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GENETICS

Family misfortune caused by hereditary bias: a reflection on mitochondrial disease diagnosis in a family

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Abstract

Aim Assisted reproductive technology (ART) is an invaluable strategy for preventing the inheritance of genetic disorders and promoting the birth of healthy children. Nevertheless, the general public's limited understanding of genetics and low awareness of available services obstruct effective utilization of genetic counseling. Our analysis of a family affected by mitochondrial genetic disease aims to improve public understanding of genetic knowledge and the importance of genetic counseling.

Methods We gathered comprehensive data on a family with mitochondrial disease and scrutinized the genetic sequencing and diagnostic procedures used to identify mitochondrial disease within the family.

Results In a case involving a family with two daughters, both began to exhibit symptoms such as abnormal gait, myodystonia, and excessive fatigue at the age of 4. These symptoms were incorrectly assumed to be paternally inherited, as the mother believed the father had a mild intellectual disability. As a result, the family opted for ART, specifically in vitro fertilization (IVF) with donor sperm, without thorough genetic counseling or a conclusive diagnosis for the children. Despite these precautions, the son born from IVF presented with symptoms mirroring his sisters' at the age of 6, including typical MRI abnormal signals in the bilateral basal ganglia. Furthermore, the eldest daughter's naturally conceived child also started to show identical symptoms by the age of 3. Subsequent genetic testing revealed a homoplasmic pathogenic mutation in the MT-ND6 gene (m.14459G>A), confirming that the dystonia was maternally inherited, with the mother exhibiting an 89.2% heteroplasmic variation in the same gene.

Conclusions This case study demonstrates the significant consequences of a lack of genetic knowledge and prevailing misconceptions when applying ART. It underscores the urgent need to bolster genetic literacy and emphasizes the vital importance of informed decision-making within genetic healthcare services.

Keywords Mitochondrial disease · Genetic literacy · Genetic counseling · Assisted reproductive technology

Introduction

Since the landmark achievement of the first successful in vitro fertilization (IVF) birth in 1978, an estimated 0.1% of the global population has been conceived through assisted reproductive technology (ART) [[1]]. The decision to pursue ART is influenced by various factors, with the desire to prevent genetic diseases being a significant consideration. With advancements in prenatal testing, genetic counseling (GC) has become a critical component of the preimplantation genetic testing (PGT) process within ART [[2]]. However, there is a general lack of genetic knowledge among the public, which can impede their access to and utilization of genetic services [[3]]. Adequate GC is particularly critical for families who have experienced the birth of children with

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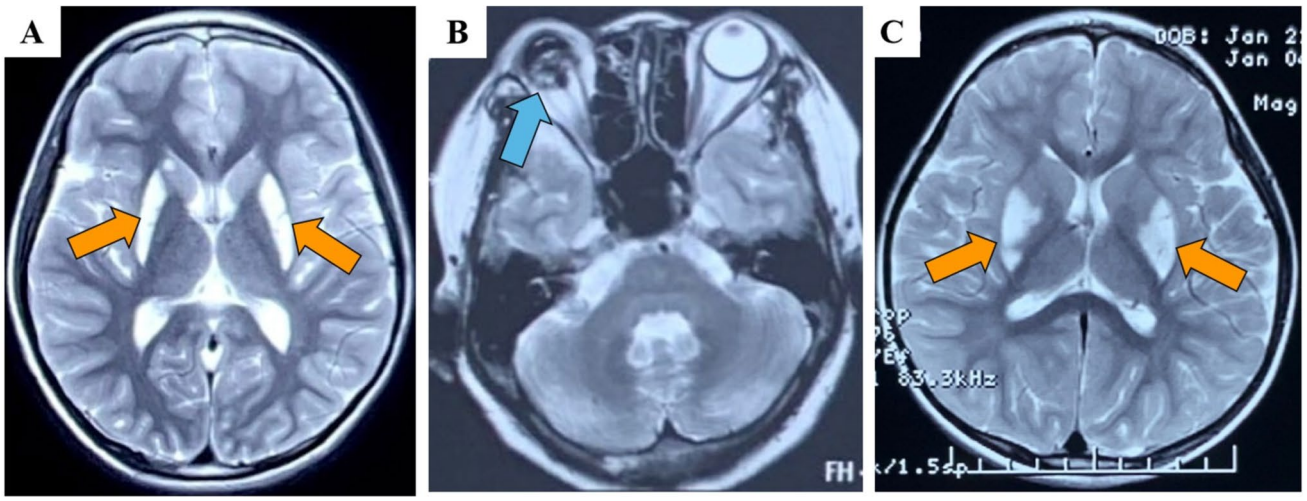
A
B
C
D
I
1
2
Sperm bank
3
II
1
2
3
4
III
1
E
The proband (F_{II-4})
MT-ND6 (m.14459G > A)
The eldest sister (F_{II-2})
MT-ND6 (m.14459G > A)
The mother (F_{I-2})
MT-ND6 (m.14459G > A)
The second sister (F_{II-3})
MT-ND6 (m.14459G > A)
The father (F_{I-1})
Wild-type
The niece (F_{III-1})
MT-ND6 (m.14459G > A)

◂**Fig. 1** **A** Brain MRI of the proband showing abnormally high signals in the bilateral basal ganglia on T2WI (indicated by yellow arrows); **B** Brain MRI of the mother displaying an abnormality in the right eyeball on T2WI (indicated by a blue arrow); **C** Brain MRI of the niece revealing abnormally high signals in the bilateral basal ganglia on T2WI (indicated by yellow arrows); **D** Pedigree genetic map of the family; **E** Genetic testing chromatogram: the proband carried a 100% homoplasmic variant of MT-ND6 (m.14459G > A). The mother exhibited an 89.2% heteroplasmic variant of MT-ND6 (m.14459G > A). The father displayed the wild type. The proband's two sisters and niece also carried a 100% homoplasmic variant of MT-ND6 (m.14459G > A)

genetic disorders; without it, the outcomes can be disheartening when using ART.

We present a family where two girls successively inherited the same disease, mistakenly believed to be inherited from the father because the mother perceived him to have mild intellectual disability. She decided to pursue ART, choosing IVF with donor sperm in the hopes of having a healthy child. Unfortunately, she skipped adequate GC or a definitive genetic diagnosis for the children before the procedure. This led to the birth of a third child, a son, who also inherited the same condition as his sisters. Compounding the situation, the eldest daughter later naturally conceived a child who also inherited the condition. Subsequent genetic testing revealed that the family's health issues were due to a mitochondrial disease passed down maternally. The mother's limited knowledge of genetics contributed to a situation where her children and her grandchild inherited a mitochondrial disease. This has understandably led to emotional and financial challenges for the family. It underscores the importance of accessible genetic education and counseling to help individuals make informed decisions about family planning and healthcare.

Methods

Pedigree data collection

Detailed information regarding clinical manifestations, imaging findings, laboratory test results, family history, and pedigree analysis was meticulously recorded.

Mitochondrial DNA sequencing and genetic data analysis

After obtaining written informed consent from the family, peripheral blood samples were collected from the child, his parents, two sisters, and the niece, totaling six individuals (F_{I-1}, F_{I-2}, F_{II-2}, F_{II-3}, F_{II-4}, F_{III-1}). Mitochondrial DNA (mtDNA) was analyzed in the patient and his mother, while Sanger sequencing was performed to verify the results for the father, sisters, and niece.

Pathogenic variant databases (ClinVar, HGMD, DECIPHER, ISCA, NCBI) and normal population databases (gnomAD, ExAC Browser, OMIM) were employed for comprehensive variant analysis and interpretation. Functional prediction software, including Polyphen-2, VEP, SIFT, REVEL, and Mutation Taster, was employed to predict variant function. The pathogenicity of genetic variants was assessed and analyzed based on the classification criteria and guidelines set forth by the American College of Medical Genetics (ACMG).

Results

A 10-year-old boy, a G3P3, was delivered via cesarean section at 37 weeks of gestation without any perinatal complications. Initially, his psychomotor development followed a normal trajectory until the age of 6, when he began to exhibit an abnormal walking posture characterized by myodystonia and easy fatigue. Upon referral to a local hospital, a brain MRI revealed abnormal signals in the bilateral basal ganglia (Fig. 1A). Despite conducting a dystonia gene panel test, no pathogenic variations were identified, and his symptoms progressively worsened. Consequently, the patient was referred to our hospital for further diagnosis and treatment.

Considering the family history, it was noted that the father was in good health but had a borderline intelligence. On the other hand, the mother had congenital abnormalities of the right eyeball and utilized a prosthetic eye (Fig. 1B). The boy has two sisters, aged 20 and 28, respectively, who have also experienced an abnormal walking posture characterized by myodystonia and easy fatigue since the age of 4. Unfortunately, they have not received a formal diagnosis or treatment, and their symptoms have progressively worsened. While the parents were aware of their daughters' genetic disorder, the mother mistakenly assumed that the condition was paternally inherited due to the father's borderline intelligence. Consequently, she was determined to have a healthy child and pursued ART, but skipped GC and genetic testing for both children before the procedure. Through IVF using sperm from a sperm bank, she gave birth to a boy, who is the proband.

Analysis of the pedigree genetic map strongly suggests that the proband and his two sisters inherited their condition from their mother. Based on the clinical manifestations and imaging studies, mitochondrial disease was considered. Subsequent mitochondrial genetic test confirmed that the proband and his two sisters carried a homoplasmic variant of MT-ND6 (m.14459G > A), suggesting pathogenic variant in line with ACMG guidelines. These were inherited from

their mother, who exhibited an 89.2% heteroplasmic variant of MT-ND6 (m.14459G > A). However, the father displayed the wild type. Tragically, the misfortunes did not end there. The eldest sister gave birth to a girl 3 years ago, who began exhibiting abnormal walking posture and dystonia symptoms at the age of 3. Brain MRI also revealed abnormal signals in the bilateral basal ganglia (Fig. 1C), and subsequent Sanger sequencing validation confirmed a homoplasmic variant in MT-ND6 (m.14459G > A) (Fig. 1E). The pedigree is summarized in Fig. 1D.

Discussion

The subject of this report is a mitochondrial disorder linked to a pathogenic mutation in the MT-ND6 gene (m.14459G > A). The initial family carrying the m.14459G > A mutation was described in 1994, spanning four generations of Hispanic descent with a diverse clinical spectrum that includes asymptomatic individuals, those with dystonia, Leber's hereditary optic neuropathy (LHON), or a combination of LHON and dystonia[[4]]. This mutation has since been identified in multiple families and sporadic cases, revealing that the variability in clinical presentation does not correlate directly with either heteroplasmic or homoplasmic states of the mutation[[5–7]]. Additionally, the m.14459G > A mutation is associated with Leigh syndrome, which is characterized by an earlier onset and more severe symptoms compared to those with dystonia alone[[8,9]]. The proband, along with his sisters and niece, was diagnosed with mitochondrial genetic-associated dystonia based on their symptoms. Initially, when the proband sought medical help, a dystonia gene testing panel was conducted. Unfortunately, this panel did not include mitochondrial genes, leading to a missed opportunity for an accurate and timely diagnosis. In relation to the mother, there were no indications of dystonia or vision impairment. Furthermore, upon reviewing the images, despite her congenital abnormalities of the right eyeball and use of a prosthetic eye, there was no evidence of optic nerve atrophy in another eye or basal ganglia lesions. Diagnoses such as Dystonia, LHON, and Leigh syndrome were not confirmed in her case. It remains unclear if the congenital eye abnormality is associated with the m.14459G > A mutation. Nonetheless, she did exhibit an 89.2% heteroplasmic variant of m.14459G > A, hinting at a potential correlation between the two.

The family in question has encountered difficulties stemming from a limited understanding of genetics and unintentional misconceptions about heredity. The lack of comprehensive genetic counseling (GC) and genetic testing prior to assisted reproductive technology (ART) has had significant repercussions. The American Society for Reproductive Medicine (ASRM) indeed advocates for a thorough assessment before embarking on any ART treatment, including physical examinations and laboratory tests[[10]]. This assessment should encompass a meticulous examination of the individual's and family's genetic history and review any existing genetic test results that might influence the ART process. It is also crucial for patients to be informed about the potential need for additional genetic testing prior to beginning ART procedures.

Studies have consistently shown that a gap in genetic literacy is common among adults, with a general lack of understanding about genetics in the broader public[[11]]. An inadequate grasp of genetics and medical genetics can limit people's access to and pursuit of genetic services. Even in advanced nations such as the USA, Canada, and Japan, awareness of GC is relatively low, with only 20–30% of the population having familiarity with the concept. The lack of widespread knowledge about GC means that many who could benefit from these services might not be informed or motivated to seek them out[[3]]. This challenge can be linked to shortcomings in formal education, insufficient coverage of genetic topics in media and online resources, and a need for more proactive engagement from healthcare providers in educating their patients.

Mitochondrial diseases are among the most prevalent and severe genetic disorders, affecting approximately 1 in 5000 individuals [[12]]. About 15–25% of cases are caused by mutations in mtDNA [[13]]. Two important characteristics of mtDNA mutations that play a significant role in understanding the complexity of mtDNA disease transmission are mitochondrial heteroplasmy and the genetic bottleneck. The majority of pathogenic mtDNA mutations that lead to severe diseases are heteroplasmic, meaning there is a mixture of mutant and wild-type mtDNA within a cell, tissue, or individual. The level of heteroplasmy can vary both between and within tissues of an individual carrying the mutations. Symptoms only manifest when the proportion of mutant mtDNA exceeds a certain threshold, known as the threshold effect. The severity of the disease in patients with heterogeneous mtDNA mutations is often associated with the mutation load [[14]]. Carriers of these mutations may exhibit clinical symptoms and potentially develop severe maternally inherited mitochondrial diseases that can be debilitating and fatal. Therefore, natural fertility is generally not recommended for carriers of such mutations. Preimplantation genetic testing (PGT) can identify eggs or embryos with a low mutation load, offering a potential solution for mtDNA mutation carriers to have healthy offspring. A single human oocyte contains approximately 100,000 mtDNA molecules. During oocyte maturation, most of the mtDNA is lost, and only a small fraction (ranging from 5 to 200 molecules) is randomly selected to be passed on to the offspring. This reduction in mtDNA quantity during egg cell formation is known as the "genetic bottleneck" effect. According to this principle, individuals carrying

disease-causing mtDNA mutations are likely to produce eggs with minimal or no mtDNA mutations, increasing the likelihood of having healthy offspring through PGT. Additionally, donor oocyte IVF-embryo transfer (ET) stands as a secure method to prevent the transmission of mitochondrial DNA (mtDNA) diseases to offspring. Mitochondrial replacement therapy (MRT) has also emerged as a novel technique to prevent the passage of both heteroplasmic and homoplasmic mtDNA mutations[[14]]. However, MRT is a relatively new procedure and, as of now, is primarily available in the UK to women who are unlikely to see benefits from PGT. This includes individuals who carry a pathogenic mutation at homoplasmic levels or with very high levels of heteroplasmy. In the case of the family discussed, the mother carries a pathogenic mutation with high levels of heteroplasmy, and all three children have homoplasmic mutations. Therefore, for this family wishing to have a healthy child, we would recommend considering the option of donor oocyte in vitro fertilization-embryo transfer (IVF-ET).

So, it is indeed possible for individuals with maternally inherited mitochondrial diseases to have healthy children. However, a lack of awareness about genetics and inherent biases in understanding heredity can have serious consequences for families. There is a pressing need to expand genetic education to the general public through accessible channels such as the Internet and media. This effort is essential to improve the overall understanding and awareness of genetic inheritance.

As genetic testing technology has improved, the cost of these tests has significantly decreased. Despite this, in our country, the financial burden of genetic testing still falls on individuals. This cost can be prohibitive for many families, causing some to skip genetic testing altogether. To address this issue, we suggest that the state should consider subsidizing genetic testing and counseling, particularly when there is a suspicion of genetic disorders. Such a policy would help to reduce the financial stress on families and increase access to these important healthcare services.

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Author contributions L-Y H and Y M conceptualized and designed the study and critically drafted and reviewed the manuscript. Y M, L W, X–Y Y, F H, M–N Z, W H, and X–Y S collected data and drafted and revised the manuscript. G Y and L-P Z coordinated and supervised data collection, carried out the initial analyses, and reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Data availability The original contributions generated for the study are included in the article; further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate. This study was performed in accordance with the Declaration of Helsinki; the written informed consent was obtained from the patients for publication of information related to the patient's medical condition in the manuscript. The study was exempt from ethics board approval by the Medical Ethics Committee of the Chinese PLA General Hospital.

Competing interests. The authors declare no competing interests.

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