

ternative explanation. Also, with the exception of AAO, the clinical symptoms of all MC were in line with classical PD.

For comparison of AAO data, we used published AAO of a large population-based cohort.⁶ The AAO of 197 idiopathic PD patients was 70 ± 11 years, whereas the AAO of MC with one mutation in our meta-analysis was 42 ± 16 years ($P < 0.0001$). It should be noted however, patients with young onset of PD are more likely to be included in genetic studies, leading to a bias in the observed AAO. In the present meta-analysis, MC with two mutations had a significantly earlier AAO, possibly indicating a dose effect of the mutation. These findings had not yet been demonstrated for *PINK1*, however, a similar effect is known for *Parkin*, another recessive PD gene.⁷

In conclusion, (1) two mutations within *PINK1* lead to a decreased AAO compared to one mutation; (2) the clinical picture is otherwise independent of the number of mutated alleles and comparable to that of idiopathic PD.

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Meike Kasten, MD
Section of Clinical and Molecular Neurogenetics
Department of Neurology, University of Lübeck
Lübeck, Germany
Department of Psychiatry and Psychotherapy
University of Lübeck, Lübeck, Germany

Charlotte Weichert, MD
Katja Lohmann, PhD
Christine Klein, MD*
Section of Clinical and Molecular Neurogenetics
Department of Neurology, University of Lübeck
Lübeck, Germany
*E-mail: christine.klein@neuro.uni-luebeck.de

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Sepiapterin Reductase Deficiency: Two Indian Siblings with Unusual Clinical Features

Video



Sepiapterin reductase deficiency (SRD) is a recently recognized potentially treatable inborn error of tetrahydrobiopterin (BH₄) metabolism without hyperphenylalaninemia.¹ It presents as an early onset autosomal recessive psychomotor retardation with dopa responsive mixed—motor and cognitive disorder.² Cerebrospinal fluid (CSF) neurotransmitter investigations are required for its diagnosis. The sepiapterin reductase (SPR) gene maps to chromosome 2p14-p12.³ We report two Indian siblings with SRD who masqueraded as “hypotonic cerebral palsy” and had severe hypersomnia as a presenting feature. We provide video documentation of their dramatic response to levodopa (L-dopa)/carbidopa therapy and continued long-term benefit. Genomic DNA analysis revealed a new mutation in these siblings.

A boy aged 10 years (Patient 1) and his sister aged 11 months (Patient 2) born to consanguineous parents were referred with diagnosis of “hypotonic cerebral palsy.” Patient 1 was found to have psychomotor retardation, floppy state, and hypersomnia at the age of 3 months. Frequent episodes of oculogyric crisis occurred from the age of 1 year. Mild spasticity and dystonic posturing appeared in the hands and feet at the age of 7 years. The motor symptoms showed sleep benefit. His global intelligence quotient was 36. He remained disabled and dependent for activities of daily living. Patient 2 was found to be floppy and hypersomnic at the age of 3 months. Oculogyric crisis occurred from the age of 4 months. Sleep benefit of the motor symptoms was not evident. There was no history of epileptic seizures in either of the patients. Video segment 1 shows the clinical status of the patients at the time of diagnosis. Routine haematological, biochemical investigations, and magnetic resonance imaging (MRI) of the brain were normal in both. Electroencephalograms (EEG) showed evidence of asymptomatic spike wave discharges in both the patients. CSF neurotransmitter investigations confirmed the diagnosis of SRD (Ta-

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TABLE 1. Biogenic amines and pterins in CSF

Patient 1 (10 yr)			Patient 2 (<1yr)	
Value (nmol/L)	Ref range	Test	Value (nmol/L)	Ref range
6	88–178	5HIAA	12	114–336
103	144–801	HVA	189	295–932
17	1.5–3.5	HVA/5HIAA	16	1.5–3.5
36	10–30	Bio	45	15–40
5.2	<0.5	Sepiapterin	12.4	<0.5

Raised sepiapterin levels in the CSF along with very low neurotransmitter metabolites and slightly elevated biopterin are correlative with the diagnosis of sepiapterin reductase deficiency.

5HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; Bio, biopterin.

ble 1). Genomic DNA analysis revealed the mutation c.413T>A or p.V138D which was found in the homozygous state in the 2 patients and in the heterozygous state in the parents. It was absent in the healthy sibling.

Both patients were treated with L-dopa/carbidopa (2 mg/kg/day). The response to treatment was dramatic and appeared within 12 hours of initiating treatment (video segment 2). They showed improvement in muscle tone, motor activity, and sleep pattern. Patient 1 needed downregulation of the dosage in view of drug-induced facial and limb dyskinesias. His cognition improved marginally. Both patients have been followed up periodically for the last 3 years and found to have persistence of clinical improvement (video segment 3).

SRD is a potentially treatable disease but may remain undiagnosed for several years due to lack of neonatal screening tests. Favorable response to L-dopa is observed even when the treatment is initiated late in the course of the disease.⁴ Prominent motor manifestations of SRD include a variable combination of spasticity, hypotonia, dystonia, parkinsonian tremors, and oculogyric crisis which may show diurnal fluctuation and sleep benefit.² The observations made in our patients widen the scope of phenotypic presentation of this disease. Generalized hypotonia was the dominant (Patient 1) or only (Patient 2) motor symptom in these siblings who were mistaken for “hypotonic cerebral palsy.” Hypersomnia which is a rare nonmotor symptom of SRD⁵ was also a presenting feature in these siblings increasing their disease burden. The presence of oculogyric crisis and sleep benefit drew our attention to a possible dopa responsive disease and lead to CSF neurotransmitter investigations. The video segments highlight the gratifying immediate and continued effects of treatment. The SR mutant allele p.V138D which has not been described previously may be related to the deficient SR activity in our patients.

In summary, a trial of L-dopa therapy may be justified in patients presenting as hypotonic cerebral palsy especially when other features like hypersomnia, oculogyric crisis, and sleep benefit coexist.

Legends to the Video

Segment 1. This segment depicts the clinical presentation of the siblings. The initial part of the segment shows the gross floppy state of Patient 1 along with mild dystonic pos-

turing of the hands and feet. In the latter part of this segment Patient 2 is seen sitting with a head drop and a floppy trunk.

Segment 2. This segment recorded one day after initiation of treatment with levodopa/carbidopa shows the dramatic improvement in the motor state of the siblings. Patient 1 is noticed to have drug induced facial and limb dyskinesias.

Segment 3. This segment was recorded after 3 years of continued treatment. The motor improvement has persisted in both the siblings.

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Gurusidheshwar M. Wali, MD, DM*
Neurospecialities Centre
Belgaum, Karnataka State
India
*E-mail: walidoc@hotmail.com

Beat Thony, PhD
Nenad Blau, PhD
Laboratory of Clinical Chemistry and Biochemistry
University Children's Hospital
Zurich, Switzerland

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