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Mitochondrial DNA Depletion Syndrome 1 (MTDPS1)—A Novel Cause of Premature Ovarian Insufficiency

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ABSTRACT

Mitochondrial DNA depletion syndrome 1 (MTDPS1) is a rare autosomal recessive disorder caused by mutations in the *TYMP* gene, leading to mitochondrial failure. Hallmark features include gastrointestinal dysmotility, cachexia, peripheral neuropathy, ocular signs, hearing loss, and leukoencephalopathy. We present a 39-year-old woman with premature ovarian insufficiency (POI) as a novel endocrine manifestation of MTDPS1. She had normal pubertal development with menarche at age 10. In her mid-20s, she developed fatigue, nausea, vomiting, abdominal pain, weight loss, and amenorrhoea at age 29. Investigations revealed POI with elevated FSH levels, a normal karyotype, negative autoimmune markers. Imaging showed a thin endometrium, small ovaries, osteoporosis, severe gastroparesis. An incidental renal angiomyolipoma prompted an MRI of the brain, revealing symmetrical abnormal white matter changes, suggestive of leukodystrophy. Given diagnostic uncertainty and a history of consanguinity she was referred to clinical genetics and underwent whole genome sequencing which identified a novel homozygous variant (c.559C > T; p.(Gln 187*)) in the *TYMP* gene, confirming MTDPS1. Though POI is not a well-established feature of MTDPS1, mutations in other genes linked with mitochondrial function are known to be associated with POI and we postulate that this is an endocrine manifestation of MTDPS1. Genetic assessment should be considered in unexplained POI, particularly if associated with other clinical features/consanguinity.

1 | Introduction

Mitochondrial DNA depletion syndrome 1 (MTDPS1) (also known as mitochondrial neurogastrointestinal encephalomyopathy, MNGIE) is a rare autosomal recessive multisystem disorder. It is caused by biallelic pathogenic variants in the gene encoding thymidine phosphorylase (*TYMP*), which results in the accumulation of mitochondrial DNA defects and ultimately mitochondrial failure. MTDPS1 is a progressive degenerative disease whose cardinal features are gastrointestinal dysmotility, cachexia, peripheral neuropathy, ocular signs (ptosis, ophthalmoplegia), sensori-neural hearing loss and leukoencephalopathy (see Figure 1) [1]. Symptom onset is usually in childhood/adolescence and average life expectancy is 35–37 years [2]. Primary hypogonadism is not widely recognized as a manifestation of MTDPS1. We report a case of premature ovarian insufficiency (POI) presenting as an endocrine manifestation of this disorder. A very pronounced insulin resistance was also observed.

2 | Case Presentation

A 39-year-old woman was referred to the endocrine clinic in 2015 to investigate secondary amenorrhoea.

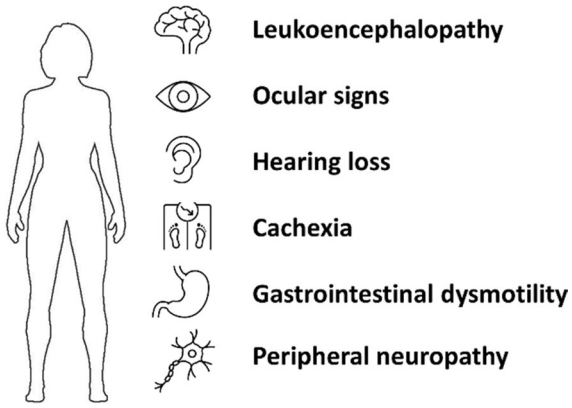

FIGURE 1 | Cardinal symptoms of mitochondrial DNA depletion syndrome 1 (MTDPS1).

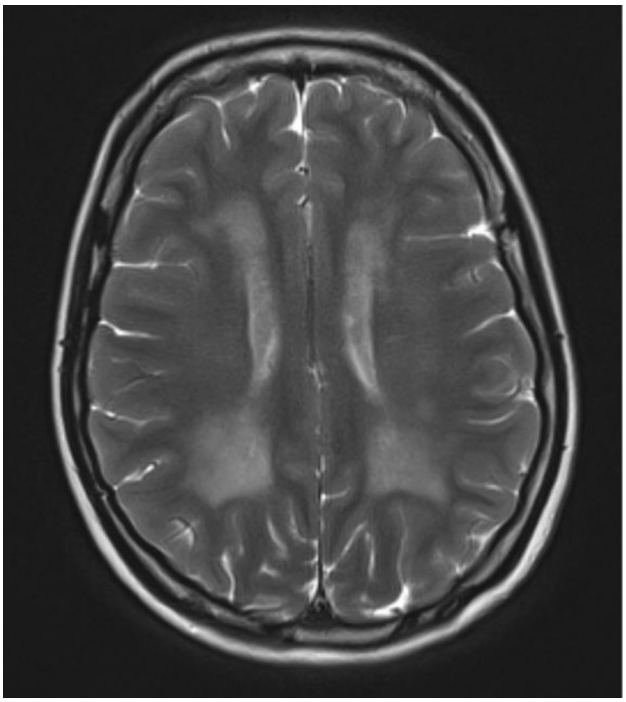

FIGURE 2 | T2-weighted MRI head -symmetrical confluent T2 hyperintensities in the periventricular, deep and subcortical white matter in fronto-parietal regions.

She had a normal childhood and pubertal development and reached menarche aged 10. Her menstrual cycle was originally regular, and up until her mid-20s, she felt entirely well.

However, she then described the onset of an unusual constellation of symptoms, which included marked fatigue and troublesome gastrointestinal symptoms. She developed ongoing issues with nausea, vomiting, abdominal bloating, epigastric pain and borborygmi, that were mainly postprandial. Her abdominal symptoms limited her oral intake, and she had lost weight leading up to her referral—with a weight of 47 kg and a BMI of 17 kg/m^2 when she was first seen in clinic. At around the same time, her periods started to become irregular, and her periods stopped entirely at age 29.

A few years prior to her referral to endocrinology, she had been reviewed in the metabolic medicine clinic with hirsutism and a notable absence of subcutaneous fat in the lower extremities with acanthosis nigricans. Investigations at that time revealed marked insulin resistance with a high serum level of fasting insulin (2085 pmol/L, NR 18–77 pmol/L) and C-peptide (3.76 nmol/L, NR 0.27–1.28 nmol/L). HbA1c was normal (35 mmol/mol, 5.4%), with a normal fasting lipid profile and normal testosterone (1.3 nmol/L, NR 0.5–2.6), androstenedione (2.3 nmol/L, NR 3–8), and DHEAS (0.8 micromol/L). A possible diagnosis of acquired partial lipodystrophy had been made, although the cause was unclear (genetic analysis was negative for archetypical causes [LMNA, PPARG and PLIN1]). Despite her normal HbA1c, pioglitazone was commenced in view of the marked insulin resistance and this resulted in an immediate drop in fasting serum insulin and C-peptide (611 and 1.99 nmol/L, respectively) followed by a normalization after some years (67 and 1.04 nmol/L). The latest insulin and C-peptide values occurred on continued pioglitazone treatment and stable HRT treatment (see later).

She had no other medical problems. She was the oldest child of consanguineous first-cousin parents of Pakistani origin. She had five younger siblings. They were all reported to be well apart from one brother who died at age 21 years, with a history of generalized weakness and failure to thrive throughout childhood.

3 | Diagnostic Assessment

Hormone profile at diagnosis confirmed POI (FSH 81.5 IU, LH 98.4 IU/L and low oestradiol 40 pmol/L). Autoantibody screen was negative (negative thyroid peroxidase, ovarian, adrenal cortex antibodies, and negative coeliac serology). She had a normal karyotype (46XX), with a normal repeat size for FMR1.

An ultrasound pelvis demonstrated a thin endometrium and small ovaries. Bone densitometry (DEXA) scan from 2019 demonstrated osteoporosis, with the lowest T score of −3.0 at the total hip.

Given her marked abdominal symptoms and ongoing weight loss, she was also concurrently reviewed in the gastroenterology clinic. Upper gastrointestinal endoscopy revealed LA grade A oesophagitis only. She had a barium swallow that showed dysmotility in the distal esophagus. Gastric emptying studies showed features in keeping with moderate to severe gastroparesis. Cross-sectional imaging (CT and MRI abdomen/pancreas) revealed no obvious structural findings, other than mild atrophy of the distal pancreatic parenchyma and an incidental 9.9 mm angiomyolipoma of the right kidney. There was no evidence of hepatomegaly or hepatic steatosis.

In light of the renal angiomyolipoma, MRI head was performed to rule out tuberous sclerosis. This incidentally demonstrated symmetrical abnormal diffuse T2/FLAIR hyperintensities in the white matter suggestive of a leukodystrophy (Figure 2).

4 | Treatment

Following the identification of leukodystrophy on the MRI brain scan, a unifying diagnosis for this multi-system disorder remained unclear, but in view of the complex pattern of associated features and the history of consanguinity, an underlying genetic cause was strongly suspected.

She was referred to the clinical genetics team and in light of the diagnostic uncertainty and her continuing weight loss and progression of symptoms underwent singleton whole genome sequencing (parental samples were not available). This identified homozygosity for the c.559C > T; p.(Gln 187*) variant in the thymidine phosphorylase gene (*TYMP*). The variant is predicted to lead to a premature termination codon and loss of protein function, a known mechanism of disease for the *TYMP* gene. This was a novel variant, not previously reported in the literature. The variant was analyzed using the Congenica Decision Support Software platform as part of the Genomic Medicine Service WGS. The Association for Clinical Genomic Science (ACGS) best practice guidelines for variant classification were applied, resulting in a PVS1 at very strong weighting, and PM2 at moderate weighting. Using the ACGS guidelines, these two weighted criteria combined classify the variant as pathogenic and associated with mitochondrial DNA depletion syndrome 1 (MTDPS1).

Currently, there are no approved specific treatments for MTDPS1—management revolves around a multidisciplinary approach to managing specific disease complications. She was referred onwards to a specialist clinic for Rare Mitochondrial disorders, ophthalmology, cardiology and metabolic bone clinics.

5 | Outcome and Follow-Up

There was an 8-year period between her original referral to the endocrine clinic, and her formal diagnosis of MTDPS1, which is a reflection of the rarity of the diagnosis and high index of suspicion required.

With regard to POI, she was commenced on hormone replacement therapy (initially commenced on a continuous combined oral HRT (Kliofem) and then switched to transdermal HRT with oestradiol patch 100 mcg twice a week, and utrogestan 100 mg at night). At her last review in the endocrine clinic she was tolerating HRT well with variable compliance, but at times she was taking this regularly; her serum oestradiol levels were acceptable (270 pmol/L—June 2021). Her repeat bone densitometry scan in April 2022 demonstrated a 1.9% and 6% decline in bone density at the spine and total hip respectively, with no fracture. She was referred to the metabolic bone clinic and is being considered for adjunctive intravenous zolendronate. She remains on pioglitazone, and HbA1c remains normal, with a normal lipid profile and liver function.

On review in the Mitochondrial Disorders clinic, she was found to have mild upper limb weakness throughout with absent reflexes. She had normal vibration sensation. On lower limb examination, she could get up from the chair without using her arms. Her gait was normal and she was able to walk on heels and toes. There was no ataxia. She had very mild weakness of hip flexion on examination. Her lower limb reflexes were absent, and vibration sense was normal. These examination findings were stable for the duration of follow-up.

For optimization of nutrition following gastroenterology investigations, she was commenced on 2–3 Ensure drinks per day to supplement oral intake, and her weight stabilized, with no ongoing weight loss. She had no vomiting over the last 12 months.

She did not have any visual symptoms, but on review in the ophthalmology clinic, she was noted to have a mild ptosis on the left with mild ophthalmoplegia, mainly manifesting in difficulties in upgaze when looking to the left. There was very mild weakness of eyelid closure, and no other facial weakness.

Her ECG and corrected QT interval were normal. An echocardiogram in June 2022 showed normal biventricular sizes and function, with no significant valvular abnormalities.

6 | Discussion

Our patient presented with many of the cardinal symptoms of MTDPS1. POI however, is not previously known to be a feature of this disorder. Although the etiology of most cases of POI is unexplained, between 10%–20% of cases are known to be caused by genetic variants or chromosomal abnormalities, such as Turner syndrome and Fragile X-associated POI, as well as a growing number of monogenic disorders. Of the monogenic disorders associated with POI, variants in over 50 genes have been identified, among which many genes are known to function within mitochondria. These include variants in CLPP, MRPS22, TWNK, POLG, LARS2, HARS2, AARS2, and LRPPRC, which play critical roles in various mitochondrial processes such as DNA replication, gene expression, protein synthesis and protein degradation [3]. Mitochondrial dysfunction plays an intuitive role in POI. Among all cell types, oocytes contain the largest number of mitochondria which play a key role in proper oocyte maturation and fertilization, as well as controlling reactive oxygen species and antioxidant defense mechanisms. Mitochondrial dysfunction may be associated with oxidative stress, which can impair follicular oocyte development, accelerate ovarian aging, and ultimately lead to depletion of the primordial follicular pool and POI [4]. We therefore postulate that the cause of POI in our patient was related to the mitochondrial disorder. To our knowledge, there have only been two other case reports of premature gonadal failure (1 male and 1 female) in this disorder, both in patients of Turkish descent. Kalkan et al. describe a 23-year-old male patient, eventually diagnosed with MTDPS1, who had been investigated from age 17 with episodic vomiting and abdominal pain, cachexia, generalized muscle weakness and mild ophthalmoplegia. He was also noted to have gynaecomastia, loss of pubic hair and small testicular volumes and endocrine investigations demonstrated primary hypogonadism [5]. Gautheron et al. describe a patient with MTDPS1 who had striking similarities to our case. She was born from first-cousin healthy parents and presented with generalized

lipoatrophy, hirsutism in adolescence, severe insulin-resistant diabetes at the age of 18, acanthosis nigricans and premature ovarian failure at age 16. She subsequently developed the classical neurological and gastrointestinal symptoms of MNGIE and died at age 24 [6].

Our case adds further evidence supporting the evolving understanding of the importance of mitochondrial function in oocyte development and ovarian function [7]. Further data from future cases may help establish a clearer genotype–phenotype correlation. This patient's investigations were performed as part of routine clinical diagnostic genomic medicine service and thus no formal functional assessment of the variant was undertaken; however this would be an interesting area of future work.

The case also highlights the importance of considering an underlying genetic cause for an unusual constellation of symptoms, particularly if there is a history of consanguinity, and the value of involving the clinical genetics team and whole genome sequencing in such circumstances.

7 | Learning Points

- Mitochondrial DNA Depletion syndrome 1 is a rare, autosomal recessive disorder; gastrointestinal dysmotility is a hallmark symptom of the disease
- Premature ovarian insufficiency may be an associated feature of the disease.
- Consider the role of whole genome sequencing to aid diagnosis in unusual multisystem presentations, particularly if there is a history of consanguinity.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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