CASE REPORT

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A Novel Mitochondrial DNA Deletion in Patient with Pearson Syndrome

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ABSTRACT

Introduction: Arteriovenous Pearson syndrome is a very rare multisystemic mitochondrial disease characterized by sideroblastic anemia and exocrine pancreatic insufficiency. It is usually fatal in infancy. **Case report:** We reported a four-month-old infant presented with fever and pancytopenia. Bone marrow examination showed hypoplastic changes and sideroblastic features. Molecular Study showed a novel hetroplasmic mitochondrial deletions (m. 10760 -m. 15889+) in multiple genes (ND4,ND5,ND6, CYTB). In our patient the pathogenic mutation was 5.1 kb heteroplasmic deletions in multiple genes that are important and crucial for intact oxidative phosphorylation pathway and ATP production in the mitochondrial DNA. This mutation was not reported in literature including the mitomap.org website (which was last edited on Nov 30, 2017 and accessed on Jan 13, 2018).

Keywords: mitochondrial deletions, mitochondrial disease, Pearson syndrome, exocrine pancreatic insufficiency.

1. INTRODUCTION

Pearson syndrome is a rare fatal disease that presents in infancy, characterized by refractory sideroblastic anemia, exocrine pancreatic insufficiency, hepatic and renal impairment (1). Anemia is the most common and prominent clinical finding in these patients (2). Infants may present with failure to thrive, diarrhea, neurological symptoms and weakness (1).

The syndrome is a subset of mitochondriopathy which occur due to mitochondrial DNA mutations which could result from mtDNA duplication/deletion, depletion and point mutation (2, 3). These mutations usually occur sporadically but rare cases may have germline mutations (4, 5, 6). These mutation affect the respiratory chain in mitochondria which results in defective energy production and development of clinical features (7, 8). The severity of disease depends on the degree of heteroplasmy which is the amount of mutant mtDNA in cells (9). The incidence of Pearson syndrome is uncertain, there is only about 100 cases reported in literature (4). Most of the patients with this syndrome die early in life mainly due to metabolic acidosis (1, 10). Some patients may survive and recover from hematological manifestation to develop clinical manifestation of Kearne-Sayre syndrome (1, 8). Diagnosis of Pearson syndrome is confirmed by genetic analysis of mtDNA (11). Treatment is symptomatic mainly blood transfusion, pancreatic enzymes replacement, G-CSF and erythropoietin (12).

2. CASE REPORT

A 3-month-old male infant presented to Queen Rania Hospital, King Hussein Medical Center, Amman, Jordan with pallor, patient is a product of normal vaginal delivery after smooth full term uneventful pregnancy to healthy no consanguineous parents. He is the first baby in his family with negative family history for genetic and metabolic disorders. No history of admission to neonatal intensive care unit, his birth weight was 3 KG, head circumference 35 cm and length 49 cm. He had normal developmental milestones.

He presented to Pediatric clinic at the age of 3 months with pallor, found to have low Packed Cell Volume (PCV) which was 19%, Hb=6 g/dL, MCV=87 fL, MCH=29 pg, Retic=1%, WBC=15x103/uL, Neutrophils=1000x103/uL, PLT=23x103/ul. On physical examination, our patient found to have hepatomegaly. Bone marrow examination was done to elucidate the underlying cause of anemia. The bone marrow aspirate was hypocellular and showed erythroid precursors exhibited cytoplasmic vacuolization. Perl's stain for iron revealed 20% ring sideroblasts, so Pearson syndrome was suspect-

ed and blood samples for mtDNA study confirmed the suspected diagnosis and showed heteroplasmic mtDNA deletions (m.10760-m.15889+) in multiple genes (ND4, ND5, ND6 and CYTB). The patient was given blood and discharged. After 2 weeks he developed shortness of breath and cyanosis. The patient was ill, hypoactive, tachypnic and dehydrated so he was admitted to pediatric intensive care unit and central venous line was inserted. His weight was 4.4 KG, PCV=21%, WBC=3.8x103/uL, PLT=19x103/uL. Liver enzymes was elevated. O2 saturation was 70%, arterial blood gases performed and revealed metabolic acidosis, low bicarbonate level and low O2 sat. Lactate level was elevated 16.96 mmol/L. Calcium, blood sugar, creatinine, BUN, Na and K were normal.

Patient was given blood, NaHCO3 and IV antibiotics. He slightly improved regarding the respiratory distress, multiple blood, platelets and fresh frozen plasma were transfused. Suddenly patient became bradycardic HR=32 bpm and O2 sat dropped to 30%, CPR done and the patient was intubated. After that his condition got worse, dopamine infusion and adrenaline started. Within a few days he died due to severe lactic academia.

3. DISCUSSION

Mitochondrion is energy producing cytoplasmic organelle found in all body cells except mature red blood cells (2, 13). Its main function is to generate ATP which is the main source of energy to cells through a oxidative phosphorylation process. It's the only cellular organelle that harbor its own DNA molecule which is the mitochondrial DNA (mtDNA) (14). MtDNA is circular double stranded small molecule (16,569 base pairs) that contains 37 genes encoding enzymes involved in oxidative phosphorylation (8, 14). Any mutation in mtDNA will cause a defect in the oxidative phosphorylation pathway (8). Mutations in mtDNA includes deletion/duplication, depletion and point mutation (2, 6). There are some peculiar characteristics in mtDNA that differ from nuclear DNA. First, it is maternally inherited and have many copies reaching thousands of single genome within a single cell (polyploidy) (10, 13). Some of features made this molecule highly exposed to risk of damage and mutations which are 10-17 folds more than nuclear DNA molecule, and due insufficient repair system which cannot get rid of all oxygen radicals molecules (10, 14). Also there is no protective histone in mtDNA (14).

MtDNA mutations classified into two major categories: Firstly; Point mutations which are usually maternally inherited, mostly recessive and heteroplasmic with clinical heterogenity. The other one is through Rearrangement, the most common is deletion which either single deletions which occur sporadically, or multiple deletions which may be inherited (10). Phenotypic expression of mtDNA mutations varies according to many factors including: mitotic segregation, threshold effect, clonal expansion, mtDNA bottleneck (10, 15). The most important factors that determine the phenotype of mtDNA mutations are amount and tissue distribution of mutant mtDNA rather than the size and location of the mutation (10).

There are many clinical syndromes result from mtDNA mutations which can be classified according to the age of presentation into: early onset (infancy/childhood) like Pearson syndrome and Kearns-Sayre syndrome, and late onset (late childhood or adulthood) like chronic progressive external ophthalmoplasia (8, 10).

Pearson syndrome (PS) was firstly described in 1979 by a pediatric oncologist Howard Pearson in infants with sideroblastic anemia (4). It is a rare multisystemic fatal disease that present in early infancy with anemia, neutropenia, thrombocytopenia, pancreatic insufficiency, hepatic, renal, neurological and endocrine failure (1, 15, 16). Sideroblastic anemia is the main finding that present in all patients with PS (15, 16). Sideroblastic anemia is a congenital or acquired anemia with presence of bone marrow ring sideroblasts which are erythroblasts with five or more siderotic granules encirculating at least one third of nuclear circumference of erythroid precursor cells (6, 17). Other chief finding in PS is striking vacuolization of hematopoietic precursors which was the clue for PS suspicion (1, 9, 16). The most frequent non hematological manifestation is low birth weight presenting in 63% of neonates with PS. Exocrine pancreatic dysfunction presents in 12.7% of patients at presentation, which increases with time reaching up to 18% at the age of 4 years. Less than 20% of patients presented with other symptoms rather than hematological and gastrointestinal symptoms (16). Renal problems is also a common finding in PS which result from proximal tubulopathy or decreased glomerular filtration rate (1, 16).

The diagnosis of PS syndrome is made in suspicious cases through intergrating biochemical results, histological findings and mtDNA analysis (8). For our patient the last test done to confirm the diagnosis was mtDNA analysis which was done using multiplex ligation amplification probe (MLPA) method and the was a heteroplasmic deletions (m.10760-_m.15889+) del in multiple genes (ND4, ND5, ND6 and CYTB) in the mitochondrial DNA.

ND4, ND5, ND6 are genes that encode for NADH-ubiquinone oxidoreductase chain 4, 5 and 6 protein respectively (18). The ND4, ND5 and ND6 protein are a subunit of NADH dehydrogenase (ubiquinone), which is located in the mitochondrial inner membrane and is the largest of the five complexes of the electron transport chain. Mutations in the MT-ND4 gene are associated with age-related macular degeneration (AMD), Leber's hereditary optic neuropathy (LHON) and mesial temporal lobe epilepsy (MTLE) (19-22). Mutations in MT-ND5 are associated with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) as well as Leigh's syndrome and Leber's hereditary optic neuropathy (LHON) (23, 24). Mutations in MT-ND6 are associated with Leigh's syndrome, Leber's hereditary optic neuropathy (LHON) and dystonia (25).

Large-scale deletions in mitochondrial DNA are associated with Kearns-Sayre syndrome and progressive external ophthalmoplegia (26) as well as with Pearson's syndrome in addition to adult onset diabetes and deaf-

ness of maternal inheritance (2). Several studies showed the underlying genetic defect of Pearson syndrome, which is the de novo large-scale deletions or in rare cases genetic mitochondrialduplication. Rotig et al reported 21 patients with Pearson syndrome carrying the most common mtDNA deletion which is 4.9 kb deletion. Report from Tunisia (Bemayed et al) reported the common 4.977kb deletion and two novel heteroplasmic deletions (5.030 and 5.234kb) of the mtDNA; these deletions affect several protein-coding and tRNAs genes and might effect the mitochondria structure and function, and impair oxidative phosphorylation and energy metabolism in the respiratory chain. Another report from the Middle East (Arzanian et al); of an infant with severe neurological and hematologic manifestation who showed 8.5 kb mtDNA deletion.

4. CONCLUSION

In our patient the pathogenic mutation was 5.1 kb heteroplasmic deletions in multiple genes that are important and crucial for intact oxidative phosphorylation pathway and ATP production in the mitochondrial DNA. This mutation was not reported in literature including the mitomap.org website (which was last edited on Nov 30, 2017 and accessed on Jan 13, 2018).

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- **Conflict of interest:** none declared.

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