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CASE REPORT

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Connective tissue involvement in an m.10191 T > C carrier with Leigh-like syndrome

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Abstract

Background Connective tissue involvement in a mitochondrial disorder has been only rarely reported.

Case presentation A 32-year-old female with Leigh-like syndrome extending into adulthood due to the mtDNA variant m.10191 T > C developed various connective tissue abnormalities, which manifested as hyperlaxity of joints, decreased clivo-axial angle, subluxations of various joints, scoliosis, hyperextensibility of skin (stretchy skin), easy tearing, papyraceous scarring, frequent petechiae, very easy bruising, impaired wound healing, blood pooling in feet, and tiny veins. She received symptomatic treatment and physiotherapy, which provided some sort of relief.

Conclusions The phenotypic spectrum of the m.10191 T > C variant is broader than previously anticipated.

Keywords mtDNA, Multisystem, Respiratory chain, Movement disorders, Amantadine

Background

Mitochondrial disorders (MIDs) are clinically characterized by multisystem involvement (Yang et al. 2022). Multisystem involvement may be present already at onset or may develop during the disease course (Finsterer 2021). Most commonly affected are the brain, muscle, peripheral nerves, eyes, ears, endocrine organs, heart, guts, and kidneys (Finsterer 2018). There is increasing evidence that also the connective tissue can be involved (Sugimoto et al. 2000; Blackburn et al. 2017). Here, we report a patient with complex-I deficiency who manifested with multisystem disease including the connective tissue.

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Case presentation

The patient is a 32-year-old female who was diagnosed at age 23 with adult Leigh-like syndrome due to the mtDNA variant m.10191 T > C in *MT-ND3*. Since age 3 she recognized joint hypermotility (hyperextensibility). Hyperlaxity concerned the finger, wrist, intervertebral, and knee joints and manifested as knee extension, thumb to the wrist and fingers far back phenomenon (Fig. 1). Her Beighton score was 8/10. At age 18 craniocervical instability and Chiari-I malformation with normal CINE flow study were diagnosed. The clivo-axial angle that was decreased on neutral position (< 135°) was slightly better on flexion and normalized to more than 30° greater on head extension (Fig. 2). The Sharp–Purser test was positive. At age 26 she was diagnosed with dextro-scoliosis of the thoracic spine. The Cobb angle was 16°. Up to now, the patient had never experienced a joint luxation, but highly frequent subluxation of skull base, cervical vertebrae, distal and proximal phalanges of hands and feet, ankles, sacroiliac joint, temporo-mandibular joint, hips, elbows, shoulders, and knees. She also complained of abnormal movements of her ribs when bending down to the side to pick up

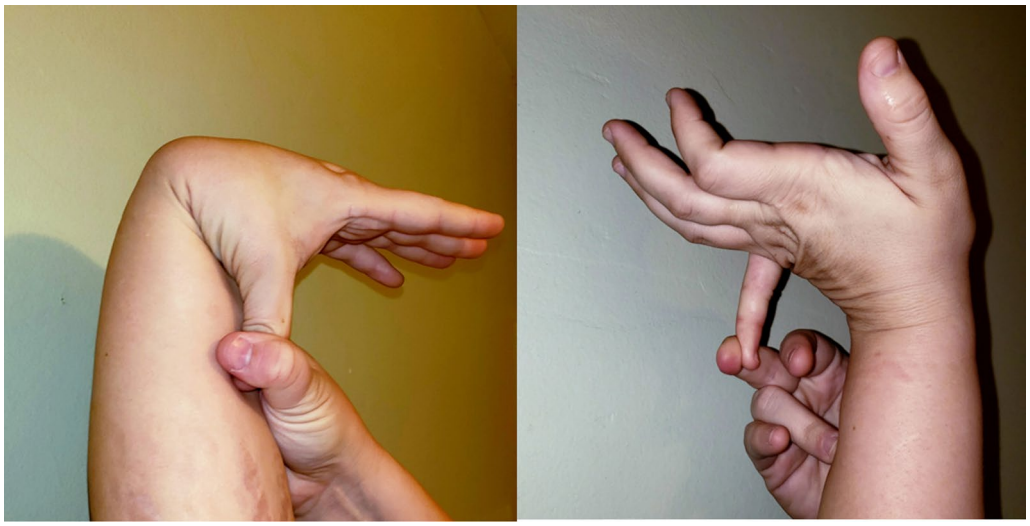

Fig. 1 Hyperlaxity of joints manifesting as thumb-to-the-wrist phenomenon, and fingers far back

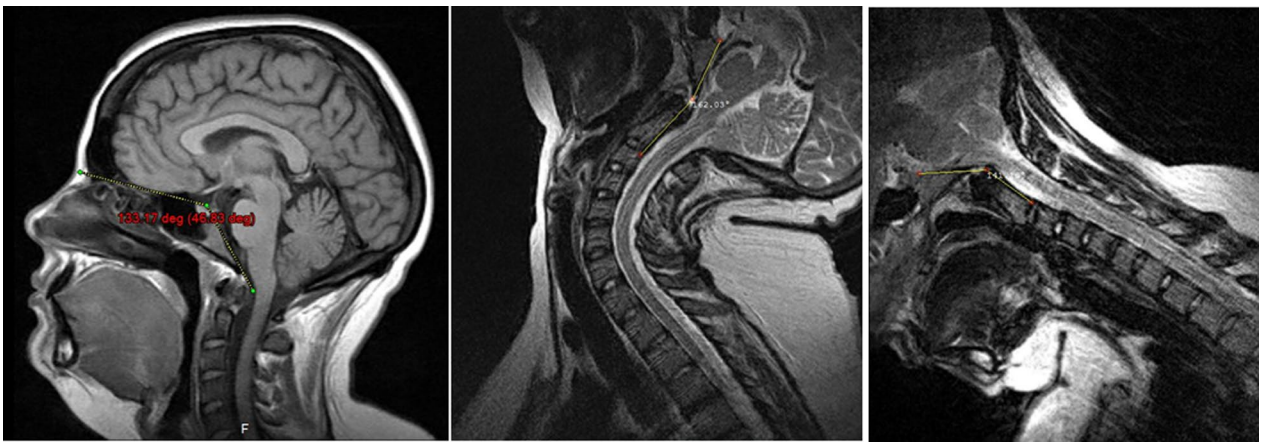

Fig. 2 Decreased clivo-axial angle in neutral position, which normalized upon retro-flexion and antero-flexion

something off the ground. Also cranio-cervical instability, crowding of foramen magnum, and small diameter of foramen magnum were diagnosed, which was complicated by subluxation of the skull base being painful and rather frightening. Magnetic resonance imaging (MRI) of the cervical spine revealed anterolisthesis 2-4 mm C2-C7.

Additionally, she complained about hyperextensibility of skin (skin stretch back of hand 3 cm) (Fig. 3). There was easy tissue tearing, papyraceous scarring, stretchy skin, frequent petechiae, very easy bruising, impaired wound healing, blood pooling in feet, and tiny veins. She had an unilateral palmar crease, bilateral clinodactyly of index fingers, brachydactyly, and excessive ulnar loops, but her karyotype came back 46-XX, ruling out Down syndrome.

To rule out causes of the connective tissue abnormalities other than the m.10191 T > C variant, various investigations had been carried out. Differentials diagnosed that have been ruled out by whole exome sequencing (WES) and whole genome sequencing (WGS) included Loeys–Dietz syndrome, osteogenesis imperfecta, COL3A1 disease, Marfan syndrome, Larsen syndrome, Ullrich muscular dystrophy, and all types of Ehlers–Danlos syndrome (EDS) except the hypermobile kind where the gene is not known. Even though COL3A1 disease was ruled out, the patient complained about many of its symptoms.

Examination for multisystem involvement revealed cerebral, ocular, otologic, endocrine, cardiac, renal, hematologic, muscle, and nerve involvement. Cerebral involvement manifested as mild cognitive impairment,

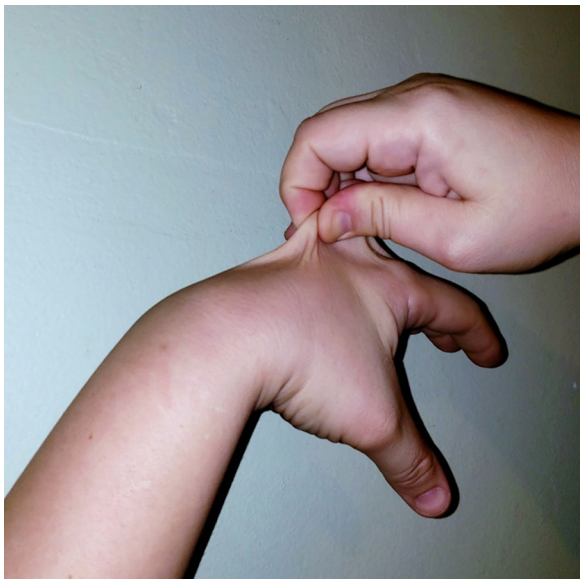

Fig. 3 Stretchy skin at the dorsum mani

migraine, pseudotumor cerebri, epilepsy, spasticity, chorea-hemiballism, ataxia, stroke-like episodes, and nystagmus. Ocular involvement manifested as visual impairment, micropsia, papilledema, and optic atrophy. Otologic involvement manifested itself as hearing impairment. Endocrine involvement was manifested by short stature, empty sella, hypogonadism, amenorrhea, and adrenal insufficiency. Cardiac involvement was manifested by brady-arrhythmias, orthostatic hypotension, and cardiomyopathy. Renal involvement manifested itself as kidney stones and renal insufficiency. As previously reported, peripheral nervous system involvement included large and small fiber neuropathy and neuropathic pain. Muscle involvement was manifested by ptosis, ophthalmoparesis, exercise intolerance, exercise-induced myalgia, cramps, and lactic acidosis [6.7].

The patient's mother suffered from myalgias, hyperlaxity, and bilateral progressive visual impairment and also tested positive for the m.10191 T > C variant. The patient's half-brother (same mother) suffered from moderate left ptosis, cyclic vomiting syndrome, epilepsy, and rhabdomyolysis. He has so far refused to undergo genetic testing.

Connective tissue involvement leading to hyperlaxity of joints and increased skin stretch has been only rarely reported in MIDs (Sugimoto et al. 2000; Blackburn et al. 2017) and definitively not in a MID due to the variant m.10191 T > C. Therefore, the presented patient is unique and provides evidence for a novel phenotypic feature of this variant. Though it is challenging to prove a causal relation between the m.10191 T > C variant and hyperlaxity, the exclusion of almost all other causes of hyperlaxity speaks for a causal relationship.

Why complex-I deficiency results in weak connective tissue remains unknown, but it can be speculated that impaired respiratory chain function results in dysfunction of connective tissue cells, impaired production of collagen fibers, and reduced adhesion of connective tissue cells. Unfortunately, no functional studies of connective tissue cells had been carried out to prove or disprove this assumption. Because MIDs can also manifest in the cellular immune system (Finsterer and Zarrouk-Mahjoub 2017) and can lead to rheumatological disease (Finsterer et al. 2019), it is conceivable that joint problems in the index patient were due to arthritis. However, there were no clinical indications for arthritis in the index patient, why weakness of connective tissue was regarded as causative for the clinical presentation.

Conclusions

This case shows that the mtDNA variant m.10191 T > C in *ND3* can manifest with connective tissue involvement, resulting in hyperlaxity of joints, frequent subluxations of various joints and hyperextensibility of skin. This novel phenotypic feature in adult Leigh-like syndrome contributes to the understanding of complex, multisystem MID phenotypes and should be included in the diagnostic considerations and in genetic counseling of patients at risk for developing a MID.

Abbreviations

EDS	Ehlers–Danlos syndrome
LLS	Leigh-like syndrome
MIDs	Mitochondrial disorders
MRI	Magnetic resonance imaging
WES	Whole exome sequencing
WGS	Whole genome sequencing

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None.

Author contributions

All authors have read and approved the manuscript. xx contributed to design, literature search, discussion, first draft, critical comments, final approval, xx helped in literature search, discussion, critical comments, final approval.

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Availability of data and materials

All data are available from the corresponding author.

Declarations

Ethics approval and consent to participate

Was in accordance with ethical guidelines. The study was approved by the institutional review board.

Consent for publication

Was obtained from the patient.

Competing interests
The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.'

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