Behavioral and Histological Hallmarks of a Mucopolysaccharidosis Type IIIA Mouse Model

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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

A Body Weight

B Activity

C Social Interaction Approach

D Latency to Reach Target

E Probe Trial Target Quadrant %

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

A Activated Microglia

B Astrogliosis

C Lysosomal and Endosomal Membranes

D Iba1

E GFAP

F LIMP2

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.