Sepiapterin reductase deficiency (SRD) is a dopa-sensitive neurotransmitter disorder, caused by mutation of the SPR gene located on chromosome 2p14-p12.1 To date, 31 patients with 14 mutations have been diagnosed (BIODEF database, update November 2010, www.biopku.org).

While classic tetrahydrobiopterin deficiencies present with hyperphenylalaninemia and deficiency of monoamine neurotransmitters, SRD is typically associated with normal phenylalanine levels in blood and pterins in urine2 and not detectable by neonatal screening for phenylketonuria. This implies how important it is to diagnose this condition clinically, in order to provide timely and proper treatment. A summary of the pathophysiology and biochemical pathway is provided by Bonafé et al.2

With the following case report and review of 21 published cases,2–10 we elucidate the clinical features of SRD as well as the diagnostic strategy and therapeutic approach.

CASE REPORT We present a 5-month-old girl, the first and only child born to consanguineous Turkish parents. The parents described the girl’s abnormal movements at 3 months of age as sudden stiffening of the whole body, extension of the extremities, upward gaze, and chewing movements lasting for several minutes often after meals, which we also could observe during her hospital stay. Pregnancy and delivery were uneventful. Birthweight, length, and head circumference were within normal ranges. During EEG, a few episodes with chewing movements could be recorded, but no epileptic discharges were evident. The brain MRI was unremarkable. We suspected gastroesophageal reflux and started therapy with omeprazole. The parents reported that the episodes be

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ministration to 3 times per day, at the age of 17 months, without any problems.

To date, our patient is developing within the normal range. At the age of 21 months, our patient has become a vivid girl with a strong will, who is very clingy to her mother. Worth mentioning are rather sweaty hands and feet, drooling, especially when the girl is focused, and behavioral issues with a tendency toward hyperactivity and distractibility.

**DISCUSSION AND REVIEW**

**Diagnostic workup.**

The diagnosis of SRD is straightforward via CSF analysis, showing a specific pattern: the levels of the pterins, in particular sepiapterin, are elevated, whereas the 5-hydroxyindolacetic acid and homovanillic acid concentrations are extremely low. This is a consistent finding, also in our case.

Additional fibroblast analysis confirms the enzymatic inactivity of sepiapterin reductase. Mutation analysis of the patient and parents is helpful for genetic counseling.

**Symptoms.** Data were available in all cases. SRD causes symptoms which are related to a disturbed dopamine and serotonin metabolism such as dystonia, speech problems, hypersomnia, and neurocognitive deficits. The spectrum of symptoms is listed in figure 1.

Figure 1 Summary of reported symptoms in patients with sepiapterin reductase deficiency in 22 cases sorted by frequency of occurrence (%)

Particular symptoms seem to be age specific. The triad upward gaze (often described as oculogyric crises in previous reports), paroxysmal stiffening, and hypotonia tend to occur early in infancy as one of the first symptoms, which was also the case in our patient, and should be defined as early clinical hallmarks of SRD. Other symptoms requiring higher motor skills and coordination, such as ataxia and dystardia, can be seen in later course. In adolescents and adults, hypersomnia seems to be one of the main complaints, next to dystonia. Figure 2 summarizes the age-related clinical hallmarks of SRD.

One interesting finding, which has not been reported previously, was the interruptability of the symptoms by voluntary movements. This phenomenon can perhaps be explained by the fact that the girl was still young and probably did not yet have significant neuronal damage. We do not have an explanation why, in a few cases, some symptoms like oculogyric crises disappear spontaneously in later course.

**Therapy.** The therapy strategy is straightforward by substituting both precursor substances L-dopa and 5-hydroxytryptophan, enabling a normalization of the CSF profile.
Data were available in 20 cases, including our case. In 9/20 cases, a combination therapy with L-dopa/carbidopa or benserazide (median 5 mg/kg/day; range 1.45–20 mg/kg/day) and 5-hydroxytryptophan (median 2.5, range 0.75–16 mg/kg/day) was administered. Eleven of 20 patients were treated with L-dopa/carbidopa (median 2 mg/kg/day, range 0.65–5.9 mg/kg/day) alone. The frequency of application was 2–5 times daily. Rarely, other substances were administered, such as selegiline and sertraline.2,4 Hypersomnia was treated well with melatonin in one case.4 Clinically the therapy provides a significant and rapid improvement (within hours) of the motor deficits, in some cases enabling immediate sitting, walking, and talking in patients who were not able to stand independently and speak more than a single word before treatment.3,7,8 Fourteen of 20 cases showed partial improvement of motor symptoms, whereas 6/20 cases could achieve a normalization of motor skills. Unfortunately, there are dosage-dependent side effects such as facial and limb dyskineties which were observed in 5/20 cases and chorea in one case, especially when the dosage of L-dopa was elevated too fast.7,9 In one case, L-dopa had to be discontinued due to transaminase elevations.4 Severe vomiting occurred in 2/8 cases with 5-hydroxytryptophan.2

Most patients seem to respond to a combination therapy with L-dopa and 5-hydroxytryptophan. Since some patients might easily get side effects, we recommend a very low starting dosage of about 0.5 to 2 mg/kg/day. Because of the short half-life period of L-dopa, the ideal application rate would be at least 3 times daily. For follow-up the analysis of prolactin levels in serum has shown to be a useful surrogate parameter for dopamine metabolism, if it was elevated prior to therapy.4,6

Neurodevelopmental outcome. To date, our patient is developing well within normal range. Though we observe a certain hyperactivity and distractibility, at this time it is very difficult to interpret and too early to try to define the neuropsychological profile of affected individuals.

In 18/21 previously reported cases, treatment with L-dopa alone or with 5-hydroxytryptophan did not have any significant influence on cognitive performance.2–10 The cognitive impairment ranges were defined as mild to severe, with an IQ ranging between 36 and 60 in 4 tested cases.4,9,10 There are only 2 patients who received treatment under 1 year of age. The first patient from Malta did not show an improvement in cognitive performance.7 For the other patient from India there were no data regarding the cognitive outcome.10 Three of 21 cases, 2 Greek siblings3 and 1 Dutch patient,9 had minor cognitive delay prior to treatment with L-dopa and were able to attend normal school in later course upon treatment.3

SRD shows specific clinical findings which may present in infancy as the triad of paroxysmal stiffening, upward gaze, and hypotonia. Later, childhood and adulthood dystonia with hypersomnia and ataxia may be striking. A combination therapy with L-dopa and 5-hydroxytryptophan improves the motor symptoms significantly in the majority of cases. The cognitive skills seem to be less influenceable if the patients already show significant neurocognitive impairment.

This highlights the importance of early diagnosis and treatment of this disorder as there is a chance of a normal developmental outcome.

AUTHOR CONTRIBUTIONS
Dr. Dill: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Wagner: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Somerville: study concept or design, analysis or interpretation of data, acquisition of data. Dr. Thony: analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, study su-
pervision. Dr. Blau: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Weber: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

ACKNOWLEDGMENT
The authors thank the parents for giving permission to publish this case report and David Meili and Anahita Rassi for technical assistance.

DISCLOSURE
Dr. Dill, Dr. Wagner, Dr. Somerville, and Dr. Thöny report no disclosures. Dr. Blau serves on a scientific advisory board for and receives research support from Merck Serono and serves on the editorial board of Molecular Genetics and Metabolism and as Communicating Editor for the Journal of Inherited Metabolic Disease. Dr. Weber serves on a scientific advisory board for Eli Lilly and Company; has received funding for travel or speaker honoraria from Eli Lilly and Company and Pfizer Inc; serves on the editorial boards of Arzneimittelforschung and Pädiatrie; and receives research support from Mepha (Teva Pharmaceutical Industries, Ltd.), Swiss National Foundation, Marie-Anna-Stiftung, and Stiftung für das kranke kind.

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Neurology 2012;78:e29-e32
DOI 10.1212/WNL.0b013e3182452849

This information is current as of January 30, 2012

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