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Skin nerve α-synuclein deposits in a parkinsonian patient with heterozygous parkin mutation

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α-Synuclein (α-syn) is the main pathological hallmark of Lewy body diseases, a group of diseases that includes idiopathic Parkinson's disease (iPD), Dementia with Lewy body (DLB), and Multiple System Atrophy. α-Syn forms pathological aggregates that can be detected in central and peripheral nervous system [4]. Even though α-syn is strongly associated with iPD, there are genetic forms of PD like homozygous parkin mutation (HoPM) that lacks α-syn deposits and are not thought to be related to LB pathology. Nevertheless, a small number of LB and Lewy neurites may sometimes be present in HoPM patients as the result of "incidental Lewy body disease", a condition observed in almost 25% of healthy elderly subjects. Even though HoPM is not thought to be related to LB pathology, assessment of α-syn in the brain from subjects carrying heterozygous parkin mutation (HePM) yielded controversial results. A 93 year-old healthy subject and a 82 year-old patient with progressive supranuclear palsy (PSP) did not show α-syn pathology [1,2] whereas two patients with HePM and typical PD phenomenology showed diffuse brain α-syn pathology [3].

Skin nerve phosphorylated α-syn (Pα-syn) has recently been validated as a diagnostic biomarker for iPD and DLB [4]. Indeed skin biopsies of healthy controls and patients affected by several forms of parkinsonisms (like vascular parkinsonism, PSP, corticobasal syndrome and HoPM) [4] lack Pα-syn deposits. To date there is no report on skin biopsy in subjects with HePM.

Using a disposable 3-mm punch, a skin biopsy sample was taken from cervical C7-C8 paravertebral area in a HePM man. This patient had PD onset at the age of 40 years with micrographia and right hand bradykinesia and tremor. Thereafter, motor impairment became bilateral but predominated on the right side of the body. He developed early levodopa-related motor fluctuations that were well-controlled by bilateral subthalamic nucleus deep brain stimulation. The patient had no family history of parkinsonism and his parents were not consanguineous. Multiplex ligation-dependent probe amplification and next generation sequencing analysis showed a single deletion of exon 4 of the parkin gene and excluded other genetic mutations in *SNCA*, *PINK1*, *DJ1*, *LRRK2*, *GCH1*, *ATP13A2* and *UCHL1* genes. Skin biopsy was performed when the patient was 53 years old and was in stage 2 of H&Y scale. Cervical skin biopsy was also performed in a 51 years-old iPD patient (positive control) with a disease duration of about 6 years and in a 50 years-old HoPM (compound heterozygous) parkinsonian patient with a deletion of exon 2 and exon 5 and a disease duration of 33 years (negative control). Genetic phase could not be determined in the latter patient but the early age of onset and the absence of other mutations suggested a compound heterozygous condition. This case report was approved by the ethics committee and patients gave their written informed consent to skin biopsy. Double immunofluorescence staining for PGP 9.5 and P-α-syn was performed as previously reported [4].

As expected, the iPD patient showed Pα-syn skin deposits in isolated nerve fibers within small nerve bundles located in deeper dermal layers, while the HoPM patient did not (Fig. 1 A and B). Similar to the iPD patient, positive Pα-syn deposits were detected in the skin from the exon 4 deletion HePM patient (Fig. 1 C). Since Pα-syn deposits tend to increase with increasing age and disease duration in PD, and with increasing age in normal subjects, age and disease duration might have confounded our results. However, the bias was unlikely, given the similar age at biopsy shared by patients and the longer disease duration of Pα-syn negative HoPM patient.

This finding may have several explanations. Because HePM could not be the cause for familial PD, our patient carrying exon 4 deletion HePM may have coincidentally developed an early-onset synuclein-related PD (iPD). Alternatively, exon 4 deletion HePM might be a risk factor for iPD. Arguments supporting this view may be the lower 18F-dopa basal ganglia uptake observed in asymptomatic HePM carriers in comparison with control subjects; and the intermediate age at disease onset showed by HePM carriers as compared with HoPM and iPD patients [5]. Finally, the presence of α-syn pathology could also be ascribed to an "incidental Lewy body disease" [3]. This seems however unlikely in our young adult patient, since incidental Lewy body disease is an aging-related condition.

This report provides evidence that skin biopsy may be a valuable in vivo tool to study α-syn pathology in symptomatic and asymptomatic HePM carriers. The hypothesis that skin Pα-syn is associated with HePM needs to be verified in larger samples.

Authors's roles

LF, FT: conception and organization of research project.
LF,RL, PS, GLP: organization and execution of research project.

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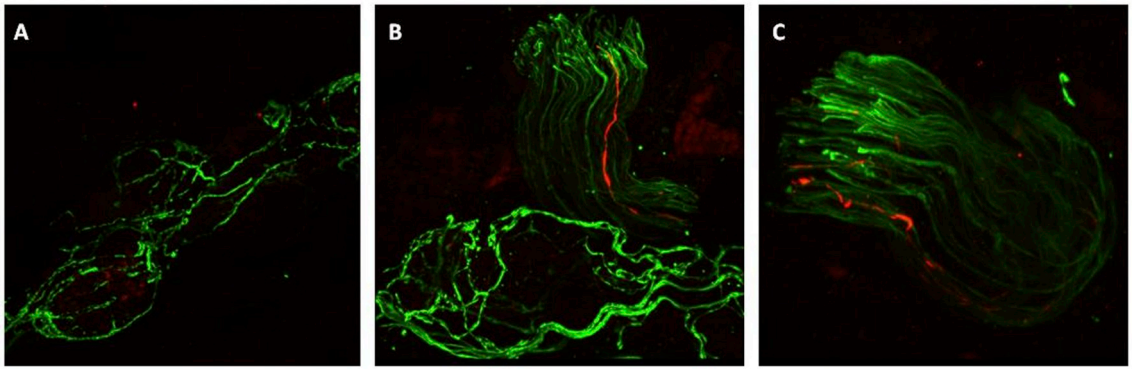

Fig. 1. Confocal microscopy (40X) study of cervical skin biopsy from a patient with compound heterozygous parkin mutation (A), a patient with idiopathic Parkinson's disease (B), and a patient with exon 4 deletion heterozygous parkin mutation (C). Nerve fibers are marked in green using a pan-neuronal marker (PGP 9.5) and P-a-synuclein deposits are marked in red. The merging images demonstrates P-a-synuclein intraneural deposits in a small dermal nerve bundle only in idiopathic Parkinson's disease (B) and in exon 4 deletion heterozygous parkin mutation (C). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

LF, FT,GLP, GD: results observations, paper review and Critique.

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