Previously Unreported Biallelic Mutation in *DNAJC19*: Are Sensorineural Hearing Loss and Basal Ganglia Lesions Additional Features of Dilated Cardiomyopathy and Ataxia (DCMA) Syndrome?

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Abstract Background: Dilated cardiomyopathy (DCM), non-progressive cerebellar ataxia (A), testicular dysgenesis, growth failure, and 3-methylglutaconic aciduria are the hallmarks of *DNAJC19* defect (or DCMA syndrome) due to biallelic mutations in *DNAJC19*. To date DCMA syndrome has been reported in 19 patients from Canada and in two Finnish siblings. The underlying pathomechanism is unknown; however, *DNAJC19* is presumed to be involved in mitochondrial membrane related processes (e. g., protein import and cardiolipin remodeling). Here, we report an additional patient with progressive cerebellar atrophy and white matter changes.

Patient and Methods: A Turkish boy presented at age 2 months with dilated cardiomyopathy (initially worsening then stabilizing in the second year of life), growth failure, bilateral cryptorchidism, and facial dysmorphism. Mental and motor developmental were, respectively, moderately and severely delayed. Profound intentional tremor and

dyskinesia, spasticity (particularly at the lower extremities), and dystonia were observed. Sensorineural hearing loss was also diagnosed. MRI showed bilateral basal ganglia signal alterations. Plasma lactate levels were increased, as was urinary excretion of 3-methylglutaconic acid. He deceased aged 3 years.

Results: Sanger Sequencing of *DNAJC19* confirmed the clinical diagnosis of *DNAJC19* defect by revealing the previously unreported homozygous stop mutation c.63delC (p.Tyr21*). Investigation of enzymes of mitochondrial energy metabolism revealed decreased activity of cytochrome *c* oxidase in muscle tissue.

Discussion: Sensorineural hearing loss and bilateral basal ganglia lesions are common symptoms of mitochondrial disorders. This is the first report of an association with *DNAJC19* defect.

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Introduction

Dilated cardiomyopathy with ataxia (DCMA syndrome, MIM #610198, *DNAJC19*) is one of the inborn errors of metabolism with 3-methylglutaconic aciduria (3-MGA-uria) as a discriminating feature (Wortmann et al. 2013). It was first described in the Canadian Dariusleut Hutterite population in 18 patients (Davey et al. 2006). The major clinical features of DCMA include a severe, early onset dilated cardiomyopathy (DCM), in some cases accompanied by long QT syndrome, and an ataxia (A) due to non-progressive cerebellar atrophy. Prenatal or postnatal growth failure is universally seen, as is significant motor delay, and

a cerebellar syndrome with ataxia. Male genital anomalies are also frequently reported and range from isolated cryptorchidism to severe perineal hypospadias. Additional features include optic atrophy, a mild increase in hepatic enzymes with microvesicular hepatic steatosis, a normochromic microcytic anaemia, and mild to borderline non-progressive mental retardation.

The precise function of DNAJ19 in human mitochondria is unknown. An effect on mitochondrial protein import or cardiolipin remodeling via prohibitin proteins has been suggested (Davey et al. 2006; Richter-Dennerlein et al. 2014). This is in line with other inborn errors of metabolism with 3-methylglutaconic aciduria (3-MGA-uria) (e.g., TAZ defect or Barth syndrome, SERAC1 defect or MEGDEL syndrome) affecting phospholipid remodeling (Wortmann et al. 2013) and can show more or less mitochondrial dysfunction in muscle (Wortmann et al. 2012; Thiels et al. 2016).

Till date only three further patients have been described (Ojala et al. 2012; Al Teneiji et al. 2016). Interestingly, white matter alterations and progressive (in contrast to non-progressive) bilateral basal ganglia lesions have been reported as additional features in one of these patients (Al Teneiji et al. 2016). Here we report the case of a Turkish boy and expand the mutational and biochemical abnormalities and the clinical spectrum.

Methods

Measurements of the Respiratory Chain Enzymes in Muscle

Skeletal muscle tissue samples were homogenized in extraction buffer (20 mmol/l Tris-HCl, pH 7.6, 250 mmol/l sucrose, 40 mmol/l KCl, 2 mmol/l EGTA) and subsequently centrifuged at 600 g to generate the post-nuclear supernatant (600 g homogenate), which was used for measurement of OXPHOS enzyme activities and Western blot analysis. Citrate synthase (CS) and OXPHOS enzyme activities were determined as published elsewhere (Berger et al. 2003; Feichtinger et al. 2014; Mayr et al. 2004; Meierhofer et al. 2004). Briefly, rotenone-sensitive complex I activity was measured spectrophotometrically as NADH/decylubiquinone oxidoreductase. The enzyme activities of citrate synthase, complex IV (ferro-cytochrome c/oxygen oxidoreductase), and the oligomycin-sensitive ATPase activity of the F_1F_0 ATP synthase (complex V) were measured in buffer conditions as previously described (Rustin et al. 1994). Succinate dehydrogenase activity (SDH; complex II) was determined as described (Rustin et al. 1994) with slight modifications (Feichtinger et al. 2014). Buffer conditions and the procedure for determina-

tion of complex III activity were as reported previously (Feichtinger et al. 2014). All spectrophotometric measurements were performed at 37°C.

Immunoblotting

For western blot analysis, a total of 10 µg protein of 600 g homogenate (generated as described above) or fibroblast mitochondria was separated on 10% acrylamide/bisacrylamide gels and transferred to nitrocellulose membranes using the Biorad Trans-Blot Turbo Blotting System. Washing and blocking procedures were performed as previously described (Feichtinger et al. 2014).

The following primary antibody dilutions, incubation times, and temperatures were used: monoclonal mouse anti-NDUFS4 (1:1,000; 1 h, room temperature; Abcam; ab55540), monoclonal mouse anti-VDAC1 (Porin) (1:1,000; 1 h, room temperature, Abcam, ab17734), and polyclonal rabbit anti-MT-CO2 (COX2) (1:1,000; overnight, 4°C; Abcam, ab79393). After washing, the membranes were incubated with primary antibodies as follows: NDUFS4, VDAC1, and MT-CO2. Since NDUFS4 and MT-CO2 have the same molecular weight, the western blot was incubated two times for 15 min in stripping buffer (25 mmol/l glycine, 2% SDS, pH 2) after VDAC1. The clean blot was blocked again and incubated with MT-CO2.

NDUFS4 and VDAC1 were labeled with polymer-HRP-antimouse (1:100; 1 h, room temperature, EnVision kit, Dako), MT-CO2 with labeled polymer-HRP-anti-rabbit (1:100; 1 h, room temperature, EnVision kit, Dako). Detection was carried out with Lumi-Light PLUSPOD substrate (Roche).

Genetic Investigations

A karyogram and Sanger Sequencing of *DNAJC19* (NM_145261.3, primers available upon request) were performed using standard methods. Parental DNA and DNA from siblings were unavailable.

Case Report and Results

Clinical and Neurological Presentation, Cerebral MRI Findings

The boy was the sixth child of Turkish parents who are first degree cousins (Fig. 1). Two older brothers and two older sisters died before the age of 13 months; however, no details were available. He was born with a low birth weight (−2.5 SD) at 38 weeks of gestation. Placental abruption was reported, no more details were available.

Fig. 1 The pedigree of the family and results from index patient's Sanger Sequencing of the genomic DNA

At age 2 months a systolic murmur was detected, subsequent echocardiography revealed a spherical configuration of the left ventricle (end diastolic diameter 2.7 cm (ref. range: 1.8–2.3 cm)) and a diminished ejection fraction (45%, (ref. range: 56–78%)). Treatment with digoxin, furosemide, and an ACE inhibitor was initiated. Two months later an increase in the trabeculation of the left ventricle was detected. The ejection fraction initially improved to 57% (4 months) and 68% (12 months), but later worsened to 50% (1.5 years) and then stabilized around age 2 years. The left ventricular end diastolic diameter at follow-up was 3.3 (ref. range: 2.4–3.1 cm) cm and 3.2 cm (ref. range: 2.5–3.2 cm), respectively. ECG did not reveal conduction defects.

Motor development was severely delayed (supported seating at 10 months, rolling over at 20 months) and he has not learned to walk. At age 2 years he made eye contact for a short time and recognized his mother and spoke only one word. He reacted to and laughed at bright colored objects (toys, mobile phones, etc.). Seizures were not reported. The cerebral MRI (at 2.5 years) showed reduced cerebellar volume and increased basal ganglia signal on the T2-weighted images (particularly putamen and globus pallidus), with correspondingly reduced signal on the T1-weighted images. In the same level diffusion-weighted imaging was characterized by diffusion restriction (Fig. 2).

Currently he is aged 2 years and 5 months, anthropometrics are within normal limits. The minor facial features are shown in Fig. 2. He has a 2/6 systolic murmur with punctum maximum at 3rd - 4th intercostal space. Bilateral cryptorchidism and a short penis length (2.3 cm (–2 SD)) were noted. The patient can only follow the gaze for a short time and babbles. He has no head control, shows mild muscular atrophy, spasticity (particularly of the lower extremities), profound intentional tremor, dystonia, and dyskinesia, and has no fine motor skills (e.g., no grasping). He has severe hyperkinetic involuntary movements such as jerky explosive “rolling over.”

Auditory evoked potential (AEP) performed at 2.5 years revealed a bilateral sensorineural hearing loss (Fig. 2). The parents did not agree to treatment until this time. The pelvic ultrasound scan failed to detect the presence of testicles in the channel and in the pelvis.

The patient deceased during the reviewing process of this manuscript due to aspiration aged 3 years.

Clinical Chemical, Metabolic, and Endocrine Findings

The patient had a microcytic, hypochromic anemia (hemoglobin 11.4 g/l (ref. range: 12–15), erythrocyte count $5.34 \times 10^{12}/l$ (ref. range: 3.78–5.4), mean red cell volume 64.5 fl (ref. range: 77–95), mean red cell hemoglobin 21.4 pg (ref. range: 23–31.2), and red cell distribution

Fig. 2 Main physical, imaginary, and auditory findings of our patient at the age of 2.5 years. **(I)** Picture of the patient: **(IA)** Thick diffuse eyebrows, short palpebral fissures with upper eyelid retraction and prominent forehead, **(IB)** Large, low set protruding ears, thin and parrot-like nose, long curly eyelashes, and hypertrichosis, **(IC)** Spasticity of the lower limbs. **(II)** Magnetic resonance imaging of the brain: **(IIA)** Axial T2-weighted image shows bilateral hyperintense aspect of basal ganglia (putamen and globus pallidus), **(IIB)** Sagittal T1-weighted image shows a globally reduced cerebellar volume. The axial dark flue image demonstrates a prominence of cerebellar folias, **(IIC)** The flair coronal image demonstrates bilateral basal ganglia

hyperintensities, **(IID)** Diffusion-weighted image (DWI b1000) shows an impaired diffusion in the bilateral basal ganglia. White matter alterations were not seen. **(III)** Auditory evoked potential (AEP) results: The cut-off of hearing loss was defined according to the mean hearing loss at frequencies of 250, 500, and 2,000 Hz as follows (normal hearing ≤ 20 dB hearing loss): **(A)** Threshold detected by click acoustic warning was 65 dB for left ear and 90 dB for right ear, **(B)** At frequencies of 500 Hz the threshold for both ears was 90 dB, **(C)** There was no response at the frequency of 2,000 Hz in both ears. *Abbreviations:* L left ear, R right ear

width 21% (ref. range: 11.6–14.6%). He received no iron therapy. The plasma alanine aminotransferase (141 U/L (ref. range: 5–45 U/L)), aspartate aminotransferase (149 U/L (ref. range: 15–55 U/L)), and gamma-glutamyl transferase (324 U/L (ref. range: <55 U/L)) were elevated. Ammonia was slightly elevated 73 $\mu\text{mol/L}$ (ref. range: 21–50). Total and conjugated bilirubin were within the normal range. Serum total cholesterol level was low 2.87 mmol/l (ref. range: 3.36–5.09 mmol/l). Albumin and CK were normal. The plasma lactate (4.07 mmol/l (ref. range: <2.1 mmol/l)) and lactate–pyruvate ratio 97.39 (redox state, ref. range: <20) were high. Urinary organic acid analyses revealed elevated excretion of 3-methylglutamic acid (120–130 mmol/mol creatinine, ref. range: <15), 3-methylglutarate (95 mmol/mol creatinine, ref. range: <5), ethylmalonic acid (116–120 mmol/mol creatinine, ref.

range: <14.6), and succinate (162 mmol/mol creatinine, ref. range: <5). FSH was elevated 9.34 mIU/ml (ref. range: 0.26–3.0) before puberty, LH as well as free and total testosterone was within the normal range.

Measurements of the Respiratory Chain Enzymes in Muscle

The investigation of enzymes of mitochondrial energy metabolism in muscle showed activities at the lower range of normal in relation to the protein content of most enzymes, however, cytochrome *c* oxidase was significantly decreased (53% of the lower limit of the reference range 79 mUnits/mg protein, reference range 148–392). In relation to the mitochondrial marker enzyme citrate synthase a similar decrease of cytochrome *c* oxidase to 0.48 mUnits/

mUnits citrate synthase (reference range 0.83–2.4) was also observed (more details in the supplementary material).

Genetic Investigations

The chromosome analysis on the karyogram was 46, XY. Sanger Sequencing of *DNAJC19* (NM_145261.3) revealed a previously unreported variant c.63delC (p.Tyr21*) in homozygous state (Fig. 1). This frameshift mutation is predicted to initiate a premature stop codon. This finally leads to the production of a severely truncated protein, if any. This mutation is neither present in the ExAC (<http://exac.broadinstitute.org>) nor KAVIAR (<http://db.systemsbiology.net/kaviar>) databases.

Discussion

It is often challenging and time-consuming to obtain a specific diagnosis in pediatric patients with multi-organ disease without using exome sequencing. In the patient reported here the combination of early onset dilated non-compaction cardiomyopathy with global developmental delays led to metabolic screening. The finding of 3-MGA-uria reduced the list of (known) differential diagnoses to: DNAJC19 defect (or DCMA syndrome), AGK defect (or Sengers syndrome, frequent additional finding cataracts), and TAZ defect (or Barth syndrome, frequent additional finding neutropenia). The latter two were considered less likely given the movement disorder and cryptorchidism of the patient reported here.

DNAJC19 defect was first described in a Canadian Hutterite population (Davey et al. 2006, Sparkes et al. 2007). In 2012 Ojala et al. reported a second affected family (Ojala et al. 2012) and recently another patient (Al Teneiji et al. 2016) was described. Table 1 gives an overview of all patients reported to date.

Sensorineural hearing loss, dysmorphic facial feature, and basal ganglia alteration were the three differences between our patient and those previously described.

Based on the similarity of DNAJC19 and yeast Tim14 protein it was suggested that DCMA phenotype might be the result of defective import and assembly of mitochondrial proteins through the TIM23 translocase pathway (Davey et al. 2006). Abnormal gathering of TIM23 transporter is the underlying pathomechanism of another (mitochondrial) disorder, Mohr–Tranebjaerg syndrome (biallelic mutations in *TIMM8A*) (Rothbauer et al. 2001). Sensorineural deafness, visual loss, intellectual disability, and movement disorders are the main components of this progressive neurodegenerative disorder (Tranebjaerg et al. 1995). Deafness is also found in another inborn error of metabolism with 3-MGA-uria as a discriminating feature (SERAC1 defect (Wortmann

et al. 2012)) and is frequently seen in mitochondrial disorders (Ammar et al. 2016) which could indicate that it is a part of the clinical spectrum of DNAJC19 defect. Alternatively, isolated hearing loss is a frequent finding and could also be due to a second (genetic) disorder.

The dysmorphic features described in our patient are probably consistent with the heterogeneous clinical presentations of children with mitochondrial disorders (Nissenkonr et al. 1999).

Reduced cerebellar volume, described as non-progressive in the original Hutterite family (Davey et al. 2006) and as progressive cerebellar atrophy (Al Teneiji et al. 2016), was also present (Fig. 2). Additionally, our patient showed bilateral basal ganglia alterations, another well-known and common feature of mitochondrial disorders (Baertling et al. 2016). No white matter involvement was seen. The latter may have been a transient finding, as it was seen only in one MRI taken at the age of 4 years in one patient (Al Teneiji et al. 2016).

Gathering more patient data also allows more insight into the underlying pathomechanism. We report clearly reduced cytochrome *c* oxidase (complex IV) activity in muscle tissue and fibroblast cell cultures. In previously reported patients with DNAJC19 defect alterations in the respiratory chain activity have been reported. Ojala et al. (2012) described diminished complex I, II, and IV activity in skeletal muscle (not in cardiac muscle) and Al Teneiji et al. (2016) reported reduced activity of both NADH-Q1-reductase (complex I) and NADH-cytochrome *c* reductase (complex II) in fibroblasts in one patient. In general, mitochondrial dysfunction not affecting a specific enzyme (complex) is in line with the findings in other disorders of the biosynthesis and remodeling of phospholipids (TAZ defect, SERAC1 defect) (Thiels et al. 2016).

Finally, our presentation of another patient suggests that DNAJC19 defect may not be as rare as previously thought but presumably still under diagnosed.

In conclusion, we report the fourth family with DNAJC19 defect (or DCMA syndrome), with details of the mutational spectrum and describing sensorineural hearing loss, dysmorphic features, and basal ganglia alterations on MRI for the first time in this disorder. This report further supports a thorough clinical investigation in the presence of a strong biomarker which can lead to a swift diagnosis without performing exome sequencing.

Synopsis

Sensorineural hearing loss and bilateral basal ganglia lesions may be additional features of dilated cardiomyopathy and ataxia syndrome.

Table 1 Clinical features of the present patient and the previously described patients

	Davey et al. (2006) (<i>N</i> = 18)	Ojala et al. (2012) (<i>N</i> = 2)	Al Teneiji et al. (2016) (<i>N</i> = 1)	This report (<i>N</i> = 1)
Ancestry	Canadian Hutterite	Finnish	Not reported	Turkish
Gender	11 male, 7 female (11/7)	Male	Female	Male
Current age	<i>N</i> = 11 alive (median age 18 m, range 4–96 m), 7 deceased (median age 13 y, range 10–22 y)	One alive 17 m, one deceased 13 m	Alive 13 y	Deceased 3 y
c.DNA change	Homozygous c.130-1G>C	Homozygous c.300delA, (p.Ala101Profs*10)	Homozygous c.280+1_280+5delGTAAG	Homozygous c.63delC, (p.Tyr21*)
Mutation type	Splice site	Frame shift	Splice site deletion	Stop
Consanguinity	$F_r = 0.0445^a$	No	Yes	Yes
IUGR	8/18 (44%)	No	Not reported	Yes
Growth failure	18/18 (100%)	Yes	Yes	Yes
Dysmorphic features	Not reported	No	Not reported	Yes, low set ears, thick eyebrows, parrot nose, fish-mouth
Cardiac findings	DCM (12/18 (67%))	DCM with non-compaction	DCM of left ventricle with non-compaction	DCM
Mental Retardation	10/18 (55%)	Not reported	Yes	Yes
Cerebral imaging	Not reported	P1: normal MRI (3 y), P2: normal ultrasound (age was not reported), marginally reduced neuronal density of the dentate nucleus (autopsy)	Normal MRI (2 y); cerebellar atrophy and white matter changes (4 y), progressive cerebellar atrophy no white matter changes (10 y)	MRI: reduced cerebellar volume; basal ganglia alterations (2.5 y)
Seizures	2/18 (11%)	No	No	No
Hypotonia	Not reported	Yes	Yes	Yes
Deafness	Not reported	No	No	Yes
Optic atrophy	4/18 (22%)	No	Not reported	No
Oculomotor apraxia	2/18 (11%) ^b	No	No	No
Cryptorchidism	12/18 (66%)	P1: Not reported P2: right sided cryptorchism, chorda penis	Not reported	Testicular dysgenesis
Microcytic, hypochromic anemia	12/18 (66%)	Yes	Not reported	Yes
Liver dysfunction	8/18 (44%)	1/2	Yes	Yes
3-Methylglutaconic acid	“Five to ten-fold increase” (data not shown)	P1: 130 mmol/l creatinine (NR<15 mmol/l creatinine) P2: no excretion (at 10 m)	Initially moderately elevated (value was not reported), later undetectable	120 mmol/mol creatinine (NR<20 mmol/mol creatinine)

Abbreviations: P patient, IUGR intrauterine growth failure, DCM dilated cardiomyopathy, m months, y years, NR normal range

^aThis value of random inbreeding shows that high inbreeding in the Hutterite population is not the result of any preference for consanguineous marriage, but instead is a reflection of the small and isolated nature of the population, resulting in a situation where most available mates are related (Relethford 2012)

^bBenson et al. 2016 followed up two patients from the Davey et al. (2006) series and reported oculomotor apraxia as a feature

Compliance with Ethics Guidelines

Conflict of Interest

Sema Kalkan Ucar, Johannes A. Mayr, René G. Feichtinger, Ebru Canda, Mahmut Çoker, and Saskia B. Wortmann declare that they have no conflict of interest.

Informed Consent

The parents consented for case report.

Author Contributions

Sema Kalkan Ucar diagnosed the patient, drafted the manuscript, reviewed the literature, and approved final version of the manuscript.

Johannes A. Mayr performed the laboratory investigations, drafted laboratory information details, and approved final version of the manuscript.

René G. Feichtinger performed the laboratory investigations, drafted laboratory information details, and approved final version of the manuscript.

Ebru Canda participated in the clinical follow-up of the patient and approved final version of the manuscript.

Mahmut Çoker is a senior clinician and provided supervision in data analysis and completing the manuscript.

Saskia B. Wortmann is a senior clinician and provided supervision in data analysis and completing the manuscript.

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