



Dopa-responsive hypersomnia and mixed movement disorder due to sepiapterin reductase deficiency

Abstract—Sepiapterin reductase deficiency (SRD) is a rare, treatable disorder of monoamine metabolism with cognitive delay and L-dopa responsive movement disorder. We describe a patient with SRD and distinctive phenotypic feature of marked hypersomnolence. Our patient showed improvement with therapies directed at both serotonergic and dopaminergic deficiencies. This case illustrates symptoms that characterize the SRD phenotype and demonstrates the importance of systematic treatment trials addressing the various biochemical abnormalities present.

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Defects in monoamine biosynthesis are associated with various phenotypes including developmental delay, diurnal variation in symptom severity, and dystonia that may improve with levodopa.¹ The best known of these disorders is dopa-responsive dystonia (DRD) due to mutations in the GTP-cyclohydrolase gene (figure).¹ Recently, a smaller number of patients with a dopa-responsive motor disorder, diurnal variation, and cognitive delays due to sepiapterin reductase gene (*SPR*) mutations have been reported.^{2,3} We describe a patient with dopaminergic and serotonergic-responsive hypersomnolence and movement disorder with bi-allelic alterations in the *SPR* transcript.

Case report. A 27-year-old woman was referred for re-evaluation of “cerebral palsy.” In childhood, she had delayed milestones, abnormal gait, and hypersomnolence. In adulthood, gait disorder and incoordination improved. However, hypersomnolence became disabling, requiring 13 hours sleep per 24 hours. Diurnal fluctuation in motor and cognitive function left her unable to perform tasks after 8 hours without sleep. Menarche was at 16 years, but menses were irregular and infrequent. Family history was remarkable for mild hemi-body posturing in the patient’s mother. Other maternal relatives were reported to display abnormal limb posturing but declined formal evaluation. Parents were nonconsanguineous.

Physical examination revealed mild cognitive dysfunction (full scale IQ 60), ptosis, punctate cataracts, oculomotor

apraxia, dysarthric speech, diffuse weakness, bradykinesia, generalized dystonia, myoclonus, and choreoathetosis. Cognitive and motor impairment was incapacitating in the afternoon and improved markedly after a nap. Cranial MRI, ¹⁸F-deoxyglucose, and ¹⁸F-fluorodopa PET were normal. Sleep study revealed abnormal sleep architecture with low sleep efficiency, shift toward lighter stages, and recurrent awakenings. Periodic limb movements were absent. Multiple sleep-latency testing was unremarkable.

CSF contained markedly reduced 5HIAA and HVA and elevated 7,8-dihydropterin consistent with SRD. Assays of neopterin and biopterin in cytokine-stimulated fibroblasts and sepiapterin reductase (SR) activity in non-stimulated fibroblasts revealed elevated neopterin and markedly reduced biopterin levels as well as SR activity below the level of detection.⁴ Mutational analysis of *SPR* gene revealed a homozygous change (c.448A>G) predicted to cause missense alteration (p.R150G) (table 1).⁴

Sequential treatment trials of L-dopa/carbidopa (6.25 to 100 mg/day L-dopa), sertraline (50 to 150 mg/day), and selegiline (5 to 10 mg/day) markedly improved alertness, decreased sleep time, and decreased dystonia. L-Dopa/carbidopa was limited by intolerable dyskinesias. Sertraline produced only modest benefit and akathisia. Combination therapy with selegiline and sertraline led to more significant benefit than sertraline alone, but was limited by myoclonic jerks and oral-buccal dyskinesia. Carbidopa/5-hydroxytryptophan (5-HTP; 1.7 mg/kg/day 5-HTP) also markedly improved sleep and dystonia related symptoms but was discontinued due to transaminase elevation. Video documentation of the patient’s baseline and response to these medications is available on the *Neurology* Web site at www.neurology.org. Interestingly, bromocriptine (0.05 to 0.10 mg/day) induced menses that were associated with worsened symptomatology. Melatonin (2 mg/day) decreased nighttime cervical dystonia and eased sleep transition. Tetrahydrobiopterin (BH₄; 20 mg/kg/day) produced no benefit, but was given for only 1 week due to cost. Trihexyphenidyl, Lioresal, and benztropine were not tolerated. Maximal benefit was obtained on combination of selegiline and melatonin.

Discussion. This patient shares with other SRD cases core features of dopa-responsive, diurnally fluctuating movement disorder and motor and cognitive delay (table 2)^{1–3,5} yet displays several unique features. Oculogyric crises, in contrast to most previous cases, were absent.^{2,3,5} Remarkably, hypersomnolence, this patient’s primary symptom, has not been previously reported. Hypersomnolence and disordered sleep have been noted in other disorders of monoamine biosynthesis.¹ This symptom may be related to impaired dopaminergic or serotonergic influences on sleep and wakefulness. This patient also displays minor features noted in patients with non-SRD disorders of monoamine metabolism.¹ Ptosis, likely due to sympathetic defect, was present. In addition, there were

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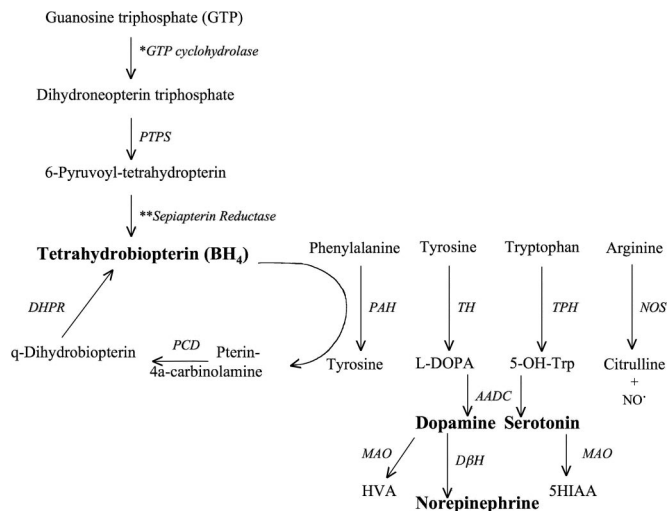


Figure. Pathway for synthesis of monoamine neurotransmitters: dopamine, serotonin, and norepinephrine. *Site of defect in dopamine responsive dystonia (DRD). **Site of defect in this patient. PTPS = 6-pyruvoyl-tetrahydropterin synthase; DHPH = dihydropteridine reductase; PCD = pterin-4 α -carbinolamine dehydratase; PAH = phenylalanine-4-hydroxylase; TH = tyrosine-3-hydroxylase; TPH = tryptophan-5-hydroxylase; NOS = nitric oxide synthase; AADC = aromatic L-amino acid decarboxylase; D β H = dopamine beta-hydroxylase; MAO = monoamine oxidase; 5-OH-Trp = 5-hydroxy tryptophan; HVA = homovanillic acid; 5HIAA = 5 hydroxyindoleacetic acid.

irregular menses/amenorrhea, which likely resulted from increased prolactin levels due to loss of pituitary dopamine release. As the core features of SR deficiency are nonspecific and diurnal fluctuation may not always be present, it is crucial to be cognizant of subtle signs, as in our patient, that may suggest monoamine dysfunction. When these are present, further investigation including L-dopa trial, and CSF neurotransmitter and pterins analysis should be undertaken.

Though patients with SRD show dramatic response to L-dopa/carbidopa supplementation, improvement is incomplete.^{2,4,6,7} Despite the imperfect clinical response there has previously been no systematic attempt to explore strategies to address the variety of other neurotransmitter and pterin abnormalities present in these patients (table 2). In this case, we report a variety of treatments: 1) cofactor replacement (BH₄); 2) neurotransmitter precursor supplementation (L-dopa and 5-HTP); 3) strategies to block reuptake or reduce catabolism of neurotransmitters (sertraline, selegiline); 4) agonist (bromocriptine); and 5) symptomatic therapy (trihexyphenidyl, Lioresal, benzotropine, melatonin). For this patient hypersomnolence was the most disabling feature. Melatonin is a downstream byproduct of serotonin production and we hypothesized that disordered sleep patterns were related to reduced melatonin levels. Therapy with melatonin reduced dystonic neck spasms at bedtime and thus eased transition to

sleep. No change in overall sleep time or alertness was noted. Interestingly, both serotonergic and dopaminergic agents (5-HTP, sertraline, L-dopa, and selegiline) led to increased arousal and decreased total sleep time. This is consistent with a growing appreciation for the role of both of these neurotransmitters in modulating arousal and sleep/wake states. BH₄ deficiency may lead to impaired nitric oxide (NO) production, as demonstrated in CSF from SR and BH₄ deficiency patients.⁸ Though the role of NO in the CNS is not fully understood, reduced levels may impact a variety of functions including learning, memory, and sleep through NO's role in modulating the release of neurotransmitters or itself acting as an atypical neurotransmitter. Empiric treatment with BH₄ replacement is unfortunately problematic as very small amounts are able to cross the blood-brain barrier.

Several of this patient's responses to pharmacologic intervention are not consistent with current understanding of dopaminergic/serotonergic roles in the CNS. Though abnormal involuntary movements and dystonic postures improved with L-dopa/carbidopa, sertraline, and selegiline, most marked improvement was noted with 5-HTP. This is of interest because, though a few reports have demonstrated impaired CNS serotonin metabolism in patients with dystonia,⁹ the serotonergic system is not traditionally thought of as playing a prominent role in the generation of dystonia. In addition, levodopa/carbidopa therapy was associated with intolerable dyskinesias, even at very low doses. Dyskinesias have been reported rarely in patients with genetically confirmed DRD¹⁰ as well as SRD.² These observations suggest that nigrostriatal denervation may not be necessary for development of dyskinesia. We hypothesized that dyskinesia likely resulted from receptor supersensitivity due to chronic dopamine deficiency. We speculated that reduction of L-dopa dose and administration over prolonged time periods would lessen dyskinesias. Though dose reduction has resulted in improvement of dyskinesias in other SRD patients² in our patient, this was, unfortunately, not the case. The etiology of dyskinesia in this and other patients with SRD remains unclear.

SRD is the most recently described disorder of monoamine biosynthesis. Thus far 13 other cases, including 7 from a presumed founder, have been tabulated in the BIODEF database^{2,3,5,7} (tables 1 and 2). Other than mutations from a single founder, most are homozygous, unique mutations in patients with severe phenotype.^{3,5} The mutation present in this case was previously reported in a heterozygous form where it was shown that when expressed recombinantly in *E coli*, the mutant protein is inactive.³ Though in most cases, SRD is a recessive disorder, one report describes haploinsufficiency resulting in a mild DRD phenotype.⁷ No other symptomatic heterozygotes have been reported. The presence of posturing in the patient's mother and several other maternal relatives raises the possibility that haplo-

Table 1 Biochemical/molecular findings in this case compared to other reported patients with sepiapterin reductase deficiency^{2,3,5-7}

	This case	Normal values	BIODEF patients*
Blood			
Phenylalanine (μmol/L)	Normal		Normal
Prolactin (mg/mL)	41.8 ↑	(2.8–29.2)	NA
Serotonin (nmol/L)	17.2–265 ↓	(454–971)	NA
Phenylalanine load	Abnormal		Abnormal
CSF			
Neopterin, total (nmol/L)	22	(7–65)	Normal
Biopterin, total (nmol/L)†	—		↑
Biopterin (nmol/L)	6 ↑	(<2)	↑
Dihydrobiopterin (nmol/L)	35 ↑	(<10)	↑
BH ₄ (nmol/L)	—		Low normal
5HIAA (nmol/L)	<10 ↓	(79–140)	↓
HVA (nmol/L)	25 ↓	(145–324)	↓
Urine			
Neopterin (mmol/mol creatinine)	0.54	(0.2–1.7)	Normal
Biopterin (mmol/mol creatinine)	0.26 (↓)	(0.5–2.7)	Normal
Fibroblasts			
Neopterin (pmol/mg)‡	389 ↑	(18–98)	↑
Biopterin (pmol/mg)‡	12 ↓	(154–303)	↓
SR activity (mU/mg)	<10 ↓	(99–185)	↓
Red blood cells			
SR activity (mU/mg)§	—		Normal
Nucleotide aberration¶			
	g.1397A>G		#229: g.1397A>G/g.1397_1401del5
	c.448A>G		#360: g.1303_1304TC>CT
			#439: g.1397_1401del5
			#447: g.1437C>T
			#491: g.395G>A
			#492: g.751A>T
			#509-515: c.596-2A>G
Location in gene	Exon 2		
Type	Substitution		
Effect on protein¶¶	R150G/R150G		#229: R150G/R150fs #360: Q119X/Q119X #439: R150fs/R150fs #447: P163L/P163L #491: -13G>A/wt #492: K251X/K251X #509-515: IVS2-2A>G/ IVS2-2A>G***

* BIODEF (international database of tetrahydrobiopterin deficiencies) (www.bh4.org).

† Total biopterin = biopterin + dihydrobiopterin + tetrahydrobiopterin.

‡ After stimulation with cytokines.

§ Assay not specific for sepiapterin reductase (SR).

¶ BIOMDB (database of mutations causing tetrahydrobiopterin deficiencies) (www.bh4.org).

|| Mechanism unknown.

*** Presumed aberrant splicing.²

NA = not available; BH₄ = tetrahydrobiopterin; 5HIAA = 5-hydroxyindolacetic acid; HVA = homovanillic acid; — = not assayed; # = case number designations in BIODEF/BIOMDB databases.

Table 2 Signs, symptoms, and therapy trials in patients with SR deficiency

	This case	BIODEF* patients (n = 13)
Age at diagnosis, y	25	0.5–26
Age at first symptom	<6 mo	<6 mo
Sex	F	6F/7M
Clinical features†		
Core features		
Motor delay	+	12/13
Cognitive delay	+	12/13
Diurnal fluctuation	+	9/13
Other frequent features		
Dystonia	+	9/13
Oculogyric crises	–	8/13
Speech delay	+	8/13
Sleep benefit	+	7/13
Axial hypotonia	+	7/13
Limb hypertonia	+	6/13
L-dopa induced dyskinesias	+	5/13
Tremor	–	4/13
Weakness	+	4/13
Therapy trials		
L-dopa/carbidopa	+	13/13
5-OH-Trp/carbidopa	+	5/13
BH ₄	+	3/13
Selegiline	+	1/13
Sertraline	+	0/13
Bromocriptine	+	0/13
Melatonin	+	0/13
Trihexyphenidyl	+	0/13
Lioresal	+	0/13
Benzotropine	+	0/13

* Obtained from published reports as well as BIODEF database (www.bh4.org).^{2,3,5-7}

† Signs/symptoms which have been seen in other disorders of monoamine metabolism (autosomal dominant and recessive GTP cyclohydrolase deficiency, 6-pyruvoyl-tetrahydropterin synthase deficiency, dihydropteridine reductase deficiency, pterin-4 α -carbinolamine dehydratase deficiency, tyrosine hydroxylase deficiency, aromatic L-amino acid decarboxylase deficiency, dopamine β -hydroxylase deficiency).

SR = sepiapterin reductase.

insufficiency of the R150G mutation may also cause symptoms.

Further investigation will be necessary to define genotype/phenotype relationships, to optimize pharmacologic therapy, to understand pathogenesis of dyskinesias, to clarify the role of individual monoamines in the sleep/wake disturbance, and to determine how BH₄ deficiency contributes to the phenotype. SRD and other disorders of monoamine metabolism should be considered in all childhood, motor/cognitive disorders and cases of unexplained hypersomnolence. Therapies should be directed at not only dopamine deficiency, but also other biochemical deficiencies present in this disorder.

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