An in situ hybridisation procedure to reveal albumin mRNA on formalin fixed hepatic tissue using a digoxigenin labelled oligonucleotide probe has been developed by Murray *et al.*[4] In our case a 2 kb cDNA sequence corresponding to a coding sequence of human albumin provided by ATCC (Rockville, Maryland, USA) was used to produce a SP6 transcribed, digoxigenin 11 UTP labelled anti-sense riboprobe. The cytospin preparations were formalin fixed and the method of in situ hybridisation developed by Stewart *et al*[5] was employed. The patient had clinical signs strongly suggestive of hepatocellular carcinoma, supported by serological, ultrasound, and computerised tomography findings. The peritoneal effusion contained single neoplastic cells and groups of neoplastic cells showing nuclear pleomorphism and granular chromatin surrounded by moderate amounts of rather granular cytoplasm. These cytological features were certainly in keeping with the appearances of hepatocellular carcinoma as described in fine needle aspirate,[6] and after demonstrating human albumin mRNA in these cells we felt that the diagnosis of hepatocellular carcinoma in the ascitic fluid was certain.

We feel that application of this rapid, reliable, and specific technique of in situ hybridisation for human albumin can confirm the diagnosis of hepatocellular carcinoma on cytospin preparations of ascitic fluid, thus making further invasive diagnostic procedures unnecessary.

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Dilutional hyponatraemia: a cause of massive fatal intraoperative cerebral oedema in a child undergoing renal transplantation

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Accepted for publication 12 February 1997

Abstract

A four year old boy with polyuric renal failure resulting from recurrent urinary tract infections and vesicoureteric reflux from birth underwent renal transplantation. In the past he had had five ureteric reimplant operations and a gastrostomy, as he ate nothing by mouth. He required peritoneal dialysis 13 hours a night, six nights a week. His fluid requirements were 2100 ml per day. This included a night feed of 1.5 litres Nutrizon. Before operation he received 900 ml of Dioralyte instead of the Nutrizon feed, and peritoneal dialysis was performed as usual. The operation itself was technically difficult and there was more blood loss than anticipated, requiring intravenous fluids and blood. The operation ended about four hours later but he did not wake up. Urgent computed tomography revealed gross cerebral oedema. He died the next day. At necropsy the brain was massively oedematous and weighed 1680 g.

(*J Clin Pathol* 1997;**50**:444–446)

Keywords: cerebral oedema; operation; intravenous fluids

There are various causes of cerebral oedema including inflammatory conditions, ischaemia, trauma, space occupying lesions, anoxia, toxins, and metabolic disorders—in particular hyponatraemia[1] and water intoxication.[2] Cerebral oedema has been defined as an increase in brain volume due to an increase in its water content.[3] It can be localised or generalised. In the conscious patient it produces symptoms of raised intracranial pressure, but in the unconscious the symptoms are masked. Cerebral oedema developing as a result of hyponatraemia is well documented[4–6] but most of these cases have developed postoperatively or following intravenous administration of fluids in a conscious patient. The event described here occurred during anaesthesia, and at the end of the operation—about four hours later—the patient, a child, did not wake up and had developed papilloedema. Urgent computerised tomography showed gross cerebral oedema with slit-like ventricles. Brain stem tests were carried out and he was declared dead the next day, about 26 hours from the start of the operation. This case illustrates the complexity of fluid management in an intraoperative fatality. To pathologists carrying out these necropsies—most probably at the behest of the coroner—it is important to realise that asymptomatic dilutional hyponatraemia can occur intraoperatively when the symptoms of hyponatraemia and cerebral oedema are masked due to anaesthesia and unconsciousness. Arieff *et al*[4] studied 16 cases of symptomatic postoperative

hyponatraemia. In 13 cases symptoms were present, one was too young to assess, and two were intubated. This is the first case to document this well recognised postoperative complication occurring rapidly during an operation with fatal results. The clinical management and the treatment of hyponatraemia will not be discussed.

Past medical history and preoperative care

This child developed recurrent urinary tract infections and vesicoureteric reflux from birth, which resulted in polyuric renal failure. He had had five ureteric reimplant operations, a fundoplication for gastro-oesphageal reflux, was fed through a gastrostomy because he ate nothing by mouth, and his most recent operation was an orchidopexy in the month before his death. All of these were uneventful. He required peritoneal dialysis 13 hours a night, six nights a week. His normal fluid requirements were 2100 ml a day, including a night feed of 1.5 litres of Nutrizon. The night before the operation routine investigations showed blood pressure 108/56 mm Hg, haemoglobin 10.5 g/dl, sodium 139 mmol/l, potassium 3.6 mmol/l, and urea 16.8 mmol/l. On anaesthetic advice he was given 900 ml Dioralyte (4% dextrose, 0.18% saline) instead of the Nutrizon feed. Peritoneal dialysis was performed as usual.

Operation

The child arrived in theatre at 0645. General anaesthesia was induced using thiopentone, atropine, and atracurium. Intravenous access was difficult and attempts were made to pass a central venous pressure catheter. Three attempts were made into the left subclavian vein and one into the left internal jugular vein, and then the catheter was successfully passed into the right subclavian vein. A lumbar epidural was sited between L1 and L2 with the administration of bupivicaine and fentanyl. In addition to the anaesthetic drugs, co-amoxyclav (Augmentin), prednisolone, azathioprine, and a continuous infusion of dopamine were given intravenously.

Central venous pressure was recorded as 17 mm Hg. Three 500 ml bags of intravenous dextrose-saline (4%/0.18%) were given between 0700 and 0830. The operation was technically difficult because of previous surgical procedures, and blood loss was calculated at 1200 ml. Further fluids given were 500 ml Hartmann's solution, 1000 ml of human plasma protein fraction, and 500 ml of packed red blood cells. At 0932 a blood analysis showed a sodium concentration of 123 mmol/l (normal 135–145) and a packed cell volume of 18% (normal 35–40%). During the operation the central venous pressure rose to 20–21 mm Hg and the haemoglobin fell to 6.1 g/dl, rising again to 10.1 g/dl at the end of the operation. The systolic blood pressure rose to 150 mm Hg and the pulse rate gradually fell, but rose steadily from 1015 onwards.

After perfusion of the donor kidney the operation was completed. The neuromuscular block was reversed with neostigmine but the child did not wake up. At midday his pupils were fixed and dilated. He was transferred to the paediatric intensive care unit at 1205, intubated, hand ventilated, treated with intravenous mannitol, and intravenous fluids were restricted. On cerebral computerised tomography there was gross cerebral oedema. The central venous pressure was now 30 mm Hg, heart rate 120 beats/min, and systolic pressure 120 mm Hg. Plasma sodium was 119 mmol/l. A chest *x* ray showed pulmonary oedema. Neurologists carried out brain stem tests and the child was declared dead the next day, about 26 hours after the start of the operation.

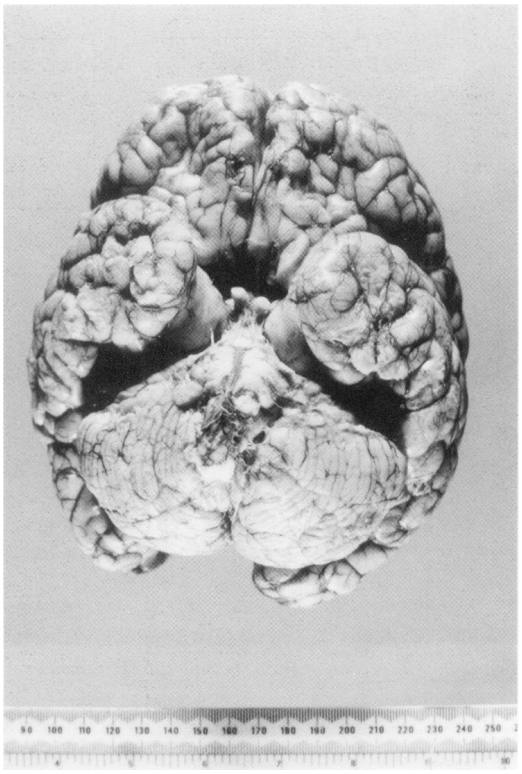

Figure 1 Marked uncal swelling and swelling of cerebellar tonsils.

Pathological findings

The brain was grossly swollen with loss of sulci and uncal swelling. The swelling was symmetrical, with swelling of the cerebellar tonsils (fig 1). There was no evidence of cortical venous thrombosis or uncal necrosis or necrosis of the cerebellar tonsils. The brain, after fixation, weighed 1680 g; the cerebellum and brain stem weighed 176 g and the cerebellum alone 154 g. On cut section there was massive brain swelling with constriction of the ventricles (fig 2). There was congestion of the white matter and blood vessels in the basal ganglia and deep grey matter. There was no evidence of necrosis of the midbrain or brain stem.

There was a suture in situ on the left side of the neck at the junction of the internal jugular vein and the subclavian vein.

There was no evidence of pulmonary oedema. The native kidneys were markedly contracted, scarred, and contained a number of cysts. Both ureters were hugely distended and dilated. The transplanted kidney was in the right pelvis, the ureter drained freely, and the vascular attachments were intact.

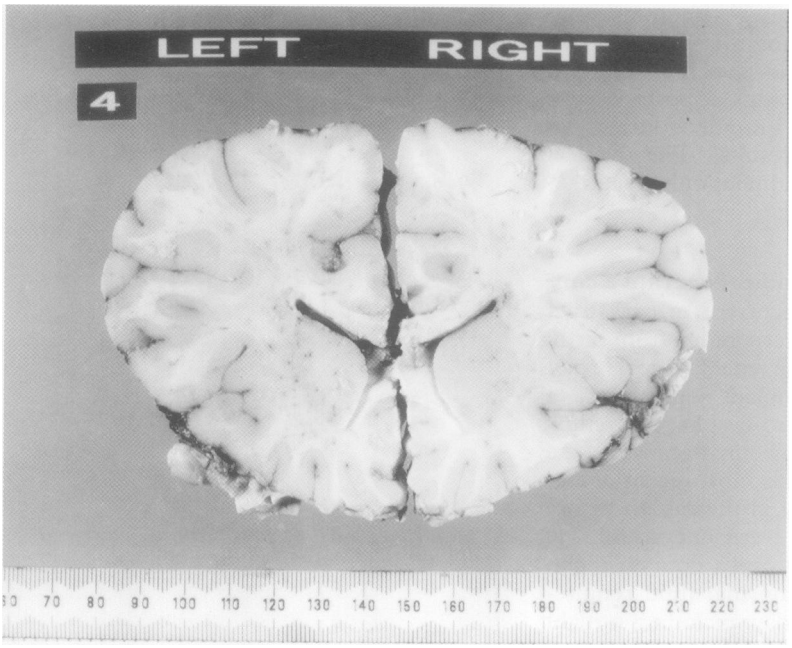

Figure 2 Cut section of brain showing slit-like ventricles.

Histologically there was massive oedema of the cerebral cortex and white matter. There was no evidence of terminal hypoxia or of central pontine myelinolysis.

Discussion

The signs of raised intracranial pressure include a rising blood pressure and falling pulse rate. Hyponatraemia, if chronic, may be asymptomatic and may not result in cerebral oedema.[3] However, the symptoms of hyponatraemia following intravenous administration of fluids include lethargy, headache, nausea, and emesis, with the onset of respiratory arrest.[4 5] In the anaesthetised and unconscious patient these symptoms are obviously masked. Hyponatraemia has been defined as a serum sodium level concentration 130 mmol/l[5] and severe hyponatraemia with a serum sodium concentration below 125 mmol/l.[6] The latter is associated with cerebral oedema[7 8] and it appears that it is the excess water content of the brain which is important in influencing consciousness.[9] In this case the serum sodium was 139 mmol/l at 2300 the night before the operation. At 0932 during the operation it had fallen to 123 mmol/l. It fell further to 119 mmol/l on admission to ICU around midday, and it did not rise again. At necropsy the brain was massively oedematous and when fixed it weighed 1680 g. The normal brain weight (unfixed) for boys aged four to five years is 1300 g. Thus the brain weight had increased by almost 30%, which is greatly in excess of other cases documented by Arieff *et al.*[4] In that study the investigators proposed that it was neither the actual concentration of the serum sodium nor the rapidity of the development of hyponatraemia that determined the ultimate outcome in these children. However, our case was associated with extremely rapid development of cerebral oedema and a correspondingly rapid fall in serum sodium concentration. It shows that dilutional hyponatraemia can occur intraoperatively, with rapidly fatal results. Dilutional hyponatraemia can occur with a minimal positive fluid balance when fluids containing small amounts of sodium are given, for example dextrose-saline as was given in this case.[4] It is the usual practice in routine elective operations to give Hartmann's solution, which contains no glucose. However, this case was not routine. It involved complex fluid management in a child who produced large quantities (75 ml/h) of dilute urine and was fed through a gastrostomy at night, therefore producing a high insulin requirement. Before the operation, to avoid the possibility of aspiration, the 1.5 litre feed was replaced by 900 ml of clear fluids. Therefore there was a fluid deficit before the operation. There was also concern about the intraoperative glucose management, and about the fact that renal transplant operations require adequate fluids for the graft to take. For these clinical reasons it was decided to use dextrose-saline though in retrospect it might have been better to give isotonic sodium chloride with glucose.

The brain was so grossly swollen at necropsy that it is possible that an additional factor was involved to account for the findings. The internal jugular vein on the left side had been tied off at its junction with the subclavian vein after the removal of a long line. This obstruction to the venous drainage from the brain could have led to increased engorgement of the brain which can be associated with oedema.[4] It is possible therefore that this factor may have played a role in the severity and rapid development of the cerebral oedema.

SUMMARY

Symptomatic dilutional hyponatraemia is a well recognised postoperative complication, particularly in children. This case shows that it can occur intraoperatively, thus masking the symptoms of cerebral oedema and the low serum sodium level. This makes its detection more difficult for the clinical staff involved, but for the pathologist the rapidity of onset with massive fatal cerebral oedema should be noted.

I thank Dr E Sumner, Consultant Paediatric Anaesthetist, Great Ormond Street Hospital, for his expert opinion, Dr Bob Taylor, Consultant Paediatric Anaesthetist, Royal Belfast Hospital for Sick Children, for his helpful comments, and HMC for Greater Belfast, Mr John Leckey, for his permission to use this case.

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