Journal of Inherited Metabolic Disease / Volume 39, Issue 2

Original Article

Succinate-CoA ligase deficiency due to mutations in *SUCLA2* and *SUCLG1*: phenotype and genotype correlations in 71 patients

Rosalba Carrozzo, Daniela Verrigni, Magnhild Rasmussen, Rene de Coo, Hernan Amartino, Marzia Bianchi, Daniela Buhas, Samir Mesli, Karin Naess, Alfred Peter Born, Berit Woldseth, Paolo Prontera, Mustafa Batbayli, Kirstine Ravn, Fróði Joensen, Duccio M. Cordelli, Filippo Maria Santorelli, Mar Tulinius, Niklas Darin, Morten Duno, Philippe Jouvencel, Alberto Burlina, Gabriela Stangoni, Enrico Bertini, Isabelle Redonnet-Vernhet, Flemming Wibrand, Carlo Dionisi-Vici, Johanna Uusimaa, Paivi Vieira, Andrés Nascimento Osorio, Robert McFarland, Robert W. Taylor, Elisabeth Holme, Elsebet Ostergaard

First published: 16 October 2015
https://doi.org/10.1007/s10545-015-9894-9
Cited by: 32

Communicated by: Johan Lodewijk Karel Van Hove

Electronic Supplementary Material:

The online version of this article (doi:10.1007/s10545-015-9894-9) contains supplementary material, which is available to authorized users.

Abstract

Background

The encephalomyopathic mtDNA depletion syndrome with methylmalonic aciduria is associated with deficiency of succinate-CoA ligase, caused by mutations in *SUCLA2* or *SUCLG1*. We report here 25 new patients with succinate-CoA ligase deficiency, and review the clinical and molecular findings in these and 46 previously reported patients.

Patients and results

Of the 71 patients, 50 had *SUCLA2* mutations and 21 had *SUCLG1* mutations. In the newly-reported 20 *SUCLA2* patients we found 16 different mutations, of which nine were novel: two large gene deletions, a 1 bp duplication, two 1 bp deletions, a 3 bp insertion, a nonsense mutation and two missense mutations. In the newly-reported *SUCLG1* patients, five missense mutations were identified, of which two

were novel. The median onset of symptoms was two months for patients with *SUCLA2* mutations and at birth for *SUCLG1* patients. Median survival was 20 years for *SUCLA2* and 20 months for *SUCLG1*. Notable clinical differences between the two groups were hepatopathy, found in 38 % of *SUCLG1* cases but not in *SUCLA2* cases, and hypertrophic cardiomyopathy which was not reported in *SUCLA2* patients, but documented in 14 % of cases with *SUCLG1* mutations. Long survival, to age 20 years or older, was reported in 12 % of *SUCLA2* and in 10 % of *SUCLG1* patients. The most frequent abnormality on neuroimaging was basal ganglia involvement, found in 69 % of *SUCLA2* and 80 % of *SUCLG1* patients. Analysis of respiratory chain enzyme activities in muscle generally showed a combined deficiency of complexes I and IV, but normal histological and biochemical findings in muscle did not preclude a diagnosis of succinate-CoA ligase deficiency. In five patients, the urinary excretion of methylmalonic acid was only marginally elevated, whereas elevated plasma methylmalonic acid was consistently found.

Conclusions

To our knowledge, this is the largest study of patients with *SUCLA2* and *SUCLG1* deficiency. The most important findings were a significantly longer survival in patients with *SUCLA2* mutations compared to *SUCLG1* mutations and a trend towards longer survival in patients with missense mutations compared to loss-of-function mutations. Hypertrophic cardiomyopathy and liver involvement was exclusively found in patients with *SUCLG1* mutations, whereas epilepsy was much more frequent in patients with *SUCLA2* mutations compared to patients with *SUCLG1* mutations. The mutation analysis revealed a number of novel mutations, including a homozygous deletion of the entire *SUCLA2* gene, and we found evidence of two founder mutations in the Scandinavian population, in addition to the known *SUCLA2* founder mutation in the Faroe Islands.

Citing Literature

Supporting Information

Filename	Description

Filename	Description
jimd0243-sup-0001.docx application/docx, 17.3 KB	(DOCX 17 kb)
jimd0243-sup-0002.docx application/docx, 70.5 KB	(DOCX 70 kb)
jimd0243-sup-0003.docx application/docx, 55.5 KB	(DOCX 55 kb)
jimd0243-sup-0004.docx application/docx, 72.1 KB	(DOCX 72 kb)
jimd0243-sup-0005.docx application/docx, 17 KB	(DOCX 17 kb)

Please note: The publisher is not responsible for the content or functionality of any supporting information supplied by the authors. Any queries (other than missing content) should be directed to the corresponding author for the article.

About Wiley Online Library

Privacy Policy
Terms of Use
Cookies
Accessibility

Help & Support

Contact Us

Opportunities

Subscription Agents
Advertisers & Corporate Partners

Connect with Wiley

The Wiley Network
Wiley Press Room

Copyright © 1999-2019 John Wiley & Sons, Inc. All rights reserved