Author's response to reviews

Title: Blood-Brain Barrier Impairment in MPS III Patients: Case Report

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Version: 2 Date: 21 March 2013

Author's response to reviews: see over
To: Josefino M. Rodis  
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Dear Dr. Rodis,

On March 20th, you noted that the article type of our manuscript titled *Blood-Brain Barrier Impairment in MPS III Patients: Case Report* by Svitlana Garbuzova-Davis et al. had been changed from a case report to a research article. In accordance with this change we have reformatted our manuscript. Also, as requested, we have added an ethics statement and a consent statement (see below) to Methods.

The aim of our study was to determine integrity of the blood-brain barrier (BBB) in various brain structures of post-mortem tissue from MPS III patients: MPS III A (the most common subtype) and MPS III D (the rarest subtype). A specific focus was analyzing endothelium barrier competence.

Results from our study are the first showing severe BBB damage in both MPS III cases. Major findings are ultrastructural endothelial and pericyte cell degeneration due to extensive lysosomal accumulation compromising the barrier and resulting in vascular leakage. Significant extracellular edema, perivascular collagen accumulation, and reduction of tight junction protein expressions were also determined. Although microvascular structural abnormalities were similar in MPS III A and III D, variations in functional BBB impairment were determined between MPS III types. These new findings of BBB alterations, although from only two cases, MPS III A and III D, may have implications for disease pathogenesis by accelerating neuropathological manifestations and should be considered in treatment development.

Ethics statement: We included the following text in Methods: “Although IRB approval was not required for our studies since we used post-mortem tissue, we followed ethical guidelines for the protection of human subjects as stated in the Helsinki Declaration.” (page 5, first paragraph in Methods)

Consent statement: We included the following text in Methods: “The NICHD Brain and Tissue Bank obtained informed consent from the tissue donors or from their parents or guardians. Other than age, gender, race, health histories, and neuropathological exam results, no personally identifiable information was released to the authors by the Bank.” (page 5, first paragraph in Methods)

We are very excited about our study results and hope that this manuscript will be found acceptable for your journal. *Our findings of barrier damage in MPS III mark the BBB as a target of critical interest to neurodegenerative disease researchers and clinicians not only for the development of new therapeutic strategies for drug delivery across the barrier, but also for understanding the potential contribution of BBB dysfunction to disease neuropathology.*
This work has not been published previously and is not under consideration for publication elsewhere. None of the authors have had any prior discussions with an editor from *BMC Neurology* about the work described in the manuscript. All the authors have read and agree with the contents of the submission and all the authors have contributed substantially to this work. Please address any prepublication correspondence to me at the above address. I look forward to hearing from you in the near future.

**Potential reviewers:**

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Sincerely,

Svitlana Garbuzova-Davis, Ph.D., D.Sc.