MITOCHONDRIAL DNA DEPLETION SYNDROMES: Two Tunisian Cases

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Background:
Mitochondrial DNA depletion syndromes (MDS) are a heterogeneous group of autosomal recessive disorders with a broad genetic and clinical spectrum that are characterized by a severe reduction in mitochondrial DNA (mtDNA) content in affected tissues and organs. It’s associated with defects in mtDNA maintenance caused by mutations in nuclear genes that function in either mitochondrial deoxyribonucleoside triphosphate synthesis or mtDNA replication. We report two patients: TK2-related myopathic MDS and SUCLG1-related encephalomyopathic MDS.

Case 1: A 30 months-old girl, born from consanguineous parents, the mother died 10 days after delivery, was seen for increasing hypotonia since the age of 18 months with difficulty walking, motor regression and muscle weakness. CPK: 211 UI/l, LDH: 1103 UI/l, ALAT: 29 UI/l, ASAT: 23 UI/l EMG showed myogenic impairment, Echocardiography without abnormalities and Muscle biopsy showed muscle lipidosis. We underwent a Muscular Dystrophy Molecular Panel in the following genes (ANOS, DYSF, GAA, SGCB, SGCD) and finally a CentoXome Solo (including NGS-based CNV analysis) that identified a homozygous pathogenic variant in the TK2 gene c.3G>A p.(Met1?), associated with autosomal recessive mitochondrial DNA depletion syndrome 2 (Myopathic type).

Case 2: A newborn from consanguineous parents, developed at H12 neurological distress and hyperlactacidemia (19.8 mmol/l), without hypoglycemia, hyperammonemia or ketonuria. The outcome showed recurrent metabolic acidosis with hyperlactacidemia, deep anemia and infections, and on neurological exam, extra pyramidal syndrome, spasticity, polycinetic reflex and neurological cry. Brain MRI showed an intense lactate signal on spectroscopy. Urine organic acids tests detected lactates (54%), high 2-cetoglutarate and methylmalonic acid (4%) and small amount of methylcitric acid. Echocardiography was normal. CentoXome Solo (Including NGS-based CNV analysis) identified a homozygous pathogenic variant in the SUCLG1 gene, c.41T>C p.(Met14Thr). The genetic diagnosis of autosomal recessive mitochondrial DNA depletion syndrome type 9 was confirmed.

Conclusions:
MDS are genetically and clinically heterogeneous group characterized by a severe reduction in mtDNA content in affected tissues. MDS in our patients are due to a defect in mtDNA maintenance caused by mutations in nuclear genes which function in either mitochondrial dNTP synthesis. With the high consanguinity in Tunisia, these kinds of diseases are relatively frequent. Genetic analysis will speed up the diagnosis. Despite that in most case there is no curative therapy; dNTP supplementation could help TK2-Related Myopathic MDS.