Case Report

Amino acid intolerance during prolonged total parenteral nutrition reversed by molybdate therapy[1,2]

Naji N. Abumrad,[3] M.D., Albert J. Schneider, M.D., Dinah Steel, R.N./N.P., and Lloyd S. Rogers, M.D.

ABSTRACT This report describes a patient suffering from intolerance to amino acids, mainly L-methionine, while on prolonged total parenteral nutrition. The patient displayed tachycardia, tachypnea, central scotomas, night blindness, and irritability, leading to coma while on total parenteral nutrition. The symptoms disappeared with discontinuation of the administered L-amino acid solutions. Biochemical abnormalities included high plasma methionine (110 to 130 μmol/L, normal 10 to 55 μmol/L) and low serum uric acid levels (0.5 to 1.4 mg/dl) associated with increased urinary excretion of sulfite (strong positive colorimetric reaction on Machery Nagel strips versus absent reaction in controls), thiosulfate (4.4 to 9.5 mM/d day or 30 to 50% of total sulfur excretion versus normal = 0.4 ± 0.1 mM/day or <2%), hypoxanthine (150 to 750 mg/24 h, normal <50 mg/24 h) and xanthine (700 to 2100 mg/24 h, normal <50 mg/24 h), with a decreased urinary excretion of uric acid (<100 mg/24 h, normal 300 to 520 mg/24 h) and inorganic sulfate (2.9 to 5.5 mM/day or 10 to 40% of total sulfur excretion versus 18.3 ± 1.2 mM/day in normal or 80% of total sulfur excretion). These abnormalities indicated that the underlying defect in sulfur amino acid metabolism occurred at the level of transformation of sulfite to sulfate, while that in uric acid production was at the level of transformation of xanthine and hypoxanthine to uric acid. The two enzymes catalyzing these reactions are sulfite oxidase, and xanthine oxidase, two metallo-enzymes containing molybdenum as part of their prosthetic groups. Treatment with ammonium molybdate (300 μg/day) improved the clinical condition, reversed the sulfur handling defect, and normalized uric acid production. This may represent the first case of diet-induced molybdenum deficiency in man. *Am. J. Clin. Nutr.* 34: 2551–2559, 1981.

KEY WORDS Total parenteral nutrtion, trace metal deficiency, molybdenum, sulfur-amino acids, uric acid

Introduction

The prolonged use of total parenteral nutrition (TPN), utilizing concentrated solutions of glucose and L-amino acids has been associated with several metal deficiency syndromes notably zinc (1), copper (2), and chromium (3). We describe in this report a unique case of TPN-associated molybdate deficiency.

Molybdenum has been known to have a functional role in the enzymes xanthine oxidase, aldehyde oxidase, and sulfite oxidase. It has been shown that molybdenum is incorporated into the apoprotein of these enzymes rendering them active (4). Xanthine oxidase functions in the disposal of the purine and pyrimidine metabolites in mammals (5). Sul-

[1] From the Departments of Surgery and Pediatrics, Upstate Medical Center, Syracuse, NY 13210 and the Departments of Surgery and Medicine, Vanderbilt University, Nashville, TN 37232.

[2] Address reprint requests to: Naji N. Abumrad, M.D., Clinical Research Center, Vanderbilt Medical School, 21st and Garland Avenue, Nashville, TN, 37232.

[3] Recipient of a Clinical Investigator Award (2M1-RR95) from the Division of General Clinical Centers Program, Division of Research Resources, National Institute of Health.

fite oxidase is essential in the handling of cystine and methionine, the sulfur-containing amino acids in the diet (6). Aldehyde oxidase is important in the oxidation of a wide variety of nitrogen containing heterocycles that are either abundant in nature or are manufactured in man (7). However, there are no reported cases where a dietary deficiency of this element has been directly implicated as a cause of poor growth, and subsequently it is still unknown whether this metal is essential in animal nutrition.

This report involves a patient who was maintained on TPN as the sole mode of nutrition for 18 months of his life. He developed recurrent mental disturbances leading on occasions to coma. These symptoms were also produced by the infusion of different solutions of amino acids and protein hydrolysates and by the infusion of a sodium bisulfite solution. The clinical symptoms were associated with the biochemical findings of mild hypermethioninemia, hypouricemia, hypouricosuria, and a very low excretion of inorganic sulfate in the urine. These and other findings indicated an acquired defect in the handling of sulfur-containing amino acids and in the catabolism of purines and pyrimidines, indirectly suggesting a deficiency of molybdenum. Treatment with ammonium molybdate (300 μg/day) greatly improved the clinical conditions with complete correction of the biochemical abnormalities.

Case report

The patient was a 24-yr-old man with Crohn's Disease of 12 yr duration. He underwent multiple small bowel resections with a resultant short bowel syndrome. His transit time from the mouth to the jejunostomy was 45 s. As a result he required maintenance on TPN solution as the sole method of nutritional support in the last 18 months of his life.

In the last 6 months of TPN administration, the patient developed a syndrome characterized by tachycardia, tachypnea, severe headache, night blindness, nausea, vomiting, and central scotomas, which progressed in 24 to 48 h to severe generalized edema, lethargy, disorientation, and coma. These symptoms were associated with high plasma methionine levels (250 to 300 versus normal <55 μmol/L) and low serum uric acid (0.5 to 0.9 versus normal 2.8 to 7.4 mg/dl). The syndrome was precipitated by the use of the commercially available amino acid preparations on the market (Freamine, Aminosyn, and Travasol). Protein hydrolysate solutions required a longer period to precipitate these symptoms. Albumin, fresh frozen plasma, fat emulsion, and dextrose solutions of various concentrations failed to produce the syndrome.

Infusion of a 0.05% solution of sodium bisulfite (1.8 g/day) led to the same syndrome over a 4-day period. Bisulfite is the antioxidant used in commercial preparations of amino acids intended for intravenous use. A modified antioxidant-free TPN solution (**Table 1**), prepared locally, and containing varying amounts of L-methionine was equally capably of causing the appearance of the above mentioned syndrome.

Metabolic studies performed, utilizing the modified TPN solution, showed hypermethioninemia, low urinary inorganic sulfate

TABLE 1
Amino acid concentrations of the TPN solutions used*

Amino Acids	Solution A†		Solution B‡
	mmol/L		
L-Threonine	28.5		14.3
L-Serine	47.6		23.8
L-Proline	41.3		41.3
L-Alanine	67.3		33.7
L-Valine	47.8		24.0
L-Cysteine	0.416		
DL-Methionine	30.2	L-methionine	4–10
Glycine	226.5		33.3
L-Isoleucine	45.0		22.5
L-Leucine	58.7		29.4
L-Phenylalanine	29.1		14.5
L-Tryptophan	6.4		3.2
L-Lysine	37.6		21.1
L-Histidine	12.6		7.7
L-Arginine	14.7		8.9

* All solutions consisted of 500 ml of 50% dextrose in water and 500 ml of amino acid solution, an electrolyte solution containing KCl 40 mEq/L, $MgSO_4$ 10 mEq/L, $CaCl_2$ 2.5 mEq/L, K_3PO_4 10 mEq/L and a trace element solution containing zinc 2.0 mg/ml, copper 0.04 mg/ml, manganese 0.20 mg/ml, and iodide 0.056 mg/ml. Each liter of TPN solution contained ~500 mg of ascorbic acid and 0.5 mg of folic acid. Vitamins A, D, and E were given once a week in the form of a multivitamin preparation (5 ml).

† A commercially produced amino acid solution and used prior to metabolic studies.

‡ Locally produced and Food and Drug Administration approved solution. The amounts of L-methionine were varied as described in the text.

excretion, and a high level of thiosulfate in the urine. Hypouricemia and hypouricosuria were also observed. Since the two enzymes involved in the catabolism of sulfur and purine compounds, sulfite and xanthine oxidase, are both molybdenum-containing proteins, the possibility of molybdenum deficiency was entertained. Consent for tissue assay of molybdenum and enzyme activity was refused. Therefore ammonium molybdate (300 μg/day) was started intravenously. After this treatment the patient showed no adverse clinical or biochemical signs to the TPN solution. Serum uric acid and plasma methionine levels and the excretion of sulfur, purine, and pyrimidine metabolites returned toward normal.

Methods

Individual amino acids concentrations in plasma were analyzed in a Technicon Amino Acid Analyzer. Urine was analyzed using a two-dimensional separation of amino acids by combined high voltage electrophoresis and solvent chromatography (8). Urinary thiosulfate was assayed using Sorbo's colorimetric method (9). Urinary inorganic sulfate and total sulfur were measured by titration (10). Urinary sulfite was assayed qualitatively using sulfite screening strips (Machery, Nagel and Co., Germany). Serum and urine uric acids were measured using a modified uricase enzyme method (10). Urinary levels of xanthines and hypoxanthines were measured using a high pressure liquid chromatography (Waters Instruments, MA) (11).

Three surgical subjects (diagnoses—gastric outlet obstruction, chronic ulcerative colitis, and chronic pancreatitis) necessitating prolonged TPN maintenance acted as controls. These subjects were placed on the modified TPN solution for a period of 3 wk. Biochemical determinations on plasma and urine were performed in the last 3 days of the maintenance period.

Results

Biochemical abnormalities

All metabolic studies were performed utilizing the modified TPN solution containing variable amounts of L-methionine. Plasma studies (**Fig. 1**) showed elevated methionine levels (110 to 130 μmol/L) well above those measured in the control subjects (10 to 55 μmol/L). Plasma taurine (~15 μmol/L) was slightly lower than normal (normal for taurine 20 to 100 μmol/L). Serum uric acid (0.5 to 1.4 mg/dl) was very low compared to the normal controls (2.8 to 7.4 mg/dl) as shown in **Figure 2**. Screening of the patient's urine revealed abnormalities in methionine metabolites (**Table 2**) and in oxypurines and uric acid excretion. Thiosulfate constituted the major sulfur metabolite excreted: 47% of urinary sulfur versus 2% in controls while inorganic sulfate excretion was only 30% of normal (versus 80 ± 2% in the control subjects). Sulfite, detected qualitatively, was strongly positive in our patient and negative in the control subjects. Urinary uric acid levels were very low as shown in Figure 2 (<100 versus control values of 300 to 500 mg/24h), while those of oxypurines were elevated as shown in **Figure 3** (xanthine excretion was equal to 700 to 1200 mg/24 h and that of hypoxanthine was equal to 150 to 750 versus an excretion <50 mg/24 h for xanthine or hypoxanthine in control subjects).

Dietary manipulations

In an attempt to improve the clinical condition of the patient a Food and Drug Administration approval was obtained for the local preparation of a modified TPN solution as already described and containing 12.3 instead of 23.7 mmol/day of the sulfur-containing amino acids. This resulted in a transient improvement in the clinical condition of the patient. Subsequently the symptoms recurred on the low sulfur load (12.3 mmol/day), and were only reversed by the discontinuation of the infusion. Plasma methionine levels were still 2- to 2.5-fold higher than normal (Fig. 1, period between −10 and 0 days). Urinary excretion of sulfur related metabolites improved yet no detectable improvement in oxypurine or uric acid excretion was observed for the same time period. After a 4-day period off TPN, an infusion of sodium bisulfite-TPN free solution (0.05%) in amounts similar to those contained in the commercially available amino acid preparations (1.80 g/day) resulted in a 2-fold increase in plasma methionine (**Fig. 4**) with a decrease in taurine (~5 μmol/L) and cystine levels (16 μmol/L, data not shown). By the 4th day of the infusion, the patient's symptoms recurred and the sodium bisulfite had to be discontinued.

Ammonium molybdate supplementation (300 μg/day) with a daily intake of sulfur amino acids equal to 12.3 mmol/day produced a progressive reversal of all biochemical abnormalities. Plasma methionine, cys-

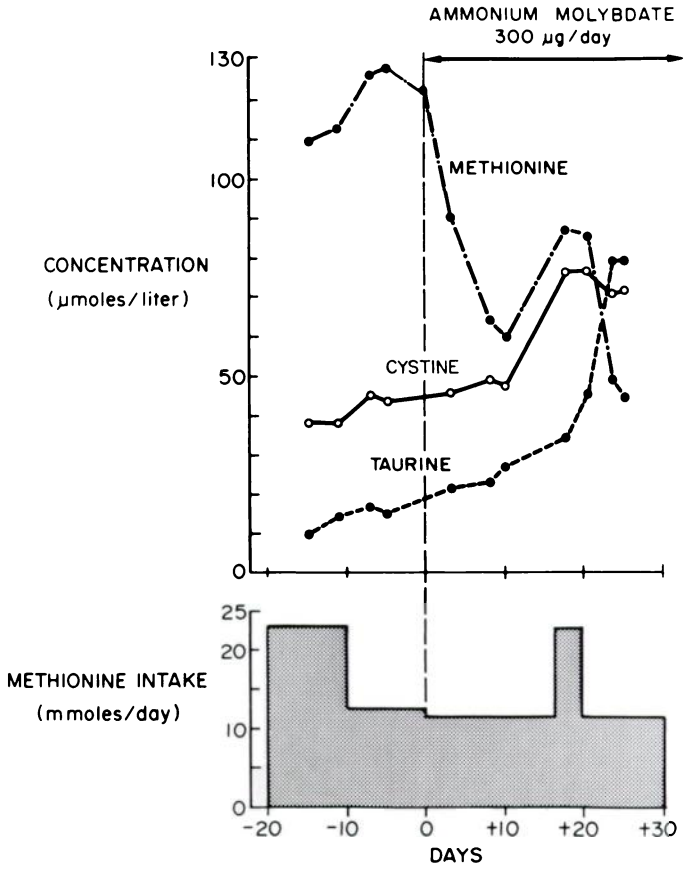

FIG. 1. Plasma levels of methionine, cystine, and taurine in response to TPN solution containing different loads of methionine, before and after treatment with 300 µg/day of ammonium molybdate. Each *point* represents a mean of two determinations. (Refer to Table 1 for amino acid content of the TPN solution.)

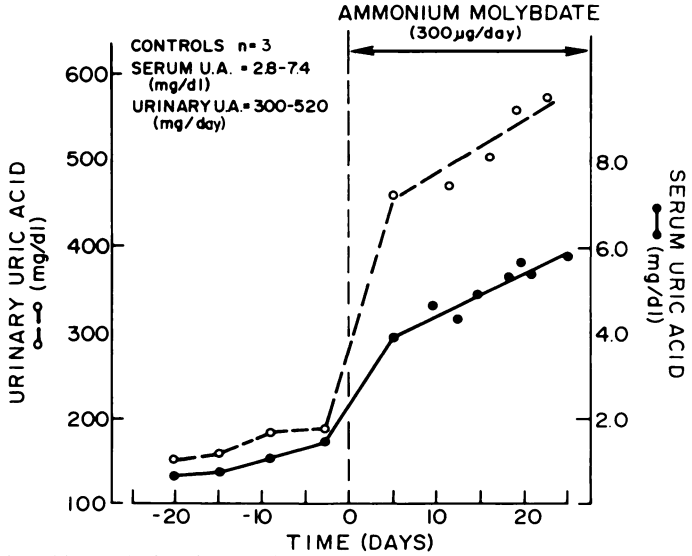

FIG. 2. Serum uric acid and 24-h urinary uric acid excretion before and after treatment with ammonium molybdate (300 µg/day). Methionine intake is the same as in Figure 1. Three surgical subjects maintained on the same TPN solution as in Table 1 (methionine intake = 23.9 ± 1.2 mM/day) acted as controls.

TABLE 2
Urinary excretion of sulfur-containing metabolites in response to different loads of methionine intake while on TPN*

	Control period			Ammonium molybdate			Controls†
				300 μg/day			
Study period (days)	−30	−15	−5	+12	+18	+21	3 days
Methionine intake (mM/day)	50.5	23.7	12.3	11.3	22.7	11.3	23.9 ± 1.2
Total sulfur excretion (mM/day)	29.2	14.8	10.2	11.1	12.5	17.8	23.1 ± 1.4 (97.3 ± 2%)‡
Inorganic SO_4 excretion (mM/day)	3.1 (11%)	5.5 (37%)	2.9 (28%)	9.1 (83%)	8.4 (67%)	15.9 (89%)	18.3 ± 1.2 (80 ± 2%)
Thiosulfate excretion (mM/day)	9.5 (33%)	7.1 (48%)	4.4 (43%)	1.1 (10%)	0.9 (7%)	0.9 (5%)	0.4 ± 0.1 (1.9 ± 0.9%)
Sulfite excretion (qualitative)	++	++	++	Faint	Faint	Faint	Absent

* For amino acid content in the TPN solution refer to Table 1.
† Three surgical subjects maintained on the same TPN solution acted as controls.
‡ All values in parenthesis denote the amount of the metabolites as percentage of total sulfur excreted.

tine, and taurine showed significant trends toward normal values. Urinary excretion of sulfur metabolites normalized with inorganic sulfate now becoming the major metabolite excreted. Thiosulfate excretion decreased from 30 to 50% to 5 to 10% of total sulfur excretion while sulfite excretion was qualitatively much lower. Uric acid production increased from <1.5 to 4 to 6 mg/dl and that of oxypurines decreased from >1000 to <200 mg/24 h (normal <200 mg/24 h) as shown in Figure 3. The metabolic clearance rate of methionine (calculated by dividing the infusion rate by the difference between the basal and steady-state plasma concentrations) increased from 100 to 250 ml/min before molybdenum supplementation to 400 to 600 ml/min after the metal was administered. The general improvement in the biochemical abnormalities was maintained even when the methionine load was doubled to 22.7 mmol/day (days + 18 to 20 in Figs. 1 and 2, and Table 1). An increase in plasma methionine was observed, however, the new levels stayed well below those preceeding the ammonium molybdate therapy. The patient was then maintained on the molybdate supplemented TPN (300 μg/day) solution containing the lower sulfur load (12.3 mmol/day). He showed no further intolerance to TPN administration.

Discussion

Molybdenum is utilized in small amounts in animal tissues for the function of sulfite, xanthine, and aldehyde oxidases (12). Sulfite oxidase is important in the assimilation and utilization of the sulfur-containing amino acids cystine and methionine that are present in the dietary proteins of mammals. It catalyzes the conversion of sulfite to sulfate the major excretory product of the transsulfuration pathway (5, 7) as shown in Figure 5. The effect of this enzyme on the recently described methionine transamination pathway (13, 14) is not clear. Aldehyde and xanthine oxidases belong to a group of enzymes collectively known as the molybdenum-sulfur flavin hydroxylases. Xanthine oxidase catalyzes the oxidation of xanthine to hypoxanthine to uric acid (5, 7) while aldehyde oxidase catalyzes the hydroxylation of a wide variety of heterocyclic nitrogenous compounds, aldehydes, purines, pteridines and pyrimidines (5, 7).

Despite the fact that these enzymes have been thoroughly investigated, their biological significance in many species is not very well understood. Individuals found to be genetically deficient in xanthine oxidase (15, 16) suffer from a mild myopathy secondary to deposition of hypoxanthine and xanthine crystals in muscle, and from the formation of renal xanthine calculi. Moreover inhibition of human xanthine oxidase by allopurinol causes no distress. Rats fed sufficient amounts of molybdenum antagonist tungsten to inhibit all xanthine and sulfite oxidase activities were observed to grow and reproduce normally (4). Sulfite oxidase deficiency however has very deleterious consequences in humans. Irrevere et al. (17) described the first case of

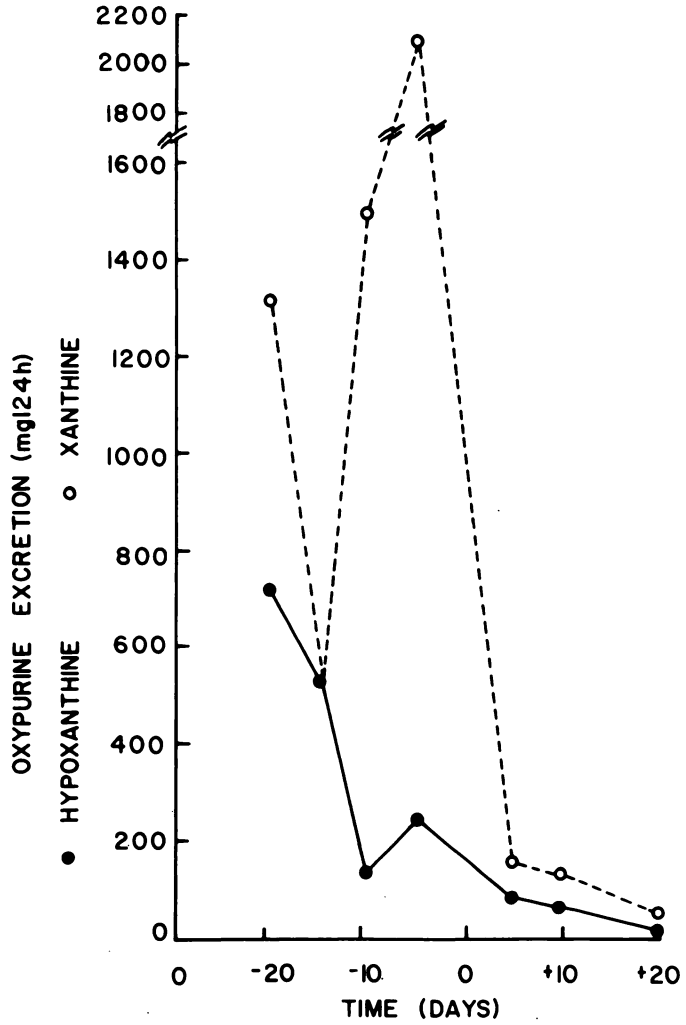

FIG. 3. Daily urinary oxypurine excretion (hypoxanthine—*closed circles* and xanthine—*open circles*) before and after treatment with ammonium molybdate (300 μg/day). Methionine intake is the same as in Figure 1. Levels of urinary xanthine excretion = <50 mg/day and hypoxanthine excretion = <50 mg/day in three surgical control subjects receiving same TPN solution for 3 wk.

hereditary sulfite oxidase deficiency. It involved a 2½-yr-old child with severe neurological abnormalities. The main biochemical feature was the virtual absence of excreted inorganic sulfate (18). More recently Shih et al. reported a hereditary partial sulfite oxidase deficiency in a 4-yr-old child with similar neurological findings and half of the normal sulfate excretion (19).

The clinical and biochemical findings in our patient are very similar to those described in the two cases of sulfite oxidase deficiency (17–19). Our patient manifested severe neurological abnormalities when stressed with a sulfur load. The relevant biochemical abnormalities included low inorganic sulfate excretion (≤30% of normal) with elevated excretion of sulfite and the abnormal sulfur metabolite, thiosulfate. Two differences are, however, worth noting in our patient. The first is the absence from the urine of the abnormal amino acid, S-sulfocystine, and second the persistent hypermethioninemia observed before molybdate supplementation.

High plasma methionine levels, without accompanying adverse reactions have been

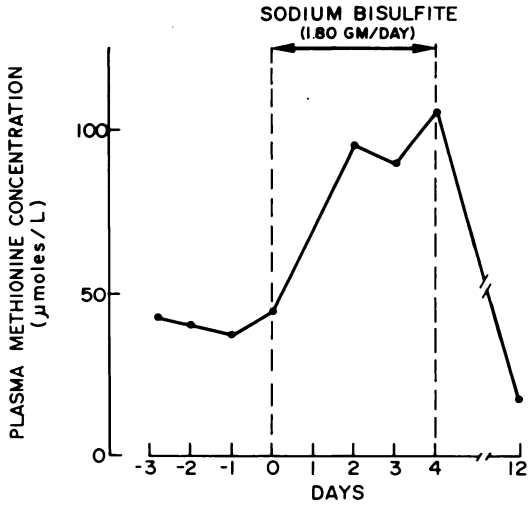

FIG. 4. Plasma methionine levels in response to a 0.05% sodium bisulfite–TPN-free solution (1.8 g/day) for a period of 4 days. No ammonium molybdate therapy was given. On day 4 the patient developed tachycardia, tachypnea, and mental irritability. The symptoms abated within 10 h of discontinuation of the solution.

previously observed in infants (20) and adult obese subjects (21) maintained on prolonged TPN using the amino acid solution Freamine. Plasma methionine levels in our patient increased to 270 to 280 μmol/L with the infusion of Freamine (data not shown). The hypermethioninemia has been attributed to the presence in Freamine of the nonmetabolizable D-form of methionine (20). The persistently elevated methionine levels we observed with the modified TPN solution (Table 1), containing only L-methionine, before molybdate therapy, argue in our case against the latter interpretation. The elevated methionine levels in our patient must have resulted primarily from a deficiency of sulfite oxidase precipitated by a prolonged inadequate molybdenum intake. In effect decreasing the sulfur load in the TPN solution infused did not improve methionine clearance and did not lower the plasma methionine levels except when supplemented with ammonium molybdate (Fig. 1). In addition we can postulate

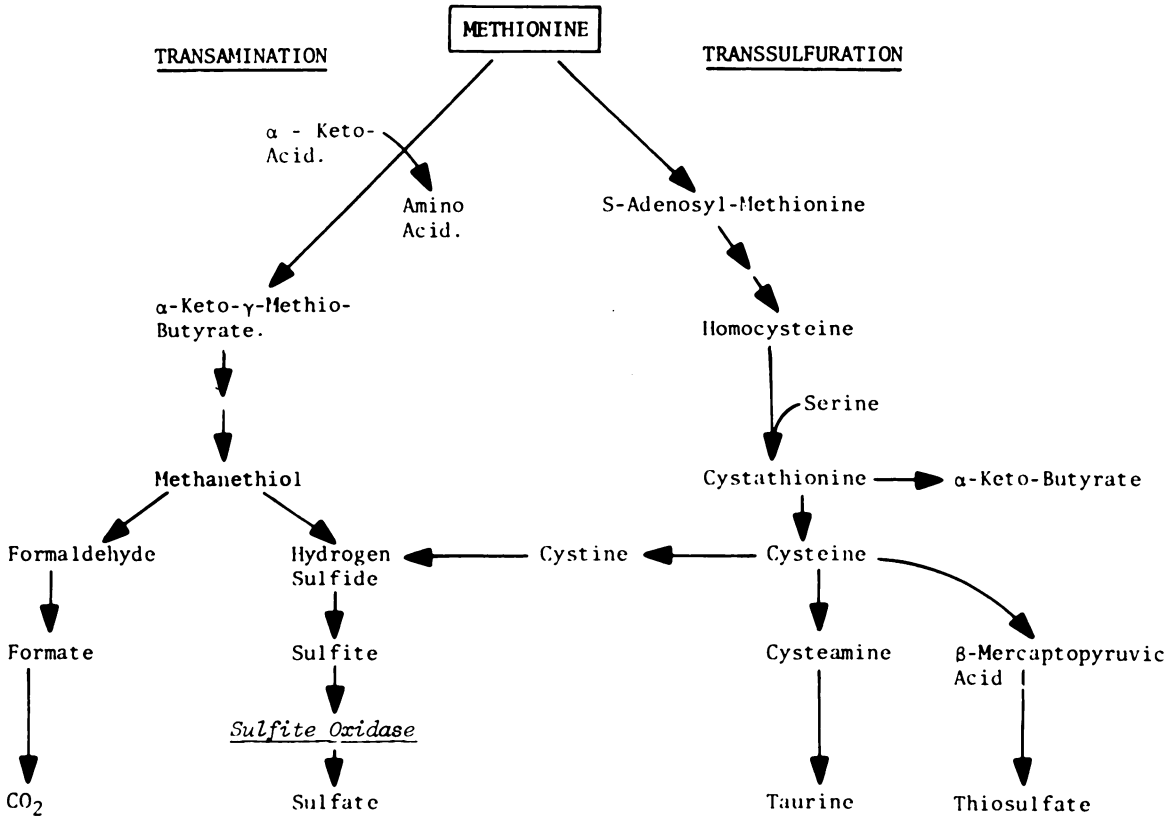

FIG. 5. Metabolic pathway of the sulfur containing amino acids, methionine and cystine (modified from References 14 and 19).

that the hypermethioninemia could partially be secondary to a block of methionine conversion to cystine, possibly as a result of accumulated sulfite. This would explain the low levels of cystine and taurine noted before molybdate therapy as well as the hypermethioninemia and subnormal cystine and taurine levels seen with a separate infusion of sodium bisulfite.

The mental disturbances and occasional coma seen with this patient are likely related to the deficiency of sulfite oxidase, since the few subjects reported to have xanthine oxidase deficiency have no associated neurological abnormalities (15, 16). It is not clear, however, how the deficiency of the enzyme leads to these neurological problems. Animals depleted of tissue sulfite oxidase were significantly more susceptible to neurological toxicity from injected sulfite (22). It is conceivable that the excess sulfite accumulating in the plasma could lead to the observed symptoms by a direct action on the central nervous system or through the formation of S-sulfonates which are toxic to the brain (23, 24). Low circulating levels of cystine (25) or inorganic sulfate (26) are other possible causes. In addition, hypermethioninemia cannot be ruled out (27). Recently Steele and Benevenga (13, 14) have shown that the transaminative pathway of methionine catabolism can lead to the formation of hydrogen sulfite and methanethiol, two compounds that are extremely toxic (14).

In summary, abnormalities of sulfur and uric acid metabolism in a patient maintained on TPN pointed to a diet-induced combined deficiency of two molybdo-enzymes, sulfite and xanthine oxidases. A similar but hereditary condition has been reported recently by Johnson et al. (28). Their patient exhibited neurological abnormalities associated with high levels of urinary sulfite, thiosulfate, xanthine, and hypoxanthine and with low levels of sulfate and urate. He was completely unresponsive to low sulfur diets or to molybdenum supplementation. The plasma molybdenum level was judged normal, while the liver molybdenum and cofactor levels were undetectable. The authors attributed the condition to an inborn deficiency in the molybdenum cofactor. The poor nutritional history of our patient and his response to a low methionine load supplemented with molybdenum suggest that his condition was TPN induced by the combined effect of high sulfur amino acid loading and very low molybdenum intake. This would then represent the first case of a diet-induced molybdenum deficiency in humans.

The authors thank Dr. Vivian E. Shih, from the Department of Neurology, Massachusetts General Hospital for assaying some of the urinary sulfur metabolites and the revision of the manuscript and for her continuous advice. Thanks is also extended to Dr. Kenneth Hande from the Department of Medicine, Vanderbilt Medical School for assaying the urinary oxypurines.

References

1. Abou-Mourad NN, Farah F, Steel D. Dermopathic changes in hypozincemia. Arch Dermatol 1979;115:956–58.
2. Vilter RW, Bozian R, Hess E, et al. Manifestation of copper deficiency in a patient with systemic sclerosis on intravenous hyperalimentation. N Engl J Med 1974;291:188–91.
3. Jeejeebhoy KN. Chromium deficiency, glucose intolerance and neuropathy reversed by chromium supplementation, in a patient receiving long term parenteral nutrition. Am J Clin Nutr 1977;30:531–8.
4. Johnson JL, Rajagopalan KV, Cohen HJ. Molecular basis of the biologic function of molybdenum: effect of tungsten on xanthine oxidase and sulfite oxidase in the rat. J Biol Chem 1974;249:859–66.
5. Bray, RC. Molybdenum iron sulfur flavin hydroxylases and related enzymes. Enzymes 1975;12:299–419.
6. Heimberg M, Fridovich I, Handler P. The enzymatic oxidation of sulfite. J Biol Chem 1953;204:913–26.
7. Krenitsky TA, Shannon MN, Elion GB, Hitchings GH. A comparison of the specificites of xanthine oxidase and aldehyde oxidase. Arch Biochem Biophys 1972;150:585–99.
8. Shih VE. Laboratory techniques for the detection of hereditary metabolic disorders. Cleveland, OH: CRC Press, 1973:20–5.
9. Sörbo B. A colorimetric method for the determination of thiosulfate. Biochim Biophys Acta 1957;23:412–16.
10. Hawk PB, Oser B, Summerson W. Practical physiological chemistry. New York: Blakiston, 1947:887–9.
11. Putterman GJ, Shaikh B, Hallmark MR, et al. Simultaneous analysis of substrates, products, and inhibitors of xanthine oxidase by high pressure liquid chromatography and gas chromatography. Anal Biochem 1979;98:18–26.
12. Coughlan MP. Aldehyde oxidase, xanthine oxidase and xanthine dehydrogenase: Hydroxylases containing molybdenum, iron-sulphur and flavin. In: Coughlan M, ed. Molybdenum and molybdenum containing enzymes. New York: Pergamon Press, 1980:119–86.
13. Steele R, Benevenga N. Identification of 3-methylthiopropionic acid as an intermediate in Mammalian methionine metabolism *in vitro*. J Biol Chem 1978;253:7844–50.

14. Steele R, Benevenga NJ. The metabolism of 3-methylthiopropionate in rat liver homogenates. J Biol Chem 1979;254:8885–90.
15. Watts RW, Englemann K, Klineberg JR, et al. Enzyme defect in xanthinuria. Nature (Lon) 1964;201: 395–6.
16. Wyngaarden JB. Hereditary xanthinuria. In: Stanbury JB, Wyngaarden JB, Frederickson DS, eds. Metabolic basis of inherited disease. New York: McGraw-Hill, 1978:1037–44.
17. Irrevere F, Mudd SH, Heizer WC, et al. Sulfite oxidase deficiency: studies of a patient with mental retardation, dislocated ocular lens, and abnormal excretion of S-sulfo-L-cysteine, sulfite and thiosulfate. Biochem Med 1967;1:187–217.
18. Mudd HS, Irrevere F, Laster L. Sulfite oxidase deficiency in man: demonstration of the enzymatic defect. Science 1967;156:1599–602.
19. Shih VE, Abrahms I, Johnson J, et al. Sulfite oxidase deficiency; biochemical and clinical investigations of a hereditary metabolic disorder in sulfur metabolism. N Engl J Med 1977;297:1022–8.
20. Winters RW, Heird WC, Dell RB, et al. Plasma amino acids in infants receiving parenteral nutrition. In: Greene HL, Holliday MA, Munro H, eds. Clinical nutrition update-amino acids. Chicago: AMA Publications, 1978:147–54.
21. Stegink LD. D-Amino acids. In:Greene HL, Holliday MA, Munro H, eds. Clinical nutrition update-amino acids. Chicago: AMA Publication, 1978:198–205.
22. Cohen HJ, Drew RT, Johnson JL, Rajagopalan KV. Molecular basis of the biologic function of molybdenum. The relationship between sulfite oxidase and the acute toxicity of bisulfite and SO_2. Proc Nat Acad Sci 1973;70:3655–9.
23. Gunnison AF, Palmes ED. Persistence of plasma S-sulfonates following exposure of rabbits to sulfite and sulfur dioxide. Toxicol Appl Pharmacol 1973;24: 266–78.
24. Olney JW, Misra CH, deGubareff T. Cysteine-S-sulfate: brain damaging metabolite in sulfite oxidase deficiency. J Neuropathol Neurol 1975;34:167–77.
25. Sturman JA, Gaull G, Reiha NCR. Absence of cystathionase in human fetal liver: Is cystine essential? Science 1970;169:74–6.
26. Percy AK, Mudd SH, Irrevere F, et al. Sulfite oxidase deficiency: Sulfate esters in tissues and urine. Biochem Med 1968;2:198–208.
27. Finkelstein JD. Enzyme defects in sulfur amino metabolism in man. In: Greenberg DM, ed. Metabolism of sulfur compounds. Vol VII. New York: Academic Press, 1975:587–90.
28. Johnson JL, Waud WR, Rajagopalan KU, et al. Inborn errors of molybdenum metabolism: combined deficiencies of sulfite oxidase and xanthine dehydrogenase in a patient lacking the molybdenum cofactor. Proc Nat Acad Sci 1980;77:3715–19.