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Anderson–Fabry disease — no histological signs of pathological accumulation in arterial and venous endothelium during pegunigalsidase alfa therapy

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Short title: Anderson–Fabry disease and pegunigalsidase alfa therapy

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A 43-year-old male patient with Anderson–Fabry disease (AFD) diagnosed in adulthood during a family screening (mutation c.734DEL61) [1] was indicated for a surgical removal (phlebectomy) of varicosities. This enzymatic defect results in pathological accumulation of glycoplipids in lysosomes of the vascular endothelium and several cell types. [2]
Since 2003 the patient received an intravenous biweekly enzyme replacement therapy (ERT) for the classic form of AFD, with skin involvement, hypertrophic cardiomyopathy, severe gastrointestinal symptoms, arthralgias, and peripheral neuropathy. The indications for starting

ERT in different countries are covered by national guidelines, e.g. a position statement in Poland [3]. Within 2003 and 2006 the patient was treated by agalsidase beta (Sanofi/Genzyme, Cambridge, MA, USA), followed by agalsidase alfa (Shire/Takeda, Lexington, MA, USA). In 2017, he was successfully screened into the Bridge study (Protalix BioTherapeutics) fulfilling inclusion criteria of persistent symptoms and disease progression, The "Bridge" study (PB-102-F30 NCT03018730) is an ongoing phase III, open label, switch-over study, assessing the safety and efficacy of pegunigalsidase alfa in AFD patients previously treated with agalsidase alfa for at least 2 years [4].

From November 2017, the patient´s treatment was started according to the study protocol by biweekly infusions of the enzyme pegunigalsidase alfa (1 mg/kg). This enzyme is a chemically modified pegylated plant cell culture-expressed version of the recombinant alpha-galactosidase-A enzyme. As compared to currently available enzymes, its half- life is substantially longer. In a pivotal trial the enzyme was shown to reduce globotriaosylceramide deposits within the kidney [5]. Of note our patient's kidney function stabilized during more than 2 years of the study medication administration, and gastrointestinal symptoms, arthralgias and peripheral pain improved.

In December 2019, the patient underwent a surgical removal of varicosities of the great saphenous vein of the right leg due to the clinical worsening. Tissue samples were taken and referred for an electron microscopic examination. The lysosomal storage characterized by typical lamellar inclusions was demonstrated neither in venous nor in arterial endothelial cells. In contrast, inclusions were detectable in arterial and venous smooth muscle cells (Figure 1A–D) and massively in the perineurial cells of the small peripheral nerves (Figure 1F–G). More discrete accumulation was demonstrated in fibroblasts and in Schwann cells.

These results suggest potential benefits of pegunigalsidase alfa on endothelial storage of AFD patients currently being treated with the available ERT.

Author contributions

All co-authors have read the final manuscript within their respective areas of expertise and participated sufficiently in the study to take responsibility for it and accept its conclusions.

Informed consent was obtained from the patient.

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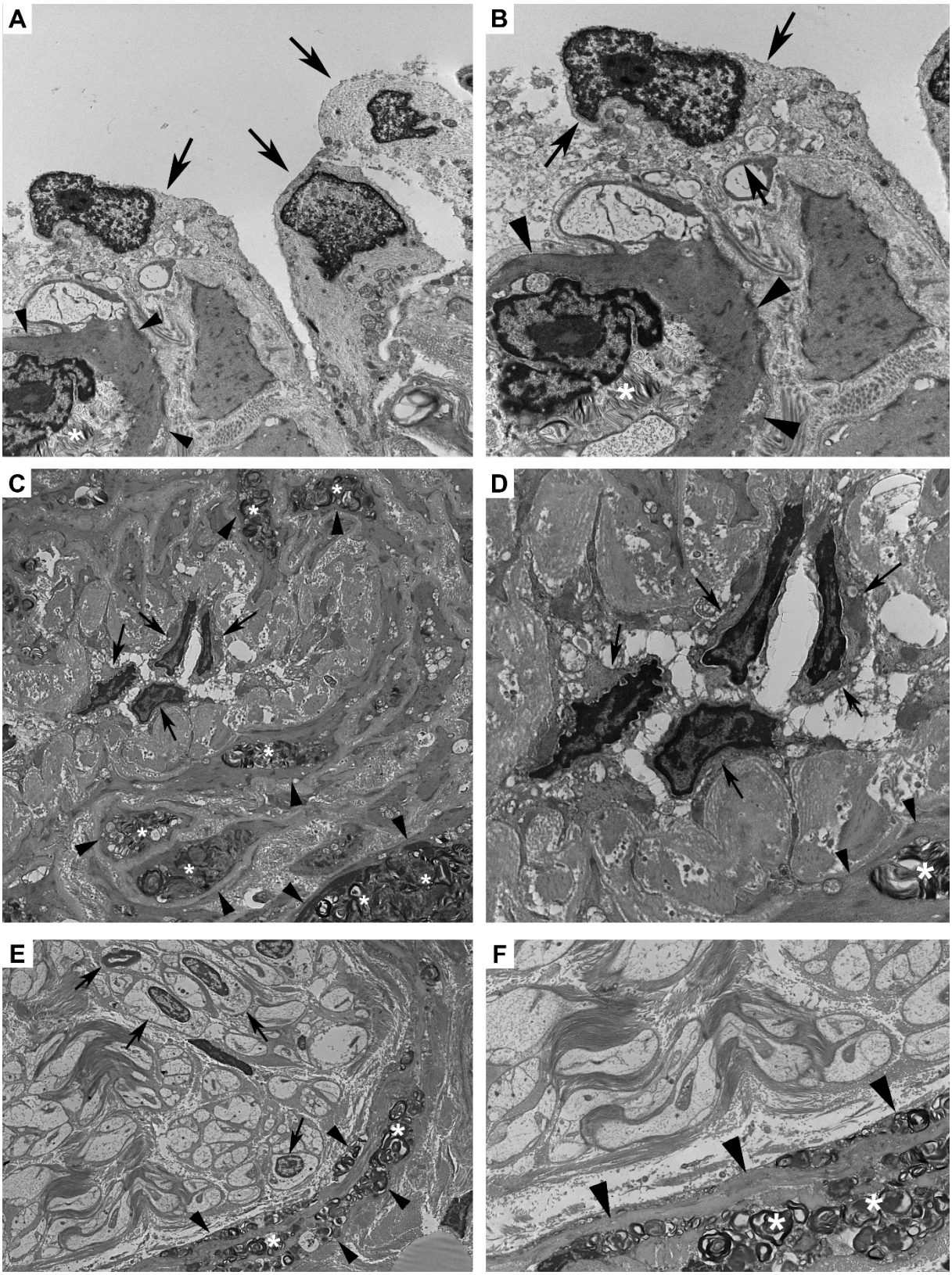

Figure 1. Ultrastructural analysis of lysosomal storage in vena saphena magna, small artery and peripheral nerve. **A–B.** Vena saphena magna. Absence of lysosomal storage in endothelial cells together with clearly detectable lysosomal storage of membranous parallel structures (zebra-like) in a vascular smooth muscle cell. **A.** Magnification ×8000. **B.** Magnification

×12000. Endothelial cells are marked by arrows, smooth muscle cells by arrowheads. **C–D.** Small artery. Absence of lysosomal storage in endothelial cells. Vascular smooth muscle cells reveal lysosomal storage of membranous concentric or parallel structures. **C.** Magnification ×5000. **D.** Magnification ×12000. Endothelial cells are marked by arrows, smooth muscle cells by arrowheads. **E–F.** Peripheral nerve. Conspicuous lysosomal storage of osmiophilic membranous material typical for Fabry disease in a perineurial cell. Cytoplasm of demonstrated Schwann cells is without detectable lysosomal storage. **E.** Magnification ×3000. **F.** Magnification ×6000. Schwann cells are marked by arrows, the perineurial cell by arrowheads. Storage material is marked by asterisks in all pictures