63. S-adenosylhomocysteine hydrolase deficiency with associated masseter hypertrophy, bradykinesia, and cerebellar atrophy and alterations of creatine and choline homeostasis. Expansion of cerebrohepatomuscular phenotype

J. PIPO-DEVEZA[1], R. JOBLING[2], S. BLASER [3], A. CARNEVALE[4,5], W. LANGBURT[1], G. YOON[1,2,5], I. TEIN [1,6]
[1]Division of Neurology and [2]Division of Clinical & Metabolic Genetics, Dept of Pediatrics, Hospital for Sick Children, University of Toronto
[3]Division of Neuroradiology, Dept. of Diagnostic Imaging, The Hospital for Sick Children, University of Toronto,
[4]Dept. of Genetic Counseling, The Hospital for Sick Children, Toronto,
[5]Dept. of Molecular Genetics, University of Toronto, Toronto
[6]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

ICNC 2022
17th INTERNATIONAL CHILD NEUROLOGY CONGRESS
ANTALYA, TURKEY I OCTOBER 3-7, 2022

INTRODUCTION

S-adenosylhomocysteine hydrolase catalyzes the reversible hydrolysis of S-adenosylhomocysteine to adenosine and homocysteine. Its deficiency results from mutations of the *AHCY* gene. This is a rare autosomal recessive disease with variable cerebrohepatomuscular phenotype.

AIM

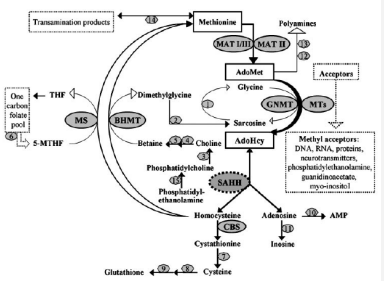
To report two cases of S-adenosylhomocysteine hydrolase deficiency with unique additional features which expand the cerebrohepatomuscular phenotype.

METHOD

Cases: We report siblings, an 18-year old male and 12-year old female with S-adenosylhomocysteine hydrolase deficiency who presented with varying intellectual disability, hypotonia, myopathy, and hepatopathy and the additional novel feature of masseter hypertrophy. There was significant phenotypic variability; the older brother had greater intellectual disability, bradykinesia and ataxia and the sister manifested with additional obesity, hyperphagia, obstructive sleep apnea and visual impairment.

RESULTS

Both had marked elevations of creatine kinase; the brother had a 120-fold increase and the younger sister had a 110-fold increase. Liver enzymes were elevated but liver involvement was more prominent in the obese sister who also had increased methionine concentrations in blood and urine, as well as elevated serum homocysteine. Their brain imaging revealed cerebellar atrophy with decreased cerebellar N-acetyl aspartate peak on MRS and marked hypertrophy of the muscles of mastication. A novel homozygous mutation, c.142G>A, p.Ala48Thr in the *AHCY* gene was detected by WES in both. There was low residual S-adenosylhomocysteine hydrolase activity in fibroblasts



Taken from Baric I. J Inherit Metab Disease 2009; 32: 459-471

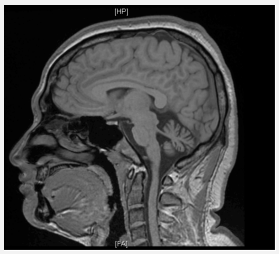


Fig. 1. Brain MRI of sibling 1. Saggital section, T1 showing moderate to severe atrophy of cerebellar vermis and moderate atrophy of cerebellar hemispheres.

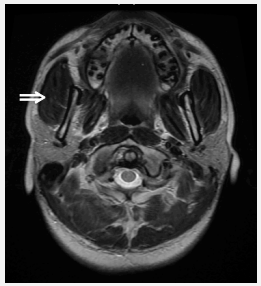


Fig. 2. Axial section showing marked and symmetrical hypertrophy of the masseter muscles in sibling 1.

Phenotypic features	Sibling 1	Sibling 2
Sex	Male	Female
Age at diagnosis	17 years	12 years
Age of onset	Infancy	Infancy
Developmental delay	+++	++
Intellectual disability	+++	++
Visual symptoms	+ exotropia/ astigmatism	++ RP/ foveal schisis
Bradykinesia	++	-
Cerebellar ataxia	+++	+
Hypotonia	+	+
Myopathy	+++	+
Hypertrophy of muscles of mastication	++	++
Liver dysfunction	++	++
Obesity	-	+++
Blood Metabolites (control)		
Methionine (11-16 µmol/L)	15 - 27	337 - 588
Homocysteine (3.4 -8.5 µmol/L)	6.4 - 9.6	11.5 – 14.0
Methylmalonic acid (< 0.37 µM)	normal	< 0.40 – 1.21
CK (55-370 U/L)	3,532- 20, 952	7,248 – 19, 220
ALT (< 40 U/L)	123 - 175	141 - 245
AST (< 31 U/L)	96 - 290	106 - 169
Neuroimaging		
Brain MRI	Moderate to severe cerebellar atrophy, FLAIR hyperintensity of cerebellum, Hypertrophy of muscles of mastication	Mild cerebellar atrophy, FLAIR hyperintensity of cerebellum, Hypertrophy of muscles of mastication
Brain MRS	⇓ NAA/Cho in cerebellum	⇓ NAA/Cho in cerebellum

CONCLUSIONS

Increased S-adenosylhomocysteine levels may cause secondary inhibition of multiple different S-adenosylmethionine-dependent methyltransferases. Clinical manifestations can be explained in part by derangements in creatine and choline metabolism as well as in DNA hypermethylation. It is unclear whether the unique feature of masseter hypertrophy in these sibs is a separate or associated feature of this disorder.

REFERENCES

1. Barić I, Fumic K, Glenn B et al. S-Adenosylhomocysteine hydrolase deficiency in a human: A genetic disorder of methionine metabolism. Proc Natl Acad Sci 2004; 101:4234-4239
2. Barić I, Cuk M, Fumic K et al. S-Adenosylhomocysteine hydrolase deficiency: A second patient, the younger brother of the index patient, and outcomes during therapy. J Inherit Metab Dis 2005; 28:885-902.
3. Motzek A, Knežević J, Switzeny OJ et al. Abnormal Hypermethylation at Imprinting Control Regions in Patients with S-Adenosylhomocysteine Hydrolase (AHCY) Deficiency. PLoS ONE 2016; 11: e0151261
4. Stefanello FM, Matte´ C, Pederzolli CD et al. Hypermethioninemia provokes oxidative damage and histological changes in liver of rats. Biochimie 2009; 91: 961-968.
5. Strauss KA, Ferreira C, Bottiglieri T et al. Liver transplantation for treatment of severe S-adenosylhomocysteine hydrolase deficiency. Mol Genet Metab 2015; 116:44-52

ACKNOWLEDGEMENTS

Funding for this project was obtained through the following grant - University of Toronto McLaughlin Centre: Next Generation Diagnostics: Advancing the Clinical Application of Genomic Analysis, grant ID MC-2012-13A. We gratefully acknowledge the family for generously agreeing to the publication of this study.

CONTACT INFORMATION

Ingrid.tein@sickkids.ca