

Review Article

Polycystic ovary syndrome in mitochondrial disorders due mtDNA or nDNA variants

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Abstract: Objectives: Whether polycystic ovary syndrome (PCOS) is associated with mtDNA or nDNA mutations causing mitochondrial disorders (MIDs) or not is under debate. This review aims at summarising and discussing previous and recent findings concerning the frequency, diagnosis, and treatment of PCOS in MIDs. Methods: Systematic literature review using appropriate search terms. Results: Currently, no reports are available which document a causal relation between PCOS and specific or non-specific MIDs. However, reports about the presence of various mtDNA point mutations, mtDNA deletions, and mtDNA depletion in females with PCOS have been published by a single Chinese group, without being confirmed by other study groups. Arguments against a causal relation between these mtDNA variants and PCOS are that all variants were homoplasmic and that none of the patients carrying any of these variants presented with a phenotype characterised by features other than PCOS or diabetes. Conclusions: Currently, there is no evidence that PCOS is a phenotypic feature of MIDs. mtDNA variants reported by a single centre in association with PCOS need to be confirmed by multicentre studies. In case of hereditary PCOS, whole exome (genome) sequencing is recommended.

Keywords: Polycystic ovary syndrome, mitochondrial, mitochondrion, mtDNA, mutation, phenotype, genotype

Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in females, and it is the main cause of infertility in women of reproductive age [1]. PCOS is characterised by chronic anovulation, hyperandrogenism, and polycystic ovaries [2]. Females with a PCOS carry an increased risk to develop cardiovascular disease or diabetes [1]. Etiology and pathogenesis are unclear but hereditary, environmental, and embryonic factors have been identified as possible causative factors [1]. Genetic disorders associated with PCOS are manifold but one group in which this abnormality is pretended to occur with an increased prevalence are the mitochondrial disorders (MIDs) [3]. MIDs are genetically and phenotypically heterogeneous disorders due to mutations in genes located in either the mitochondrial DNA (mtDNA) or the nuclear DNA (nDNA). Proteins, tRNA, or rRNAs encoded by these genes are involved in the metabolism, maintenance, or signalling of mito-

chondria. This review aims at summarising and discussing previous and recent findings concerning the frequency, diagnosis, and treatment of PCOS in MIDs.

Materials and methods

Data for this systematic review were identified by searches of MEDLINE for references of relevant articles. Search terms used were all acronyms known for specific MIDs (n=50) and the terms “mitochondrial disorder”, “mtDNA”, “encephalomyopathy” and “mitochondrion” in individual combination with the terms “ovarian”, “ovarial”, “PCOS”, and “cysts”. Results of the searches were screened for potentially relevant studies by application of inclusion and exclusion criteria for the full texts of relevant studies. Included were only original articles about humans, published between 1966 and 2017. Only randomised controlled trials (RCTs), observational studies with controls, case series, and case reports were considered. Reviews, editori-

als, and letters were excluded. Additionally, reference lists of retrieved studies were checked for reports of studies not detected on the electronic search. Websites checked for additional information with regard to spinal cord involvement in MIDs were MITOMAP (<https://www.mitomap.org/foswiki/bin/view/MITOMAP/ClinicalPhenotypesRNA>), Neuromuscular Disease Center Database (<http://neuromuscular.wu-stl.edu/mitosyn.html#merrf>), and MitoTools (<http://www.mitotool.org/database.html>).

Results

When searching for the combinations “polycystic ovary syndrome” and any of the 50 acronyms tagging specific MIDs, no hit could be achieved, suggesting that PCOS is not a frequent phenotypic feature of specific MIDs. When searching for the terms “polycystic ovary syndrome” and “mtDNA”, “mitochondrial”, “mitochondrion”, or “leucoencephalopathy” respectively, no suitable paper could be identified either. On the other hand, carriers of the PGC-1 α rs8192678 “Ser” allele carried an increased risk to develop PCOS in a case control study of 108 PCOS females [4]. In a study of 80 Chinese females with PCOS, PCOS with insulin resistance was attributed to the presence of the mtDNA variants m.3302A>G or m.3275C>A in the mt-tRNA^{Leu(UUR)} gene, to the variants m.4363T>C or m.4395T>C in the mt-tRNA^{Gln} gene, to the variant m.7492C>T in the mt-tRNA^{Ser(UCN)} gene, to the variant m.7543A>G in the mt-tRNA^{Asp} gene, to the variant m.8343A>G in the mt-tRNA^{Lys} gene, to the variant m.10454T>C in the mt-tRNA^{Arg} gene, and to the variant m.14693A>G in the mt-tRNA^{Glu} gene [5]. In a study of 57 females with PCOS, 23.5% carried a homoplasmic 9pb deletion of the mtDNA [3]. Interestingly, also 2 healthy controls carried this deletion. Investigating the same number of females, the same authors found six variants in the tRNA(Gln), tRNA(Cys), tRNA(Asp), tRNA(Lys), tRNA(Arg), and tRNA(Glu) genes respectively [6]. In a study of eight females with PCOS and insulin resistance, mitochondrial mass and rate of ATP synthesis with and without the use of ATP did not differ between PCOS patients and controls [7]. The study suggested that there is no evidence for primary impaired mitochondrial function or content in myotubes of patients with PCOS [7]. Reduced expression of oxidative genes in PCOS patients was regarded

as an adaptive trait [7]. In a study on the question if BCL2-associated X protein (BAX) and B-cell leukase (BCL2) expression in cumulus cells affect the competency of in-vitro mature oocytes, it turned out that BAX’ and BCL2 expression are strongly associated with the ability of oocytes to complete nuclear maturation and to be fertilized [8]. When comparing gene expression in PCOS patients (n=16) with healthy controls it turned out that OXPHOS-related genes were downregulated in PCOS patients, manifesting as reduced levels of PGC-1 α [9]. It was concluded that there is an early association between insulin-resistance and impaired mitochondrial oxidative metabolism in PCOS patients mediated by reduced PGC-1 α [9].

Discussion

An argument against a causal relation between MIDs and PCOS is that PCOS has not been reported in a patient with a specific or non-specific MID so far. Arguments against the mtDNA variants repeatedly reported by the group of Ding and Zhuo [2-4] are that the variants were all homoplasmic, that mutation carriers did not manifest with abnormalities other than PCOS or diabetes, and that these variants had been reported in association with MIDs but not with PCOS so far. Arguments against mtDNA depletion as the cause of PCOS, as reported by Ding et al. [10] are that mtDNA depletion syndromes are usually associated with severe clinical manifestations, which often lead to premature death, and that the reported patient only manifested with PCOS and diabetes. Arguments against the findings in Zhuo’s study from 2010 [3] are that single mtDNA deletions are usually associated with specific clinical manifestations, such as Kearns-Sayre syndrome, Pearson syndrome, or CPEO, and that the mutation was homoplasmic. A further argument against the 9bp deletion to be causative is that it also occurred in healthy controls [3]. Another argument against a causal relationship between PCOS and mitochondrial dysfunction is that mitochondrial functions in the skeletal muscle are not impaired in these patients [11].

An argument in favour of a causal relation between PCOS and MIDs is that in a study of 50 females with PCOS the mtDNA copy number in blood lymphocytes was significantly reduced

compared to healthy females [12]. The reduced mtDNA copy number was independent of the presence or absence of insulin resistance [12]. Absence of PCOS in any specific or non-specific MID not necessarily excludes that PCOS is truly absent in MIDs. This is because MIDs are usually not prospectively investigated for PCOS. An argument in favour for the occurrence of PCOS in MIDs is that MIDs are frequently associated with endocrine abnormalities [13]. However, to finally answer the question about the causality, MIDs must be prospectively investigated for PCOS irrespective if there is amenorrhoea, infertility, or diabetes in these patients. Finally, there are some indications that PCOS is rather an autoimmune disease than a genetic disease [14]. In a study of 113 consecutive patients with PCOS, autoimmune thyroiditis was found in 27% of these patients [14].

In conclusion, this review shows that PCOS is not present in specific or nonspecific MIDs and that the association between PCOS and various mtDNA variants is not a strong argument for causality, since most of these variants were homoplasmic and since none of the so far reported patients developed a phenotype compatible with a MID.

Disclosure of conflict of interest

None.

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