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Correspondence

Letter to the Editors: Concerning "Divergent clinical outcomes of alpha-glucosidase enzyme replacement therapy in two siblings with infantile-onset Pompe disease treated in the symptomatic or pre-symptomatic state" by Takashi et al. and Letter to the Editors by Ortolano et al.

Dear Editors,

With interest, we read the article by Matsuoka et al., and the response of Ortolano and colleagues, emphasizing improved outcome of siblings with infantile Pompe disease (IPD) starting early with enzyme replacement therapy (ERT) compared to those commencing later [1,2]. We fully agree that early start of ERT in cross reactive immunostained material (CRIM)-positive subjects together with immune tolerance induction in CRIM-negative individuals will improve the chances to reach significant effects of ERT [3,4]. However, we like to stress that an early begin of recombinant human alpha glucosidase (rh-GAA) treatment does not guarantee a positive outcome. We illustrate this by reporting two brothers with the CRIM-positive GAA mutation p.A694Gfs*43. The older one was diagnosed with IPD due to typical clinical symptoms at age 5 months, and ERT with 20 mg/kg rh-GAA every other week was begun 2 weeks later. At age 7 years, he is still walking and not ventilated. In his younger brother, diagnosis was established prenatally. He was born by cesarean section at 38 weeks gestational age, and ERT with 40 mg/kg every week was commenced on day 3. GAA-antibodies were determined regularly, and the highest titer was 1:400. Despite a distinctly earlier start of ERT, low antibody titers, and high enzyme dosage, the boy did not achieve free sitting. His respiratory function substantially worsened during an upper respiratory infection, necessitating tracheostomy and assisted ventilation from age 10 months on.

The reason why the younger brother responded poorly to ERT remains elusive. But a muscle biopsy taken at age one month displayed substantial extralysosomal glycogen storage, distinct ultrastructural abnormalities, and enhanced autophagy (Fig. 1), demonstrating that ERT in this new-born targeted to treat an already advanced stage of myopathy [5,6].

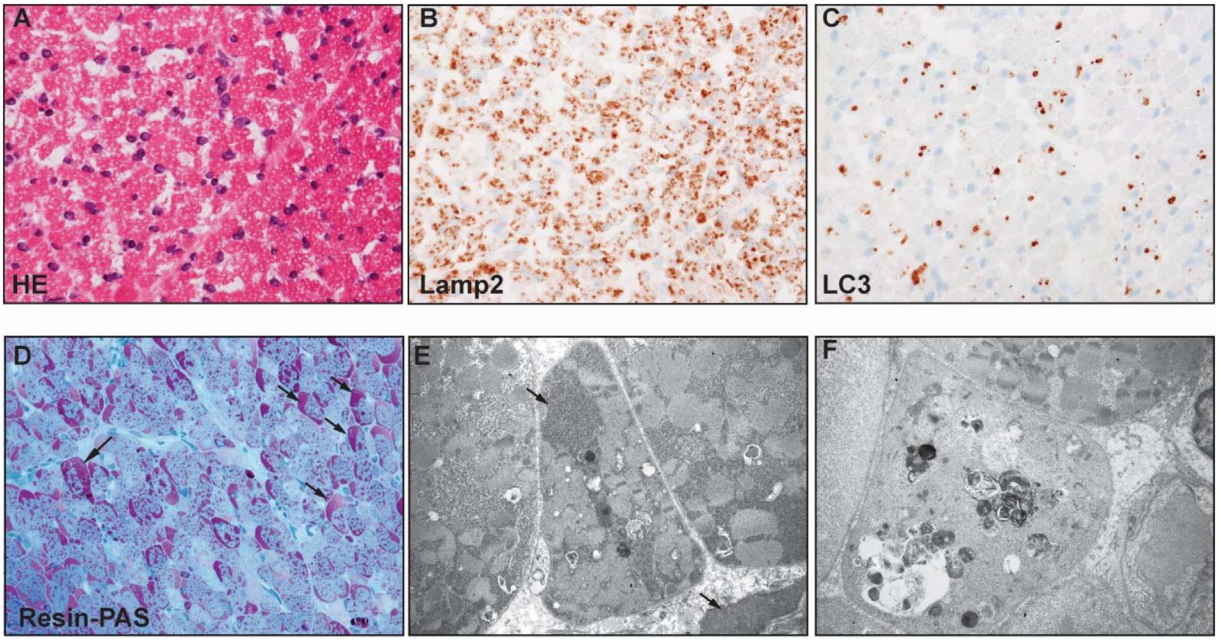

Fig. 1. A muscle biopsy taken at age 1 month depicts a vacuolar myopathy (A). Immunostaining for LAMP2 reveals strong lysosomal activity (B), and immunostaining for LC3 demonstrates increased autophagic activity in many muscle fibers (C). PAS stained resin sections show that all muscle fibers contain pathological accumulations of glycogen (magenta color). Extralysosomal subsarcolemnal glycogen deposits are seen in most muscle fibers (arrows) (D). Electron microscopy confirms abundant extralysosomal glycogen (E), and displays autophagic vacuoles in muscle fibers with myofibril disintegration (F). (A–C cryosection × 400, D resin section × 400, E + F electron microscopy × 3000). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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