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Increase in urinary purines and pyrimidines in patients with methylmalonic aciduria combined with homocystinuria

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ABSTRACT

Background: Methylmalonic aciduria combined with homocystinuria (MMA–HC) is the biochemical trait of a metabolic disorder resulting from impaired conversion of dietary cobalamin (cbl, or vitamin B_{12}) to its two metabolically active forms. Effects on urinary purine and pyrimidine levels have not been described for this condition.
Methods: Urine samples were collected from three patients with methylmalonic aciduria combined with homocystinuria and from 70 healthy subjects. Urinary purine and pyrimidine levels were quantitated by the use of LC/UV–Vis and LC/ESI/MS.
Results: Higher urine levels of pyrimidines were detected with both methods in patients compared to controls.
Conclusion: Methylmalonic aciduria with homocystinuria is due to deficiency of the enzyme, cobalamin reductase. The enzyme defect leads to altered hepatic metabolism, which appears to modify circulating pyrimidine levels.

1. Introduction

Inherited disorders of cobalamin metabolism are rare conditions that have been classified on the basis of eight somatic cell complementation groups (cblA to cblH). Methylmalonic aciduria combined with homocystinuria (MMA–HC) is most frequently associated with cblC, in which there is reduced conversion of dietary cobalamin (cbl, or vitamin B_{12}) to methylcobalamin (MeCbl) and adenosylcobalamin (AdoCbl). CblC mutations inhibit production of MeCbl and AdoCbl through defects in cobalamin reductase [1].

In normal hepatic cells, MeCbl is produced in the cytosol, whereas AdoCbl is made in mitochondria. AdoCbl and MeCbl are the essential coenzymes for methylmalonyl-CoA mutase and homocysteine methyltransferase (also known as methionine synthase), respectively. Impaired biosynthesis of AdoCbl and MeCbl reduces activity of these enzymes [1,2].

Defective metabolism of several essential amino acids and other important metabolites occurs in MMA–HC. For example, methylmalonyl-CoA, the substrate of methylmalonyl-CoA mutase, is derived mainly from propionyl-CoA, a compound formed through breakdown of isoleucine, valine, threonine, methionine, thymine, uracil, cholesterol, and odd-chain fatty acids [3,4]. Further, higher plasma homocysteine and urine homocystine levels and lower plasma methionine levels occur due to lower homocysteine methyltransferase activity from impaired synthesis of MeCbl [2].

Clinical presentations of MMA–HC vary widely. Manifestations may include lethargy, vomiting, hyperammonemia, and metabolic acidosis. Progression to coma is not uncommon. If the patient survives the initial metabolic decompensation, failure to thrive, developmental retardation, chronic renal failure, and/or strokes may follow [5]. Treatment includes dietary protein restriction, intramuscular hydroxycobalamin administration, and oral supplementation with folic acid and betaine.

Neuropathophysiological studies have focused on effects of accumulation of putatively toxic organic acids, such as methylmalonate, propionate, and 2-methylcitrate. These compounds are believed to inhibit mitochondrial energy metabolism, involving the pyruvate dehydrogenase complex, the tricarboxylic acid cycle, the mitochondrial respiratory chain, and the mitochondrial salvage pathway of deoxyribonucleoside triphosphates. Inhibition of these processes may

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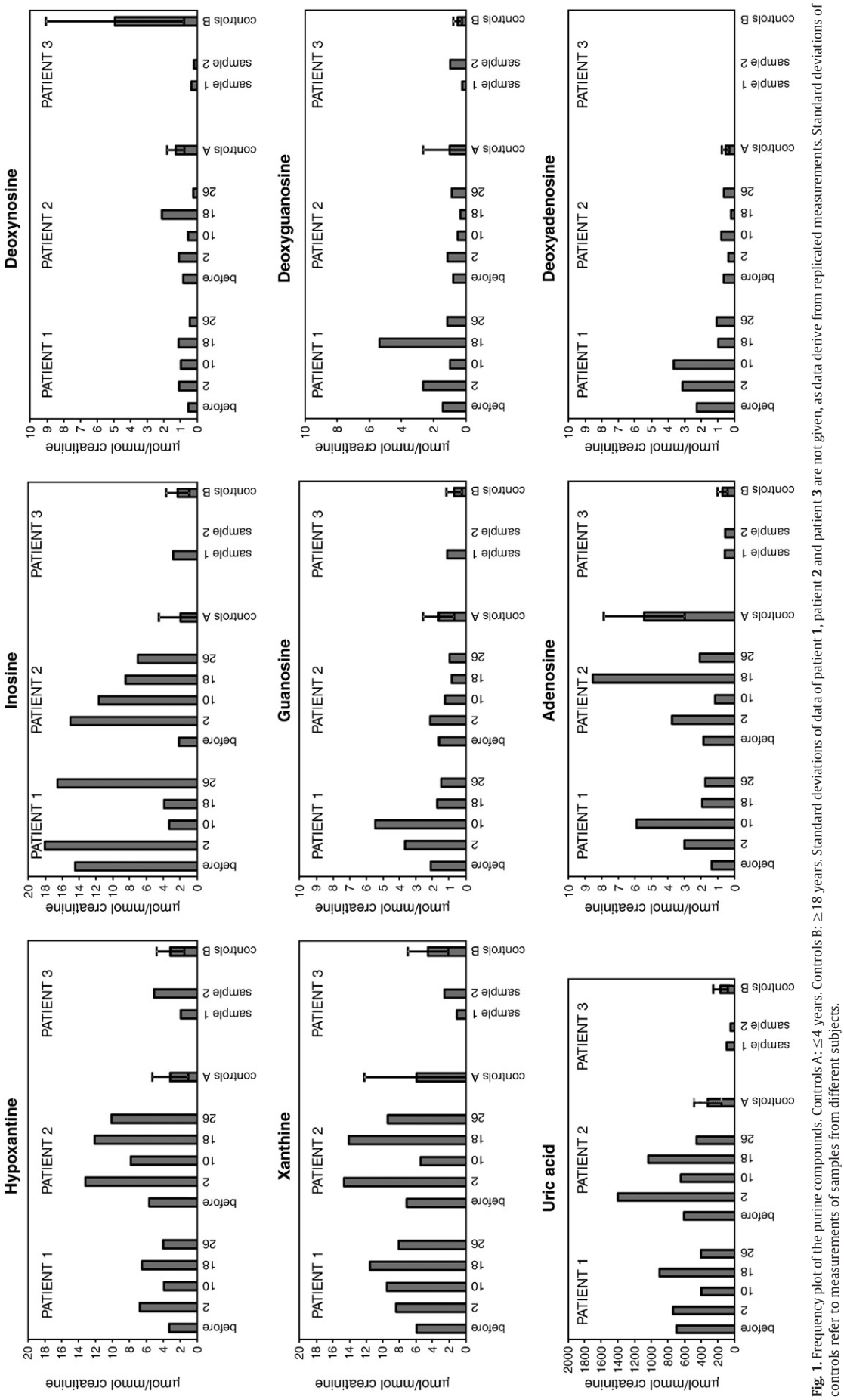

Fig. 1. Frequency plot of the purine compounds. Controls A: ≤4 years. Controls B: ≥18 years. Standard deviations of data of patient **1**, patient **2** and patient **3** are not given, as data derive from replicated measurements. Standard deviations of controls refer to measurements of samples from different subjects.