

Sepiapterin Reductase Deficiency: Clinical Presentation and Evaluation of Long-Term Therapy

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Sepiapterin reductase deficiency has recently been recognized as a treatable, inborn error of pterin metabolism. This investigation is the first long-term clinical study demonstrating impressive positive, long-term effects of treatment in two cases of sepiapterin reductase deficiency after 2 and 5 years of treatment respectively. The two patients were not diagnosed before 7 and 13 years of age. These results highlight the importance of cerebrospinal fluid neurotransmitter investigations in childhood encephalopathy, in cases of unexplained early-onset neurologic handicap. Such a widened approach to the diagnostic efforts in early-onset encephalopathy with motor delay during childhood is important, as we have at our disposal a simple and effective treatment. © 2006 by Elsevier Inc. All rights reserved.

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Introduction

Sepiapterin reductase deficiency, the latest of the known inborn errors of pterin deficiencies, was only fully recognized in 2001 [1,2]. As the disease does not lead to hyperphenylalaninemia, and as cerebrospinal fluid analysis of neurotransmitter metabolites is only performed in a few specialized laboratories in the world, the incidence of the disease is still unknown.

Diagnosis is made by analyzing the metabolites of the biogenic monoamines, dopamine and serotonin, and individual pterin species in the cerebrospinal fluid, revealing decreased concentrations of homovanillic acid, 5-hydroxyindolacetic acid, and elevated levels of 7,8-dihydrobiopterin. Sepiapterin is not detected by the regularly used methods applied in the investigation of biogenic monoamines metabolites in cerebrospinal fluid. It must be determined by specialized methods [3] indicating a marked and abnormal increase of sepiapterin in cerebrospinal fluid. Confirmation of the diagnosis is by demonstration of high levels of cerebrospinal fluid sepiapterin and finally by a marked decrease of sepiapterin reductase activity of the fibroblasts along with sepiapterin reductase gene (*SPR* gene) molecular analysis [1,2]. Since the original description, 14 cases of sepiapterin reductase deficiency have been described or collected in the database [1,2,4-7].

The present study describes two patients affected with sepiapterin reductase deficiency and describe the positive results of long-term treatment, using levodopa/carbidopa and 5-hydroxytryptophan, with several years of follow-up. These results highlight the importance of diagnosing this neurotransmitter disease, otherwise leading to progressive neurologic symptoms that could be misdiagnosed as an unrecognized neurodegenerative disorder or cerebral palsy.

Patients and Methods

The first patient was born from first-cousin parents of Turkish ancestry. After a transitory neonatal distress secondary to maternal infection, the development was considered normal, until a first prolonged afebrile seizure occurring when he was 6 months old. A progressive global delay became obvious during the following months, associated

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Table 1. Metabolite levels before and under treatment (see Fig 1)

First Patient	Control Ranges (nmol/L)	Before Treatment	After 1.5 yr Treatment	After 3 yr Treatment	After 5.5 yr Treatment
Medication (mg L-Dopa/Cardidopa/kg)		0	10.0	6.2	8.0
Medication (5-OH-tryptophan mg/kg)		0	0	3.5	2.9
5-OH-tryptophan	<15	<15	n.d.	73	44
5-HIAA	87-247	<5	5	95	36
L-Dopa	<15	<2	<2	<2	<2
3-metoxo-dopa	<50	<50	476	780	459
HVA	240-713	84	346	181	109
BH ₄	20-49	22	26	24	14
BH ₂	<18	85	38	48	60
Neopterin	7-27	28	26	17	37
Sepiapterin	<0.5	N/A	4.4	2.4	0.8
Serotonin in serum	583-1811	n.d.	353	4611	2373
Prolactin in serum	43-375 mU/L	n.d.	57	564	698

Second Patient	Control Ranges (nmol/L)	11/03	02/04	03/05	01/06
Medication (mg L-Dopa/cardidopa/kg)		0	4	6.2	9.3
Medication (5-OH-tryptophan mg/kg)		0	1.6	1.6	2.3
5-OH-tryptophan	<15	<2	<2	<2	985
5-HIAA	87-247	8	7	6	136
L-Dopa	<15	<2	<2	<2	<2
3-metoxo-dopa	<50	<2	<2	1123	1352
HVA	240-713	50	31	87	95
BH ₄	20-49	27	18	11	<2
BH ₂	<18	34	66	33	46
Neopterin	7-27	22	71	17	14
Sepiapterin	<0.5	131	n.d.	n.d.	n.d.
Serotonin in serum	583-1811	277	317	n.d.	1138
Prolactin in serum	2-20 ng/mL	36	153	20.6	32.2

All metabolite levels are given in nmol/L (except for prolactin in the second patient).
Abbreviations:
BH₂ = Dihydrobiopterin
BH₄ = Tetrahydrobiopterin
5-HIAA = 5 Hydroxyindolacetic acid
HVA = Homovanillic acid
L-dopa = Levodopa
n.d. = Not determined

with abnormal movements (intermittent dystonic movements of arms and legs, lateral or upper deviation of the eyes, of brief duration, without loss of consciousness). Atypical absences were suspected, but electroencephalograms and cerebral magnetic resonance imaging were normal. The routine biologic investigations were normal: lactate, pyruvate, amino acids, carnitine, acylcarnitine, organic acids. The neurologic status worsened. At 18 months of age, he had generalized spasticity and pyramidal signs, persistence of generalized and localized dystonic movements, and abnormal ocular movements lasting a few seconds but occurring many times a day. These ocular movements, in retrospect oculogyric crises, were initially misinterpreted as atypical absences. The motor symptoms exhibited diurnal variations, becoming worse at the end of the day. When the patient was 7 years old, he could only walk in the morning with a dystonic gait and spasticity. Later in the day, he had to use a wheelchair. Language delay and mental retardation were obvious. When the ocular movements were considered as nonepileptic oculogyric crises, the diagnosis of neurotransmitter disease was suspected and confirmed by cerebrospinal fluid analysis (Table 1). Growth has always been normal, initially between the 10th and 25th percentile, as was his weight, initially the 50th percentile then between the 75th and 90th percentile. His head circumference at birth was 32 cm, 54 cm at 9 years of age, and 54.4 cm at 12 years of age. Sexual maturity at age 12: pubic 2-3, genitals 2-3.

The second patient was born after a second normal pregnancy and delivery of nonconsanguineous Caucasian parents. Early development

appeared normal, but at 5 months of age, delayed motor and cognitive performances were suspected. This female manifested a generalized hypotonia; brief oculogyric crises occurred at the same age. Intensive etiologic investigations (including plasma acylcarnitines, carnitine, lactate and pyruvate, urinary organic acids, muscle biopsy, electroencephalograms, cerebral magnetic resonance imaging) were normal. When she was 1 year old, dystonic movements of brief duration, generalized or localized, appeared during rest or voluntary movement. Swallowing difficulties developed; the oculogyric crises persisted. During the following years, a slow improvement occurred: she walked on her own at 3 years of age, the hypotonia diminished and was replaced by pyramidal signs, always with dystonic movements and oculogyric crises. Mental delay was obvious, requiring special education (full intelligence quotient-Wechsler scale: 46). A marked diurnal sleepiness was frequently observed which was not epileptic. Oculogyric movements spontaneously disappeared when she was 10 years old. Growth and sexual maturity were normal (50th percentile and pubic 3, breast 2 respectively). Head size always was normal (50th percentile). Cerebral palsy was suspected despite normal electroencephalograms and cerebral magnetic resonance imaging. Three years later, a cerebrospinal fluid neurotransmitter study was performed, leading to the diagnosis of sepiapterin reductase deficiency.

For both patients, the neurotransmitter metabolites 5-hydroxyindolacetic acid, homovanillic acid, 3-metoxo-dopa, and levodopa as well as tetrahydrobiopterin were measured in cerebrospinal fluid with high-

performance liquid chromatography and electrochemical detection as described elsewhere [2]. Dihydrobiopterin and neopterin were separated by reversed phase high-performance liquid chromatography using column switching and fluorimetric detection [2]. Levels of cerebrospinal fluid sepiapterin were determined by reversed phase high-performance liquid chromatography and fluorimetric detection with settings 425/530 nm [3]. These studies were completed by cerebrospinal fluid amino acid chromatography, plasma and fibroblast assays for sepiapterin reductase activity, and *SPR* gene mutation analysis [1,2].

Results

Cerebrospinal fluid neurotransmitter levels were highly pathologic, demonstrating a severe deficiency of the dopaminergic as well as the serotonergic neurotransmission (Table 1). There was a marked increase of cerebrospinal fluid sepiapterin. In the cerebrospinal fluid, 5-methyltetrahydrofolate was normal. Plasma amino acids were slightly increased or normal. Phenylalanine and tyrosine levels were normal, but a phenylalanine loading test (second patient) indicated a marked increase of phenylalanine (phenylalanine/tyrosine ratio at 1 hour (8.5 [normal = 4.1])).

Plasma serotonin levels were decreased (<360 nmol/L; normal \geq 580 nmol/L) in both patients, also in accordance with the diagnosis of sepiapterin reductase deficiency. Plasma prolactin levels were highly increased. A finding of elevated plasma prolactin points to a central dopamine deficiency as the release of prolactin is normally inhibited by central dopamine concentrations. The excretion of neopterin and biopterin in urine were repeatedly normal in both patients, as were activities of dihydropteridine reductase and aromatic L-amino acid decarboxylase. Sepiapterin reductase activity was deficient in fibroblasts of both patients (no detectable activity in each case). A homozygous mutation (g. 1397-1401 del AGAAC) in the *SPR* gene was present in the first patient, the parents being heterozygous for the same mutation. A homozygous nonsense mutation in exon 3 of the *SPR* gene was demonstrated in the second patient (mutation g. 751 A > T, not described so far). Lysine 251 is charged to a premature codon stop leading to a putative protein truncation (p. K251X). The familial study is ongoing.

Evolution Under Treatment

The first patient was treated from the age of 7 years, initially with levodopa during a short period and then with levodopa/carbidopa. The doses were slowly increased up to 10 mg/kg/day in 4 or 5 doses. Initiation of therapy was followed by a steady improvement of gross and fine motor abilities, a disappearance of oculogyric crises, and progress in intellectual abilities. A transitory worsening of the neurologic status occurred, with a loss of ambulation, during a too rapid increase of levodopa. One year and 3 months after the initiation of therapy, 5-hydroxytryptophan was added to levodopa/carbidopa, and progressively increased up to 4 mg/kg/day. Overall the improvement

was spectacular: pyramidal signs, dystonic gait, and tremor disappeared and muscle tone normalized during the two following years. Dystonic movements still persist but are diminished, appearing only during voluntary movement. After a total follow-up of 5 years under treatment, the child can now walk and run; he is playing soccer with his friends. He has normal handwriting and he speaks in normal, complete sentences in both German and Turkish. At age 12 his intelligence quotient was 57. Prolactin levels as well as cerebrospinal fluid neurotransmitter analysis were used to tailor and monitor therapy. Prolactin is still elevated but cerebrospinal fluid sepiapterin has decreased (2.4 nmol/L) but not normalized (Table 1).

With the second patient, specific rational therapy was initiated when she was 12 years old. A marked improvement was observed after only 2 months of therapy: she became more active and alert, with improvement of language (previously reduced to some words and some short nonsyntactic sentences) and of motor abilities, with a decrease of dystonic movements and improvement of motor skills. After a transitory worsening with again marked hyperkinesias, and even choreic movements, probably secondary to a too rapid increase of doses of levodopa/carbidopa, she improved again. The 5-hydroxytryptophan was introduced after 1 year of monotherapy (progressively, up to 3 mg/kg/day). With a total follow-up of 2 years, the neurologic status has completely changed: disappearance of pyramidal signs, marked improvement of language performance and school level (she was introduced in a normal school, with a delay of 4 years but with good results), and moreover, of intellectual abilities. She can now read, and her mathematics level corresponds to the third grade of primary school. There only persists a slight action dystonia, but handwriting and drawing are normal. She is now receiving 5 mg/kg/day of levodopa/carbidopa, and 3 mg/kg/day of 5-hydroxytryptophan, both in four daily doses. Prolactin is at the upper-normal level (431 μ UI/mL). It seems, however, that the marked intellectual and cognitive improvement observed during the first months of treatment is actually less impressive. School performances are better (a second-grade special high school instead of an establishment for deficient children). However, her intelligence quotient declined to a low subnormal level (full intelligence quotient 60, then 54, Wechsler Intelligence Scale for Children III), and moreover, the biologic controls manifested persistent cerebrospinal fluid abnormalities, despite apparent good treatment compliance and at a proper dose (Table 1).

Discussion

Sepiapterin reductase catalyzes the nicotinamide adenine dinucleotide phosphate-dependent reduction of various carbonyl substances including derivatives of pteridines. It plays an important role in the biosynthesis of tetrahydrobiopterin and thereby in the synthesis of cerebral neurotransmitters (Fig 1).

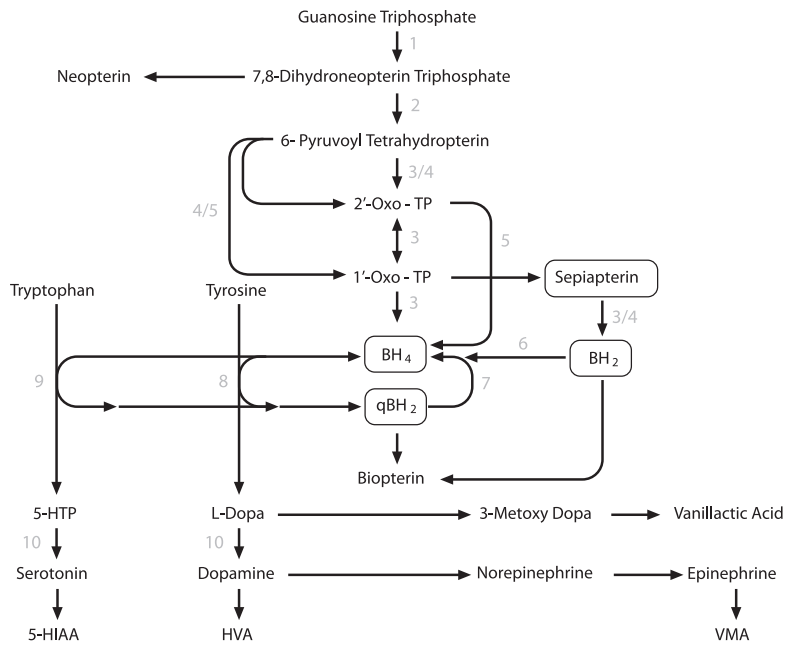


Figure 1. Pathways for the biosynthesis and catabolism of the biogenic monoamine neurotransmitters serotonin, dopamine, norepinephrine, and the pterins. 5-HTP = 5-hydroxytryptophan; 5-HIAA = 5-hydroxyindolacetic acid; HVA = homovanillic acid; 1 and 2-oxo TP = 1 and 2-oxo-hydroxytetrahydropterin; BH₄ = tetrahydrobiopterin; qBH₂ = quinonoid dihydrobiopterin; BH₂ = dihydrobiopterin; VMA = vanillylmandelic acid; 1 = guanosine triphosphate cyclohydrolase; 2 = 6-pyruvoyl-tetrahydropterin synthase; 3 = sepiapterin reductase; 4 = carbonyl reductase; 5 = aldose reductase; 6 = dihydrofolate reductase; 7 = dihydropteridin reductase; 8 = tyrosine hydroxylase; 9 = tryptophan hydroxylase; 10 = aromatic L-amino acid decarboxylase.

Pediatric neurotransmitter diseases cause severe, often progressive neurologic symptoms. An important subgroup are pterin defects generally resulting in progressive extrapyramidal movement disorders, especially parkinsonism-dystonia and chorea; however, the spectrum of individual symptoms and course of disease is wide, ranging from intermittent focal dystonia to severe, lethal infantile encephalopathies. Diagnosis of pterin defects is often facilitated by hyperphenylalaninemia but some depend on reliable quantification of metabolites in cerebrospinal fluid.

Sepiapterin reductase deficiency has been recently described in patients with a severe biogenic amine deficiency presenting without hyperphenylalaninemia [1,2]. Two forms of tetrahydrobiopterin deficiency presenting without hyperphenylalaninemia are known: dopa-responsive dystonia due to autosomal dominant mutations in the guanosine triphosphate cyclohydrolase I gene, i.e. Segawa disease [8], and the recently discovered sepiapterin reductase deficiency. This disorder can only be diagnosed by cerebrospinal fluid investigations of dopamine and serotonin metabolites (5-hydroxyindolacetic acid, homovanillic acid, 3-methoxy-dopa), and pterins (neopterin, dihydrobiopterin, tetrahydrobiopterin) (Fig 1).

The cerebrospinal fluid pterin profile in sepiapterin reductase deficiency is similar to that of dihydropteridin reductase deficiency (reduced dopamine and serotonin metabolites) with normal levels of dihydrobiopterin and tetrahydrobiopterin, this being at a low-normal or slightly lowered level. However, patients with the dihydropteridin reductase deficiency also present with hyperphenylalaninemia. The determination of cerebrospinal fluid sepiapterin and of the respective enzymatic activities differentiates the two conditions.

The normal level of biopterin is explained by the existence of a "salvage pathway" of biopterin synthesis [3] leading to reduction of the intermediate 6-pyruvoyl tetrahydropterin to dihydrobiopterin by additional reductases (carbonyl and aldose reductases). These enzymes are primarily active in the liver [2,3], which may explain the almost normal pterin availability in the liver. This fact also explains why cerebrospinal fluid dihydrobiopterin is elevated; but the levels of tetrahydrobiopterin remain at the low normal level because dihydrobiopterin is not efficiently converted to tetrahydrobiopterin owing to the low activity of dihydrofolate reductase in the brain.

The patients with sepiapterin reductase deficiency published so far exhibited clinical features similar to our patients, except in one case [6]. Development may be delayed from the first month of life, but in most cases, the neurologic abnormalities appear shortly afterward, between the second and the sixth month of life. The abnormalities consist of delayed milestones, generalized hypotonia, which may persist (2/14) or be replaced by limb spasticity, and pyramidal signs (often with proximal weakness). Three patients became stiff without being floppy before (Patients 3 and 7 of Neville et al. [7] and our first patient). Spasticity was lacking in only two patients [7]. Moreover, two major clinical signs were found: first, oculogyric crises, consisting of brief or long lasting upper or lateral deviation of the eyes, without loss of consciousness or abnormal movement (except for sometimes dystonic postures of the neck and trunk). They appear between the first and the tenth month of life. They were lacking in two cases. Secondly, dystonic movements were observed, appearing between 6 months and 2 years of life. They corresponded to action dystonia in most cases (10 of 12 cases for whom the information is available). A

marked diurnal variation of the motor abnormalities was observed in 9 of 11 patients in whom this sign was recorded. A Parkinsonian tremor was observed in six cases, often of early onset; choreic movements were also observed in four cases, essentially during a too rapid increase of levodopa treatment. Dysautonomic signs were observed in six patients (excessive sweating, diurnal sleepiness).

The other clinical abnormalities are less frequent: "bulbar" signs [7] (drooling, dysarthria, abnormal tongue movements; 4/14), "ataxia", probably not cerebellar ataxia nor sensory ataxia, but dystonic gait (4/14), occasional seizure (4/14), growth retardation (2/14), and Gowers' sign (1/14). Microcephaly was observed in two patients (the information was available for 7 patients). In one, presentation was initially with toe-walking. This condition disappeared before puberty, but at 15 years of age abnormal finger movements developed, followed by gait abnormalities, dystonia, and tremor [6].

In most cases, the diagnosis of cerebral palsy was suspected, despite usually normal magnetic resonance imaging cerebral investigations. A slow progression of motor abilities was observed in most cases, but in two, a progressive worsening of the neurologic signs occurred, suggesting a progressive degenerative disease. Finally, the motor handicap was more often severe, most of the patients, except for three, being unable to walk alone before the start of treatment.

Although most of these clinical signs are nonspecific, the early occurrence of oculogyric crisis and dystonic movements, as in other diseases affecting the neurotransmitters [9], may evoke the diagnosis of sepiapterin reductase deficiency and lead to a careful examination of neurotransmitters in cerebrospinal fluid.

If abnormalities in the metabolic pathways of dopamine, serotonin, bipterin, and their metabolites are revealed, a specific determination of cerebrospinal fluid sepiapterin is required and, if necessary, further enzymatic assays (dihydropteridin reductase, sepiapterin reductase) in fibroblasts. The phenylalanine loading test can reveal an abnormal increase of phenylalanine [10,11], and hyperprolactinemia is a useful indicator of the disease as well as helpful in tailoring treatment.

Such a widened approach to the diagnostic efforts in early-onset encephalopathy with motor delay during childhood is important, as we have at our disposal a simple treatment that provides spectacularly good results in long-term follow-up.

Some discrepancies, however, seem to exist between our results and those of Neville et al. [7]. Under levodopa therapy, exceptional positive results in relation to motor skills have always been obtained, often after only some days or even during the following hours after the onset of treatment. Dystonic postures decreased; spasticity, pyramidal signs, and oculogyric crisis disappeared. All the patients who were wheelchair bound became able to walk alone, to run, and even to practice sports. Only minor

residual motor dysfunction may persist, such as slight action dystonia, moderate chorea, or mild writer's cramp [7]. However, differences were observed concerning cognitive abilities. All the patients described by Neville et al. [7] exhibited moderate learning difficulties or significant cognitive impairment after several years of treatment, and in some cases despite an early onset of therapy (two patients were less than 13 months old). Unfortunately, Neville's study is a retrospective study, without biochemical data, and no intelligence quotient quantification or school levels were reported concerning those patients. In the present study, a marked improvement of cognitive abilities was observed especially concerning language and even school performances. Nevertheless, these children did not reach a normal intellectual or school functioning level, and intellectual difficulties persist; in addition, the clinical phenotype seems less severe than in Neville's patients, perhaps in relation with the different gene deletion. Overall in severely handicapped children, it is unusual to face such a situation in which a striking improvement of motor, language, and even, cognitive skills may be obtained.

Treatment of sepiapterin reductase deficiency following diagnosis relies on levodopa in combination with carbidopa and 5-hydroxytryptophan. Amounts administered have varied between 1 and 10 mg/kg/day in 3 or 4 doses. 5-hydroxytryptophan is administered similarly but usually in lesser amounts (1 to 8 mg/kg/day in 3 or 4 doses). Levodopa/carbidopa/5-hydroxytryptophan therapy should be introduced slowly and increased in steps of not more than 1 mg/kg over days or weeks. Some patients develop extrapyramidal symptoms with hyperkinesias as with both patients described herein. Some do not tolerate 5-hydroxytryptophan owing to gastrointestinal side effects. In the latter cases, monotherapy with levodopa/carbidopa may be sufficient. Additional supplementation of tetrahydrobiopterin may be considered. The effectiveness of treatment is monitored clinically by repeated careful evaluation by a pediatric neurologist including video documentation and follow-up of metabolite concentrations by consecutive lumbar punctures. In patients with high prolactin before levodopa supplementation, prolactin levels can aid monitoring of therapy. Levodopa/carbidopa/5-hydroxytryptophan therapy may reduce cerebrospinal fluid folates (CH₃-group trapping by levodopa to 3-methoxy-dopa) requiring folinic acid (5-formyltetrahydrofolate) substitution (15 mg/day).

Sepiapterin reductase deficiency is an autosomal recessive disease. Different types of the *SPR* gene mutations have been demonstrated up to now (g. 1397_1401del-AGAAC, g. 1437C >T, g. 1397 A > G, g. 1303 _ 1304 TC > CT in our first patient [1-4], mutation g. 751 A > T in the second patient) [1-4].

Another as yet open field of research concerns possible consequences of dominant mutations in the *SPR* gene. Studying patients with dopa-responsive dystonia not carrying a mutation in the guanosine triphosphate cyclohy-

drolase gene, Steinberger et al. [6] determined in one patient (out of 95 with primary generalized dystonia) that a heterozygous mutation in the *SPR* gene could be found in this adult patient, whose development had been normal during infancy. In this patient, the first neurologic signs appeared between 15 and 19 years; the major findings were partial dystonia of legs and arms, and intermittent voice tremor. The phenotype spectrum of sepiapterin reductase gene defects will probably become larger in the future and may include autosomal dominant haploinsufficiency, similar to guanosine triphosphate cyclohydrolase deficiency.

Addendum

The evolution of one of the two first patients described with sepiapterin reductase deficiency (pt 229 database) [1,4] is similar to those of our patients. After initiation of therapy, when he was 5 years old, paroxysmal dystonia and oculogyric crises disappeared and global development slowly improved. With a follow-up of 9 years, he is now able to speak in short sentences, but he was not able to attend a normal school, and persistent mental delay is obvious. Fine motor skills are poor. However, even if on walking and running he exhibits increased associated movements of the arms, he is now able to play some soccer and ride a bicycle. Somatic development is normal (weight, height, head circumference are on the 50-90th percentile) and he manifests normal signs of puberty. Parents' compliance with treatment (in addition to levodopa/carbidopa, e.g. 5-hydroxytryptophan and tetrahydrobiopterin) was poor; nevertheless, the improvement under levodopa therapy was effective for the patient's neurological and mental status.

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