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Pediatric Ptosis as a Sign of Treatable Autonomic Dysfunction

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Introduction

Dopamine beta-hydroxylase deficiency is a rare congenital type of autonomic failure caused by an abnormality in the enzyme that converts dopamine to norepinephrine. It is inherited in an autosomal recessive manner, so that both parents are asymptomatic carriers of one mutant allele for the *Dbh* gene, and siblings of affected individuals have a 25% chance of being affected. Dopamine beta-hydroxylase deficiency was first described in 1986, with the absence of plasma norepinephrine and epinephrine, and elevated levels of dopamine.^{1–3} Parasympathetic and sympathetic cholinergic functions remain intact while sympathetic noradrenergic functions are affected. It can be treated successfully with L-threo-dihydroxyphenylserine, which is converted to norepinephrine without the presence of dopamine beta-hydroxylase.

Although dopamine beta-hydroxylase deficiency is present from birth, the diagnosis is usually not made until late in childhood or early adulthood.⁴ Infants may experience multiple episodes of dehydration, hypotension, hypothermia, hypoglycemia, and vomiting. Children have low exercise tolerance. Other signs and symptoms include significant orthostatic hypotension, nasal stuffiness, ptosis,^{1–4} and pupil abnormalities.⁵ The diagnosis of dopamine beta-hydroxylase deficiency is still made based upon a collection of clinical and laboratory findings indicative of impaired sympathetic noradrenergic function, intact sweating, and absent or minimal plasma norepinephrine with at least a five-fold elevation of plasma dopamine.⁴ The combination of childhood ptosis and systemic hypotension is suggestive of dopamine beta-hydroxylase deficiency. Therefore, three young patients with dopamine beta-hydroxylase deficiency underwent an ophthalmologic examination to determine whether ocular findings could assist in the earlier detection and treatment of dopamine beta-hydroxylase deficiency.

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Methods

This was a prospective study design. The Vanderbilt University Institutional Review Board approved the protocol before the start of this study. The study and data accumulation were carried out in accordance with this approval. Written informed consent was obtained from each subject prior to participating in the study. This study is registered in the public database of the National Institute of Health maintained site at <http://www.clinicaltrials.gov> with ID: NCT00338065. This study was conducted in compliance with regulations of the Health Insurance Portability and Accountability Act and the Declaration of Helsinki. Three patients with dopamine beta-hydroxylase deficiency were taken off medications, including L-threo-dihydroxyphenylserine, 1-deamino-8-D-arginine vasopressin or fludrocortisone, during their admission to Vanderbilt's Clinical Research Center inpatient unit. While off medications, they received an ophthalmic examination including intraocular pressures (IOP) and blood pressures (BP) while supine, sitting, and standing, eyelid function and pupillary function testing. Table 1 lists each patient's demographics. The mean age of the three patients was 18.7 ± 3.5 years with mean age of diagnosis at 17.7 ± 3.8 years and symptom onset during the first decade of life. One-way repeated measures analysis of variance was performed on the mean arterial blood pressures (MAP), heart rates, and IOP (SigmaStat 2.03, SPSS, Inc.).

Patient One

Patient 1 is a 19 year-old female who experienced episodes of syncope at 3 years old and was diagnosed with dopamine beta-hydroxylase deficiency at 16 years old. Her symptoms are adequately controlled with L-threo-dihydroxyphenylserine 400 mg twice daily and 1-deamino-8-D-arginine vasopressin 0.6 mg once daily. She is homozygous for c. [301G>A]; [1033G>A] mutations in the *Dbh* gene.

Patient Two

Patient 2 is a 17 year-old male who reported muscle weakness and fatigue "since a very young age". Testing at the Clinical Research Center confirmed dopamine beta-hydroxylase deficiency. His symptoms initially were treated with fludrocortisone 0.1 mg twice daily prior to admission to the Clinical Research Center, but were better controlled when switched to L-threo-dihydroxyphenylserine 300 mg three times daily. He also has continuous nasal congestion without a seasonal pattern. His older brother also has dopamine beta-hydroxylase deficiency and is Patient 3 in this case series.

Patient Three

Patient 3 is a 23 year-old male with type I diabetes with a similar presentation as his younger brother with regard to fatigue onset at a young age. At 5 months old, he was hospitalized for aseptic meningitis and documented to have ptosis. Subsequently, he had levator advancement surgery for the ptosis. Like his brother, testing at the Clinical Research Center confirmed the preliminary diagnosis of dopamine beta-hydroxylase deficiency. He was also treated with fludrocortisone 0.1 mg twice daily prior to admission to the Clinical Research Center. Symptoms were better controlled when switched to L-threo-dihydroxyphenylserine 300 mg three times daily.

Patients Two and Three are compound heterozygotes for c. [348+2T>C];[1033G>A] in the *Dbh* gene.

Results

Blood Pressure and Intraocular Pressure

All 3 patients exhibited a profound reduction in orthostatic BP with MAP (mm Hg) averaging 90.1 ± 18.5 supine, 79.1 ± 25.7 sitting, and 45.8 ± 11.6 standing ($P=0.021$, Table 2). There were corresponding elevations in heart rates (beats per minute) averaging 55 ± 6 supine, 73 ± 8 sitting, and 89 ± 1.7 standing ($P=0.028$, Table 2). Intraocular pressures were also found to markedly decrease in all 3 patients with standing ($P=0.03$, Table 2). Intraocular pressures (mm Hg) averaged 15.8 ± 1.0 supine, 15.0 ± 3.6 sitting, and 7.7 ± 2.3 standing.

Eyelid Function

The mean palpebral fissure width was 8.2 ± 1.0 mm (Table 3). The margin reflex distance was reduced in all patients with a mean of 2.8 ± 0.6 mm (Table 3). Patient 1 and Patient 2 (Figure, top) had mild ptosis, defined as a reduction in the margin reflex distance. Patient 3 (Figure, bottom) had palpebral fissures within the normal range, but he had a history of ptosis surgery as a child and his margin reflex distance was still slightly diminished. All 3 patients had intact levator function with a mean of 16 ± 0 mm (Table 3). A small increase averaging 1.5 ± 0.5 mm in palpebral fissure width occurred after instillation of 2.5% phenylephrine (Table 3).

Pupillary Function

Pupils reacted to light and accommodation in all 3 patients (Table 3). Mild miosis of 4 mm constricting to 3 mm in room light was present only in Patient 3. Phenylephrine (2.5%) caused dilation approximately 1 mm in Patient 1 (Table 3), 2 mm in Patient 2 (Figure, top right), and 3 mm in patient 3 (Figure, bottom right).

Discussion

Dopamine beta-hydroxylase deficiency is a rare but debilitating disease that, if diagnosed, can be successfully treated with L-threo-dihydroxyphenylserine. Fewer than 25 patients have heretofore been recognized worldwide, but indeterminate numbers may go undiagnosed. Many untreated patients with dopamine beta-hydroxylase deficiency can only remain standing for a few minutes before BP falls to levels causing syncope. It is especially important to identify these patients because a specific and efficacious medication, L-threo-dihydroxyphenylserine, can enable these patients to stand indefinitely. Indeed, one young woman with dopamine beta-hydroxylase deficiency, once treated with L-threo-dihydroxyphenylserine, was able to successfully run the New Orleans Marathon.⁶ Intraocular pressure screening of children presenting with ptosis and orthostatic or exercise intolerance may lead to earlier diagnosis and recognition of additional cases.

Symptoms and signs of dopamine beta-hydroxylase deficiency begin in childhood and include ophthalmic manifestations. Intraocular pressure is one measurement that has not been studied in this unique group of patients. Intraocular pressure is slightly altered by 1–4 mm Hg with a change in a normal subject's gravity-dependent body position from supine to standing.^{7–9} Intraocular pressure also is influenced by systemic BP.¹⁰ The magnitude of IOP change with standing in these three patients is consistent with positional IOP changes in patients with adult-onset autonomic dysfunction diagnoses, including multiple system atrophy, pure autonomic failure, and baroreflex failure.^{8,11} Measuring supine/sitting and standing IOPs may represent a simple clinical screen for dopamine beta-hydroxylase deficiency in a child presenting to an ophthalmologist with mild ptosis and a history of exercise intolerance. Alternatively, orthostatic BP measurements could be performed with

measurements in both the supine and standing postures. Orthostatic intolerance is an important part of the clinical features of dopamine beta-hydroxylase deficiency.

Ptosis is an ophthalmic sign of dopamine beta-hydroxylase deficiency.^{1,12–16} The mild ptosis was bilateral in all patients. However, Patient 3 had lid surgery when he was younger. All patients had a mild decrease in margin reflex distance. By definition, the condition could be confused with a bilateral Horner syndrome. Horner syndrome is caused by a lack of sympathetic innervation to both the lid and eye. Since patients with DBH deficiency lack intrinsic sympathetic function, they would be expected to have symptoms similar to bilateral Horner syndrome (ptosis and miosis). Since bilateral Horner syndrome is quite rare, the diagnosis of DBH deficiency should also be entertained in patients presenting with mild bilateral ptosis and miosis. A slight improvement in ptosis was observed with phenylephrine. However, the patients in this case series showed no supersensitivity to phenylephrine in palpebral fissure widening, unlike patients with blepharoptosis.¹⁷ The levator function was normal in all patients as expected since it is innervated by cranial nerve III, which contains parasympathetic fibers. In contrast, Muller's muscle is innervated by sympathetic nerves and is thus affected by dopamine beta-hydroxylase deficiency. This may explain why only mild ptosis is observed, since the levator palpebrae function remains intact.

Previous studies in adults reported pupils measuring 2–3mm in diameter with normal reaction to light and accommodation.^{1,12,13} As expected, the parasympathetic system was unaffected as exhibited by no supersensitivity to methacholine, a non-selective muscarinic receptor agonist.^{1,14,18} It has been reported that the pupils have no response to hydroxyamphetamine,¹⁴ because a functional postganglionic sympathetic neuron is required. However, pupils would dilate with 1% epinephrine or phenylephrine, consistent with alpha adrenergic supersensitivity.^{18,19} A study of a sibling pair with dopamine beta-hydroxylase deficiency revealed severe bilateral redilation lag, consistent with sympathetic neuropathy.¹⁹ In this case series, the patients did not exhibit pupil supersensitivity to phenylephrine. In addition, only the oldest subject (Patient 3) had pupil sizes consistent with dopamine beta-hydroxylase-deficient subjects in other studies.^{1,12,13} Perhaps, pupillary function may be a less reliable screening test in young patients.

Adult case reports suggested that several ophthalmic signs are present in this treatable deficiency. However, in this case series of young patients, miosis was not overly impressive. Mild ptosis was observed, which may be explained by levator muscle compensation as it is driven by the parasympathetic system. There may be varying degrees of ptosis as demonstrated by Patient 3, who required levator advancement surgery as a child. This patient was also the only one with miosis. Orthostatic reductions in BP and IOP occurred in all three young patients consistent with other adult-onset autonomic dysfunction disorders. Given the results of this study, dopamine beta-hydroxylase deficiency should be considered in pediatric patients presenting with mild ptosis and symptoms of orthostatic hypotension such as exercise intolerance. Newer tonometry instruments such as the ICare (ICare Finland, Helsinki, Finland) and the TonoPen-XL (Mentor, Norwell, MA) aid in obtaining these IOP measurements in young children.^{20,21} Measuring orthostatic BP and/or IOP represents a simple clinical screen to provide earlier diagnosis of this debilitating, yet treatable deficiency.

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Biographies

Figure 1.

Pediatric ptosis as a sign of treatable autonomic dysfunction: pupillary response to phenylephrine in 2 patients. Patient 2 before (top left) and after (top right) the instillation of phenylephrine drops. His pupils dilated by 2 mm in response to 2.5% phenylephrine. Patient 3 before (bottom left) and after (bottom right) the instillation of phenylephrine drops. His pupils dilated by 3 mm in response to 2.5 %phenylephrine. Patients did not exhibit pupil supersensitivity to phenylephrine.

Table 1
Pediatric Ptosis as a Sign of Treatable Autonomic Dysfunction: Demographics

	Patient One	Patient Two	Patient Three
Age	19 years	17 years	23 years
Sex	Female	Male	Male
Age of symptoms onset	3 years	Young age	5 months
Age of diagnosis	16 years	17 years	23 years
Prior eye surgery	None	None	Levator advancement
Medications on admission	L-threo-dihydroxyphenylserine 1-deamino-8-D-arginine vasopressin	Fludrocortisone	Fludrocortisone
Medications on discharge	L-threo-dihydroxyphenylserine 1-deamino-8-D-arginine vasopressin	L-threo-dihydroxyphenylserine	L-threo-dihydroxyphenylserine

Table 2

Pediatric Ptosis as a Sign of Treatable Autonomic Dysfunction: Positional Intraocular Pressure (mm Hg), Blood Pressure and Heart Rate Measurements

		Patient One					Patient Two					Patient Three				
		IOP	OD	IOP	OS	HR	BP	MAP	IOP	OD	IOP	OS	HR	BP	MAP	MAP Average
Standing	9			9		88	46/34	38.9	10		8		88	55/33	40.3	45.8±11.6
Sitting	12			12		65	97/58	49.5	20		19		72	129/73	91.7	79.1±25.7
Supine	15			15		50	103/52	69	17		15		54	139/86	103.6	90.1±18.5

IOP = intraocular pressure; OD = right eye; OS = left eye; HR = heart rate; BP = blood pressure; MAP = mean arterial pressure.

One-way repeated measures analysis of variance: IOP ($P=0.03$), HR ($P=0.028$), MAP ($P=0.021$)

Table 3

Pediatric Ptosis as a Sign of Treatable Autonomic Dysfunction: Testing of Eyelid and Pupillary Function for Autonomic Dysfunction

	Patient One		Patient Two		Patient Three	
	OD	OS	OD	OS	OD	OS
Palpebral fissure (reference: 9–10 mm)	8 ^a	9	7	7	9	9
Levator function (reference: 14–18 mm)	16	16	16	16	16	16
Margin reflex distance (reference: 4–4.5 mm)	3	3	2	2	3	3.5
Palpebral fissure after 2.5% phenylephrine	9	10	9	9	10	10
Reaction to light under the following conditions:	OD	OS	OD	OS	OD	OS
Light	4–4 ^b	4–4	6–4	6–4	3–2	3–2
Dark	7–5	7–5	7–4	7–4	4–2	4–2
Accommodation	5–3	5–3	6–4	6–4	3–2	3–2
After 2.5% phenylephrine	5–4	5–4	8–7	8–7	6–5	6–5

^a All measurements are in millimeters.

^b Measurement of 4–4 means that the pupil was at 4 mm at baseline in a lit room and stayed at 4 mm after exposure to light.
mm = millimeter; OD = right eye, OS = left eye.