Pigmentary degenerative maculopathy in a CYP2U1/SPG56 family

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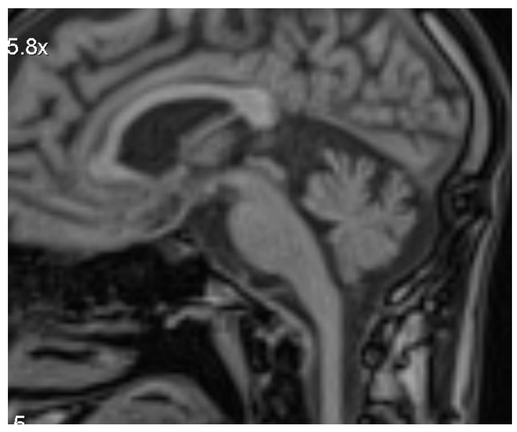
Introduction: SPG56 is an autosomal recessive form of Hereditary Spastic Paraplegia (HSP) caused by mutations in *CYP2U1*, a gene involved in lipid metabolism and mitochondrial function. Herein, we report three SPG56 patients with pigmentary degenerative maculopathy as a prominent clinical feature.

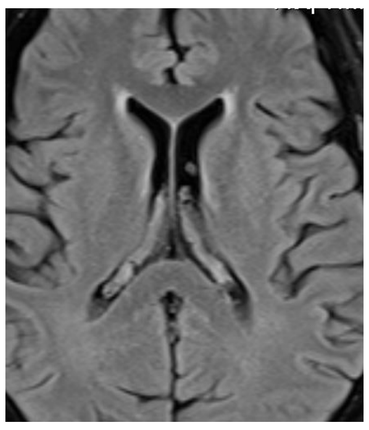
Materials/Methods: Patient 1 is a 50 year-old man, with progressive walking unsteadiness and progressive visual loss after age 30 years. His healthy consanguineous parents originated from a small village in Campania. He showed paraparetic gait, lower limbs spasticity and brisk tendon reflexes, bilateral Babisnki sign (SPRS 8/52) and mild cerebellar signs. EMG/NCS disclosed a subclinical axonal motor and sensory polyneuropathy. MRI showed mild brainstem and cerebellar atrophy as well as a moderately thinned corpus callosum. His 46-year-old sister was similarly affected with onset after age 30 years. Patient 3 is their 42 year-old first cousin on both mother's and father's side.

After extensive genetic analyses (ARSACS, SPG7, SPG11, SPG15), **a homozygous c.1168C>T (p.R390*) pathogenic mutation in the coding region of *CYP2U1*** was detected in all three patients, allowing a diagnosis of SGP56. As visual acuity of all patients was severely reduced (1/10 and 2/10, in patients 1 and 3 respectively), complete ophthalmologic evaluation, including (ocular fundus, OCT scan, PEV and PERG, was undertaken, which disclosed a pigmentary degenerative maculopathy

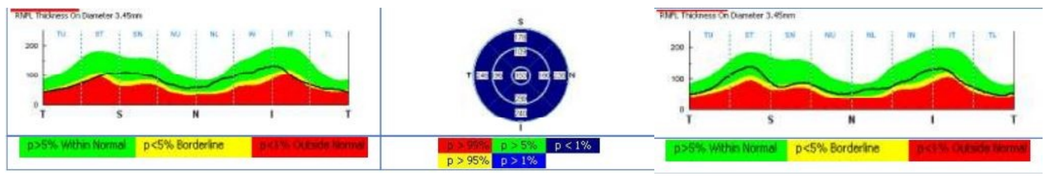
Pat 1 – Brain MRI

- Brainstem and cerebellar atrophy
- Thinned corpus callosum
- White matter changes





OD Pat. 1 OCT OS



Visus lontano	Visus vicino
OD: -2,50 sf= -0,50 Cyl:(45): 1,0/10	**OD:** -1,50 sf= -0,50 Cyl:(45): V carattere
OS: -2,75 sf= Cyl:( ): 1,0/10 (T)	**OS:** -1,75 sf= Cyl:( ): V carattere (T)

Esame senso Cromatico: Ishihara	
OD: 22/22	**OS:** 22/22

Esame del Fondo Oculare	
OD:	Maculopatia atrofica. Papilla ottica rosea e a margini netti.
OS:	Maculopatica atrofica, Lieve pallore temporale del nervo ottico.

OCT (Optical Coherence Tomography)

	Spessore Fibre Nervose Peripapillari (RNFL th)				
	temporale (µm)	**superiore (µm)**	**nasale (µm)**	**inferiore (µm)**	**totale (µm)**
OD:	51,33	95,25	67,09	104,80	79,62
OS:	61,76	100,20	62,32	104,61	81,95

OCT (Optical Coherence Tomography)

	Volume Maculare (mm^3)	
	OD: 5,21	**OS:** 5,48
	Descrizione	
OD:	Difficoltà operative per deficit di fissazione: spessore medio globale delle fibre nervose parapapillari nella norma con significativo deficit settoriale Temporale . Volumetria maculare ridotta per atrofia centrale	
OS:	Difficoltà operative per deficit di fissazione: spessore medio globale delle fibre nervose parapapillari nella norma con modesto deficit settoriale Temporale . Volumetria maculare ridotta per atrofia centrale	

Risposte elettrofunzionali - OD
PERG a 60' (stimolazione extramaculare) e a 15'(stimolazione maculare): tracciati: morfologicamente ben strutturati, con tempi di latenza nella norma ed ampiezze ridotte. PEV a 60' (stimolazione extramaculare) e a 15'(stimolazione maculare): tracciati morfologicamente ben strutturati, con aumento dei tempi di latenza ed ampiezze nei limiti della norma. Tempo retino corticale superiore ai limiti della norma a 60' e a 15' di stimolazione.

Risposte elettrofunzionali - OS
PERG a 60' (stimolazione extramaculare) e a 15'(stimolazione maculare): tracciati: morfologicamente ben strutturati, con tempi di latenza nella norma ed ampiezze ridotte. PEV a 60' (stimolazione extramaculare) e a 15'(stimolazione maculare): tracciati morfologicamente ben strutturati, con aumento dei tempi di latenza ed ampiezze nei limiti della norma. Tempo retino corticale superiore ai limiti della norma a 60' e a 15' di stimolazione.

Conclusioni - OD
Si rilevano alterazioni funzionali degli strati interni retinici (cellule e fibre ganglionari). Si rileva ritardo della conduzione nervosa post-retinica lungo gli assoni di grosso calibro e lungo il fascio papillo-maculare

Conclusioni - OS
Si rilevano alterazioni funzionali degli strati interni retinici (cellule e fibre ganglionari). Si rileva ritardo della conduzione nervosa post-retinica lungo gli assoni di grosso calibro e lungo il fascio papillo-maculare

Discussion/Conclusion: Mutations in *CYP2U1* are associated with both pure and complicated forms of HSP. White matter lesions, basal ganglia calcifications, thin corpus callosum, mental retardation , infraclinical axonal motor and sensory neuropathy have been described. "Maculopathy" has been only found in one female patient in the original paper describing SPG56. This is the first formal report of pigmentary degenerative maculopathy associated with *CYP2U1* mutation, which may reasonably be explained by the mitochondrial pathogenesis of the disorder.

References

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