Brachydactylia As A Phenotypic Feature of Mitochondrial Disorder

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Abstract- Mitochondrial disorders (MIDs) may occasionaly go along with dysmorphism but hand deformities, as in the following case, have been only rarely reported. A 72 year old female with ptosis, hypoacusis, tremor, myopathy, diabetes mellitus, arterial hypertension, severe cardiac disease, pulmonary hypertension, gastric carcinoid, hepatopathy, generalised atherosclerosis, anemia, polyarthrosis, and hyperlipidemia, additionally presented with brachydactylia. Upon neurological work-up a MID was suspected. The family history was positive for diabetes but negative for brachydactylia or other features of a MID. MIDs may be associated with brachydactylia. Skeletal deformities may be a phenotypic manifestation of MIDs.

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Keywords: Dysmorphism; Hand deformity; Mitochondrial disorder; Myocardial infarction; Myopathy; Multisystem disease; Respiratory chain

Introduction

Though a number of skeletal deformities have been reported in association with mitochondrial disorders (MIDs) (Table 1), they are usually not recognised as a common feature of a MID. Brachydactylia is an uncommon feature of MIDs and has been reported only once (1). Here we present a second patient with brachydactylia and MID.

Case Report

The patient is a 72 year old Caucasian female, height 158 cm, weight 68.7 kg, with a history of diabetes mellitus since age 21 y resulting in micro- and macroangiopathy, diabetic retinopathy, renal insufficiency, and stocking-type paresthesias, nocturnal myalgias on the lower limbs, cramps of the calve muscles, anemia, arterial hypertension, coronary heart disease, heart failure, atrial fibrillation, high-grade tricuspid insufficiency, moderate mitral insufficiency, pulmonary hypertension, aorto-coronary bypass grafting in 2002, a gastric carcinoid successfully resected in May 2008, polyarthrosis, hepatopathy, and hyperlipidemia. Electrical cardioversion was unsuccessful in February 2010. In 2009 and March 2011 she had experienced a myocardial infarction with placement of a drug-eluting stent into the right coronary artery in March 2011. Since then she was on a triple therapy with phenprocoumon, acetyl-salicylic acid, and clopidogrel during 6 months. The family history was positive for diabetes in her mother and all her children and all children of her brother and sister (Figure 1). The family history was negative for brachydactylia.

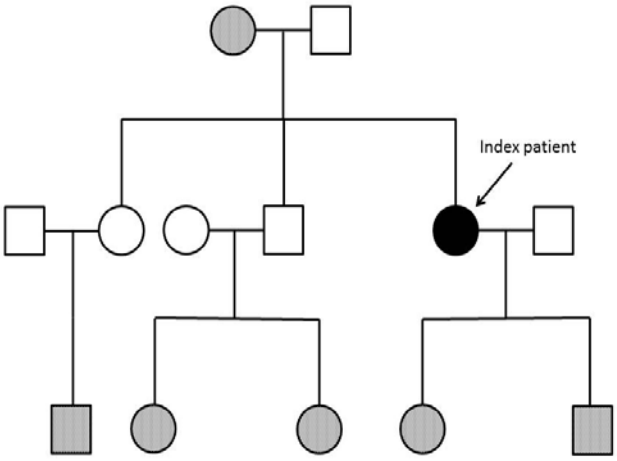

Figure 1. Pedigree chart of the index patients's family showing hereditary diabetes in several relatives. Except of the index patient, none of the other family members was investigated for MID. Shaded symbols represent diabetic patients

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Table 1. Skeletal dysmorphic features in MIDS.

Dysmorphism	Syndrome	Mutated gene	Reference
Facial dysmorphism	Non-syndromic	ATPsynthase	(11)
	PDH-deficiency	E1-alpha	(12)
	French-Canadian Leigh-syndrome	LRPPRC	(2)
	Non-syndromic	TMEM70	(13)
	MELAS	tRNA(Leu)	(14)
	Non-syndromic	nr	(15)
	Leigh-syndrome	SURF-1	(16)
	CPEO/KSS	mtDNA deletion	(17)
	Wolf-Hirschorn syndrome	LETM1	(18)
High (arched) palate	Non-syndromic	nr	(5)
	MLASA	nr	(19)
	KSS	mtDNA deletion	(9)
Microcephaly	Non-syndromic	POLG1	(4)
	Cardioencephalopathy	COX15	(3)
	PDH-deficiency	nr	(20)
	Amish microcephaly	SLC25A19	(21)
	Amish microcephaly	SCL25A22	(22)
	MELAS	tRNA(Leu)	(23)
	PCH	nr	(24)
	Non-syndromic	ATP-synthase	(11)
	PDH-deficiency	E1-alpha	(12)
	Hepatocerebral depletion	DGK	(25)
	Non-syndromic	EFG1	(26)
	Leigh-syndrome	E3	(27)
	MLASA	nr	(19)
Epiphyseal dysplasia	Wolcott-Rallison syndrome	EIF2AK3	(6)
Arachnodactily	KSS	mtDNA deletion	(9)
Brachydactylia	Non-syndromic	nr	(1)
Scoliosis	mtDNA depletion syndrome	SUCLA2	(7)
	Leigh syndrome	nr	(2)
	MNGIE	nr	(8)
	CPEO	nr	(29)
Camptocormia	Non-syndromic	tRNA(Phe)	(30)
	Non-syndromic	nr	(31)
Pes cavus	MNGIE	nr	(8)
	MERRF	nr	(32)
	MSL	nr	(33)
	MELAS	nr	(34)

Nr: not reported

In October 2011 she was admitted for pacemaker implantation. Blood work revealed anemia, HbA1c of 8.9% (normal <6.0%), renal insufficiency (glomerular filtration rate 23 ml/min (normal > 90ml/min), hyperuricemia, and slightly elevated proBNP. Transthoracic echocardiography revealed akinesia of the basal and middle interventricular septum, slight dilatation of both atria, high-grade tricuspid insufficiency, moderate mitral insufficiency, pulmonary hypertension, and a fractional shortening of 15%. Clinical neurologic investigation revealed bilateral ptosis, hypoacusis, reduced tendon reflexes, discrete positional tremor, bilateral hypoesthesia of all fingers, and absent arterial pulses. Muscle biopsy showed ragged-red fibers and COX-negative fibers. A CT scan of the cerebrum was normal except for severe atherosclerosis of the internal carotid artery. Interestingly, she presented also with bilateral brachydactylia (Figure 2).

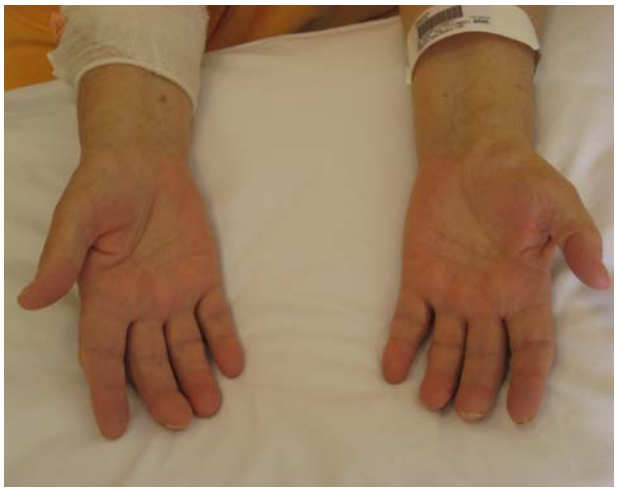

Figure 1. Palmar side of the left hand of the presented patient showing marked brachydactylia of all fingers

Discussion

The patient was suspected to suffer from a MID based on the multisystem nature of her condition. She had indications for myopathy (ptosis, muscle cramps, myalgias and reduced tendon reflexes), hypoacusis, diabetes, short stature, cardiac involvement (atrial fibrillation, pulmonary hypertension), hepatopathy, anemia, hyperlipidemia, generalised atherosclerosis and a family history positive for diabetes. The diagnosis of a MID was further supported by the presence of brachydactylia, which has been previously reported in association with a MID (1). Brachydactylia was attributed to the MID after exclusion of various previously published differential diagnoses (1).

Though rather rarely reported as a phenotypic feature of MIDs, skeletal dysmorphism is occasionally associated with MIDs (Table 1). It may manifest as facial dysmorphism (2), microcephaly (3,4), high arched palate (5), epiphyseal dysplasia (6), scoliosis (7), foot deformity (8) or deformity of the hands (9). Hand deformities reported in patients with MIDs include brachydactylia (1) and arachnodactylia (9). Arguments for a causal relation between MID and brachydactylia in the presented patient are that brachydactylia has been previously reported in a patient with MID, that dysmorphic features may be phenotypic feature of MIDs, and that brachydactylia together with multisystem disease was found only in the index patient and not in her relatives. Further evidence for the association of morphological defects with mutations in genes causing a MID comes from animal models showing that knock-out of the MFN2 gene results in various morphological defects (10). The causal relation between skeletal abnormalities and MIDs is not fully proven but genes, which govern cell differentiation, could play a pathogenetic role. It is also conceivable that energy depletion or increased oxidative stress following mitochondrial dysfunction contribute to the pathogenesis although these scenarios remain unproven so far.

This case shows that MIDs may be rarely associated with brachydactylia. Morphological abnormalities and skeletal abnormalities should not be neglected as phenotypic manifestations of a MID.

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