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A NARRATIVE REVIEW ON ANALYSIS OF CHROMOSOMAL ANOMALIES FREQUENCY AND VARIETIES IN PHENOTYPICALLY FEMALE PATIENTS EXPERIENCING AMENORRHEA.

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ABSTRACT

Amenorrhea, characterized by the absence of menstrual periods, affects a significant portion of the female population, signaling potential underlying genetic, anatomical, or hormonal disorders. Chromosomal abnormalities are pivotal in understanding the etiology of amenorrhea, especially in phenotypically female patients experiencing primary or secondary forms of the condition. The review aims to analyze and synthesize research findings on the frequency and types of chromosomal abnormalities in phenotypic females with amenorrhea, highlighting the correlation between specific chromosomal anomalies and the manifestation of amenorrhea. Studies across India have underscored the importance of cytogenetic analysis in diagnosing and managing amenorrhea, revealing a diverse range of chromosomal abnormalities contributing to this condition. Key findings include the necessity of cytogenetic analysis for accurate diagnosis and management, the clinical utility of karyotyping in primary amenorrhea cases, and the broad spectrum of genetic variations contributing to amenorrhea. The review suggests directions for future research, emphasizing the need for improved diagnostic approaches and therapeutic strategies. Understanding the genetic underpinnings of amenorrhea is crucial for developing personalized medicine approaches, optimizing hormone replacement therapy, and employing assisted reproductive technologies based on the patient's genetic and hormonal profile. The findings advocate for the integration of cytogenetic analysis into the standard diagnostic workflow for amenorrhea, enhancing patient care through precise identification of chromosomal abnormalities and informed management strategies.

Keywords: *Amenorrhea, Chromosomal Abnormalities, Cytogenetic Analysis, Turner Syndrome*
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INTRODUCTION

Amenorrhea, the absence of menstrual periods, is a clinical symptom that affects a significant portion of the female population at some point in their lives. It is categorized into two main types: primary amenorrhea, where menstrual periods have not started by the age of 15, and secondary amenorrhea, defined as the cessation of periods for three months or more in women who have previously menstruated regularly [1]. This condition not only poses a challenge to reproductive health but also serves as an indicator of underlying genetic, anatomical, or hormonal disorders. Among the various etiological factors contributing to amenorrhea, chromosomal abnormalities play a critical role, particularly in phenotypically female patients who experience primary or secondary amenorrhea.

Chromosomal abnormalities, including numerical and structural variations, are significant contributors to congenital anomalies and reproductive disorders. These abnormalities can lead to a wide range of clinical manifestations, from minor physical anomalies to severe developmental disorders, impacting an individual's health and fertility [2]. The study of these chromosomal anomalies in amenorrheic patients is crucial for understanding the genetic basis of reproductive disorders, enabling accurate diagnosis, management, and counseling.

While there are differences in the frequency of chromosomal anomalies in people with amenorrhoea, Turner syndrome (45, X) is the most common, affecting about 1 in 2,500 live female births[3]. Other chromosomal disorders, such as mosaicisms and structural anomalies like translocations or inversions, also contribute to the etiology of amenorrhea, albeit less frequently. The identification of these chromosomal abnormalities is essential for the clinical management of amenorrhea, as it can influence treatment decisions, including hormone replacement therapy and fertility options.

Understanding the genetic foundations of amenorrhoea requires examining chromosomal anomalies in phenotypically feminine patients. It aids in the accurate diagnosis, informs treatment strategies, and provides valuable information for genetic counseling. As research in this area continues to evolve, it is expected to offer deeper insights into the complex interplay between genetics and reproductive health, ultimately improving outcomes for individuals affected by amenorrhea.

The review aims to comprehensively analyze and synthesize existing research findings on the frequency and types of chromosomal abnormalities observed in phenotypically female patients with amenorrhea. By examining the correlation between specific chromosomal anomalies and the manifestation of amenorrhea, this review seeks to elucidate the genetic underpinnings that contribute to this condition. Furthermore, it aims to highlight potential gaps in the current understanding and suggest directions for future research, with the ultimate goal of improving diagnostic approaches and therapeutic strategies for affected individuals.

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METHODOLOGY

A narrative search was done to find relevant studies released up to this point, from electronic databases including PubMed, Scopus, Web of Science, and Google Scholar was carried out. A combination of keywords and MeSH terms about "amenorrhoea," "chromosomal abnormalities," "karyotype," "hormonal profiles," and "genetic causes of amenorrhoea" were used in the search approach. A selection of English-published studies was subjected to filters. To locate further research that was not discovered through database searches, reference lists of papers that were found were also examined. The search was conducted in research articles published from 2001 to 2023.

Original research articles focusing on chromosomal abnormalities in phenotypically female patients with amenorrhoea, studies examining the relationship between karyotype and hormonal profiles, studies involving human subjects, and articles published in peer-reviewed journals were all considered for inclusion. Review papers, case reports, conference abstracts, studies that were not available in English, and studies that used non-human participants were among the exclusion criteria.

A standardized data extraction form was utilized to extract data from all the included studies. The following data were gathered: chromosomal abnormality types found, hormonal profile analysis, main findings regarding the correlation between karyotype and hormonal profiles, study location, study design, sample size, age range of participants, author(s), year of publication, study design, hormonal profiles analyzed, and any noted implications for diagnosis, treatment, or management.

The main conclusions on the relationship between karyotype and hormonal profiles in phenotypically female patients with amenorrhoea were highlighted through a narrative synthesis of the data. The synthesis's main objectives were to spot trends, parallels, and discrepancies among the studies and to engage in discussion about how these conclusions might affect future research and clinical practice.

DISCUSSION

Etiologies of Amenorrhea

The etiology of amenorrhea encompasses a broad spectrum of genetic, endocrine, and anatomical disorders, each contributing to the disruption of the normal menstrual cycle through distinct mechanisms. A thorough understanding of these causes is essential for accurate diagnosis, effective treatment, and management of amenorrhea, facilitating improved reproductive health outcomes for affected individuals.

Genetic and Chromosomal Etiologies

Turner Syndrome and Variants: Turner syndrome, arising from a complete or partial absence of one X chromosome (45, X karyotype), is a pivotal genetic cause of primary amenorrhea. It accounts for a significant proportion of cases, with phenotypic manifestations ranging from short stature to gonadal dysgenesis [4]. Variants like mosaic Turner syndrome (e.g., 45, X/46, XX) may present with a milder phenotype but similarly result in amenorrhea due to impaired ovarian function.

X Chromosome Structural Anomalies: Structural anomalies of the X chromosome, such as deletions, isochromosomes, and ring chromosomes, can disrupt gene expression critical for ovarian development and function, leading to primary amenorrhea [3].

Hypothalamic-Pituitary Axis Disorders

Functional Hypothalamic Amenorrhea (FHA): FHA is a condition where external stressors, including psychological stress, extreme weight loss, and excessive physical activity, suppress the hypothalamic secretion of GnRH, leading to reduced gonadotropin levels and amenorrhea. This condition underscores the sensitivity of the reproductive axis to metabolic and emotional cues.

Pituitary Adenomas: Prolactin-secreting pituitary adenomas (prolactinomas) can cause amenorrhea by inhibiting GnRH release through the elevation of serum prolactin levels. This hyperprolactinemia disrupts the ovarian cycle, leading to anovulation and amenorrhea [5].

Ovarian Causes

Premature Ovarian Insufficiency (POI): POI is characterized by the premature depletion of ovarian follicles before the age of 40, leading to amenorrhea, infertility, and menopausal symptoms. Genetic factors, autoimmune disorders, and environmental toxins have been implicated in its etiology.

Polycystic Ovary Syndrome (PCOS): PCOS is a complex endocrine disorder marked by hyperandrogenism, ovarian dysfunction (oligo- or anovulation), and the presence of polycystic ovaries. It is a common cause of secondary amenorrhea or oligomenorrhea in women of reproductive age.

Uterine and Anatomical Causes

Müllerian Anomalies: Congenital absence or malformation of the uterus and vagina (Müllerian agenesis) can result in primary amenorrhea in females with a normal karyotype and functioning ovaries. This condition, also known as Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, highlights the role of anatomical factors in amenorrhea [6].

Asherman's Syndrome: Acquired intrauterine adhesions or scarring, often resulting from surgical procedures or infections, can obstruct menstrual flow, leading to secondary amenorrhea. The severity of amenorrhea correlates with the extent of the adhesions.

Major Cytogenetic Abnormalities

Major cytogenetic abnormalities play a crucial role in the etiology of various clinical conditions, including congenital disorders, infertility, and cancer. These abnormalities involve significant changes in chromosome structure or number, which can disrupt gene function and lead to disease. Understanding these abnormalities is

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essential for diagnosis, prognosis, and treatment planning in affected individuals.

Aneuploidy

One common cytogenetic anomaly is aneuploidy, which is the occurrence of an abnormal number of chromosomes in a cell. Among the most well-known disorders brought on by aneuploidy are trisomy 13 (Patau syndrome), trisomy 18 (Edwards syndrome), and trisomy 21 (Down syndrome). These conditions are typified by a broad spectrum of developmental and physical difficulties, with the most prevalent hereditary cause of intellectual disability being Down syndrome [7].

Structural Abnormalities

Structural abnormalities involve deletions, duplications, inversions, or translocations of chromosome segments. These changes can lead to various genetic disorders depending on the genes affected. For example, deletions in part of chromosome 5 lead to Cri-du-chat syndrome, characterized by intellectual disability and a high-pitched, cat-like cry in infancy [8]. Translocations, where parts of one chromosome are transferred to another, can lead to disorders such as chronic myelogenous leukemia (CML), which is often associated with the Philadelphia chromosome, a result of a translocation between chromosomes 9 and 22.

Microdeletions and Microduplications

Microdeletions and microduplications are submicroscopic changes involving small pieces of chromosomes. These can lead to various syndromes, such as DiGeorge syndrome (22q11.2 deletion syndrome), which affects multiple body systems and can result in heart defects, immune deficiencies, and cleft palate [9]. Similarly, Williams syndrome, caused by a deletion on chromosome 7, includes features like distinctive facial characteristics, cardiovascular disease, and a unique cognitive profile with strong verbal abilities but weak spatial reasoning.

Sex Chromosome Abnormalities

Conditions like Turner syndrome (45, X), in which females have a single X chromosome and experience short stature and ovarian failure [3], and Klinefelter syndrome (47, XXY), in which males have an extra X chromosome and experience hypogonadism and infertility, can be caused by abnormalities in the number of sex chromosomes.

Major cytogenetic abnormalities, including aneuploidy, structural changes, microdeletions, and microduplications, as well as sex chromosome imbalances, are fundamental to understanding the genetic basis of many diseases. Advances in cytogenetic techniques, such as fluorescent in situ hybridization (FISH) and array comparative genomic hybridization (aCGH), have improved the detection of these abnormalities, facilitating early diagnosis and intervention.

Acquired abnormalities

Acquired chromosomal abnormalities refer to genetic changes that occur after conception, as opposed to those that are inherited. These abnormalities can arise at any point during an individual's life and are often associated with various diseases, including cancers and disorders of the blood. Unlike inherited chromosomal abnormalities, acquired changes

Hematological Malignancies

Acquired chromosomal abnormalities are hallmark features of many hematological malignancies, such as leukemia, lymphoma, and myelodysplastic syndromes (MDS).

- Philadelphia Chromosome (Ph): The Philadelphia chromosome, resulting from a translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)), is a well-known acquired abnormality in chronic myeloid leukemia (CML) and a subset of acute lymphoblastic leukemia (ALL). This translocation leads to the formation of the BCR-ABL fusion gene, which has a critical role in the pathogenesis of these leukemias [10].
- Deletions and Translocations in Lymphomas: Non-Hodgkin lymphomas (NHL) often exhibit specific chromosomal translocations that result in the juxtaposition of an oncogene next to a highly active promoter or enhancer, leading to dysregulated gene expression. For example, the t(14;18)(q32;q21) translocation involving the BCL2 gene is common in follicular lymphoma, promoting cell survival by inhibiting apoptosis.
- Complex Karyotypes in MDS: MDS are characterized by a wide range of cytogenetic abnormalities, including deletions (e.g., del(5q), del(7q)), duplications, and complex karyotypes. These abnormalities are crucial for diagnosis, prognosis, and therapeutic decision-making in MDS patients.

Solid Tumors

In solid tumors, acquired chromosomal abnormalities can drive tumorigenesis through mechanisms such as gene amplification, deletion, or rearrangement.

- HER2 Amplification in Breast Cancer: Amplification of the HER2 (ERBB2) gene on chromosome 17q is found in approximately 20% of breast cancers and is associated with a more aggressive disease course and a poorer prognosis. HER2-targeted therapies have significantly improved outcomes for patients with HER2-positive breast cancer.
- EGFR Mutations in Lung Cancer: Mutations and amplifications of the EGFR gene are common in non-small cell lung cancer (NSCLC), leading to constitutive activation of the EGFR signaling pathway. EGFR-targeted therapies have become a cornerstone in the treatment of patients with EGFR-mutant NSCLC [11].

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Cytogenetic abnormalities in amenorrhea-Indian scenario

The investigation into cytogenetic abnormalities in amenorrhea within the Indian context has yielded significant insights, as evidenced by several studies conducted across different regions of the country. These studies collectively underscore the critical role of cytogenetic analysis in diagnosing and managing amenorrhea, revealing a diverse range of chromosomal abnormalities that contribute to this condition.

The study in South India retrospectively reviewed 637 patients with amenorrhea, making it one of the largest studies in the region focusing on this condition. The key finding was the identification of a significant incidence of chromosomal abnormalities among these patients, which underscores the necessity of cytogenetic analysis for all individuals presenting with amenorrhea [12]. This study not only highlighted the prevalence of chromosomal abnormalities but also suggested that such analysis is crucial for accurate diagnosis and effective management, particularly in cases with or without short stature, indicating a broad spectrum of genetic variations contributing to amenorrhea.

In Kerala, the study focused on the proportion and pattern of chromosomal abnormalities in primary amenorrhea. This retrospective study emphasized that a significant number of primary amenorrhea cases were due to cytogenetic abnormalities, advocating for karyotyping as an essential component of the diagnostic evaluation. The study pointed out the clinical utility of karyotyping in resource-limited settings, especially for cases characterized by hypogonadotropic hypogonadism, highlighting the importance of accessible and accurate genetic testing in the diagnosis and management of amenorrhea [13].

A study in Eastern India emphasized the importance of cytogenetic analysis as a part of the diagnostic protocol for primary amenorrhea. This study reinforced the notion that precise identification of chromosomal abnormalities through cytogenetic analysis is crucial for the appropriate management and counseling of patients [14]. By identifying specific genetic factors contributing to amenorrhea, healthcare providers can offer targeted interventions and support, underscoring the personalized nature of medical care required for these patients.

A study of 100 cases at a tertiary center, further supported the critical role of cytogenetic evaluation in primary amenorrhea. This study highlighted the necessity of integrating cytogenetic analysis into the diagnostic process to accurately identify chromosomal abnormalities. Such detailed genetic insights are essential for formulating appropriate reproductive management strategies and providing comprehensive counseling to affected individuals, demonstrating the value of cytogenetic analysis in enhancing patient care [15].

The extensive investigation into 1843 referral cases of disordered sexual development, including amenorrhea, infertility, and sexual ambiguity, in Andhra Pradesh, underscored the mandatory need for cytogenetic evaluation. This study illuminated the wide array of cytogenetic abnormalities encountered in such cases, advocating for routine cytogenetic analysis as part of the diagnostic workflow. The findings highlight the complexity of genetic factors involved in sexual development disorders and the critical role of cytogenetic evaluation in understanding and managing these conditions effectively [16].

Correlation between Karyotype and Hormonal Profiles

The correlation between karyotype and hormonal profiles in individuals with various medical conditions, including disorders of sexual development (DSD), amenorrhea, and infertility, has been the subject of extensive research. Understanding this correlation is crucial for accurate diagnosis, effective treatment, and comprehensive management of affected individuals. Karyotyping provides essential genetic information, while hormonal profiles offer insights into the functional status of the endocrine system. Together, they can elucidate the underlying causes of clinical symptoms and guide therapeutic interventions.

Karyotype and Hormonal Profiles in Disorders of Sexual Development

Disorders of sexual development (DSD) present a complex challenge, where the correlation between karyotype and hormonal profiles is particularly significant. Karyotyping in DSD cases often reveals chromosomal anomalies such as Turner syndrome (45, X), Klinefelter syndrome (47, XXY), and mixed gonadal dysgenesis (45, X/46, XY), among others. These chromosomal configurations are closely associated with specific hormonal profiles. For instance, individuals with Turner syndrome typically exhibit elevated gonadotropin levels due to ovarian dysgenesis, while those with Klinefelter syndrome have increased plasma levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), alongside reduced testosterone levels, reflecting testicular dysfunction [17].

Amenorrhea and Hormonal Imbalances

In cases of amenorrhea, the correlation between karyotype and hormonal profiles aids in distinguishing between various etiologies, such as primary ovarian insufficiency (POI) and polycystic ovary syndrome (PCOS). Chromosomal abnormalities like X chromosome deletions or mosaicism can lead to POI, characterized by amenorrhea, elevated gonadotropins, and low estrogen levels. Conversely, PCOS is often associated with normal karyotypes but is characterized by hormonal imbalances, including hyperandrogenism, insulin resistance, and elevated LH levels.

Infertility and Genetic-Hormonal Interactions

Infertility investigations also benefit from analyzing the correlation between karyotype and hormonal profiles. Chromosomal anomalies, such as Y chromosome microdeletions, can directly impact spermatogenesis and result in altered testosterone levels, FSH, and LH, guiding the diagnosis and management of male infertility [18]. Similarly, in females, karyotype analysis can identify chromosomal causes of infertility, with corresponding hormonal profiles providing insights into ovulatory function and ovarian reserve.

Clinical Implications and Management

Understanding the correlation between karyotype and hormonal profiles has profound clinical implications. It enables personalized medicine approaches, allowing healthcare providers to tailor interventions based on the specific genetic and hormonal underpinnings of each condition. For example, hormone replacement therapy can be optimized based on an individual's hormonal status and assisted reproductive technologies can be employed with consideration of the patient's karyotype and endocrine function.

CONCLUSION

The review has highlighted the critical role of cytogenetic analysis in understanding the etiology of amenorrhea among phenotypically female patients. Through a comprehensive examination of studies conducted across India, it has been established that a diverse range of chromosomal abnormalities significantly contributes to both primary and secondary amenorrhea. The findings underscore the necessity of incorporating cytogenetic evaluation into the diagnostic process for amenorrhea, facilitating accurate diagnosis, effective management, and personalized treatment strategies. Future research should focus on filling the existing gaps in knowledge, particularly in understanding the complex interplay between genetics and reproductive health, to improve outcomes for individuals affected by amenorrhea. The integration of genetic insights into clinical practice is essential for advancing diagnostic approaches and developing targeted therapeutic interventions, ultimately enhancing patient care and reproductive health outcomes.

Limitations

The study is limited by its focus on research conducted primarily in India, which may not fully capture the global landscape of chromosomal abnormalities in amenorrhea. Additionally, the review's reliance on existing literature introduces the possibility of publication bias, potentially overlooking unpublished or inaccessible studies. Furthermore, variations in study methodologies and participant demographics across the included studies may affect the generalizability of the findings. Finally, the review's scope is limited to phenotypically female patients, excluding other populations that may also experience chromosomal abnormalities contributing to amenorrhea.

Recommendations

The study underscores the crucial role of cytogenetic analysis in diagnosing and managing amenorrhea in phenotypically female patients. A comprehensive review of research findings in India, reveals a diverse range of chromosomal abnormalities contributing to both primary and secondary forms of the condition. It advocates for integrating cytogenetic evaluation into the diagnostic process to enable accurate diagnosis, personalized treatment, and improved reproductive health outcomes. Future research should focus on addressing knowledge gaps to enhance understanding and management strategies for affected individuals, emphasizing the importance of genetic insights in clinical practice.

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List of abbreviations

PCOS - Polycystic Ovary Syndrome
POI - Premature Ovarian Insufficiency
FHA - Functional Hypothalamic Amenorrhea
FISH - Fluorescent In Situ Hybridization
aCGH - Array Comparative Genomic Hybridization
DSD - Disorders of Sexual Development
MDS - myelodysplastic syndromes
GnRH - Gonadotropin-Releasing Hormone
MRKH - Mayer-Rokitansky-Küster-Hauser Syndrome
CML - Chronic Myelogenous Leukemia
ALL - Acute Lymphoblastic Leukemia
NHL - Non-Hodgkin Lymphoma
NSCLC - non-small cell lung cancer

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Conflict of interest

The authors have no competing interests to declare.

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