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REVIEW

"Las Meninas" in the clinical description of genetic disorders

"Las Meninas" en la descripción clínica de los trastornos genéticos

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ABSTRACT

Introduction: las Meninas (The Family of Philip IV) continues being a topic of active research in the field of Medical Sciences. In this painting, three distinct planes can be differentiated, the foreground features the Infanta and her ladies-in-waiting and two court jesters along with a mastiff; and in the background, we find the image of the Monarchs reflected in a mirror.
Objectives: to analyze the characters portrayed in the foreground of "Las Meninas", using contemporary clinical genetics concepts. Additionally, it seeks to explore the potential genetic significance of the reflection of the royal couple in the mirror, highlighting its relevance in the era of Genomic Medicine.
Method: documentary research was conducted, identifying 47 documents through three independent searches in the following databases: PubMed/Medline, Google Scholar and OMIM. Moreover, recommendations from experts in the field were incorporated. Subsequently, two researchers scrutinized independently the articles in their entirety, and both concurred on the recommendation of the inclusion of 32 articles. After conducting a qualitative evaluation, a comprehensive review was generated.
Results: within this painting, there are depicted clinical signs that are sufficient to suggest diagnoses of achondroplasia, Laron syndrome and McCune-Albright syndrome. Furthermore, it serves as an illustrative tool to distinguish the characteristics associated with autosomal dominant inheritance in the Habsburg Syndrome; the observation of this artwork provides an invaluable exercise for honing clinical skills.
Conclusions: in the foreground of the painting "Las Meninas," discernible clinical signs in the depicted characters lead us to propose dysmorphic disorders of genetic origin as potential diagnostic hypotheses. The visual observation of Velázquez's genius, captured in this artwork is still decisive as part of the clinical examination in the diagnostic process, especially in the era of Genomic Medicine.

Keywords: Medicine In The Art; Velázquez; Meninas; Medical Education; Diagnosis; Physical Examination; Achondroplasia; Habsburg Syndrome; Laron Syndrome; Mccune-Albright Syndrome.

RESUMEN

Introducción: las Meninas (La familia de Felipe IV) sigue siendo un tema de investigación activa en el campo de las ciencias médicas. En esta pintura se pueden diferenciar tres planos distintos: en primer plano, la infanta y sus damas de compañía y dos bufones de la corte junto con un mastín; y al fondo, la imagen de los monarcas reflejada en un espejo.
Objetivos: analizar los personajes representados en primer plano en Las Meninas, utilizando conceptos contemporáneos de genética clínica. Además, se busca explorar el posible significado genético del reflejo de

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la pareja real en el espejo, destacando su relevancia en la era de la medicina genómica.
Método: se llevó a cabo una investigación documental, identificando 47 documentos a través de tres búsquedas independientes en las siguientes bases de datos: PubMed/Medline, Google Scholar y OMIM. Además, se incorporaron recomendaciones de expertos en la materia. Posteriormente, dos investigadores examinaron de forma independiente los artículos en su totalidad, y ambos coincidieron en la recomendación de la inclusión de 32 artículos. Después de realizar una evaluación cualitativa, se generó una revisión exhaustiva.
Resultados: en esta pintura se representan signos clínicos suficientes para sugerir diagnósticos de acondroplasia, síndrome de Laron y síndrome de McCune-Albright. Además, sirve como herramienta ilustrativa para distinguir las características asociadas a la herencia autosómica dominante en el síndrome de Habsburgo; la observación de esta obra de arte proporciona un ejercicio inestimable para perfeccionar las habilidades clínicas.
Conclusiones: en primer plano del cuadro «Las Meninas», los signos clínicos perceptibles en los personajes representados nos llevan a proponer trastornos dismórficos de origen genético como posibles hipótesis diagnósticas.
La observación visual del genio de Velázquez, plasmado en esta obra de arte, sigue siendo decisiva como parte del examen clínico en el proceso de diagnóstico, especialmente en la era de la medicina genómica.

Palabras clave: Medicina En El Arte; Velázquez; Meninas; Educación Médica; Diagnóstico; Exploración Física; Acondroplasia; Síndrome De Habsburgo; Síndrome De Laron; Síndrome De Mccune-Albright.

INTRODUCCIÓN

Throughout human history, the fields of art and medicine have maintained a profound interplay; visioners in the art world, such as Leonardo da Vinci (1452–1519), significantly contributed to the understanding of human anatomy; a discipline meticulously explored by those aiming to showcase its creativity and aesthetics. Artists have used the human figure as a foundational element in diverse forms of artistic expression.

In contemporary times, the presence of medical signs within artworks continues captivating, and at times, these signs permit the identification of specific diseases, some of which were portrayed by artists even before their formal scientific description. This demonstrates that the acute observation of artists has served as enduring visual records of diseases.[1,2]

"Las meninas" or "The Family of Phillip IV", created in 1656, stands as the pinnacle work of the painter Diego Velázquez, who was primarily a portraitist. This masterpiece presents us with what appears to be an ordinary scene, in which the artist offers not explanations but rather data.[3,4,5] These data have led to numerous interpretations, making it a topic of contemporary research, even within the field of Medical Sciences.[6]

In this painting (figure 1), a total of 10 individuals and a dog are depicted, and experts categorize them into three distinct planes. The foreground, symbolizing innocence and childhood, prominently features the Infanta Margaret, who serves as the central focal point of the work. She is accompanied by her two ladies-in-waiting or "meninas" (María Agustina Sarmiento and Isabel de Velasco), as well as the court jesters (Mari Bárbola and Nicolasito Pertusato), who are accompanied with the mastiff. In the middle ground Velázquez contrasts the intellectual and superficial elements; in this plane he portrayed himself on the left side, while Marcela de Ulloa and the keeper of the women, Diego Ruiz Azcona, are depicted on the right. Moving to the background, we find José Nieto Velázquez, the Queen's lodging master and ingeniously incorporated into the scene, a mirror that reflects the images of Philip IV and Mariana of Austria, the royal couple.[7]

The objective of this review is to employ contemporary clinical genetics concepts to analyze the characters portrayed in the foreground of "Las Meninas". Additionally, it aims to explore the potential genetic significance of the reflection of the royal couple in the mirror depicted in the painting. Furthermore, this study seeks to exhibit the relevance of this artwork in the context of the era of Genomic Medicine.

METHOD

This investigative study adopted a bibliographic review approach, employing three separate searches to identify relevant documents for analysis. The initial search was conducted in the "PubMed/Medline" bibliographic database using a combination of the following keywords: "medicine in the arts", "Velázquez" and "meninas", and connecting them with the Boolean operators "AND" and "OR". The search query structure was as follows: ["Medicine in the Arts" AND Velazquez] OR [meninas AND Velazquez]. Language filters were applied, restricting the search results to English or Spanish language publications. Concurrently, a search was carried out in the Google Scholar database using the following strategy: "medical education" AND "physical examination" AND "fine art". The activated filters for this search included: language (English or Spanish), publication date no older than five years and a focus on review articles.

In addition to these database searches, visual information pertaining to the primary characters within the painting was collected. A deliberate search was made to identify dysmorphic signs in accordance with current medical nomenclature, allowing for the formulation of diagnostic hypotheses.[8] Subsequently, documents related to specific diseases were added using the Online Mendelian Inheritance in Man database,[4] and expert-recommended articles were also incorporated into the investigation.

To summarize the investigation findings, an analysis of the discernable signs crucial for diagnosing the characters depicted in the painting was conducted. This analysis was framed within the context of the current significance of integrating the study of art into medical education.

In accordance with the defined objectives, two of the researchers independently conducted a comprehensive examination of the found articles in their entirety. Before proceeding with the review, a careful assessment of the article titles and abstracts was conducted, and the recommendations for inclusion in the review process were integrated only after confirming that the articles precisely addressed the intended topic and provided pertinent information. Figure 1 illustrates the process of article inclusion in the analysis.

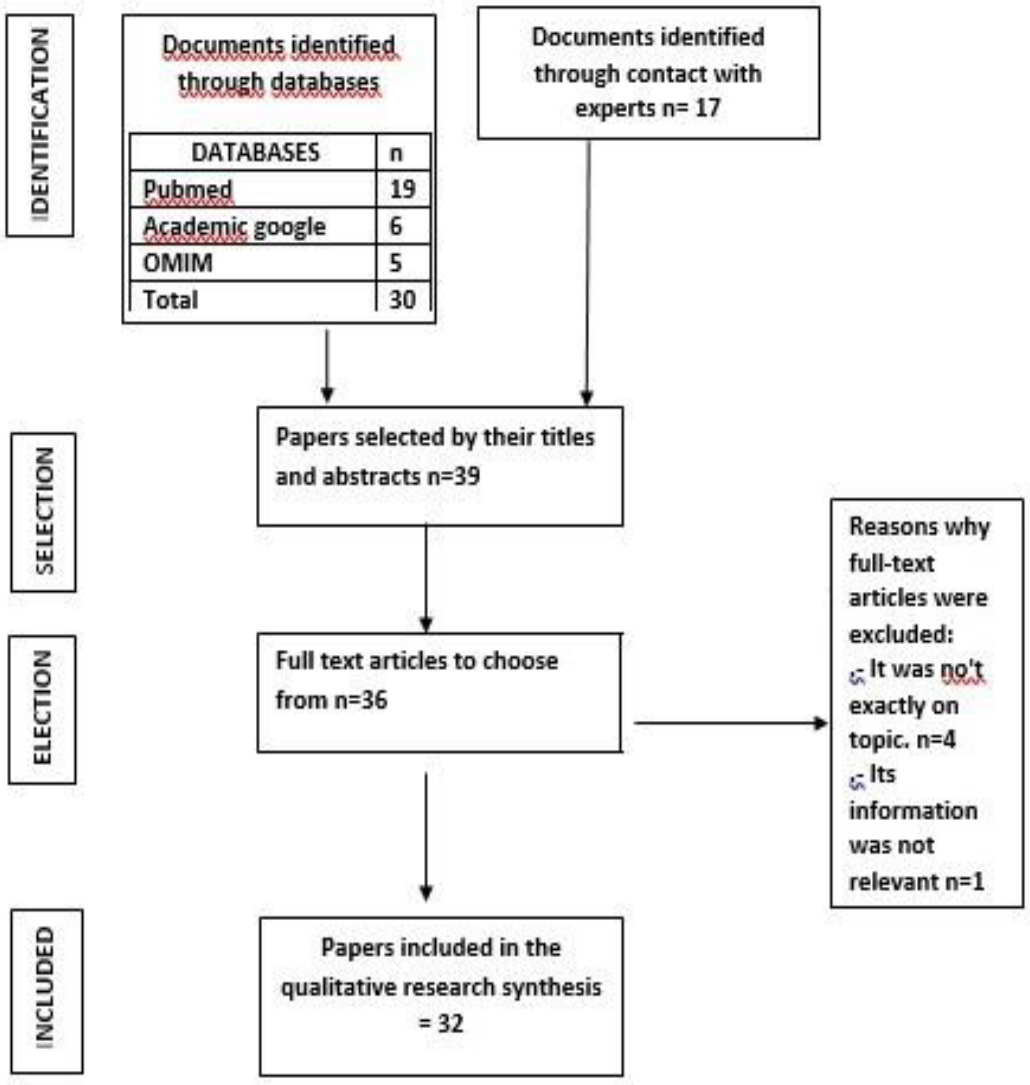

Figure 1. Flow diagram followed in the research carried out

These articles were identified through three primary sources: "PubMed/Medline", "Google Schoolar" and "Online Mendelian Inheritance in Man (OMIM)", from which 19, 6 and 5 documents were identified, respectively. Additionally, 17 documents recommended by experts in the field were considered. Of all these, a total of 39 were initially selected based on their titles and abstracts, and subsequently, 36 full – text articles were retrieved. During the analysis, five were excluded from consideration; four due to the content that did not precisely align with the topic of interest, and one was excluded because the information it contained was deemed irrelevant. Therefore, the final number of studies included in this review was 32.

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Ethical approval

The study protocol was approved by Local Ethical Committee of National Center of Medical Genetics of Cuba, according to the guidelines of The Cuban Society of Human Genetics.

RESULTS

Analysis of the characters depicted in the painting "Las Meninas", in accordance with contemporary clinical genetics concepts

"Las Meninas" stands as an unparalleled source in illustrating the diagnostic process of conditions marked by dysmorphisms or morphological alterations that manifest during growth. These are often unusual signs, occasionally converging into what is denominated as a dysmorphic pattern, what presence of which suggests specific medical conditions. The ability to understand, possess the skills to investigate, and comprehend the significance of these indicators within the diagnostic process constitutes integral aspects of the medical profession.[8,10]

At the time Velázquez painted the canvas (figure 2), the central figure, Infanta Margaret Theresa of Spain was five years old, while Maria Bárbola and Nicolasito Pertusato were estimated to be 20 and 18 years old, respectively.[11] Upon close examination of the painting, particularly in comparison to the Infanta, it becomes evident that both Maria Bárbola and Nicolasito Pertusato presented stunted growth relative to their ages.

Figure 2. Las Meninas or family of Philip IV from: Wikipedia (Public domain)

In the case of Maria Bárbola, this disproportionality is striking, especially when applying the canon or rule of proportions followed by painters, which takes the height of the head as a reference measurement. – ideally, the height should be approximately eight times greater.[5] This observation suggests that Maria Bárbola had macrocephaly. Additionally, her limbs appeared shortened, particularly in the proximal regions. Her facial features show a depressed nasal bridge and mid – face retraction, with relative prognathism.[6,7]

Pabo Ruiz Picasso, a fervent admirer of Velázquez, conducted an extensive study of "Las Meninas". In 1957, he decided to create his own version, which ultimately comprised a series of 58 interpretations. The first and most prominent work in this series (figure 3) masterfully portrays a complete scene using shades of grey.

Picasso ingeniously captured the primary clinical signs, which combined, constitute the dysmorphic pattern characteristic of achondroplasia: short stature, macrocephaly, a depressed nasal bridge, relative prognathism and shortened extremities. Thus, within Picasso's initial painting of "Las Meninas" series, as represented through the character of Maria Bárbola, a definitive indication of her affliction with achondroplasia emerges.[8,9,10,11]

Conversely, Nicolasito's proportionate short stature hints at a potential diagnosis of pituitary dwarfism, a condition described in several forms. Velázquez's depiction of him with a slightly protruding forehead, a depressed nasal bridge, and full cheeks suggests that he might specifically have suffered from pituitary dwarfism type II, or Laron syndrome. Laron syndrome is an autosomal recessive disorder characterized by insensitivity to growth hormone.[12]

Figure 3. First work in the series "Las Meninas" by Pablo Picasso/ Canes, 1957

Returning to Infant Margaret Theresa of Spain and her ladies-in-waiting: María Agustina Sarmiento de Sotomayor holds a red ewer; although she could make the unexpert eye confuse her with an individual with short-stature (because she is in the first plane and at first sight looks the same stature as the others); she clearly appears making a reverent gesture. While Isabel de Velasco gazes attentively at the Infanta with a graceful inclination. Some have suggested that the ewer contains water, which holds significance. However, the depiction of insistence in this scene, along with the evident interest of her ladies-in-waiting, raises the question that many have pondered: Could this have been a remedy? In the painting, the Infanta Margaret exhibits remarkably pale skin, which could be a sign of anemia, she also has protruding eyes, and on her right temple, there is a cafe-au-lait spot, which is also present in later portraits. The five-years-old Infanta is dressed in adolescent attire, with a bust that appears notably rigid, possibly achieved through the use of rigid lead plates, in accordance with the customs of the time, concealing perhaps an early breast development.[13] Some believe it is likely that she experienced precocious puberty, and the interested shown by her ladies-in-waiting could be attributed to their involvement in providing something that might have delayed a potential premature menstruation, during that era, it was a common practice to chew small pieces of clay and mud as a means of achieving this effect.[14] This has led to the suggestion of a possible diagnosis of McCune-Albright syndrome, has a post-zygotic etiology, it means that it is no heritary. Clinically this disease is characterized by a triad, consisting of irregular skin pigmentation, multiple endocrinopathies including: precocious sexual development (and early menstruation), hyperthyroidism supported by the presence of exophthalmos, where a more pronounced goiter also becomes evident (figure 4), and polyostotic fibrous dysplasia.[20,21]

Although facial asymmetry could be observed in McCune Albright syndrome, it is not observed in all persons suffering this disease; besides it would be evidence later in life. Infanta Margaret was a five-years-old girl when "Las Meninas" painting was painted; by analyzing other paintings made by Velazquez, as the one showed in figure 4, perhaps it could be identified.[15,16]

King Philip IV and his wife, Mariana of Austria, are perceptible in the reflection within the mirror in the third plane. Subtle brushstrokes hint at some characteristics of the Habsburg Syndrome, which are more prominently

depicted in other portraits of the monarchs executed by Velázquez. Habsburg Syndrome is characterized by mandibular prognathism, a flat malar area, slight eversion of the lower eyelids, and a thick lower lip.[17] Nevertheless, it is remarkably illustrative in the painting that this autosomal dominant disorder manifests in each generation (in the parents of the Infanta and in the Infanta herself), affecting both females and males, irrespective of gender. While this may not be as evident in the Infanta in 'Las Meninas,' it becomes more evident in later portraits of Margaret Theresa of Spain (figure 4), and is expressed with increased severity in males. Hence, this painting provides yet another detail that, from a genetic perspective, represents the importance of family history in the diagnostic process.

Figure 4. Infanta Margarita Teresa de España from: Wikipedia (Free content)

Relevance of "Las Meninas" in the era of Genomic Medicine

Research frequently reaches its conclusion when it successfully addresses the problem that initially instigated it, as exemplified by the Human Genome Project.[23] Nevertheless, "Las Meninas" leaves behind numerous unanswered questions or mysteries. From the standpoint of medicine in general and the clinical investigation of genetic disorders in particular, genetic research findings continue appearing in established bibliographic data, these findings seek to provide explanations for what was formulated, something that was reflected in this Velázquez´s artwork.[18]

Moreover, this painting maintains its relevance in the present, both in the broader context of Medicine and within the specific field of clinical study of genetic disorders. This pertinence is underscored by what has regrettably been referred to as a crisis in the clinical method, given that there is a growing inclination to order tests, whether they are laboratory-based or imaging, without first establishing a clinical judgement to justify them. While these tests are undoubtedly important and sometimes essential for diagnosis, the practice of medicine in this manner can result in the erosion of the scientific essence of the medical profession, especially in the era of Genomic Medicine.[19]

The clinical method serves as the diagnostic process, representing the application of the scientific method to medical practice. In the scientific method, information is systematically gathered, hypotheses are formulated, and then tested. In medical diagnosis, the gathering of information primarily relies on the application of essential tools that have long characterized the medical profession: patient history and physical examination, These crucial aspects require the honing of the senses through training.[19] From that, medical education encompasses the concept of "visual literacy", which is the ability to find meaning from images. It has been demonstrated that formal training in the observation of artworks in interdisciplinary courses, not only provides an enjoyable experience but also enhances the clinical skills of medical students. Such training teaches them not only to observe but also how to do it effectively. The integration of concepts from the fine arts into clinical diagnosis cultivates professionals who excel in their medical practice.[20,21,22,23,24]

It remains crucial for medical trainees to receive comprehensive training that equips them with the skills which have characterized the medical profession, using the tools that have been in use for centuries, these tools are far from obsolete, instead, they are evolving and expanding. Contemporary advancements in medical science, for instance, new DNA-level study techniques, are enhancing our ability to comprehend genotypes and facilitate molecular-level diagnosis, this contributes to a deeper understanding of the significance of genetic variations. The use of these essential medical skills and tools is pivotal in guiding the selection of appropriate molecular studies to conduct and, once the results are obtained, plays a role in their accurate interpretation.[25]

"Las Meninas" represents an invaluable teaching tool offering a unique opportunity for medical trainees.

Its detailed description serves as an exercise of immense value, providing medical students with a visual representation of human variability.[26,27]

The primary limitation of this review was the inability to retrieve all publications related to the topic.

CONCLUSIONS

In the foreground of the painting "Las Meninas," discernible clinical signs in the depicted characters lead us to propose dysmorphic disorders of genetic origin as potential diagnostic hypotheses.

The visual observation of Velázquez's genius, captured in this artwork is still decisive as part of the clinical examination in the diagnostic process, especially in the era of Genomic Medicine.

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CONFLICTS OF INTEREST

All the authors have no conflicts of interest regarding this submission.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are openly available, these could be found by using the references appearing in it.

AUTHORSHIP CONTRIBUTION

Conceptualization: Estela Morales Peralta, Javier Gonzalez-Argote, Miguel Alfonso Alvarez Fornaris.
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