New approaches towards laboratory diagnosis of isolated sulphite oxidase deficiency

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Abstract

Background Molybdenum cofactor deficiency (resulting in combined deficiencies of the enzymes sulphite oxidase, xanthine dehydrogenase and aldehyde dehydrogenase) and isolated sulphite oxidase deficiency are inherited metabolic diseases which follow an autosomal recessive trait of inheritance. Detection of these diseases in selective screening for inborn errors of metabolism is not easy because relevant metabolites are either not routinely determined or are unstable.

Methods We have searched for additional markers for these diseases and studied plasma total homocysteine (determined by enzyme immunoassay) and S-sulphonation of transthyretin (assessed by electrospray ionization mass spectrometry).

Results and conclusion We found total homocysteine concentrations below the limit of quantification (< 1 μmol/L) in all samples of patients with sulphite oxidase deficiency studied in this regard and that the proportion of S-sulphonated transthyretin is clearly increased in such samples. Our observations suggest additional tools for selective screening and diagnostic work-up of patients suspected of having sulphite oxidase deficiency.

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Introduction

Although there is some variability in the severity of symptoms and age of onset, patients with molybdenum cofactor deficiency and isolated sulphite oxidase deficiency generally present with a severe and often fatal disease.¹ Key clinical symptoms include untreatable severe convulsions starting soon after birth. Although molybdenum cofactor deficiency can often, but not always, be diagnosed following the detection of pronounced hypouricaemia³ because it results in combined deficiencies of sulphite oxidase, xanthine dehydrogenase and aldehyde dehydrogenase, isolated sulphite oxidase deficiency is easily missed because relevant metabolites such as sulphocysteine (detectable in the analysis of urinary amino acids) and sulphite are either not routinely determined or are unstable. After ahomocystinaemia had been reported for a patient with molybdenum cofactor deficiency³ and the accumulation of S-sulphonated transthyretin in patients with molybdenum cofactor deficiency had been found,⁴ we examined the use of total homocysteine and S-sulphonated transthyretin as markers for isolated sulphite oxidase deficiency.

Patients and methods

Three patients with isolated sulphite oxidase deficiency proven by mutation analysis and their parents participated in the study and provided plasma samples with heparin (two families) or EDTA (one family) as the anticoagulant. They were of Mexican-American, Chinese and Turkish origin. Clinical information on two of the patients has been published.⁵,⁶ Plasma homocysteine levels were determined with a commercially available enzyme immunoassay (Axis Shield AS, Oslo, Norway). S-Sulphonated transthyretin was determined in plasma by a recently described method using electrospray ionization mass spectrometry.⁷

Results

In the samples of all three patients, the concentration of total homocysteine was below the quantification limit of 1.0 μmol/L. In contrast, their parents’ total...
Figure 1. Deconvoluted spectra obtained by electrospray ionization mass spectrometry of transthyretin from a patient with isolated sulphite oxidase deficiency (a) and from a control individual (b). A, free transthyretin; S, sulphonated transthyretin; B, cysteinyltransthyretin; C, cysteinylglycinyltransthyretin; D, glutathionyltransthyretin. For peak assignment see also Ref. 6.
homocysteine concentrations in plasma appeared normal (median 7.8 µmol/L, range 2.9–11.7 µmol/L). Only the patients’ samples presented with high signals of S-sulphonated transthyretin (see Fig. 1). The peak height ratio of S-sulphonated transthyretin and other oxidized isoforms [(S)/(B+C+D); see Fig. 1] was increased for all three patients’ samples, yielding values of 8.5, 3.3 and 8.3 compared to recently reported control values of 0.14 (standard deviation 0.09, n = 57), which can be applied here. For the parents, the ratios (median 0.34, range 0.13–0.59) were close to normal values.

Conclusion
Undetectable total plasma homocysteine has previously been reported in molybdenum cofactor deficiency only. That disease and isolated sulphite oxidase deficiency have in common the accumulation of reactive sulphite, which may result in degradation of thiol compounds such as homocysteine.

Quantification of total homocysteine in plasma is widely available and inexpensive. A sample volume of less than 100 µL is needed for analysis in duplicate. We recommend considering this measurement for selective screening for metabolic disorders, not only with regard to hyperhomocysteinaemias, but also for detection of sulphite oxidase deficiency by hypohomocysteinaemia. Furthermore, in view of the phenotypic variations of isolated sulphite oxidase deficiency (and molybdenum cofactor deficiency), any pronounced hypohomocysteinaemia observed in another context deserves careful investigation. Assessment of the peak height ratio of S-sulphonated transthyretin and other oxidized isoforms provides another tool which can contribute to the diagnosis of sulphite oxidase deficiency. Notably, S-sulphonated transthyretin in plasma may be more stable than S-sulphocysteine in urine.

Any laboratory diagnosis using this approach should, however, be confirmed by enzyme and DNA analyses which will allow distinction between isolated sulphite oxidase deficiency and molybdenum cofactor deficiency.

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References

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