SHORT REPORT

Hyperammonaemia in critically ill septic infants

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Abstract

Three infants with subphrenic abscess, pyonephrosis, and obstructive ureterocolic respectively had grossly increased concentrations of plasma ammonia. This was considered to be a result of infections with urea splitting organisms. All died in spite of intensive care support, including specific measures to reduce plasma ammonia.

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Keywords: infant sepsis; urea splitting organisms; hyperammonaemic encephalopathy

Markedly raised plasma ammonia has been described in children with infections caused by urea splitting organisms in obstructive uropathy,¹⁻⁶ and after surgical procedures on the urinary tract.⁷ The only child who did not make a full recovery sustained a cerebral infarct.⁷

This report describes three infants who presented with critical septic illness, and plasma ammonia sufficiently raised to lead to consideration of an inborn error of metabolism. Hyperammonaemic encephalopathy is likely to have contributed to the fatal outcome.

Case 1

A 6 month old girl required ventilatory and cardiovascular support following the development of septicaemia secondary to Hirschprung's enterocolitis and laparotomy for peritonitis.

Initial plasma ammonia concentration was 469 $\mu\text{mol/l}$ (reference range $<70 \mu\text{mol/l}$), which rose to 912 $\mu\text{mol/l}$ on treatment with sodium benzoate, sodium phenylbutyrate, and haemofiltration. Despite intensive support the infant's condition continued to deteriorate and treatment was withdrawn following signs of irreversible cerebral damage.

During the course of her illness positive cultures included *Corynebacterium species*, *Escherichia coli*, and *Enterococcus faecalis* from blood culture; *Pseudomonas aeruginosa*, enterococcus, and coliform species from peritoneal fluid; *P aeruginosa* and *E coli* from endotracheal secretions; and *Clostridium difficile* from faeces.

Postmortem examination showed a subphrenic abscess, and a collection in the pouch of Douglas. Brain pathology showed widespread oedema and neuronal hypoxia.

Case 2

An 8 month old boy with an antenatal diagnosis of hydronephrosis presented with a two day history of vomiting, irritability, poor feeding, and convulsions. Initial ammonia of 299 $\mu\text{mol/l}$ was treated with sodium benzoate. Following an increase to 453 $\mu\text{mol/l}$, sodium phenylbutyrate and arginine were added, percutaneous nephrostomy was performed, and ammonia fell to $<50 \mu\text{mol/l}$. *Proteus mirabilis* was cultured from nephrostomy urine.

Despite intensive care support, fits continued, an electroencephalogram showed grossly decreased amplitude throughout, there was no response to pain, and active management was withdrawn.

Autopsy showed a grossly obstructed right pyonephrosis. Brain pathology showed ischaemic cell change in the cerebrum and cerebellum.

Case 3

A male infant presented at 16 days with a two day history of poor feeding, irritability, and loose stools. He was hypothermic and shocked and required ventilatory and inotropic support. Ultrasound showed duplex kidneys and increased parenchymal echogenicity. Blood culture grew *Staphylococcus aureus*; urine was sterile. Plasma ammonia of 458 $\mu\text{mol/l}$ rose to 716

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Table 1 Hyperammonaemia in children following infections

Reference	Age (y)	Sex	Pathology	Peak ammonia ($\mu\text{mol/l}$)	Organism	Outcome
1	3	Male	Prune belly	112	<i>Proteus mirabilis</i>	Normal
2	11	Male	Hydronephrosis	409	None found	Normal
3	10/12	Male	Ureterocolic	185	<i>Proteus</i>	Normal
4	2	Male	Prune belly	139	<i>Proteus mirabilis</i>	Normal
5	4	Male	Prune belly	175	<i>Proteus</i>	Normal
5	2	Male	Prune belly	61	<i>Proteus</i>	Normal
6	4	Male	Prune belly	217	<i>Proteus mirabilis</i>	Normal
7	6	Male	Antireflux surgery	320	None found	Blind, spastic tetraparesis

$\mu\text{mol/l}$ despite peritoneal dialysis and sodium benzoate. Acidosis progressed, pupils became fixed and dilated, and life support was withdrawn.

Autopsy showed bilateral duplex kidneys, pyelonephritis, renal infarction, and a large ureterocoele obstructing the vesicoureteric junctions. Brain pathology showed widespread hypoxic change.

Discussion

Gross elevations of ammonia are found in primary metabolic defects, specifically urea cycle disorders and organic acidaemias. Amino acid analysis detects the abnormal metabolites found in citrullinaemia and arginosuccinic aciduria. The presence of orotic acid distinguishes ornithine transcarbamylase deficiency from carbamyl phosphate synthetase deficiency. In none of our cases was there any abnormality of amino or organic acid profiles or orotic acid. In case 1 hepatic ornithine transcarbamylase and carbamyl phosphate synthetase activities were within normal limits.

Hyperammonaemia may also result from urea cycle impairment following hepatic failure, malignant disease, or toxin exposure. Hepatic mitochondrial failure resulting in hyperammonaemia, increased transaminases, and acute fatty change is seen in Reye's syndrome. Alanine transaminase (ALT) was normal in cases 1 and 3, rising to a maximum of 112 IU/l in case 2 (reference range <65 IU/l). In no case was there histopathological evidence of liver disease.

A greatly increased urea load, such as that produced by *Proteus* and other urea splitting bacteria, may occur as a result of increased production and absorption of ammonia as NH_3 from a reservoir of infected stagnant urine with an increased pH. This is the likely mechanism in cases 2 and 3. In case 1 the purulent collection was in the peritoneal cavity. Hyperammonaemia has not previously been reported from a site outside the urinary tract.

Our three cases showed severe hyperammonaemia in infants with critical septic illness and collections of pus. Urea splitting organisms were cultured in case 1 (*Corynebacterium*) and case 2 (*Proteus*), and were likely in case 3.

Hyperammonaemia results in an encephalopathy secondary to astrocyte swelling, increased permeability of the blood-brain barrier, mitochondrial changes, and cerebral oedema. Our cases showed global hypoxic change, and while specific changes of a metabolic encephalopathy were not seen, it is possible that metabolic derangement may have contributed to the neuropathology.

Only eight cases of hyperammonaemia in children secondary to infection have been reported, all with conditions predisposing to urinary tract infections (table 1). Relief of urinary tract obstruction and specific therapies improved the hyperammonaemia, and the outcome was generally favourable. In no reported case was the hyperammonaemia as severe, or intractable, as in the cases reported here.

Plasma ammonia should be measured in all critically ill and potentially septic children in whom the clinical signs and symptoms of encephalopathy may not be readily apparent because of their critical illness and intensive support. If hyperammonaemic, primary urea cycle disorders and organic acidurias should be excluded. Identification and drainage of any infected collection or obstructed viscus should be considered, including sites outside the urinary tract. Whatever the cause, a progressive rise in ammonia requires active treatment to forestall encephalopathy.

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