November 2013

Diagnosis, treatment and follow-Up in four children with biotinidase deficiency from Pakistan

Bushra Afroze
Aga Khan University

Mohammad Wasay
Aga Khan University

CASE REPORT

Diagnosis, Treatment and Follow-Up in Four Children with Biotinidase Deficiency from Pakistan

Bushra Afroze[1] and Mohammad Wasay[2]

ABSTRACT

Biotinidase deficiency is an inherited disorder in which the vitamin biotin is not recycled. If untreated, affected individuals develop neurological and cutaneous symptoms. Untreated individuals with biotinidase deficiency either succumb to disease or are left with significant morbidity. We describe clinical course and follow-up of 4 children from Pakistan. All 4 presented with classical symptoms of biotinidase deficiency and responded dramatically to oral biotin within days to weeks. Biotinidase deficiency is reported in Pakistani children from different part of world, however; there is no such report from Pakistan. This highlights lack of awareness of biotinidase deficiency among physicians in Pakistan.

Key Words: *Biotinidase deficiency. Clinical course. Pakistan. Children.*

INTRODUCTION

Biotinidase deficiency (OMIM 253260) is an autosomal recessive metabolic disorder with an estimated global incidence of 1:60,000 newborns.[1] Most individuals with untreated biotinidase deficiency (BD) show progressive clinical features, including neurological abnormalities such as seizures, hypotonia, ataxia, developmental delay, sensorineural hearing impairment and optic atrophy.[2] BD is treated with 5 – 20 mg of biotin daily independent of age.[3] All symptomatic children show clinical improvement within days to weeks,[4] except for visual abnormalities, hearing loss and developmental delay, which are usually irreversible.[5]

In Pakistan, patients with BD are almost never diagnosed early and often remain misdiagnosed. We present two families with 4 children diagnosed as BD and their follow-up. Family 2 highlights the importance of first degree relatives screening for BD once a proband is diagnosed as having BD.

CASE REPORT

Patient 1: This boy was born as the third child to first-cousins parents at full-term after an uneventful pregnancy and delivery. At the age of 3 years and 4 months, he developed conjunctivitis followed by ataxia and a tendency to fall while walking with significant thinning of scalp hair and loss of eye lashes and eye brows. In addition, scaly and erythematous skin rashes in the perioral, periorbital, periungual area and buttocks developed. A day before admission to our hospital, he developed tachypnea and stridor, which progressed to severe respiratory distress. The main biochemical laboratory evaluation showed metabolic acidosis (pH 7.2, BE -12), raised lactate 4.3 mmol/L (normal < 2 mmol/L), ketonuria (+2); serum ammonia 36 µmol/L (normal range: 50 – 80 µmol/L), liver and renal functions were normal.

Patient 2: This girl was born as first child of first-cousin once removed parents at full-term after an uneventful pregnancy. She attained normal developmental milestones time till 18 months of age when she developed high grade fever and seizure. CSF bio-chemistry and culture was normal. At discharge, she was grossly hypotonic and had lost all her motor mile stones. Subsequently, the physician at that time started her on oral biotin 10 mg twice daily without any investigation or diagnosis. Mother reported that she improved substantially on biotin over 3 – 4 months duration and regained neck holding and sitting. She started walking with support at 3 years. Family was not compliant to the regular use of oral biotin. Whenever oral biotin intake was interrupted, she would develop total alopecia including loss of eyebrows and eyelashes, which would recover within weeks of resuming oral biotin. She was 16 years old and her mother reported her strong refusal to visit hospital. She was seen in metabolic clinic only once at the age of 16 years and was mobile using crutches. She refused any kind of investigation. The only laboratory investigation done was dried blood spots for biotinidase assay. We could not carry out visual evoked potential study (VEP) or brainstem auditory evoked potential (BAEP).

Patient 3: Patient 3 is the sister to patient 2. She was born as the second child of the family at full-term uneventful pregnancy and delivery. Her early childhood including development was normal. She started to lose scalp hair first at the age of 12¼ years, which progressed

Department of Paediatrics and Child Health[1] / Medicine[2], The Aga Khan University Hospital, Karachi.

Correspondence: Dr. Bushra Afroze, A-281, Block 5, Gulshan-e-Iqbal, Karachi.
E-mail: bushra.afroze@aku.edu

Received: April 02, 2012; Accepted: January 05, 2013.

Table I: Clinical presentation and outcome of 4 patients with profound biotinidase deficiency.

Patient	Age at onset	Presenting symptoms	Alopecia/ skin rash	Ataxia	Blood lactate (mmol/L)	Age at diagnosis	Follow-up period	Outcome
1	3 years 4 months	Respiratory distress, stridor	+/+	+	4.3	3 years 4 months	1 year 5 months	Normal development and hearing.
2	18 months	Seizures	+/-	-	NA	Confirmed diagnosis at 16 years	8 months	Spastic paraplegia
3	12 years 3 months	Severe visual impairment and inability to walk	+/+	+	3.8	13 years	8 months	Clinical improvement in visual acuity and regained independent ambulation
4	7 years 6 months	Visual impairment and inability to walk	+/+	+	4.2	8 years 6 months	8 months	Clinical improvement in visual acuity and regained independent ambulation

NA = Data not available.

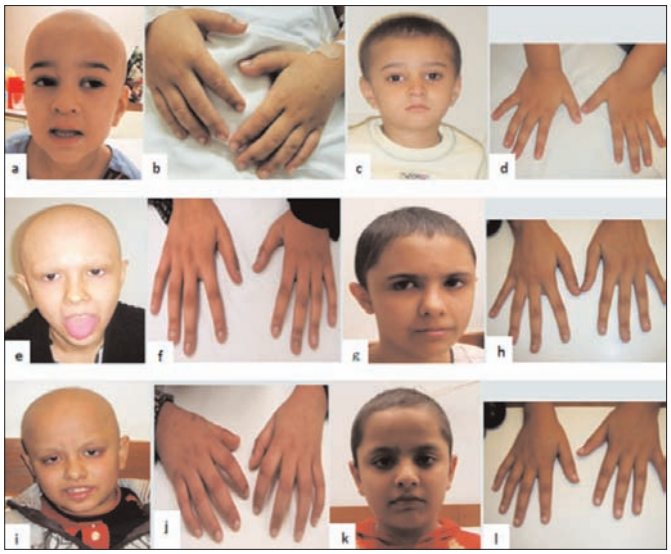

Figure 1: (a-d) Patient 1. **(e-h)** Patient 3. **(i-l)** Paitent 4. **(a,e,i)** Alopecia, perioral and periorbital rashes before treatment. **(b,f,j)** Periungual rashes before treatment. **(c,g,k)** Resolved perioral, periorbital rashes and growth of scalp hair after treatement. **(d,h,l)** Resolved periungual rashes after treatment.

to total alopecia including loss of eyelashes and eyebrows by 12½ years. She faced visual difficulty in reading by 12¾ years and became ataxic. Symptoms progressed over next 3 months. She was seen at metabolic clinic at the age of 13 years. She was wheel chair bound and had left school because of poor vision and alopecia. Her skin examination showed scaly and erythematous rashes in the perioral, periorbital and periungual area. Focused laboratory investigation showed plasma lactate 3.8 mmol/L and optic pathways dysfunction predominantly demyelinating in nature on VEP and normal BAEP.

Patient 4: Patient 4 is the youngest brother of patients 2 and 3. He was born at full-term uneventful pregnancy and delivery. His early childhood including development was normal. His symptoms started at 7½ years of age with skin rashes in the perioral, periorbital, periungual area, buttock, oral ulcers and thinning of scalp hair. At the same time he complained of poor vision and became ataxic. He was seen in metabolic clinic at the age of 8½ years. At that time he had total alopecia including loss of eyelashes and eye brows. He was able to walk only with support. Focused laboratory investigations showed plasma lactate 4.2 mmol/L; VEP showed optic pathways dysfunction predominantly demyelinating in nature. BAEP was normal.

Clinical and biochemical features of patients are summarized in Table I. Dried blood spots for biotinidase activity of all 4 patients were sent to NSW Biochemical Genetic Services at New Children's Hospital, Adelaide, Australia, where biotinidase activity was determined with a semiquantitative colorimeteric method using N-biotinyl-p-aminobenzoic acid as substrate. Absent BD activity was found in all 4 patients, so all of them were diagnosed as profound BD.

Patient 1 was started on oral biotin 20 mg/day initially. He showed clinical and biochemical improvement within 2 days. His skin rash disappeared along with improvement of metabolic acidosis, normalization of lactic acidemia and ketonuria. But his ataxia did not improve, therefore; oral biotin was increased to 30 mg/day. He responded to increased dose and was ambulatory within 3 days of increased dose of biotin. Growth of eyebrows, eye lashes and scalp hair was seen by the end of 3 weeks. Photographs of patient 1, 3 and 4 are shown in Figure 1. Patient 2, 3 and 4 were treated with oral biotin 20 mg/day. Most symptoms disappeared 1 – 3 weeks after the initiation of treatment. For patient 3 and 4, skin rashes disappeared within first week. Growth of eyelashes, eyebrows and scalp hair was seen by second week of treatment. Patient 4 was walking independently by the end of third week. Independent ambulation was seen in patient 3 by the end of 5th week. In Patient 3, vision also improved significantly as she was able to read even small prints.

DISCUSSION

Biotinidase deficiency remains underdiagnosed in Pakistan. Biotinidase deficiency meets many of the criteria for newborn screening; an inexpensive and reliable screening test is available, untreated individuals have high morbidity and mortality and effective and cost effective/economical treatment is available.[6] There are no prior cases of BD reported from Pakistan but a number of Pakistani children are reported in literature.[7-9]

In Pakistan, due to high rate of consanguinity, incidence of BD is expected to be high. In countries like Turkey with high consanguinity incidence of BD is reported to be 1 in 14800.[10] Incidence of BD in Pakistan needs to be studied, because the treatment of BD is much more cost-effective then the expense and resources needed to support a blind, deaf or mentally challenged individual. The presently described cases also showed marked improvement following appropriate therapy with reversal of visual handicap in one patient.

Hence, Pakistani physicians need to be made aware of such a metabolic deficiencies which are both easily diagnosable and easily treatable to avoid long-term irreversible handicap.

REFERENCES

1. Wolf B. Worldwide survey of neonatal screening for biotinidase deficiency. *J Inherit Metab Dis* 1991; **14**:923-7.
2. Wolf B. The neurology of biotinidase deficiency. *Mol Genet Metab* 2011; **104**:27-34.
3. Wolf B. Clinical issues and frequent questions about biotinidase deficiency. *Mol Genet Metab* 2010; **100**:6-13.Epub 2010 Jan 11.
4. Wolf B, Grier RE, Allen RJ, Goodman SI, Kien CL, Parker WD, *et al.* Phenotypic variation in biotinidase deficiency. *J Pediatr* 1983; **103**:233-7.
5. Wolf B, Spencer R, Gleason T. Hearing loss is a common feature of symptomatic children with profound biotinidase deficiency. *J Pediatr* 2002; **140**:242-6.
6. Wolf B, Heard GS, Jefferson LG, Proud VK, Nance WE, Weissbecker KA. Clinical findings in four children with biotinidase deficiency detected through a statewide neonatal screening program. *N Engl J Med* 1985; **313**:16-9.
7. Wastell HJ, Bartlett K, Dale G, Shein A. Biotinidase deficiency: a survey of 10 cases. *Arch Dis Child* 1988; **63**:1244-9.
8. Grunewald S, Champion MP, Leonard JV, Schaper J, Morris AA. Biotinidase deficiency: a treatable leukoencephalopathy. *Neuropediatrics* 2004; **35**:211-6.
9. Mc Sweeney N, Grunewald S, Bhate S, Ganesan V, Chong WK, Hemingway C. Two unusual clinical and radiological presentations of biotinidase deficiency. *Eur J Paediatr Neurol* 2010; **14**:535-8. Epub 2010 Feb 12.
10. Pomponio RJ, Coskun T, Demirkol M, Tokatli A, Ozalp I, Hüner G, *et al*. Novel mutations cause biotinidase deficiency in Turkish children. *J Inherit Metab Dis* 2000; **23**:120-8.