A two-day-old newborn girl presented with intermittent episodes of hypertonia and hypotonia, increasing in frequency and intensity. Her parents were distant cousins, and her two sisters showed a normal development after a normal pregnancy. On admission, an EEG combined with video recording showed no focal epileptic activity during repeated short contractions in both arms and/or limbs. Seven days later, repeat EEG showed diffusely slowed monomorphic trace of rather low voltage, but again without epileptic characteristics. Brain ultrasound, performed on admission, revealed hypoplasia of the corpus callosum, enlarged lateral ventricles, and cystic formations in the white matter. MRI, performed at age 3 days, confirmed the hypoplasia of the corpus callosum found on ultrasound and showed a diffuse cystic degeneration of the supratentorial white matter, mainly involving the frontoparietal regions (Fig. 1).

The subsequent diagnostic work-up was based on a differential diagnosis between a possible metabolic disease and hypoxic-ischemic-related multicystic encephalopathy. Biochemical examinations revealed undetectable homocysteine plasma levels (0 mol/L, reference value: 15-100 micromol/L) in two separate occasions. Analysis of freshly catheterized urine was positive for sulphite (+/-40 mg/L), and showed an increased S-sulfo cysteine and taurine. A normal value of uric acid was measured in the plasma (4.6 mg/dL, reference 2.0 to 5.5 mg/dL), and there were no elevated urinary levels of xanthine (8 mmol/mol creat., reference value ≤ 66 mmol/mol creat.) or hypoxanthine (≤ 99 mmol/mol creat.). The latter measurements ruled out molybdenum cofactor deficiency and a diagnosis of isolated sulfite oxidase deficiency was established.

**Discussion**

Sulphite oxidase is a mitochondrial enzyme that plays a role in the oxidation of sulfite to sulfate, which is the final step in the metabolism of sulfur-containing amino acids (methionine, homocysteine) (1). With this step, two electrons are released, and these are mediated by cytochrome c to the electron transport chain, enabling the production of ATP (oxidative phosphorylation). Molybdenum is a necessary co-factor for the
Table I. — The metabolic pathway of sulfur-containing amino acids (methionine, homocysteine) and the role of sulfite oxidase.

activation of sulphite oxidase, and is also necessary for the activation of xanthine oxidase and aldehyde dehydrogenase. Reduced function of sulphite oxidase may either result from an isolated deficiency (SUOX gene, located on chromosome 12q) or from defective synthesis of molybdenum (MOCS1, MOCS2, and MOCS3 GEPH genes) (2). Regardless of the affected gene, the clinical presentation is almost identical.

When sulfite oxidase is deficient, homocysteine and methionine are metabolized via an alternative pathway, causing an accumulation of sulfite and its metabolites: taurine, S-sulfocysteine and thiosulfate (Table I). To date, the neuropathogenesis of this disease has not been fully clarified; it has been hypothesized that the accumulation of neurotoxic products or the lack of sulfate may eventually lead to energy failure at a cellular level (1, 2).

This hypothesis also explains the similarities in both clinical and neuroimaging appearance between sulfite oxidase deficiency and hypoxic-ischemic encephalopathy (3, 4). In fact, neuroimaging findings in isolated sulfite oxidase deficiency include cerebral and cerebellar atrophy, ventricular dilatation, cystic leukomalacia, hypoplasia of the corpus callosum, and cystic changes in the basal ganglia, resulting in a multicystic encephalomalacia similar to that found in the context of severe perinatal hypoxic-ischemic injury and twin-to-twin transfusion syndrome (4, 5). The clinical context and laboratory investigations are therefore crucial to make the diagnosis. Among biochemical assays, determination of total plasma homocysteine is considered a first-line investigation and shows greatly decreased values ($\leq 1$ mol/l); it is a sensitive and specific indicator of sulphite oxidase deficiency. This parameter can help the clinician and may lead to more specific investigations. For example, a specific analysis of plasma amino acids can be performed, demonstrating an increased concentration of sulfocysteine. Also, an increased concentration of thiosulphate in the urine supports the diagnosis. A low level of uric acid in serum and urine and an increased concentration of xanthine and hypoxanthine in the urine allow to differentiate between molybdenum cofactor deficiency and isolated sulfite oxidase deficiency (1, 2).

References