Phenotypic heterogeneity of a compound heterozygous SUCLA2 mutation

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<td>Published Version</td>
<td>doi:10.1016/j.ymgmr.2017.01.015</td>
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Sibling 1 at presentation had severe dystonia and very high plasma lactic acidosis. Treatment at 6 months of age with DCA was not inappropriate, especially given its initial diagnosis of PDC deficiency. Soon after initiation of treatment his dystonia resolved and his lactate levels normalized. We are well aware of the side effects of DCA, mostly related to the development of peripheral neuropathy. Patients with lactic acidosis are treated according to an IRB protocol and follow-up entails repetitive nerve conduction studies. Sibling 1 had nerve conduction testing on a regular basis. The dose of DCA was adjusted in this case, as the peripheral neuropathy is largely dose dependent and reversible. On the most recent study, sibling 1 showed improvement in his nerve conduction velocities. Most recently, he developed additional neurologic signs, yet his disease has had a milder course than that of his younger sibling. We have no evidence that neurological deterioration is associated with DCA use in sibling 1. On the contrary, his less severe course of his disease may be attributed, at least in part, to him being maintained on DCA that had normalized or decreased his lactate levels. While a ketogenic diet is recommended for patients with PDC deficiency, it is not a standard of care for other mitochondrial disorders. In fact, the relatively brief exposure to a ketogenic diet may have been responsible for the much more severe illness in sibling 2. Sibling 1 was not treated with a ketogenic diet, as his plasma lactate levels greatly improved on DCA.

Administration of a ketogenic diet may not be effective to control metabolism and/or may be harmful in cases where PDC deficiency is secondary to impairment of formation of acetyl-CoA in defects of fatty acid β-oxidation, or decreased oxidation of acetyl-CoA due to primary oxidation defects distal to PDC (e.g., the tricarboxylic acid (TCA) cycle including succinyl-CoA synthetase deficiency), or combined defects of PDC and KDC (e.g., E3, thiamine pyrophosphate, or lipoate deficiencies). It is clear that ketogenic diet usage is beneficial in cases with primary mutations in PDHA1 and mutations in other PDC specific genes. Efficacy of ketogenic diet usage may be totally different for seizure disorders, where PDC, TCA, and respiratory chain functions are still intact, and one can safely use a ketogenic diet.

Please note that the diagnosis of succinyl-CoA synthetase (SUCLA2) deficiency was not established until sibling 1 and 2 were 7 years and 3 years old, respectively. Patients with a primary lactic acidosis usually are followed with multiple brain MRI/MRS studies over time. Repeat MRIs could not be performed in sibling 1 or were complicated because of the fact that he had a cochlear implant.

There was no evidence of a primary disorder of calcium or phosphate metabolism. Both of the siblings spent most of their life lying in bed. And, as is well known, this non-ambulatory state is usually associated over time with a net loss of calcium from bone and osteopenia.

There are many questions that remain unanswered in the patients. They spent most of their life in the intensive care unit and/or in hospice care. As per the wishes of the family, at some point in time, tests that were not deemed absolutely necessary by the intensive care physicians were not performed. An autopsy was not performed on sibling 2. We would have liked to address and answer many of the items that you noted in your letter but unfortunately this was not possible.

Sincerely,

Xiaoping Huang, Jirair Bedoyan, Irina Anselm, Gerard T. Berry and co-authors

References


Gerard T. Berry
Boston Children’s Hospital/Harvard Medical School, 3 Blackfan Circle CLS Suite 14070, Boston, MA 02115, United States
E-mail address: gerard.berry@childrens.harvard.edu

26 January 2017
Available online xxxx