizing rare disease definitions is and should continue to be the primary priority of rare disease groups in Latin America [41].

Without a doubt, each country sets its own rules, but the existence of rare diseases in each region of the world is undeniable. On the other hand, Gorini & Ferreira add that,

In the European Union, any life-threatening or chronically debilitating disease that affects fewer than 5 people in 10,000 is considered rare, while in the United States, any disease affecting fewer than 200,000 people is considered rare, corresponding to a prevalence of approximately 1 in 1,630 people [16].

Lu & Han highlight that, "In China, a rare disease is defined as a condition with an incidence of less than 1/10,000 among newborns, a prevalence of less than 1/10,000, or an affected population of less than 140,000" [26]. It should be noted that authors such as Wainstock & Katz argue that "the lack of a universal definition in the lives of people with rare diseases disrupts government funding, international research and development partnerships, and market access" [41]. It is therefore understood that there is no universal scientific definition for rare diseases, which makes it difficult for new generations of doctors to train to understand, diagnose, and treat them. Concerning this issue, authors such as Abozaid et al. argue the following,

The qualitative criteria used to define RDs are primarily subjective and include terms such as "life-threatening," "alternative treatment options," "disease severity," and "neglected." Some of these criteria have important emotional impacts, such as the severity of the disease, its potential lethality, heritability or the lack of effective therapies [1].

Orphan disease statistics

Although rare on an individual level, collectively, rare diseases (RDs) are common, with a prevalence of 3.5% to 5.9% equating to 263 to 446 million people being affected at any time point. This includes an estimated 36 million people in the European Union (EU) and 30 million people in the United States [34,18].

Authors such as Darretxe et al., Tambuyer, highlight that,

Depending on the disease, the diagnosis of RD may be possible before birth, at a very young age, or it can be made between 5 and 30 years of age, in most cases, a period of between 10 and 15 years [12].

In a study to investigate the factors associated with mortality due to orphan diseases in Chile in the period 2002-2017, Ávila & Martínez [6] found that 10,718 deaths were attributed to orphan diseases, 53.2% of which occurred in women. The average annual mortality was 3.9 per 100,000 inhabitants: 4.1 in women and 3.8 in men. The main causes of death were Creutzfeldt-Jakob disease, anencephaly, and autoimmune hepatitis. While in men, the main causes of death were Creutzfeldt-Jakob disease, muscular dystrophy, and anencephaly. According to these authors, women are 1.75 times more likely to die from this group of diseases compared to men (adjusted OR=1.75; 95% CI 1.69-1.82). The highest probability of dying occurred in children aged 0 to 4 years (adjusted OR=15.30; 95% CI 14.10-19.20).

Challenges for the promotion of medical knowledge in orphan diseases

The current challenges that medical schools have in promoting medical knowledge through research and clinical trials in orphan diseases are highly relevant to increasing the life expectancy of many patients with these diseases. For this reason, it is vital to identify the factors that can be a problem for the advancement in the research, treatment, and care of orphan diseases in patients by the new generation of doctors in training, according to existing needs. For example, in Latin America, authors such as Gonzaga et al., Díaz et al. argue that,

"*Rare and undiagnosed diseases pose a significant challenge to the region's health systems; timely diagnosis, access to appropriate care, prevention, and the provision of effective treatments are some of the main challenges" [15]. Along these lines, Wainstock & Katz [41] state that "the vast majority of those who can obtain diagnosis and access to treatment belong to the middle and upper classes". Gonzaga et al. [15] agree that "access to treatments is another major challenge for patients with rare diseases in Latin America and the Caribbean" (p.4).*

However, the most transcendental challenge for the promotion of medical knowledge is the lack of knowledge about research and treatment of orphan diseases among medical students. For example, Hristova explains that,

They conducted a study to assess medical students' knowledge and awareness of rare diseases, as well as their perceptions of potential measures to enhance education on these diseases, using a cross-sectional survey at the Medical University of Plovdiv in Bulgaria in 2019. Through the study, researchers found that respondents believed society as a whole was largely unaware of rare diseases as a significant public health issue. The study was conducted through a cross-sectional survey with 12 questions divided into three categories: sociodemographic profile, knowledge and awareness of rare diseases, and attitudes about measures to improve training in rare diseases. In the study, 1,189 medical students participated in the survey, yielding an overall response rate of 56.4%. 13% of participants knew the

correct definition of rare diseases. However, a low overall level of knowledge about orphan drugs was identified 20.3%, and genetic counseling and testing 0.5% [20].

Flores et al. found in a study whose objective was to identify the level of knowledge of students from a non-state university in Lima, Peru, about rare diseases through a cross-sectional analytical survey that most (68.1%) of students and 48.7% of physicians had heard of the term rare disease. It should be noted that only a few individuals claimed to have received any specific training on it. Of the doctors, 46% considered that there should be a course on rare diseases in the medical plans. More than 60% considered rare diseases to be a public health problem [14]. On the other hand, Flores et al. [14] concluded that "due to the low level of general knowledge among students and doctors about rare diseases, it is necessary to raise awareness and improve education about these pathologies, as this would have beneficial effects on patient care."

Regarding the limited knowledge about orphan diseases, Walkowiak et al. explain that,

Although national plans or strategies for rare diseases have been implemented in many jurisdictions, the low level of knowledge and experience among medical professionals in diagnosing, treating, and rehabilitating rare diseases is one of the main barriers faced by patients during the medical encounter [40].

For their part, Hristova et al. [19] highlight that the incorporation of training in rare diseases should be considered in university curricula. This is essential to motivate the various stakeholders to play a proactive role and to collaborate with these activities. It should be noted that Walkowiak et al. concluded in a study whose objective was to identify the knowledge about rare diseases in health professionals in the Republic of Kazakhstan that,

The majority of respondents agreed that rare diseases are a public health problem for medical students and physicians due to insufficient knowledge about etiology, epidemiology, and prevalence of rare diseases. Many respondents had difficulty distinguishing them from common diseases. They also lacked the knowledge of central patient registration and reimbursement of orphan drugs in Kazakhstan. Almost half of the respondents reported having received classes on rare diseases during their studies; however, most considered that their knowledge about rare diseases was insufficient or scarce, so they did not feel prepared to deal with them. The study was conducted between March and May 2021 through a survey of 207 medical students and 101 physicians at the Marat Ospanov Medical University of West Kazakhstan in Aktobe [40].

Stoller states that "the challenge of researching and treating orphan diseases primarily involves diagnosis, receiving optimal care, and the cost of specific drugs for the disease" [37]. Likewise, Jahanshahi et al. [22] state their opinion stating that "rare diseases pose a serious challenge to the healthcare system that should not be ignored. Patients with rare diseases often experience a lack of treatment alternatives, psychological stress, and financial burden in addition to the burden of disease."

Similarly, Ahmed et al conclude that among there are more challenges than we think; they list elements such as,

Limited resources, the need to balance research requirements and curriculum, and the importance of cultivating a research-oriented institutional culture. Successful strategies involve curriculum updating, teacher motivation, and interdisciplinary collaboration [2].

Finally, Lancet Global Health [25] adds that "due to the low possibility of the disease in orphan diseases and the lack of knowledge among patients and health workers of its typical signs and symptoms, it is difficult to achieve an accurate and early diagnosis".

Need for scientific research in orphan diseases

Research is the primary function of any scientist, and teaching doctors are part of that community that trains future doctors for the common welfare. Even so, research is an expensive activity that requires financial, academic, and social support. Therefore, the absence of any of these three elements deprives the teacher of their motivation to undertake new research projects, especially if such research is aimed at understanding a phenomenon with little information revealed or shared. As a result of this reality, Puyol [30] postulates that,

Rare diseases are also referred to as orphan diseases due to the limited scientific research dedicated to them, resulting in equally scarce treatments. They are orphan diseases because they are abandoned by research (p. 354).

On the other hand, Yoo [43] adds that, "orphan diseases are called orphan diseases because pharmaceutical companies and researchers tend to neglect them, because they do not generate enough revenue to justify the cost of developing treatment strategies." For their part, Ayyappan et al. (2022), about this topic, state that, "many rare diseases lack sufficient knowledge and data to prefer an Evidence-Based Medicine (EBM) framework in patients with rare diseases". They state that "in this regard, students must make clinical decisions when faced with diseases or conditions for which evidence is limited" [3].

On the importance of medical knowledge in orphan diseases, Suarez-Obandob postulates the following,

Given the conditions of clinical care in RD and its importance in the field of public health, this group of diseases should play a preponderant role in the evolution of medical education and the preparation of academic content received by both medical students and specialty students [36].

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To address these unique challenges, Berry et al. [7] explain that the National Institutes of Health (NIH) established the Rare Disease Clinical Research Network. For their part, Zhou and Yang identified through their study the need for research into orphan diseases. They initiated their study to examine the fundamental knowledge, information, and educational needs of emergency physicians in China. These researchers found that,

Most emergency physicians prefer to get information through search engines on websites specializing in rare diseases. The primary reason for the delay in diagnosing rare diseases is the lack of established practice guidelines and consensus. The lack of practice guidelines or consensus was considered the most significant reason for the delay in diagnosing rare diseases. The sample in the study was composed of 539 emergency physicians, 200 women, and 339 men. 4.27% of respondents correctly estimated the prevalence of rare diseases. A total of 98.5% of respondents rated their knowledge of rare diseases as minimal or insufficient [44].

According to Fehr & Prütz [13] "the heterogeneity of rare diseases, which span all medical disciplines, has long since left rarity in the background as a common denominator and as the cause of particular infrastructure problems" (p.3). On the other hand, Ramírez & Muñoz; Roth & Marson [33] explain that "the lack of adequate treatments for the set of rare diseases highlights the urgency of promoting research aimed at accurately addressing conditions and providing palpable solutions to those facing these challenging realities" [33].

The author Hristova et al. [19] explain that "medical universities are autonomous and have the prerogative over the organization, structure, and contents of undergraduate medical courses" (p.2). Groft et al. state that,

It is important that students in early childhood faculty internships in rare disease research are included for their professional development and the advancement of knowledge in this field, given that a person at this stage of their career cannot carry out a large-scale prospective research project, it is essential to identify appropriate and viable studies [17].

On the other hand, Dunne et al. conducted a literature review of articles to identify current rare disease education in different databases since June 2021 using the "rare disease" and "education or teach" strategy. According to them,

The search yielded 8,557 results in English as available text. After being verified by title and abstract, ten publications were identified that they considered educational resources on a specific therapy for a rare disease. However, the educational resources identified do not relate to the management of rare undiagnosed diseases as a general theme; they only identify specific diseases and learning situations [11].

Similarly, Somanadhan et al. & the European Commission Rare diseases state that "research on rare diseases is a top priority: to date, more than 1,400 million euros have been invested in 200 or more research and innovation projects" [38]. "Rare diseases are currently under-researched in Europe, there is a lack of resources and there is no uniformity in the rules governing the collection, management and use of rare disease information registers" [38].

Jahanshahi et al., on the other hand, conducted a cross-sectional, survey-based study from September 2021 to January 2021 through convenience sampling in health professional students who had completed two years of education and had access to the internet in Iran. The purpose of the study was to investigate the knowledge and opinions of future Iranian health professionals about rare diseases. To this end, it was found that,

Out of a total of 6,838 students, mostly nursing and medical students, 85% rated their knowledge of rare diseases as scarce and insufficient. 70% of those surveyed took courses on rare diseases at university. While 72.7% of future professionals did not feel prepared to care for a patient with a rare disease [22].

Therefore, these studies prompt us to reflect on the health challenges faced by patients with orphan diseases in the face of the uncertainty surrounding an accurate diagnosis. According to Fanny, studies carried out in the United States report that "patients with these conditions can visit between 6 and 13 doctors before achieving a definitive diagnosis, and the delay in their diagnosis is often greater than 5 years from the onset of symptoms. This is what has been called the diagnostic odyssey of patients affected by Rare Diseases" [13].

Role of the Pharmaceutical Industry in Orphan Disease Research

The development of drugs to treat orphan diseases can impact the dissemination of research in academia and discourage its importance. According to Fasseeh et al. [10] "in the 1970s, availability to treat rare diseases was limited to only 10 drugs." According to Budarapu [8] "pharmaceutical industries show negligible interest in the development of drugs and treatments for rare diseases as the drug development process is an expensive process." Mitschang [27] states that one of the primary challenges in developing orphan drugs is the limited capacity to enroll, engage, and retain patients in clinical trials. Because patients are scarce and generally geographically dispersed, it is difficult to recruit enough candidates for trials and expensive to organize logistics. Galindo (2024) stresses that companies' pharmaceutical companies regularly have less incentive to invest in the research and development of orphan drugs, which represents a first challenge.

One of the limitations of disseminating medical knowledge in medical schools to promote research into orphan diseases is the development of drugs. However, for drugs to be developed for orphan diseases, the pharmaceutical industries depend on research. On this issue, authors such as Yates & Hinkel [42] state that the "large number of rare diseases and the scarcity of research available on many of them has created enormous challenges in drug development". For these authors (p.810), "a large number of rare diseases are never investigated for treatment because they affect very few people" [42]. On the other hand, Orpha Net (2024) states that "orphan drugs are aimed at treating conditions so rare that manufacturers are

not willing to market them under standard market conditions". About economic investment in the development of orphan drugs, Sultana et al. state that,

In the last two decades, initiatives have emerged to encourage pharmaceutical companies to invest in the development of orphan drugs. The Orphan Drug Act in the United States in 1983 and followed by similar legislation in Japan, Australia and the European Community, marked a milestone in this direction and the European Community was a fundamental step in this direction [39].

In this regard, concern arises about the scope that the Orphan Drugs Act has had to promote research in medical schools as an inherent regulation of research. According to Sultana et al. (2024) "strategies have been used to stimulate research aid, the streamlining of authorization procedures and the extension of commercial exclusivity". Regarding the aspect of exclusivity, Sultana et al. (2024) add that in "Europe, commercial exclusivity has raised doubts about the need for additional incentives to ensure profitability". Therefore, the relationship of research for the development of orphan drugs by pharmaceutical industries in terms of cost/effectiveness seems to be an unstimulating variable in the construction of medical knowledge in medical students.

Development of research skills in medical students

For medical educators, cultivating collaborative research skills is essential for trainees to treat orphan diseases in the future effectively. In this regard, Noller & Cain explain that,

A vital skill for students in the health professions to develop is collaboration. Developing tolerance for diverse viewpoints, as well as valuing an understanding of the lived experiences of others, is critical to learning how to deliver a patient-centered experience. The educator must promote these meetings to defend the principles of academic freedom and civility in achieving optimal educational outcomes. [31].

Regarding research competencies, Barbero [8] highlight that it is "fundamental for the practice of professional practice not only because conducting research must constitute an important part of practice, but also because research-related competencies go beyond research"(p.283). In this line Ahmed & Khayal [4] state that "the integration of skills de research in medical study programs is becoming a critical component, to equip future medical professionals with the ability to contribute to the scientific community effectively" (p.3).

Therefore, research must be the north to follow if we want to move forward to solve what ails us. More emphatically, Barbero and Anzola, for their part, postulate that,

Research should be understood as the activity aimed at the search, production and generation of knowledge and the development of critical and argumentative capacity that makes it possible to update and contextualize the knowledge taught, shared, discussed and updated in the teaching-learning process, capable of responding to the challenges of the time and health problems [8].

Creating new perspectives that generate hope is crucial if we want to attract more young doctors to research. From the perspective of medical research, some researchers explain that,

They carried out a bibliographic study in different databases with the purpose of systematically categorizing and analyzing current trends and future directions in research training in medical education and their influence on the training of medical students' skills. The results revealed a diverse perspective in medical research, with significant emphasis on research training. The study showed various methodologies and approaches used globally, where the thematic focus and geographical distribution of the studies were highlighted [4].

These researchers put all their effort into researching what was being done to investigate. On the other hand, Asghar et al., concerning this topic, state that,

Transferable research skills, such as critical thinking and problem-solving, can be easily integrated into the curriculum. However, due to the time and resource requirements needed for authentic research experiences, such as extended research projects, it may not be possible to offer them to all students [5].

Research activities can develop the research skills required in orphan diseases. In this regard, Kaur et al. (2023) state that in "the career of medicine, research activities have the potential to encourage or deter future participation in research". These researchers conducted a study whose objective was to determine the experiences of medical students, the perceived development of research skills, and satisfaction related to the completion of research projects.

Experience helps but above all encourages you to continue. In their study, Kaur et al. concluded that,

Most respondents consider mandatory research projects to be positive. Regarding satisfaction, respondents believe that it can be improved by ensuring conducive research environments, high-quality supervision, and the inclusion of dedicated research time in the curriculum. The study was conducted through an online survey of five cohorts of 1,375 students in total between 2017 and 2021. A univariate study was employed to understand students' perceptions of the development of research skills, in conjunction with a linear regression model to identify the factors that influence satisfaction with their research projects [21].

On the development of research skills in medical students, Qamar et al. and Bhate Loh explain that "teaching medical students about the social determinants of health without equipping them with the essential skills and resources to bring about meaningful change is inadequate" [32].

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Along the same lines, Ramalle et al. carried out a study whose objective was to report on the training needs and perceived shortcomings of Spanish doctors in the public health system in the diagnosis, treatment, and follow-up of patients with rare diseases. Their findings were that,

Less than one-third of physicians have received training in rare diseases during their undergraduate or graduate studies. In the case of hospital professionals, they received more postgraduate training. The study was a cross-sectional descriptive survey conducted through an "ad hoc" questionnaire with 26 questions, which were completed by 132 primary care physicians and 37 specialists in April and May 2018. The researchers concluded that primary care physicians and specialists showed a low level of training in rare diseases. Among its recommendations was the establishment of an academic and continuous program on rare diseases, and multidisciplinary units and high-quality practical guidelines for prevention and support for clinical practice [33].

According to Bai et al. (2023) "in recent years, China began to pay more attention to the prevention, diagnosis, and treatment of early diseases, especially rare diseases, which had been ignored for a long time." To these ends, Bai et al. [6] indicate that "the Construction of Gold Courses that impose greater demands on teachers and students" was established. These authors highlight that "the inclusion of common diseases with atypical symptoms and rare diseases in the typical case scenarios of Problem-Centered Learning increases the challenge, enriches the variety of cases and improves the learning skills of students".

Results

The literature review reveals the challenges faced by educational institutions in training medical students to treat orphan diseases. The lack of knowledge about orphan diseases invisible the seriousness of this issue, which should be considered a threat to the lives of those with no way out or answers to their disease, and therefore, to the decrease in human capital. From the perspective of medical knowledge development, spaces for research and discussion are not being created to raise awareness among medical students about these diseases. If the teaching doctor does not provide spaces for the discussion and construction of medical knowledge, the question is what we are doing to contribute to the health of patients with orphan diseases, and how we can correct the suffering of these patients and their families.

Conclusion

The development of medical knowledge is the basis of teaching in educational institutions. The thinking that is transferred as part of the teaching-learning process, where the teaching physician serves as a mentor, is vital and pertinent for creating viable scientific solutions. There is currently an opportunity to identify research opportunities through 'Grants' or grants aimed at finding new diagnoses and treatments for orphan diseases. Primary management rests in the hands of institutions aimed at training doctors in the present and the next generations with a creative and free mentality in search of concrete scientific truths that serve to preserve the life of those who suffer from orphan disease. Similarly, these medical resources will enable better services and longer life expectancy, thereby enhancing human capital and the economy.

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Declarations:

Authors' Contribution:

- [a]Conceptualization, data collection, interpretation, drafting of the manuscript and intellectual revisions
- [b]Data collection, interpretation, and drafting of manuscript
- The authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed

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