

Dopamine beta-hydroxylase deficiency

Authors: Prof. Jean-Michel Senard^{1*} and Dr. Philippe Rouet²

^{1*}Corresponding author: Club d'Etude du Système Nerveux Autonome, Autonomic Unit of the Department of Clinical Pharmacology and INSERM U586, Faculté de Médecine, 37 allées Jules Guesde, 31073 Toulouse cedex, France. senard@cict.fr

²INSERM Unit 586, Institut Louis Bugnard, C.H.U. Rangueil, 31054, Toulouse cedex, France

Section Editor: Prof. F. C. Luft

Creation Date: July 2005

[Abstract](#)

[Key-words](#)

[Definition/diagnostic criteria](#)

[Epidemiology](#)

[Aetiology](#)

[Clinical description](#)

[Diagnostic methods](#)

[Differential diagnosis](#)

[Genetic counselling](#)

[Management including treatment](#)

[Prognosis](#)

[References](#)

Abstract

Dopamine beta-hydroxylase (DβH) deficiency is a very rare form of primary autonomic failure characterized by a complete absence of noradrenaline and adrenaline in plasma together with increased dopamine plasma levels resulting from heterogeneous molecular alterations of DBH gene. It is inherited in an autosomal recessive manner. The prevalence of DβH deficiency is unknown. Only limited number of cases with this disease has been reported. DβH deficiency is mainly characterized by cardiovascular disorders and severe orthostatic hypotension. First symptoms often start during a complicated perinatal period with hypotension, muscle hypotonia, hypothermia and hypoglycaemia. Children with DβH deficiency exhibit reduced ability to exercise because of blood pressure inadaptation with exertion and syncope. Symptoms usually worsen progressively during late adolescence and early adulthood with severe orthostatic hypotension, eyelid ptosis, nasal stuffiness and sexual disorders. Limitation in standing tolerance, limited ability to exercise and traumatic morbidity related to falls and syncope may represent later evolution. Restoration of plasma noradrenaline to the normal range can be achieved by precursor therapy with L-threo-dihydroxyphenylserine (DOPS). Administration of 100 to 500 mg DOPS orally twice or three times daily increases blood and reverses the orthostatic intolerance.

Key-words

sympathetic failure, orthostatic hypotension, plasma catecholamines, dopamine, noradrenaline, adrenaline, L-threo-dihydroxyphenylserin, DOPS, *DBH gene*

Disease name and synonyms

Dopamine beta-hydroxylase deficiency
Norepinephrine deficiency
Noradrenaline deficiency

Definition/diagnostic criteria

Dopamine beta-hydroxylase (DβH) deficiency is a very rare form of primary autonomic failure characterized by a complete absence of noradrenaline and adrenaline in plasma together with increased plasma dopamine levels, first described in 1986 [1]. This congenital rare

disease is caused by a series of mutations in the *DBH* gene, mapped to chromosome 9q34, encoding the key enzyme in noradrenaline synthesis.

The diagnosis has to be evoked when a pure sympathetic autonomic failure is associated with absence of both noradrenaline and adrenaline and accumulation of dopamine in plasma.

Epidemiology

The very limited number of cases of DβH deficiency in humans suggests that the disorder is very rare. However, since deficiency in DβH is lethal in embryos or shortly after birth in mice [2], the prevalence of the disorders may be higher than expected. It should be kept in mind that history of spontaneous abortions and stillbirths has been noted in parents of DβH deficient patients. Among the cases reported, in one family only two members were found to present the disease [3].

Aetiology

Despite the fact that the *DBH* gene was cloned a long time ago [4], the molecular defects in DβH deficiency are poorly understood. Access to extensive data concerning *DBH* gene is available on the Web [5]. In three unrelated patients, a common mutation has been identified in intron 1 (IVS1+2T→C) leading to aberrant splicing and premature stop codon probably involved in noradrenaline deficiency [3,6]. In one patient, a mutation in exon 4 (764G>T) that leads to alteration of a sequence specific to copper type II ascorbate-dependent monooxygenase was also described [3]. A summary of identified mutations in *DBH* gene is given in Table 1. However, these mutations cannot entirely explain the phenotype since some of them are also found in healthy subjects [7]. It is possible, for instance, that combination of IVS1+2T→C allele with other missense mutations necessary for clinical expression of the disorder. Clearly, further studies are needed to explain how the identified mutations can lead to the absence of detectable enzyme protein [for a review see ref 8].

From a pathophysiological point of view, whatever the nature of the mutations leading to DβH enzyme inactivity, the consequence in patients is a large accumulation of dopamine, the precursor of noradrenaline, in sympathetic nerves. This biochemical pattern probably explains cardiovascular paradoxical responses such as increase in dopamine but not in noradrenaline levels with standing or during hypoglycaemia or tyramine infusion. It is however, rather surprising, in view of the role of central nervous system DβH in mood and

behaviour [8,9], that only mild changes have been reported in DβH patients.

Table 1. Summary of discovered mutations in *DBH* gene (extracted from www.genetest.org).

Nucleotide change	Location	Amino acid change	Mutation type
C-1021T	5' flanking		Noncoding
G259A	Exon 1	V87M	Missense
IVS1+2T→C	Intron 1		Noncoding
C300A	Exon 2	D100E	Missense
IVS3+8C→T	Intron 3		Noncoding
G991A	Exon 6	D331N	Missense
IVS10+415A 0→G	Intron 10		Noncoding

Clinical description

The available data come from clinical description of the known cases reported (see Table 2). First symptoms often start during a complicated perinatal period with hypotension, muscle hypotonia, hypothermia and hypoglycaemia. Delay in opening of the eyes and ptosis of eyelids and vomiting have also been reported. Children with DβH deficiency exhibit reduced ability to exercise because of blood pressure inadaptation with exertion and syncope. Symptoms usually progressively worsen during late adolescence and early adulthood with severe orthostatic hypotension, eyelid ptosis, nasal stuffiness and sexual disorders.

Table 2. Main clinical characteristics of DβH deficiency (Adapted from Robertson D *et al*, 1991).

Feature	(%)
Severe orthostatic hypotension	100
Impaired ejaculation	100
Ptosis of eyelids	67
Complicated perinatal course	67
Nocturia	67
Hyperextensible/hyperflexible joints	50
High palate	50
Nasal stuffiness	50
Mild behavioural changes	33
Seizures (with hypotension)	33
Bradydactyly	33
Sluggish tendon reflexes	33
Weak facial musculature	33
Hypotonic skeletal muscles	33
Atrial fibrillation	16

Examination indicates low blood pressure in standing position, small but light- and accommodation- reactive pupils and normal sweating. Mild behavioural changes have also been reported in some patients.

Some biochemical abnormalities have also been reported such as hypoprolactinemia, hypomagnesemia, raised blood urea nitrogen.

Diagnostic methods

The clinical exploration of autonomic nervous system activity indicates a pure and isolated sympathetic failure with normal cholinergic function. Orthostatic hypotension is profound, and blood pressure does not increase as expected during usual tests such as Valsalva manoeuvre (phase IV), isometric handgrip or cold exposure. When pharmacological testing is performed some responses clearly indicate adrenergic cardiac and vascular receptor supersensitivity. Drug challenge confirms the sympathetic failure with a lack of pressor response to tyramine or a significant and apparently paradoxical elevation of blood pressure with clonidine.

Since the key enzyme that catalyses the conversion of dopamine to noradrenaline, D β H, is undetectable in 4% of the population with normal concentrations of catecholamines [12], definite diagnosis of D β H deficiency is evident when plasma levels of catecholamines and metabolites are measured. In D β H deficient patients, circulating levels of noradrenaline and adrenaline are undetectable whereas dopamine levels are elevated [13]. Metabolites of noradrenaline have also been shown to be absent in plasma, urine and cerebro-spinal fluid.

Differential diagnosis

A typical flare reaction to intradermal histamine together with normal tearing sensory function, normal taste and smell, normal intact corneal and deep tendon reflexes, and lack of Askenazi Jewish extraction allow exclusion [familial dysautonomia](#) [10]. Absence of profound mental retardation or hypopigmentation makes confusion with [Menkes syndrome](#) improbable [11].

Genetic counselling

D β H deficiency is inherited in an autosomal recessive manner [6]. At conception, the sibs of an affected individual have a 25% chance of being affected, a 50% chance of being asymptomatic carriers, and a 25% chance of being unaffected and not carriers. The optimal time for determination of genetic risk is before pregnancy. *DBH* molecular genetic testing is available on a research basis only.

Management including treatment

As orthostatic hypotension is the main symptom of patients with D β H deficiency, most of the

available information on treatment focuses on this aspect. Many empirical therapies using mineralocorticoids or adrenergic receptor agonists have been reported to have mild effects. Because of the identified biochemical defect, the treatment of choice is dihydroxyphenylserine (L-Threo-DOPS, DOPS), a synthetic precursor of noradrenaline which has been proposed for the management of orthostatic hypotension with controversial results [14]. Administration of DOPS in mice lacking *Dbh* gene restores normal plasma noradrenaline levels and reverses behavioural abnormalities [15]. It was also shown to be able to restore sensitivity to antidepressants in the same model [9]. In humans with D β H deficiency, L-Threo-DOPS administration results in dramatic increase in blood pressure and postural symptoms [16].

Prognosis

Little is known about prognosis. Retrospective data indicate that in most described cases, the perinatal period is complicated by episodes of hypotension, hypoglycaemia and hypothermia. Later evolution seems to be marked by progressive orthostatic hypotension with limitation in standing tolerance, limited ability to exercise and traumatic morbidity related to falls and syncope. L-threo-DOPS has been described a very effective to restore noradrenergic tone and to correct postural hypotension [1]. Effects of L-threo-DOPS on other aspects of autonomic failure have not been reported.

References

1. Robertson D, Goldberg MR, Hollister AS, Onrot J, Wiley R, Thompson JG, Robertson RM. Isolated failure of autonomic noradrenergic neurotransmission. Evidence for impaired b-hydroxylation of dopamine. *New Engl J Med* 1986;314:1494-7.
2. Thomas SA, Matsumoto AM, Palmiter RD. Noradrenaline is essential for mouse foetal development. *Nature* 1995;374:643-6.
3. Deinum J, Steengergen-Spanjers GCH, Jansen M, Boomsma F, Lenders JWM, van Ittersum FJ, Hück N, van den Heuvel LP, Wevers RA. DBH gene variants that cause low plasma dopamine b hydroxylase with or without a severe orthostatic syndrome. *J Med Genet* 2004;41:e38.
4. Lamouroux A, Vigny A, Faucon Biguet N, Darmon MC, Franck R, Henry JP, Maleet J. The primary structure of human dopamine-beta-hydroxylase: insights into the relationship between the soluble and the membrane-bound forms of the enzyme. *EMBO J* 1987;6:3931-7.

5. National Center for Biotechnology Information: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=Graphics&list_uids=1621
6. Kim CH, Zabetian CP, Cubells JF, Cho S, Biaggioni I, Cohen BM, Robertson D, Kim KS. Mutations in the dopamine b-hydroxylase gene are associated with human norepinephrine deficiency. *Am J Med Genet* 2002;108:140-7.
7. Zabetian CP, Romero R, Robertson D, Sharma S, Padbury JF, Kuivaniemi H, Kim KS, Kim CH, Köhnke MD, Kranzler HR, Gelernter J, Cubells JF. A revised allele frequency estimate and haplotype analysis of the DBH deficiency mutation IVS1+2T→C in African- and European-Americans. *Am J Med Genet* 2003;123A:190-2.
8. Cubells JF, Zabetian CP. Human genetics of plasma dopamine b-hydroxylase activity: applications to research in psychiatry and neurology. *Psychopharmacology* 2004;174:463-76.
9. Cryan JF, O'Leary OF, Jin SH, Friedland JC, Ouyang M, Hirsch BR, Page ME, Dalvi A, Thomas SA, Lucki I. Norepinephrine-deficient mice lack responses to antidepressant drugs, including selective serotonin reuptake inhibitors. *PNAS* 2004;101:8186-91.
10. Axelrod FB. Familial dysautonomie. *Muscle Nerve* 2004;29:352-63.
11. Kaler SG. Metabolic and molecular bases of Menkes disease and occipital horn syndrome. *Pediatr Dev Pathol* 1998;1:85-98.
12. Weinshilboum RM, Schorott HG, Raymond FA, Weidman WH, Elveback LR. Inheritance of very low serum dopamine-beta-hydroxylase activity. *Am J Hum Genet* 1975;27:573-85.
13. Robertson D, Haile V, Perry SE. Dopamine b-hydroxylase deficiency. A genetic disorder of cardiovascular regulation. *Hypertension* 1991;18:1-8.
14. Freeman R, Landsberg L. The treatment of orthostatic hypotension with dihydroxyphenylserine. *Clin Neuropharmacol* 1991;14:296-304.
15. Thomas SA, Marck BT, Palmiter RD, Matsumoto AM. Restoration of norepinephrine and reversal of phenotypes in mice lacking dopamine b-hydroxylase. *J Neurochem* 1998;70:2468-76.
16. Biaggioni I, Robertson D. Endogenous restoration of noradrenaline by precursor therapy in dopamine-beta-hydroxylase deficiency. *Lancet* 1987;2:1170-2.