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RESEARCH REPORT

Dopamine-Responsive Growth-Hormone Deficiency and Central Hypothyroidism in Sepiapterin Reductase Deficiency

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Abstract Sepiapterin reductase (SR) deficiency is a rare autosomal recessively inherited error of tetrahydrobiopterin (BH_4) biosynthesis, resulting in disturbed dopaminergic and serotonergic neurotransmission. The clinical phenotype is characterized by dopa-responsive movement disorders including muscular hypotonia, dystonia, and parkinsonism. Due to the rarity of the disease, the phenotype of SR deficiency is far from being completely understood. Here, we report a 7-year-old boy, who was referred for diagnostic evaluation of combined psychomotor retardation, spastic tetraplegia, extrapyramidal symptoms, and short stature. Due to discrepancy between motor status and mental condition, analyses of biogenic amines and pterins in CSF were performed, leading to the diagnosis of SR deficiency. The diagnosis was confirmed by a novel homozygous mutation c.530G>C; p.(Arg177Pro) in exon 2 of the *SPR* gene. Because of persistent short stature, systematic endocrinological investigations were initiated. Insufficient growth-hormone release in a severe hypoglycemic episode after overnight fasting confirmed growth-hormone deficiency as a cause of short stature. In addition, central hypothyroidism was present. A general hypothalamic affection could be excluded. Since dopamine is known to regulate growth-hormone excretion, IGF-1, IGF-BP3, and peripheral thyroid hormone levels were monitored under L-dopa/carbidopa supplementation. Both growth-hormone-dependent factors and thyroid function normalized under treatment. This is the first report describing growth-hormone deficiency and central hypothyroidism in SR deficiency. It extends the phenotypic spectrum of the disease and identifies dopamine depletion as cause for the endocrinological disturbances.

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Abbreviations

3-OMD	3-*O*-methyldopa
5-HIAA	5-Hydroxyindoleacetic acid
5-HTP	5-Hydroxytryptophan
BH_2	Dihydrobiopterin
BH_4	Tetrahydrobiopterin
CSF	Cerebrospinal fluid
HVA	Homovanillic acid
L-dopa	Levodopa
Phe	Phenylalanine
SR	Sepiapterin reductase

Introduction

Sepiapterin reductase (SR) deficiency is a rare levodopa-responsive disorder due to an autosomal inherited error in pterin metabolism (Bonafe et al. 2001; Blau et al. 2001). The molecular basis is an inherited deficiency of sepiapterin reductase, which is caused by two disease-causing mutations in the *SPR* gene locus located on chromosome 2p14-p12 (Thöny and Blau 2006). SR catalyzes the last step in

the tetrahydrobiopterin (BH_4) synthesis pathway converting 6-pyruvoyl-tetrahydropterin to BH_4 in a two-step NADPH-dependent reaction (Hyland 1999; Pearl et al. 2004). BH_4 is an essential cofactor necessary for the function of phenylalanine hydroxylase (PAH), tyrosine hydroxylase (TH), tryptophan hydroxylase (TPH), and nitric-oxide synthase. TH and TPH are rate limiting in the biosynthesis of the biogenic amines dopamine and serotonin, which play important roles in the generation and regulation of motor movements, sleep maintenance, learning, memory, and emotional behavior (Hyland 1999; Surtees 1999). Dopamine exerts some of its functional effects via D2 receptors. In recent years, evidence was gathered that D2 receptors are crucial in the regulation of growth-hormone-dependent body growth as well as thyroid hormone secretion (Díaz-Torga et al. 2002; Lewis et al. 1987; Samuels et al. 1992).

Patients with SR deficiency exhibit characteristic symptoms. While the early clinical phenotype is dominated by axial muscular hypotonia or developmental delay, older patients present with cardinal features of dopamine-responsive disorders including dystonia, sleep disorders, and oculogyric crises, most of them with diurnal fluctuations (Friedman et al. 2011). However, due to the rarity of the disease and lack of systematic investigations, the phenotype of SR deficiency is far from being completely understood.

Diagnosis of SR deficiency is depending on the analysis of biogenic amines and pterins in CSF. SR deficiency must be suspected finding an increased dihydrobiopterin (BH_2) concentration combined with low levels of both homovanillic (HVA) and 5-hydroxindolacetic acid (5-HIAA). Diagnosis can be confirmed biochemically by elevated CSF sepiapterin and molecular genetic studies (Blau et al. 2001). Here, we report a 7-year-old boy with newly diagnosed SR deficiency who presented with severe endocrinological disturbances.

Case Summary

History and Examination

The male patient was born spontaneously after an uneventful pregnancy at term to healthy consanguineous parents (1st-degree cousins; target height SDS −1.59) of Kuwaiti ancestry. He is the 6th child of 9 children. There was no history of genetic disorders in the families. Growth parameters at birth were small for gestational age (birth weight 2,500 g, SDS −2.55, birth length 46 cm, SDS −2.83). Perinatal adaption was normal without any signs of neonatal infection or early metabolic decompensation. Newborn screening for inherited metabolic diseases was not performed. At age 6 months, the boy was evaluated for the first time by a neuropediatrician due to developmental delay, axial muscular hypotonia, and short stature without finding a specific underlying diagnosis. In the further course, growth parameters remained under the 3rd centile. During the first year of life, successively increasing limb spasticity, predominantly on the left side, was observed associated with episodes of generalized tonic hyperextensions. The clinical examination at age 12 months was dominated by significantly reduced head control and truncal muscular hypotonia with increased limb stiffness. Hyperreflexia, widened reflex zones and foot clonus led to the initial diagnosis of spastic tetraparesis. Cerebral palsy was suspected. Ocular movements described as frequent uprolling of eyes were regarded as epileptic. Anticonvulsant therapy with valproic acid was initiated, but stopped after a total of 1 month since follow-up EEG examination did not reveal epileptic discharges. Expanded metabolic analyses including blood ammonia level, amino acid and acylcarnitine profiles, biotinidase activity, and analysis of lysosomal enzymes performed at the age of 3 years were all negative. Repeated MRI scans of the brain were unremarkable. An underlying neuropathy was excluded by normal nerve conduction studies. Under regular physical therapy, the boy mildly progressed in his development.

At the time of presentation at the University Children's Hospital, Heidelberg, at the age of 7 years, the patient still had poor head control with severe axial muscular hypotonia, was unable to sit or walk, and did not use spoken language. There was a striking contrast between his motor disabilities and his cognitive capacities. The boy was alert and interactive, exploring his environment attentively. On physical examination, he showed apart from a severe generalized muscular hypotonia extrapyramidal symptoms with rigor and bradykinesia associated with generalized hyperreflexia and pes equinus. Bilateral striatal toe was noted. Typical dystonic movements were absent. Body height, weight, and head circumference were under the 3rd centile (height 99.0 cm, SDS −5.17, weight 11.0 kg, SDS −7.89, head circumference 48.0 cm, SDS −3.52). Because of the marked discrepancy between his motor status and mental condition, analyses of biogenic amines and pterins in CSF were included in the metabolic workup. CSF analysis revealed significantly decreased concentrations of HVA 22 nmol/l (normal range 260–713 nmol/l) and 5-HIAA 27 nmol/l (normal range 110–247 nmol/l). BH_2 and sepiapterin concentrations in CSF were highly elevated (BH_2 91 nmol/l, normal range 0–18 nmol/l; sepiapterin 24 nmol/l, normal range < detection limit), while BH_4 concentration was low at 6 nmol/l (normal range 20–49 nmol/l). Plasma and CSF phenylalanine (Phe) concentrations were within the normal range: plasma, 59 μmol/l (normal range 26–91 μmol/l), and CSF, 8.7 μmol/l (normal range 6.4–11.5 μmol/l). Surprisingly, plasma prolactin concentration was found within the normal

Table 1 Endocrinological data before and during treatment

Biochemical marker	Before therapy	After 2 weeks of therapy (L-dopa/carbidopa 2.7 mg/kg/day)	After 4 weeks of therapy (L-dopa/carbidopa, 4.1 mg/kg/day)	After 8 weeks of therapy (L-dopa/carbidopa, 6.8 mg/kg/day and 5-hydroxytryptophan, 5.5 mg/kg/day)	Control range
IGF-1 (ng/ml)	nd ↓	36 ↓	33 ↓	27 ↓	62–248
IGF-1 (SDS)	na ↓	−3.1 ↓	−3.3 ↓	−3.8 ↓	
IGF-BP3 (mg/l)	1.08 ↓	1.15 ↓	1.36 ↓	1.69	1.66–3.59
IGF-BP3 (SDS)	−3.8 ↓	−3.4 ↓	−2.6 ↓	−1.7	
TSH (mU/l)	0.98	1.33	0.98	1.80	0.7–3.7
T3 (ng/ml)	0.56 ↓	0.92 ↓	0.95 ↓	0.97 ↓	1.18–2.14
fT3 (ng/l)	2.42 ↓	4.14	3.15 ↓	3.95	3.4–6.6
T4 (ng/ml)	65.82	59.55 ↓	65.54	63.63	60.61–117.02
fT4 (ng/l)	10.37	8.88	7.70	9.45	7.5–18.7

nd not detectable, *na* not available, *IGF-1* insulin-like growth factor 1, *IGF-BP3* insulin-like growth factor binding-protein 3, *TSH* thyroid-stimulating hormone, *T3* total triiodothyronine, *fT3* free triiodothyronine, *T4* total thyroxine, *fT4* free thyroxine, ↓ below control range

range. For confirmation of the biochemical findings, genetic analysis of the SR gene (*SPR*) was initiated, which identified a novel homozygous mutation c.530G>C; p.(Arg117Pro) in exon 2. Taking the phenotype into consideration, the mutation has to be judged as functionally relevant, thereby affirming the diagnosis of SR deficiency. Diagnostic workup of short stature (SDS −5.17) showed a strikingly decreased concentration of IGF-1 and IGF-BP3 (Table 1). Growth-hormone deficiency was confirmed by inadequate growth-hormone release (max. 1.31 ng/ml) in hypoglycemia (plasma glucose 27 mg/dl, normal range 45–100 mg/dl) that spontaneously occurred after overnight fasting. Further systematic endocrinological investigations revealed central hypothyroidism (Table 1). The analysis of steroid metabolites in urine, 24-h cortisol–ACTH profile, as well as gonadotropin concentrations were within the normal range, thereby excluding a panhypopituitarism as concomitant disease. Brain MRI was unremarkable, particularly showing no evidence of morphological alteration of hypothalamic–pituitary axis.

Treatment and Follow-Up

Treatment with L-dopa/carbidopa [4:1] was started immediately after diagnosis with a slow dose increase up to a total L-dopa dosage of 6.8 mg/kg body weight per day. After 1 month, 5-hydroxytryptophane was added with doses slowly increased up to 5.5 mg/kg body weight per day. Growth hormone and thyroid function were monitored carefully. L-dopa/carbidopa supplementation led to a prompt increase of the very low IGF-1 and IGF-BP3 concentrations (Table 1). Similarly central hypothyroidism significantly improved. Specific supplementation of L-thyroxin was not necessary. After 2 months of therapy, overall thyroid function was euthyroid (Table 1). Clinically at the 2-month follow-up visit, the boy presented with improved alertness and improved motor function. Prone position was tolerated well; in addition the patient was partially supporting his own weight when held and showed improved hand–hand and hand–mouth contact. However, orofacial dyskinesia as side effect of treatment was noted. On 6-month follow-up examination, laboratory testing showed marked hyperprolactinemia (prolactin 450.9 mIU/l, normal range 57–281 mIU/l).

Discussion

SR deficiency is a rare inherited neurological disease in the biosynthesis of BH_4 leading to monoamine neurotransmission deficiency. Due to the missing hyperphenylalaninemia, SR deficiency fails early identification by newborn screening, which results in a significantly delayed diagnosis (Opladen et al. 2012). Within the inherited BH_4 deficiencies, apart from SR deficiency, only the autosomal dominant and a subgroup of the autosomal recessive inherited GTP cyclohydrolase deficiencies are characterized by normal phenylalanine levels (Opladen et al. 2011; Segawa 2011). The phenotype of SR deficiency is mainly characterized by an affection of the motor and cognitive system. Patients exhibit psychomotor retardation and neurologic symptoms dominated by axial muscular hypotonia, dystonic movements, spasticity, and parkinsonism with diurnal fluctuation (Abeling et al. 2006; Dill et al. 2012; Neville et al. 2005). In infancy, muscular hypotonia and developmental delay are usually the only clinical findings. Therefore, due to mimicking characteristics, infantile cerebral palsy is one of the most important differential diagnoses of SR deficiency (Friedman et al. 2011). The underlying pathophysiological basis of SR deficiency is a defect in the

synthesis of BH_4 leading to severe depletion in monoamines serotonin and dopamine. In the central nervous system, dopamine exerts its effects mainly through the activation of dopamine D2 receptors. Recent in vivo studies, using genetically modified mice that lack dopamine D2 receptors ($Drd2^{-/-}$), revealed dopamine as a crucial regulator of growth-hormone-dependent body growth. $Drd2^{-/-}$ mice exhibit deficiency of pituitary somatotrophs associated with decreased growth hormone and IGF-1 serum levels, ultimately resulting in dwarfism (Díaz-Torga et al. 2002; Noaín et al. 2013). In addition, mice deficient in the *SPR* gene ($Spr^{-/-}$) display a phenotype comparable to $Drd2^{-/-}$ mice with severely reduced concentrations of IGF-1 in serum and growth retardation (Yang et al. 2006). Growth-hormone deficiency is thereby not specific for SR deficiency but related to all primary deficiencies in dopamine synthesis. Mice deficient in the *PTS* gene ($Pts^{-/-}$), coding 6-pyruvoyl-tetrahydropterin synthase, and homozygous DDC knock-in mice (Ddc(IVS6/IVS6)), deficient in aromatic L-amino acid decarboxylase, exhibit dwarfism and low IGF-1 concentration (Elzaouk et al. 2003; Lee et al. 2013). Interestingly, analogous to transgenic $Pts^{-/-}$ and $Spr^{-/-}$ mice, where administration of dopaminergic substances rescued dwarfism and concentration of IGF-1 (Elzaouk et al. 2003; Yang et al. 2006), treatment with L-dopa/carbidopa led to a significant increase of IGF-1 and IGF-BP3 serum levels in our patient. The results demonstrate for the first time that growth-hormone deficiency in human SR deficiency is caused by dopamine depletion and can be sufficiently treated by restoring dopamine concentration in the central nervous system.

While changes of thyroid functions were not documented in either animal models, endocrinological evaluation revealed central hypothyroidism in our SR-deficient patient. Concerning the regulation of hypothalamic–pituitary–thyroid axis by dopamine, evidence was gathered implicating opposite effects of D2 receptor activation on the hypothalamus and the pituitary thyrotroph. Whereas dopamine suppresses TSH pulse amplitude in healthy volunteers (Samuels et al. 1992), in vitro studies illustrated that dopamine stimulates the release of TRH by acting via the same D2 receptors (Lewis et al. 1987). It is appropriate to hypothesize that basal activation of D2 receptors in the hypothalamus is required for sufficient TRH release. Interestingly, it was recently shown that levodopa-induced hyperkinesia is associated with increased TRH expression in the striatum (Cantuti-Castelvetri et al. 2010). Similar to the effect on IGF-1 and IGF-BP3 concentrations, supplementation with L-dopa/carbidopa significantly improved thyroid hormone levels with TSH and fT3 within the normal range. This supports the hypothesis that central hypothyroidism is caused by dopamine depletion in SR deficiency. As hypothyroidism is a known cause for mental retardation in children, central hypothyroidism might contribute to the severe cognitive deficits in patients with SR deficiency. Prolactin concentrations in the periphery are known to inversely correlate with the dopamine levels in the central nervous system and therefore are expected to be elevated in the case of dopamine depletion. The normal prolactin level in our patient, measured once before supplementation with L-Dopa, reflects the diurnal fluctuations of plasma prolactin levels. Recently, it has been shown that prolactin levels in blood range from normal values to severe hyperprolactinemia in the BH_4 biosynthesis disorders 6-pyruvoyl-tetrahydropterin synthase deficiency and dihydropteridine reductase deficiency (Porta et al. 2009; Porta et al. 2012). Follow-up evaluation after 6 months showed marked hyperprolactinemia, emphasizing the fact that repeated examinations of plasma prolactin levels are necessary for the reliable, indirect assessment of dopamine homoeostasis in the central nervous system.

Given their pathophysiological basis, it is likely that growth-hormone deficiency and central hypothyroidism are part of the general phenotype of SR deficiency. The fact that patients with growth-hormone deficiency have a higher risk to develop life-threatening hypoglycemic episodes, as seen in our patient, highlights the importance of an early diagnosis of SR deficiency and immediate start of treatment with dopaminergic substances. As hypoglycemic episodes are known and potentially lethal complications in several inherited neurotransmitter disorders including aromatic L-amino acid decarboxylase (AADC) deficiency (Arnoux et al. 2013; Manegold et al. 2009), analyses of biogenic amines and pterins in CSF should be taken into consideration in children presenting with fasting hypoglycemia and neurologic symptoms.

Conclusion

Analyses of biogenic amines in CSF should be considered in the metabolic workup of children with fasting hypoglycemia and neurologic symptoms.

Synopsis

Systematic endocrinological investigations should be performed in patients with sepiapterin reductase deficiency as dopamine depletion might result in growth-hormone deficiency and central hypothyroidism associated with cognitive impairment and life-threatening hypoglycemic episodes. Analyses of biogenic amines in CSF should be considered in the metabolic workup of children with fasting hypoglycemia and neurologic symptoms.

References to Electronic Databases

Phenylalanine hydroxylase, EC 1.14.16.1; tyrosine hydroxylase, EC 1.14.16.2; tryptophan hydroxylase, EC 1.14.16.4; nitric-oxide synthase, EC 1.14.13.39

Competing Interest Statement

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Details of Contributions of Individual Authors

All authors contributed to clinical care and diagnostic evaluation of this patient. The manuscript was prepared and written by Matthias Zielonka and Thomas Opladen. All authors contributed to the critical revision of the manuscript for intellectual content and gave final approval for the version to be published.

Name of One Author Who Serves as Guarantor

Thomas Opladen accepts full responsibility for the work and/or conduct of the study, had access to the data, and controlled the decision to publish.

Ethical Approval

No approval from the institutional review board was necessary as this is a case report without inclusion of any identifying information.

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