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ORIGINAL COMMUNICATION

Pigmentary degenerative maculopathy as prominent phenotype in an Italian SPG56/*CYP2U1* family

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Abstract SPG56 is an autosomal recessive form of hereditary spastic paraplegia (HSP) associated with mutations in *CYP2U1*. There is no clear documentation of visual impairment in the few reported cases of SPG56, although this form is complex on clinical ground and visual deficit are extremely frequent in complicated HSP. We report three patients in a consanguineous family harboring the novel homozygous c.1168C>T (p.R390*) in SPG56/*CYP2U1,* and showing a pigmentary degenerative maculopathy associated with progressive spastic paraplegia. Furthermore, we characterized precisely the ophthalmologic phenotype through indirect ophthalmoscopy, retinal optical coherence tomography and visual evoked potentials. This is the first formal report of pigmentary degenerative maculopathy associated with a *CYP2U1* homozygous mutation.

Keywords HSPs · SPG56 · CYP2U1 · Pigmentary degenerative maculopathy

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Introduction

Hereditary spastic paraplegias (HSPs) are genetically determined neurodegenerative disorders characterized by progressive spasticity and weakness of lower limbs. The occurrence of additional neurological and non-neurological manifestations defines if HSPs are pure or complex forms, although complex phenotypes are increasingly detected among previously defined pure forms. Rapid technological progress in the molecular genetics of HSPs has allowed the identification of 84 different disease loci and the cloning of 67 corresponding genes [1]. SPG56 (HGNC nomenclature, http://www.genenames.org), previously named as SPG49, is an autosomal recessive (AR) form of HSP associated with mutations in *CYP2U1* [2]. There is no clear documentation of visual impairment in the few reported cases of SPG56 [2, 3], although this form is complex on clinical ground and visual deficit are extremely frequent in complicated HSP [1]. Herein, we report three patients in a consanguineous family harboring a homozygous mutation in *CYP2U1* and showing a pigmentary degenerative maculopathy associated with progressive spastic paraplegia.

Patients and methods

Patient 1 is a 50-year-old man who complained of progressive unsteady gait with onset after age 30 years. At neurological examination, he showed spastic gait, increased muscle tone in the legs, brisk tendon reflexes in the lower limbs, and bilateral Babisnki sign. Spastic paraparesis rating scale score [4] was 8/52. The patient also presented mild cerebellar signs, consisting in difficulties in tandem gait, bilateral intentional hand tremor, dysarthria and fixation nystagmus. Electromyography and nerve

conduction studies disclosed a subclinical axonal, sensory motor polyneuropathy. Brain MRI showed mild brainstem and cerebellar atrophy as well as a moderately thinner corpus callosum (Fig. 1). The similarly affected 46-year-old sister had onset of her motor problems after age 30 years. Her SPRS score is 7/52. Patient 3, a 42-year-old man, is the first cousin of Patient 1 on both paternal and maternal sides. This patient started complaining of gait difficulties and urinary urgency since his late 30s. At examination, he showed a mild spastic gait with moderate spasticity and brisk reflexes in the lower limbs. Bilateral foot clonus and Babinski sign were also noted. SPRS was 5/52. No other neurological signs were disclosed and there was no neurophysiological evidence of axonal neuropathy. Brain MRI was unremarkable. After obtaining a written informed consent, genomic blood DNA from the three propositi was included among samples from a group of undiagnosed patients with sporadic or familial spastic paraparesis to be analyzed by *SpastoPlex2.0*, a customized targeted gene panel in next-generation sequencing able to investigate the coding regions of all genes thus far linked to HSP, spastic ataxias or related motor diseases. In the three patients we identified the novel homozygous c.1168C>T (p.R390*) in SPG56/*CYP2U1* predicting a premature protein truncation. Interestingly, all patients complained of visual impairment. It started before the onset of motor manifestations in Patient 1 (at the age of 25 years) and at the age in Patients 2 and 3. Patients 1 and 3 underwent comprehensive ophthalmologic examinations including best-corrected visual acuity (BCVA), measurement with the Early Treatment Diabetic Retinopathy Study (ETDRS) charts, expressed as a logarithm of the minimum angle of resolution (logMAR), slit-lamp biomicroscopy, intraocular pressure (IOP) measurement, indirect ophthalmoscopy with 90D non-contact lens (Volk), color testing by monocular administration of Ishihara pseudoisochromatic plates (24 plates edition, Kanehara Trading Inc., Tokyo, Japan) in natural daylight, Amsler grid test. Retinal optical coherence tomography (OCT) was performed in Patients 1 and 3 with the RTVue Model-RT100 version 3.5 (Optovue Inc,

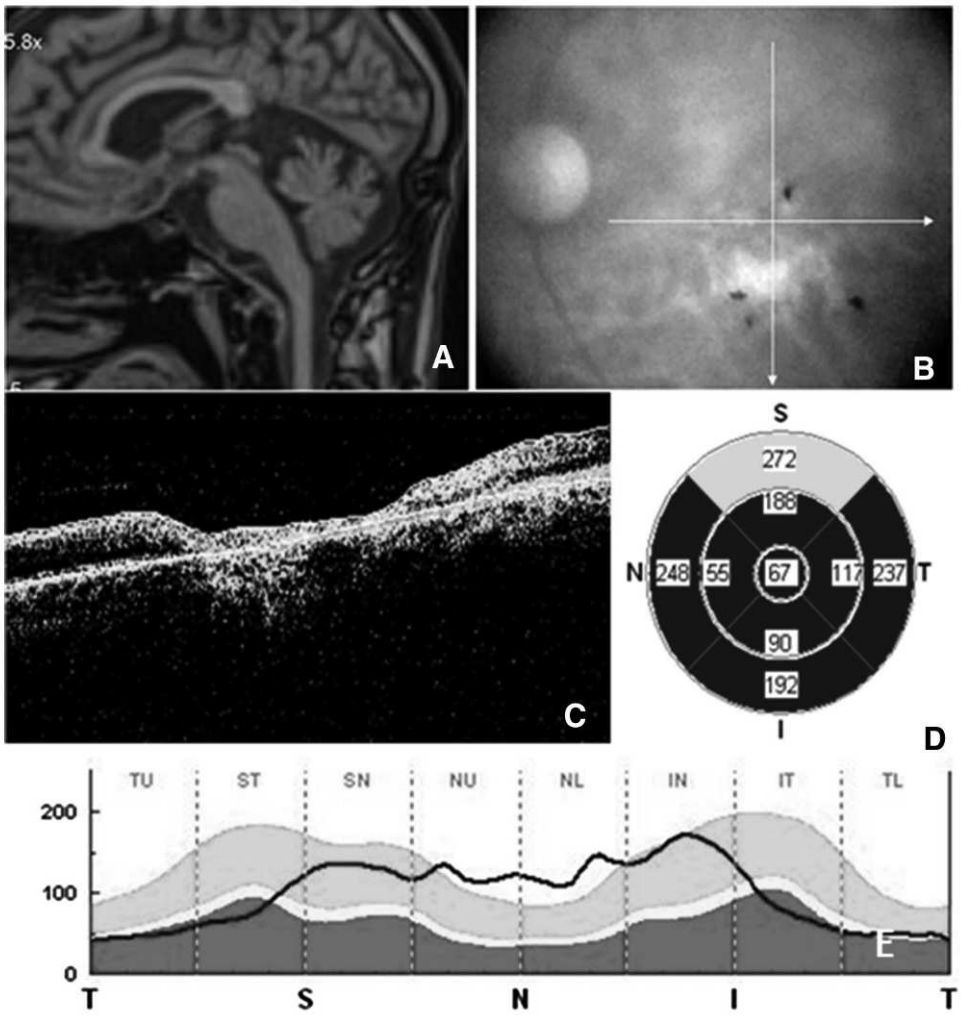

Fig. 1 Representative images from Patient 1. Sagittal brain MRI scan showing brainstem and cerebellar atrophy and the moderately thinner corpus callosum (**a**), left eye fundus (**b**), the *red*-free image provided by the OCT system (**c**), the OCT line scan from the macula (**d**), and the macular thickness map and the RNFL thickness profile (**e**)

Fremont, CA, USA). Patients were also submitted to electrophysiological tests by recording the visual evoked potentials (VEP). Both patients presented a reduced central visual acuity with bilateral BCVA of 0.1 LogMAR (ETDRScharts) (or 20/200 or 0.1 Snellen), with the ability to fix a target at the distance of 114 cm during the VEP recordings. The color test and the intraocular pressure measurement were normal. The Amsler grid test denoted metamorphopsia in the superior sector in both eyes. Indirect ophthalmoscopy showed absence of optical media opacities, ocular fundus appearance of macular atrophy with pigmentary changes of the retinal pigmented epithelium, and mild paleness of the temporal sector of the optic nerve in both eyes. Upon manual acquisitions of the scans, we observed that OCT lines passing through the fovea showed reduced central retinal thickness (CRT RE = 80 μm, LE = 60 μm in Patient 1, RE = 97 μm, LE = 80 μm in Patient 3) and disruption of the whole outer retina elements, with loss of the inner segment/outer segment (IS/OS) junction and of the external limiting membrane (ELM). Macular volume was also reduced (RE = 4.87 mm^3 and LE = 5.03 mm^3 in Patient 1, RE = 5.21 mm^3 and LE = 5.48 mm^3 in Patient 3) (Fig. 1). The retinal nerve fiber layer (RNFL) scans showed normal thickness values in all sectors but the temporal one, that was markedly reduced in both eyes compared to the normal values provided by the system database (Fig. 1). We also found VEP abnormalities consisting of increased P100 implicit times and reduced N75-P100 amplitude values in response to 60′ and 15′ checkerboards in both eyes with respect to the 95 % confidence limits previously observed in control subjects [5]. The VEP abnormalities suggested an impairment involving both the large and the small axons of the optic nerve [5]. These clinical and instrumental findings were indicative of bilateral chronic pigmentary degenerative maculopathy. We examined the four heterozygous healthy parents as well as several additional relatives (even non carriers of the pathogenic mutation in SPG56/*CYP2U1*) and found no other individual with either neurological or visual problems.

Discussion and conclusion

Mutations in SPG56/*CYP2U1* are associated with both pure and complicated forms of AR HSP. White matter lesions, basal ganglia calcifications, thinning of corpus callosum, mental retardation and infraclinical axonal motor and sensory neuropathy are the complicated features already described [2, 3]. “Maculopathy” was only shortly cited in one woman in the original describing report, without any thorough characterization or documentation [2]. This is the first formal report of pigmentary degenerative maculopathy associated with a *CYP2U1* homozygous mutation, with an extensive characterization of the ophthalmological phenotype. The occurrence of retinal degeneration seems consistent with the mitochondrial dysfunction hypothesized in SPG56 [2] and the predictive role of the gene product in lipid metabolism [1], fully placing it within the spectrum of mitochondrial disorders. Finally, pigmentary degenerative maculopathy was the initial manifestation of the disease in Patient 1 years before the onset of other neurological features and is the cause of major complaints in all patients. This report should increase the awareness of such a complex phenotype among both neurologists and ophthalmologists.

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Compliance with ethical standards

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

Ethical standards This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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