Small fiber neuropathy in Amyotrophic Lateral Sclerosis: a skin biopsy and laser evoked potential combined study

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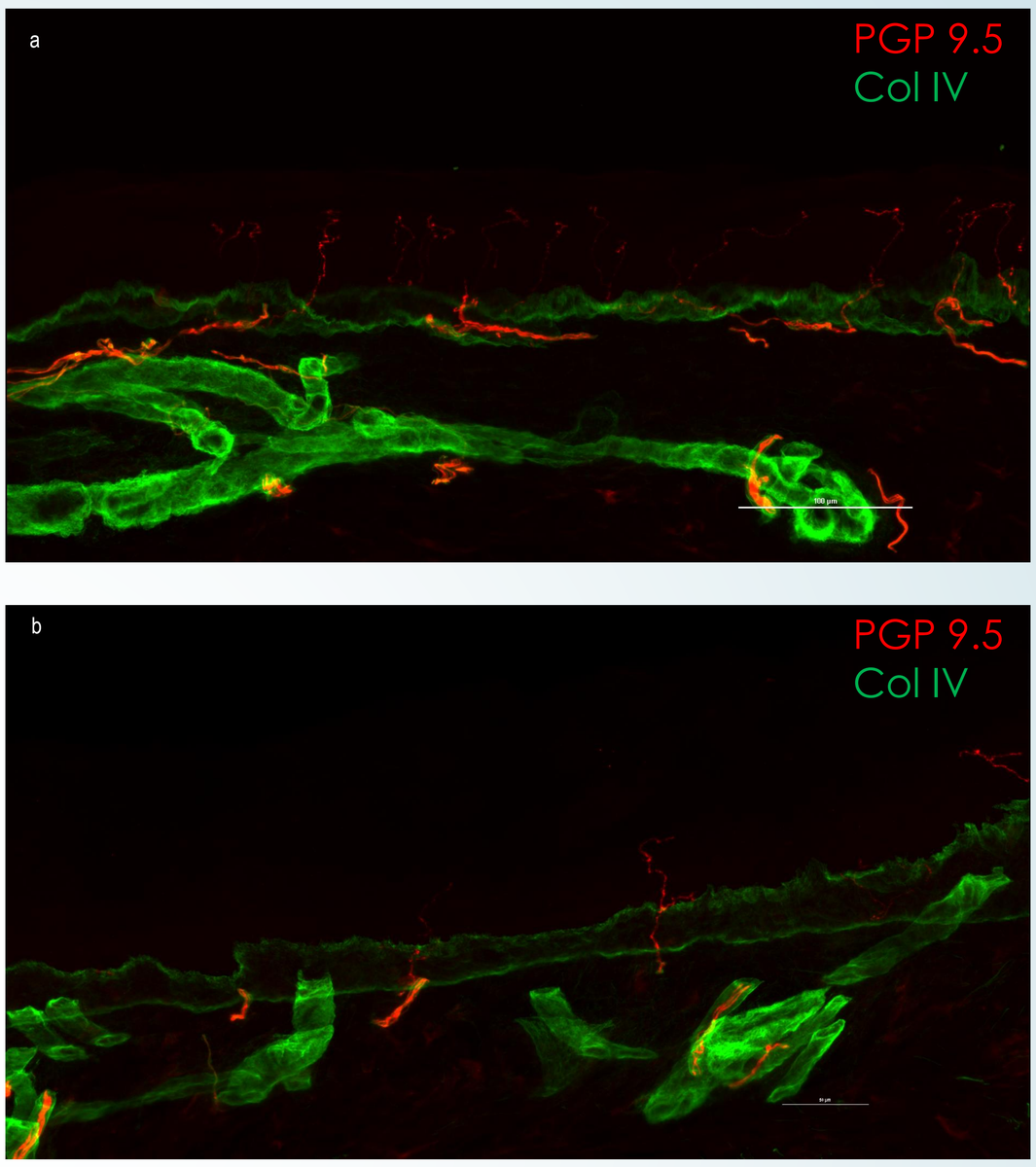
Objectives

Increasing evidence suggests that Amyotrophic lateral sclerosis (ALS) is a multisystem neurodegenerative disorder with prominent involvement of motor neurons. Skin biopsy studies have already showed a subclinical loss of intraepidermal nerve fibers in distal legs, occurring in ALS patients irrespective of the disease duration [1,2,3]. This study aimed at evaluating the performance of a battery of neurophysiological and morphological tests assessing the small fiber loss occurring in ALS.

Patient No.	Age	Sex	Height	Type of onset	Sural nerve conduction	Sensory complaints at onset	Duration of symptoms (months)	Foot LEPs	Hand LEPs	C-fiber LEPs	Trigeminal LEPs
1	72	M	174	Bulbar	Normal	None	60	Altered (< AMP)	Normal	Normal	Altered (> LAT)
2	65	M	178	Bulbar	Normal	None	18	Normal	Normal	Normal	Normal
3	72	F	162	Bulbar	Normal	None	12	Absent	Normal	Absent	Not tolerated
4	65	F	165	Pyramidal	Amplitude right>left	None	15	Normal	Normal	Absent	Normal
5	63	M	174	Flail limb	Normal	None	40	Normal	Normal	Normal	Altered (> LAT)
6	52	F	150	Flail limb	Normal	None	30	Normal	Normal	Normal	Altered (> LAT)
7	60	M	174	Spinal	Normal	Hypoestesia bilateral foot	60	Normal	Normal	Normal	Normal
8	60	M	177	Flail limb	Normal	None	60	Normal	Normal	Normal	Normal
9	55	F	168	Flail limb	Normal	None	24	Altered (< AMP)	Normal	Normal	Normal
10	73	F	155	Spinal	Normal	None	13	Normal	Normal	Altered (> LAT)	Normal
11	67	M	175	Spinal	Normal	None	11	Normal	Normal	Normal	Normal



Skin biopsy representative findings. Confocal double-stained images (40 x magnification) showing intraepidermal nerve fibre density at the distal leg in (a) a control subject and (b) a patient with amyotrophic lateral sclerosis (ALS). Nerve fibres are stained in red (protein-gene product 9.5) and basement membrane and the blood vessels are stained in green (collagen IV). Bar = 100 µm.

Materials and methods

Consecutive patients referred to our clinics for ALS were screened. Patients diagnosed as having definite or clinically probable or laboratory-supported ALS (according to the revised El Escorial criteria) took part to the study. We investigated large myelinated fibers with sural nerve conduction studies (NCS) and small fibers with laser-evoked potentials (LEPs) and skin biopsy in eleven consecutive patients (6 M, age 64,9±7,3 years, duration of symptoms 29,1±20,7 months), 3 with bulbar-onset, 3 with spinal-onset, 4 with flail limb onset and 1 with pyramidal syndrome. Only one patient complained of foot paresthesias. LEPs using a Nd:YAP laser stimulator of face, hand dorsum and distal leg were recorded in all patients. Skin biopsy was performed at the proximal and distal leg and intraepidermal nerve fiber (IENF) density was quantified according to the available published guidelines [4]. Findings were referred to age- and sex-adjusted normative values.

Results

Sural NCS was normal in all patients. Absence or reduced amplitude of Aδ-LEPs by foot stimulation was revealed in 27% of our sample. C-LEPs were absent in 27% patients. Alteration of both Aδ and C-LEPS was detected in only one patient. IEFN density was altered in 100% of patients (proximal leg: 7,9±3,2; distal leg: 3,9± 1,8).

Discussion

As previously suggested by several lines of evidence, our study has confirmed a small fiber involvement in our small cohort. Moreover, no difference in ALS subtypes was disclosed according to previous findings [3]. Neurodegenerative processes probably share similar molecular pathways, affecting both motor and sensory fibers. To our knowledge this is the first study using Nd:YAP LEPs and skin biopsy assessment in ALS patients. Between neurophysiological instruments, LEPs have been revealed as the most sensitive tool to detect small fiber loss in several neurological disorders. However, although a positive correlation between LEPs and skin biopsy has already been detected in single case reports and diabetic patients, sensitivity of skin biopsy appeared much higher than LEPs in diagnosing asymptomatic small fiber neuropathy in ALS patients.

References

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