Molecular Genetics and Metabolism Reports 5 (2015) 33–35

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: http://www.journals.elsevier.com/molecular-genetics-and-metabolism-reports/

Outcomes of oral biotin treatment in patients with biotinidase deficiency — Twenty years follow-up

Edyta Szymańska [a], Małgorzata Średzińska [a], Agnieszka Ługowska [b], Magdalena Pajdowska [c], Dariusz Rokicki [a], Anna Tylki-Szymańska [a,*]

[a] Department of Pediatrics, Nutrition and Metabolic Disorders, The Children's Memorial Health Institute, Warsaw, Poland
[b] Department of Genetics, Institute of Psychiatry and Neurology, Warsaw, Poland
[c] Department of Biochemistry, Radioimmunology and Experimental Medicine, The Children's Memorial Health Institute, Warsaw, Poland

ARTICLE INFO

Article history:
Received 29 August 2015
Received in revised form 21 September 2015
Accepted 22 September 2015
Available online 6 October 2015

Keywords:
Biotinidase deficiency
Biotin
Newborn screening

ABSTRACT

Introduction: Biotinidase deficiency (BTD) is an inborn error of biotin metabolism inherited as an autosomal recessive trait. Due to the, biotinidase deficiency, biotin is not recycled. Individuals with BTD usually exhibit neurological and cutaneous abnormalities unless treated with biotin. Supplementation with biotin may either ameliorate or if early introduced even prevent symptoms when introduced presymptomatically.
Patients and methods: Since 1991, 22 Polish patients from 19 families have been diagnosed with BTD. In 16 children the diagnosis had been suspected on the basis of clinical signs: skin lesions, hyperventilation, seizures, spasticity, and laboratory investigation (elevated lactate and metabolites on urine organic acids profile).
The defect was enzymatically (serum biotinidase activity measurement) and genetically (tested for mutations in the *BTD* gene) confirmed afterwards. All patients were treated with biotin. Urine organic acids analysis (GC/MS) for 3-hydroxizovaleric acid was used for patients' monitoring. Neurological, audiological and ophthalmological evaluation has been conducted once a year.
Results: In 5 symptomatic patients a progressive optic nerve atrophy had already been noted at the time of treatment initiation. In these patients sensorineural hearing loss has also been diagnosed despite biotin supplementation. Asymptomatic patients treated with biotin supplementation presented no signs or symptoms of BTD. Supplementation with biotin slows the progression of BTD in symptomatic patients, but does not reverse nerve atrophy. Nonetheless, introduction of the treatment with biotin during presymptomatic stage of the disease prevents the onset of symptoms including optic atrophy and hearing loss. Homozygosity for the p.Leu215Phe mutation in *BTD* gene seems to be frequent in patients from the North-Eastern region of Poland and is connected with the hearing loss.
Conclusion: Since the prognosis for individuals diagnosed with BTD is good, provided they are treated before symptoms occur, it is justified to add this metabolic disorder to the panel of conditions screened under the national newborn screening programme in Poland.

1. Introduction

Biotinidase deficiency (BTD) is a late-onset form of multiple carboxylase deficiency (LMCD; OMIM 253260), an inborn error of biotin metabolism. The disorder is inherited as an autosomal recessive trait, and more than 150 mutations in the *BTD* gene have been identified. Pathogenic mutations lead to either reduced or absent biotinidase activity [1]. This enzyme (EC 3.5.1.12) is involved in the reutilization of biotin, a necessary nutrient required for multiple biotin-dependent metabolic processes. Biotinidase removes biotin from biocytin, a complex of biotin and carboxylase enzymes, and makes it available to be reused by other enzymes.

Prevalence of BTD is estimated to be 1/61,000 in European population [2,3]. Biotinidase deficiency is classified into early and late forms. In the early form the symptoms appear within the first few months of life. Unless treated, individuals develop seizures, breathing difficulties, hypotonia, skin rash, alopecia, hearing loss, delayed development and elevated serum lactic acid [4,5]. Patient's urinary organic acids (GC/MS) analysis shows an excretion of 3-hydroxyisovaleric acid and 3-hydroxypropionic acid. Their plasma biotin concentration is decreased, however, it can be normal in early forms [6]. Ketolactic acidosis and mild hyperammonemia may also be present. Patients with partial BTD (10% to 30% of mean normal BTD activity) may be asymptomatic.

* Corresponding author at: Department of Pediatrics, Nutrition and Metabolic Disorders, Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-730 Warsaw, Poland.
E-mail address: a.tylki@czd.pl (A. Tylki-Szymańska).

http://dx.doi.org/10.1016/j.ymgmr.2015.09.004

The aim of this study was to assess the clinical outcomes and efficacy of oral biotin supplementation introduced in various disease stages in the group of 22 Polish patients who have been followed-up for the period of time of 1–20 years.

2. Patients and methods

Since 1991, 22 Polish paediatric patients from 19 families have been diagnosed with BTD. In 16 individuals, BTD was suspected because of: skin lesions, hyperventilation, seizures, spasticity, and lactic acidosis. The diagnosis was then confirmed by serum biotinidase activity measurement with quantitative colorimetric assay (with N-biotinyl-p-aminobenzoate, B-PABA, as the substrate) [7]. Apart from the enzymatic studies, patients were also tested for the presence of mutations in the *BTD* gene.

Sanger sequencing was used for the analysis of the whole coding region of *BTD* gene to detect both common and rare mutations in this gene. The results were processed with the Mutation Surveyor® software (the analyses were performer at MedGen Laboratory, Warsaw, Poland). Four children were identified by family screening (Table 1).

The study was approved by the Ethics Committee of the Children's Memorial Health Institute. An informed consent from parents or guardians of the patients undergoing molecular investigation was obtained.

All patients were treated with oral biotin supplementation. Symptomatic children received an initial dose of 20 mg/daily gradually reduced to 5 mg. Asymptomatic patients received the treatment with a dose of 5 mg a day (Table 1). Urine organic acid analysis (GC/MS) for 3-hydroxizovaleric acid was used for patients' monitoring. Neurological, audiological and ophthalmological evaluation was performed once a year. Hearing assessment included impedant audiometric tests, tympanometry and auditory brainstem response (ABR) assessment. A direct ophthalmoscopy was performed to assess patient's vision.

3. Results

Median age of diagnosis in symptomatic patients was 14 months (3 months–14 years).

Median age of symptoms onset was 10 months (3 m–4 years). As soon as the diagnosis of BTD was established the treatment with oral biotin was administered.

In most symptomatic patients rapid improvement in psycho-motor skills was observed after biotin initiation. There were two patients who needed rehabilitation due to significant hypotonia and walking disorders. In all patients with skin involvement, the rash disappeared. Most patients exhibited behavioural disorders and slight intellectual retardation even following the treatment.

A progressive optic nerve atrophy had already been noted at the time of treatment initiation. In these individuals, however, no further optic deterioration was observed when the treatment had been introduced. In all symptomatic patients sensorineural hearing loss did not reverse despite biotin supplementation, however no progression was observed either. Alopecia, which is considered to be a common and characteristic feature of BTD was found 4 patients (18.2%). Asymptomatic patients, who began the treatment with oral biotin did not present with any signs nor symptoms of BTD.

Twelve patients had profound biotinidase activity (<10% BT activity) and all of them were symptomatic. Among 10 patients with partial BT activity, 5 exhibited symptoms of BTD (Table 1).

Molecular analysis has demonstrated that the most common mutation in the analysed group was p.Leu215Phe mutation. It was found in homozygous state in 4 individuals (patient's reference Nos.: 13, 14, 15, 16) who were not related but lived in the same region of Poland (North-Eastern Poland). Homozygosity for other mutations was found in 3 patients (patient's reference Nos.: 4, 6, 9,), namely for the mutations: p.Arg79Cys, p.Thr532Met and p.Asp444His. Four individuals were compound heterozygotes with the following genotypes:

Table 1
Study group characteristics, n = 22.

Patient's ref. no.	Age at diagnosis (S/P)	Serum lactic acid normal values (0–20 mg/dl	GC/MS	Serum BT activity normal range: 6–12 (nmol/min/ml)	Hearing	Optic nerve atrophy	Partial (10–30% activity) profound (<10% BT activity)	Mutation in allel 1	Mutation in allel 2	Follow-up (years)
1.	36 months (S)	48	+	0.09	L	N	Profound	p.Cys33PhefsTer36	c.1052delCfs	20
2.	3 months (S)	Lack of data	+	0.5	L	L	Profound	p.Cys33PhefsTer36	p.Gly313Ser	Lack of data
3.	21 months (S)	18.8–54.9	+	4.17	N	N	Partial	Lack of data	–	7
4.	14 months (S)	33	–		N	N		p.Arg79Cys	p.Arg79Cys	8
5.	3 years (S)	Lack of data	+	1.63	N	N	Partial	–	–	1
6.	14 months (S)	18.6	+	0.00	N	N	Profound	p.Thr532Met	p.Thr532Met	1
7.	18 months	28–61	+	6.69	N	N	Partial	–	–	2
8.	36 months (S)	28–60.2	–	0.13	Lack of data	Lack of data	Profound	p.Gly45Arg	p.Asp444His	2
9.	54 months (S)	Lack of data	–	0.05	N	N	Profound	–	–	2
10.	5 months (S)	29–37,8	+	0.068	L	Lack of data	Profound	p.Asp444His	p.Asp444His	2
11.	7 years (S)	Lack of data	+	0.25	N	N	Profound	–	–	9
12.	10 months (S)	32–46	+	0.14	N	N	Profound	p.Arg538Cys	–	10
13.	36 months (S)	24	–	0.85	N	N	Partial	p.Leu215Phe	p.Leu215Phe	20
14.	4 years (S)	13	+	0.44	N	L	Profound	p.Leu215Phe	p.Leu215Phe	20
15.	6 months (S)	77.3–95.8	+	0.74	L	L	Partial	p.Leu215Phe	p.Leu215Phe	20
16.	7 months (S)		+		L	L		p.Leu215Phe	p.Leu215Phe	20
17,	Newborn (Canadian newborn screening (P))	Lack of data	–	0.0	N	N	Profound	p.Cys33PhefsTer36	p.Tyr438Cys	20
18.	Newborn (Turkish newborn screening (P))	Lack of data	+	0.73	N	N	Partial	–	–	20
19. Sibling to 5	14 years (P)	14	+	1.96	L	L	Partial	–	–	15
20. Sibling to 4	3 months (P)	nd	–	0.0	Lack of data	L	Profound	–	–	17
21.	2 months (P)	14	–	6.0	Lack of data	L	Partial	–	–	6
22. Sibling to 10	15 months (P)	Lack of data	–	0.24	N	L	Profound			3.5

Legend: L—loss, N—normal, S—symptomatic, P—presymptomatic.

p.Cys33PhefsTer36/c.1052delCfs; Cys33PhefsTer36/p.Gly313Ser; p.Cys33PhefsTer36/p.Tyr438Cys; p.Gly45Arg/p.Asp444Hist (patient's reference Nos.: 1, 2, 17, 21). In 11 patients either no mutation or mutation in 1 allele was found. In patients with most common p.Leu215Phe mutation, hearing loss was present in 2 individuals (15,16), and optic atrophy was present in 3 of them (14,15,16) (Table 1). Molecular and clinical data of patients ref. Nos. 1, 2, 17 have already been published in 2002, in the report by Wolf et al. on seventeen novel mutations causing profound biotinidase deficiency [8].

4. Discussion

Biotinidase deficiency is one of these inborn errors of metabolism in which we can either alleviate the existing symptoms or prevent their occurrence if the biotin treatment is introduced in the presymptomatic stage of the disease. Therefore, early diagnosis during presymptomatic period is crucial. According to literature treatment with oral biotin administration reversed symptoms such as alopecia, skin rash, ataxia, and developmental delay [9]. In our study group supplementation with biotin, slowed disease progression in symptomatic patients, while treated asymptomatic individuals did not develop clinical signs. In our 5 symptomatic patients with optic nerve atrophy and sensorineural hearing loss present at the time of treatment initiation, the symptoms did not reverse despite biotin supplementation, which is consistent with the literature [10,11]. However, following the treatment no further progression of both optic complication and hearing complication was observed either, which means that since biotin was administered, hearing and sight status was stable without neither progression nor regression. This only supports the fact, that the prognosis for individuals diagnosed with BTD is good, provided that they are treated before symptoms occur. It is therefore justified to add BTD activity measurement to the panel of the national newborn screening programme.

Most patients from our population who were homozygous for p.Leu215Phe mutation presented with hearing loss and/or optic atrophy. It seems that this mutation is characteristic of North- Eastern region of Poland since 3 out of 4 patients diagnosed with this particular mutation originate from this part of our country. These individuals claimed no consanguinity. Our observations are consistent with the data published so far [12,13]. Alopecia, considered to be a typical feature of BTD, did not occur in all symptomatic patients from our study group, although was one of the symptoms in majority of them. Therefore, it is not an obligatory symptom to establish a diagnosis of BTD.

However, based on our experience and on the literature, presentation of BD is highly variable and cases of patients in whom biotin supplementation prevented neurological symptoms have been reported [9]. Therefore, it is very important to include BTD in the newborn screening programme.

5. Conclusion

Our 20 years follow-up has proved that in 7 symptomatic patients supplementation with oral biotin alleviates most of clinical symptoms of BTD in symptomatic patients, but does not reverse neither optic nerve atrophy nor hearing loss.

Introduction of biotin treatment during presymptomatic stage of the disease prevents the occurrence of symptoms including optic atrophy.

Since the prognosis for individuals diagnosed with BTD is promising, provided they are treated before symptoms occur, it is recommended to add this BTD assessment to the national newborn screening programme.

Moreover, we have observed that homozygosity for the p.Leu215Phe mutation in *BTD* gene seems to be frequent in patients from the North-Eastern region of Poland and is connected with the hearing loss.

References

[1] http://www.orpha.net/Biotinidase-deficiency.
[2] B. Wolf, biotinidase deficiency, in: R.A. Pagon, T.D. Bird, C.R. Dolan, K. Stephens, et al., (Eds.),GeneReviews, 2011.
[3] P. Weber, S. Scholl, Baumgartner ER outcome in patients with profound biotinidase deficiency: relevance of newborn screening, Dev. Med. Child Neurol. 46 (7) (2004) 481–484.
[4] L. Bottin, S. Prud'hon, S. Guey, et al., Biotinidase deficiency mimicking neuromyelitis optica: initially exhibiting symptoms in adulthood, Mult. Scler. 22 (2015) (pii: 1352458515596457. [Epub ahead of print]).
[5] S. Cabasson, S. Rivera, S. Mesli, E. Dulubac, Brainstem and spinal cord lesions associated with skin changes and hearing loss: think of biotinidase deficiency, J. Pediatr. 166 (3) (2015), 771-1.e1http://dx.doi.org/10.1016/j.jpeds.2014.11.023 (Epub 2014 Dec 30).
[6] D. Mukhopadhyay, M.K. Das, S. Dhar, M. Mukhopadhyay, Multiple carboxylase deficiency (late onset) due to deficiency of biotinidase, Indian J. Dermatol. 59 (5) (2014) 502–504.
[7] T.M. Cowan, M.G. Blitzer, B. Wolf, Working Group of the American College of Medical Genetics Laboratory Quality Assurance Committee. Technical standards and guidelines for the diagnosis of biotinidase deficiency, Genet. Med. 12 (7) (2010) 464–470.
[8] B. Wolf, K. Jensen, G. Hüner, et al., Seventeen novel mutations that cause profound biotinidase deficiency, Mol. Genet. Metab. 77 (1–2) (2002) 108–111.
[9] B. Wolf, G.S. Heard, K.A. Weissbecker, et al., Biotinidase deficiency: initial clinical features and rapid diagnosis, Ann. Neurol. 18 (1985) 614–617.
[10] B. Wolf, R.E. Grier, G.S. Heard, Hearing loss in biotinidase deficiency, (Letter) Lancet 322 (1983) 1365–1366.
[11] L.P. Thuy, B. Zielinska, E. Zammarchi, et al., Multiple carboxylase deficiency due to deficiency of biotinidase, J. Neurogenet. 3 (1986) 357–363.
[12] H.S.K. Sivri, G.A. Genc, A. Tokatli, et al., Hearing loss in biotinidase deficiency: genotype–phenotype correlation, J. Pediat. 150 (2007) 439–442.
[13] M. Karaca, R.K. Özgül, Ö. Ünal, et al., Detection of biotinidase gene mutations in Turkish patients ascertained by newborn and family screening, Eur. J. Pediatr. 174 (8) (2015) 1077–1084.