

Thiamine deficiency and oxalosis¹

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SYNOPSIS Type I hyperoxaluria results from reduced activity of α -ketoglutarate: glyoxylate carboxylase, which is necessary for the synergistic decarboxylation of glyoxylate and α -ketoglutarate to α -hydroxy- β -keto-adipate.

Since thiamine pyrophosphate is a cofactor in the reaction, thiamine deficiency might be expected to result in tissue oxalosis. However, there was no significant increase in the incidence of renal oxalosis in 15 patients with Wernicke's encephalopathy at necropsy compared with controls.

It is possible that hyperoxaluria was present in these thiamine-deficient patients but at a urine concentration below that necessary for calcium oxalate deposition. It is also possible that the severity of the thiamine deficit required for hyperoxaluria exceeds that for the neuronal and cardiac manifestations.

Tissue calcium oxalate may be deposited as a result of increased intake, increased synthesis, or decreased excretion of oxalate or its precursors. Endogenous oxalate is derived primarily from glyoxylate (Williams and Smith, 1968a). Theoretically, increased quantities of oxalate may be produced if any of the alternative pathways of glyoxylate metabolism are defective.

One of these alternative pathways involves transamination with L-glutamate to glycine and α -ketoglutarate. The reaction requires pyridoxal phosphate as a cofactor (Williams and Smith, 1968a). Pyridoxine deficiency in animals results in hyperoxaluria and oxalosis (Gershoff, Faragalla, Nelson, and Andrus, 1959). In man, it leads to increased levels of oxalate excretion (Faber, Feitler, Bleiler, Ohlson, and Hodges, 1963). Administration of pyridoxine to normal persons and to patients with calcium oxalate stones causes decreased urinary oxalate (Gershoff, 1964). A second alternative pathway of glyoxylate metabolism is reduction of glyoxylate to glycolate. It is this reaction which is thought to be impaired due to a deficiency of D-glyceric dehydrogenase in so-called type II primary hyperoxaluria (Williams and Smith, 1968b). In a third alternative pathway, glyoxylate and α -ketoglutarate are synergistically decarboxylated to α -hydroxy- β -keto-adipate. The activity of an enzyme necessary for this reaction, soluble α -ketoglutarate: glyoxylate carboxylase, is markedly reduced in

patients with type I hyperoxaluria (Koch, Stokstad, Williams, and Smith, 1967). Thiamine pyrophosphate is a cofactor in this reaction. Therefore, thiamine deficiency might be expected to result in hyperoxaluria and oxalosis (Williams and Smith, 1968a).

In the following study, the tissues of patients with anatomical evidence of thiamine deficiency were examined for the presence of calcium oxalate crystals with particular attention given to the kidney, since the kidney is the common site for oxalate deposits in other types of oxalosis (Salyer and Keren, 1973). However, no increased incidence of oxalosis in presumed thiamine-deficient patients compared with controls was found.

Observation

At least five routinely prepared, haematoxylin-and-eosin-stained sections of kidneys from each case were examined for calcium oxalate crystals using partially polarized light. Sections of myocardium, bone, lung, pancreas, adrenals, and brain were also studied. The appearance of the crystals has been described previously (Salyer and Keren, 1973). Their calcium oxalate content was confirmed histochemically (Johnson and Pani, 1962).

Fifteen cases of presumed thiamine deficiency were found in the necropsy files (group A), ranging in age from 33 to 62 with an average of 49. All of the patients had anatomical evidence of Wernicke's encephalopathy, regarded as characteristic of

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thiamine deficiency (Pinkerton, 1971). In addition, two of the patients had clinical and anatomical findings consistent with beri-beri heart disease. Four of the patients developed acute renal failure terminally with serum urea nitrogen measurements greater than 50 mg/100 ml. Renal function was normal in the remaining 11 patients.

Control group B consisted of 50 patients with no renal disease and a terminal serum urea nitrogen less than 50 mg/100 ml. They ranged in age from 7 to 87 with an average of 56. Control group C was composed of 50 patients with terminal acute renal failure, defined by the presence of a serum urea nitrogen concentration greater than 50 mg/100 ml but of less than two months' duration (Salyer and Keren, 1973).

Focal deposits of calcium oxalate crystals were observed in the kidneys of three of the 15 patients with presumed thiamine deficiency. Two of these cases had terminal acute renal failure. In group B, the patients with normal renal function terminally, focal renal oxalosis was present in four of 50 cases. Calcium oxalate was found in 28 of 50 patients with terminal acute renal failure.

Discussion

This study was performed in an attempt to provide morphological evidence of hyperoxaluria in patients with presumed thiamine deficiency. Since thiamine pyrophosphate serves as a cofactor in the decarboxylation of glyoxylate, the metabolic pathway which is blocked as a result of an enzyme deficiency in type I primary oxalosis (Koch *et al.*, 1967), it would be expected that hyperoxaluria would result from thiamine deficiency (Williams and Smith, 1968a).

Although thiamine levels were not measured in these patients, characteristic findings of thiamine deficiency were present in all. However, calcium oxalate crystals were identified in the kidneys of only three of the 15 patients, two of whom had acute renal failure. This number does not differ significantly from either of the control groups. Kidney dysfunction of any aetiology is frequently associated with renal oxalosis, presumably due to decreased oxalate excretion (Salyer and Keren, 1973).

Thus, this study failed to demonstrate anatomical evidence of hyperoxaluria in thiamine-deficient patients. It is possible that hyperoxaluria was present in these patients but at a level below that required

for crystal deposition. However, urinary oxalate was stated to be normal in an unpublished study of patients with the clinical findings of the Wernicke-Korsakov syndrome (Williams and Smith, 1968a). Thiamine deficiency in the rat has been shown to lead to increased urinary glyoxylate but not oxalate (Liang, 1962). These biochemical studies do not completely rule out the possibility of hyperoxaluria secondary to thiamine deficiency. Conceivably, elevated plasma levels and urinary excretion of oxalate could be intermittent and variable, analogous to normocalcaemic hyperparathyroidism with urinary tract lithiasis (Wills, Pak, Hammond, and Bartter, 1969). The findings of this morphological study, however, provide additional evidence of the failure of thiamine deficiency to result in oxalosis.

Although, theoretically, hyperoxaluria should occur as a result of thiamine deficiency, it is possible that the severity of the deficit required for hyperoxaluria to develop is greater than that for the neuronal and cardiac manifestations. This would be in contrast to pyridoxine, since it appears that the level of pyridoxine needed to ensure minimal oxalate excretion is greater than the amount needed to protect against other manifestations of pyridoxine deficiency (Williams and Smith, 1968b).

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