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Comprehensive Report &
Remote Second Opinion

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Prepared on June 9, 2025

About Dr. Melinda Peters

Clinical Expertise
Biochemical Genetics

Education
MD, University of Massachusetts Medical School, 2015

Residency
Residency, 2021, Stanford Hospital, Medical Genetics and Genomics
Residency, 2019, Harbor-UCLA Medical Center, Pediatrics

Fellowship
Fellowship, 2022, Boston Children's Hospital, Harvard Medical School, Medical Biochemical Genetics

Your Expert Opinion

Case Brief

This is a 12 year old female in Egypt diagnosed with Biotinidase Deficiency in January 2023 after rapid neurological decline. She began biotin, with slow improvement, regaining vision and partial motor/sensory function after prior loss. Biotin dosage was gradually increased (currently 300 mg/day), resulting in regained vision, some lower limb sensation/motor control, ability to sit independently and stand with support, however she is still incontinent and spastic in lower limbs. Upper limbs are functionally normal. The family seeks diagnostic confirmation, prognosis insight, and treatment optimization guidance.
This case includes 15 pages of indexed medical records, in addition to imaging available for review in the DICOM viewer.

Patient's Questions and Answers

Background Information Related to the Patient's Condition.

Biotin is a cofactor for 5 important carboxylase enzymes in the body which affect metabolism of several pathways involved in gluconeogenesis, fatty acid metabolism and amino acid catabolism. Biotin must be covalently bound to these enzymes to activate them. The role of and enzyme called holocarboxylase synthetase is to bind biotin to these 5 carboxylases in order to activate them. The 5 carboxylases affected by holocarboxylase synthetase deficiency are: acetyl-CoA carboxylase (acetyl-CoA carboxylase 1, the cytolsolic form and acetyl-CoA carboxylase 2, the mitochondrial form), 3-methyl-crotonyl-CoA carboxylase, pyruvate carboxylase and propionyl-CoA carboxylase. Acetyl-CoA carboxylase catalyzes the carboxylation of acetyl-CoA to malonyl-CoA which represents the first committed step in fatty acid synthesis. There are two isoforms of acetyl-CoA carboxylase (acetyl-CoA carboxylase 1 the cytolsolic form and Acetyl-CoA carboxylase 2 the mitochondrial form). Pyruvate carboxylase catalyzes the carboxylation of pyruvate to oxaloacetate. Propionyl-CoA carboxylase catalyzes the carboxylation of propionyl-CoA to methylmalonyl-CoA. 3-methyl-crotonyl-CoA carboxylase catalyzes the carboxylation of 3-methylcrotonyl-CoA to 3-methylglutaconyl-CoA. When the enzyme 3-methyl-crotonyl-CoA carboxylase is not functioning properly, 3-methyl-crotonyl-CoA accumulates and is subsequently converted into 3-hydroxyisovaleryl-CoA by the enzyme enoyl-CoA hydratase in a side reaction.
The accumulation of both propionyl- (C3) and 3-hydroxyisovaleryl- (C5-OH) carnitine indicates that both propionyl-CoA carboxylase and 3-methyl-crotonyl-CoA carboxylase are not functioning properly.
Thus, biotin is extremely important for normal metabolism. Another enzyme called biotinidase is responsible for obtaining biotin through the diet and recycling biotin so that it may be used for these crucial carboxylase enzymes. Profound biotinidase deficiency occurs when biotinidase activity is less than 10% of the mean normal serum biotinidase activity. It usually appears between ages one week and ten years, with a mean age of three and one-half months (GeneReviews). The majority of biotin obtained through the diet is bound biotin and must be 'freed' in order to be used.

Biotin must be covalently attached to the enzymes we discussed above (propionyl-CoA carboxylase (PCC), beta-methylcrotonyl-CoA carboxylase (MCC), pyruvate carboxylase (PC), and acetyl-CoA carboxylase (ACC)) in order to activate them. This covalent attachment is done by holocarboxylase synthetase. Biotin must be 'freed' and reused in order to keep these carboxylases working. The enzyme, biotinidase, generates free biotin from dietary sources and biotinylated enzymes by cleavage of biocytin or biotinyl-peptides. Without sufficient biotinidase activity, biotin cannot be recycled and becomes a limiting factor in the major carboxylase reactions listed above. Biotin supplementation is critical in this condition and is given as free biotin in order to allow holocarboxylase synthtase to biotinylate the carboxylases. It is encoded by BTD gene and is an autosomal recessive condition.

1. **Do you concur with the diagnosis of Biotinidase Deficiency given the timeline and response?**
   Yes, I do concur with the diagnosis of profound biotinidase deficiency. Sila's enzyme activity confirms this. Even though the exome classifies her genetic changes as variants of uncertain significance, they are pathogenic (disease-causing) since the biochemical enzyme activity supports this diagnosis. Her enzyme activity is very low and indicates profound biotinidase deficiency. Sila's clinical presentation is also consistent with late-onset biotinidase deficiency. There are patients who present with neuromyelitis optica and there are many case reports in the literature of late-onset biotinidase deficiency presenting this way. Sila's lack of response to immunomodulation therapies and improvement with biotin also support this diagnosis.

2. **Is high-dose biotin supplementation (current dose 300mg/day) the most appropriate and sufficient treatment or would suggest alternative treatments or modifications?**
   High-dose biotin supplementation (current dose of 300mg/day) seems like an appropriate treatment for Sila and the amount of biotin that each person with profound biotinidase requires can vary. It could be useful to perform biochemical testing for Sila to determine if she has any markers of abnormal carboxylase enzyme function. This means obtaining urine organic acids and urine acylglycine analyses to determine if there are any residual compounds such as 3-hydroxyisovaleric acid, 3-methylcrotonic acid, 3-methylcrotonylglycine and 3-hydroxy-propionic acid. If these are present, it means that the carboxyalse enzymes are having difficulty functioning normally and a dose increase could be considered. Biotin is the only treatment for biotinidase deficiency and is the standard of care in the United States.

3. **Are there any clinical trials that she would qualify for?**
   There are no clinical trials that are currently enrolling patients for treatment of biotinidase deficiency. However, please check the website https://clinicaltrials.gov/ periodically as new clinical trials are being posted daily and in the future, new opportunities for clinical trials may become available.

4. **Is the slow recovery (over 27 months) typical, or does it suggest an additional or complicating factor?**

My comments on timeline for recovery: due to the varied nature of each individual's symptoms and response to treatment, every individual with profound biotinidase deficiency will have a different recovery course and timeline. Sila started biotin in January of 2023 and during that time, she started to show signs of improvement. Her biotin dose has been gradually titrated upwards and now in April 2024, she has shown improvement. Over the time, she has started biotin, she has gone from complete loss of mobility and vision to standing with support and regaining her vision. This is a great improvement in my opinion.

My comments on additional or complicating factors: there are a few features of Sila's clinical presentation that make me puzzled. Features that are not common for this condition would be that Sila requires a very high biotin dose. However, it has been reported in the medical literature that some patients require biotin doses that are very high so this still can be explained by profound biotinidase deficiency. The finding of osteoporosis in a 12 year old female and the need for bisphosphonates makes me concerned that Sila has a second diagnosis. That is very atypical, especially since she is starting to walk again. Sila has proband-only exome. It might be beneficial to do trio exome sequencing (both parents contribute samples for analysis) to see if she has a second condition due to the consanguinity in the family.

5. **What is the expected likelihood for her regaining full mobility and continence and what is the typical outlook for patients similar to her?**

It is not known how much function Sila will recover but her body will need time to heal on high-dose biotin. She has made great improvements but in cases like hers, there are reports of children who make a full recovery and there are also reports of children who still have some residual neurological deficits. Every child with this condition can have a different recovery course and timeline.

6. **Are there adjunct medications or therapies that could improve sensation or bladder/bowel control?**

This question is best answered from a neurologist who specializes in spinal cord dysfunction. I cannot answer this question.

7. **Could the use of rituximab and IVIG have affected the expected recovery time, and are there ways to counteract that?**

The impact these interventions had on Sila cannot be known. For other immunomodulation therapies like steroids, some individuals showed improvement and some did not. For Sila's particular case, the impact of IVIG and rituximab cannot be determined.

8. **Does BCH offer any advanced treatments or expertise on this condition that would not be available in Egypt or other parts of the world? Do you see the benefit for us to be seen in person in Boston?**
There are no advanced treatments for biotinidase deficiency except for administration of biotin by mouth daily. At Boston Children's Hospital, we would treat Sila in the same manner with high-dose biotin. I do not see a benefit for Sila to come to Boston for an evaluation by a medical biochemical geneticist (physicians who specialize in biotinidase deficiency) as she is receiving biotin already but I do think it could be helpful for Sila to see neurologists either in her home country or abroad to see if there are any treatments that would help for Sila's spasticity and incontinence. Boston Children's Hospital has a clinic for these treatments. I also think that Sila should have her hearing checked if this was not already done as hearing can be affected in these cases.

9. **Please include any links to research reports or helpful resources.**
Please see the attached literature articles of neuromyelitis optica and biotinidase deficiency. It is also important to note that each case had its own unique features and treatment response and recovery are very variable.
A comprehensive review for this condition can be found at:
GeneReviews for Biotinidase Deficiency
https://www.ncbi.nlm.nih.gov/books/NBK1322/#

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Boston Children's Hospital is ranked among the top children's hospitals in the nation by U.S. News & World Report and is the primary pediatric teaching affiliate of Harvard Medical School. Home to the world's largest research enterprise based at a pediatric medical center, its discoveries have benefited both children and adults since 1869. Today, 3,000 researchers and scientific staff, including 10 members of the National Academy of Sciences, 25 members of the National Academy of Medicine and 12 Howard Hughes Medical Investigators comprise Boston Children's research community. Founded as a 20-bed hospital for children, Boston Children's is now a 415-bed comprehensive center for pediatric and adolescent health care. For more, visit our Answers blog and follow us on social media @BostonChildrens, @BCH_Innovation, Facebook and YouTube.

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