Skin nerve phosphorylated α-synuclein deposits in Parkinson's disease with orthostatic hypotension

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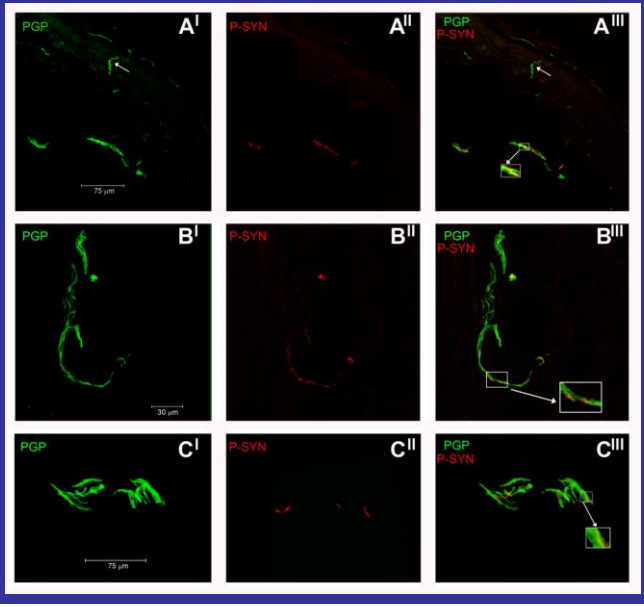
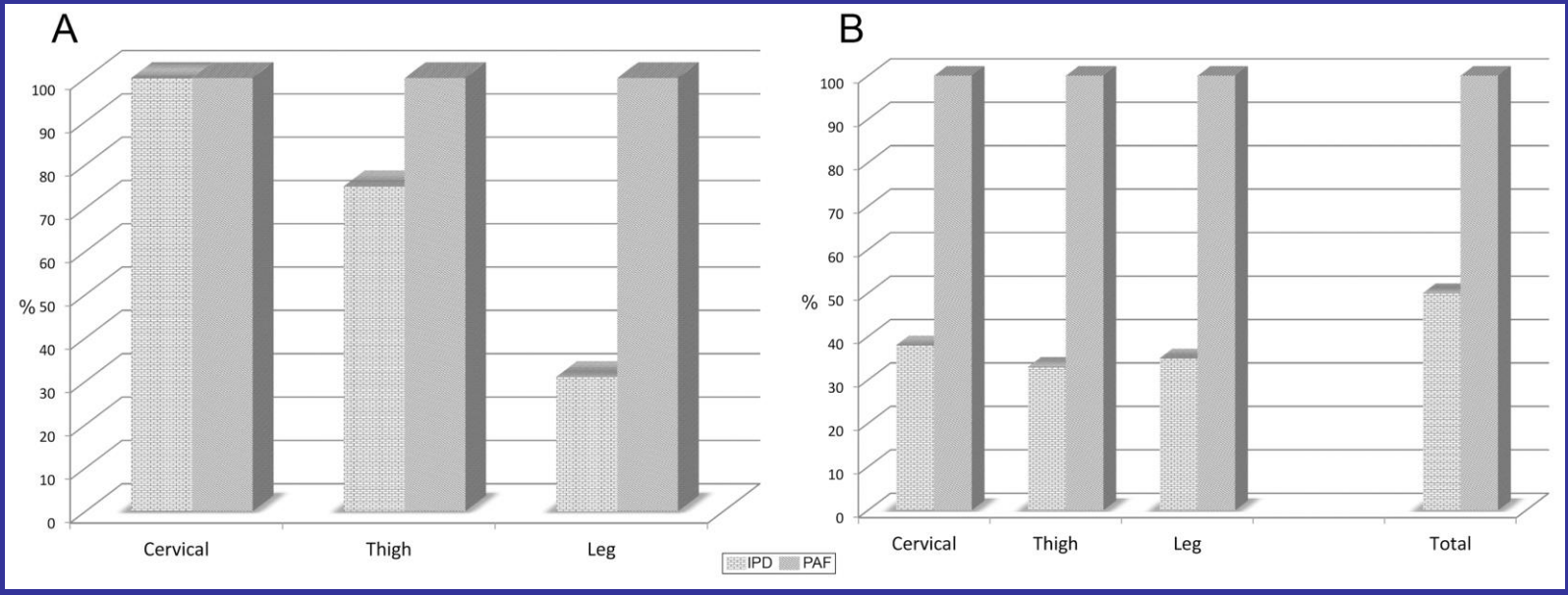
Orthostatic hypotension (OH) in Parkinson disease (PD)

- A minority of PD patients have OH (Velseboer et al, 2011)
- OH developed concurrent with or soon after the onset of the movement disorder (Goldstein 2006)
- Survival and disease progression of PD+ OH patients is much worse than in PD No OH (Stubendorff et al, 2012; Fereshtehnejad et al, 2015)

Idiopathic Parkinson disease and Pure autonomic failure: skin biopsy studies



Neurology 2014



Annals of Neurology 2016

Aims of the study

To investigate the distribution of phosphorylated α-synuclein (p-syn) deposits in skin nerves and clinical characteristics in idiopathic Parkinson disease patients with orthostatic hypotension (PD+OH) and a matched group of PD patients without dysautonomia (PD-OH)

Materials and methods

- 28 well-characterized IPD patients fulfilling diagnostic criteria according to the National Institute of Neurological Disorders and Stroke
  - late onset disorder (> 45 years-old)
  - L-dopa induced a good control of motor symptoms
  - No positive familiarity and normal MMSE excluding cognitive impairment
  - Diagnosis supported in all patients by cardiac uptake of [123-I])-MIBG and/or nigrostriatal dopamine transporter ligand [123I]ioflupane-DatScan

- 14 patients showed OH (BP fall >20 mmHg for systolic and 10 mmHg for diastolic BP during tilt test)

- 14 patients showed no OH during tilt test or standing; 7 of them were re-evaluated over a follow-up (4±2 years)

Materials and methods

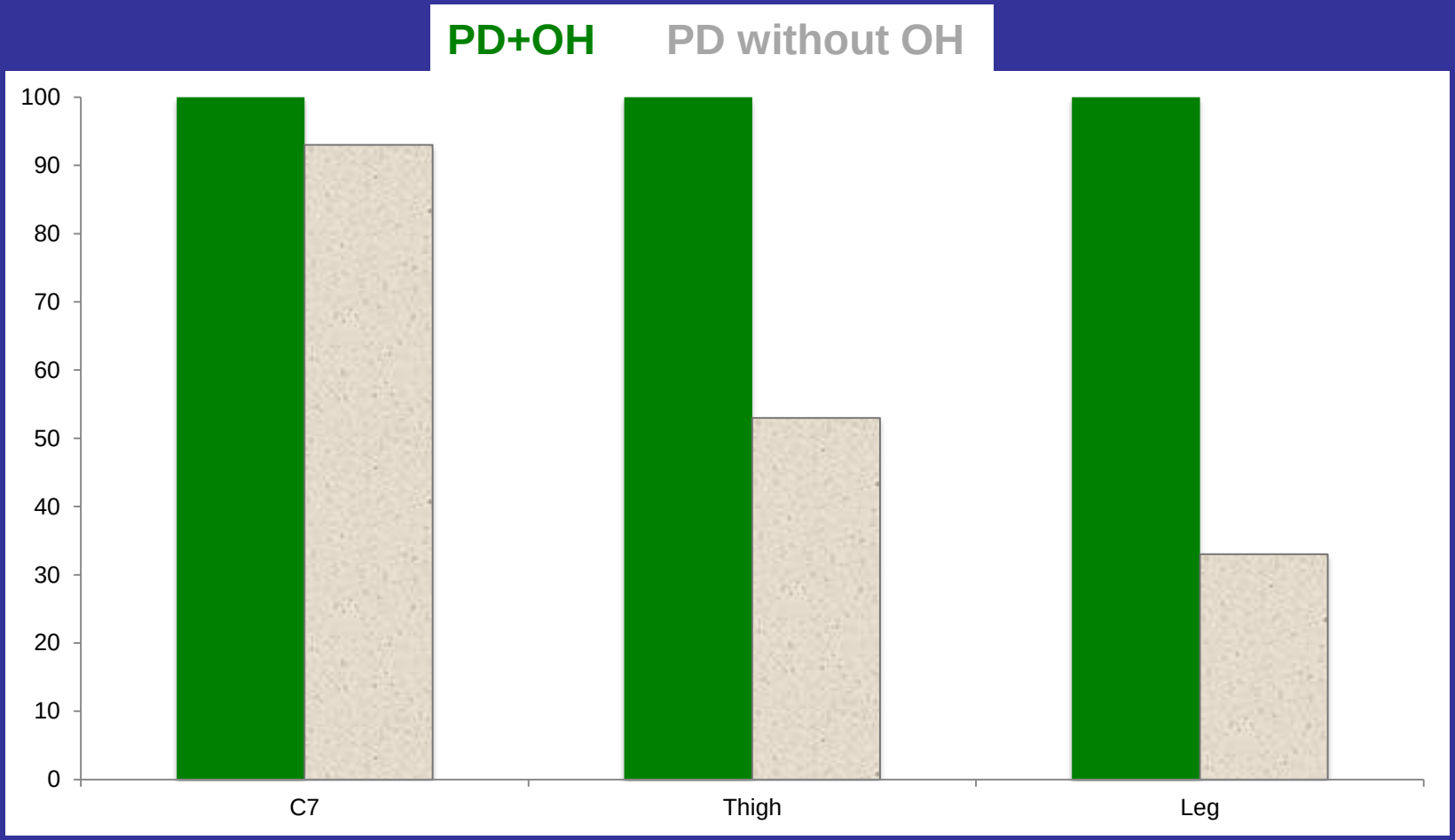
- Skin biopsy from proximal (i.e. cervical) and distal (i.e. thigh and leg) sites to study deposits of **phosphorylated α-synuclein**, considered the pathological form of α-synuclein. A second skin biopsy was taken 3-4 centimetres away from the first sample to assess the pattern of α-synuclein deposits

RESULTS

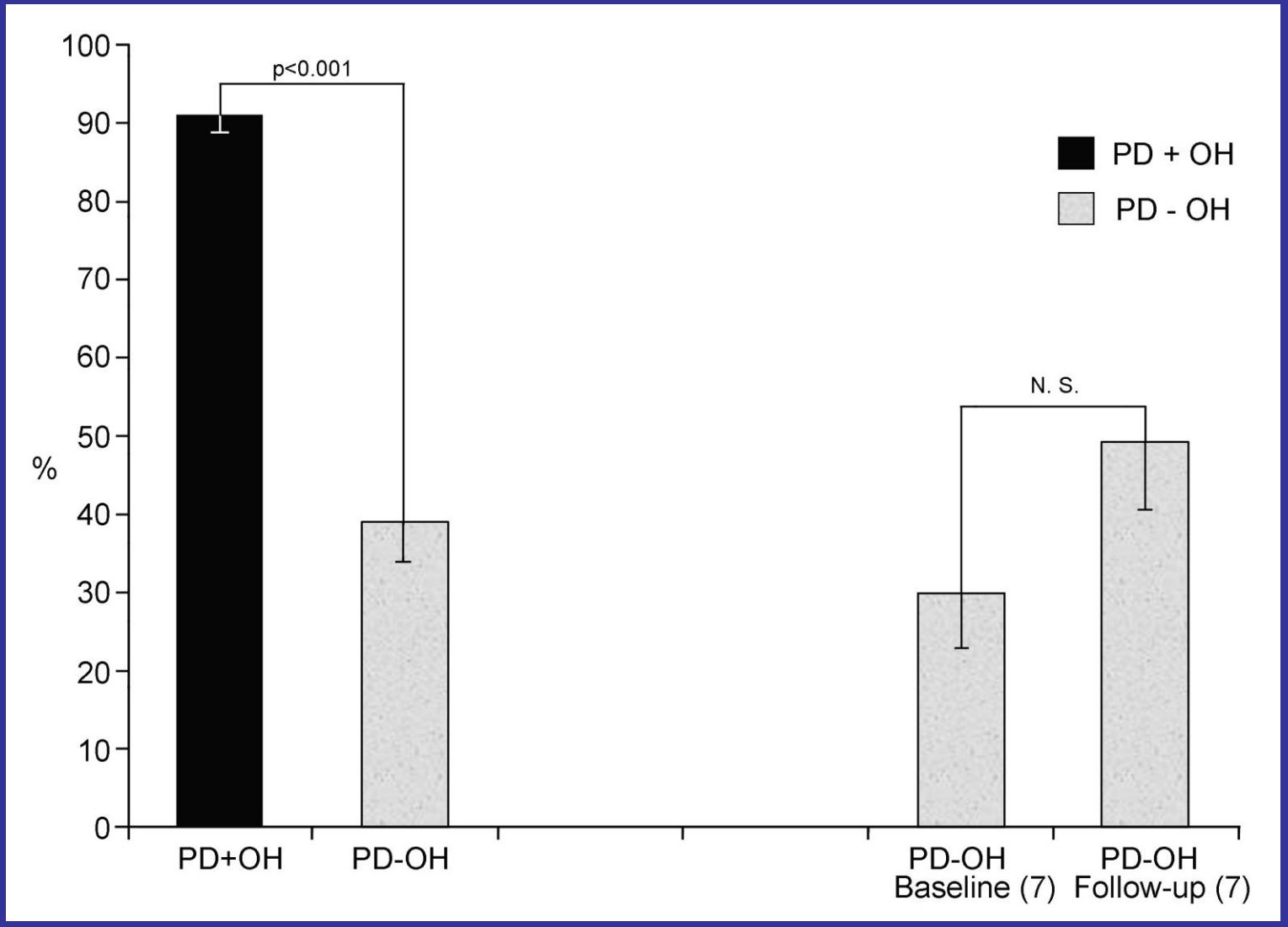
Clinical and demographic characteristics of recruited patients

PD+OH	Age	Sex	DD	UPDRS	H&Y	Aut. symp start*	Aut. symp	MMSEc	L-dopa		RBD	DatScan	MIBG	M.sub.
	(years)	male:female	(years)			(years)			mg/die					
1	76	F	6	30	2	1	OH	27	400		Present +	Ab	Ab	T
2	74	M	13	30	2	6	OH, UI, SL	27	500		Present	Ab	NP	both
3	81	M	22	45	5	3	OH	28	650		Present	Ab	NP	A
4	82	M	4	16	1	1	OH	24.4	300		Present	Ab	Ab	both
5	71	F	6	25	2	1	OH	24.7	600		-	Ab	NP	both
6	78	M	5	30	2	3	OH	26	250		Present	Ab	Ab	A
7	65	M	20	20	1	5	OH, UI	28	0		Present	Ab	Ab	A
8	73	M	12	30	2	2	OH, UI	25.4	800		Present	Ab	Ab	A
9	75	M	15	40	3	5	OH	24.7	200		Present	Ab	NP	A
10	68	F	9	23	1,5	4	OH	26.2	750		Present	Ab	NP	A
11	72	M	14	40	2,5	2	OH	26.4	300		-	Ab	Ab	A
12	82	M	12	35	2	3	OH, ID, UI, SL	27	750		Present	Ab	Ab	Both
13	72	M	8	25	1,5	0	OH	25	600		Present +	Ab	Ab	T
14	66	F	8	35	2,5	2	OH	26.2	750		Present	Ab	Ab	A
Mean±SD	74±6	10:04	11±5	30±8	2±1	3±2		27±1	489±249	%	**86§**	100	100	57^
PD-OH														
1	64	M	2	14	1	-	None	27.5	100		-	NP	Ab	A
2	59	M	1	15	1.5	-	None	27	100		Present	Ab	Ab	T
3	79	F	10	22	2	-	None	25	800		-	Ab	NP	A
4	72	F	2	33	2	-	None	26	400		Present	Ab	Ab	T
5	78	M	3	14	1.5	-	None	26.5	200		-	Ab	Ab	T
6	60	M	13	16	2.5	-	None	29	750		Present	Ab	Ab	T
7	64	M	3	11	1	-	None	27.5	300		Present	Ab	Ab	A
8	82	M	17	28	2	-	None	27.7	300		-	Ab	Ab	A
9	78	F	5	30	2	-	None	25	800		-	Ab	NP	A
10	74	M	10	41	4	-	None	25.4	650		-	Ab	NP	A
11	77	M	12	17	1	-	None	26	250		-	Ab	Ab	A
12	64	F	14	37	2.5	-	None	26.7	800		Present	Ab	NP	A
13	78	M	14	30	3	-	None	28.7	850		-	Ab	NP	T
14	73	M	25	32	3	-	None	29.3	600		-	Ab	NP	A
Mean±SD	72±8	10:04	10±7	24±10	2±1	-	-	26±2	493±284	%	36	100	100	64^

RESULTS: p-syn distribution

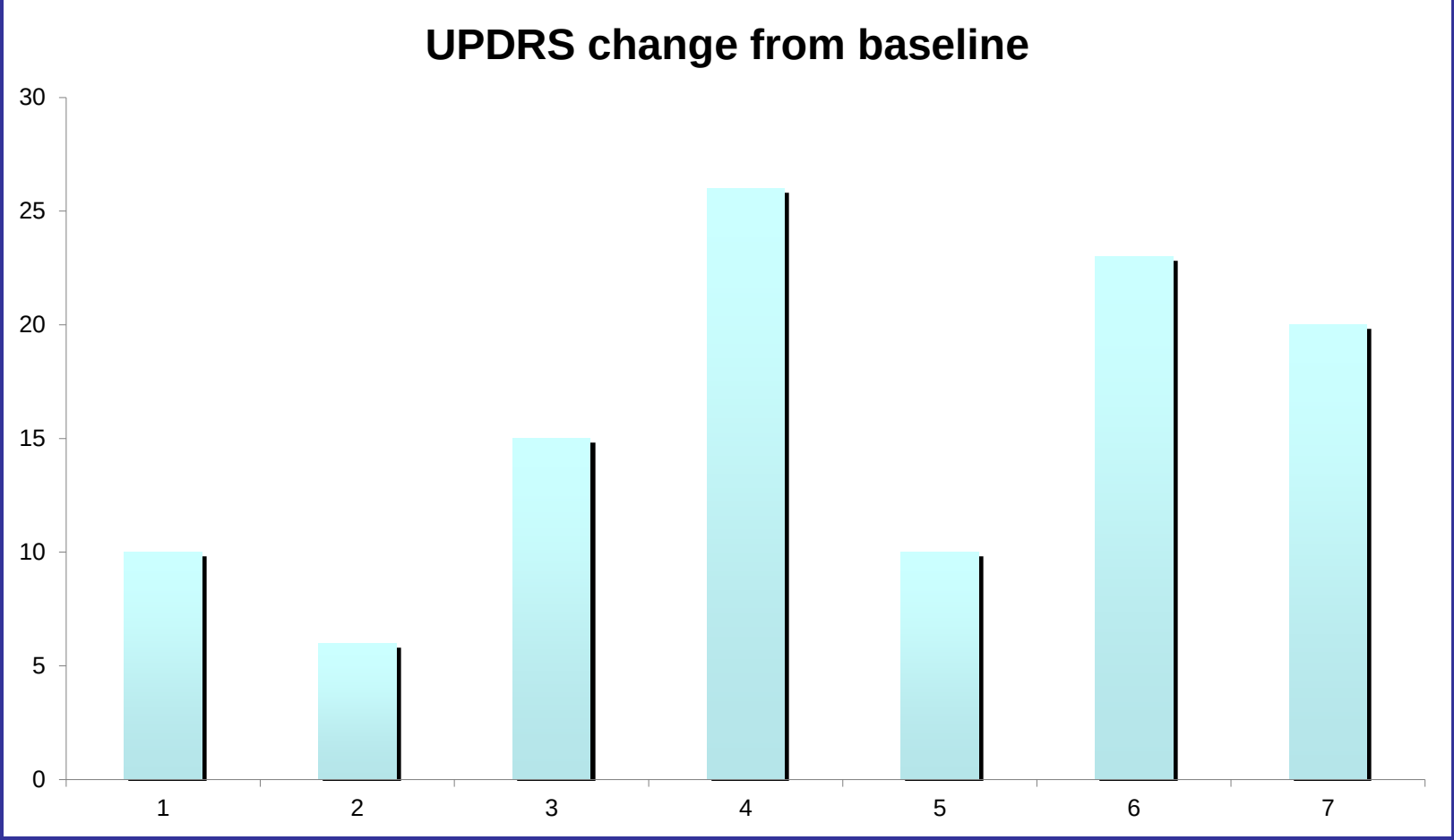


RESULTS: p-syn distribution



RESULTS

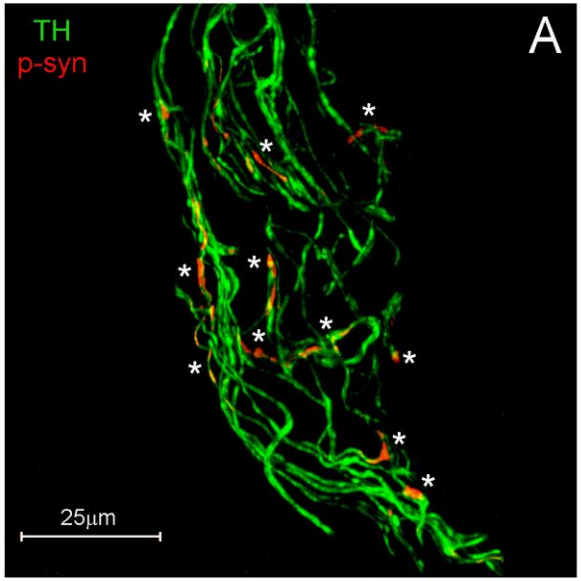
Follow-up in 7 PD-OH patients

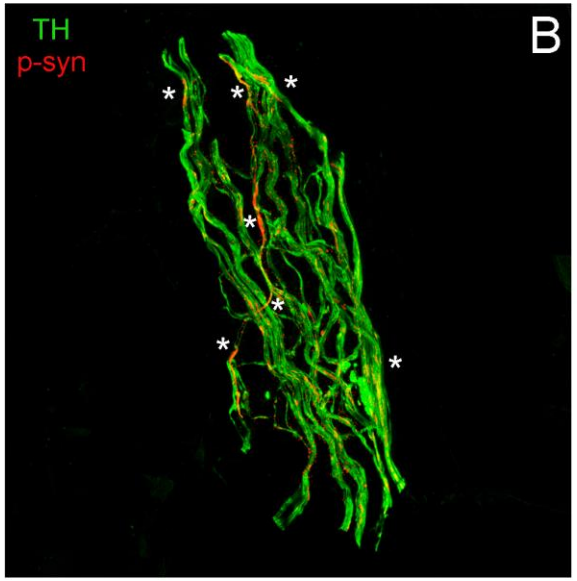


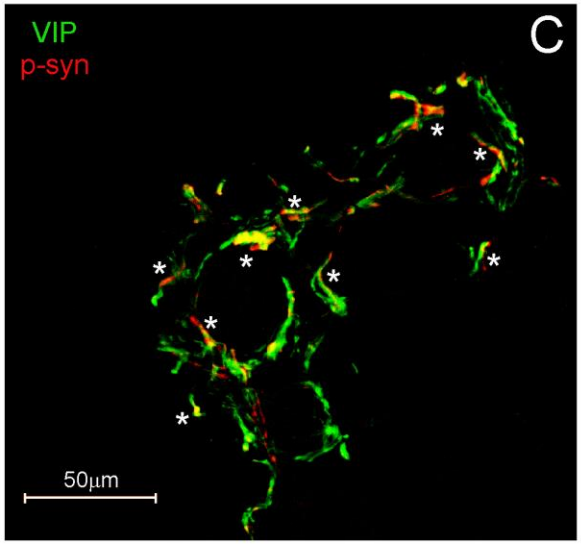
RESULTS

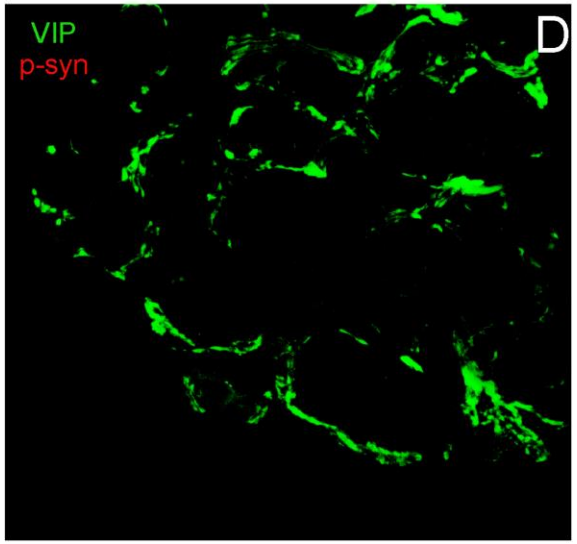
PD+OH

PD-OH

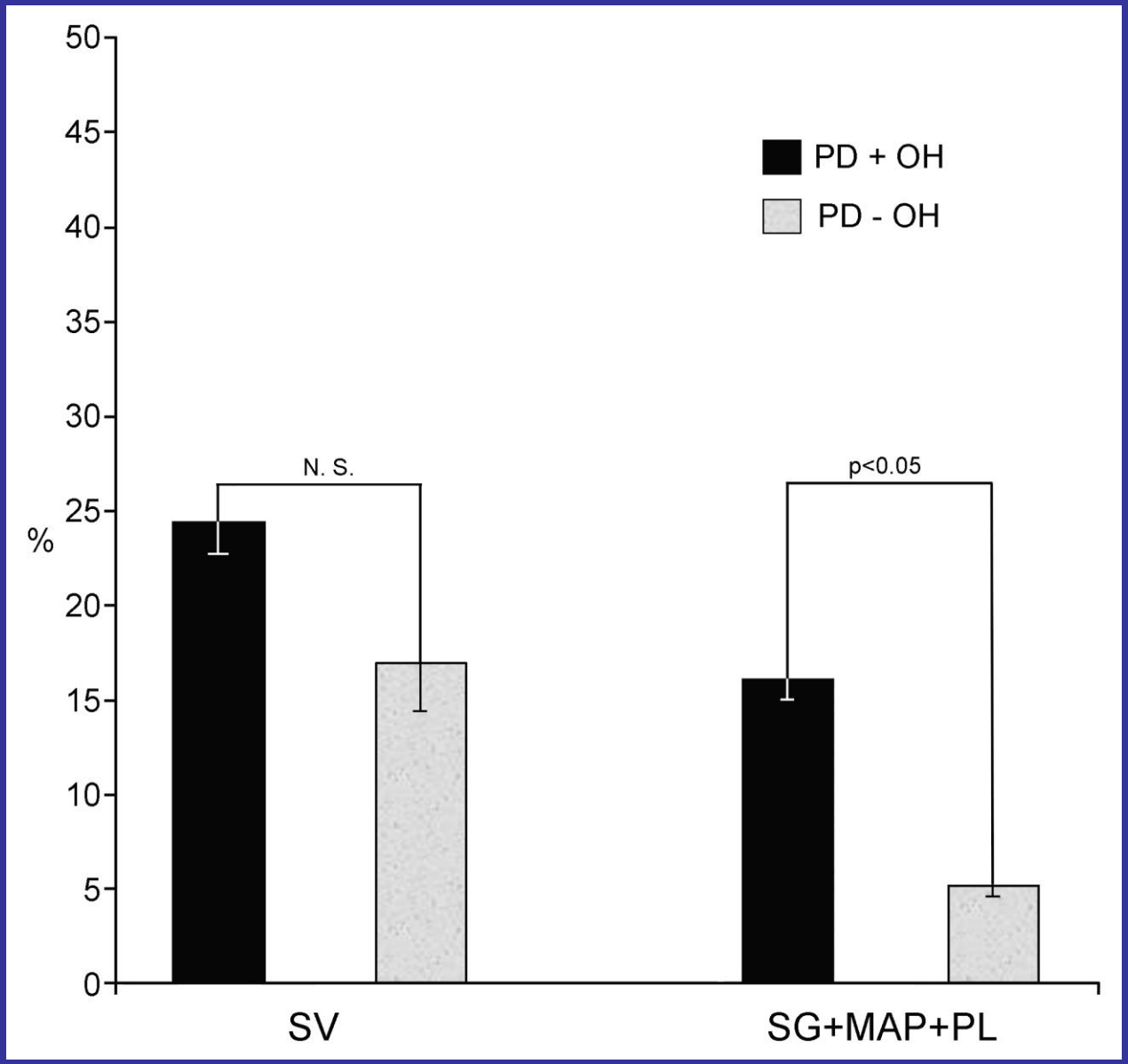








RESULTS: skin annexes involvement



Conclusions

- PD+OH showed a wide involvement of p-syn deposits in cholinergic and adrenergic autonomic skin nerves and higher incidence of RBD compared to PD-OH

- PD-OH showed a lower load of skin p-syn mainly restricted to adrenergic fibers of skin vessels still persisting over a follow-up, despite a worsening of motor performances.

- these data demostrated that skin p-syn is differently expressed in PD+OH than PD-OH and that skin biopsy is a potentially useful tool to differentiate these disorders