MEDICAL REPORT

Adam STRAIN

Dob: 14th August 1991

Prepared by Dr Fenella Kirkham MB BChir FRCPCH

Professor of Paediatric Neurology
Institute of Child Health, London

&

Consultant Paediatric Neurologist
Southampton General Hospital

Prepared under the instruction of the Hyponatraemia Enquiry

My name is Dr Fenella Jane Kirkham and I qualified MBChir in 1978. I trained in paediatrics from 1979 and in paediatric neurology from 1982. I worked as an SHO in paediatric renal medicine in 1982 and covered emergencies in that service as a registrar and senior registrar from 1986-1990. I obtained the MRCP in 1982 and was awarded FRCP in 1994. I was a founding member of the Royal College of Paediatrics and Child Health in 1997. I have been a Consultant Paediatric Neurologist since 1990. From 1990 to 2001, I was Senior Lecturer in Paediatric Neurology at the Institute of Child Health, London, with an honorary contract at Great Ormond Street Hospital. I am currently working part-time as a Consultant Paediatric Neurologist at Southampton General Hospital (6 PAs) and part-time as a clinical academic (6PAs). I was promoted to Reader at the Institute of Child Health in 2002 and to Professor in 2006. I have a research interest in coma, intracranial hypertension and ischaemic brain damage in childhood and have published widely on these subjects. I obtained my MD on 'Cerebral haemodynamics in children in coma' from the University of Cambridge in 2009. I was senior editor for the book 'Cerebrovascular Disease and Stroke in childhood' published by MacKeith Press in 2011.

I have been asked to provide a report on Adam Strain (Date of birth: 14th August 1991). I have had access to the photocopied notes from Royal Belfast Children's Hospital, to some of the general practice and community paediatric notes, to the expert reports and to various depositions.

1. Adam Strain was born by emergency Caesarian section for delayed second stage at Term on the 14th August 1991 after an antenatal diagnosis of abdominal cysts. Apgar scores were 5 at 1 minute and 8 at 5 minutes (050-022-061) i.e. there was no evidence of significant birth asphyxia. He had renal problems from birth, clinically diagnosed as renal dysplasia with posterior urethral valves, but possibly secondary to medullary cystic kidneys (050-022-061). He had a large number of operations on his urinary tract in the first four years of life, but despite all attempts to prevent this, he gradually developed chronic renal failure.

2. Adam's head circumference at his 6 week check was 38 cm, around the 50th centile and continued to grow along the 50th centile (016-095-139; 016-098-149) i.e. his head growth was normal so he is unlikely to have sustained a major hypoxic-ischaemic event in infancy.

3. Adam was fully gastrostomy-fed and had had a fundoplication on 19th March 1992 because he would not take any food orally and had evidence of gastro-oesophageal reflux. He did suck on bread and underwent some intensive feeding clinic (speech therapy) input when he was felt to have an immature up and down (rather than rotator) chewing action as well as reluctance to swallow.

4. Adam had brief apnoeas (050-023-068, 050-023-069, 051-023-128), episodes of jitteriness (050-023-073, 051-023-132, 051-

023-136), jerking of the head and transient twitching of the left eye (e.g. on 8th February 1992 050-023-088) as an infant which were probably within normal limits or may have been brief seizures. He had rigors in the context of fever on 18th January 1995 (057-105-264) and further rigors are mentioned in Dr Savage's letter of 02/02/95 (016-039-070) attributed to having his central line flushed. On the balance of probabilities I do not think that any of these episodes were diagnostic of epilepsy.

5. On 5th September 1994, Adam had a headache and was hearing noises in his ears (057-105-264). This appeared to settle and is probably not relevant.

6. Adam was intermittently noted to be puffy or generally oedematous (e.g. 054-057-150) sometimes with facial oedema (050-031-290) but this is not likely to be relevant to his death.

7. Adam had cardiomegaly on chext X-ray, probably in relation to his chronic anaemia.

8. Adam developed some evidence of renal osteodystrophy on serial X-rays of his bones.

9. Adam was sitting unsupported by 7 months and walked at exactly 18 months according to the developmental checklist from his general practice notes (016-098 2.3.92 5.2.93). At his 30 month check (016-098 16.3.94) there is no place for circling as before or after but his gross motor/locomotion skills appear to have been satisfactory. His gross motor skills were under observation at his 4 year check (016-098 18.8.95), which was

undertaken after the admission for pyrexia of unknown origin during which he was noted to be limping on his left leg.

10. Adam had expressive language delay under observation documented in the developmental checklists from his general practice notes (016-098 16.3.94) and by his 4 year check he was documented to be receiving treatment for this and social and behavioural problems (016-098 18.8.95). A report from the speech therapist from February 1995 noted that he had mild expressive language delay in the areas of phonology and syntax (016-037-067). In September 1995 he was referred for formal speech and language assessment (016-020-042). There is a brief report from this assessment, which took place on 10th November 1995, stating that he had mild expressive language delay and would be reviewed in March 1996 (016-016-035).

11. I also note that, although he was of average and perhaps superior intelligence, he was said to need input to improve his attention (016-037-067). I have requested to see the full report of his formal developmental assessments by Dr Cosgrave on 12th September 1995.

12. Adam was an inpatient with a pyrexia of unknown origin and a raised C-reactive protein (around 150 when normal is <5). He was irritable and also intermittently limping on his left leg at this time (058-033-133) having apparently experienced a fall involving the left leg 3 weeks before. His haemoglobin fell steadily from 10.5 to 5.5 g/dL during this admission (058-033-

121). Adam had a CT scan of the head (016-026-050) on 7th July 1995 as part of the work-up to exclude localised infections. Dr Anslow, the expert neuroradiologist engaged by the Hyponatraemia Inquiry, reported this CT scan with contrast as normal. Lumbar puncture was not successful when attempted on 6th July 1995 (058-033-017).

13. Adam was followed by the Community Medical Officer, Dr Burns. He was due to start mainstream school in Reception at St Patrick's Primary school in January 1996 (016-013-032, 058-015-43) where the plan was that he would have a statement of educational needs because of his toileting needs. There were also behavioural issues reported by mother at the renal clinic appointments. He had been referred to the Educational Psychologist for a full assessment.

14. On the 26th November 1995 a transplant kidney became available from a sixteen year old in Glasgow and the kidney was offered to Adam's family for Adam. After some thought, mother consented to allow Adam to undergo the transplant.

15. On the day before the kidney transplant Adam had a haemoglobin of 10.5 g/dl with a haematocrit of 0.32 (32%). His fibrinogen was 3.58 g/l. The day before his transplant, his sodium was recorded as 139 (058-035-144) and 133 mmol/l (INQ-0450-11) and he had evidence of chronic renal failure with a urea of 16 mmol/l and a creatinine of 702 µmol/l.

16. Adam was peritoneally dialysed as usual overnight on the night of 26th November 1995. He was supposed to have clear fluids through the gastrostomy overnight (058-035-133) and fluid intravenously pre-operatively, but although venous access was achieved initially for a short period, the cannula tissued in the early hours of the morning (057-101-13) and venous access was not re-established. He was therefore given an increased rate of fluid, apparently Dextrose Saline, through his gastrostomy feed. Prior to his admission on 26th November 1995 he would already have had his three 200mls bolus feeds of Nutrison and his sodium bicarbonate supplements because he had a tendency towards hyponatraemia. Because of the transplant it was decided that he should have clear fluids overnight, which according to Dr. Maurice Savage did not contain sodium supplements, which would be stopped two hours before the transplant, to avoid having a stomach full of food.

17. Adam's transplant was delayed until the morning of the 27th November 1995 so that the surgical and anaesthetic team would be fresh. He went to theatre at 07:00 for pre-transplant preparation by the anaesthetist.

18. Although intravenous access was achieved easily as was intubation of the trachea and a right radial line, placement of a central venous line proved very difficult for Dr Taylor, the anaesthetist, who tried several times on the left-hand side (011-010-035, 011-010-037, 011-010-040), but could not insert a

catheter properly, perhaps because the left jugular vein had been ligated (011-010-031, 011-010-041), although I note that this issue remains unresolved. Eventually a cannula was placed in the right subclavian vein (011-010-035) and the central venous pressure (CVP) was recorded at 17 mmHg (058-008-023). This reading was considered by Dr Taylor, the anaesthetist, to be inaccurate with a response to increased venous pressure suggestive that it was up against a vessel wall (093-038). Adam's head was turned in theatre, potentially leading to some obstruction of the venous return from the head, also accounting in part for the difference in CVP between theatre (20-22 mmHg) and the Paediatric Intensive Care Unit (PICU; 10-12 mmHg) (011-014-101). Adam had been dialysed overnight and as he had difficulty in cannulating the left subclavian vein, a sign of dehydration, Dr Taylor did not consider him to be fluid overloaded. The CVP was therefore used as a measure of change rather than as an absolute value and when a chest X-ray was done later, the line was found to be in the right internal jugular vein in the neck rather than the heart.

19. Induction was with Atropine 0.3 and sodium thiopentone 125 mg and Atracurium 10 mg. Adam was anaesthetised with Halothane and in theatre was gven 500 mg Augmentin, 200 mg of Methyl Prednisolone and 25 mg Azathioprine (057-021-033) as well as a further 35 mg of Atracurium to maintain paralysis. His eyelids were taped to prevent damage to the cornea. He was on a low

dose Dopamine infusion (5 mcg/kg/min) throughout the procedure in an attempt to maintain perfusion of the donor kidney. He was started on a Cyclosporin infusion 3 mcg/kg/hr, I think post-operatively (058-005-012, 057-018-026) rather than intra-operatively. Azathioprine 25 mg daily and Methyl Prednisolone 10 mg bd were continued post-operatively.

20. Adam was given 500 ml of 0.18% saline 4% Dextrose between 0700 and 0730, 500 ml of 0.18% saline 4% Dextrose between 0730 and 0845 and 500 ml of 0.18% saline 4% Dextrose between 0845 and 1100 (058-003-005).

21. Adam's operation was complicated because of the number of previous operations that he had had and he lost a considerable amount of blood, around 1000-1200 ml according to Dr Taylor and the experts Drs Haynes, Coulthard and Gross, when his total blood volume was 1600 ml. His haematocrit had fallen from 0.32 to 0.18 (32% to 18%) by 0930 on 27th November 1995 and he had an estimated haemoglobin of 6.1 g/dL according to the blood gas machine. This required replacement with 500 ml of packed cells, 250 ml given at 0930 and 250 ml given at approximately 1045 as well as 1000 ml of human plasma protein fraction (HPPF) given between 0830 and 1045. His haemoglobin at the start of the procedure was 10.5 g/dL, fell to the estimated 6.1 g/dL during the case and was 10.1 g/dL at the end of the procedure. Post-operatively on PICU, the haemoglobin was 14.4 g/dL.

22. Oxygen saturation (99-100%) and end-tidal carbon dioxide tension (38-43 mmHg) were maintained within normal limits throughout the procedure and the blood gas at 0930 showed normal arterial carbon dioxide tension (44.1 mmHg) and oxygen tension (125 mmHg) with a normal pH (7.348) and base excess (-0.3).

23. At 9.30 in the morning a low sodium of 123 mmol/l was recorded from the blood gas machine. Post-operatively the sodium was 119 mmol/l.

24. During the operation Adam's blood pressure increased from an initial systolic measurement of 90 mmHg (diastolic c.50 mmHg; mean c.70 mmHg) to an eventual systolic pressure of 120 mmHg (diastolic c.80 mmHg; mean c.100 mmHg) (058-008-023), at least in part response to 2 small boluses of Dopamine (1 mcg/kg) to increase the perfusion pressure to the donor kidney without increasing fluids (011-014). There were no large brief increases in blood pressure or heart rate suggestive of acute seizures or Cushing responses to intracranial hypertension. It is possible that his slightly enlarged heart was not functioning quite as well as a normal heart, reducing the ability to compensate by increasing blood pressure acutely in response to seizures or intracranial pressure waves. Post-operatively Adam's blood pressure continued to rise to hypertensive levels (058-008-022) and he was given Diazepam on PICU (058-005-011) in case this increase in blood pressure

was secondary to seizures. His blood pressure was then treated with Nifedipine (058-005-011). Adam's central venous pressure, which was initially reading 17 mmHg and read 20-22 mmHg for most of the operation, read 28 mmHg after the table was raised but the dripstand with the transducer was not but then returned to the stable baseline of 20-22 mmHg when re-zeroed (011-014). Adam's heart rate increased from 130 to 160 beats per minute.

25. Adam failed to breathe or wake up at the end of the surgery and at midday on the 27th November 1995 his pupils were noted to be fixed and dilated. He was transferred to PICU and Drs Savage and Taylor spoke to Adam's mother.

26. Chest x-rays post-transplant at 1320 on the 27th November 1995 and at 2130 on the same day were thought by the clinicians to show pulmonary oedema but on review by Dr Landes the lung fields appear to be clear. I am not an expert in pulmonary physiology but my interpretation is that the chest X-ray is not helpful in determining the cause of Adam's death.

27. An emergency CT scan of the brain was carried out at approximately 1415 on the 27th November 1995. As reported at the time, this apparently showed marked generalised cerebral swelling with effacement of the lateral ventricles with obliteration of the third ventricles, basal cisterns and sulci. Dr Anslow has noted that the changes were particularly severe in the posterior fossa. There was descent of the cerebellar tonsils through the

foramen magnum. The appearances were in keeping with the development of acute cerebral brain oedema particularly involving posterior cerebral structures.

28. Adam was seen by Dr David Webb at 19:30 on the 27th November 1995. He noted (058-035-139) severe extensive bilateral retinal haemorrhages suggesting an acute rise in intracranial pressure and that the CT scan showed diffuse generalised cerebral oedema with obliteration of basal cisterns, fulfilling the radiological criteria for cerebral swelling. He felt that Adam's signs suggested that he fulfilled the clinical criteria for brain stem death.

29. Adam's ventilation was discontinued on the 28th November 1995 and he died in his mother's arms.

30. A post mortem was carried out on the 29th November 1995 (011-010-034) by Dr Armour who reported the cause of Adam's death as cerebral oedema secondary to dilutional hyponatraemia and impaired cerebral perfusion during the transplant. The case was reported in the literature. Dr Squier, the expert neuropathologist instructed by the Inquiry, feels that the brain weight was not greater than expected for a 4 year old child. She has pointed out that the majority of the swelling involves the posterior structures. She has not found any evidence of hypoxic brain damage or ischaemic brain damage in a distribution consistent with reduced cerebral perfusion pressure.

31. Acute reduction in conscious level associated with cerebral oedema on neuroimaging has been reported in water intoxication in childhood (Boetzkes et al 2010, Radojevic et al 2012).

32. In addition to data with his collaborator, Dr Ayus, as first author in menstruating women, Arieff et al (1992) reported 16 apparently normal children given hypotonic fluids, mainly post-operatively, who had reduction in plasma sodium over several days and either died or were left with severe neurological handicap. I have not been able to ascertain from his paper or that of Mortiz and Ayus (2005) quoting these cases which of the patients were administered Glucose 280 mmol/L in water (similar to 5% Dextrose as used in the UK) or and which Glucose 280 mmol/L sodium chloride 38 mmol/L (similar to 0.18% saline 4% Dextrose as used in the UK).

33. The data from the Toronto papers (Halberthal et al 2001, Hoorn et al 2004), again summarised by Moritz and Ayus (2005), are also lacking data either on the precise nature of the hypotonic fluid given or on the cause of death in those who died.

34. Recent work from the research group which includes Arieff, Ayus and Moritz has emphasised the role of additional factors in determining the severity of cerebral oedema in women and children, particularly hypoxia (Moritz and Ayus 2005, Ayus et al 2008).

35. In his 1992 paper, Arieff noted that most of the infants and children reported previously had had central nervous system disorders or had water intoxication. In fact, the patients in Arieff's series had pre-existing risk factors for central nervous system disorders, including apparently minor trauma and orchidopexy (undescended testes are common in neurological disorders), or risk factors for hypoxia (tonsillitis, adenotonsillectomy, pneumonia).

36. I have not been able to find full blood count data from Arieff's series or the 2 Toronto series although 11/16 in Arieff's paper had relatively low arterial pO2 immediately after respiratory arrest. It is not clear whether these were the children with risk factors for hypoxia or risk factors for central nervous system disease.

37. The series reporting most of these childhood deaths was from 20 years ago (Arieff et al 1992). Neuroimaging was less sophisticated in the 1990s so that cerebral co-morbidities, e.g. pre-existing congenital malformations of the brain potentially epileptogenic or predisposing to cerebral herniation, or vascular pathologies such as venous sinus thrombosis or so-called 'posterior reversible encephalopathy syndrome' (PRES), would not have been excluded. In fact, although CT was available from 1977, there was no neuroimaging reported for the cases in Arieff's 1992 series and in the data pulled together for the review

by Moritz and Ayus (2005), neuroimaging is discussed mainly in the context of demyelination rather than cerebral oedema.

38. Arieff's paper cited previous papers and has subsequently been extensively cited as well as being reproduced in the paper by Moritz and Ayus (2005) which summarises the literature up that point. I have looked at this literature as well as entering search terms into Pubmed e.g. 'hyponatraemia' and 'brain death' or 'fatal' or 'CT or 'magnetic' or 'cerebral oedema' and have tabulated it looking at co-existing cerebral disease known prior to the administration of hypotonic fluids and at risk factors for hypoxia. As venous sinus thrombosis might be a hidden central nervous system condition associated with the dehydration consequent on conditions such as gastroenteritis which precipitate fluid prescription, I have also included these diagnoses in the excel spreadsheet.

39. There are a number of children with pre-existing central nervous system disease who appear to have developed cerebral oedema associated with hyponatraemia (reviewed in Arieff et al 1992 and Moritz and Ayus 2005).

40. I have found 4 cases of cerebral oedema in children without pre-existing central nervous system disease, 3 fatal and one with severe neurological sequelae, where the fluid administered was 0.18%-0.3% sodium chloride in 4 or 5% Dextrose. One had had a tonsillectomy (McRae quoted in Moritz and Ayus 2005) and was therefore at risk of hypoxia and there were 2 with

gastroenteritis and one with dehydration (Moritz and Ayus 2005) in whom the diagnosis of venous sinus thrombosis was not considered.

41. Apart from these 4 cases, I have only been able to find case reports of fatal cerebral oedema in children without central nervous system disorders with water intoxication (e.g. Radovejic 2012) or the use of 5% Dextrose post-operatively (Paut et al 2000, Sicot 2006) or in influenza or dehydration (e.g. Jackson, Keating quoted in Moritz and Ayus 2005).

42. Seizures have been reported in hyponatraemic children with central nervous system conditions, e.g after scoliosis or craniofacial surgery (Moritz and Ayus 2005) or respiratory syncytial virus infections, a risk factor for hypoxia (Hanna et al 2003).

43. A simple way of reviewing the reported cases of hyponatraemia associated with hypotonic fluids is to divide those with:

a. Pre-existing central nervous system disease

b. Risk factors for hypoxia

c. Risk factors for venous thromboembolism e.g. dehydration

And to look at whether there was

(i) excessive water intake

(ii) administration of intravenous Dextrose without sodium

(iii) administration of hypotonic intravenous Dextrose with sodium

And to determine whether neuroimaging and/or autopsy was adequate to exclude cerebral venous sinus thrombosis and posterior reversible encephalopathy syndrome

44. I have not been able to find any other case of documented cerebral oedema or brain death in a child without a central nervous system condition given 0.18% saline 4% Dextrose intra-operatively as Adam was. The other children who died having been given hypotonic intravenous Dextrose with sodium had risk factors for hypoxia (n=1), which Adam did not have, or risk factors for cerebral venous sinus thrombosis without having this condition excluded (n=3), as in Adam's case.

45. Even now neuroimaging is not necessarily able to exclude all possible comorbidities: for example the child with fatal hyponatraemia after renal transplant described by Cansick et al (2009) had had meningitis, which may be associated with thrombosis of the venous sinuses (Sebire et al 2005, DeVeber in Ganesan and Kirkham 2011).

46. Adam's renal transplant and death associated with cerebral oedema particularly involving posterior fossa structures occurred in 1995, i.e. in a similar era to Arieff's series, with similar concerns that acute and chronic cerebral co-morbidities may not have been excluded.

47. Adam had renal dysplasia with bilateral large cysts. His kidneys were abnormally shaped and he had abnormally dilated ureters. He also had severe feeding difficulties and expressive language

delay. There is, however, no neuroimaging or post mortem evidence that he had an underlying cerebral abnormality.

48. Adam had at least four risk factors for chronic or acute venous thrombosis which could have involved the cerebral venous sinuses: (1) from November 1993 he was appropriately on erythropoietin (Finelli and Carley 2000) 1-3 times a week (16-055-096, 16-052-093, 016-045-081, 016-007-022, 016-006-021, 016-032-061, 016-027-053, 016-021-043, 016-018-039, 016-015-034) to stimulate his bone marrow as he had chronic anaemia associated with renal failure and (2) he was polyuric and therefore intermittently at risk of dehydration (3) he was given Methyl prednisolone (Stolz et al 2003) as immunosuppression for the donor kidney during his transplant and (4) he may have had an external jugular vein ligated and he had a central venous line in the neck during his renal transplant. In addition, he also had anaemia, considered at least in part to be secondary to iron deficiency. Both anaemia (Zafeiriou et al 2011 in Ganesan and Kirkham 2011) and iron deficiency (Sebire et al 2005, DeVeber in Ganesan and Kirkham 2011) have been associated with venous sinus thrombosis in childhood. In one series red cell indices consistent with iron deficiency were associated with non-recanalisation of previously thrombosed cerebral venous sinuses (Sebire et al 2005). Venous sinus thrombosis associated with iron deficiency is also a differential diagnosis for deteriorating conscious level despite appropriate

fluid management in diabetic ketoacidosis (Keane et al 2002). This condition may present with chronic neurological symptoms e.g. difficulty in using one arm and/or leg (Sebire et al 2005) and is associated with acute cerebral (Sebire et al 2005) and cerebellar (Eng et al 1990) swelling, status epilepticus and brain death (Sebire et al 2005, DeVeber in Ganesan and Kirkham 2011). Venous sinus thrombosis is difficult to exclude even in 2012 as CT scan misses up to 40% (DeVeber 2011 in Ganesan and Kirkham 2011) and there are few recent autopsy data (DeVeber in Ganesan and Kirkham 2011). Dr Squier cannot find evidence for cerebral venous sinus thrombosis but she does not consider that venous sinus thrombosis was excluded at the post mortem. It would be helpful to ask Dr Anslow if venous sinus thrombosis and/or subarachnoid haemorrhage can be excluded on the post-operative CT scan. If cerebral venous sinus thrombosis cannot be excluded either from the available neuroimaging or the autopsy then I think that, on the balance of probabilities, chronic venous sinus thrombosis is a likely cause of Adam's previous rather subtle neurological problems. In addition I think it likely that further acute thrombosis in the venous sinuses was associated with acute posterior cerebral oedema during the operation.

49. Even if there was no venous sinus thrombosis, the difficulty experienced in cannulating the jugular vein on the left, perhaps related to previous tying off of this vessel, together with the

position of the central venous pressure line in the right jugular vein, would have reduced the opportunity for compensating for increasing cerebral oedema by drainage of blood into the jugular veins (see figure 1). In addition the reduced jugular venous drainage would have increased the chances of increased intracerebral venous pressure with engorgement of these vessels with an additional volume of blood and consequent increase in the volume of the contents of the skull and the intracranial pressure if the reserve capacity was exceeded (see paragraph).

50. Adam required a blood transfusion because of the blood losses during transplantation. He was started on Azathioprine 25 mg during the renal transplant. Posterior Reversible Encephalopathy Syndrome (PRES), which is not always reversible and may be fatal, has been described in renal disease (Sebire et al 2005, Gumus et al 2009, Yamada and Ueda 2012), specifically after transfusion (Sato et al 2011). Blood transfusion associated PRES is also well recognised in other conditions where there is chronic anaemia (Zafeiriou et al in Ganesan and Kirkham 2011). Immunosuppression with Azathioprine (Foocharoen et al 2006), as well as Cyclosporin (Ganesan and Kirkham 2011), is also a common association with PRES. PRES can be associated with the development of more generalised cerebral oedema (Ganesan and Kirkham 2011) as well as white matter oedema in the posterior part of the brain

(the parietal and occipital lobes) and seizures. Dr Armour's report mentions white matter oedema but Dr Squier's expert Neuropathology report makes it clear that the aetiology of the oedema is difficult to determine. Unless Dr Squier or Dr Anslow can exclude PRES on neuroradiological or neuropathological grounds, I consider it likely that the development of PRES, for which Adam had at least 3 risk factors (anaemia, blood transfusion, immunosuppression) contributed to the rapid development of mainly posterior cerebral oedema in his case.

51. CVST and PRES were not widely recognised in 1995, although a review in 2011 pointing out their similarities stated 'These diagnoses should be at the forefront of the differential diagnosis when confronted with otherwise unexplained brain edema' (Petrovic et al 2011).

52. If Adam developed any primary cerebral problem, such as cerebral venous sinus thrombosis and/or PRES, during 26th-27th November, he would have been at risk of hyponatraemia secondary to cerebral salt-wasting as well as antidiuretic hormone secretion. There are no urinary sodium readings which might help to resolve the possibility of a cerebral component to Adam's acute hyponatraemia.

53. Adam's blood pressure rose a little during the operation (058-008-023) and substantially post-operatively (058-008-022). It is possible that this was related to seizures but it is now impossible to prove or disprove this. During a seizure, cerebral blood flow

increases, which increases the cerebral blood volume and therefore increases the risk of intracranial hypertension if the reserve intracranial volume is exceeded. Seizures can cause brain damage in unconscious patients by excitotoxic mechanisms and also if the cerebral blood flow increase does not match the increase in cerebral metabolic demand (Kirkham MD thesis 2009).

54. The argument that Adam's acute cerebral oedema and brain death was caused by dilutional hyponatraemia is based on:

a. The fall in sodium. Adam had experienced similar levels of hyponatraemia on a number of previous occasions (brief for expert neurologist p.7).

b. The evidence for generalised oedema in the lungs and the rest of the body. It is now clear that Adam did not have pulmonary oedema

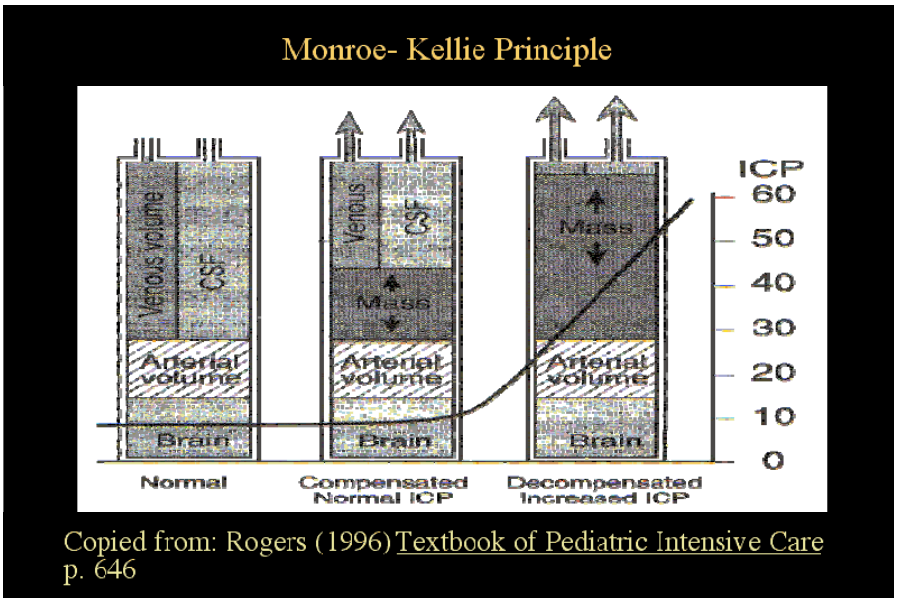
c. Dr Armour's autopsy evidence for massive generalised cerebral oedema. It is now clear that there are discrepancies in brain weight increases which mean that the cerebral oedema may not have been as severe as previously assumed and that the cerebral oedema involved the posterior fossa structures more than the forebrain.

d. The apparently extensive literature showing fatal cerebral oedema in children who had received hypotonic fluids containing 4-5% Dextrose and 0.18-0.3% sodium chloride, when many of the fatal cases appear to have received 5%

Dextrose or to have had other risk factors for developing acute cerebral oedema.

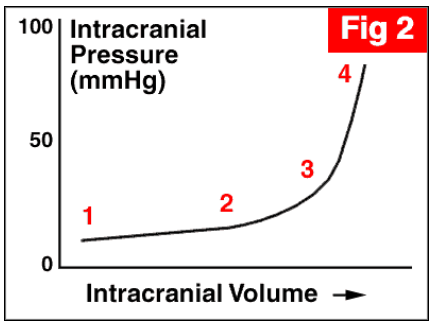
Although it is possible that the compensatory mechanisms were overwhelmed because of the rapidity of the fall in sodium and the associated shift of water into the brain along an osmotic gradient, on the balance of probabilities the rapid development of fatal posterior cerebral oedema was secondary to acute on chronic cerebral venous thrombosis, probably with the additional development of posterior cerebral oedema similar to that seen in cases of PRES.

55. The intracranial contents consist of three components; brain, blood (arterial and venous) and cerebrospinal fluid (Figure 1).



If there is a mass lesion or the volume of one of these components increases e.g. there is cerebral oedema leading to increased volume of the brain, there is some reserve capacity related to (i) reduction of venous blood volume by compression and/or drainage into the jugular veins and (ii) reduction of CSF

volume by increased absorption in the subarachnoid space over the brain and around the spinal cord. This is difficult to predict on an individual basis, but may be less in children as there is little cerebral atrophy meaning that the skull is almost completely full of brain. When the volume of the contents of the skull exceeds the reserve capacity, the intracranial pressure can go up extremely quickly because of the shape of the pressure-volume curve. The relationship between increasing volumes and intracranial pressure are shown in the enclosed diagram.



In Adam's case there was brain swelling, documented both on the CT scan of 27th November 1995 in comparison to that of 6th July 1995 and at post mortem, particularly posteriorly. There was likely to have been a reduction in both potential compensatory mechanisms: increase in venous drainage and increase in reabsorption of CSF. Firstly the ability to increase venous drainage is likely to have been compromised because there was a central line in his right jugular vein in addition to the high likelihood of acute on chronic venous sinus thrombosis and a ligated left external jugular vein. The rapid development of posterior cerebral oedema will have pushed the cerebellum down towards the foramen magnum,

thus reducing access to the the spinal sites for CSF absorption (Artru 1987) and therefore exacerbating a rapid increase in intracranial pressure which would be particularly likely to cause immediate brain death because the respiratory centre is in the posterior fossa.

56. The data on minimum cerebral perfusion pressure (Chambers et al) cited by Dr Dyer comes from children who have sustained a brain insult. Although as outlined above, I believe that Adam had sustained a primary brain insult, there is no evidence that he sustained borderzone ischaemia between the territories of the middle and anterior cerebral arteries of the type typically seen if perfusion pressure is reduced below the minimum threshold (Newton et al 1993).

57. In answer to paragraph 38 (1) under Requirements: It is very difficult to know what the expected reserve capacity in a four year old child would be. Because of variations in venous drainage and cerebrospinal fluid reabsorption it is impossible to state in an individual child (i) the reserve capacity (ii) what volume and rate of hypotonic fluid would cause death due to herniation from raised intracranial pressure. The relationship between intracranial volume and intracranial pressure is described by the diagram (Figure 2) but the precise point at which intracranial pressure starts to rise depends on the volume of blood, brain and cerebrospinal fluid and on anatomical factors such as the point at which the cerebellar tonsils fill the foramen

magnum, thus rapidly losing access to the spinal sites for CSF absorption (Artru 1987) which may be associated with rapid increases in intracranial pressure.

58. In answer to paragraph 38 (2) under Requirements: If Adam's total body water was expanded by 10% over a period of two and a half hours it would be very difficult to estimate the volume of free water sufficient to cause fatal cerebral oedema because of the large number of unknown variables.

59. In answer to paragraph 38 (3) under Requirements: It is very difficult to estimate what proportion of the free water infused would have contributed to Adam's cerebral oedema and what proportion would have diffused through other organs.

60. In answer to paragraph 38 (4) under Requirements: As Adam's pupils were fixed and dilated by 1200 on 27th November 1995 the fatal event almost certainly occurred before that time rather than after that time.

61. In answer to paragraph 38 (5) under Requirements: As discussed above I think that it is extremely likely that venous obstruction, with or without thrombosis, would have been present to a significant degree and contributed substantially to the severity of the cerebral oedema in Adam's case.

62. In answer to paragraph 38 (6) under Requirements: I think that it is likely that Adam's cerebral oedema would have progressed further after 1155 on the 27th November 1995 as there is often massive swelling after brain stem death. The cerebral oedema

could have continued to progress over that period, right up until ventilation was abandoned twenty-two hours later.

63. In answer to paragraph 38 (7) under Requirements: I think that Adam's cerebral blood flow was almost certainly compromised by obstruction to the jugular venous drainage, which would have contributed to his ultimate gross cerebral oedema. In addition, if he did have seizures intra-operatively, cerebral blood flow may not have been adequate for the increased metabolic demand, which could have led to a further vicious cycle of acute ischaemic brain swelling, seizures and ischaemia.

Declaration

I Fenella Kirkham DECLARE THAT:

1. I understand that my duty in providing written reports and giving evidence is to help the Court, and that this duty overrides any obligation to the party by whom I am engaged or the person who has paid or is liable to pay me. I confirm that I have complied and will continue to comply with my duty.

2. I confirm that I have not entered into any arrangement where the amount or payment of my fees is in any way dependent on the outcome of the case.

3. I know of no conflict of interest of any kind, other than any which I have disclosed in my report.

4. I do not consider that any interest which I have disclosed affects my suitability as an expert witness on any issues on which I have given evidence.

5. I will advise the party by whom I am instructed if, between the date of my report and the trial, there is any change in circumstances which affect my answers to points 3 and 4 above.

6. I have shown the sources of all information I have used.

7. I have exercised reasonable care and skill in order to be accurate and complete in preparing this report.

8. I have endeavoured to include in my report those matters, of which I have knowledge or of which I have been made aware, that might adversely affect the validity of my opinion. I have clearly stated any qualifications to my opinion.

9. I have not, without forming an independent view, included or excluded anything which has been suggested to me by others, including my instructing lawyers.

10. I will notify those instructing me immediately and confirm in writing if, for any reason, my existing report requires any correction or qualification.

11. I understand that;

    1. my report will form the evidence to be given under oath or affirmation;

    2. questions may be put to me in writing for the purposes of clarifying my report and that my answers shall be treated as part of my report and covered by my statement of truth;

    3. the court may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues between the parties;

    4. the court may direct that following a discussion between the experts that a statement should be prepared showing those issues which are agreed, and those issues which are not agreed, together with a summary of the reasons for disagreeing;

5. I may be required to attend court to be cross-examined on my report by a cross-examiner assisted by an expert;

6. I am likely to be the subject of public adverse criticism by the judge if the Court concludes that I have not taken reasonable care in trying to meet the standards set out above.

12. I have read Part 35 of the Civil Procedure Rules and the accompanying practice direction including the “Protocol for Instruction of Experts to give Evidence in Civil Claims” and I have complied with their requirements.

13. I am aware of the practice direction on pre-action conduct. I have acted in accordance with the Code of Practice for Experts.

Statement of Truth

I confirm that I have made clear which facts and matters referred to in this report are within my own knowledge and which are not. Those that are within my own knowledge I confirm to be true. The opinions I have expressed represent my true and complete professional opinions on the matters to which they refer.

Fenella Kirkham MD FRCPCH
Professor in Paediatric Neurology
Consultant Paediatric Neurologist
16th Feb 2012

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