Follow-up of seven Korean MCAD deficiency patients detected by newborn screening

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Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency is a rare metabolic disorder that prevents the body from converting medium chain fats to energy during fasting[1,2]. MCAD gene (ACADM) mutation 985A>G (p.K329E) common in Caucasians population is not detected in Asians[3]. In Asia, 11 cases from Japan[5], 3 cases from Korea[4], and 1 case from Hong Kong[6]have been reported so far. The first Korean patient confirmed by molecular study shows unusual novel missense mutation 843A>T (R281S) and a 4-bp deletion. We report two Korean MCAD patients detected by newborn screening.

Principles of Management : (1, 2)

Preventative Care :

- Identification of affected infants via newborn screening.
- Prevent periods of prolonged fasting and thereby avoid breakdown of fats.
  - Frequent feeding of infants (i.e. Every 3 hrs)
  - Avoid formulas with medium chain tryglycerides as the primary source of fat.
  - Complex carbohydrates at bedtime for toddlers given as 2gm/kg uncooked cornstarch.
- Maintain normal to high fluid intake, avoiding dehydration.
- Give Tylenol (15mg/kg-dose q4) or Ibuprofen (10mg/kg-dose q6) for fever or pain.

Emergency Management :

- Patients with persistent vomiting, ataxia, lethargy, weakness, hypoglycemia or acidemia should be hospitalized promptly.
- Avoid epinephrine or glucagon for the purposes of restoring blood glucose, as both cause rapid increases in free fatty acids and insulin resistance.
- Patients with fatty acid deficiencies should not receive intralipid or aspirin.
- IV Fluids:
  - Initial fluids – bolus 10-20mg/kg IV D5NS
- Give L-carnitine 100mg/kg
  - 1st12 Hrs: Glucose infusion rate of 8-10mg/kg-min. (D10 or D12.5 + 1/2NS + 10mEq/L KCl) IVF electrolytes depending upon serum electrolytes.
- For an unresponsive patient:
  - Administer IV glucose 0.5mg/kg immediately

- Wean IV fluids slowly once adequate oral caloric intake is achieved.

Case History

Case 1

A 6 year-old boy was ascertained by abnormal newborn screening result – elevation of C6, C8, C10:1 carnitine. Prenatal historywas non-specific. He was born by C-section for delayed progression of labor at full term with birth weight of 3.06kg (50^{th} percentile), length 52 cm (50^{th} percentile), and head circumference 36 cm (50^{th} percentile). Mild hyperbilirubinemia was noticed, but the size of liver was normal. He was the only son with no family history of metabolic disorder or consanguinity. He was fed formula while maintaining breast feeding. He was supplemented with riboflavin and carnitine. At two and half months of age, he was treated for brochiolitis. His growth (weight 80^{th} percentile, head circumference 5^{th}percentile, height 95^{th}percentile) and development has been normal. EKG checked at age of three months showed mild tachycardia. He is attending regular school without any problem. At night time, raw corn starch has been givenbefore going to bed.

Case 2

A 4 year-old boy was detected by newborn screening with elevation of C6, C8, C8:1, C10:1 carnitine. He has a healthy sister with normal acylcarnitine profile. There was no history of related marriage. He was born by normal spontaneous vaginal delivery (NSVD). His birth weight was 3.9 kg (98^{th} percentile), length 52 cm (50^{th} percentile), and head circumference 36 cm (90^{th} percentile). He has been breast fed,growing well with carnitine and riboflavin supplementation. At one month of age, he had an EKG with mild tachycardia (152 per minute). He had a history of recurrent respiratory infectionsbut he is growing and developing normally. EKG and Echocardiogram were normal.

Case 3

A 21 month-old boy, detected by newborn screening, was born by NSVD at 39 week with birth weight of 3.2kg. Hisunusual clinical presentation was severe atopic dermatitis, recurrent URI, intolerable fasting with sweating, mild speech development delay (he was able to speak 3 words).

Case 4

A 18 month-old girl came to attention with abnormal elevation of C6, C8, and C10:1 carnitine. She hadbeen growing normally without any problem until 1year of age. She had hypoketotic hypoglysemia, requiring IV glucose infusion.

Case 5

A 16 month-old boy detected by newborn screening had birth weight of 3.5kg. He was breast fed for 2 months and underwent mixed feeding in subsequent 10 months. Nonfat milk was given once a day and raw cornstarch was given before going to bed. He was hospitalized for rota virus gastro enteritis at 3 months of age. At 1 year of age, he was hospitalized for hand-foot-mouth disease.

Case 6

A 9 month-old girl was detected by abnormal newborn screening. She has been hospitalized twice for pneumonia and gastroenteritis. She showed normal growth and development.

Case 7

A 6 month-old baby boy, normal growth and development, breast feeding.

Diagnosis

Biochemical and molecular genetic test.

Confirmatory biochemical diagnostic tests included bloodspot acylcarnitine, urine organic acid and urine acylglycine. Molecular test was done with DNA from peripheral blood and cultured fibroblasts. We amplified and sequenced all 12 exons of the gene. Mutation analysis was performed by direct sequencing of PCR-amplified fragments. Western blot test along with the fibroblast were employed to see the expression of MCAD antigen.In addition, DNA was extracted from 50 randomly selected and anonymized Korean NBS cards.

Results

Blood ammonia, liver function test, blood gas, urine ketone were normal except in case 1 who had transienthyperbillirubinemia and elevation of alkaline phosphatase. Acycarnitine of profile showed in case 1 elevation of C6 carnitine: 0.41, C8 carnitine: 1.26, C10:1 carnitine: 0.84. In Case 2C6 carnitine: 0.64, C8 carnitine: 0.59 (N: 〈0.5), C10:1 carnitine: 0.80 (N: 〈0.5). Urine acylglycine showed elevation of hexanoylglycine in case 1 and hexanoylglycine, suberylglycine, 3-phenylpropionylglycine, and 3-OH-sevasic in case 2. Urine organic acid showed elevation of hexanolyglycine, suberylglycine, unsaturated sebacic, 3-HO-sevacic in both cases. In case 1 3-phenylpropionylglycine remarkably elevated in case 1. We found a homozygous mutation, T1190A in exon 11 that alters tyrosine-372 to asparagines in both cases.We also did a western blot with these cells. The level of expression of MCAD antigen is very low, less than 5% of normal. Therefore, this missense mutation must create an unstable MCAD protein that is rapidly degraded. It is quite surprising to find this in the homozygous state, as that would suggest either that the parents are related genetically (consanguineous) or that this mutation is relatively common in the Korean population.

Discussion

Because of the nonspecific clinical presentation of MCAD deficiency, the differential diagnosis from other FAO disorders is an increasingly complex process that can hardly be achieved by a single test. The diagnosis of MCAD deficiency, therefore, requires the integrated interpretation of multiple analyses, including consideration of the clinical status of the affected individual (acutely symptomatic vs. asymptomatic) at the time of sample collection. Initial testing should include the following analyses and their proper interpretation[2]. The external source of MCT oil can affect the

diagnosis of MCAD deficiency. The first Korean patient showed clinical manifestation before the result of newborn screening results of acylcarnitine. The molecular study showed missense mutation 843A〉T (R281S) and 4-bp deletion. In our two cases the molecular study showed novel mutation, T1190A. Whether this mutation is common mutation in Korea or not is not certain and require persistent study in the future. Early detection of MCAD deficiency is essential to prevent or minimize the complication of metabolic disorder.

Reference

1. Gregersen N, Laurizen R. Rasmussen K. Suberylglycine excretion in the urine from a patient with dicarboxylic aciduria. Clin Chim Acta 1976;70:417-425.
2. Matern D, Rinaldo P. Medium-chain acyl-coenzyme A dehydrogenase deficiency. In: GeneReviews:Genetic disease Online Reviews at GeneTests-GeneClinics [data base online: Initial posting: April 20, 2000; last update January 27, 2003] Universityof Washinton, Seattle. Availabe at : http://www.geneclincs.org Accessed Janurary 2 2005.
3. Regina MD, Wionters, Jennifer L. et al. Genotypic differences of MCAD deficiency in the Asian population: Novel genotype and clinical symptoms preceding newborn screening notification. Genetics in Medicine. 7(5):339-343, May/June 2005.
4. Hong Jin Lee. Inborn Errors of Metabolism in Korea. J Korean Neurol Assoc 22(1):1-10, 2004
5. Tajima G, Sakura N, Yofune H, Nishimura Y, Ono H, Hasegawa Y, Hata I, Kimura M, Yamaguchi S, ShigematsuY, Kobayashi M. Enzymatic diagnosis of medium-chain acyl-CoA dehydrogenase deficiency by detecting 2-octenoyl-CoA production using hyigh-performance liquid chromatography: a practical confirmatory test for tandem mass spectrometry newborn screening in Japan. J Chromnatogr B Analyt Technol Biomed Life Sci. 2005 Sep 5;823(2):122-30.
6. C. P. Pang, L.K. Law, et al. Biochemical investigation of young hospitalized Chinese children: Results over a 7-year period. Am. J. Med. Genet. 72:417-421, 1997.