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Case study

Sepiapterin reductase deficiency: Report of 5 new cases

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ABSTRACT

Background: Sepiapterin reductase deficiency is a rare, under-recognized, autosomal recessively inherited disorder of neurotransmitter metabolism.
Case report: Five new patients from 3 unrelated Saudi consanguineous families are reported. Symptoms began at 6 months, with delay to diagnosis averaging 8 years. All 5 patients presented with severe symptoms including axial hypotonia, dystonia, and cognitive impairment, associated with hyper-reflexia (4 patients), spasticity (4 patients), bulbar dysfunction (4 patients), and oculogyric crisis (2 patients) with diurnal fluctuation and sleep benefit. Cerebrospinal fluid neurotransmitters analysis showed a typical pattern with increased sepiapterin and increased 7,8-dihydrobiopterin. Analysis of the *SPR* gene identified 3 novel mutations: c.1A > G, c.370T > C, and c.527C > T. Patient one, with early diagnosis, is currently developing within the normal range. The 4 other patients showed significant improvement in their motor function, but only mild improvement in their cognitive dysfunction.
Conclusion: Our cases illustrate the difficulties in the diagnosis of sepiapterin reductase deficiency in infancy, and the importance of early recognition and management.

1. Introduction

Sepiapterin reductase deficiency (SRD) is a rare, inherited dopa sensitive neurotransmitter disorder, caused by autosomal recessive mutations in the sepiapterin reductase (*SPR*) gene. The sepiapterin reductase enzyme is the last step in the tetrahydrobiopterin cofactor biosynthesis pathway, and this tetrahydrobiopterin cofactor is required, among others, for catecholamine and serotonin biosynthesis.[1] In the early stages, the triad of paroxysmal stiffening, oculogyric crises and hypotonia are highly suggestive in some patients.[2,3] In other patients features are nonspecific, and usually remain under-recognized and misdiagnosed as cerebral palsy with hypotonia or

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dystonia.[1] In reporting the following 5 new cases identified from Saudi Arabia, we stress the importance of early diagnosis of this condition to provide timely and proper treatment.

2. Case reports

2.1. Illustrative case report (case 1)

We present a 24-month-old boy, the second child born to consanguineous Saudi parents. His 4-year-old sister, was diagnosed with hypotonic cerebral palsy with dystonia and received rehabilitation treatment. The parents described the boy's abnormal movements at 3 months of age as sudden stiffening of the whole body, extension of all extremities, and upward gaze lasting for several minutes often after meals, which we also observed during his hospital stay (video 1). These abnormal movements were, initially, mistaken for seizures. The pregnancy and delivery were uneventful. The birth weight was 3 kg, the length 49 cm, and head circumference 35 cm. He was seen for the first time at the age of 10 months. The growth parameters were normal, but there was significant developmental delay; mainly motor. He could not hold his neck, could not sit even with support, and was not reaching for objects. He had severe axial hypotonia, with normal deep tendon reflexes. He had a social smile, and could fix and follow. There was no babbling. The systemic examination was unremarkable, no dysmorphism, no organomegaly, or skin stigmata. Several episodes were recorded in the 24 h video-EEG, but no epileptiform discharges or any EEG correlate could be identified. The brain MRI was unremarkable, as was as tandem mass spectrometry, urine organic acid, ammonia, and lactic acid.

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The cerebrospinal fluid (CSF) neurotransmitter pattern was abnormal with elevated levels of sepiapterin, 14 nmol/l (normal range: not detectable), and 7,8-dihydrobiopterin 138 nmol/l (0–18 nmol/l), and low levels of 5-hydroxyindolacetic acid (5-HIAA), 57 nmol/l (170–412 nmol/l), homovanillic acid (HVA), 69 nmol/l (403–919 nmol/l), and a ratio of HVA to 5-HIAA, 1.2 (1.8–3.0).

Mutation analysis revealed a novel homozygous mutation in the *SPR* gene: c.527C > T (p.A176V), in exon 2, probably causing a nonfunctional enzyme. Both parents were confirmed carriers for the same mutation. His sister was tested, and found to have the same mutation (case 2).

He was started on Sinemet (L-dopa/carbidopa) at 1.5 mg/kg/day, gradually increased over 5 months until reaching 13 mg/kg/day. He showed significant improvement over one week; with complete cessation of the oculogyric crisis. Over the next month, he started to sit unsupported, communicate well by cooing, laughing, turning his head to voices, and recognizing his parents (video 2). Currently, he is 24 months old. His motor, language, and cognitive development are within the normal range. The medication was well, tolerated with no side effects observed; and he was recently started on 5-hydroxytryptophan.

2.2. Summary of the 5 cases

The main clinical, and genetic findings of our cohort of 5 patients from 3 unrelated Saudi consanguineous families, are summarized in Table 1. Symptoms began at 6 months (range: 3–12 months), with a delay to diagnosis averaging 8 years. All 5 patients presented with severe symptoms including axial hypotonia, dystonia, and cognitive impairment (only patient 1 had mild cognitive impairment), associated with hyper-reflexia in 4 patients, spasticity in 4 patients, bulbar dysfunction in 4 patients (drooling, dysphagia, dysarthria), and oculogyric crisis in 2 patients with diurnal fluctuation and sleep benefit. One patient showed microcephaly. The brain MRI and EEG findings were normal in all patients. Analysis of the *SPR* gene identified 3 novel mutations: c.1A > G, c.370T > C, and c.527C > T.

All 5 patients were treated with L-dopa/carbidopa (dose ranging from 1 mg/kg/day to 13 mg/kg/day) and 2 patients received a combination of L-dopa and 5-hydroxytryptophan. Patient 1 who had an early diagnosis is currently developing within the normal range, including the motor, language, and cognitive milestones. The 4 other patients had shown a significant improvement in their motor function, starting to walk, improvement of dystonia and spasticity, improvement of their sleep, but only mild improvement in their cognitive dysfunction.

3. Discussion

These 5 new patients share with the other approximately 50 cases of SRD reported in the literature[4] the core features of dopa-responsive, diurnally fluctuating movement disorder, and motor and cognitive delay (Table 1). Interestingly, oculogyric crises, in contrast with most previous cases, were absent in 3 patients.

The clinical presentation of SRD seems to be age specific. The triad of paroxysmal stiffening, oculogyric crises, and hypotonia, as observed in patient 1, tends to occur early in infancy, and should be defined as early clinical hallmarks of SRD.[1–5] Oculogyric crises, when present, are a good distinguishing sign. Over time, there is development of limb hypertonia, hyper-reflexia, dystonia, and more apparent diurnal fluctuation and sleep disturbance. Patients with SRD may pose a diagnostic challenge especially early and in those with milder phenotypes, or normal intelligence, or both. As pointed out by Friedman et al., SRD is commonly misdiagnosed as cerebral palsy.[1] The developmental delay and hypotonia may be the only initial symptoms without prominent movement disorder adding to difficulties in early recognition.

The diagnosis of SRD relies on CSF analysis of neurotransmitters and *SPR* gene analysis. Typically CSF analysis of neurotransmitters shows very low levels of neurotransmitter metabolites HVA, 5-HIAA and increased sepiapterin and increased 7,8-dihydrobiopterin and total biopterin. It was recently shown that urine sepiapterin excretion can be used as diagnostic marker for SRD.[6]

Twenty pathogenic variants have been reported in *SPR* (including our 3 mutations).[4] Known pathogenic variants are missense, nonsense, and frame-shift. Pathogenic variants have been found in all 3 exons, the 5′ untranslated region, and