Pigmentary retinopathy can indicate the presence of pathogenic *LAMP2* variants even in somatic mosaic carriers with no additional signs of Danon disease

Running title: Pigmentary retinopathy can indicate Danon disease

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ABSTRACT

Purpose: Danon disease (DD) is a rare X-linked disorder caused by pathogenic variants in *LAMP2*. DD primarily manifests as a severe cardiomyopathy. An early diagnosis is crucial for patient survival. The aim of the study was to determine the usefulness of ocular examination for identification of DD.

Methods: Detailed ocular examination in 10 patients with DD (3 males, 7 females) and a 45-year-old asymptomatic female somatic mosaic carrier of a *LAMP2* disease-causing variant.

Results: All patients with manifest cardiomyopathy had pigmentary retinopathy with altered autofluorescence and diffuse visual field loss. Best corrected visual acuity (BCVA) was decreased (<0.63) in 8 (40%) out of 20 eyes. The severity of retinal pathology increased with age, resulting in marked cone-rod involvement overtime. Spectral-domain optical coherence tomography in younger patients revealed focal loss of photoreceptors, disruption and deposition at the retinal pigment epithelium/Bruch´s membrane layer (corresponding to areas of marked increased autofluorescence), and hyperreflective foci in the outer nuclear layer. Cystoid macular oedema was seen in one eye. In the asymptomatic female with somatic mosaicism, the BCVA was 1.0 bilaterally. An abnormal autofluorescence pattern in the left eye and diffuse bilateral visual field loss were present; while full-field electroretinography was normal.

Conclusions: Detailed ocular examination may represent a sensitive and quick screening tool for the identification of carriers of *LAMP2* pathogenic variants, even in somatic mosaicism. Hence, further investigation should be undertaken in all patients with pigmentary retinal dystrophy as it may be a sign of a life-threatening disease.

Keywords: Danon disease – *LAMP2* – somatic mosaicism – spectral-domain optical coherence tomography – autofluorescence – pigmentary retinopathy

INTRODUCTION

Danon disease (DD; OMIM #300257) is a rare X-linked disorder caused by mutations in the lysosomal-associated membrane protein type 2 gene (*LAMP2*, Xq24). DD is characterized by cardiomyopathy, skeletal muscle myopathy and mild cognitive impairment; with male patients having earlier onset and more severe disease. Most patients require heart transplantation, which in males is usually before the age of 25 years (Boucek et al. 2011; Brambatti et al. 2019).

The majority of *LAMP2* casual variants result in the absence of the protein. LAMP2 deficiency is uniform in tissues of male individuals. In heterozygous female patients, cellular expression of the alternative *LAMP2* alleles is mosaic (unless influenced by events like formation of syncytia (citace)) as a result of X-chromosome inactivation (XCI). Although not fully mechanistically understood at the molecular level, *LAMP2* deficiency is presumed to compromise lysosomal processing of autophagic substrates (Rowland et al. 2016; Chi et al. 2019).

A growing number of reports suggest that females, who are somatic (and possibly also germinal) mosaics for *LAMP2* variants represent a specific and under-detected patient/carrier group. Some of these carrier females have been reported to express the phenotype (Meinert et al. 2019) but others remain free of clinical DD symptoms (Chen et al. 2012; Majer et al. 2014).

Although a number of individual case reports demonstrate impaired vision in patients with DD, detailed ocular findings have been, to the best of our knowledge, reported in less than 20 patients, and of these only 10 underwent imaging with spectral-domain optical coherence tomography (SD-OCT) and 7 had fundus autofluorescence imaging (Prall et al. 2006; Schorderet et al. 2007; Thiadens et al. 2012; Mack 2014; Thompson et al. 2016; Fukushima et al. 2019; Majer et al. 2019; Meinert et al. 2019).

Based on functional and clinical imaging testing, DD has a variable ocular phenotype, but a pigmentary retinopathy is commonly present, associated with generalised loss of cone and rod function (Schorderet et al. 2007). Occasionally fine lens opacities can be observed (Prall et al. 2006).

In this study we report detailed ophthalmic examination including SD-OCT imaging in a cohort of 10 Czech patients with DD and one asymptomatic female with somatic mosaicism for a *LAMP2* disease-causing variant. Documented ocular findings highlight the fact that the pigmentary retinopathy may be the only sign of this potentially life threatening cardiac condition, warranting further clinical and laboratory investigation in all cases with a phenotype suggestive of an inherited retinal disease (IRD).

METHODS

The study was approved by the Institutional Ethical Committee and adhered to the tenets of the Declaration of Helsinki. All patients or their legal guardians provided signed, informed consent prior to inclusion in the study.

Ten Czech patients with DD (3 males, 7 females) and one asymptomatic female with somatic mosaicism were included (Table 1). In all affected individuals, the diagnosis of DD was based on the following criteria: clinical (primarily cardiological) symptoms, cardiac histopathology if endomyocardial biopsy or explanted heart were available, absence of the LAMP2 protein in peripheral blood granulocytes and monocytes and/or cardiac tissue, and presence of a pathogenic variant in the *LAMP2* gene. The detailed description of clinical and molecular findings in individuals 1, 5, 6, 8, 9, 10, and 11, as well as protocols of cardiac tissue histopathological and LAMP2 immunohistochemical (IHC) analyses, HUMARA XCI assay in peripheral white blood cells (WBC), flow cytometric (FC) LAMP2 expression testing in

WBCs, and *LAMP2* mRNA/cDNA and gDNA analyses are provided in previous reports (Majer et al. 2012, 2014 and 2018).

Briefly - LAMP2 deficit in granulocytes and monocytes was uniform in all three male patients (8−10) and mosaic in females (1−7). WBC XCI ratios were in all females within or close to the prevalent 20:80 – 80:20 range (Amos-Landgraf et al. 2006). Only one of the females (5) was not informative for the HUMARA assay (Majer et al. 2012). Myocardial histopathological abnormalities and IHC *LAMP2* expression patterns in four females (2, 3, 5, and 7), and one male patient (10) were compatible with changes observed in male and female DD patients (Majer et al. 2012). Detailed information about *LAMP2* expression profiles in WBCs and *LAMP2* pathogenic variants in patients 2, 3, 4, and 7 have not yet been reported but are available upon request from the authors.

Female 11 was previously reported to be a clinically asymptomatic mother of two sons affected by DD (Majer et al. 2014). Her genotype was characterized as somatic (and presumably also germinal) mosaicism for a tandem duplication of *LAMP2* exons 4 and 5. Her WBC HUMARA XCI ratio value was 30:70. The population of her LAMP2def leukocytes was, however, extremely small (0.06% of granulocytes and 0.13% monocytes) (Majer et al. 2014). She underwent ocular examination at the age of 45 years. She is currently 48 years old and remains asymptomatic with normal heart function.

All eleven individuals underwent comprehensive ophthalmic examination comprising best corrected visual acuity (BCVA) tested using ETDRS charts (extrapolated to decimal values), standard slit-lamp biomicroscopy including dilated retinal assessment. Colour, red free and autofluorescence photographs of the fundus were taken using FF 450 plus IR and Visucam 200 (Carl Zeiss Meditec AG, Jena, Germany) and automated perimetry was performed with the M700 (Medmont International, Nunawading, Australia). Macular architecture and BluePeak blue laser autofluorescence imaging were studied using SD-OCT (Spectralis,

Heidelberg Engineering GmbH, Heidelberg, Germany). Colour vision was assessed with Lanthony desaturated D-15 test, more than one diametrical crossing was considered as abnormal (Shoji et al. 2009).

Full-field electroretinography (ERG), multifocal ERG (mfERG) and pattern ERG were performed in the somatic mosaic female (11) according to the standards recommended by International Society for Clinical Electrophysiology of Vision (Hood et al. 2012; Bach et al. 2013; McCulloch et al. 2017).

RESULTS

Summary of demographic and ophthalmic findings in the 10 patients with DD, is shown in Table 1. The detailed ocular imaging and static perimetry findings are provided in Supporting Information.

The mean age of female subjects at ocular examination was 32.0 ± 9.6 years and the mean age of male subjects was 23.3 ± 8.3 years.

None of the patients reported nyctalopia and only one male (10) admitted subjective symptoms; reduced visual acuity and impaired perception of colours. Visual acuity was normal, i.e. ≥0.63 in 12 (60%) eyes of 7 individuals. The most severe BCVA decrease down to 0.1 was observed in the left eye of male 10, aged 35 years, this eye also had impaired colour vision (Table 1).

Dilated fundus examination revealed mainly symmetrical pathological findings. Typically, pigmentary retinopathy (punctate areas of hypopigmentation and hyperpigmentation) was observed (Table 1, Fig. 1). Additional findings included a bilateral peripheral band of chorioretinal atrophy in female 2, a large area of peripheral chorioretinal atrophy in the left eye of female 5, cystoid macular oedema (confirmed by SD-OCT) in the right eye of male 6 (Fig. 2D), and bilateral foveal retinal pigment epithelial (RPE) clumping in all 3 male

individuals - the severity of which seemed to increase with age (Fig. 1, Supporting Information).

Fundus autofluorescence imaging demonstrated an abnormal pattern with hypo- and hyperautofluorescent mottling in all eyes of patients with DD, except for male 8 (aged 17 years) who had normal autofluorescence bilaterally. The foveal region was relatively spared, except for the right eye of female 6 (Fig. 1C), left eye of female 7, and both eyes of male 10 (Fig. 1F, Supporting Information). Individuals 2, 3, 5, 6, 7, 9, and 10 had markedly hyperautofluorescent dots located predominantly in the macular region and in the mid-peripheral retina (Fig. 1A–C,E,F, Supporting Information). On SD-OCT these dots corresponded to round and oval deposits at the interface of the RPE and ellipsoid zone (EZ) layers, measuring from 60 to 294 μm in diameter at their base, and from 43 to 87 μm in height (Fig. 2C,F, Table 2).

In addition to deposits in the RPE/EZ layers, SD-OCT documented a range of findings from variation of signal intensity of the interdigitation and EZ in mildly affected individuals with normal or nearly normal BCVA; to focal disruptions of these two bands in more advanced disease. Atrophy of the neuroretina, with total loss of the photoreceptor layers and RPE, were observed in the most severely affected individuals; female 7 aged 47 years and male 10 aged 35 years. Correspondingly, the total central subfield retinal thickness was below normal values in these two patients (Table 2). An interesting finding were foci of increased signal in the outer nuclear layer in all examined patients. A summary of SD-OCT findings and representative images are provided in Table 2 and Fig. 2.

Static automated perimetry was abnormal in all 10 patients with DD. Visual field changes were characterized by patchy areas of decreased retinal sensitivity, more pronounced in the periphery. In males, the loss of sensitivity was more profound and extensive compared to similarly aged females (Fig. 1, Supporting Information).

Except for tiny and visually insignificant lens opacities found in 8 eyes of 4 females, the anterior segment appeared normal. Intraocular pressure was also within the normal range (under 21 mmHg) in all eyes.

The BCVA of individual 11 was 1.0 in both eyes. She denied any subjective eyesight related problems including nyctalopia. The right fundus appeared normal (Fig. 3A), in the left eye there were few scattered yellow deposits (Fig. 3C). Static perimetry was performed but was unreliable due to poor fixation and her underlying anxiety disorder . Autofluorescence imaging identified one hyperautofluorescent spot in the right eye (Fig. 3B), whereas in the left eye, there was a number of hypoautofluorescent and a few hyperautofluorescent spots (Fig. 3D). SD-OCT imaging (Fig. 3E,F) revealed only discrete irregularities of the RPE band in areas corresponding to these hyperautofluorescent foci (Fig. 3F). The central retinal thickness was 277 μm and 275 μm in the right and left eye, respectively (normal values 280.1 ± 35 μm) (Invernizzi et al. 2018). Light and dark-adapted full-field ERGs were bilaterally normal (Fig. 3G–J). No abnormalities were detected on pattern ERG (Fig. 3K,M). Multifocal ERG showed mild bilateral decreased foveal responses (75% of normal) which potentially could be attributed to poor fixation (Fig. 3L,N).

DISCUSSION

Herein we describe ocular findings of 10 patients with DD and one asymptomatic female with an extremely low-level somatic mosaicism for a pathogenic *LAMP2* variant (Majer et al. 2014). We show that pigmentary retinopathy associated with DD is readily visible on autofluorescence imaging in all individuals and that there are detectable changes on SD-OCT even when the fundus appears normal on clinical examination.

At the cellular level, pigmentary retinopathy in DD has been suggested to be a sequela of the accumulation of outer segment remnants, ineffective mutant mitochondria and undegradable

lipofuscin in lysosomes of the RPE cells (Thompson et al. 2016). Furthermore, a recent experimental study in *Lamp2-KO* mice demonstrated altered autophagy and phagocytosis in RPE cells, age-dependent accumulation of lipids, basal laminar deposits, and thickening of Bruch's membrane, which resulted in RPE and photoreceptor cell loss. (citace) Thus available evidence supports that outer retinal deposits and both rod and cone degeneration are typical clinical findings in DD patients.

The severity of retinal pathology in our cohort generally increased with age, although females, when compared to similarly aged male patients, seemed to be less severely affected. The most advanced findings were present in the oldest male (10), who had the lowest BCVA, marked cone-rod involvement, in addition to pigmentary retinopathy. Bearing in mind the limits of XCI testing in WBCs for predicting pathology in non-hematologic tissues, we presume that the ocular/retinal abnormalities in female patients with DD reflect the XCI-induced mosaic expression of the mutant *LAMP2* allele.

Females with non-homogenous distribution of heterozygous *de novo LAMP2* mutations in their tissues (somatic mosaicism) represent a specific and diagnostically neglected patient/carrier group (Majer et al. 2014; Sikora et al. 2015). Clinical presentation in these individuals is likely very variable. A *de novo* somatic mosaic for a *LAMP2* variant in a symptomatic female with DD presenting with cardiomyopathy and also exhibiting peripheral pigmentary retinopathy has been recently reported by Meinert et al. (2019). In contrast, in female 11 from our cohort, retinal pathology was the only detectable DD-associated abnormality.

High resolution SD-OCT allowed for more detailed visualization of retinal pathology. We demonstrate for the first time, that DD manifests, apart from previously reported abnormalities of the RPE and photoreceptor layers, with focally increased signals in the outer nuclear layer corresponding histologically to photoreceptor nuclei. The biological explanation

of these observations is currently uncertain. We also extend the spectrum of autofluorescence imaging abnormalities associated with DD.

Unlike non-syndromic retinitis pigmentosa (Strong et al. 2017), the finding of cystoid macular oedema in pigmentary retinopathy associated with DD is uncommon. In this study it was present in only one eye, and previously has been observed bilaterally in one other individual with DD (Mack 2014).

In summary, this study provides deep ocular phenotyping in the largest cohort of patients with DD reported to date, highlighting the utility of detailed ophthalmic examination and imaging in the identification of *LAMP2* variant carriers, including individuals with very low somatic mosaicism. It also provides a rationale for molecular genetic and/or further functional investigation in individuals with pigmentary retinopathy since this may be the only sign of a life threatening condition such as DD. High resolution imaging with SD-OCT and autofluorescence imaging should become an integral part in the overall diagnostic multidisciplinary approach in families with DD.

ACKNOWLEDGEMENTS

This work was supported by AZV-MZ 15-27682A, NU20-07-00182, NV19-08-00122 and SVV UK 260516. Institutional support was provided by UNCE 204064 and PROGRES Q26 /LF1 research programs of the Charles University and RVO-VFN 64165/2012 program of the General University Hospital in Prague. MM is supported by a grant from the National Institute for Health Research Biomedical Research Centre at Moorfields Eye Hospital National Health Service Foundation Trust and UCL Institute of Ophthalmology.

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FIGURE LEGENDS

Fig. 1. Ocular imaging and static perimetry in selected patients with Danon disease. For each subject fundus photographs (left column), magnified areas of the retinal periphery (left middle column), fundus autofluorescence (right middle column), and 50° visual field sensitivity map (right column), of the right eye is shown. Images are ordered by increasing age and sex. Female 2 (A), female 3 (B), female 6 (C), male 8 (D), male 9 (E), and male 10 (F). Note the pigmentary retinopathy, predominantly in the peripheral retina. Fundus autofluorescence imaging demonstrates hypo- and hyperautofluorescent changes corresponding to the mottled areas of retinal pigment epithelium. Diffuse loss of sensitivity, more profound in males, can be observed on static perimetry. The severity of findings increases with age.

Fig. 2. Variability of spectral-domain optical coherence tomography (SD-OCT) findings in Danon disease. Female 1 (19 years) (A), female 3 (27 years) (B), female 5 (39 years) (C), female 6 (41 years) (D), male 8 (17 years) (E), and male 10 (35 years) (F). Note the hyperreflective areas in the outer nuclear layer (asterisks), focal disruptions of the ellipsoid zone (EZ) (triangles), and hyperreflective deposits (arrows) at the interface of the retinal pigment epithelium and EZ layers.

Fig. 3. Ocular phenotyping in an asymptomatic female (11) – a somatic mosaic for a *LAMP2* pathogenic variant. Normal appearance on fundus photography of the right (A) and left (C) eye. Fundus autofluorescence of the right (B) and left (D) eye, note only one hyperautofluorescent spot in the right eye (arrow), abnormal fundus autofluorescence pattern in the left eye with a number of hypoautofluorescent (asterisks) and a few hyperautofluorescent (arrows) spots. Spectral-domain optical coherence tomography images of the right (E) and left (F) eye, with the area corresponding to the hyperautofluorescent spot denoted by an asterisk. Normal full-field ERG responses in the right (G – scotopic), (H – photopic), (K – pattern) and left (I – scotopic), (J – photopic), (M – pattern) eye, and decreased foveal responses, to a lesser extent in the right (L) than left (N) eye on multifocal ERG.