Behavioral and Histological Hallmarks of a Mucopolysaccharidosis Type IIIA Mouse Model

Vera Niederkofler[1], Ewald Auer[1], David Amschl[1], Joerg Neddens[1], Elisabet Ohlin Sjöström[2], Susanne Gustavsson[2], Birgit Hutter-Paier[1]

[1]QPS Austria GmbH, Parkring 12, 8074 Grambach, AUSTRIA

[2]Research & Translational Science, Swedish Orphan Biovitrum AB, Stockholm, SWEDEN

OBJECTIVE

Mucopolysaccharidosis IIIA (MPS IIIA), also known as Sanfilippo syndrome A, is an autosomal recessive lysosomal storage disorder. The disease is characterized by severe and progressive loss of cognitive and motor functions, behavioral deficits and eventually death in the second decade of life, although the severity and progression of the disease varies widely. MPS IIIA is caused by mutations in the SGSH gene that result in deficiency of the N-sulfoglucosamine sulfohydrolase enzyme and subsequent accumulation of undegraded heparan sulfate, lysosomal enlargement as well as cellular and organ dysfunction.
To model the disease, a MPS IIIA mouse strain with spontaneous Sgsh mutation, resulting in an almost complete loss of N-sulfoglucosamine sulfohydrolase activity, was characterized.

MATERIALS & METHODS

Male MPS IIIA mice (JAX#003780) were analyzed at an age of 28 to 30 weeks for body weight changes, activity, social interaction and cognition. Afterwards, neuropathology was evaluated by using a LIMP2 antibody, labeling lysosomal and endosomal membranes, and GFAP and IBA1 antibodies to analyze neuroinflammation.

General Health & Behavior

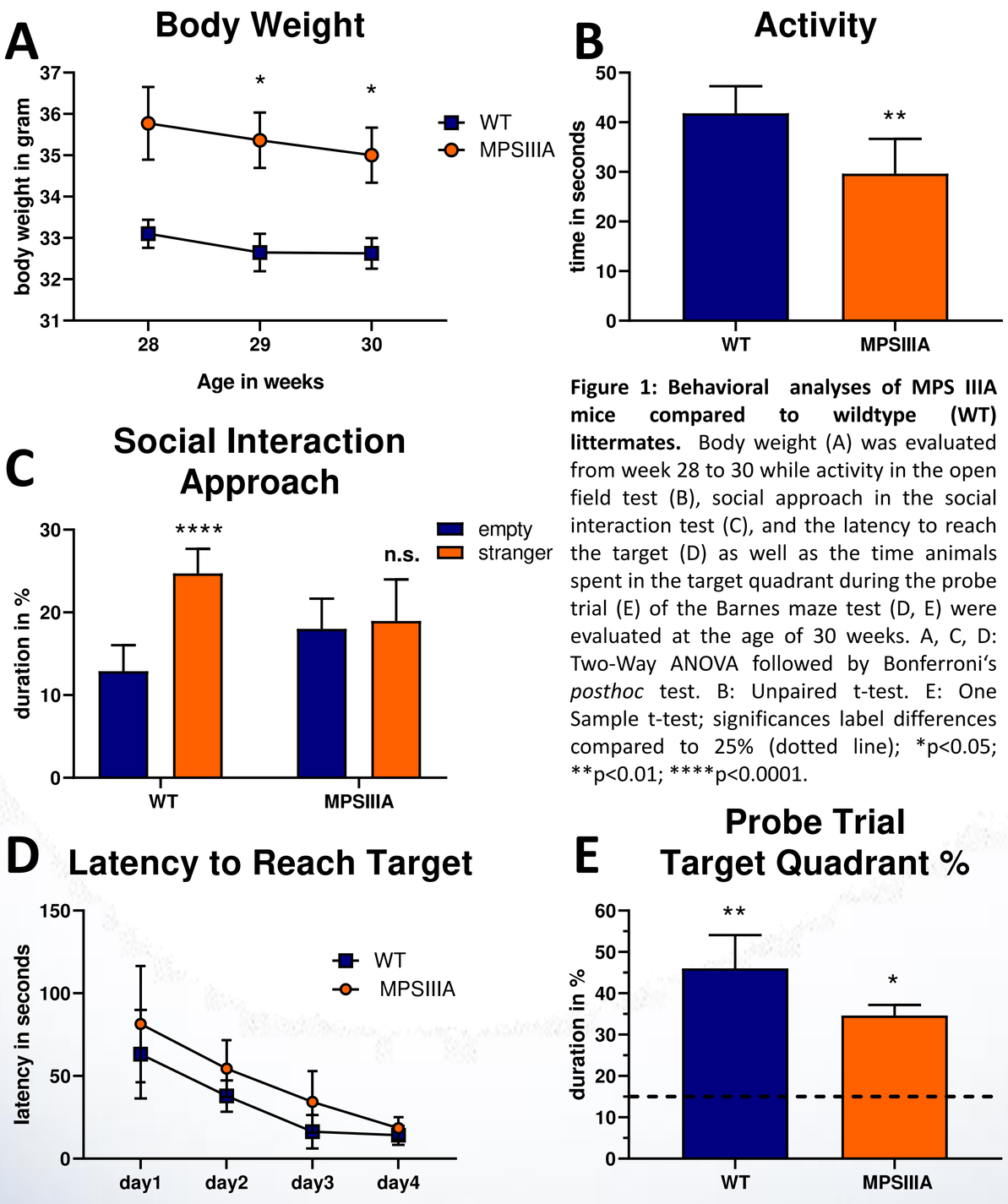

Figure 1: Behavioral analyses of MPS IIIA mice compared to wildtype (WT) littermates. Body weight (A) was evaluated from week 28 to 30 while activity in the open field test (B), social approach in the social interaction test (C), and the latency to reach the target (D) as well as the time animals spent in the target quadrant during the probe trial (E) of the Barnes maze test (D, E) were evaluated at the age of 30 weeks. A, C, D: Two-Way ANOVA followed by Bonferroni's *posthoc* test. B: Unpaired t-test. E: One Sample t-test; significances label differences compared to 25% (dotted line); *p<0.05; **p<0.01; ****p<0.0001.

RESULTS

MPS IIIA mice demonstrated an increased body weight, combined with a decreased activity in the open field test. Social interaction of MPS IIIA mice was reduced and animals presented weak memory deficits in the Barnes maze test. Histological analyses revealed a strong increase in astrogliosis but only a slight increase of activated microglia. Quantification of LIMP2 showed a severe signal increase in MPS IIIA mice compared to wildtype animals.

Neuroinflammation & Lysosomal Pathology

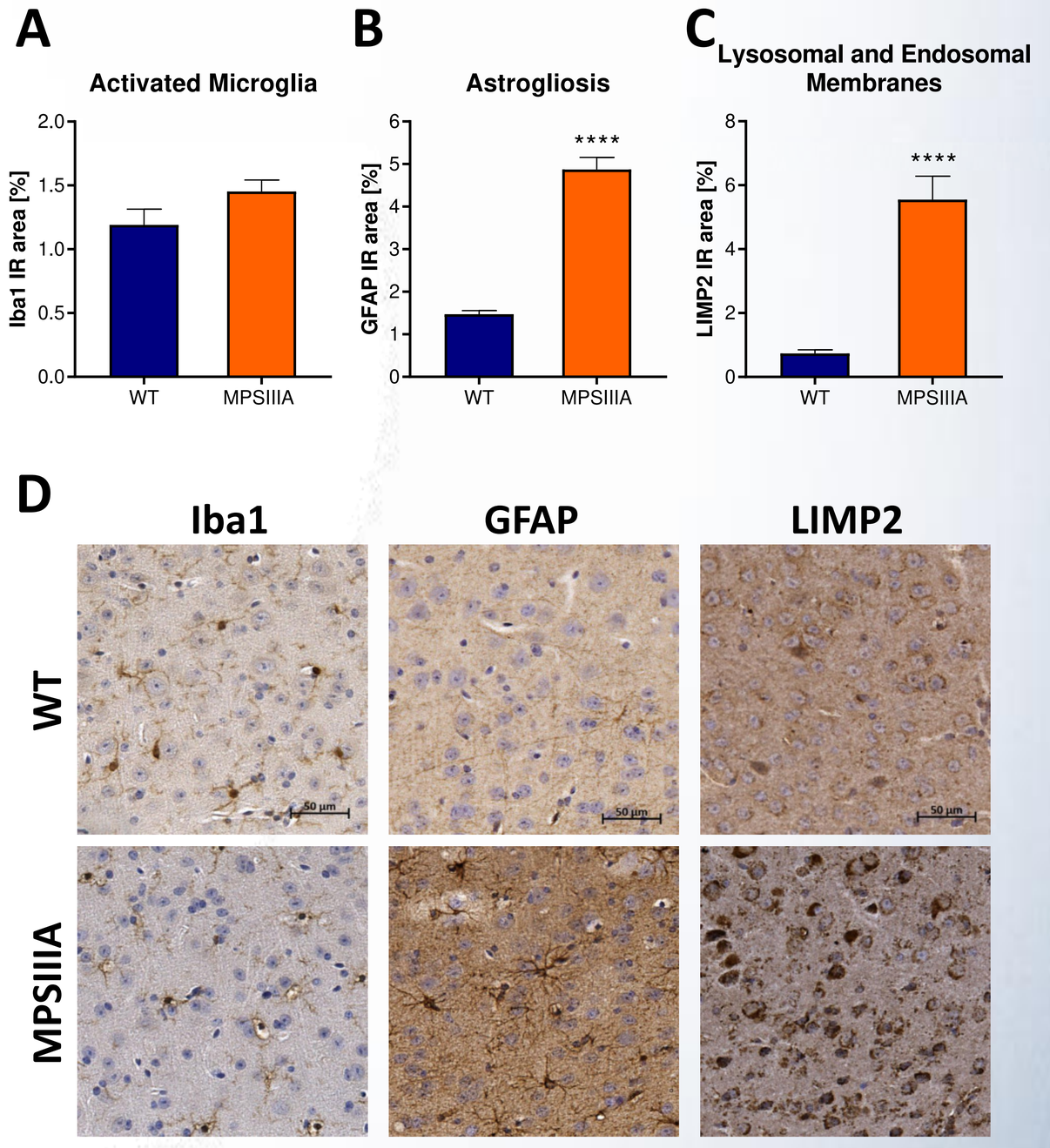

Figure 2: Histological analysis of MPSIIIA mice compared to wildtype (WT) littermates for neuroinflammation and lysosomal/endosomal membrane alterations in the cortex. Immunoreactive area (IR) in percent of Iba1 (A), GFAP (B) and LIMP2 (C) labeling. Mean+SEM; unpaired t-test. ****p<0.0001. D: Representative images of Iba1, GFAP and LIMP2 labeling in the cortex of MPSIIIA and WT animals at the age of 30 weeks.

DISCUSSION

In summary, these results confirm that MPS IIIA mice present a similar phenotype as observed in Sanfilippo syndrome A patients. The mouse is therefore a valuable model for preclinical research.

QPS Austria GmbH, Parkring 12, 8074 Grambach, AUSTRIA

Web www.qpsneuro.com

Email office-austria@qps.com

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