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Chronic renal failure in methylmalonic acidaemia

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Abstract. The renal function of 12 patients with non vitamin B_{12} responsive methylmalonic acidaemia has been investigated. Eight patients had reduced glomerular filtration rates, but the plasma creatinine concentration was only raised in those with values of less than 40 ml/min per 1.73 m^2 surface area. The reduction in glomerular filtration was a function of the age and the severity of the disease. Plasma urate concentrations were increased in four patients but this may be secondary to the renal disease rather than its cause.

Key words: Methylmalonic acidaemia – Chronic renal failure – Tubulo-interstitial nephritis

Introduction

With early diagnosis and appropriate treatment an increasing number of patients with the more severe forms of methylmalonic acidaemia (MMA) are surviving longer. As a result, longer term complications that may have an important influence on outcome are becoming apparent. During episodes of metabolic decompensation patients with MMA are often dehydrated with raised plasma concentrations of urea and creatinine which normally resolve with treatment. However, chronic renal impairment in MMA is now becoming increasingly recognised, although only a few cases have been documented [4, 14, 15], and it has usually been assumed to be due to a secondary urate nephropathy. After one of our patients with mutase° MMA was found to be in chronic renal failure, we studied the renal function of a further 11 children with this disorder.

Case report

A male infant presented at the age of 3 months with weight loss and acidosis. The diagnosis of MMA was made at 7 months when a gross excess of methylmalonic acid was detected in his urine and confirmed by finding no methylmalonyl CoA mutase activity in white cells (Dr. K. Bartlett). There was no response to a trial of hydroxycobalamin. He was treated with a low protein diet and made good progress, growing and developing normally. However he had recurrent episodes of vomiting and acidosis requiring numerous hospital admissions and intravenous therapy. His plasma levels and urinary excretion of methylmalonic acid remained markedly raised (plasma methylmalonate 2–4 mmol/l, urine methylmalonate > 10 mmol/mmol creatinine). At the age of 4.5 years he was noted to have a persistently raised creatinine (> 200 μmol/l). Further investigations showed a glomerular filtration rate (GFR) of 9 ml/min per 1.73 m^2 surface area (SA), a tubular reabsorption of phosphate of 81% and a plasma urate of 213 μmol/l (normal 60–240). Renal imaging was normal. A renal biopsy showed a tubulo-interstitial nephritis (Fig. 1). There was no birefringent material seen on unstained cryostat sections under polarised light thus excluding the presence of urate or oxalate crystals. Immunofluorescence was negative. Following 18 months of greatly improved metabolic control his GFR has increased to 20 ml/min per 1.73 m^2 SA with a corresponding fall in his plasma creatinine from 224 μmol/l to 141 μmol/l.

Patients and methods

Twelve patients (including the child described above) with non vitamin B_{12} responsive methylmalonic acidaemia aged between 1 and 9 years were investigated (Table 2). Patients were studied when well and clinically stable.

Investigations

Renal function was assessed using standard methods. Random urine samples were collected for microscopy, culture and dipstick analysis for glycosuria and proteinuria. GFR was estimated from the plasma clearance of ^{51}-chromium ethylenediamine tetraacetic acid (^{51}Cr-EDTA) [5] and albuminuria assessed by the urinary albumin/creatinine concentration ratio (Ua/Uc) [3]. Renal tubular function was assessed from the tubular reabsorption of phosphate (TRP) [8], and the urinary lysozyme/creatinine ratio (Ul/Uc) [2]. In addition to the above, blood was taken for the measurement of plasma electrolytes, urate, and methylmalonate concentrations, the latter estimated by high performance liquid chromatography [13]. Urinary excretion of methylmalonate was also measured using this method. All children underwent abdominal ultrasound scanning to exclude structural renal abnormalities.

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Abbreviations: 51 Cr-EDTA = 51-chromium ethylenediamine tetraacetic acid; GFR = glomerular filtration rate; MMA = methylmalonic acidaemia; SA = surface area; TRP = tubular reabsorption of phosphate; Ua/Uc = urinary albumin/creatinine concentration ratio; Ul/Uc = urinary lysozyme/creatinine concentration ratio

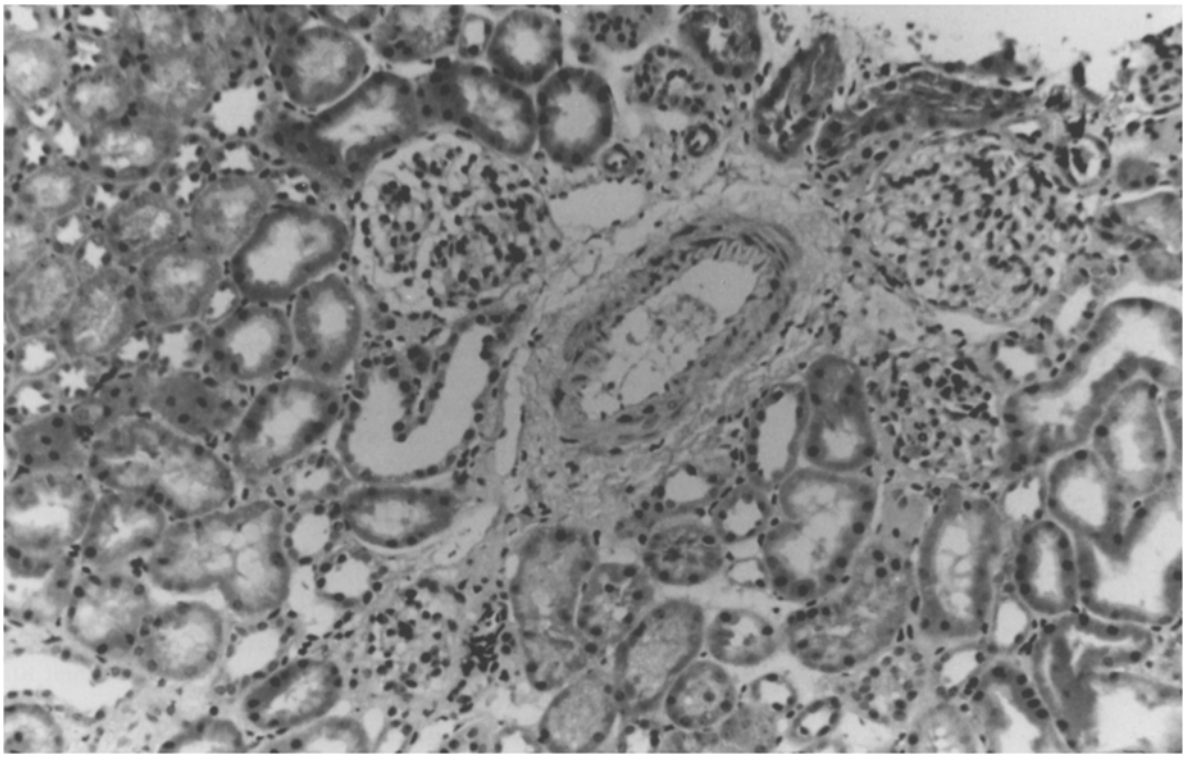

Fig. 1. Renal biopsy from patient 10 (MSB stain). The renal biopsy consisted of renal cortex and medulla. A small proportion of the glomeruli were sclerosed and many of the remainder showed an immature morphology with prominence of epithelial cells covering the capillary loops. There was, however, no tuft hypercellularity, capillary loops were widely patent and there was no thickening of tuft capillary walls. There were foci of tubular atrophy and occasional eosinophilic casts. The interstitium contained a patchy but prominent cellular infiltrate consisting of lymphocytes and histiocytes with occasional well formed lymphoid follicles containing germinal centres. Blood vessels appeared normal. The appearances were of a tubulo-interstitial nephritis with focal glomerulosclerosis, but with no evidence of primary glomerular disease

Table 1. Clinical severity score

Score	+0	+1	+2
IQ	> 80	60–80	< 60
Height	> 3rd percentile	< 3rd percentile	
Appetite	Normal	Partially tube fed	Fully tube fed
Protein tolerance (g/kg/day)	> 2.0	1.2–1.9	< 1.2
Acute episodes of acidosis requiring iv therapy in 2 years prior to investigations	None	< 3	> 3

Severity score

As the enzyme activity in vitro does not correlate well with clinical severity in non vitamin B12 responsive MMA [9] we have devised a scoring system (Table 1) based upon IQ, appetite, protein tolerance, growth, and the number of episodes of acute illness. These factors, in our [9] and others [11] experience, are a reflection of both long term and acute metabolic control. The maximum score is 9 (severe disease) and the minimum 0 (mild disease). The severity score for each child is listed in Table 2.

Table 2. Clinical details of patients studied

Patient	Age at diagnosis[a]	Age when investigated (years)	Protein tolerance (g/kg/day)	Severity score
1	1 week	1.6	2.0	3
2	3 days	2.1	1.0	9
3	10 months	4.9	1.5	4
4	2 months	2.5	1.0	9
5	3 months	2.1	1.0	8
6	9 months	5.8	2.2	0
7	8 months	2.4	1.9	2
8	2 weeks	1.5	2.0	5
9	3 days	6.0	1.2	4
10	7 months	4.8	1.0	5
11	4 days	1.0	1.2	2
12	4 months	8.6	1.4	5

[a] In all cases the diagnosis of MMA had been made by finding persistently raised concentrations of methylmalonic acid in urine. In addition, six patients had specific tissue enzyme assay; patients 4 and 5 had some residual methylmalonyl CoA mutase activity but no activity was found in patients 3, 6, 9, and 10. All these patients had been shown to be non responsive to a trial of hydroxycobalamin

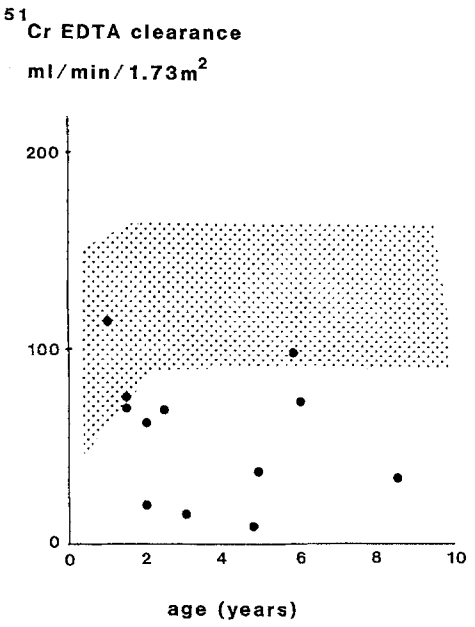

Fig. 2. ^{51}Cr-EDTA plasma clearance against age for each patient. The *shaded area* represents the normal range

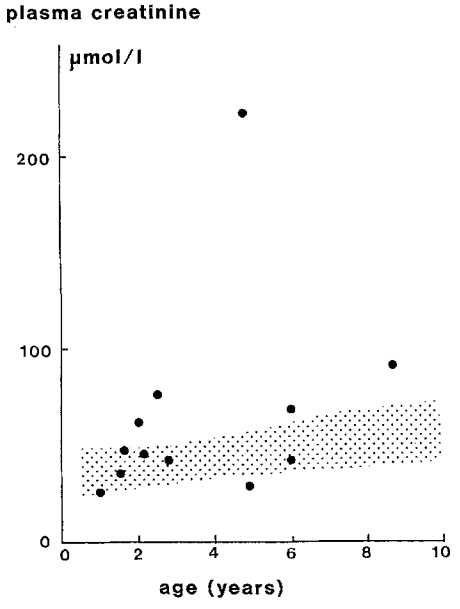

Fig. 3. Plasma creatinine against the age for each patient. The *shaded area* represents the normal range

Results

Glomerular function

Eight of the 12 children had a significantly reduced GFR as measured by ^{51}Cr-EDTA plasma clearance (Fig. 3). Five children (patients 2, 3, 4, 10 and 12) had clearance values of less than 40 ml/min per 1.73 m^2 SA, and these patients were the only ones with raised plasma creatinine concentrations (Fig. 3). Plasma clearance of ^{51}Cr-EDTA was repeated in 4 children (patients 1, 2, 4, and 10) following an interval of 6 months or more. In 2 children the clearance was unchanged and in 1 it had fallen from 74 to 53 ml/min per 1.73 m^2 SA. In only 1 child (patient 10, the child described in the case report) had the GFR increased. Only 2 children (patients 4 and 10) had a raised Ua/Uc ratio, both of whom had a GFR of less than 20 ml/min per 1.73 m^2 SA.

Table 3. Concentrations of methylmalonate (plasma and urine), urate (plasma) and glomerular filtration rates

Patient	Urinary MMA (mmol/ mmol creat)	Plasma MMA (mmol/l)	Plasma urate (µmol/l)	GFR (ml/min/ 1.73 m^2 SA) [repeat values]
1	7.3	0.1	126	74 [53]
2	5.5	5.0	670	19 [18]
3	3.6	0.6	678	38
4	1.1	0.7	703	16 [14]
5	9.5	0.3	137	62
6	0.7	<0.5	129	99
7	7.7	<0.5	228	69
8	2.7	<0.5	152	73
9	7.0	<0.5	228	72
10	22.5	8.4	235	9 [16, 18, 20]
11	10.6	<0.5	173	117
12	1.0	0.2	320	32

Tubular function

No patient had glycosuria or casts. The Ul/Uc ratio was raised in the same 2 patients with a raised Ua/Uc ratio, but only 1 child (patient 4) had a decreased TRP of 51% (Normal >80%).

Plasma urate

Four children (patients 2, 3, 4 and 12) had raised plasma urate concentrations (>240 µmol/l). There was little correlation between the urate concentration and the reduction in the GFR (Table 3).

Methylmalonate concentrations

There was no correlation between the random urinary methylmalonate/creatinine concentrations and the reduction in the GFR (Table 3). Very high concentrations of plasma methylmalonate were found in 2 of the children (patients 2 and 10) with GFRs of less than 20 ml/min per 1.73 m^2 SA.

Urine microscopy and renal ultrasonography

Urine microscopy and culture were negative in all the children at the time of study. No patient had structural abnormalities detected on renal ultrasound.

Discussion

This study suggests that renal impairments is common in patients with MMA. Of the 12 children investigated, 8 had reduced glomerular filtration rates, and of these, 5 had values of less than 40 ml/min per 1.73 m^2 SA. Of the 4 patients with a normal GFR, 3 had levels towards the lower limit of normal

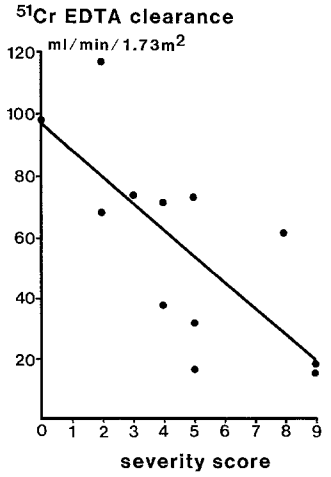

Fig. 4. The severity score against the GFR for each patient. The regression co-efficient is −0.71

and may have had some degree of renal impairment. The reduction was not due to a temporary disturbance of renal function since in the 4 children in whom the 51 Cr-EDTA clearance was repeated after an interval of more than 6 months, the GFR remained abnormally low. The degree of renal impairment appeared to be related to the clinical severity of the disease (Fig. 4).

In earlier reports it has been suggested that the nephropathy in MMA is secondary to a hyperuricaemia [4, 14]. However in 4 of the patients with a reduced GFR plasma urate levels were normal. Furthermore the renal biopsy from patient 10 (as described in the case report), who was in renal failure, showed no evidence of urate nephropathy. The aetiology of chronic renal disease in MMA, is not apparent from this study. Although it seems unlikely that uric acid nephropathy is the primary cause, it cannot be entirely excluded, since a non specific interstitial nephritis, initially caused by urate deposition, may persist after crystals have disappeared [6]. The renal biopsy from patient 10 showed a chronic tubulo-interstial nephritis. This was also the finding in a renal biopsy from a child with vitamin B_{12} responsive methylmalonic acidaemia reported by Broyer et al. [4]. Wolff et al. [15] reported a 3-year-old child who at the age of 5 months developed evidence of a proximal renal tubular acidosis. Creatinine clearance was within normal limits (101 ml/min per 1.73 m^2 SA.) as were clearances of Ca, PO_4, and uric acid. They postulated that this isolated proximal RTA might be causally related to methylmalonyl CoA mutase deficiency and might be due to a direct toxic effect of methylmalonate on renal tubular function. They also pointed out the structural similarity between maleic acid and methylmalonic acid. Maleic acid, when administered to animals, produces a generalised tubular transport defect closely resembling the Fanconi syndrome [7] and also results in a reduction in the GFR. It is thought that the effect of maleic acid on renal transport is due to its interference with renal mitochondrial metabolism while the effect on the glomerular filtration may be due to an increase in intrarenal adenosine [1]. In our study we did not look for evidence of renal tubular acidosis (which, in any case, may have been masked, since the majority of children were being treated with sodium bicarbonate): no child had a Fanconi-like tubular defect. However in renal disease the degree of tubular damage is known to correlate closely with a reduction in glomerular filtration [12] so that the reduced renal function in these children may have been a result of tubular damage caused by tubulo-interstial nephritis. Tubular function was not extensively investigated. In particular neither the ability to concentrate nor acidify the urine were studied, so that tubular disease may have been present even in those children with a normal Ul/Uc or TRP.

Plasma creatinine was a poor screening test of renal function in these patients. Mackensen et al. [10] found a positive correlation between the degree of interstitial fibrosis in renal biopsies from patients with interstitial nephritis and their serum creatinine concentrations, with the exception of a patient with anorexia nervosa and muscle wasting. In our study only those children with a very low GFR had a raised plasma creatinine. This might also be explained by a decreased muscle bulk and low protein diet with creatinine production subsequently reduced.

Although we have been unable to demonstrate a correlation between the reduction in renal function and the results of single plasma or urinary methylmalonic acid levels, it is possible that the reduction in glomerular filtration may be related either to plasma methylmalonate concentrations or the filtered methylmalonate load over a prolonged period of time. If this is the case, an improvement in the management of these children, leading to a reduction in the plasma methylmalonate would have a beneficial effect upon renal function. Indeed in patient 10 an improvement in his metabolic control has been associated with an initial doubling of his GFR from 9 to 18 ml/min per 1.73 m^2 and there has been no further deterioration in renal function over the past year.

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