Original Article

DOI: 10.7860/JCDR/2015/12958.6941

Clinical, Biochemical and Outcome Profile of Biotinidase Deficient Patients from Tertiary Centre in Northern India

Paediatrics Section

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ABSTRACT

Introduction: Biotinidase deficiency is an inherited metabolic disorder with estimated birth incidence of 1 in 61,000 for profound and partial deficiency. Estimated incidence of profound and partial biotinidase deficiency is 1 in 1, 37,000 and 1 in 1, 10,000 respectively. The carrier frequency in general population is 1 in 120. We attempt to study clinical, biochemical and outcome from 10 Biotinidase deficient patients.

Materials and Methods: A retrospective case record study was conducted to record Clinical, biochemical and outcome profile from genetic records. Biotinidase level was measured using spectrophotometric method.

Results: Study group comprised of 8 males and 2 females with median age of presentation 6 (2-45.75) months. Median (interquartile range) Biotinidase level in study group 0.3 (0.08—1.5) nmol/ml/min. Study group was further divided in to early onset group (< 12 months, n-6) and late onset group (> 12 months, n-4). Seizure, alopecia and hearing loss were predominant phenotypes in study group. The other rare presentations were: hypotonia, ataxia, skin rash, seborrhoea. The most common seizure type was focal seizure. Control of seizure activity was important immediate outcome measured in study group. Median duration (interquartile range) of seizure control in early onset group was 3 (2-4)days against 13.5 (12.25-14.75) days in late onset group.

Conclusion: This study highlights the need of early diagnosis for favourable outcome for a potentially treatable inherited metabolic disorder.

Keywords: Hypotonia, Rash, Seizures

INTRODUCTION

Biotinidase deficiency is a multisystem disorder, predominantly manifesting with necurocutaneous features: seizures, hypotonia, ataxia, skin rash, alopecia, hearing loss, optic atrophy and sepsis like metabolic crisis. If detected late, it can cause irreversible brain damage, coma and even death [1]. It can manifest from neonatal period to adulthood. Several adults with profound biotinidase deficiency identified through family studies have never exhibited symptoms [2]. It is autosomal recessive inherited metabolic disorder which is amenable to treatment with pharmacological doses of biotin. Biotin is cofactor for four carboxylases (propionyl-CoA carboxylase, β-methylcrotonylCoA carboxylase, pyruvate carboxylase, acetyl CoA carboxylase) in human that are essential for glucose, fatty acid and amino acid metabolism. The major function of Biotinidase is to recycle biotin liberated from biocytin and small biotinyl–peptides from degraded holocarboxylases. The causative enzyme deficiency was first described by Wolf et al., [3]. Mutation in biotinidase gene was localised to chromosome 3p25 [4]. There are more than 150 mutations reported till now in literature [2]. It has been a part of newborn screening programme for many countries to screen asymptomatic newborns and extends the benefit of biotin supplementation in asymptomatic stage. The burden of Biotinidase deficiency has not been studied in our population. Various studies have found congenital hypothyroidism, Congenital Adrenal hyperplasia, G6PD Deficiency are the other common metabolic disorders that requires screening and treatment. The reported frequency of congenital hypothyroidism and Congenital Adrenal hyperplasia are 1 in 1700 and 1 in 2575 respectively [5]. Many case reports have been presented from India, highlighting the clinical features and response to treatment. We undertook present study to depict clinical, biochemical and outcome profile from ten biotinidase deficient patients and highlight need of early diagnosis for favourable outcome in symptomatic cases.

MATERIALS AND METHODS

A retrospective study was conducted at genetic centre at tertiary level hospital after obtaining Institute ethical committee approval. Genetic records of all biotinidase deficient patients were searched from January 2012 to August 2013. A predesigned performa was filled for age of onset, sex ratio, parental consanguinity, clinical features, biochemical and outcome (where available). One millilitre of serum was extracted and stored at -80 degree Celsius till analysis. Biotinidase level was estimated, following a standard protocol using spectrophotometric technique [6]. Normal levels of biotinidase have not been established in our population, so levels provided by American college of medical genetics were used to classify them as biotinidase deficient [7]. Reference biotinidase activities reported by ACMG (Americal College of Medical Genetics) are as follow: Unaffected individual - 7.57±1.41 nmol/min/ml of serum, profound BD (biotinidase def) excluding NBS - 0.12± 0.18 (less than 10% of mean normal serum enzyme activity), partial BD -1.47 ± 0.41nmol/min/ml serum (between 10% and 30% of mean normal serum enzyme activity). To study outcome of seizure control; study group was divided in to early onset group (presentation < 12 months, n- 6) and late onset group (presentation >12 months, n-4). Outcome was number of days required to seizure control after initiation of biotin therapy.

RESULTS

There were ten cases with male to female ratio of 8:2. All cases were unrelated except one family in which three members were affected. All cases were from Northern India. Median (interquartile range) age of presentation in study group was 6 (2-45.75) months. Demographic characteristics, clinical features, biochemical profile were summarised in [Table/Fig-1]. Median (interquartile range) biotinidase level in study group 0.3(0.08--1.5) nmol/min/ml. Frequency of common clinical and biochemical features were:

Patient	Age (mon)	Sex	Seizure	Hypotonia	Ataxia	Alopecia	Skin rash	Seborroea	Hearing loss	Organic Aciduria	Lactate	Ammonia	Biotinidase (nmol/min/ ml)	Days of seizure control
1	4	m	+	+	-	+	--	+	nd	+	n	n	0.057	3
2	84	m	+	+	+	+	na	+	+	nd	abn	n	0.30	12
3	45	m	+	+	+	+	na	+	+	nd	n	n	0.00	14
4	1	m	-	-	-	+	-	-	-	n	n	n	0.30	2
5	48	m	+	+	+	+	-	-	+	n	n	n	1.67	15
6	2	f	+	+	-	+	-	-	nd	+	abn	n	1.32	4
7	3	m	+	+	-	+	+	+	nd	nd	n	abn	1.67	3
8	8	m	+	-	-	+	+	-	+	nd	abn	n	1.5	4
9	2	f	+	n	-	-	+	-	nd	+	abn	n	0.228	2
10	26	m	+	+	+	+	+	-	+	+	n	abn	0.08	13

[Table/Fig-1]: Clinical, biochemical and outcome profile of ten Biotinidase deficient patients.
Foot note: m-male; f- female; na-not available, nd- not done; n-normal; abn- Abnormal

parental consanguinity (6/10); seizures (9/10); hypotonia (7/10); ataxia (4/10); alopecia (9/10); skin rash (4/8); seborrhoea (4/10); sensorineural hearing loss (5/6); organic aciduria (4/6); high lactate (4/7); high ammonia (2/7). Median (interquartile range) duration of seizure control in study group was 4 days (3-13). Median duration (interquartile range) of seizure control in early onset group was 3 (2-4) days against 13.5 (12.25-14.75) days in late onset group ($p< 0.05$) .

DISCUSSION

Study included ten Biotinidase deficient cases over a span of 20 months, referred to genetic centre for enzyme assay. Study demonstrates male preponderance of cases with median age of presentation 6 months. The commonest neurological, cutaneous and biochemical manifestations were: seizure (9/10); alopecia (9/10); organic aciduria (4/6). This observation has been seen previously in various ethnic populations and in case reports from India [8-12]. Iranian case series found that seizures (13/16), alopecia (8/16), abnormal auditory brainstem response (4/16), abnormal lactate and ammonia (8/16) were the common manifestations [13]. Seizures and alopecia are the commonest manifestation in our cohort unlike Iranian cohort where alopecia was found in only 50% of cases. Hearing abnormality was found in five of six cases in our series which higher than Iranian cohort. This may be attributed to nonscreening of all cases in our cohort or small sample size. Ammonia and lactate abnormality was comparable in both case series. We could not find any case series from India to compare our findings. There have been case reports citing common findings of this disorder. Ours is the largest cohort of biotinidase deficient patients from India, depicting their clinical and biochemical profile. Median age of presentation was 6 months with interquartile range (2-45.75 months). Most of cases (6/10), onsent of symptoms was infantile with death in one case that presented with sepsis like episodes. High index of suspicion in presence of constellation of seizures, hypotonia, and alopecia led to early referral for prompt diagnosis and institution of appropriate treatment in rest of five infantile onset cases. All our cases responded to supplementation of biotin (10-20 mg per day). The most important marker of disease control was cessation of seizure activity. The most important long term complication in late onset group cases was irreversible sensorineural hearing loss as previously reported by Genc et al., [10]. This may be attributed to, lack of suspicion on part of clinicians, delay in early diagnosis, lack of appropriate facilities for enzyme assay, affordability or related to genotype as stated by Sivri [14]. This observation necessitates the need of early referral and diagnosis in symptomatic cases to start timely treatment to the prevent complications.

In one family in which 2 children were already affected, mother was started on biotin therapy since conception. The child, born to mother, was started on biotin supplement soon after birth and tested for enzyme assay at 1 month of age. He was found to be deficient. So, biotin therapy continued. Currently, he is asymptomatic with achievement of normal development. The strategy of supplementing biotin to mother, who already has affected children, has worked in preventing symptoms of biotinidase deficiency [2]. The low dose biotin therapy does not does interfere with enzyme assay and thus leading to correct diagnosis in suspected cases. This strategy is important for resource poor countries like ours where prenatal testing (enzyme or genotype) is not available at most of centres.

Biotinidase, encoded by BTD gene, helps in recycling biotin from food by releasing biotin from biocytin or small biotinylated peptides [15]. Mutation in BTD gene leads to altered enzyme activity. There are nearly 165 mutations have been reported in literature so far [16]. We could not genotype our cases as this facility was not available at our centre. Further genotype would have provided the prevalent mutations in our population, chance for genotype and phenotype correlation and diagnosis in borderline cases. Another drawback of study was that we could measure only immediate outcome rather than long term neurodevelopmental outcome.

There are case reports from India highlighting the need for early diagnosis and treatment in symptomatic cases [11,12]. It is an inherited metabolic disorder that fulfils the Wilson & Jeugner criteria for Newborn screening [17]. It is part of newborn screening programme of many American and European countries unlike ours [18]. Asymptomatic screening of newborns has yielded satisfying results. With estimated birth prevalence of 1 in 60,000, there lays huge burden on public and private agencies to diagnose and treat symptomatic cases [19]. We need to develop infrastructure and manpower to enable screening of asymptomatic newborns through dried blood spot enzyme assay for a potentially treatable inherited metabolic disease. As this was retrospective case record study, long term outcome was not found in case records except irreversible hearing loss. No specific indices were used. Only clinical control of seizure was recorded. Some of patients were also reported appearance of new hairs and improvement in cutaneous symptoms. Most of families were satisfied with diagnosis as their children were seizure free, cutaneous symptoms and alopecia were disappeared.

There is no large scale population based study to know exact burden of problem in our country. However, the situation may be alarming for a hugely populous country like ours due to high birth rate, high rate of consanguious marriages in sections of society, practices of same caste and same gotra marriages. So, there is need of opening more government aided centres for enzyme assays to offer timely treatment for a potentially treatable metabolic disorder.

CONCLUSION

Our study is the largest cohort of symptomatic Biotinidase deficient children from India. The study has highlighted clinical features,

biochemical profile and outcome in Biotinidase deficient patients. Outcome was favourable in cases where early diagnosis was made and prompt treatment was instituted. So, early and timely supplementation of biotin improves the neuro devlopmental outcome.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Jan 11, 2015**
Date of Peer Review: **Jun 04, 2015**
Date of Acceptance: **Sep 20, 2015**
Date of Publishing: **Dec 01, 2015**