Adult mitochondrial DNA depletion syndrome with mild manifestations

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Abstract

Mitochondrial DNA depletion syndrome (MDS) is usually a severe disorder of infancy or childhood, due to a reduced copy number of mtDNA molecules. MDS with only mild, non-specific clinical manifestations and onset in adulthood has not been reported. A 47-year-old Caucasian female, height 158 cm, weight 60 kg, who developed day-time sleepiness, exercise intolerance, and myalgias in the lower-limb muscles since age 46y. She slept 9-10 hours during the night and 2 hours after lunch daily. Her individual history was noteworthy for a number of previous disorders. In 3/96 an ovarian endometriotic cyst, a follicular ovarian cyst, and a hydatid cyst of the left Fallopian tube were resectioned and an adhesiolysis carried out. In 10/96 she experienced a gastro-intestinal haemorrhage time-linked to menstruation. Endomietrosis was suspected. Since 1997 she was diagnosed with migraine with up to 3-4 non-triggered attacks per month. In 2/99 she experienced a second gastro-intestinal haemorrhage, this time requiring 6 blood transfusions. Colonoscopy did not detect any source of bleeding. In 5/02 a periapicotic abscess developed and was adequately treated. In 3/03 erythema nodosa of the lower legs occurred, preceded by diarrhoea. Upon histological examination of the colonic mucosa, Crohn’s disease was diagnosed and a therapy with steroids (initially aprednisolone, since 10/03 budesonide) and mesalazine initiated, resulting in remission of the enteritis. In 10/06 a chronic anal fistula was diagnosed requiring surgical intervention. In 12/08 budesonide was discontinued. Since 08 she was taking the pill for endometriosis. Cerebral MRI in 5/09, carried out for work-up of headache, was normal. MRI of the cervical and lumbar spine, carried out for dorsal pain, revealed only slight degenerative abnormalities.

The family history was noteworthy for thyroid cancer (grandmother from the mother’s side, sister), gastric cancer (second sister), clinically multysystem mitochondrial disorder (2 sisters, niece, aunt (sister of mother, mother), Hashimoto thyroiditis, recurrent synkopes, restless-leg syndrome, tinnitus, endomietrosis, easy fatigability), and sudden cardiac death (mother). Upon a family screening in 4/10 for thyroid carcinoma she, her sister, and her niece were found positive for the rearranged NCP (n, 112-351 U/g NCP). Southern blot and PCR were negative but real-time NCP (n, 15.8-42.81 U/g NCP), succinate/ 

Case Report

The patient is a 47-year-old Caucasian female, height 158 cm, weight 60 kg, who developed day-time sleepiness, exercise intolerance, and myalgias in the lower-limb muscles since age 46y. She slept 9-10 hours during the night and 2 hours after lunch daily. Her individual history was noteworthy for a number of previous disorders. In 3/96 an ovarian endometriotic cyst, a follicular ovarian cyst, and a hydatid cyst of the left Fallopian tube were resectioned and an adhesiolysis carried out. In 10/96 she experienced a gastro-intestinal haemorrhage time-linked to menstruation. Endomietrosis was suspected. Since 1997 she was diagnosed with migraine with up to 3-4 non-triggered attacks per month. In 2/99 she experienced a second gastro-intestinal haemorrhage, this time requiring 6 blood transfusions. Colonoscopy did not detect any source of bleeding. In 5/02 a periapicotic abscess developed and was adequately treated. In 3/03 erythema nodosa of the lower legs occurred, preceded by diarrhoea. Upon histological examination of the colonic mucosa, Crohn’s disease was diagnosed and a therapy with steroids (initially aprednisolone, since 10/03 budesonide) and mesalazine initiated, resulting in remission of the enteritis. In 10/06 a chronic anal fistula was diagnosed requiring surgical intervention. In 12/08 budesonide was discontinued. Since 08 she was taking the pill for endometriosis. Cerebral MRI in 5/09, carried out for work-up of headache, was normal. MRI of the cervical and lumbar spine, carried out for dorsal pain, revealed only slight degenerative abnormalities.

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Deletion of mtDNA results from a replication defect, which may be caused by mutations in at least nine different nDNA-located genes. MDS with only mild clinical manifestations and onset in adulthood has not been reported.

Introduction

Mitochondrial DNA depletion syndrome (MDS) is usually a severe disorder of infancy or childhood due to a reduced copy number of mtDNA molecules within a mitochondrion. Depletion of mtDNA results from a replication defect, which may be caused by mutations in at least nine different nDNA-located genes. MDS with only mild clinical manifestations and onset in adulthood has not been reported.
Discussion

MDSs are characterised by severe reduction of the mtDNA copy number. Residual mtDNA copy levels may be as low as 1-2% of that of normal. In up to 50% of the cases, mtDNA depletion may be caused by mutations in at least nine different genes (POLG1, PEO1, RRM2B, SUCLA2, TK2, TYMP). Among these, mtDNA depletion is most commonly caused by mutations in the POLG1 gene, encoding the catalytic subunit of DNA polymerase-gamma, the only polymerase to replicate mtDNA. In the majority of the cases with MDS, however, the underlying genetic defect remains undetected. The phenotypic expression of mutations in these 9 genes is quite variable. Usually, infants or children are affected and the cerebrum, the liver, or the skeletal muscles are predominantly affected, alone or in combination (myopathic, encephalomyopathic, or hepato-cerebral MDS). Patients with POLG1 mutations manifest as non-syndromic hepato-cerebral depletion syndrome, Alpers-Buttgenlocher syndrome (AHS), infantile onset spinocerebellar ataxia (IOSCA), non-syndromic encephalomyopathic depletion syndrome, or Leigh-syndrome. Whether the MDS in the presented patient was due to long-term treatment with infliximab remains speculative but previous studies have shown that infliximab at least induces apoptosis of monocytes. An argument against the presence of a MDS in the presented case is that the family history suggests a maternal trait of inheritance whereas all other MDS so far reported follow an autosomal recessive trait.

Contrary to previous descriptions, the phenotype in the presented patient was mild. Why mtDNA depletion in the presented patient resulted in only minor abnormalities, remains speculative but could be explained by the low rate of depleted mtDNA in tissues other than the muscle or by a mutation in a gene so far not reported in association with MDS. Probably, mtDNA depletion was absent or only mild in tissues other than the muscle. Possibly, the mild phenotype at onset will turn into a more severe presentation during the disease course, but given the stable presentation during the first year after onset and the benign course in other family members, such a scenario is rather unlikely. Assuming, that any of the nine genes so far associated with MDS was mutated in the presented patient, the ones most likely involved are the TK2, SUCLA2, RRM2B, SUCLA1, POLG, or TYMP genes since they have been found most frequently associated with myopathy. Among these, mutations in TYMP were found in adult patients with MNGIE. Also twinkle mutations were associated with adult-onset MDS. Exercise intolerance has been reported as a phenotypic feature of DGUOK mutations and migraine or migraine-like headache as a feature of PEO1 mutations. Hyperpronia or other sleep disorders and myalgias have not been reported in association with MDS. It must be admitted, however, that the phenotype of the presented patient fitted to none of those previously described in MDS. However, muscle biopsy was taken from the sternocleidomastoid muscle and though it showed some changes, myopathological alterations may vary considerably between muscles.

Whether the C-cell carcinoma was causally related to the MDS remains speculative, but preliminary observations in our cohort of patients with mitochondrial disorders suggest that the prevalence of malignancies is increased among these patients. It remains also unclear if endometriosis was causally related to the mitochondrial disorder. Arguments for a causal relation are that mtDNA polymorphisms were made responsible for the development of endometriosis and that mitochondrial biomarkers are increased in eutopic endometriosis. It remains also unclear, if Crohn’s disease was causally related to the MDS. Since some of the mitochondrial disorders go along with non-specific colitis, it is possible that the gastrointestinal problem was actually a manifestation of the MDS, but missing reports about an association between MDS and enteritis and unequivocal histological abnormalities argue against such an assumption.

Conclusions

In conclusion, MDS may start in adulthood, may be associated with a mild phenotype, and may not significantly progress during the first year after onset. In an adult patient with severe tiredness, exercise intolerance, hyperpronia, and a family history positive for mitochondrial disorder, MDS should be considered. Endometriosis, colitis, or malignancy may be a phenotypic feature of a mitochondrial disorder.

References

3. Spinazzola A. Mitochondrial DNA muta-