

# Acute optic neuropathy associated with a novel *MFN2* mutation

Luca Leonardi<sup>1</sup> · Christian Marcotulli<sup>1</sup> · Eugenia Storti<sup>2</sup> · Alessandra Tessa<sup>2</sup> ·  
Mariano Serrao<sup>1</sup> · Vincenzo Parisi<sup>3</sup> · F. M. Santorelli<sup>2</sup> · Francesco Pierelli<sup>4</sup> ·  
Carlo Casali<sup>1</sup>

Received: 19 March 2015 / Revised: 15 April 2015 / Accepted: 17 April 2015  
© Springer-Verlag Berlin Heidelberg 2015

**Abstract** Mutations in the mitofusin 2 (*MFN2*) gene cause CMT2A the most common form of autosomal dominant axonal Charcot–Marie–Tooth (CMT). In addition, mutations in *MFN2* have been shown to be responsible for Hereditary Motor Sensory Neuropathy type VI (HSMN VI), a rare early-onset axonal CMT associated with optic neuropathy. Most reports of HSMN VI presented with a sub-acute form of optic neuropathy. Herein, we report a CMT2A patient, who developed very rapidly progressing severe optic neuropathy. A 40-year-old Caucasian man was evaluated for gait disturbance and lower limbs weakness, slowly progressed over the last 2 years. Due to clinical data and family history, a diagnosis of CMT2 was made. The novel heterozygous c.775C > T (p.Arg259Cys) mutation in *MFN2* was detected in the patient and his clinical affected mother. Interestingly, the patient developed a severe sudden bilateral visual deterioration few years early, with clinical and instrumental picture suggestive of acute bilateral optic neuropathy. Our report expands the spectrum of *MFN2*-related manifestation because it indicates that visual symptoms of HSMN VI may enter in the differential with acquired or hereditary acute optic neuropathies, and that severe optic neuropathy is not invariably an early manifestation of the disease but may occur as disease progressed. This report could have an

impact on clinicians who evaluate patients with otherwise unexplainable bilateral acute-onset optic neuropathy, especially if associated with a motor and sensory axonal neuropathy.

**Keywords** CMT2A · HSMN VI · *MFN2* · Bilateral acute optic neuropathy

## Background

Mutations in the mitofusin 2 gene (*MFN2*) cause CMT2A (MIM 609260), the most common form of autosomal dominant axonal Charcot–Marie–Tooth (CMT) [1]. In addition, mutations in *MFN2* have been shown to be responsible for Hereditary Motor Sensory Neuropathy type VI (HSMN VI, MIM 601152), a rare early-onset axonal CMT associated with optic neuropathy [2–4]. Most reports of HSMN VI presented patients with bilateral visual acuity deterioration, central scotoma, and color vision defects, developing over weeks or months, as in a sub-acute form of optic neuropathy [2–4]. Herein, we report a CMT2A patient, who developed very rapidly progressing severe optic neuropathy.

## Case report

A 40-year-old Caucasian man was admitted to our neurological rehabilitation unit for lower limbs weakness and gait disturbance. Symptoms had started a few years earlier, and progressed slowly over the last 2 years. The patient used a cane to walk and required intermittent unilateral support. At examination, the patient showed unsteady, stepping gait. Walking on his toes and heels was impossible as well as in

✉ Luca Leonardi  
leonardi.luca89@gmail.com

<sup>1</sup> Dept. Scienze e Biotecnologie Medico-Chirurgiche, Rome Sapienza University Polo Pontino, Rome, Italy

<sup>2</sup> Molecular Medicine, Department of Developmental Neuroscience, IRCCS Stella Maris, Pisa, Italy

<sup>3</sup> G.B. Bietti Foundation-IRCCS, Rome, Italy

<sup>4</sup> IRCCS Neuromed Institute, Pozzilli, IS, Italy

tandem. He did not get up from the squatting position. He maintained the Romberg position, but with multidirectional swaying upon eyes closure. Deep tendon reflexes were reduced in the legs but not in the arms. There was no Babinski sign. Muscle strength was reduced distally with MRC scores of 2 on foot dorsal flexion, 0 on toe dorsal flexion, and 4 on foot plantar flexion, bilaterally. Pin-prick sensation was symmetrically reduced at the ankles and feet; deep sensation was severely reduced at the knees and absent at the ankles. Upper limbs strength and sensation were normal. A complete NCS/EMG evaluation showed reduced cMAP and SNAP amplitudes with normal NCVs, consistent with motor and sensory axonal neuropathy. His 64-year-old mother was similarly affected upon neurological examination. The patient's CMTNS (Charcot–Marie–Tooth Neuropathy Score) was 14 (moderately affected) [5]. Direct gene testing in peripheral blood showed that both the patient and his mother carried the novel heterozygous c.775C > T (p.Arg259Cys) mutation in *MFN2*. The mutation was not found in 300 healthy, ethnically matched control chromosomes and not listed in the large exome collection from the Exome Aggregation Consortium (ExAC) (Exome Aggregation Consortium, Cambridge, MA, <http://exac.broadinstitute.org>, last accessed January 2015). In silico analyses using Polyphen2 ([genetics.bwh.harvard.edu/pph2](http://genetics.bwh.harvard.edu/pph2)) and MutPred ([mutpred.mutdb.org/](http://mutpred.mutdb.org/)) showed that the p.Arg259Cys mutation is probably damaging with a score of 0.999 (sensitivity: 0.14; specificity: 0.99). Of note, a different mutation at the same residue (p.Arg259Leu) has been associated with a CMT2A phenotype with upper motor signs [6].

However, the major point of interest in our patient's medical history was the occurrence of acute-onset optic neuropathy. A few months before we had a chance to first see him, the patient, while working as a street advertiser, started complaining of visual deterioration over the entire visual field with a rapid progression within a few hours without significant ocular pain. His visual acuity was severely impaired when he was examined in the emergency eye clinic. At that time, the patient was unable to recognize faces and read road signs and banners. General physical examination was reported as normal, even though his pre-existing neurological condition was clearly overlooked. Routine blood tests and brain CT scan were unremarkable and brain MRI did not show structural alterations nor enhancements in cortical–subcortical regions nor in the optic nerves. The patient received a diagnosis of bilateral retrobulbar optic neuritis and was put on high dose steroid treatment without any improvement over the next few days. Admitted in the ophthalmological department a week later, his visual acuity was 2/30 (right), and 1/30 (left). Ishihara color test showed impaired color perception (1/22, bilaterally). Ocular fundus was first examined at that time and

reported as pale and with excavated optic discs. Visual field examination revealed bilateral central scotoma. Retinal fluorangiography did not show vascular alteration. Heart and epiaortic Eco-color-Doppler scanning were negative. Risk factors for acute optic neuropathy such as smoking, alcohol use and other social and personal habits were excluded. Blood tests, including C-reactive protein, erythrocyte sedimentation rate, angiotensin converting enzyme, thyroid function tests, VDRL, TPHA, B12 vitamin, B1 vitamin, ANA, ENA, p-ANCA, c-ANCA test, were all normal. Optical coherence test (OCT) scan showed bilateral reduction of macular thickness, due to selective depletion of ganglionic cells and reduction of retinal fiber layers thickness, more severe over the temporal sectors. Pattern electroretinography (PERG) and visual evoked potentials (VEPs) showed a dysfunction of retinal ganglion cells associated with a delay in neural conduction along both large and small optic nerve axons [7]. Direct gene testing of the *OPA1* gene (MIM 165500), whole mitochondrial DNA sequencing in blood as well as direct testing for the mtDNA mutations associated with Leber Hereditary Optic Neuropathy (LHON, MIM 535000) were all normal. Over the following 18 months, his visual problems remained essentially unchanged. Ophthalmological examination of the proband's mother did not reveal any abnormality.

## Conclusions

Mutations in *MFN2* are associated with a spectrum of clinical manifestations wider than CMT2 neuropathy alone, such association with pyramidal signs [6, 8], early-onset stroke [9], hearing loss [4] and optic neuropathy (as in the HMSN VI form). Visual manifestations in the patients usually develop over weeks or months as in a sub-acute or chronic form of optic neuropathy [2–4]. Conversely, the patient we described developed a form of sudden and severe acute bilateral optic neuropathy that was reminiscent of the visual phenotype usually associated with LHON. Our report expands the spectrum of *MFN2*-related manifestation because it indicates that visual symptoms of HMSN VI may enter in the differential with acquired or hereditary acute optic neuropathies, and that severe optic neuropathy is not invariably an early manifestation of the disease but may occur as disease progressed. It is possible to speculate that in this family, the specific mutation in *MFN2* presents variable penetrance accounting for a less severe phenotype in the mother and that it may specifically impact on mitochondrial dynamics in the retinal ganglion cells, justifying at least in part the acute loss of central vision resembling what is described in young LHON patients [10].

**Acknowledgments** The contribution of the Fondazione Bietti in this paper was supported by Ministry of Health and Fondazione Roma.

**Conflicts of interest** The authors declare that they have no conflict of interest or financial relationship to disclose.

**Ethical standards** Written informed consent was taken from patients, and therefore, this study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## References

- Züchner S, Mersiyanova IV, Muglia M et al (2004) Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. *Nat Genet* 36:449–451
- Züchner S, De Jonghe P, Jordanova A, Claeys KG, Guergueltcheva V, Cherninkova S, Hamilton SR, Van Stavern G, Krajewski KM, Stajich J, Tournev I, Verhoeven K, Langerhorst CT, de Visser M, Baas F, Bird T, Timmerman V, Shy M, Vance JM (2006) Axonal neuropathy with optic atrophy is caused by mutations in mitofusin 2. *Ann Neurol* 59:276–281
- Verhoeven K, Claeys KG, Züchner S, Schröder JM, Weis J, Ceuterick C, Jordanova A, Nelis E, De Vriendt E, Van Hul M, Seeman P, Mazanec R, Saifi GM, Szigeti K, Mancias P, Butler IJ, Kochanski A, Ryniewicz B, De Bleecker J, Van den Bergh P, Verellen C, Van Coster R, Goemans N, Auer-Grumbach M, Robberecht W, Milic Rasic V, Nevo Y, Tournev I, Guergueltcheva V, Roelens F, Vieregge P, Vinci P, Moreno MT, Christen HJ, Shy ME, Lupski JR, Vance JM, De Jonghe P, Timmerman V (2006) MFN2 mutation distribution and genotype/phenotype correlation in Charcot-Marie-Tooth type 2. *Brain* 129:2093–2102
- Chung KW, Kim SB, Park KD, Choi KG, Lee JH, Eun HW, Suh JS, Hwang JH, Kim WK, Seo BC, Kim SH, Son IH, Kim SM, Sunwoo IN, Choi BO (2006) Early onset severe and late-onset mild Charcot-Marie-Tooth disease with mitofusin 2 (MFN2) mutations. *Brain* 129:2103–2118
- Shy M, Blake J, Krajewski K, Fuerst D, Laura M, Hahn A, Li J, Lewis R, Reilly M (2005) Reliability and validity of the CMT neuropathy score as a measure of disability. *Neurology* 64(7):1209–1214
- Ajrroud-Driss S, Fecto F, Ajroud K, Yang Y, Donkervoort S, Siddique N, Siddique T (2009) A novel de novo MFN2 mutation causing CMT2A with upper motor neuron signs. *Neurogenetics* 10(4):359–361
- Ziccardi L, Sadun F, De Negri AM, Barboni P, Savini G, Borrelli E, La Morgia C, Carelli V, Parisi V (2013) Retinal function and neural conduction along the visual pathways in affected and unaffected carriers with Leber's hereditary optic neuropathy. *Invest Ophthalmol Vis Sci* 54(10):6893–6901
- Zhu D, Kennerson ML, Walizada G, Züchner S, Vance JM, Nicholson GA (2005) Charcot-Marie-Tooth with pyramidal signs is genetically heterogeneous: families with and without MFN2 mutations. *Neurology* 65:496–497
- Chung KW, Cho SY, Hwang SJ, Kim KH, Yoo JH, Kwon O, Kim SM, Sunwoo IN, Züchner S, Choi BO (2008) Early-onset stroke associated with a mutation in mitofusin 2. *Neurology* 70:2010–2011
- Carelli V, Chan DC, Mitochondrial DNA: impacting central and peripheral nervous systems. *Neuron*. 2014; 84(6):1126–1142. ISSN 0896-6273