CASE REPORT

Biotinidase Deficiency with Hypertonia as Unusual Feature

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We report 3 cases of biotinidase deficiency presenting in early infancy with neurological and cutaneous manifestations. All of them had hypertonia (spasticity). Response to oral biotin was excellent. One of the cases showed 7D3I biotidase deficient mutation.

Keywords *: Biotinidase deficiency, Hypertonia, Spasticity, 7D3I mutation.*

Biotinidase deficiency is one of the treatable inherited errors of metabolism. Clinically it presents with progressive neurological deterioration associated with cutaneous involvement. Presence of metabolic acidosis and ketonuria substantiate the clinical diagnosis. Final confirmation is obtained by plasma and urinary organic acid profile and enzyme assay in cultured fibroblast. Biotin therapy results in excellent therapeutic success with rapid normalization of clinical and metabolic parameters. Presence of hypertonia is unusual in these children.

Case report

Case 1: A, 3 month old boy, born out of non-consanguineous marriage, presented with generalized tonic clonic convulsions for one month, altered sensorium, and loss of milestones. Convulsions were uncontrolled despite phenytoin sodium and phenobarbitone therapy. The perinatal period was uneventful.

On examination, child was normothermic with normal pulse and blood pressure. There was tachypnea (RR 64/min) with Kussmaul breathing. The anterior fontanelle and fundus was normal. He had alopecia, scanty eyebrows and blepharitis.There was seborrheic dermatitis on scalp. He was getting seizures intermittently. He had hypertonia (spasticity) and brisk deep tendon reflexes in all four limbs. Arterial blood gases showed metabolic acidosis, with pH 7.14, PaCO2 12.5mm Hg, bicarbonate 4.3 mEq/L and base deficit of –21.3. Urine examination revealed large amount of ketones (80mg/dL). Sepsis screen, blood sugar, hemogram, serum calcium, creatinine, sodium and potassium were normal. Cranial ultrasound was normal. The child was treated with oxygen, parenteral fluids, anticonvulsants and IV sodabicarb 1mL/kg. Acidosis and seizures persisted and child lapsed into coma. A possibility of biotinidase deficiency was kept and child was empirically put on biotin tablets through nasogastric tube after collecting sample on filter paper. Within 24 hours, there was dramatic response in the form of improved consciousness, decreased acidosis and cessation of seizures. Hypertonia disappeared in 72 hours. Anticonvulsans were withdrawn after 7 days without any recurrence of seizures. Mass tandem spectroscopy revealed large amount of hydroxyl-C5-acylcarnitine supporting biotinidase deficiency. The child is on regular biotin therapy 5 mg BD and doing well. Hairs have started growing on scalp and eyebrows.

Case 2: A 3.5 month old boy born out of consanguineous marriage presented with seizures, regression of milestones, altered sensorium and

spasticity in upper and lower limbs. The child had hypotrichosis on scalp and eyebrows. There was no rash or seborrhea. Anterior fontanel, fundus and cranial ultrasound was normal. Ketonuria and metabolic acidosis were present. Sepsis screen and serum electrolytes, calcium, and sugar were normal. Child responded to empiric biotin therapy 5mg BD. Screening for biotinidase deficiency showed little or no enzyme activity in the sample. DNA analysis done at Neo Gen Screening, Bridgeville PA 15017 showed two copies (homozygous) of 7D3I Biotinidase deficient mutation.

Case 3: A 3 months old child also presented similarly with seizures, regression of milestones, alopecia (***Fig.*****1**) and total loss of eyebrows (***Fig.*** **2**). On examination child had spasticity in lower limbs with normal anterior fontanel. Sepsis screen, serum electrolytes, serum calcium, blood glucose, fundus and cranial ultrasound were normal. Arterial blood gases and urinary ketones were normal. Response to empiric biotin therapy was excellent. Enzyme assay showed severe Biotinidase enzyme deficiency with enzyme activity less than 1% of normal.

DISCUSSION

Biotinidase deficiency, a recessively inherited treatable metabolic disorder, is a defect in utilization of a water soluble vitamin, biotin. It is an autosomal recessive disorder with prevalence of 1 in 60000. Every 1 in 123 individuals is heterozygous for this disorder(1). This disorder is clinically suspected in the presence of progressive neurological deterioration (seizures, encephalopathy, neuro-developmental delay) associated with cutaneous involvement (skin rash, seborrhea, alopecia). The symptoms appear when the child is several months old, which is possibly due to presence of sufficient free biotin derived from mother.

Hypotonia is a common clinical finding in this condition, due to reversible metabolic myopathy(2-5). Hypertonia, as observed in these 3 cases remains unexplained. Raised intracranial pressure was unlikely in view of normal anterior fontanel, fundus and cranial ultrasound. In all 3 cases, hypertonia responded to Biotin therapy in 3-5 days. Hypertonia and spasticity is described in biotinidase deficiency only in cases which present in late childhood or adolescence(6,7). In such cases with late presentation, spastic paraparesis and bilateral optic atrophy are important clinical features but hypertonia is not reported in patients who present in early infancy. Hypertonia of extrapyramidal type (rigidity) is seen in biotin responsive basal ganglia disease, which presents as progressive quadriparesis, dystonia, dysarthria and subacute encephalopathy due to bilateral necrosis of basal ganglia(8). But this disorder occurs in older children and clinical

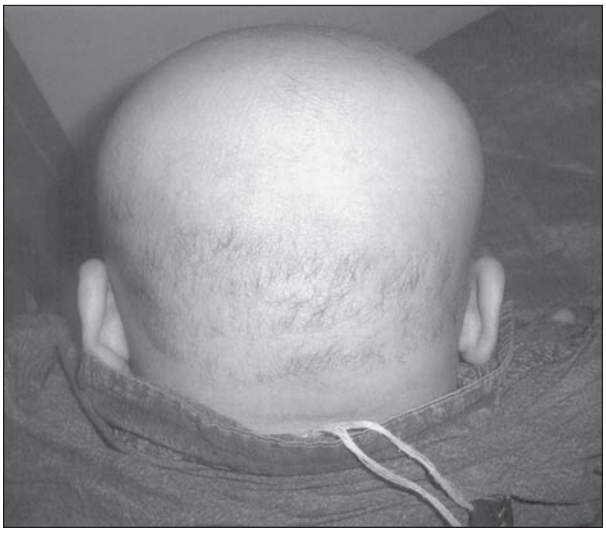

FIG. 1 *Alopecia.*

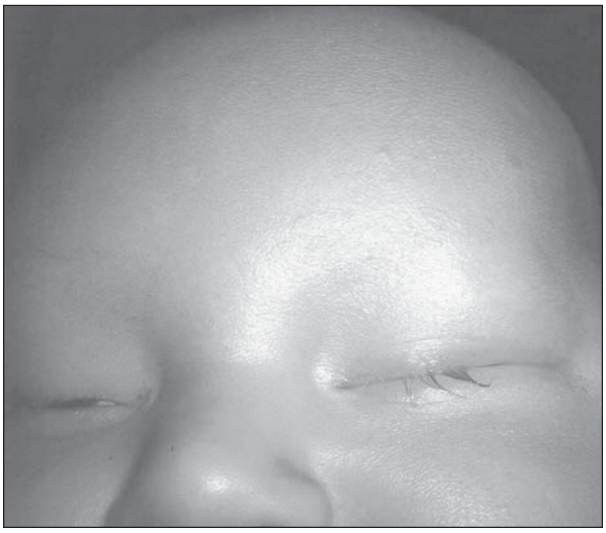

FIG. 2 *Loss of eyebrows.*

presentation is quite different from biotinidase deficiency.

In first case, enzyme estimation could not be done. Clinically and therapeutically, biotinidase deficiency cannot be differentiated from holo-carboxylase synthatase deficiency, but in last 2 cases enzyme assay proved biotinidase deficiency. The most common mutation found is deletion at chromosome 7 and insertion at chromosome 3(9), as seen in our second case. Biotin therapy needs to be continued throughout life. Prognosis is excellent if Biotin therapy is started early. Newborn screening helps for prevention of neurological damage in patients with low residual enzyme activity by early therapy. Prenatal dignosis is done by enzyme assay in cultured amniotic cells and mutation studies. Biotin administered prenatally is effectively taken up by the fetus and prevents functional deficiency of carboxylases in an affected newborn(10). Genetic counseling is offered to parents.

Biotinidase deficiency should be thought of in any child with seizures in first few months of life associated with encephalopathy, skin manifestations, developmental delay or regression, metabolic acidosis and ketonuria.

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