Hyperammonaemic coma in ureterosigmoid urinary diversion

R.M. Oliver,* S. Talbot and G. Venkat Raman

Wessex Regional Renal Unit, Department of Renal Medicine, University of Southampton, St Mary's Hospital, Portsmouth PO3 6AD, UK.

Summary: We report on a patient with ureterosigmoid anastomosis, who presented with recurrent episodes of confusion, agitation and aggressive behaviour, culminating in coma. Investigations revealed profound hyperammonaemia, which responded to treatment with sodium benzoate and sodium phenylacetate. No definite cause was found for the abnormality, apart from possible urinary tract infection. The patient remains well on a protein restricted diet with mildly elevated levels of plasma ammonia.

Introduction

Hyperammonaemic encephalopathy is rare except in association with specific inherited enzyme defects within the urea cycle. Subjects who have undergone ureterocolic diversion have a well-known predisposition for certain metabolic complications, such as hyperchloraemic acidosis, hypokalaemia and osteomalacia. We describe a patient with bilateral ureterosigmoid diversion who presented with hyperammonaemic coma and discuss the possible aetiology and treatment.

Case report

A 58 year old female born with ectopia vesicae and treated by bilateral ureterosigmoid anastomosis at the age of 5 years, presented with fever, confusion and aggressive behaviour. She had been hypertensive for 18 years and was currently on atenolol but had never been on alkali supplements. No cause for her illness was apparent on physical examination, blood pressure was 120/80 mmHg and there were no focal neurological signs. A lumbar puncture revealed normal cerebrospinal fluid, a computed tomographic brain scan showed no structural abnormality and an electroencephalogram showed 3–5 second bursts of seizure activity. She was treated with phenytoin and made a spontaneous recovery and was discharged.

Six weeks later she was readmitted with a history of gradual onset of drowsiness and confusion. On examination she was apyrexial, semicomatose and exhibited myoclonic movements of her limbs. Within

24 hours she became deeply comatose with limb extension to painful stimuli, generalized hyper-reflexia and bilateral extensor plantar responses. Brain stem reflexes were intact and pupils were mid point and sluggish in reaction to light. Optic fundi were normal. Blood pressure was 170/105 mmHg. Lumbar puncture revealed normal cerebrospinal fluid. An intravenous urogram showed normal sized kidneys with contrast passing freely into the sigmoid colon. Blood screen for common poisons was negative. Blood counts and haemoglobin were normal. Serum urea was 10.4 mmol/l, creatinine 94 μ mol/l, bicarbonate 25.8 mmol/l, sodium 141 mmol/l, potassium 3.5 mmol/l, chloride 109 mmol/l, calcium 1.80 mmol/l (adjusted calcium 1.95) and phosphate 0.47 mmol/l. Other biochemical values including liver function tests were normal (serum bilirubin 7 μ mol/l, aspartate transaminase 47 IU/l, alkaline phosphatase 98 IU/l, gamma glutamyl transpeptidase 56 IU/l). Plasma ammonia concentration (measured by a kit – 'Ammonia Checker', DIC KYOTO DAIICHI, Kyoto, Japan) was grossly elevated at 236 μ mol/l (normal range 10–47).

Culture of a urine specimen obtained from the rectum produced a pure growth of *Strep. faecalis*. Plasma amino acid analysis revealed low levels of the branched chain amino acids and those involved in the urea cycle; glutamine concentration was within the normal range (Table I). A modest diuresis was induced by administering 6 litres of intravenous fluid/24 hour. A nasogastric tube was passed and lactulose administered to reduce nitrogen absorption from the bowel. Amoxycillin was administered enterally to reduce bowel flora and to treat presumed urinary tract sepsis. A high carbohydrate intake was instituted both enterally and parenterally and protein intake restricted to 20 g/day.

Correspondence: G. Venkat Raman, M.D., M.R.C.P.

*Present address: Southampton General Hospital, Tremona Road, Southampton, UK.

Accepted: 22 December 1988

Table 1 Plasma free amino acids ($\mu\text{mol/l}$) in a patient with hyperammonaemic coma. Isoleucine, leucine and valine are branched chain amino acids; the rest are involved in the urea cycle

	Normal range	Pre-treatment	Day 4	Day 7
Glutamate	19–48	47	79	77
Glutamine	495–775	569	614	561
Citrulline	38–57	16	17	24
Arginine	68–111	31	60	56
Ornithine	72–120	34	73	74
Isoleucine	48–96	16	54	62
Leucine	107–184	29	96	122
Valine	182–311	65	146	184

Ammonia excretion was encouraged by the administration of sodium benzoate (250 mg/kg body weight) parenterally for 48 hours and subsequently enterally. Sodium phenylacetate (250 mg/kg body weight) was administered enterally. The plasma ammonia levels fell progressively during the 5 days of treatment with these agents (Figure 1). Random urine samples were analysed for orotic acid excretion, which were normal, thereby excluding inherited urea cycle abnormalities such as ornithine transcarbamylase deficiency and citrullinaemia. The anticipated rise in the principal urinary excretory products of sodium benzoate (hippurate) and sodium phenylacetate

(phenylacetyl glutamine) was observed (measured by HPLC, but not quantitated).

After the initial 24 hours her condition improved steadily. Her recovery was complicated by an episode of supraventricular tachycardia associated with hypokalaemia (serum potassium 2.4 mmol/l). As her level of consciousness improved she exhibited transient aggressive and paranoid behaviour. She was established on modest dietary protein restriction (40 g/day) and discharged well 8 days following admission. At follow-up she has remained in good health with plasma ammonia levels mildly elevated at 50–70 $\mu\text{mol/l}$. Persisting subclinical liver pathology was suspected (even though there was no biochemical abnormality) – however, a percutaneous liver biopsy showed entirely normal appearances on light and electron microscopy. The unexplained hypocalcaemia and hypophosphataemia resolved spontaneously.

Discussion

Hyperammonaemia is rare except in association with congenital urea cycle abnormalities. It was first reported in association with urinary diversion in 1957.¹ It is thought that nitrogenous compounds, particularly urea, are degraded, in the intestinal lumen by commensal or pathogenic bacteria, to ammonia which crosses the bowel wall and thus enters the portal venous circulation and passes to the liver where under normal circumstances it is rapidly removed and resynthesized to urea for urinary excretion. In the presence of impaired liver function or abnormal portal-system venous communications, ammonia is able to enter the systemic circulation resulting in hyperammonaemia. This combination of hyperammonaemia and behavioural abnormality is most commonly caused by portosystemic encephalopathy.

Most cases of hyperammonaemia in urinary diversion have been reported in association with liver dysfunction including cirrhosis^{2,3} and patchy hepatic necrosis.⁴ However, one patient with hyperammonaemia and urinary diversion did not have any demonstrable liver pathology,⁵ as in our case. Interestingly, in two of the reports it was possible to reproduce the hyperammonaemic state by balloon occlusion of the rectum presumably resulting in urinary stagnation in the colon and enhanced ammonia absorption.^{3,4}

Hyperammonaemic coma has also been reported in association with normal urinary anatomy and normal liver function in a 49 year old female with unexplained neurogenic bladder and bladder calculi;⁶ similarly an 11 year old boy developed a profound hyperammonaemic state after an episode of urinary retention and hydronephrosis.⁷ In both these patients it is postulated that urinary infection associated with urinary stagnation in a distended bladder facilitated

Figure 1 Biochemical response to treatment in a patient with hyperammonaemic coma.

the passage of ammonia across the bladder wall to enter the internal iliac veins and thus the systemic circulation, by-passing the liver. Recently hyperammonaemia has been reported in 3 patients undergoing treatment for leukaemia, in whom there were no demonstrable urinary or hepatic abnormalities.⁸

Protein catabolism involves transamination of amino acids to glutamate which feeds nitrogen into the urea cycle in the liver. Alternative biosynthetic pathways of non-urea nitrogen excretion are used in the management of hyperammonaemic coma associated with inborn errors of urea synthesis.⁹ Administered benzoate conjugates with glycine to form hippurate which is rapidly excreted in the urine. Ammonia, extremely toxic to the body in its free state, is bound to glutamate to form glutamine. Glutamine present in relative excess in hyperammonaemia can be conjugated with administered phenylacetate to form phenylacetyl glutamine which is also readily excreted in the urine. In the case we describe, both benzoate and phenylacetate resulted in effective diversion of nitrogen catabolism away from urea formation and resulted in a rapid fall in plasma ammonia.

In our patient though there was no histological or biochemical evidence of hepatic abnormality, it would be interesting to speculate that there was subclinical hepatic dysfunction or portal-systemic shunting to account for her presentation and continued elevation in plasma ammonia levels. This may be supported by the finding of a low serum urea and paradoxically low glutamine concentrations in the face of high ammonia

concentration. Furthermore, the amino acids involved in the urea cycle were also low in the plasma. All these abnormalities could be accounted for by some degree of liver dysfunction. The low level of the branched chain amino acids probably reflects inadequate dietary intake, consequent upon her illness. The pure growth of *Strep. faecalis* (which was not a urea splitting organism) from her rectal urine probably represented a real urinary tract infection which might have contributed to the precipitation of coma through increased catabolism and nitrogen production.

Treatment of the hyperammonaemic state is aimed at reducing ammonia (and urea) generation and enhancing the excretion of molecular nitrogen by routes other than urea synthesis in the liver. Treatment with benzoate and phenylacetate was successful in our patient, in conjunction with dietary protein restriction, though it can be argued that mere rehydration and antibiotics would have been successful. Hyperammonaemia remains a rare but serious complication of ureterosigmoidostomy and the importance of prompt recognition and treatment cannot be overemphasized.

Acknowledgements

We thank Dr V. Walker, Senior Lecturer in Chemical Pathology, University of Southampton, for her help in analysis of urinary organic acids. We thank Mrs Susan Morris for typing this manuscript.

References

1. McDermott, W.J. Diversion of urine to the intestines as a factor in ammoniagenic coma. *N Engl J Med* 1957, **256**: 460–462.
2. Silberman, R. Ammonia intoxication following ureterosigmoidostomy in a patient with liver disease. *Lancet* 1958, **ii**: 937–939.
3. Egense, J. & Schwartz, M. Recurrent hepatic coma following ureterosigmoidostomy. *Scand J Gastroenterol* 1970, **5** (Suppl 7): 149–152.
4. Mortensen, E., Lyng, G. & Juhl, E. Ammonia induced coma after ureterosigmoidostomy. *Lancet* 1972, **i**: 496.
5. Kaufman, J.J. Ammoniagenic coma following ureterosigmoidostomy. *J Urol* 1984, **131**: 743–745.
6. Drayna, C.J., Titcomb, C.P., Varma, R.R. & Soergel, K.H. Hyperammonaemic encephalopathy caused by infection in a neurogenic bladder. *N Engl J Med* 1981, **304**: 766–768.
7. Ullman, M.A., Haecker, T.A. & Medani, C.R. Hyperammonaemic encephalopathy and urinary obstruction. *Engl J Med* 1981, **304**: 1546.
8. Watson, A.J., Chambers, T., Kamp, J.E., Risch, V.R., Walker, W.G. & Branislava, S.W. Transient idiopathic hyperammonaemia in adults. *Lancet* 1985, **ii**: 1271–1272.
9. Brusilow, S.W., Valle, D.L. & Batshaw, M.L. New pathways of nitrogen excretion in inborn errors of urea synthesis. *Lancet* 1979, **ii**: 452–454.