MEDICAL REPORT

Adam STRAIN

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&

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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 Fellow 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) at University College London Institute of Child Health. 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 am 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 had had low or very low serum sodiums, e.g. in November 1991 (050-022-965; 049-030-166), April 1993 (055-053-120), December 1993 (055-054-159; 055-054-133; 055-054-160) and June 1995 (057-041-197) and rapid decreases of serum sodium e.g in January and February 1992 (050-024-162; 050024-128; 050-024-223; 050-024-215) but did not have seizures at these times.

10. 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 this check but his gross motor/locomotion skills appear to have been satisfactory. However, 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.

11. 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).

12. 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.

13. Adam was an inpatient during July 1995 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).

14. 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.

15. 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.

16. 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.

17. Adam had a shorter period of peritoneal dialysis than 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.

18. 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.

19. 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. Possibilities for these difficulties include intravascular volume depletion, as considered by Dr Taylor, and a vein having been ligated on this side (011-010-031, 011-010-041), although I note that these issues 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).

20. Adam had been dialysed overnight and as he had difficulty in cannulating the left subclavian vein, consistent with relatively

low intravascular volume, 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.

21. Induction was with Atropine 0.3, sodium thiopentone 125 mg and Atracurium 10 mg. Adam was anaesthetised with Halothane, an anaesthetic associated with an increase in cerebral blood flow, particularly in the occipital lobes (Reinstrup et al 1995). In theatre, Adam was also given 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.

22. Adam was started on a Cyclosporine infusion 3 mcg/kg/hr post-operatively (058-005-012, 057-018-026). Azathioprine 25 mg daily and Methyl Prednisolone 10 mg bd were continued post-operatively.

23. 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).

24. 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 in their combined table, when his total blood volume was 1600 ml. His haematocrit had fallen from 0.32 to 0.18 (32% to 18%) by 0932 on 27th November 1995 and he had an estimated haemoglobin of 6.1 g/dL according to the blood gas machine, compared with a pre-operative haemoglobin of 10.5 g/dl. This will have been associated with a reduction in arterial oxygen content of around 40%. This blood loss 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 initially 10.6 g/dL and latterly 14.4 g/dL. Although it has been suggested by Dr Haynes that this fall in haemoglobin was dilutional and not haemorrhagic, I have not been able to find any evidence that such a large fall in haematocrit is a feature of the previously reported cases who were documented to be hyponatraemic post-operatively or secondary to water intoxication (see paragraph 44). On the balance of probabilities I agree with the other experts, as

documented in the combined table, that Adam lost blood which required replacement.

25. 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 0932 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).

26. At 0932 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.

27. During the operation Adam's blood pressure was initially within the normal range (systolic 90-110 mmHg, diastolic 50-70 mmHg; mean 65-85 mmHg). From 0945, the diastolic pressure was greater than the 99.6th centile on 5 quarter-hourly readings and at 1115, the systolic pressure was also greater than the 99.6th centile (Jackson et al 1997). This was at least in part response to 2 small boluses of Dopamine (1 mcg/kg) to increase the perfusion pressure to the larger donor kidney without increasing fluids (011-014) and is an essential part of the procedure for the transplant of an adult-sized kidney into a child, as the adult kidney requires a higher perfusion pressure.

28. Although there were no large brief increases in blood pressure or heart rate suggestive of acute seizures or Cushing responses to intracranial hypertension, on the continuous recording just

before 1100 there were 2 small surges of blood pressure (058-008-023) of a similar order of magnitude documented in a deeply unconscious patient I was involved with who had an intracranial pressure monitor inserted (Kirkham and Neville 1987) and probably had circulatory compromise secondary to a thiopentone infusion.

29. Adam was already hypertensive as outlined in the paragraph above. In addition, a recent report from the CKiD study found cardiac disease in 24% of children on long-term dialysis: left ventricular hypertrophy/enlargement in 17%, congestive heart failure/pulmonary edema in 8%, cardiomyopathy in 2% and decreased left ventricular function in 2% (Chavers et al 2011). It is possible that Adam's slightly enlarged heart, likely secondary to chronic anaemia, 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.

30. Post-operatively Adam's blood pressure continued to rise (058-008-022).

31. Adam was given Diazepam on PICU (058-005-011) in case the increase in blood pressure was secondary to seizures, although this possibility was not investigated by undertaking an EEG.

32. Adam's high blood pressure was then treated with Nifedipine (058-005-011).

33. 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.

34. Adam failed to breathe or wake up at the end of the surgery and around midday on the 27th November 1995 his pupils were noted to be fixed and dilated. He was transferred to PICU where papilloedema and retinal haemorrhages were documented in addition to the fixed dilated pupils. Drs Savage and Taylor spoke to Adam's mother.

35. 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.

36. 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 and he thinks there was descent of the cerebellar tonsils

through the foramen magnum. The appearances were in keeping with the development of acute cerebral oedema particularly involving posterior cerebral structures but the cause of the cerebral oedema, e.g. excessive fluid intake or posterior reversible encephalopathy syndrome or cerebral venous thrombosis, cannot be determined without further neuroimaging (Petrovic 2011), as documented by Dr Anslow.

37. 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 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.

38. Adam was peritoneally dialysed overnight as his potassium was rising, but his blood pressure fell during dialysis and it had to be discontinued.

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

40. 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. There is ongoing uncertainty about the fresh and fixed weights of the brain. Dr Squier, the expert

neuropathologist instructed by the Inquiry, feels that the reported fresh 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 pre-existing cerebral malformation, hypoxic brain damage or ischaemic brain damage in a distribution consistent with reduced cerebral perfusion pressure. Dr Squier's report and her contributions to the expert meetings makes it clear that, although she cannot find any evidence for either venous sinus thrombosis or PRES, it is difficult to exclude these diagnoses.

41. Acute reduction in conscious level has been reported in water intoxication in childhood (Boetzkes et al 2010, Radojevic et al 2012). Interestingly, cerebral oedema was not documented on the CT scan of the 12 year old boy in Boetzkes' series, who drank 4 litres of tap water in an hour; although the weight of this child was not reported this is likely to represent a similar volume of free water ingested per kilogram per hour to the amount that Adam received before 1000 on 27th November. The results of any neuroimaging undertaken were not reported at all in the other 3 recent cases in these 2 manuscripts (Boetzkes et al 2010, Radojevic et al 2012); as publications usually include positive findings it is unlikely that these children had obvious cerebral oedema on any neuroimaging that was performed.

42. Arieff (1985) reported the neurological consequences, including fatal cerebral oedema, of hyponatraemia documented in the first

few post-operative days in young women and attributed the fall in sodium to a combination of (a) administration of excess water and (b) fluid retention in the context of antidiuretic hormone secretion. Ayus et al (1992), from the same group, published further data in a paper on post-operative hyponatraemia in menstruating women. However, this is a controversial area as studies from other centres have failed to find hyponatraemia in association with post-operative cardiac arrest (Wijdicks and Laeson 1994, Chawla et al 2011). For example, Wijdicks et al (1994) failed to identify a single case of post-operative hyponatraemia in nearly 300,000 operations in women at the Mayo clinic while Chawla et al found that mortality was higher in those with moderate compared with profound hyponatraemia (sodium <120 mmol/L) and there only one patient, who had had a stroke, who died with cerebral oedema. Many authorities now consider that sick patients die *with* rather than *from* hyponatraemia (Chawla et al 2011).

43. 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. There is no evidence that these children had papilloedema or retinal haemorrhages. Again, he discusses causation in terms of the combination of (a) administration of hypotonic fluids and (b) fluid retention in the context of antidiuretic hormone excretion. I have not been able

to ascertain from his paper or that of Moritz and Ayus (2005) from the same group, who quoted 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). I did not receive a response to my email to Dr Arieff requesting further information on the nature of the fluids given.

44. 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. Dr Bohn's email in reponse to mine requesting further information on fluids given did not contain information not already gleaned from his published papers and he made it clear that no further information is available.

45. 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).

46. In his 1992 paper, Arieff noted that most of the infants and children reported previously had had cent.ral 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 pre- and/or post-operative hypoxia (tonsillitis, adenotonsillectomy, pneumonia). Dr Haynes' paragraph 20 responding to paragraphs 35 and 36 in my previous report assumes that patients undergoing adenotonsillectomy are at greater risk of post-operative hypoxia only. I now make it clear that any pre-operative hypoxic exposure might also have affected the behaviour of the mechanisms for water and ionic balance at the membrane of brain cells by up- or down-regulating critical genes coding for key proteins in brain water balance, such as the Aquaporins (Abreu-Rodriguez et al 2011), in these previously reported patients.

47. I have not been able to find full blood count data from Arieff's series or the 2 Toronto series or the 8 French patients reported by Paut et al 2000 and Sicot. I emailed Drs Arieff and Bohn asking for haematocrit data. It is clear from Dr Bohn's reply that the data are no longer available from the Toronto series, while there has been no response to my request for further information from Dr Arieff. Since abnormal data are more likely to have been reported than normal data, on the balance of probabilities there is no evidence for dilutional anaemia in association with the hyponatraemia reported by these authors. In Boetzkes' second case, a 12 year old boy who drank 4 litres

of tap water in an hour and in who dilutional anemia was diagnosed, the haematocrit was 33% with a haemoglobin of 12g/dL when the lower limits of normal at this age are 35% and 13g/dL; alternative explanations e.g. iron deficiency were not excluded and the follow-up data were not reported. My inspection of the notes of another child under consideration by the Hyponatraemia Inquiry also found no evidence of a fall in haemoglobin (12.2 g/dL) in association with hyponatraemia and the administration of 0.18% saline 5% Dextrose. I therefore disagree with Dr Haynes that the main cause of Adam's fall in haemoglobin to 6.1 g/dL was dilutional anaemia and consider that acute blood loss is a much more likely explanation.

48. Eleven of the 16 children 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.

49. 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, which might be potentially epileptogenic or might predispose 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 neuroimaging was reported to show cerebral oedema

in all 16 cases in Arieff's 1992 series, this is reported in the Discussion and there are no details on severity or distribution. 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.

50. Arieff's paper cited previous papers and the series has subsequently been extensively cited, as well as being reproduced in the paper by Moritz and Ayus (2005) which summarises the literature up to 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 in an excel spreadsheet 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 spreadsheet.

51. 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).

52. I have found 5 cases of cerebral oedema in children without pre-existing central nervous system disease, 4 fatal and one with

severe neurological sequelae, where the fluid administered was 0.18%-0.3% sodium chloride in 4 or 5% Dextrose. Two had had a tonsillectomy (McRae 1994) and had evidence for hypoxia (blood loss in one, low saturation in the other) 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.

53. 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 in the context of child abuse involving physical trauma as well (Arieff and Kronlund 1999) or the use of 5% Dextrose post-operatively (Paut et al 2000, Sicot 2006) or in influenza or dehydration where cerebral compromise is likely (e.g. Jackson, Keating quoted in Moritz and Ayus 2005).

54. 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).

55. 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

56. 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. As discussed above, the other children who died having been given hypotonic intravenous Dextrose with sodium had risk factors for hypoxia (n=1) or risk factors for cerebral venous sinus thrombosis without having this condition excluded (n=3).

57. 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).

58. 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.

59. Adam had renal dysplasia with bilateral large cysts. His kidneys were abnormally shaped and he had abnormally dilated ureters.

60. Adam also had severe feeding difficulties and expressive language delay.

61. There is no neuroimaging or post mortem evidence that Adam had an underlying cerebral abnormality pre-operatively, although as Dr Anslow and Dr Squier point out, subtle abnormalities cannot be excluded.

62. Dr Coulthard points out that developmental delay is common in children with chronic renal failure with which I concur. Problems with general intelligence, attention, memory and executive function appear to be very common (Lawry et al 1994, Jaramillo-Solorio et al 1994, Honda et al 1998, Brouhard et al 2000, Madden et al 2003, Gerson et al 2006, Slickers et al 2007, Duquette et al 2007, Gipson et al 2007). Language problems have been reported in some series but tend to involve verbal abstraction difficulties or problems in the context of hearing loss (Fennell et al 1990 a,b, Gipson et al 2007). I have not been able to find any evidence that expressive language delay, out of proportion to receptive language ability, is a feature of chronic renal failure (CRF) in young children and on the balance of probabilities, I think that this is an important difference for Adam compared with other young children with CRF.

63. Dr Coulthard also states that many young children with CRF are fed by nasogastric tube or gastrostomy because appetite is reduced (Coulthard at al 2002) and he has very usefully provided from these data a graph illustrating this. However, I think that tube feeding in Adam was essential because he had a significant movement disorder affecting sucking, chewing and swallowing. On the balance of probabilities I think that this specific movement disorder affecting his sucking, chewing and swallowing is not that seen in other children with CRF and, together with his expressive language problems, is consistent with a neurological disorder affecting bulbar function.

64. Adam had at least four risk factors for chronic or acute venous thrombosis which could have involved the cerebral venous sinuses: (i) from November 1993 he was appropriately on erythropoietin, which has been associated with cerebral venous thrombosis (Casati et al 1987; Finelli and Carley 2000, Lage et al 2002), 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 (ii) he was polyuric and therefore intermittently at risk of dehydration. For example, Adam became dehydrated during episodes of diarrhoea e.g. on 30th April 1992 (053-027-075) and vomiting e.g. on 28th November 1992 (016-073-115) which would have put him at risk of cerebral venous sinus thrombosis

CSVT) which often recannalises spontaneously (iii) he was given Methyl prednisolone as immunosuppression for the donor kidney during his transplant. Venous thrombosis is a recognised complication of renal transplantation (Coulthard et al 2002, Moscarelli et al 2011); although the use of steroids is a recognised risk factor (Allen et al 1987) the link has received relatively little attention. Acute onset of symptoms of cerebral venous sinus thrombosis has been documented during administration of Methyl Prednisolone for multiple sclerosis (Stolz et al 2003) and leukaemia (Nowak-Gottl et al 2003) and appears to be preventable by the use of prophylactic subcutaneous heparin (Kalanie et al 2011, Mitchell et al 2011) (iv) Adam also had chronic anaemia, considered at least in part to be secondary to iron deficiency. Dr Coulthard in his response to my previous report has mainly focussed on the haematological results available at the time of the transplant. Although Adam was not iron deficient at the time of his transplant, he had previously had low Ferritins and had been appropriately been treated with iron supplementation. Both anaemia (Zafeiriou et al 2011 in Ganesan and Kirkham 2011) and iron deficiency (Sebire et al 2005, DeVeber in Ganesan and Kirkham 2011) are associated with cerebral venous sinus thrombosis in childhood. In one series red cell indices consistent with anaemia and iron deficiency were documented in 55% and 52% of children with cerebral venous sinus thrombosis

respectively and 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). In addition, Adam may have had other risk factors for venous sinus thrombosis (DeVeber in Ganesan and Kirkham 2011, Petrovic 2011). He may have had a jugular vein ligated, he had a central venous line in the neck during his renal transplant, his head was turned, and his head was down, probably reducing venous flow. Chronic renal failure is also associated with hyperhomocysteinaemia (Merouani et al 2001), another risk factor for venous sinus thrombosis (Cantu et al 2003, DeVeber 2011); it is unlikely that homocysteine would have been measured in Adam in the early 1990s. Venous sinus thrombosis may present with chronic neurological symptoms e.g. difficulty in using one arm and/or leg (Sebire et al 2005 Figure 3) and is associated with acute cerebral (Sebire et al 2005 Figure 1) and cerebellar (Eng et al 1990) swelling, status epilepticus and brain death (Sebire et al 2005 Figure 1, DeVeber in Ganesan and Kirkham 2011). Venous sinus thrombosis is difficult to exclude even in 2012 as plain CT scan misses a substantial proportion (DeVeber 2011 in Ganesan and Kirkham 2011, Petrovic 2011). As Dr Anslow says, venous sinus thrombosis cannot be excluded on Adam's post-operative CT

scan. There are few recent autopsy data (DeVeber 2011 in Ganesan and Kirkham 2011). Dr Squier cannot find evidence for cortical or cerebral venous sinus thrombosis but she does not consider that venous sinus thrombosis was completely excluded at the post mortem. Chronic venous sinus thrombosis is a possible cause of Adam's previous rather subtle neurological problems not usually seen in children with CRF (feeding difficulties, expressive language delay, limp). Further acute thrombosis in the venous sinuses may have been associated with acute posterior cerebral oedema during the operation (Petrovic 2011).

65. 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, and Adam's position, with the head down and turned, during the operation, 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.

66. I agree with Dr Coulthard that Posterior Reversible Encephalopathy Syndrome (PRES) is the same condition as hypertensive encephalopathy as recognised by renal physicians for many years. Dr Coulthard's response to my report gives an excellent account of the clinical manifestations of hypertensive encephalopathy and the neuroradiological findings in PRES. Dr Coulthard lists the clinical symptoms and signs and I agree that this list is comprehensive. Although Adam was anaesthetised and so could not have complained of headache or visual loss or have manifested vomiting or clinical seizures, he did have papilloedema and retinal haemorrhages when examined by at least 3 doctors post-operatively, including Dr Webb and he was unconscious at the end of the procedure which I consider were clinical signs consistent with PRES. Whilst I agree that Adam did not have PRES or hypertensive encephalopathy at the beginning of his renal transplant I disagree with Dr Coulthard as I think that Adam did have PRES or hypertensive encephalopathy clinically by the end of the procedure. Retinal haemorrhages are characteristic of hypertensive encephalopathy (Aryan et al 2005) while retinal haemorrhages do not appear to have been documented in fatal cerebral oedema associated with hyponatraemia (Moritz and Ayus 2005) and it has been argued that the infants reported with retinal haemorrhages and reduced conscious level in the context of

hyponatraemia may have been the victims of non-accidental injury (Krugman et al 2000, Rubin et al 2001).

67. Adam had at least 4 risk factors for PRES. (i) From the continuous recording, Adam's blood pressure rose to above the 99.6th centile towards the end of the operation (058-008-023) and rose further post-operatively (058-008-022). From the quarter hourly readings, Adam's diastolic blood pressure went above the upper limit of the normal range during the operation after 0945 and his systolic blood pressure was above the normal range at 1115. This was part of the paediatric renal transplant protocol related to the need to increase perfusion to the kidney donated by an older person. (ii) Adam required a blood transfusion (Sato et al 2011) because of the blood losses during transplantation. (iii) Adam had had Erythropoietin (Delanty et al 1997) (iv) He was started on the immunosuppressant agents Azathioprine 25 mg during the renal transplant and on a Cyclosporine infusion immediately afterwards. PRES, which is not always reversible and may be fatal (Schiff and Lopes 2005), has been described in renal disease (Gumus et al 2009, Yamada and Ueda 2012), specifically after transfusion (Sato et al 2011) as well as in association with hypertension as covered by Dr Coulthard. Blood transfusion associated PRES is also well recognised in other conditions where there is chronic anaemia (Zafeiriou et al in Ganesan and Kirkham 2011) and may be related to the rapid transfusion of blood in a chronically anaemic

patient (Huang et al 2008). Immunosuppression with Azathioprine (Foocharoen et al 2006), as well as Cyclosporine (Ganesan and Kirkham 2011, Petrovic 2011), is also a common association with PRES. PRES can be associated with the development of more generalised cerebral oedema (Bartinski et al 2008a,b, Petrovic et al 2011, 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. Neither Dr Squier or Dr Anslow can exclude PRES on neuroradiological or neuropathological grounds. Given the retinal haemorrhages, I consider it that, on the balance of probabilities, the development of PRES was the initial trigger for the development of mainly posterior cerebral oedema in Adam's case.

68. CVST and PRES were not widely diagnosed radiologically in 1995, as Dr Coulthard points out, 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).

69. If Adam developed any primary cerebral problem, such as PRES, and/or cerebral venous sinus thrombosis, during 26th-27th November, he would have been at risk of hyponatraemia secondary to compromise of the cellular sodium pumping

mechanism, which requires energy, as well as antidiuretic hormone secretion. There are no urinary sodium readings which might help to resolve the mechanism of the cerebral component to Adam's acute hyponatraemia.

70. It is possible that the further short increases in blood pressure documented just before 1100 related to increases (waves) of intracranial pressure alone or in the context of the development of seizures. However, no EEG was undertaken and it is now impossible to prove or disprove the presence of seizures intra- or post-operatively. 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 also cause brain damage in unconscious patients by excitotoxic mechanisms, i.e. by generating toxic chemicals in vulnerable regions such as the hippocampus (Scott and Kirkham 2007), and also if the cerebral blood flow increase does not match the increase in cerebral metabolic demand (Kirkham MD thesis 2009). The key question is whether the seizures were a potentially reversible factor in the finding of fixed dilated pupils after Adam failed to breathe at the end of surgery. I would have done an EEG as soon as possible after he came back from theatre to exclude status epilepticus as a potentially treatable cause of his fixed dilated pupils as I was aware of the paper by Horwitz et al (1980) on abnormal pupillary responses secondary

to seizures in bacterial meningitis. However, Diazepam, an anticonvulsant, was given and did not make any difference so either (a) there were never any seizures or (b) if seizures had been present treating them with Diazepam on PICU could not reverse the cerebral herniation.

71. 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 and similar rates of fall in sodium on a number of previous occasions (brief for expert neurologist p.7) and had not experienced seizures or loss of consciousness. I have not been able to find any literature supporting the notion that the rate of fall of sodium is critical in causing cerebral oedema. Arieff (1992) did not find any evidence for an effect of rate of fall of sodium on outcome. The 12 year old boy who drank 4 litres of water in an hour and had a sodium of 120 mmol/L at presentation, presumably a fall of at least 15 mmoles/L from the normal range of >135 mmol/L, did not have cerebral oedema on CT scan. I would be happy to review any papers on speed of fall of sodium and cerebral oedema provided by the other experts.

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. Although I have translated the French text in Sicot's case as reporting cerebellar swelling, this may have referred to herniation; this appears to be the only case where localised posterior cerebral oedema was documented in association with acute hyponatraemia.

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. The case reports on which this hypothesis are based have not usually excluded or even considered aggravating factors e.g. hypoxia (Ayus et al 2008), alternative diagnoses e.g. cerebral venous sinus thrombosis or predisposing conditions e.g. metabolic conditions or anatomical variants.

72. In Adam's case the shift of free water into the brain along an osmotic gradient will have led to a degree of cerebral swelling and I accept Prof Gross' carefully considered estimate of a 9%

increase in brain volume. However, if the brain was not compromised, the ion exchange pumps in the cell membrane should have continued to pump sodium out of the brain cells and water should then have followed down a diffusion gradient. Therefore if there was a 9% increase in brain water because of the free water crossing down the osmotic gradient, if these pumps, which require energy, were functioning, the brain water is unlikely to have exceeded the reserve capacity and I therefore disagree with the statement in Prof Gross' first report that the brain oedema alone would have been likely to lead to fatal cerebral herniation.

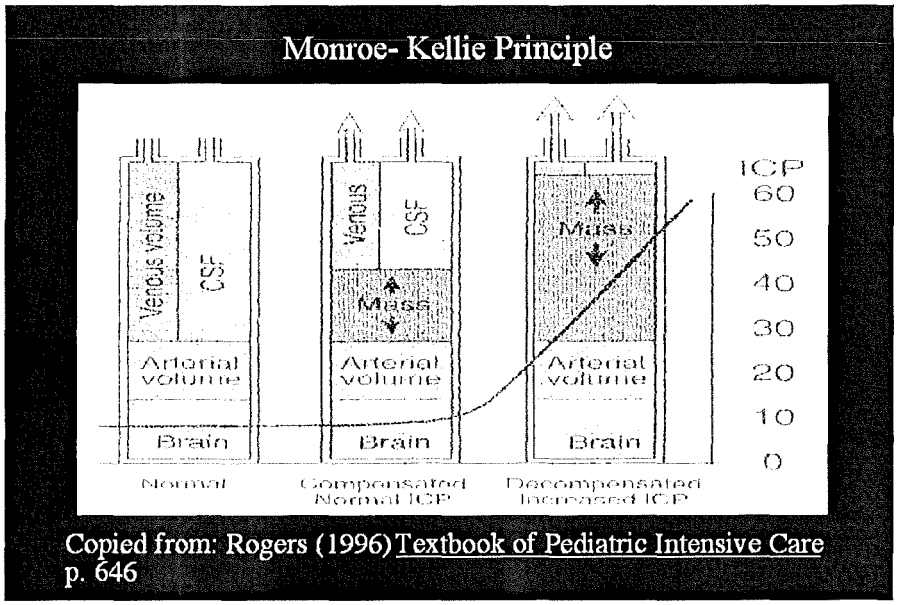
73. In the light of Dr Coulthard's view that some suggestions in my first report on the pathophysiology of Adam's failure to breathe post-operatively were speculative, I have carefully reviewed the facts of Adam's case and how they best fit the 3 possibilities that the experts have discussed (i) fatal cerebral oedema secondary to dilutional anaemia (ii) cerebral venous sinus thrombosis (iii) posterior reversible encephalopathy syndrome. We have no evidence for Adam's (a) urine output or (b) urinary sodium and (c) his CVP reading was unreliable. Dr Coulthard made the point that Adam may have stopped passing urine intraoperatively, as apparently occurs during renal transplantation and I wonder whether this may represent antidiuretic hormone secretion; however, again without accurate data for (a), (b) and (c) we do not know whether or not this occured. We do not have any

evidence that Adam had (d) seizures or (e) cerebral venous sinus thrombosis. We do not have (f) an accurate measure of his brain weight at autopsy and we cannot be sure whether or not he had had a jugular vein tied off on the left side. However, he did not have brain damage in a distribution between the borderzones between the anterior, middle and posterior cerebral arteries consistent with reduced cerebral perfusion pressure. In addition, he did have (A) cerebral oedema with affecting white matter and with a posterior predominance, (B) a blood pressure above the normal range for his age after 0945 and (C) retinal haemorrhages. I therefore think that, with the combination of this clinical presentation, including the presence of retinal haemorrhages, and the neuroradiological/ neuropathological distribution, on the balance of probabilities the rapid development of fatal posterior cerebral oedema was secondary to development of hypertensive encephalopathy/PRES. Although this was an obligatory blood pressure increase for a young child like Adam transplanted with an adult-sized kidney, it was probably the major contribution to the development of PRES. Neuroradiological abnormalities consistent with PRES have also been documented in 20-30% of patients with no evidence of hypertension and Adam also had some of these additional risk factors.

74. In fact, there is some evidence that there is less oedema in PRES if the hypertension is worse (Petrovic 2011), perhaps

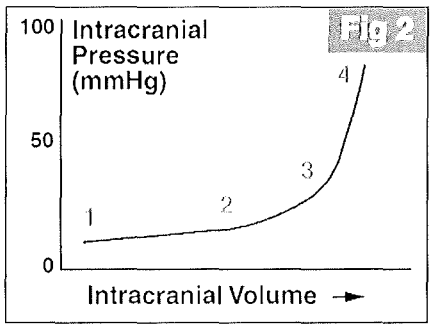
because there are vascular effects of prior hypertension which reduce the effects of intravascular volume overload. Once the vasogenic oedema of PRES had started and the brain had become compromised, the additional volume of crystalloid (free water) and perhaps of colloid (blood) is likely to have exacerbated the cerebral oedema and very recent evidence suggests that controlling fluid volume, e.g. with ultrafiltration or dialysis, may be an appropriate treatment (Gungor et al 2012). I am not an expert on whether dialysis or ultrafiltration could have been commenced in theatre during a renal transplant.

75. 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 he was head down with his head turned and there was a central line in his right jugular vein in addition to the possibility 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 spinal sites for CSF absorption (Artru 1987) and therefore exacerbating a rapid increase in intracranial pressure which would be particularly likely to cause immediate irreversible compromise to the brain stem because the respiratory centre is in the posterior fossa.

76. The data on minimum cerebral perfusion pressure (Chambers et al 2005, 2006) 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).

77. 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.

78. 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. However, as discussed above, I think that if the cellular ionic pumps had been working in a normal brain, the excess water in the brain is likely to have been less than the 9% estimated in Dr Gross' first report. I think that Adam's brain is unlikely to have been compromised from 0700 to 0945 and thus water will have diffused out of the brain as the ion exchange pumps will have been functioning and the volume of the brain is very unlikely to have exceeded the skull's reserve capacity.

79. 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.

80. In answer to paragraph 38 (4) under Requirements: As Adam's pupils were fixed and dilated by 1200 on 27th November 1995 and he had evidence of cerebellar herniation on the CT scan performed before 1400, the fatal event almost certainly occurred

before 1400, and probably before 1200, rather than after that time.

81. In answer to paragraph 38 (5) under Requirements: As discussed above I think that it is 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. I do not think that the position of Adam's head will have made a difference to the distribution of oedema in the brain by itself, e.g. by gravity. However, the vertebral venous plexus, through which blood not exiting through the jugular venous system is likely to flow, is affected by position, being more effective in the upright rather than the supine position. The head down position is likely to further restrict venous outflow through this plexus and this may be critical if a compensatory reduction in blood volume is required in the context of an increase in brain volume. In addition, there is evidence for children with acute brain insults, e.g. secondary to head injury, that maintaining a head up position reduces intracranial pressure.

82. 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 he was given cyclosporine, there may have been seizures and 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.

83. In answer to paragraph 38 (7) under Requirements: I think that Adam's cerebral blood flow was probably compromised by reduced jugular venous outflow because his head was down and turned to the side, regardless of whether a left jugular vein was tied off. Once a cerebral insult had been sustained, this is likely to 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.

84. I have been asked to comment on page 9 of Prof Gross' report as follows:

a. The possibility that Adam's blood flow was compromised reducing the oxygenation of blood

Adam's haemoglobin fell from 10.5 g/dL at the start of the operation to an estimated 6.1 g/dL at 0932. This will have been associated with a reduction in arterial oxygen content of around 40%. For the maintenance of cerebral oxygen delivery and avoidance of tissue hypoxia, the cerebral blood flow will have been required to increase by 40% and this may not have been possible in a child whose cerebral blood flow is already likely to have been increased in the context of his chronic anaemia. I

therefore think that the fall in haemoglobin, which I believe to mainly haemorrhagic rather than dilutional, is likely to have increased the risk of brain tissue hypoxia. I do not think a mechanism invoking cerebral perfusion pressure needs to be invoked and would point out (a) that the published data on cerebral perfusion pressure in children refers to those who have suffered a brain injury and (b) that Adam's scan and autopsy do not show the typical borderzone ischaemia associated with reduced perfusion.

b. *The relevance, if any, of the administration of dopamine to Adam*

I agree with Prof Gross that at the dose given, Dopamine is vasodilatory. In fact this vasodilatation, alongside the vasodilation associated with Halothane associated with increased cerebral blood flow in the occipital region, may also have reduced the capacity of the cerebral circulation to further vasodilate during acute anaemia so there is no need to invoke a vasoconstrictor mechanism for the appropriate use of Dopamine to have been a further risk factor for tissue ischaemia and hypoxia in the critical situation faced in Adam's case.

c. *Explain whether or not it is possible for hypoxia to occur without any evidence thereof on autopsy, and give the reasons for your answer.*

Hypoxia has a very wide spectrum of effects on tissues through a variety of mechanisms at a wide range of exposures over a variety of time frames and with individual responses which are currently difficult to predict, e.g. during rapid ascent to altitude. It is therefore perfectly possible for mild hypoxic exposure, e.g. during the reduction in haemoglobin, to have triggered a series of events leading to cerebral oedema without leaving autopsy evidence characteristic of e.g. birth asphyxia.

85. I have been asked by Dr Coulthard to comment on how Adam's case differed from other 4 year old boys with CRF undergoing renal transplantation. In addition to his neurological difficulties, including limp, feeding and expressive language problems, he was one of the 25% with some evidence of cardiac compromise. Dr Coulthard's 2002 paper from a contemporaneous series in the UK makes it clear that there is a mortality of 11% overall for children who are transplanted after requiring treatment for chronic renal failure in early life. In fact 4% died acutely in the context of transplanted kidneys which did not function. This compares with a total mortality of 11% but an acute mortality of 0.8% across the entire paediatric age range (Postlethwaite et al

1999). Although this series did not include Adam's case as he required dialysis at a slightly older age, it is clear that his acute death was not unique in that era.

86. I do not consider that there is any evidence that Adam's condition was irreversible between 0700 and 0945 because the additional risk factors for the development of tissue hypoxia (the blood loss) and PRES (the blood transfusion and the increase in diastolic blood pressure) did not come into play before 0930 and on the balance of probabilities, Adam's brain was functioning normally during that period of time. I think that after he became hypertensive, PRES gradually developed and the cerebellum herniated through the foramen magnum at some time between 0945 and 1400 and probably between 1100 and 1200 on 27th November 1995.

87. To summarise, I do not think that hyponatraemia was the primary cause of Adam's death. I have found no evidence in the literature that infusing a high volume of free water or developing a low sodium over 2-3 hours, either separately or together, overwhelms the brain's ability to adapt sufficiently through extrusion of sodium through the ion channel pumps with passive diffusion of water out of the cell, to cause fatal cerebral oedema unless the brain is already compromised by hypoxia or ischaemia. I think that if dilutional hyponatraemia was the primary cause, the cerebral oedema would be more equally distributed whereas the distribution of oedema in Adam's case

was posterior, more in keeping with hypertensive encephalopathy or posterior reversible encephalopathy syndrome. If Adam had had hyponatraemia without hypertensive encephalopathy and the development of posterior cerebral oedema, I think he would have survived.

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
28th Mar 2012

Author	Fluid	n
Arieff 1992 BMJ	Glucose 280 mmol/L in water or sodium chloride 38 mmol/L	16
Choong 2006 meta-analysis	Hypotonic vs isotonic	404 in 6 st
Dearlove	0.45% saline 5% Dextrose post appendicectomy	104
Hanna Tibby Murdoch		30 of 91
McRae 1994	5% Dextrose, 5% Dextrose/0.2% NaCl	3
Wilkinson E 1992 Pediatr Neurosurg	5% dextrose and electrolyte No. 48 and normal saline	2 of 56
Hoorn EJ 2004 Pediatrics		40
Halberthal M 2001 BMJ	Hypotonic'	23
Chung HM 1986 Ann Intern Med		
McCormick A 1999 Paediatr Anaesth		
Dunn K 1997 J Paediatr Child Health		21
Crumpacker AW 1973 Neurology		
Sarnaik AP 1991		
David R 1981		
Judd BA 1987 Aca Paediatr Scand		
Cowley DM 1988 Aust NZ J Surg	5% Dextrose (and 'hypotonic saline')	2 of 10
Varavithya J Pediatr 1967	?	18
Gomola 2002	Ringer's; D5 NS 0.33	1
Hughes P Aust NZ J Surg	Hartmann's; 0.18% saline 4% Dextrose	1 child
Auroy 2008	Dextrose 5%	1
Cansick	Hartmann's; 0.45% saline alternating with 0.45% saline 2.5% Dextrose	1
Bhalla 1999	Oral 'juice'	4
Playfor 2003	0.18% saline 4% Dextrose	1
Cohen ISMP	Dextrose 5% in one; ?	2
Paut 2000	Dextrose 5%	7
Sicot	Dextrose 5%	1
Donaldson McWilliam	0.45% saline	2
Walker	Water-irrigation bladder	1
Carpenter	Normal saline	1
Boetzkes	DDAVP; water	2
Fiser 1986 cited in Chen and Huang	Posterior pituitary extract, water	1
Radovejic	Water	2

AS - EXPERT

Na+	Headache	Lethargy	Confusion	Irritability	Seizures	N&V	GCS	Pallor	CT	MRI
115 (7)		+								
16/52 had Na+ <133; 7 <130		0	0	0	0	0				
30/91 <136; 10/91 <130					4					
115, 122, 119					3	2			3	
121, 122					2 of 56					
	-				-	10+25				
<130					18					
				11	3					
118, 122					1					
123 (5)		+			+			+		
			1			1				N
120							6		Oedema	
125, 121					1				Oedema	
116, 118, 119, 128 (126)					4				Oedema	
120									Oedema	
					2				Oedema	
					7				Oedema	
115					1				Oedema	
					2				Oedema	
120					1				Oedema	
									Oedema	
118, 120	1									
128										

208-007-117

ECHO	Cerebral oedema	Respiratory arrest	Brain death	Died	Predisposing to CVST?	Predisposing to PRES?
	9	16	9			
				0		
	2 of 3		2	2 of 3		
				0		
			?	1		
			5	5	?	?
		0	0	4 day 9-60		
	1	1	1	1		
			?	4		
	0		0	0		
LV dys	1	1	1	1		
	1	1	1	1		
	01-Feb	0	0	0		
	1	1	1	1	Gastroenteritis	
	2		2	2		2nd had coarctaion ?BP
			1	1	1 ear infections	
	1	1	1	1		
	2		0	1		
	1		1	1		
	1			0		
QT incr	0			0		
	1			1		
				0		

Hypoxia	Conditions predisposing hypoxia	Anaemia	Neuro
pO2 6.0 (1.5) in 11 after RA	Tonsillitis/Ts&As (7), nosebleed (1), pneumonia (1)	-	
	All bronchiolitis		
Blood loss in 1, saturation 8% in 1	Addenotonsillectomy	?	
			+
?			?
?		?	?
			3
			2
		1	7
			1
			1
			1
1	Post-op Ts and As		
2	Post-op Ts and As		3
1	Post-op Ts and As		
			1
1	Post-op Ts and As		

Conditions predisposing neuro	Renal	Gastro	Post-op	Urine	Vomiting	NG	CSF	Water xs
Hydrocephalus (1), orchidopexy (1), trauma (4)				34 (34)	10	2	1	
	-							
Adenotonsillectomy								
Craniofacial	-							
	?	?	13					
2 congenital, 1 encephalopathy	2+3 (1 died)							
Scoliosis	-							
Meningitis, meningocoele, hydrocephalus	0	7						
Cleft palate	-							
Scoliosis	-							
Meningitis, Epilepsy	1							
		1						
Squint (2); Developmental delay+epilepsy (1)	0							
Subarachnoid	0							
	0							
	0							

Abreu-Rodríguez I, Sánchez Silva R, Martins AP, Soveral G, Toledo-Aral JJ, López-Barneo J, Echevarría M. Functional and transcriptional induction of aquaporin-1 gene by hypoxia; analysis of promoter and role of Hif-1α. PLoS One. 2011;6(12):e28385.

Allen RD, Michie CA, Murie JA, Morris PJ. Deep venous thrombosis after renal transplantation. Surg Gynecol Obstet. 1987 Feb;164(2):137-42.

Arieff AI, Ayus JC, Fraser CL. Hyponatraemia and death or permanent brain damage in healthy children. BMJ. 1992 May 9;304(6836):1218-22.

Arieff AI, Kronlund BA. Fatal child abuse by forced water intoxication. Pediatrics. 1999 Jun;103(6 Pt 1):1292-5.

Artru AA. Reduction of cerebrospinal fluid pressure by hypocapnia: changes in cerebral blood volume, cerebrospinal fluid volume, and brain tissue water and electrolytes. J Cereb Blood Flow Metab. 1987 Aug;7(4):471-9.

Ayus JC, Achinger SG, Arieff A. Brain cell volume regulation in hyponatremia: role of sex, age, vasopressin, and hypoxia. Am J Physiol Renal Physiol. 2008 Sep;295(3):F619-24.

Boetzkes S, Van Hoeck K, Verbrugghe W, Ramet J, Wojciechowski M, Jorens PG. Two unusual pediatric cases of dilutional hyponatremia. Pediatr Emerg Care. 2010 Jul;26(7):503-5.

Brouhard BH, Donaldson LA, Lawry KW, McGowan KR, Drotar D, Davis I, Rose S, Cohn RA, Tejani A. Cognitive functioning in children on dialysis and post-transplantation. Pediatr Transplant. 2000 Nov;4(4):261-7.

Cansick J, Rees L, Koffman G, Van't Hoff W, Bockenhauer D. A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation. Pediatr Nephrol. 2009 Jun;24(6):1231-4.

Cantu C, Alonso E, Jara A, Martínez L, Ríos C, Fernández Mde L, Garcia I, Barinagarrementeria F. Hyperhomocysteinemia, low folate and vitamin B12 concentrations, and methylene tetrahydrofolate reductase mutation in cerebral venous thrombosis. Stroke. 2004 Aug;35(8):1790-4.

Casati S, Passerini P, Campise MR, Graziani G, Cesana B, Perisic M, Ponticelli C. Benefits and risks of protracted treatment with human recombinant erythropoietin in patients having haemodialysis. Br Med J (Clin Res Ed). 1987 Oct 24;295(6605):1017-20.

Chambers IR, Stobbart L, Jones PA, Kirkham FJ, Marsh M, Mendelow AD, Minns RA, Struthers S, Tasker RC. Age-related differences in intracranial pressure and cerebral perfusion pressure in the first 6 hours of monitoring after children's head injury: association with outcome. Childs Nerv Syst. 2005 Mar;21(3):195-9.

Chambers IR, Jones PA, Lo TY, Forsyth RJ, Fulton B, Andrews PJ, Mendelow AD, Minns RA. Critical thresholds of intracranial pressure and cerebral perfusion pressure related to age in paediatric head injury. J Neurol Neurosurg Psychiatry. 2006 Feb;77(2):234-40.

Chavers BM, Solid CA, Sinaiko A, Daniels FX, Chen SC, Collins AJ, Frankenfield DL, Herzog CA. Diagnosis of cardiac disease in pediatric end-stage renal disease. Nephrol Dial Transplant. 2011 May;26(5):1640-5.

Chawla A, Sterns RH, Nigwekar SU, Cappuccio JD. Mortality and serum sodium: do patients die from or with hyponatremia? Clin J Am Soc Nephrol. 2011 May;6(5):960-5.

Coulthard MG, Crosier J. Outcome of reaching end stage renal failure in children under 2 years of age. Arch Dis Child. 2002 Dec;87(6):511-7.

Duquette PJ, Hooper SR, Wetherington CE, Icard PF, Gipson DS. Brief report: intellectual and academic functioning in pediatric chronic kidney disease. J Pediatr Psychol. 2007 Sep;32(8):1011-7.

Eng LJ, Longstreth WT Jr, Shaw CM, Eskridge JM, Bahls FH. Cerebellar venous infarction: case report with clinicopathologic correlation. Neurology. 1990 May;40(5):837-8.

Fennell RS, Fennell EB, Carter RL, Mings EL, Klausner AB, Hurst JR. Association between renal function and cognition in childhood chronic renal failure. Pediatr Nephrol. 1990 Jan;4(1):16-20.

Fennell RS, Fennell EB, Carter RL, Mings EL, Klausner AB, Hurst JR. A longitudinal study of the cognitive function of children with renal failure. Pediatr Nephrol. 1990 Jan;4(1):11-5.

Finelli PF, Carley MD. Cerebral venous thrombosis associated with epoetin alfa therapy. Arch Neurol. 2000 Feb;57(2):260-2.

Foocharoen C, Tiamkao S, Srinakarin J, Chamadol N, Sawanyawisuth K. Reversible posterior leukoencephalopathy caused by azathioprine in systemic lupus erythematosus. J Med Assoc Thai. 2006 Jul;89(7):1029-32.

Ganesan V and Kirkham FJ (eds) Stroke and cerebrovascular disease in children. London, MacKeith Press 2011.

Gerson AC, Butler R, Moxey-Mims M, Wentz A, Shinnar S, Lande MB, Mendley SR, Warady BA, Furth SL, Hooper SR. Neurocognitive outcomes in children with chronic kidney disease: Current findings and contemporary endeavors. Ment Retard Dev Disabil Res Rev. 2006;12(3):208-15.

Gipson DS, Duquette PJ, Icard PF, Hooper SR. The central nervous system in childhood chronic kidney disease. Pediatr Nephrol. 2007 Oct;22(10):1703-10.

Gümüş H, Per H, Kumandaş S, Yikilmaz A. Reversible posterior leukoencephalopathy syndrome in childhood: report of nine cases and review of the literature. Neurol Sci. 2010 Apr;31(2):125-31.

Halberthal M, Halperin ML, Bohn D. Lesson of the week: Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. BMJ. 2001 Mar 31;322(7289):780-2.

Hanna S, Tibby SM, Durward A, Murdoch IA. Incidence of hyponatraemia and hyponatraemic seizures in severe respiratory syncytial virus bronchiolitis. Acta Paediatr. 2003 Apr;92(4):430-4.

Honda M, Kamiyama Y, Kawamura K, Kawahara K, Shishido S, Nakai H, Kawamura T, Ito H. Growth, development and nutritional status in Japanese children under 2 years on continuous ambulatory peritoneal dialysis. Pediatr Nephrol. 1995 Oct;9(5):543-8.

Hoorn EJ, Geary D, Robb M, Halperin ML, Bohn D. Acute hyponatremia related to intravenous fluid administration in hospitalized children: an observational study. Pediatrics. 2004 May;113(5):1279-84.

Huang YC, Tsai PL, Yeh JH, Chen WH. Reversible posterior leukoencephalopathy syndrome caused by blood transfusion: a case report. Acta Neurol Taiwan. 2008 Dec;17(4):258-62.

Ishikura K, Hamasaki Y, Sakai T, Hataya H, Mak RH, Honda M. Posterior reversible encephalopathy syndrome in children with kidney diseases. Pediatr Nephrol. 2012 Mar;27(3):375-84.

Jackson LV, Thalange NK, Cole TJ. Blood pressure centiles for Great Britain. Arch Dis Child. 2007 Apr;92(4):298-303.

Jaramillo-Solorio RM, Menodoza-Guevara L, Garcia-Lopez E. Intellectual output of children with chronic renal failure on continuous ambulatory peritoneal dialysis. Perit Dial Int. 1996;16 Suppl 1:S554-6.

Kalanie H, Harandi AA, Alidaei S, Heidari D, Shahbeigi S, Ghorbani M. Venous thrombosis in multiple sclerosis patients after high-dose intravenous methylprednisolone: the preventive effect of enoxaparin. Thrombosis. 2011;2011:785459. Epub 2011 Dec 25.

Keane S, Gallagher A, Ackroyd S, McShane MA, Edge JA. Cerebral venous thrombosis during diabetic ketoacidosis. Arch Dis Child. 2002 Mar;86(3):204 5.

Kirkham FJ, Neville BG. Successful management of severe intracranial hypertension by surgical decompression. Dev Med Child Neurol. 1986 Aug;28(4):506-9.

Kirkham FJ. Cerebral haemodynamics in children in coma. MD University of Cambridge 2009.

Krugman SD, Zorc JJ, Walker AR. Hyponatremic seizures in infancy: association with retinal hemorrhages and physical child abuse? Pediatr Emerg Care. 2000 Dec;16(6):432-4.

Laakkonen H, Lönnqvist T, Valanne L, Karikoski J, Holmberg C, Rönnholm K. Neurological development in 21 children on peritoneal dialysis in infancy. Pediatr Nephrol. 2011 Oct;26(10):1863-71.

Lawry KW, Brouhard BH, Cunningham RJ. Cognitive functioning and school performance in children with renal failure. Pediatr Nephrol. 1994 Jun; 8(3): 326-9.

Lage JM, Panizo C, Masdeu J, Rocha E. Cyclist's doping associated with cerebral sinus thrombosis. Neurology. 2002 Feb 26;58(4):665.

Madden SJ, Ledermann SE, Guerrero-Blanco M, Bruce M, Trompeter RS. Cognitive and psychosocial outcome of infants dialysed in infancy. Child Care Health Dev. 2003 Jan;29(1):55-61.

McRae RG, Weissburg AJ, Chang KW. Iatrogenic hyponatremia: a cause of death following pediatric tonsillectomy. Int J Pediatr Otorhinolaryngol. 1994 Nov;30(3):227-32.

Merouani A, Lambert M, Delvin EE, Genest J Jr, Robitaille P, Rozen R. Plasma homocysteine concentration in children with chronic renal failure. Pediatr Nephrol. 2001 Oct;16(10):805-11.

Mitchell L, Lambers M, Flege S, Kenet G, Li-Thiao-Te V, Holzhauer S, Bidlingmaier C, Frühwald MC, Heller C, Schmidt W, Pautard B, Nowak-Göttl U. Validation of a predictive model for identifying an increased risk for thromboembolism in children with acute lymphoblastic leukemia: results of a multicenter cohort study. Blood. 2010 Jun 17;115(24):4999-5004.

Moritz ML, Ayus JC. Preventing neurological complications from dysnatremias in children. Pediatr Nephrol. 2005 Dec;20(12):1687-700.

Moscarelli L, Zanazzi M, Bertoni E, Caroti L, Rosso G, Farsetti S, Annunziata F, Paudice N, Salvadori M. Renin angiotensin system blockade and activated vitamin D as a means of preventing deep vein thrombosis in renal transplant recipients. Clin Nephrol. 2011 May;75(5):440-50.

Newton CR, Peshu N, Kendall B, Kirkham FJ, Sowunmi A, Waruiru C, Mwangi I, Murphy SA, Marsh K. Brain swelling and ischaemia in Kenyans with cerebral malaria. Arch Dis Child. 1994 Apr;70(4):281-7.

Nowak-Göttl U, Ahlke E, Fleischhack G, Schwabe D, Schobess R, Schumann C, Junker R. Thromboembolic events in children with acute lymphoblastic leukemia (BFM protocols): prednisone versus dexamethasone administration. Blood. 2003 Apr 1;101(7):2529-33.

Paut O, Rémond C, Lagier P, Fortier G, Camboulives J. [Severe hyponatremic encephalopathy after pediatric surgery: report of seven cases and recommendations for management and prevention]. Ann Fr Anesth Reanim. 2000 Jun;19(6):467-73.

Petrovic BD, Nemeth AJ, McComb EN, Walker MT. Posterior reversible encephalopathy syndrome and venous thrombosis. Radiol Clin North Am. 2011 Jan;49(1):63-80.

Postlethwaite RJ, Johnson RJ, Armstrong S et al. for the Paediatric Task Force of United Kingdom Transplant. The outcome of pediatric cadaveric renal transplantation in the UK and Eire. Pediatric Transplantation 2002; 6(5): 367-377.

Radojevic N, Bjelogrlic B, Aleksic V, Rancic N, Samardzic M, Petkovic S, Savic S. Forensic aspects of water intoxication: Four case reports and review of relevant literature. Forensic Sci Int. 2012 Feb 3. [Epub ahead of print]

Reinstrup P, Ryding E, Algotsson L, Messeter K, Asgeirsson B, Uski T. Distribution of cerebral blood flow during anesthesia with isoflurane or halothane in humans. Anesthesiology. 1995 Feb;82(2):359-66.

Rubin D, Christian C. Retinal hemorrhages in infants with hyponatremic seizures. Pediatr Emerg Care. 2001 Aug;17(4):313-4.

Sato Y, Hirose M, Inoue Y, Komukai D, Takayasu M, Kawashima E, Koiwa F, Yoshimura A. Reversible posterior leukoencephalopathy syndrome after

blood transfusion in a patient with end-stage renal disease. Clin Exp Nephrol. 2011 Dec;15(6):942-7.

Schiff D, Lopes MB. Neuropathological correlates of reversible posterior leukoencephalopathy. Neurocrit Care. 2005;2(3):303-5.

Scott RC, Kirkham FJ. Status epilepticus: aetiology and outcome. Lancet 2007; 370: 724-6.

Sébire G, Tabarki B, Saunders DE, Leroy I, Liesner R, Saint-Martin C, Husson B, Williams AN, Wade A, Kirkham FJ. Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome. Brain. 2005 Mar;128(Pt 3):477-89.

Sicot C, Laxenaire MC. [Death of a child due to posttonsillectomy hyponatraemic encephalopathy]. Ann Fr Anesth Reanim. 2007 Oct;26(10):893-6.

Slickers J, Duquette P, Hooper S, Gipson D. Clinical predictors of neurocognitive deficits in children with chronic kidney disease. Pediatr Nephrol. 2007 Apr;22(4):565-72.

Stolz E, Klötzsch C, Schlachetzki F, Rahimi A. High-dose corticosteroid treatment is associated with an increased risk of developing cerebral venous thrombosis. Eur Neurol. 2003;49(4):247-8.

Wijdicks EF, Larson TS. Absence of postoperative hyponatremia syndrome in young, healthy females. Ann Neurol. 1994 May;35(5):626-8.

Yamada A, Ueda N. Age and gender may affect posterior reversible encephalopathy syndrome in renal disease. Pediatr Nephrol. 2012 Feb;27(2):277-83.

Safety of anticoagulants in children with arterial ischemic stroke:

Comments to the study of IPSS

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As clinicians involved in care of children with stroke, we were interested in the paper establishing safety of anticoagulants in arterial ischemic stroke (AIS)[1]. Nevertheless, we do not fully concur with its conclusion that the results warrant clinical trials with anticoagulants. Such treatment will not reach clinical equipoise vs. placebo, since observational studies argue in favour of aspirin vs. natural history for recurrence in childhood AIS. They suggest also that aspirin is equally effective as heparin in prophylaxis[2] and probably has economic benefits in terms of hospital length of stay. In addition, recent studies suggest that the recurrence rate has fallen substantially for anterior circulation stroke[3] compared with earlier cohorts[4].

Most pediatric AIS are due to non-progressive focal cerebral arteriopathies (FCA) occurring in previously healthy children, often associated with basal ganglia infarction. Patients with basal ganglia infarction were more likely to be anticoagulated in Schechter's study, and although vasculopathy was less common than in other cohorts[4,5], a substantial proportion of these patients probably had FCA not diagnosed by cerebrovascular imaging techniques available at that time. In the FCA population, the current rate of recurrence is now notably inferior to the 16-50% cited by Schechter et al., with some evidence for an effect of aspirin[5] For example, in our original paper describing FCA, 3 of the 4 patients not treated with aspirin recurred, compared with only 1 out of the 11 who received aspirin (Fisher's exact test; p=0.03)[4]. Subsequently, of 72 additional children with cryptogenic (including FCA) AIS, 85% were treated with long term aspirin alone. Five (7%) had recurrence of stroke after a mean follow-up of 27 months, and only one out of the 54 (<1%) with anterior stroke. In adult AIS also, no randomised trial demonstrated advantage of anticoagulants over aspirin in secondary prevention.

As many child neurologists are using aspirin in AIS, recurrence may now be quite rare, except in some specific circumstances such as moyamoya, where revascularisation may be a better option than either anticoagulation or aspirin. According to these arguments, it is uncertain that a therapeutic trial comparing anticoagulants vs. aspirin in the general setting of childhood AIS will be justified. It will probably be more relevant focusing on specific populations, such as children suffering from longstanding thrombotic conditions or those with extracranial dissection and/or posterior AIS.

1. Schechter T, Kirton A, Laughlin S, et al. Safety of anticoagulants in children with arterial ischemic stroke. Blood 2012;119:949-956.

2. Sträter R, Kurnik K, Heller C, Schobess R, Luigs P, Nowak-Goettl U. Aspirin versus low-dose low-molecular-weight heparin: antithrombotic therapy in pediatric ischemic stroke patients: a prospective follow-up study. Stroke. 2001;32: 2554-2558.

3. Touré A, Chabrier S, Plagne MD, et al. Neurological outcome and risk of recurrence depending on the anterior vs. posterior arterial distribution in children with stroke. Neuropediatrics 2009;40:126–128.

4. Chabrier S, Husson B, Lasjaunias P, Landrieu P, Tardieu M. Stroke in childhood: outcome and recurrence risk by mechanism in 59 patients. J Child Neurol. 2000;15:290-4.

5. Ganesan V, Prengler M, Wade A, Kirkham FJ. Clinical and radiological recurrence after childhood arterial ischemic stroke. Circulation. 200614;114:2170-7.

Cerebral Herniation in Bacterial Meningitis in Childhood

Samuel J. Horwitz, MD, Bernard Boxerbaum, MD, and John O'Bell, MD

Among 302 infants and children with acute bacterial meningitis, the syndrome of cerebral herniation occurred in 3 of 10 fatal cases and in 15 patients who survived. The interval from time of admission to herniation was 8 hours or less, and no predictive factors could be determined. Seizures occurring immediately prior to cerebral herniation made diagnosis more difficult. Early recognition of cerebral herniation and prompt treatment with osmotic diuretics can reduce the mortality of bacterial meningitis.

Horwitz SJ, Boxerbaum B, O'Bell J: Cerebral herniation in bacterial meningitis in childhood. Ann Neurol 7:524–528, 1980

The mortality of acute bacterial meningitis in childhood and in infancy beyond the newborn period has declined during the past 20 years, from 10 to 20% [8, 9] to as low as 2.0% [5, 8, 9]. In one recent series of 50 cases of *Hemophilus influenzae* meningitis there were no deaths [6]. Increased intracranial pressure and resultant cerebral herniation as a mechanism of death in some cases of bacterial meningitis has been described [4, 15]. Williams et al [17] reported the successful treatment of that complication in 6 patients. This report focuses on cerebral herniation as a possible major factor in determining the outcome of treatment of acute bacterial meningitis based upon our experience with this disease over a 10-year period.

Materials and Methods

The records of all infants and children aged 1 month to 16 years, admitted to Rainbow Babies and Childrens Hospital with bacterial meningitis during the years 1967 through 1976, were studied retrospectively. Only those patients with positive cerebrospinal fluid cultures for *H. influenzae* type B, *Streptococcus pneumoniae*, or *Neisseria meningitidis* were included in the study. Patients with previously placed ventricular shunts for hydrocephalus were omitted, but no other form of preexisting disease was cause for exclusion.

Each patient's illness was assessed according to the following features: (1) duration of illness prior to admission; (2) history of serious preexisting disease; (3) level of consciousness; (4) seizure activity; (5) vital signs (admission temperature, pulse, blood pressure, and rate and rhythm of respiration); (6) presence or absence of abnormal neurological signs; (7) abnormalities in the general physical examination; (8) results of serum sodium, potassium, chloride, carbon dioxide, and osmolality, hemoglobin, hematocrit, and blood culture tests; (9) volume, rate of administration, and content of intravenous fluids; (10) cerebrospinal fluid (CSF) cell count, protein, and glucose concentration; and (11) antibiotic therapy.

The record of each patient treated for cerebral herniation was examined for the signs of herniation, including abnormalities in level of consciousness, pupil size and reaction, respiration, motor function, and oculocephalic reflexes. Because of the difficulty of retrospectively evaluating the signs of cerebral herniation, we formulated the following criteria to increase the probability of correct diagnosis: (1) that pupillary abnormalities be restricted to unilateral or bilateral dilatation with absence of reaction to light; (2) that motor abnormality consist only of decorticate or decerebrate posture or development of hemiparesis; (3) that respiratory abnormality be confined to Cheyne-Stokes respiration, hyperventilation, or apnea; (4) that there be loss of oculocephalic response or fixed oculomotor deviation; (5) that clonic convulsive activity have ceased before the signs of cerebral herniation were recorded; and (6) that two or more of the clinical signs be present simultaneously. Those patients who did not fulfill these criteria were excluded from the clinical diagnosis of cerebral herniation.

The occurrence of any seizures within 10 minutes prior to the suspected episode of herniation was recorded. The interval from arrival at the hospital to diagnosis of herniation was estimated to the nearest half-hour.

The response to treatment with mannitol and corticosteroids was classified into three categories: rapid—improvement in level of consciousness and disappearance of the other signs of herniation within 1 hour; gradual—improvement within 1 to 6 hours; none—no improvement by 6 hours or death. Outcome of treatment was assessed by the patient's neurological condition at the time of discharge from the hospital.

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Table 1. Clinical Data in 27 Patients with Suspected Cerebral Herniation

Patient No. and Age (yr)	Interval before Diagnosis (hr)[a]	Signs of Herniation					Response to Mannitol
		Level of Consciousness	Motor Function	Respiration	Pupils	Oculocephalic Reflexes	
1. 11 mo	6	Coma	Decerebrate	Normal	BF	...	Gradual
2. 1	1	Coma[b]	...	HV	BF	...	Rapid
3. 3	2	Coma[b]	Decerebrate	HV	BF	...	Rapid
4. 6	< ½	Coma	Decerebrate	...	UF	...	Gradual
5. 1	6	Coma[b]	Normal	HV	UF	Normal	Gradual
6. 3	2	Stupor	Normal	HV	BF	Normal	Rapid
7. 6 mo	< ½	Coma	Decorticate	CS	UF	...	Rapid
8. 4	< ½	Stupor	Normal	CS	UF	...	Rapid
9. 15	< ½	Stupor	Hemiparesis	HV	BF	FD	Gradual
10. 8 mo	1	Stupor[b]	Hemiparesis	...	UF	Absent	Gradual
11. 7 mo	7	Coma[b]	Decorticate	...	UR	...	Rapid
12. 6	< ½	Coma	Decorticate	Normal	BF	...	Rapid
13. 8	1	Stupor	Normal	HV	BF	Normal	Gradual
14. 7 mo	8	Stupor	Decerebrate	HV	BF	...	Rapid
15. 4 mo	< ½	Coma	Hemiparesis	HV	UR	...	Gradual
16. 7 mo	< ½	Coma	Hemiparesis	...	BF	FD	Gradual
17. 5 mo	< ½	Coma	Decorticate	Arrest	BF	Absent	None
18. 2	1	Coma	Normal	HV	UF	Absent	None
19. 7	< ½	Clouded	Normal	Normal	UR	...	Gradual
20. 3 mo	1	Clouded[b]	Normal	Normal	NR	...	Rapid
21. 5 mo	4	Clouded[b]	Hemiparesis	Normal	NR	Normal	None
22. 7	< ½	Coma	Normal	...	LR	...	Gradual
23. 10 mo	4	Coma[b]	Normal	Normal	NR	...	Rapid
24. 7 mo	48	Clouded[b]	Normal	Normal	NR	Normal	Rapid
25. 4 mo	96	Clouded[b]	Normal	Normal	NR	...	Rapid
26. 1 mo	7	Clouded[b]	Normal	HV	NR	...	None
27. 4	< ½	Stupor	Normal	...	LR	...	Gradual

[a]Interval from time of admission to diagnosis of herniation.
[b]Patients with seizures within 10 minutes before signs of herniation.

BF = bilateral fixed; HV = hyperventilation; UF = unilateral fixed; CS = Cheyne-Stokes; FD = fixed deviation; UR = unequal reactive; NR = normal reactive; LR = large reactive.

Results

The total number of patients with meningitis was 302. Of these, 221 cases were due to *H. influenzae* type B, 35 to *S. pneumoniae*, and 46 to *N. meningitidis*. Twenty-seven patients were treated for suspected cerebral herniation (Table 1). Alteration in the level of consciousness and pupillary abnormalities were the most frequent physical signs (Table 2). Abnormalities in oculocephalic reflexes were recorded in only 5 patients. Twenty patients had two or more signs of herniation, and 7 had one or no signs. Eleven of the 27 had seizures within 10 minutes prior to suspected herniation (Table 1). Nine of the 27 patients (Nos. 19 through 27) were excluded from the diagnosis of cerebral herniation because of failure to meet the criteria we established for this diagnosis. Eight of these, including 6 patients with seizures, had fewer than two acceptable physical signs. The ninth patient (No. 21) was discarded because seizure activity was present when mannitol treatment was instituted.

Thus, 18 of the 302 patients (Nos. 1 through 18) were accepted as cases of cerebral herniation according to our criteria, a minimum incidence of 6%. Eleven of the patients had meningitis due to *H. influenzae* type B; in 7 it was due to *S. pneumoniae*. The prevalence of clinical signs and number of signs per patient are shown in Tables 2 and 3.

All 18 patients who suffered herniation did so within 8 hours of admission, and 8 within a half-hour of that point. Coma was present at the time of admission in 4 of the 18 children (22%) and in 11 of the 284 (3.9%) not diagnosed as having herniation. Nine patients suffered seizures, 4 before admission, 2 before admission and again prior to herniation, and 3 only before herniation. There were seizures in 53

Table 2. Patients with Signs of Suspected Herniation

Sign	No. of Patients	
	Suspected (N = 27)	Diagnosed (N = 18)
Level of consciousness		
Coma on admission	5	4
Deterioration[a]	15	13
Pupils		
Unilateral fixed	6	6
Bilateral fixed	10	10
Unequal or large	5	0
Respiration		
Hyperventilation	10	9
Cheyne-Stokes	2	2
Apnea	1	1
Not recorded	6	4
Motor function		
Hemiparesis	5	4
Decorticate	4	4
Decerebrate	4	4
Not recorded	1	1
Oculocephalic reflexes		
Absent	3	3
Fixed deviation	2	2
Not recorded	17	10

[a]Patients not comatose at time of admission.

Table 3. Prevalence of Signs of Herniation

No. of Signs of Herniation	No. of Patients	
	Suspected (N = 27)	Diagnosed (N = 18)
0	3	0
1	4	0
2	3	2
3	8	8
4	7	6
5	2	2

(18.7%) of the 284 remaining patients with meningitis. Hyponatremia with serum sodium concentration below 130 mEq per liter was found at the time of admission in 6 children with cerebral herniation. No patient received more than a calculated three-fourths of the normal maintenance intravenous fluid requirement, and the administration rate and electrolyte concentration of the fluid were not unusual. Subsequently, in all cases, serum sodium concentrations were above 135 mEq per liter within 48 hours after fluid restriction.

Cerebrospinal fluid (CSF) cell counts from the initial diagnostic lumbar puncture ranged from 60 to more than 20,000 leukocytes/mm^3 in the 18 patients with herniation. Six children had fewer than 1,000 cells/mm^3. Pleocytosis and changes in protein and glucose content of the CSF were no different than in the remaining 284 patients with meningitis. No cases were complicated by bacterial resistance to the antibiotic treatment.

The response to administration of mannitol followed by dexamethasone was rapid, with the signs of herniation resolving within 20 to 60 minutes in 8 patients and more gradually in 8 others. In 2 children (Nos. 13 and 15), the pupils again became fixed and dilated within 3 to 4 hours after initial treatment with mannitol, and a second course of the hyperosmotic agent induced rapid return of pupillary responses and improvement in the level of consciousness.

There were 10 deaths among the 302 patients (3%), 7 among the 284 not diagnosed as having herniation (2.5%) and 3 of the 18 with this complication (17%). One of the patients who died (No. 16) regained consciousness following treatment with mannitol and dexamethasone but collapsed and died from congestive failure 15 hours later. Two of the deaths were attributed directly to herniation. Autopsy was obtained in only 1 of the 3 patients with herniation (No. 18). The clinical signs were those of uncal herniation with rostrocaudal progression. Respiratory arrest and dilatation of the contralateral pupil had occurred immediately before administration of mannitol. Cerebral edema and uncal herniation were confirmed by postmortem examination of the brain.

Four (27%) of the 15 patients who survived the episode of cerebral herniation syndrome had severe residua at the time of discharge from the hospital, including 2 with severe spastic hemiparesis, 1 with cortical blindness, and 1 with retardation and seizures. The 3-year-old girl with cortical blindness gradually improved and 2 years later showed only mild difficulty with visual perception. By comparison, 16 of the 277 children (5.8%) who survived bacterial meningitis without ever developing signs of herniation had neurological sequelae at the time of discharge from the hospital. Two of the patients with herniation had preexisting disease; 1 had Hodgkin's disease (No. 13), and 1 had chronic mastoiditis (No. 9). In neither instance did it appear that this concomitant illness contributed to the development of cerebral herniation or affected the outcome. Among the patients who did not suffer cerebral herniation there were 6 with underlying disease, including 2 children with sickle-cell anemia and 1 each with mesenchymoma, diabetes, Down syndrome with leukemia, and CSF rhinorrhea.

Discussion

Adams et al [1] and Smith and Landing [16] found cerebral edema and cerebral herniation at postmortem examination in a few cases of bacterial meningitis. The clinical recognition of raised intracranial pressure as a serious complication of meningitis was made in the early 1960s. Among 29 fatal cases of meningitis, Dodge and Swartz [4] found 5 patients with cerebral edema at postmortem examination. Four of these showed temporal lobe or cerebellar herniation. Five patients had cerebellar herniation in the absence of unequivocal cerebral edema. The clinical history in each case suggested that brain swelling or herniation was contributory to or responsible for death. The clinical signs consisted of coma, third nerve dysfunction, respiratory arrest, or combinations of these problems. They proposed that raised intracranial pressure results from impaired circulation of CSF due to accumulation of purulent material in the subarachnoid space and ventricles, as well as from cerebral edema. Rischbieth [15] reported that 9 of 28 patients with pneumococcal meningitis had clear-cut signs of tentorial herniation, characterized by progressive deterioration of consciousness, pupillary dilatation, and extensor plantar responses. Two of his patients recovered after ventricular drainage. He concluded that profound cerebral edema was the most important factor responsible for the high mortality rate (50%) in his series. Williams et al [17] have written the only paper specifically directed at the problem of cerebral herniation as a complication of bacterial meningitis. They described 7 cases of herniation, 1 fatal. The other 6 patients survived following the use of intravenous urea. They did not report on the relative frequency of herniation in their patients. The incidence of pathologically confirmed herniation reported by Dodge and Swartz [4] was 9 (4.3%) out of 207 cases of meningitis. In our study we found a 6% incidence of cerebral herniation syndrome according to the criteria we established for clinical diagnosis. However, we were able to confirm the diagnosis by pathological correlation in only a single patient.

The clinical diagnosis of cerebral herniation, according to the descriptions of McNealy and Plum [10] and Plum and Posner [14], is usually relatively straightforward. However, when seizures occurred in our patients, it was difficult to differentiate the signs of herniation from the postictal state. Seizures were present about the time of herniation in 5 of 7 patients reported by Williams et al [17], but they did not comment on the distinction between the postictal state and cerebral herniation. The pupils may be dilated or unequal during or immediately after a seizure [13], and oculocephalic reflexes can be transiently suppressed [14]. In a study of patients with seizures due to various causes other than meningitis, 6 of 12 had postictal unilateral pupillary dilatation [13]. The pupils retained their reactivity to light. Five of our 18 patients had pupillary abnormalities subsequent to seizures, but in 4 of these the dilated pupils were unreactive. The postictal state is usually transient. Therefore we have concluded that prolonged persistence of pupillary dilatation and, more important, absence of reaction to light indicate the probability of herniation rather than postictal state in cases of meningitis. However, no more specific differential diagnostic criteria were determined from this study or from a review of the literature. It is likely that seizures with accompanying hypoxia and hypercapnia may further elevate intracranial pressure in patients with meningitis, thus precipitating central or uncal herniation.

Isolated and focal neurological abnormalities complicating meningitis were distinguished from the signs of herniation by close observation over a period of hours. Acute hemiparesis and sixth nerve paralysis were the most common. One patient with an otherwise mild case of *H. influenzae* type B meningitis had a complete third nerve paralysis that resolved in one week. We believe the requirement of two or more signs for the diagnosis of herniation will reduce the number of patients who are treated unnecessarily with hyperosmotic agents.

The occurrence of herniation within 8 hours after admission in our patients is similar to the experience of others [4, 15]. There is a possibility that diagnostic lumbar puncture may precipitate transtentorial or cerebellar herniation in some patients with meningitis [4]. One of our patients (No. 17) experienced respiratory arrest and the pupils became fixed and dilated immediately following lumbar puncture; an autopsy was not obtained. The development of signs of herniation in 7 other patients within a half-hour after admission to the hospital suggests a possible relationship to lumbar puncture; furthermore, there were no instances of herniation before this essential diagnostic procedure was performed. We do not believe the amount of CSF removed for diagnosis, 2 to 3 ml, is excessive. Recognition of the possibility of herniation within a few hours following diagnostic lumbar puncture should lead to close surveillance, prompt diagnosis, and immediate therapy.

Hyponatremia has been reported in 54% of children with *H. influenzae* meningitis and inappropriate antidiuretic hormone secretion in over 80% [5, 6]. It has thus been common practice to restrict the volume of intravenous fluid during acute treatment of meningitis. Although 6 of our 18 patients with herniation had serum sodium levels below 130 mEq per

liter, all had received a restricted amount of intravenous fluid. The quantity of fluid administered was thus not the determining factor in the early occurrence of cerebral herniation in these patients. Restriction of the quantity of intravenous fluids may be important in preventing brain swelling and herniation later in the course of the disease. In this retrospective study we were unable to determine the incidence or importance of inappropriate antidiuretic hormone secretion.

It has not been possible from our study to predict which patients will suffer herniation. Ten of our 18 children with cerebral herniation had seizures or coma early in the course of meningitis, and the presence of these findings may indicate some increased potential for herniation. However, because of the absence of these features in 8 others and the relative frequency of seizures (18.7%) among the total 284 patients without signs of herniation, we must conclude that coma and seizures are not useful predictive factors. The initial findings in CSF, including the number of cells, gave no correlation with the subsequent development of signs of herniation.

The use of mannitol as an emergency method of treatment for acute cerebral edema is well accepted. In our study, no problems were recognized with the use of this agent in the patients with herniation or in the 9 who were treated but subsequently excluded from the diagnosis of herniation. The administration of corticosteroids in cases of bacterial meningitis is more controversial. In at least two studies, corticosteroid therapy had no beneficial effect on the outcome of meningitis, although cerebral herniation was not specifically discussed [2, 3]. The use of large doses of dexamethasone together with glycerol or mannitol has been recommended for the treatment of raised intracranial pressure with bacterial meningitis [7, 12]. We have administered dexamethasone, 0.5 mg/kg intravenously, immediately following mannitol in the hope of preventing the rebound effect known to occur with the use of mannitol. In 2 of our patients it was necessary to administer a second dose of mannitol because of recurrence of the signs of cerebral herniation. Our study does not permit any conclusion that the use of large doses of corticosteroids in acute meningitis is beneficial. On the other hand, we were not able to discern any short- or long-term adverse effect.

The survival of 15 of our 18 patients diagnosed as having cerebral herniation indicates that this condition is potentially reversible, though morbidity in the survivors was high. The recognition and treatment of this complication is probably a major factor contributing to the reduced mortality of acute bacterial meningitis in recent years. Other measures, including improved anticonvulsant and fluid therapy and the emergence of intensive care units, may also be important. In spite of improved survival, the morbidity of acute bacterial meningitis remains high, and the goal for the future must be prevention of the disease by specific immunization [11]. In the interim, however, we recommend prompt recognition and treatment of cerebral herniation as an important aspect of the care of children with acute bacterial meningitis.

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References

1. Adams RD, Kubic CS, Bonner FJ: The clinical and pathological aspects of influenzal meningitis. Arch Pediatr 65: 354–376, 408–441, 1948
2. Belsey MA, Hoffpauir CW, Smith MHD: Dexamethasone in the treatment of acute bacterial meningitis: the effect of study design on the interpretation of results. Pediatrics 44:503–513, 1969
3. deLemos RA, Haggerty RJ: Corticosteroids as an adjunct to treatment in bacterial meningitis. Pediatrics 44:30–34, 1969
4. Dodge PR, Swartz MN: Bacterial meningitis. A review of selected aspects. N Engl J Med 272:898–902, 954–960, 1003–1010, 1965
5. Feigin RD, Dodge PR: Bacterial meningitis: newer concepts of pathophysiology and neurologic sequelae. Pediatr Clin North Am 23:541–556, 1976
6. Feigin RD, Stechenbert MD, Chang MJ, et al: Prospective evaluation of the treatment of *Hemophilus influenzae* meningitis. J Pediatr 88:542–548, 1976
7. Herson VC, Todd JK: Prediction of morbidity in *Hemophilus influenzae* meningitis. Pediatrics 59:35–39, 1977
8. Laxer RM, Marks MI: Pneumococcal meningitis in children. Am J Dis Child 131:850–853, 1977
9. McGowan JE, Klein JO, Bratton L, et al: Meningitis and bacteremia due to *Hemophilus influenzae:* occurrence and mortality at Boston City Hospital in 12 selected years, 1935–1972. J Infect Dis 130:119–124, 1974
10. McNealy DE, Plum F: Brainstem dysfunction with supratentorial mass lesions. Arch Neurol 7:10–32, 1962
11. Mortimer EA: Immunization against *Hemophilus influenzae.* Pediatrics 52:633–635, 1973
12. Murray JD, Fleming PC, Anglin CS, et al: Acute bacterial meningitis in childhood. Clin Pediatr 11:455–464, 1972
13. Pant SS, Benton JW, Dodge PR: Unilateral pupillary dilatation during and immediately following seizures. Neurology (Minneap) 16:837–840, 1966
14. Plum F, Posner JB: Diagnosis of Stupor and Coma. Third edition. Philadelphia, Davis, 1980
15. Rischbieth RH: Pneumococcal meningitis—a killing disease. Med J Aust 1:578–581, 1960
16. Smith JF, Landing BH: Mechanisms of brain damage in *H. influenzae* meningitis. J Neuropathol Exp Neurol 19:248–265, 1960
17. Williams CPS, Swanson AG, Chapman JT: Brain swelling with acute purulent meningitis. Pediatrics 34:220–227, 1964

Posterior Reversible Encephalopathy Syndrome and Venous Thrombosis

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KEYWORDS

• Posterior • Reversible • Encephalopathy • Syndrome • Venous • Thrombosis

Posterior reversible encephalopathy syndrome (PRES) and venous thrombosis are frequently encountered first in the emergency setting and share some common characteristics. The clinical presentation of both is vague, and the brain parenchymal findings of PRES may resemble those of venous thrombosis in some ways. Both entities often occur in a bilateral posterior distribution and may be associated with reversible parenchymal findings if the inciting factor is treated. These diagnoses should be at the forefront of differential diagnosis when confronted with otherwise unexplained brain edema, among other findings described in this article.

PRES

PRES is a clinicoradiologic entity with characteristic symptoms and imaging features.[1,2] It is classically associated with a distinct pattern of edema that is primarily posterior, including the parietal and occipital lobes (**Fig. 1**).[1] PRES occurs in the setting of neurotoxicity, and the accompanying brain edema is reversible if the underlying cause is addressed.[2]

Although these statements are true for classic cases of PRES, it is important to recognize that the term PRES is, in many ways, a misnomer for this entity. PRES is not always posterior and may occur primarily in the frontal lobes. In addition, PRES is not always reversible if the cause is not treated. Again, these factors are of prime importance when considering an unusual pattern of brain edema not otherwise explained. Also, the patient may not always present with an encephalopathy, which is usually understood as altered mental status; instead, the patient may have various clinical presentations as described later. Also, the patient may not present with a syndrome.

Clinical Presentation and Demographics

Patients with PRES often develop headaches, visual disturbances (eg, blurry vision, hemianopsia, visual neglect, cortical blindness), seizures, and/or altered mental status.[3–5] Occasionally, these patients may develop focal neurologic deficits such as paresis or hemianopsia.[1,5] Because the symptoms are nonspecific, PRES can be a diagnostic dilemma from a clinical standpoint unless one maintains a high clinical suspicion in patients with risk factors for the disease. Symptoms associated with PRES may develop acutely or over several days.[1]

PRES is more prevalent in women.[6] It can occur over a wide age range and has been reported in patients aged 2 to 90 years.[6] The overall incidence of PRES has not been established.[6] The incidence of PRES in the setting of solid-organ transplant

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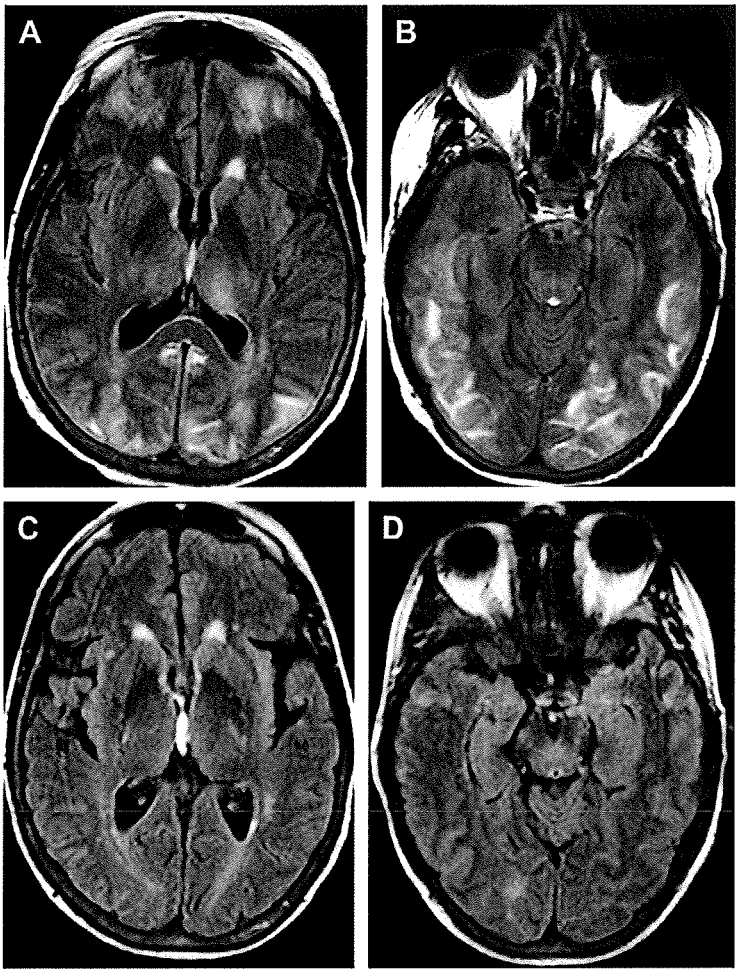

Fig. 1. A 59-year-old woman with a history of lupus presented with mental status changes and sepsis. Axial fluid-attenuated inversion recovery (FLAIR) MR images (*A*, *B*) show increased signal intensity in the cortex and subcortical white matter of the parietal and occipital lobes bilaterally and, to a lesser extent, in the bilateral frontal lobes and left thalamus. Axial FLAIR images obtained on follow-up several months later (*C*, *D*) demonstrate resolution of the findings without parenchymal sequelae such as encephalomalacia. The findings are consistent with PRES.

ranges from 0.4% to 6%.[1] In the setting of allogeneic bone marrow transplant with myeloablative marrow preconditioning and cyclosporine therapy, the incidence of PRES is 7% to 9%, although it may be as high as 16% with higher-dose myeloablative preconditioning and as low as 3% with nonmyeloablative therapy.[1]

Risk Factors and Causes of PRES

There are many conditions associated with the development of PRES. Frequently seen in the setting of moderate or severe hypertension, PRES was formerly referred to as hypertensive encephalopathy.[1] PRES, as it is now understood as a distinct clinical entity, was first described in patients with eclampsia and renal disease and in those receiving immunosuppressant therapy.[4,5] Immunosuppressive agents most commonly associated with PRES include calcineurin inhibitors such as cyclosporine A and tacrolimus (FK-506).[5] PRES is now also known to occur in patients on antineoplastic chemotherapy (especially high-dose multidrug therapy), patients with certain autoimmune diseases (eg, lupus), and in the setting of infection, sepsis, or shock.[2,5]

The pathophysiology of PRES is not well understood. Because most patients with PRES (70%–80%)[1] have moderate to severe hypertension that developed either acutely or subacutely, one of the most commonly accepted theories is that severe hypertension exceeds the compensatory ability of the autoregulatory mechanisms of cerebral blood flow, ultimately resulting in vasodilation

and edema.[5] Some investigators have asserted that the degree of hypertension required to induce PRES depends on the patient's baseline blood pressure.[5] Patients with baseline low-normal blood pressure may develop PRES if they experience a substantial increase in blood pressure, even if that elevated blood pressure is considered to be within the broad range of normal blood pressure.[5] In fact, 20% to 30% of patients with PRES may be normotensive or only minimally hypertensive.[1] Also, the upper limit of autoregulation may be increased in a chronically hypertensive patient.[7]

The major failing of the theory that is based on the collapse of the autoregulation of cerebral blood flow is that it cannot account for cases of PRES that occur in absence of severe or acute hypertension (20%–30%). Furthermore, by imaging studies, normotensive patients with PRES have been shown to develop greater edema than patients with severe hypertension.[1] Other known causes of PRES, such as cyclosporine A neurotoxicity, are also not readily explained by this theory. An alternative theory that has been proposed is that of an exaggerated cerebral autoregulatory response leading to potentially reversible vasospasm and ischemia.[8–10] More recently, the concept of a neurotoxic state has been introduced, in which circulating toxic substances induce endothelial injury or dysfunction, resulting in the breakdown of the blood-brain barrier and development of edema.[5]

Imaging Features

Although the causes of PRES are diverse, the imaging appearance is fundamentally the same regardless of the cause.[7] Typically, PRES is first encountered on computed tomography (CT) in the emergency setting; however, MR imaging is a more sensitive modality in the detection of PRES.[11] The characteristic findings in PRES are cortical and subcortical areas of hypoattenuation on CT or T2 hyperintensity on MR imaging with a predominantly posterior distribution in the parietal and occipital lobes.[5] On MR imaging, the findings are most apparent on fluid-attenuated inversion recovery (FLAIR) images.[11] The imaging hallmark of PRES is that the findings are potentially reversible. Resolution of findings on follow-up imaging often confirms the diagnosis.[6]

The reason why PRES is predisposed to involve the territory of the posterior circulation is uncertain but is thought to be related to the limited sympathetic innervation of the vertebrobasilar circulation.[12] This sympathetic innervation assists in the defense of the brain against marked increases in intravascular pressure, as might be seen with severe hypertension.[11] There is an inversely proportional relationship between the amount of sympathetic innervation and the degree of parenchymal involvement in PRES. The posterior aspects of the cerebral hemispheres are more commonly involved in PRES because there is relatively less protection via sympathetic innervation. However, in some cases, the protective efforts of sympathetic innervation in the anterior aspects of the cerebral hemispheres can also be overcome and involvement of the frontal and/or temporal lobes may be seen.[1,5] Thus, Narbone and colleagues[13] have suggested that potentially reversible encephalopathy syndrome may actually be a more appropriate term for PRES.

When areas of the brain apart from the parietal and occipital lobes are involved, it is sometimes referred to as atypical PRES.[12] However, Bartynski and Boardman[14] demonstrated that frontal lobe involvement was common as seen in 68% of patients (see **Fig. 1**). A posterior predominance can also be seen within each lobe.[11] For example, in a study by McKinney and colleagues,[11] when the frontal lobe was involved, the posterior portion of the superior frontal gyrus and the precentral gyrus were most commonly affected. The orbitofrontal region was affected only in the most severe cases.[11] Other structures that may be involved in PRES include the basal ganglia, brainstem, or cerebellum (**Figs. 2** and **3**).[1,5] The deep white matter may also be affected, including the corona radiata, splenium of the corpus callosum, or internal or external capsules.[14] In descending order, PRES most commonly involves the parietal and occipital lobes, frontal lobes, inferior temporo-occipital junction, and cerebellum.[1]

Earlier, PRES was referred to as posterior reversible leukoencephalopathy syndrome. This term has fallen out of favor because it suggests that there is a destructive process of the white matter, which is not usually the case.[10] The pathology of PRES in acute toxicity has shown nonspecific edema in the white matter but without overt inflammation, demyelination, or neuronal damage.[2] Although parenchymal changes in PRES primarily affect white matter, the cortex can also be involved.[12] In fact, FLAIR images show that the involvement of the gray matter is more extensive than was initially appreciated and that the development of edema may even commence in the cortex.[3,10] Up to 94% of patients with PRES have cortical involvement.[3]

Cerebral hemisphere involvement tends to be bilateral and symmetric. The lesions become confluent as the disease progresses.[1] Although typically bilateral, in a series by McKinney and

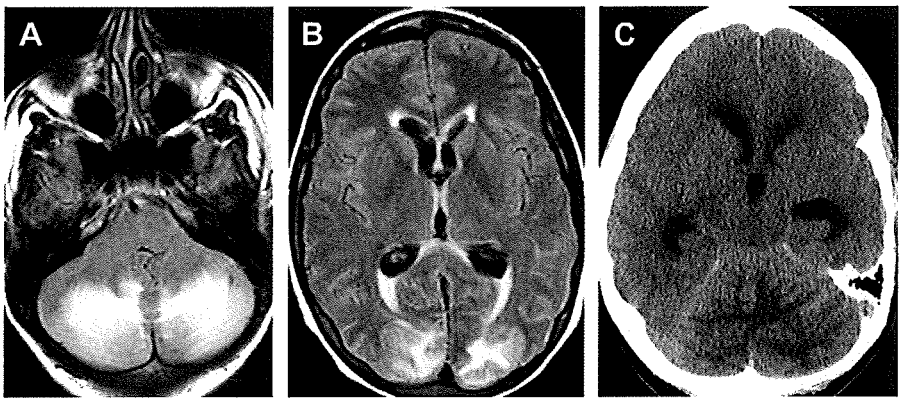

Fig. 2. A 22-year-old woman with a history of acute lymphocytic leukemia and mental status changes. Axial FLAIR MR images (*A, B*) show cortical and subcortical FLAIR hyperintensity bilaterally in the occipital lobes and the superior cerebellar hemispheres. FLAIR images also show mild hydrocephalus with dilatation of the lateral ventricles and periventricular FLAIR hyperintensity consistent with transependymal flow of cerebrospinal fluid. An axial CT image (*C*) also shows hypoattenuation in the superior cerebellum and mild hydrocephalus with dilatation of the lateral and third ventricles. After 2 months, follow-up MR image (not shown) demonstrated resolution of the findings that were attributed to PRES.

colleagues,[11] PRES was unilateral in 2.6% of patients. This unilateral involvement creates a diagnostic difficulty because differential considerations in this setting include neoplasms as well as infectious and inflammatory causes.

Although severe hypertension is a major risk factor for PRES, it should be noted that the degree of hypertension in patients with PRES does not correlate with the distribution of the imaging findings.[14] Furthermore, in a study by Mueller-Mang and colleagues,[5] there was no statistically significant difference in the location of PRES parenchymal signal abnormalities between hypertensive and nonhypertensive patients with PRES related to cytotoxic or immunosuppressive drugs.[5] In fact, there is no way to distinguish between the varied causes of PRES based on the imaging findings.[10]

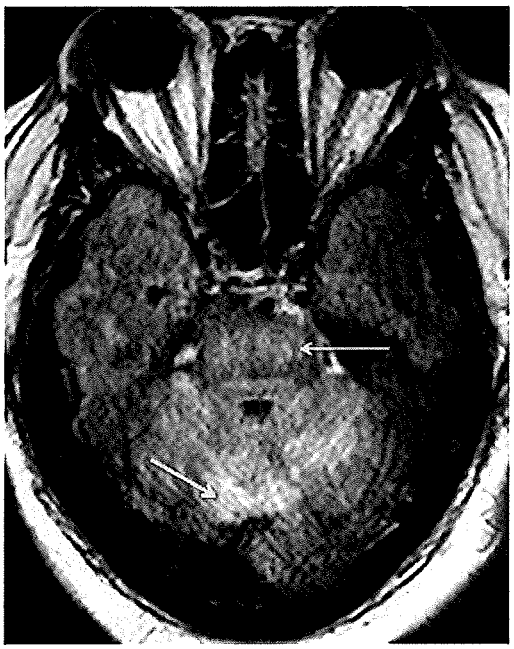

Fig. 3. Isolated posterior fossa PRES. Axial FLAIR image shows FLAIR hyperintensity in the cerebellar hemispheres, cerebellar vermis, and pons (*arrows*). The remainder of the brain (not shown) was unremarkable.

If there is marked involvement of the brainstem or cerebellum, the edema may result in hydrocephalus or even brainstem compression (see **Fig. 2**).[1] This condition is particularly true if there is localized mass effect on the cerebral aqueduct.

Slight enhancement may also be seen in PRES (**Figs. 4** and **5**), although this is not consistently present.[12] The enhancement most commonly occurs as mild, gyriform, leptomeningeal, or stippled (see **Fig. 5**) cortical enhancement. However, some reported cases have shown enhancement in the deep white matter or dura in addition to the leptomeningeal or cortical enhancement.[11] McKinney and colleagues[11] found no correlation between the presence of enhancement and the extent of FLAIR signal edema.

Diffusion-weighted MR imaging is useful in PRES because it can distinguish between vasogenic and cytotoxic edema.[12] Restricted diffusion seen with infarction or cytotoxic edema is uncommon in PRES but has been reported in 11% to 26% of patients (see **Fig. 5**).[1] When present, the typical pattern is to have small, patchy, or punctate areas of restricted diffusion,

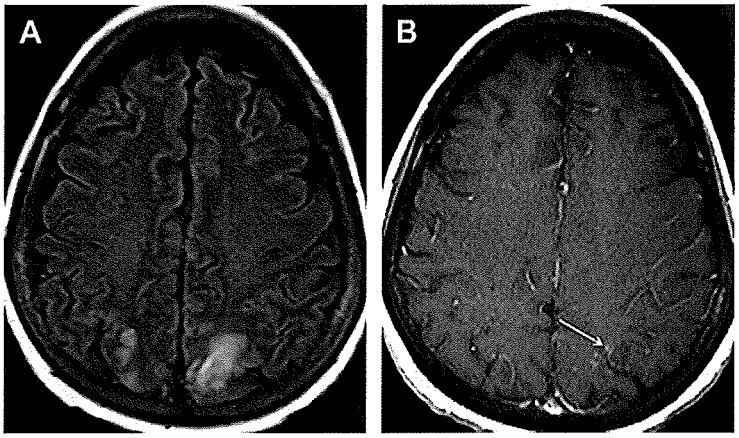

Fig. 4. PRES with enhancement. Axial FLAIR image (*A*) demonstrates FLAIR hyperintensity in the cortex and subcortical white matter of the parietal lobes bilaterally. Postgadolinium axial T1-weighted image (*B*) shows stippled cortical and subcortical enhancement (*arrow*) in the area of FLAIR hyperintensity in the left parietal lobe.

which correspond to areas of cytotoxic edema. The cytotoxic edema is considerably less extensive than the surrounding vasogenic edema.[11]

Hemorrhage is not often associated with PRES. However, intraparenchymal or subarachnoid hemorrhage can be seen in up to 15% of patients with PRES (**Fig. 6**).[1,15] In a study conducted by Aranas and colleagues,[2] most patients with PRES who developed intracranial hemorrhage had an underlying bleeding diathesis or coagulopathy. The incidence of hemorrhage does not correlate with the blood pressure at toxicity.[15]

PRES may result in vasculopathy that is demonstrable on MR angiography. The vasculopathy can appear as vessel irregularity, with focal areas of vasoconstriction and vasodilation, diffuse areas of vasoconstriction, or vessel pruning (see **Fig. 6**).[1] On catheter angiography, the vasculopathy of PRES may even result in a string of beads appearance that mimics fibromuscular dysplasia when PRES involves the internal carotid arteries or vertebral arteries.[1] Bartynski and Boardman[8] found evidence of vasculopathy in patients with PRES on 30 of 43 MR angiograms and 8 of 9 catheter angiograms. Follow-up MR angiography after treatment of PRES may demonstrate reversal of the vasculopathy.[1]

Potential Pitfalls

Accurately diagnosing PRES is important to avoid unnecessary brain biopsies or complications of PRES related to delayed treatment.[10] When the distribution of the imaging findings is archetypal and the clinical history is consistent with PRES, the diagnosis is straightforward. However, there may be isolated involvement in uncharacteristic locations (atypical PRES) such as the basal ganglia, brainstem, and deep white matter, making diagnosis difficult.[1] When atypical imaging features of PRES (eg, an uncommon distribution of parenchymal changes, contrast enhancement, or hemorrhage) are found, clinical history is indispensable in making the diagnosis. Follow-up imaging demonstrating resolution of the findings after appropriate therapy is confirmatory.

Although CT is often used in the evaluation of patients in the emergency setting, the radiologist should be cognizant that subtle or atypical lesions may be missed in patients with PRES who undergo only CT evaluation.[14] MR imaging should be considered for patients in whom there is a clinical concern for PRES without diagnostic CT findings or when there is difficulty in differentiating PRES from other conditions that can mimic its appearance. For instance, vasogenic edema from PRES and cytotoxic edema from infarction have an identical CT appearance but are readily distinguished with diffusion-weighted MR imaging.

A particularly good mimic of PRES is dural sinus thrombosis. The edema pattern of both conditions may be identical. For instance, biparietal vasogenic edema can be seen in both PRES and superior sagittal sinus thrombosis. Dural sinus thrombosis is easily excluded with CT or MR venography.

Prognosis and Treatment

The prognosis in patients with PRES is variable but is typically considered to be favorable.[2] In many patients, the clinical and imaging findings are completely reversible with appropriate therapy.[5] However, in some patients, PRES progresses to ischemia, infarction, or death.[5,16] Patients whose MR images demonstrate extensive T2 parenchymal signal abnormalities are at a greater risk

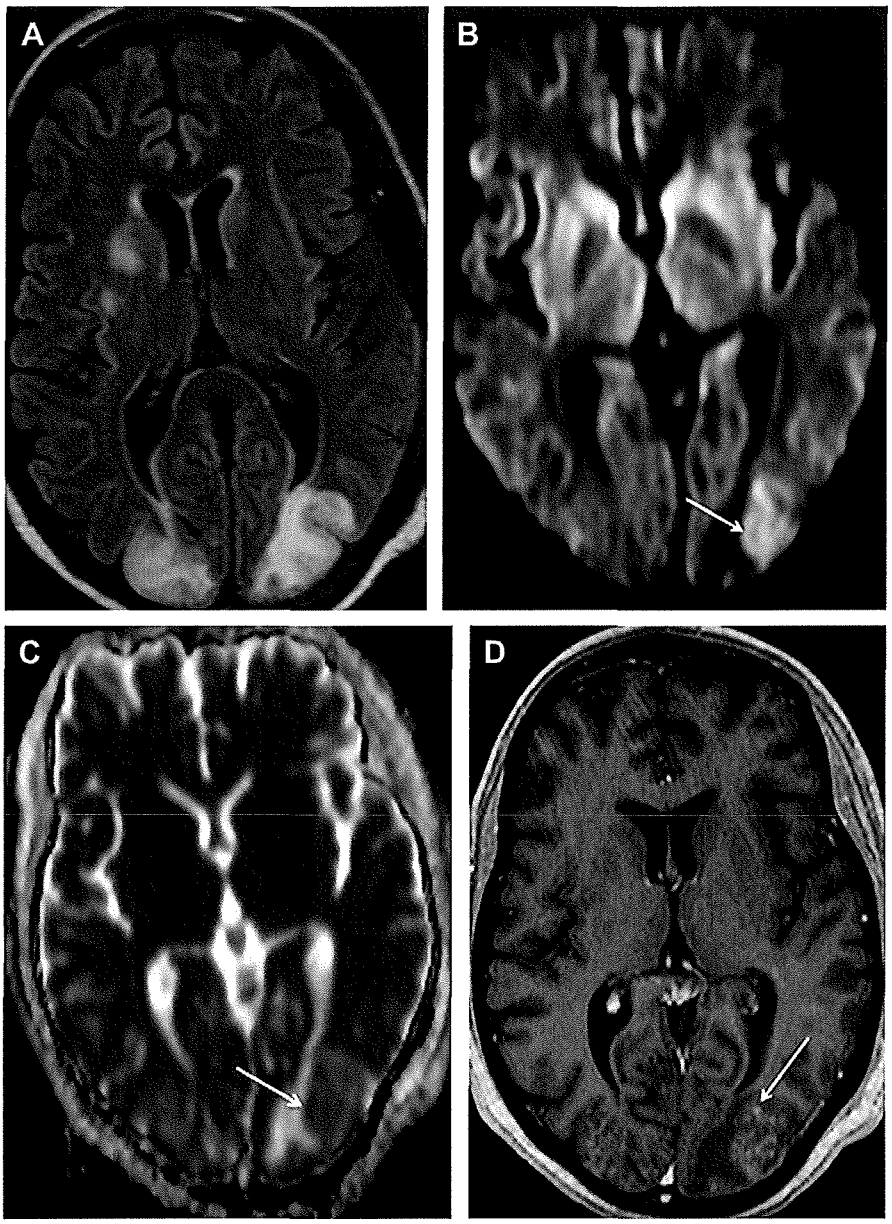

Fig. 5. PRES with restricted diffusion and enhancement. Axial FLAIR image (*A*) shows cortical/subcortical FLAIR hyperintensity in the occipital lobes bilaterally as well as within the right basal ganglia. Axial diffusion-weighted image (*B*) shows an area of increased signal intensity in the left occipital lobe (*arrow*). Axial apparent diffusion coefficient map image (*C*) shows punctate focus of low signal (*arrow*) along the medial margin of the diffusion abnormality in the left occipital lobe consistent with a small focus of restricted diffusion next to a larger area of vasogenic edema with increased signal. Axial postgadolinium T1-weighted image (*D*) shows stippled enhancement (*arrow*) in the areas of FLAIR signal abnormality in the occipital lobes.

for a poor outcome than patients whose MR images show minimal parenchymal T2 changes.[12] Prognosis for patients with PRES associated with intracranial hemorrhage may be worse than in patients without hemorrhage, with increased morbidity and mortality.[2] In a small series by Aranas and colleagues,[2] only 28% of patients with PRES and intracranial hemorrhage attained a favorable functional outcome. It is indeterminate whether the poor outcome is caused by the hemorrhage itself or it reflects the severity of the disease in these patients.[2]

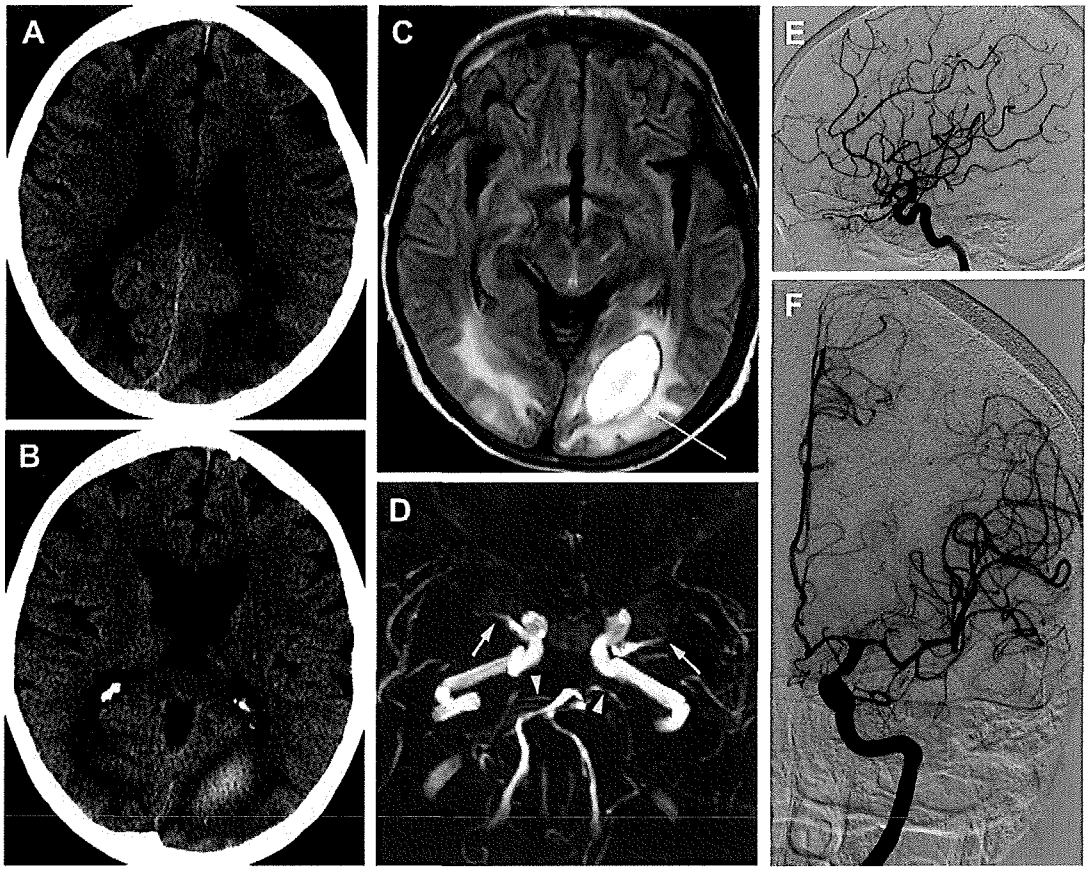

Fig. 6. A 56-year-old woman with septic shock, renal failure, and thrombocytopenia developed mental status changes. Axial noncontrast CT images (*A*, *B*) demonstrate confluent cortical/subcortical hypoattenuation involving more of the parietal and occipital lobes than the frontal lobes, in a pattern consistent with PRES. Intraparenchymal hemorrhage in the left occipital lobe is also present. Axial FLAIR MR image (*C*) demonstrates confluent cortical/subcortical FLAIR hyperintensity in the occipital lobes as well as the intraparenchymal hemorrhage in the left occipital lobe (*arrow*). Collapsed 3-dimensional time-of-flight MR angiographic image (*D*) demonstrates spasm with cutoff of the middle cerebral arteries bilaterally (*arrows*) as well as irregularity of the posterior cerebral arteries bilaterally (*arrowheads*) consistent with the vasculopathy of PRES. Follow-up catheter angiograms (*E*, *F*) display a normal left middle cerebral artery, consistent with resolution of the vasculopathy of PRES.

Timely treatment is necessary to minimize the risk of complications in PRES.[12] Treatment is aimed at the underlying causes. For example, in patients with hypertension, maintaining adequate blood pressure is a mainstay of therapy. In eclamptic patients who are refractory to medical therapy, delivery by cesarean section may be necessary.[6] In patients on tacrolimus, symptoms can often be reversed by reducing the dosage of the medication or withholding the medication for a few days.[12] Some physicians may also consider adding antiepileptic drugs or magnesium sulfate because of the risk of developing status epilepticus.[6]

CEREBRAL VENOUS THROMBOSIS

Cerebral venous thrombosis is an uncommon but serious condition first described in the early nineteenth century.[17,18] The estimated annual incidence is 2 to 7 cases per million population per year.[19] The myriad causes of cerebral venous thrombosis and the broad spectrum of clinical manifestations make diagnosis difficult.[20–22] However, rapid diagnosis is vital because appropriate therapy can significantly curtail the risk of serious complications including intracranial stroke or death.[23]

Causes and Risk Factors

The causes of cerebral venous thrombosis are protean. Cerebral venous thrombosis may be related to local conditions that directly affect the cerebral veins and dural sinuses or a systemic process leading to a hypercoagulable state. Examples of local conditions affecting the cerebral

veins and dural sinuses include trauma to the dural sinuses, infection in structures adjacent to the dural sinuses, or invasion or compression of the sinuses by neoplastic processes.[21,24] Hypercoaguable states such as protein C or protein S deficiency, presence of lupus anticoagulant, oral contraceptive use, pregnancy, or malignancy may also predispose to cerebral venous thrombosis.[21,24] Dural arteriovenous fistula is also associated with cerebral venous thrombosis,[25] although it is unclear whether this is the cause or result of cerebral venous thrombosis. In a study by Tsai and colleagues,[26] 39% of patients with dural arteriovenous fistula also had dural sinus thrombosis. In most cases, the dural sinus thrombosis was near the site of the dural arteriovenous fistula.[26]

Risk factors for cerebral venous thrombosis in children often differ from those seen in adults.[27] Perinatal complications, such as hypoxic ischemic encephalopathy, are the most common risk factors in neonates.[27] In young children, head and neck infections (eg, otitis media, mastoiditis, sinusitis) are the most frequent risk factors for cerebral venous thrombosis.[27] In older children, chronic diseases, such as connective tissue diseases, are more common causes.[27]

Demographics and Clinical Presentation

Cerebral venous thrombosis occurs in all age groups, although it chiefly occurs in patients aged 20 to 35 years.[28] Cerebral venous thrombosis is the cause of approximately 1% to 2% of strokes in young adults.[29] Among children with cerebral venous thrombosis, neonates are the most commonly affected group.[27]

Clinical signs and symptoms of cerebral venous thrombosis are often vague. Most patients with cerebral venous thrombosis develop generalized neurologic symptoms with headache, seen in 75% to 95% of patients,[21] as a common first clinical symptom[30]; nausea is also seen.[30] Papilledema may be noted on physical examination, indicating elevated intracranial pressure.[31] Some patients develop seizures or focal sensory or motor deficits (such as vision changes[30] or hemiparesis).[21] Cranial nerve palsies may occur,[30] particularly when there is involvement of the petrous sinuses.[32] In some cases, cerebral venous thrombosis may even lead to coma or death.[32]

Cerebral venous thrombosis results in elevated venous pressure.[21,31] In some instances, a robust collateral venous drainage network may mitigate against venous hypertension.[21] However, if adequate collateral venous drainage fails to materialize, the venous pressure increases. As venous pressure increases, venous congestion develops with an accompanying decline in arterial perfusion pressure[21] and a reversible compromise of oxygen and glucose consumption.[32] If reduction of arterial perfusion pressure is severe enough and prolonged enough, venous infarction occurs[21] and hemorrhage may ensue.[18] Again, if collateral venous drainage develops or recanalization occurs before cell death, the parenchymal changes identified on imaging (including vasogenic and cytotoxic edema) may partially or even completely resolve.[21,33]

Unlike arterial thrombosis, symptoms in cerebral venous thrombosis tend to develop slowly or subacutely.[30] The clinical manifestations of cerebral venous thrombosis are determined by the extent, site, and acuity of thrombosis.[21] The clinical scenario may also vary over time because of thrombosis and concurrent endogenous thrombolysis and recanalization.[21]

Imaging Modalities and Imaging Features

In patients with cerebral venous thrombosis, the superior sagittal sinus is most commonly involved, seen in approximately two-thirds of patients.[17] Many patients with superior sagittal sinus thrombosis also have thrombus extending into the transverse and sigmoid sinuses (**Fig. 7**).[17] Deep venous system thrombosis (eg, thrombosis of the internal cerebral veins, vein of Galen, or straight sinus) is seen in approximately 16% of patients with cerebral venous thrombosis (**Figs. 8** and **9**).[21] Most of these patients present with symptoms of intracranial hypertension and may rapidly deteriorate to a comatose state.[21]

Imaging of the cerebral venous structures may be performed with MR or CT venography (CTV). With time-of-flight (TOF) MR venography, normal flow results in high signal, whereas absence of flow yields low signal.[17] CTV demonstrates thrombus as a filling defect within a contrast-enhanced dural sinus or nonopacification of a cerebral vein.

The most common MR venography techniques are 2-dimensional TOF (2D-TOF) MR venography and contrast-enhanced MR venography. TOF MR venography displays flowing blood as high signal. The background is dark secondary to the suppression of signal from stationary tissues. The 2D-TOF techniques are most sensitive to the flow that is perpendicular to the plane of acquisition.[21] In areas where venous flow is parallel to the plane of acquisition, saturation effects can lead to loss of signal, which must not be mistaken for venous thrombosis.[17,21] With contrast-enhanced MR venography, the paramagnetic

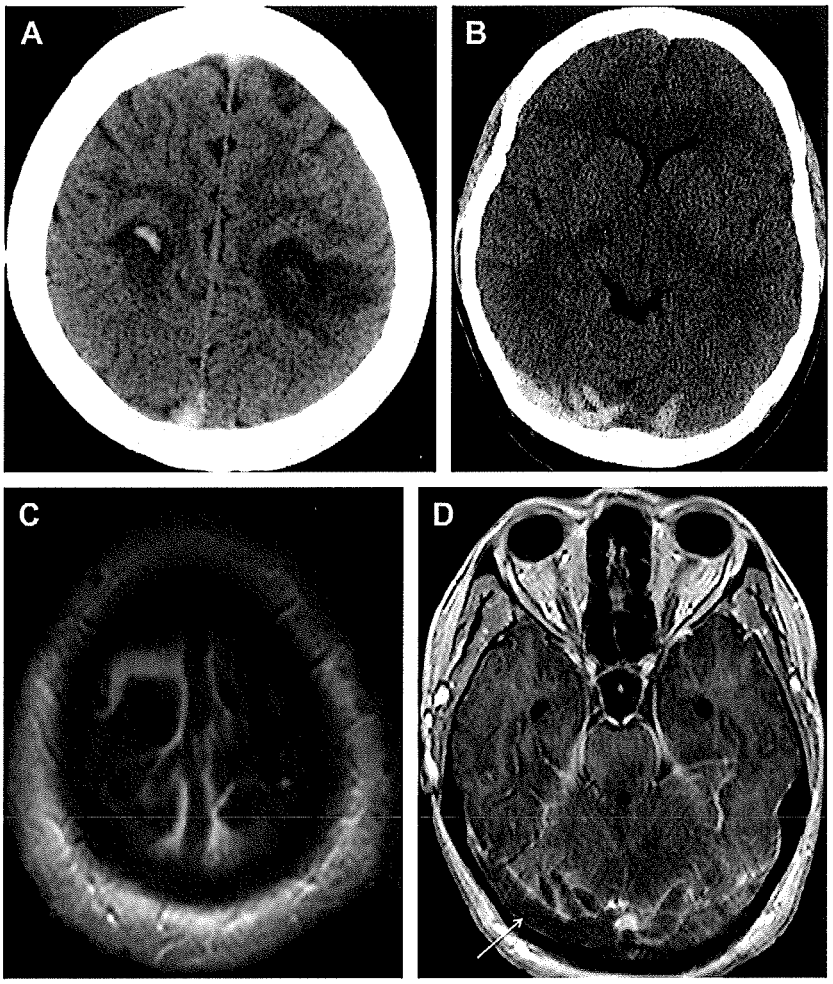

Fig. 7. Venous hemorrhagic infarction. Axial noncontrast CT image (*A*) shows biparietal intraparenchymal hemorrhages with surrounding hypoattenuation consistent with vasogenic edema. Hyperattenuation within the superior sagittal sinus suggesting hemorrhagic infarcts secondary to dural sinus thrombosis. A more caudal noncontrast axial CT image (*B*) demonstrates linear hyperattenuation along the transverse sinuses and cortical veins consistent with dural sinus and cortical venous thromboses. Postgadolinium axial 3-dimensional magnetized-prepared rapid gradient echo images (*C, D*) confirm the presence of superior sagittal sinus, transverse sinus (*arrow*), and cortical venous thrombosis with filling defects found in those locations.

effect of gadolinium shortens T1, resulting in intravascular contrast enhancement.[21] When compared with TOF MR venography, contrast-enhanced MR venography offers superior visualization of smaller vessels with fewer problematic effects of turbulent flow.[21] There are several methods for performing contrast-enhanced MR venography. Among the more common methods are the magnetized-prepared rapid gradient echo and volumetric interpolated brain examination pulse sequences. A particular advantage of these techniques is that the signal is not affected by the angle between the vessels and the scan plane.[34] This advantage is especially helpful in the evaluation of the sigmoid sinuses and jugular bulb, which are often problematic with other techniques because of artifacts and turbulent flow.

CTV is commonly used in the emergency setting because it can be performed swiftly and offers improved visualization of small vessels when compared with MR venography (eg, the inferior sagittal sinus, basal veins of Rosenthal, and nondominant transverse sinus).[30,35] In addition, CTV is not affected by the flow-related artifacts that are sometimes problematic with MR venography.[17] In the assessment of cerebral venous thrombosis, CTV has been shown to be at least as accurate as TOF MR venography.[17,21,35] One of the disadvantages of this technique is the complexity of generation of maximum intensity

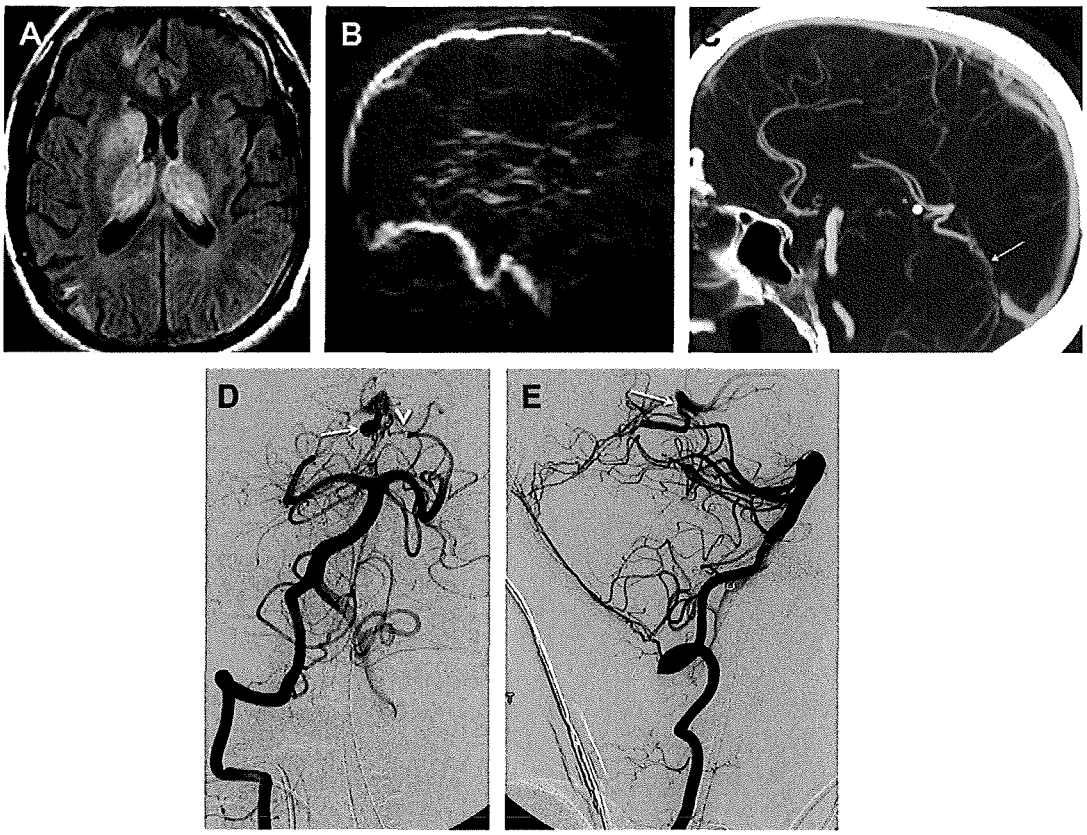

Fig. 8. Deep venous thrombosis and dural arteriovenous fistula. Axial FLAIR image (*A*) shows FLAIR hyperintensity in the right basal ganglia and bilateral thalami. Maximum intensity projection image from 2-dimensional time-of-flight MR venography (*B*) demonstrates lack of flow-related enhancement in the straight sinus consistent with dural sinus thrombosis. On the sagittal CT angiographic image (*C*), there is no visualization of most of the straight sinus (*arrow*), compatible with thrombosis. Anteroposterior and lateral catheter angiograms with right vertebral injection (*D*, *E*) show a dural arteriovenous fistula within the straight sinus with a left posterior cerebral artery branch arterial feeder (*arrowheads*) and early filling of deep veins including the vein of Galen (*arrows*). On more delayed images (not shown), there was nonvisualization of the straight sinus, compatible with dural sinus thrombosis.

projection (MIP) images from the source data secondary to the care that must be taken not to omit part of the sinus when subtracting the bone.[21] However, Wetzel and colleagues[36] showed that CTV with multiplanar reformations has increased sensitivity in depiction of the venous anatomy compared with CTV with MIP images.[30] Sensitivity and specificity of CTV for cerebral venous thrombosis approach 100%.[30] Nevertheless, a hyperdense venous thrombus can be mistaken for normal enhancing sinus, referred to as the "cord sign." Therefore, it is imperative that CTV be reviewed in conjunction with an unenhanced head CT.[30] Occasionally, chronic thrombus may also be difficult to detect on CTV because the clot may enhance, thereby failing to manifest as a filling defect.[30]

Unenhanced CT examinations can sometimes demonstrate findings that raise the possibility of cerebral venous thrombosis. Chief among these findings is a hyperdense dural venous sinus or a dense cortical vein (**Fig. 10**). However, a hyperdense sinus is seen only in 25% of patients with dural venous sinus thrombosis. Other potential causes of increased dural sinus attenuation include dehydration and polycythemia.[16,21] Comparison of the density of dural venous sinus with that of the arteries can be helpful in differentiating dural venous sinus thrombosis from physiologic causes of increased attenuation. If venous sinus hyperdensity is identified on unenhanced CT, this should be further evaluated with CTV or MR venography. Nonspecific findings, such as edema or parenchymal hemorrhage, not

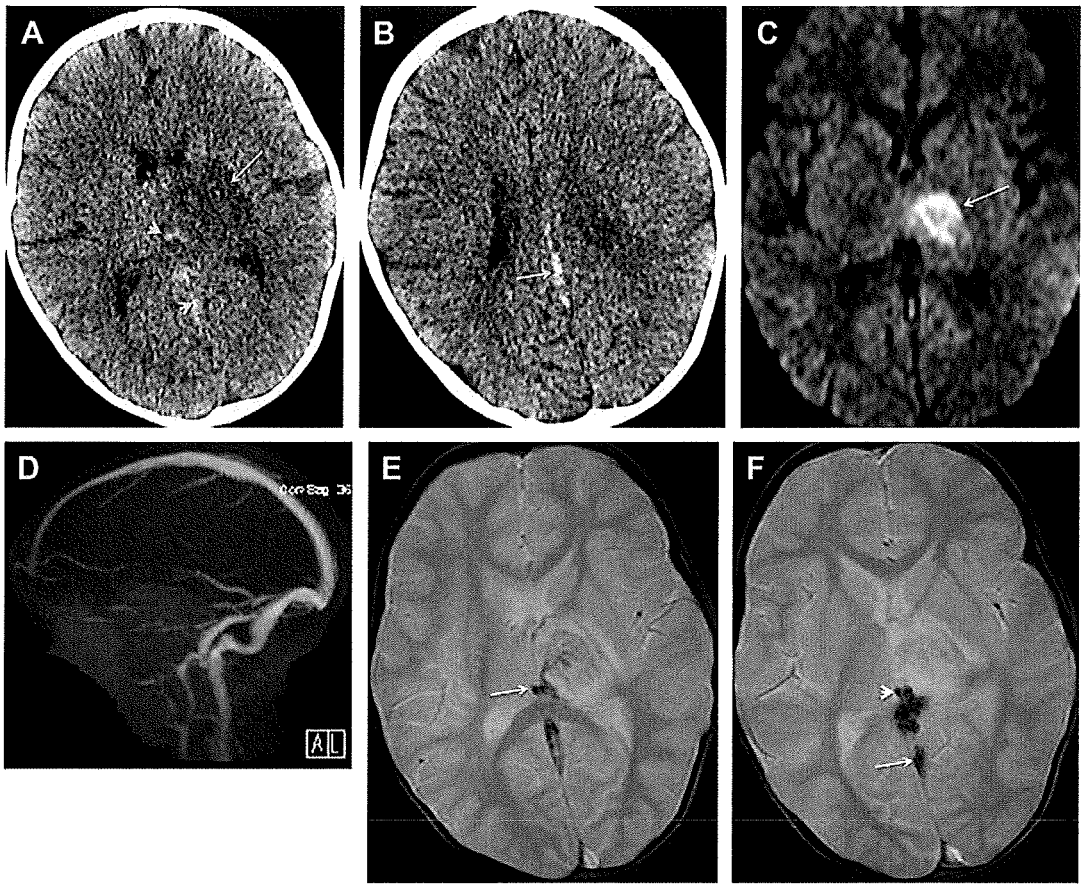

Fig. 9. Deep venous thrombosis with thalamic and basal ganglia infarcts. Axial noncontrast CT images (*A*, *B*) show confluent hypoattenuation in the left thalamus and left basal ganglia (*arrow* in *A*) as well as subtle hyperattenuation along the deep veins (*arrowheads* on *A* and *arrow* on *B*), suggesting thrombosis. Axial diffusion-weighted image (*C*) shows restricted diffusion in the left thalamus (*arrow*) consistent with acute infarction. Maximum intensity projection MR venographic image (*D*) demonstrates lack of flow-related enhancement in the internal cerebral veins, vein of Galen, and straight sinus, consistent with thrombosis. Axial gradient echo images (*E*, *F*) demonstrate blooming of susceptibility artifact within the deep veins (*arrow* in *E* and *arrowhead* in *F*) and straight sinus (*arrow* in *F*) caused by deep venous thrombosis.

conforming to an arterial territory can sometimes suggest the diagnosis of venous thrombosis and/or venous infarction. Rarely, subarchnoid hemorrhage may be the sole finding in cerebral venous thrombosis[18] and should be considered in patients without an identifiable cause for subarachnoid hemorrhage.

Unenhanced conventional MR imaging can sometimes raise the specter of cerebral venous thrombosis and is more sensitive than noncontrast CT in the identification of cerebral venous thrombosis.[21] Thrombosis should be considered when there is loss of an expected dural venous sinus flow void.[17,21] With careful review, this finding may be seen in 80% of patients with cerebral venous thrombosis.[17] However, turbulent or slow flow can also affect dural venous sinus signal and is a potential pitfall, particularly at the jugular bulb.[21] When dural venous sinus thrombosis is present, venous sinus signal abnormalities are typically seen on multiple sequences. The appearance of a venous thrombus on T1- and T2-weighted images varies with the age of the thrombus (**Table 1**). On gradient echo MR images, magnetic susceptibility artifact related to deoxyhemoglobin or methemoglobin may sometimes be a helpful diagnostic adjunct in the detection of dural venous sinus thrombosis (**Fig. 11**).[21] However, chronic thrombus may not be associated much with gradient susceptibility artifact.[19] The reason for this is unclear but may be because of elimination of blood breakdown products by macrophages during the process of thrombus organization.[19] In some cases, a dural venous

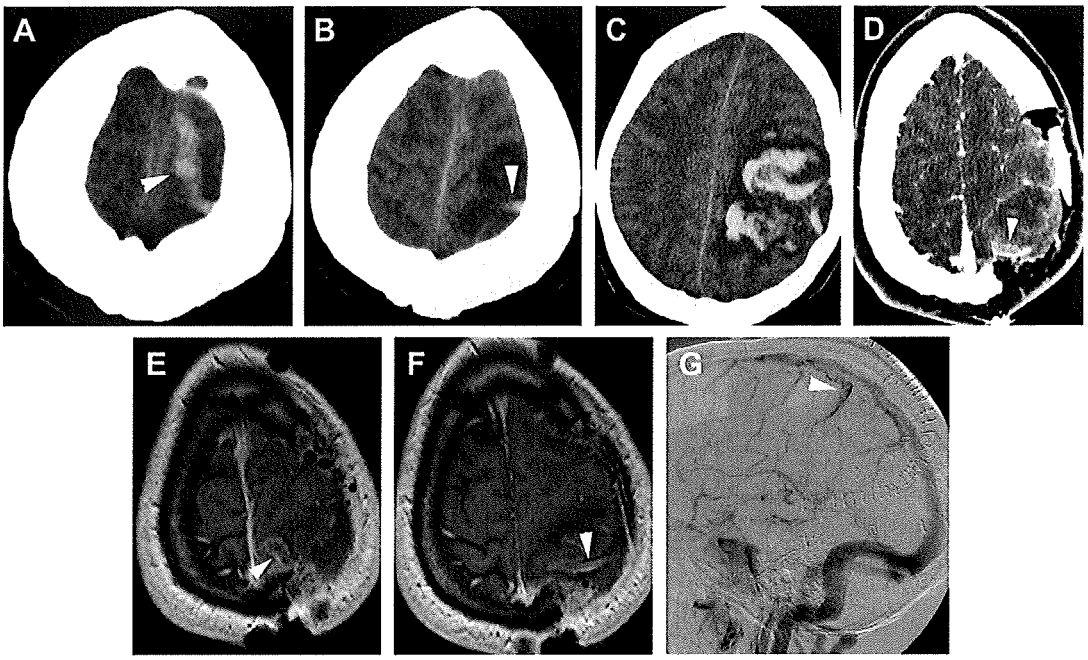

Fig. 10. Isolated cortical vein thrombosis. Axial noncontrast CT images (*A*, *B*, and *C*) demonstrate a curvilinear hyperdense structure (*arrowheads*) along the left parietal lobe consistent with a thrombosed cortical vein. A large intraparenchymal hemorrhage with surrounding hypoattenuation consistent with vasogenic edema is seen in the left parietal lobe in image C, compatible with a venous hemorrhagic infarct. Axial CT angiographic image after left parietal craniectomy for decompression (*D*) shows a filling defect (*arrowhead*) within an enlarged left parietal cortical vein consistent with thrombus. Axial postgadolinium 3D magnetized-prepared rapid gradient echo images after left parietal craniectomy for decompression (*E*, *F*) confirm the filling defect (*arrowheads*) in the left parietal cortical vein consistent with thrombus. Lateral view of a catheter angiogram in the venous phase (*G*) also shows the filling defect in the parietal vein (*arrowhead*), confirming the venous thrombosis.

sinus thrombus may demonstrate restricted diffusion.[21]

Conventional contrast-enhanced CT or MR imaging of the brain can sometimes provide clues to the diagnosis of dural venous sinus thrombosis. The empty delta sign is characterized by the presence of a central intraluminal filling defect surrounded by contrast-enhanced dural collateral venous channels and cavernous spaces in the sinus wall. This sign is diagnostic of dural venous sinus thrombosis.[21,37] Although the empty delta sign is very specific for the diagnosis of dural venous thrombosis, its sensitivity is only approximately 30%.[37] Subacute thrombus on postcontrast T1-weighted MR images may display increased signal intensity that may occasionally simulate the signal of flow.[35] However, subacute thrombus rarely achieves the very bright signal intensity of normal flow.[24,35] But chronic organized dural venous sinus thrombus may enhance.[21] As a thrombus ages, it is invaded by fibroblasts and endothelial-lined channels, converting it to a vascularized tissue that enhances.[19,21,37] Contrast enhancement in the dural venous sinuses does not definitely exclude thrombosis, and even contrast-enhanced MR venography may have a decreased sensitivity for chronic thrombus.[21,37] Because the length of time required for chronic

Table 1
MR signal characteristics of thrombus versus thrombus age

Age of Thrombus	Signal Characteristics
Acute (0–5 d)	Isointense on T1-weighted images Hypointense on T2-weighted images
Subacute (6–15 d)	Hyperintense on T1- and T2-weighted images
Chronic (>15 d)	Variable signal characteristics but typically isointense on T1-weighted images and isointense to hyperintense on T2-weighted images

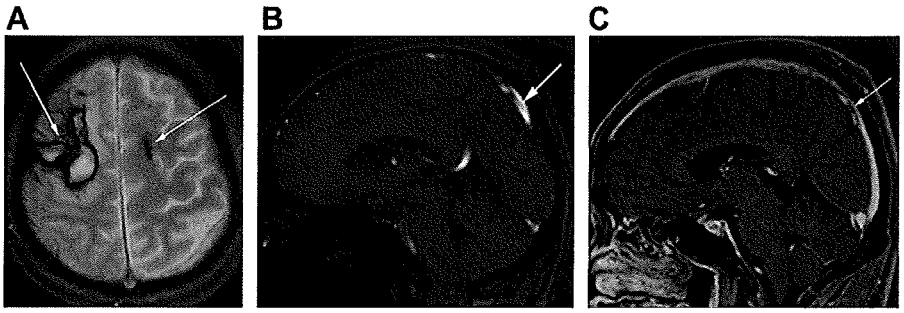

Fig. 11. Chronic superior sagittal sinus thrombus on 2D-TOF MR venography and postgadolinium volumetric interpolated brain examination (VIBE) MR venography. Axial gradient echo image (*A*) shows susceptibility artifact (*arrows*) in the frontal lobes bilaterally consistent with intraparenchymal hemorrhages. MIP image from 2D-TOF MR venography (*B*) shows subtle nonocclusive filling defect (*arrow*) within the superior sagittal sinus consistent with chronic thrombus. Postgadolinium VIBE MR venographic image (*C*) in the same patient demonstrates thrombus (*arrow*) in the superior sagittal sinus to better advantage.

thrombus to begin to demonstrate significant enhancement is unclear, it is helpful to perform both contrast-enhanced and TOF MR venography.[19]

Parenchymal abnormalities are seen in many patients with cerebral venous thrombosis. Parenchymal abnormalities include edema (vasogenic or cytotoxic), hemorrhage, or enhancement. Edema may manifest as areas of hypoattenuation (on CT) or T2 hyperintensity (on MR imaging) involving cortex, white matter, or both. Unlike arterial infarcts that are typically transcortical, intraparenchymal changes in cerebral venous thrombosis are often subcortical.[29] Mass effect is also seen in most patients,[33] but it should be noted that the edema leading to parenchymal swelling does not always manifest as parenchymal attenuation or signal abnormalities. In fact, there may be evidence of parenchymal swelling with sulcal or ventricular effacement in up to 42% of patients without associated parenchymal attenuation or signal abnormalities.[21]

Approximately one-third of patients with cerebral venous thrombosis develop intraparenchymal hemorrhages (see **Fig. 11**).[21] This development may be related to continued arterial perfusion in areas of infarction or venous hypertension beyond a critical limit.[21] The hemorrhages are typically cortical with subcortical extension.[21] Cerebral venous thrombosis may also result in subarachnoid hemorrhage[22] related to rupture of dilated cortical veins.[22]

Enhancement patterns that have been described in patients with cerebral venous thrombosis include parenchymal enhancement (often gyral in location), tentorial enhancement, leptomeningeal enhancement, and prominent cortical venous enhancement.[21]

The location of the parenchymal abnormalities usually reflects the site of thrombosis. For instance, edema or hemorrhage in the bilateral frontal, parietal, and occipital lobes is typical of superior sagittal sinus thrombosis,[23] whereas deep venous thrombosis often affects the thalami that have primary venous pathways draining into the internal cerebral veins.[21] The characteristic parenchymal finding in patients with deep cerebral venous thrombosis is thalamic hemorrhage or bilateral thalamic edema, with occasional involvement of the caudate nuclei and deep white matter.[21] Unilateral thalamic parenchymal findings in deep cerebral venous thrombosis are rare.[21] Although the distribution of parenchymal abnormalities may suggest the site of thrombosis, there are some atypical cases.[21] For example, dural sinus thrombosis may result in edema or hemorrhage in the supratentorium as well as in the cerebellum and brainstem.[23]

Isolated cortical venous thrombosis without associated dural sinus thrombosis is rare because both the thromboses are usually related, with the thrombus extending in a retrograde manner from the thrombosed sinus.[29] Many patients with isolated cortical venous thrombosis either have a coagulopathy or a chronic inflammatory disease such as inflammatory bowel disease.[21] The typical finding in cortical venous thrombosis is a hyperdense or hyperintense cortical vein that shows blooming on gradient echo images.[21] There may or may not be associated edema or hemorrhage in the parenchyma drained by the vein. Occasionally, cortical venous thrombosis may be detected on MR venography as loss of flow-related or contrast-related enhancement within the thrombosed cortical vein. The thrombosis of the main draining vein

of a developmental venous anomaly associated with a thrombosed venous varix and thrombosed cortical vein is shown in **Fig. 12**.[21]

Potential Pitfalls

With cerebral venous thrombosis, the average delay from onset of symptoms to diagnosis is 7 days.[30] Many clinical conditions including arterial stroke, brain tumors, encephalitis, and benign intracranial hypertension may mimic cerebral venous thrombosis.[18] Clinical diagnosis of cerebral venous thrombosis is further complicated by vague nonspecific symptoms. If a high index of suspicion is not maintained in such patients without a clear alternate diagnosis, then diagnosis of cerebral venous thrombosis is often missed. Cerebral venous sinus thrombosis should always be considered in young or middle-aged patients with atypical or severe headache or with strokelike symptoms in patients without the usual risk factors for stroke.[30] The diagnosis should also be suspected when imaging demonstrates localized cerebral edema or infarction that does not conform to an arterial vascular territory.[29]

Although positive findings of cerebral venous thrombosis (eg, hemorrhagic venous infarcts, the dense vein sign on unenhanced CT, and the empty delta sign on contrast-enhanced CT) are helpful, it must be kept in mind that positive findings on screening examinations are only seen in a minority of patients with cerebral venous thrombosis.[17] When there is concern for cerebral venous thrombosis, CTV or MR venography must be performed.

When evaluating for cerebral venous sinus thrombosis, the radiologist must be aware of several potential pitfalls, including dural venous sinus asymmetry, slow flow in a hypoplastic sinus on TOF MR venography, variant sinus confluence anatomy, arachnoid granulations, intrinsic thrombus signal on TOF MR venography, and sinus signal intensity variations. Dural venous sinus asymmetry is relatively common, with the right transverse sinus typically larger than the left. Furthermore, a dural venous sinus may be hypoplastic or atretic. With 2D-TOF MR venography, the radiologist may not be able to differentiate a hypoplastic or atretic sinus from dural venous sinus thrombosis.[34] Slow flow in hypoplastic dural venous sinuses may manifest as

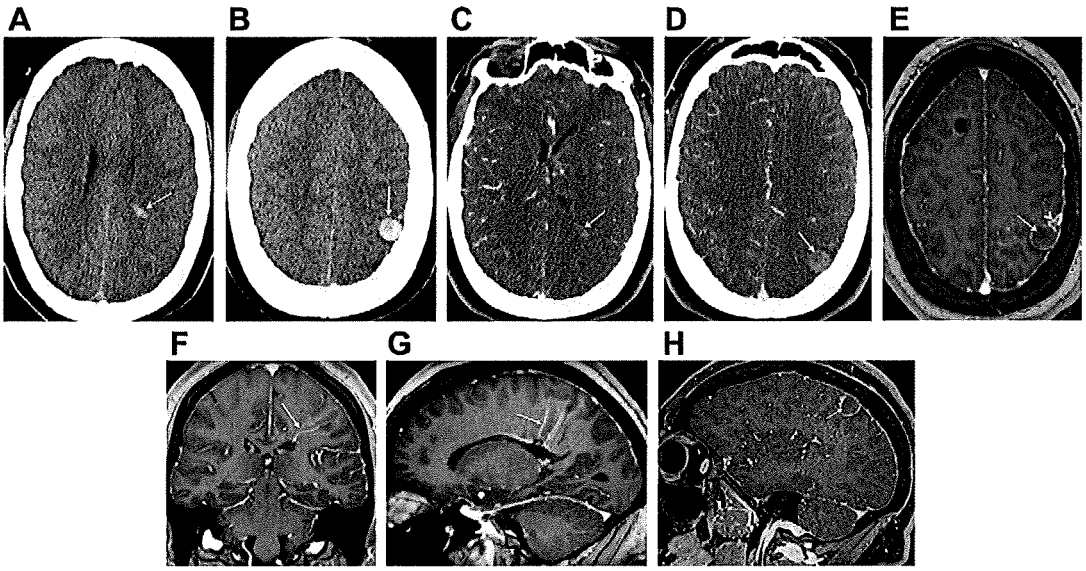

Fig. 12. A 27-year-old woman with new-onset right-sided seizures. (*A*) and (*B*) are noncontrast axial CT images demonstrating hyperdense material (*arrows*) in the left parietal lobe. CT angiographic images (*C, D*) show that this hyperdensity corresponds to a filling defect within the main draining vein of a large left parietal developmental venous anomaly (*arrow* in *C*) and an associated venous varix (*arrow* in *D*). The filling defect is consistent with thrombus. Axial postgadolinium 3D magnetized-prepared rapid gradient echo (MP-RAGE) image (*E*) shows thrombus extending into a cortical vein (*arrowhead*) associated with the left parietal venous varix (*arrow*). The left parietal developmental venous anomaly (*arrows*) is well demonstrated on coronal and sagittal postgadolinium 3D MP-RAGE images (*F, G*). Postgadolinium sagittal volumetric interpolated brain examination MR venographic image (*H*) confirms the filling defect (*arrow*) in the venous varix associated with the developmental venous anomaly.

flow gaps on TOF MR venography because the flow-related enhancement may be insufficient to distinguish it from stationary tissue.[35]

TOF MR venography is prone to signal loss from saturation effects when the direction of blood flow is parallel rather than perpendicular to the acquisition plane.[19,21] This signal loss may cause a flow gap simulating thrombosis.[19,35] Misdiagnosis of cerebral venous thrombosis can often be averted in these settings by referring to the source images as well as TOF MR venographic images obtained in an orthogonal plane.

A high or asymmetric bifurcation at the torcular Herophili can be mistaken for thrombus (pseudoempty delta sign). This pitfall can be avoided by careful evaluation of the source and reformatted images.

Lesions that protrude into or invade a dural venous sinus may mimic a thrombus. Arachnoid granulations, which normally extend into the dural venous sinuses, can cause defects that may be misdiagnosed as thrombi, particularly if they are large (**Fig. 13**). Arachnoid granulations are typically focal round defects with a signal intensity or attenuation similar to that of the cerebrospinal fluid.[21] Although the granulations may occur anywhere in the dural venous sinus system, they are most commonly seen in the transverse sinus or superior sagittal sinus. In the transverse sinus, they are commonly seen in the lateral transverse sinus, the drainage site for the vein of Labbé, and lateral tentorial sinus.[21] A tumor such as a meningioma may also invade or cause mass effects on a dural venous sinus, simulating a thrombus.[35]

Increased signal intensity associated with subacute thrombus can sometimes simulate normal flow on T1-weighted TOF or contrast-enhanced MR venography. Review of the source images usually helps in differentiation.[21,30] Also, the signal of subacute thrombus is rarely as high in signal intensity as normal flow. Organized chronic thrombus is also a potential pitfall on T1-weighted images, because enhancement related to chronic thrombus may simulate the contrast-enhanced MR venography of a patent sinus.[19] Small flow voids may be seen within chronic thrombus on T2-weighted images.

CT venograms and MR venograms are often displayed with an MIP algorithm. This technique displays the highest intensity pixel in the volume along a ray perpendicular to the viewing screen.[35] The advantage of this technique is that it enables the viewing of the high-density or high signal intensity vessels through the relative low-density or low signal intensity brain parenchyma.[35] However, because MIP images emphasize the brightest voxels in a vessel, the thrombus may be obscured by the surrounding high-density contrast on CTV or high signal intensity flow on MR venography.[35] Thus, the source images should always be consulted when reviewing MIP images.[35]

Subdural hematoma along a dural venous sinus may be mistaken for acute dural venous thrombosis on unenhanced CT or MR.[17]

Spin-echo imaging can sometimes demonstrate artifactual loss of the expected dural venous sinus flow void because of flow-related enhancement or echo rephrasing.[17] Venous signal abnormalities caused by turbulent flow are especially problematic at the level of the jugular bulb.

Prognosis and Treatment

The most severe complications of cerebral venous thrombosis include intracranial hemorrhage, venous infarct, and death. Reported mortality rates of cerebral venous thrombosis range from 5% to 30%.[18,28,29] Factors associated with a poor prognosis of cerebral venous thrombosis include infancy, advanced age, thrombus largely affecting the deep venous system or cerebellar veins, and rapid onset of coma and focal neurologic deficits.[28]

Treatment option for cerebral venous thrombosis includes intravenous heparin or intradural thrombolysis.[20,31] Anticoagulation and/or thrombolytic therapy can improve clinical outcome in cerebral venous thrombosis.[18] Anticoagulation with intravenous heparin halts the progression of thrombosis and allows the body's endogenous thrombolytic process to achieve partial or complete recanalization.[28] With heparin therapy, approximately 70% of patients achieve complete recovery.[28] Even in the presence of hemorrhage, heparin therapy can greatly improve outcome and reduce mortality.[24]

Thrombolysis is most commonly used in patients whose clinical status worsens while on anticoagulation.[20] Thrombolysis is most often accomplished with a pharmacologic agent such as tissue plasminogen activator. Hemorrhage or massive venous infarction is not a contraindication to thrombolysis in the setting of cerebral venous thrombosis, unlike with arterial occlusion.[23] In patients with poor response to intradural thrombolysis, rapid neurologic deterioration, or contraindication to pharmacologic thrombolysis, mechanical thrombectomy with a rheolytic catheter may be attempted.[28] Mechanical thrombectomy may also be considered as an adjunctive therapy in patients undergoing pharmacologic thrombolysis.[31]

Treatment of chronic thrombus is controversial because it may not respond as well to anticoagulation as acute thrombus.[19]

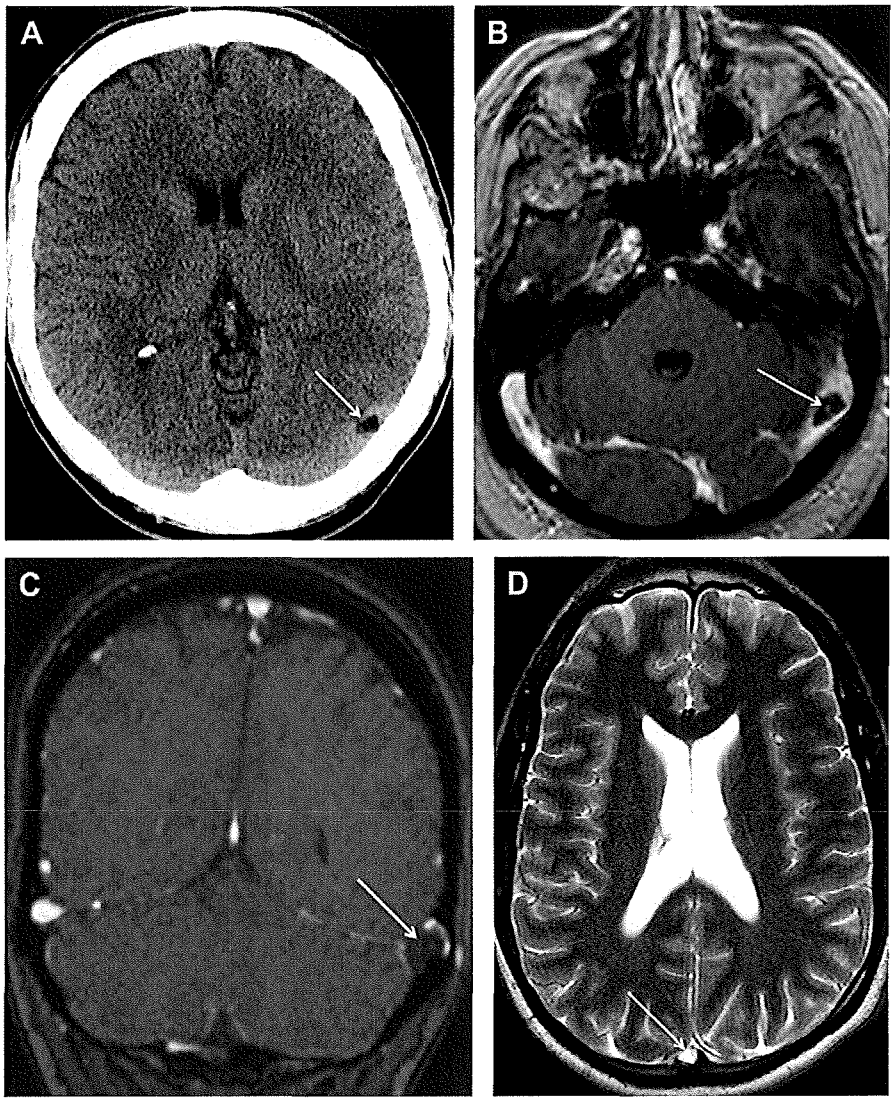

Fig. 13. Arachnoid granulations. Noncontrast axial CT image (*A*) demonstrates a focus of cerebrospinal fluid (CSF) attenuation (*arrow*) within the left transverse sinus consistent with an arachnoid granulation. Axial postgadolinium 3D magnetized-prepared rapid gradient echo (MP-RAGE) image (*B*) shows a filling defect (*arrow*) in the distal left transverse sinus with a typical location and appearance of an arachnoid granulation. Coronal postgadolinium 3D MP-RAGE image (*C*) shows an unusually large arachnoid granulation (*arrow*) as a filling defect in the distal left transverse sinus. Axial T2-weighted image (*D*) depicts a round T2 hyperintense structure (*arrow*) in the superior sagittal sinus demonstrating CSF signal and is compatible with an arachnoid granulation.

SUMMARY

PRES and venous thrombosis are discussed together in this article because both these entities have vague clinical presentations and similar imaging findings and radiologists may be the first to suggest the diagnosis. When brain edema and intraparenchymal hemorrhage occur without respecting vascular territories, or are above and below the tentorium, both entities should be considered in the differential diagnosis. It is crucial to be familiar with these entities when reading emergency neuroradiology studies.

REFERENCES

1. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. AJNR Am J Neuroradiol 2008;29(6): 1036–42.

2. Aranas RM, Prabhakaran S, Lee VH. Posterior reversible encephalopathy syndrome associated with hemorrhage. Neurocrit Care 2009;10(3): 306–12.
3. Finocchi V, Bozzao A, Bonamini M, et al. Magnetic resonance imaging in posterior reversible encephalopathy syndrome: report of three cases and review of literature. Arch Gynecol Obstet 2005;271(1): 79–85.
4. Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. N Engl J Med 1996;334(8):494–500.
5. Mueller-Mang C, Mang T, Pirker A, et al. Posterior reversible encephalopathy syndrome: do predisposing risk factors make a difference in MRI appearance? Neuroradiology 2009;51(6):373–83.
6. O'Hara McCoy H. Posterior reversible encephalopathy syndrome: an emerging clinical entity in adult, pediatric, and obstetric critical care. J Am Acad Nurse Pract 2008;20(2):100–6.
7. Bartynski WS. Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. AJNR Am J Neuroradiol 2008;29(6):1043–9.
8. Bartynski WS, Boardman JF. Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol 2008;29(3):447–55.
9. Bartynski WS, Boardman JF, Zeigler ZR, et al. Posterior reversible encephalopathy syndrome in infection, sepsis, and shock. AJNR Am J Neuroradiol 2006;27(10):2179–90.
10. Casey SO, Sampaio RC, Michel E, et al. Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. AJNR Am J Neuroradiol 2000;21(7):1199–206.
11. McKinney AM, Short J, Truwit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJR Am J Roentgenol 2007;189(4): 904–12.
12. Hodnett P, Coyle J, O'Regan K, et al. PRES (posterior reversible encephalopathy syndrome), a rare complication of tacrolimus therapy. Emerg Radiol 2009;16(6):493–6.
13. Narbone MC, Musolino R, Granata F, et al. Posterior or potentially reversible encephalopathy syndrome? Neurol Sci 2006;27(3):187–9.
14. Bartynski WS, Boardman JF. Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol 2007;28(7):1320–7.
15. Hefzy HM, Bartynski WS, Boardman JF, et al. Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. AJNR Am J Neuroradiol 2009;30(7):1371–9.
16. Healy JF, Nichols C. Polycythemia mimicking venous sinus thrombosis. AJNR Am J Neuroradiol 2002;23(8):1402–3.
17. Khandelwal N, Agarwal A, Kochhar R, et al. Comparison of CT venography with MR venography in cerebral sinovenous thrombosis. AJR Am J Roentgenol 2006;187(6):1637–43.
18. Tang PH, Chai J, Chan YH, et al. Superior sagittal sinus thrombosis: subtle signs on neuroimaging. Ann Acad Med Singap 2008;37(5): 397–401.
19. Leach JL, Wolujewicz M, Strub WM. Partially recanalized chronic dural sinus thrombosis: findings on MR imaging, time-of-flight MR venography, and contrast-enhanced MR venography. AJNR Am J Neuroradiol 2007;28(4):782–9.
20. Manzione J, Newman GC, Shapiro A, et al. Diffusion- and perfusion-weighted MR imaging of dural sinus thrombosis. AJNR Am J Neuroradiol 2000;21(1): 68–73.
21. Leach JL, Fortuna RB, Jones BV, et al. Imaging of cerebral venous thrombosis: current techniques, spectrum of findings, and diagnostic pitfalls. Radiographics 2006;26(Suppl 1):S19–41 [discussion: S42–3].
22. Oppenheim C, Domigo V, Gauvrit JY, et al. Subarachnoid hemorrhage as the initial presentation of dural sinus thrombosis. AJNR Am J Neuroradiol 2005;26(3):614–7.
23. Tsai FY, Wang AM, Matovich VB, et al. MR staging of acute dural sinus thrombosis: correlation with venous pressure measurements and implications for treatment and prognosis. AJNR Am J Neuroradiol 1995;16(5):1021–9.
24. Vogl TJ, Bergman C, Villringer A, et al. Dural sinus thrombosis: value of venous MR angiography for diagnosis and follow-up. AJR Am J Roentgenol 1994;162(5):1191–8.
25. Morales H, Jones BV, Leach JL, et al. Documented development of a dural arteriovenous fistula in an infant subsequent to sinus thrombosis: case report and review of the literature. Neuroradiology 2010; 52(3):225–9.
26. Tsai LK, Jeng JS, Liu HM, et al. Intracranial dural arteriovenous fistulas with or without cerebral sinus thrombosis: analysis of 69 patients. J Neurol Neurosurg Psychiatr 2004;75(11):1639–41.
27. deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. N Engl J Med 2001;345(6):417–23.
28. Peeters E, Stadnik T, Bissay F, et al. Diffusion-weighted MR imaging of an acute venous stroke: case report. AJNR Am J Neuroradiol 2001;22(10): 1949–52.
29. Chang R, Friedman DP. Isolated cortical venous thrombosis presenting as subarachnoid hemorrhage: a report of three cases. AJNR Am J Neuroradiol 2004;25(10):1676–9.

30. Linn J, Ertl-Wagner B, Seelos KC, et al. Diagnostic value of multidetector-row CT angiography in the evaluation of thrombosis of the cerebral venous sinuses. AJNR Am J Neuroradiol 2007;28(5): 946–52.
31. Dowd CF, Malek AM, Phatouros CC, et al. Application of a rheolytic thrombectomy device in the treatment of dural sinus thrombosis: a new technique. AJNR Am J Neuroradiol 1999;20(4):568–70.
32. Kuehnen J, Schwartz A, Neff W, et al. Cranial nerve syndrome in thrombosis of the transverse/sigmoid sinuses. Brain 1998;121(Pt 2):381–8.
33. Mullins ME, Grant PE, Wang B, et al. Parenchymal abnormalities associated with cerebral venous sinus thrombosis: assessment with diffusion-weighted MR imaging. AJNR Am J Neuroradiol 2004;25(10): 1666–75.
34. Liang L, Korogi Y, Sugahara T, et al. Evaluation of the intracranial dural sinuses with a 3D contrast-enhanced MP-RAGE sequence: prospective comparison with 2D-TOF MR venography and digital subtraction angiography. AJNR Am J Neuroradiol 2001;22(3):481–92.
35. Ozsvath RR, Casey SO, Lustrin ES, et al. Cerebral venography: comparison of CT and MR projection venography. AJR Am J Roentgenol 1997;169(6): 1699–707.
36. Wetzel SG, Kirsch E, Stock KW, et al. Cerebral veins: comparative study of CT venography with intraarterial digital subtraction angiography. AJNR Am J Neuroradiol 1999;20(2):249–55.
37. Dormont D, Sag K, Biondi A, et al. Gadolinium-enhanced MR of chronic dural sinus thrombosis. AJNR Am J Neuroradiol 1995;16(6):1347–52.

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High-Dose Corticosteroid Treatment Is Associated with an Increased Risk of Developing Cerebral Venous Thrombosis

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Anecdotal reports linked high-dose corticosteroid (CS) treatment in multiple sclerosis (MS) to an increased risk of developing cerebral venous thrombosis (CVT) [1, 2]. Because high doses of CS are routinely delivered in a wide variety of other neurological and medical disorders, such an association may have an impact on prophylactic strategies against venous thromboembolism during CS treatment. In this respect, CVT provides a better model than deep venous thrombosis of the extremities because it is less influenced by circumstantial risk factors, such as immobilization.

In a cohort of 120 consecutive patients with acute CVT, diagnosed either by digital subtraction angiography or magnetic resonance (MR) imaging and MR angiography, we identified 4 patients who developed CVT during intravenous CS treatment (≥500 mg/day over 5 days) for a relapse of a definite MS according to Poser's criteria. Furthermore, 2 patients with optic neuritis developed CVT during high-dose CS treatment. Overall, this amounts to 5% of patients who developed CVT during CS treatment, a rate as high as could be expected in protein C or S deficiency [3]. In all of the cases the temporal latency to CS treatment was striking. A causative link

Table 1. Clinical and demographic data of 120 patients with CVT

a Total patient cohort (n = 120)

Sex (M/F)	28/92 (23/77)
Age, years, means ± SD (M/F)	48 ± 18/39 ± 16
Inherited risk factors[1]	
Factor V Leiden mutation	7/67 (10.4%)
Prothrombin polymorphism	10/67 (14.9%)
Other coagulopathies	6/67 (8.9%)
Acquired risk factors	
Lupus anticoagulant[1]	8/67 (11.9%)
Pregnancy and postpartum thrombosis	23 (19.2%)
Oral contraceptives	46 (38.3%)
Malignancies	12 (10.0%)
Other	5 (4.2%)

b Six patients with CVT related to high-dose methylprednisolone treatment

Patients	
Relapse of multiple sclerosis	4
Optic neuritis	2
Dosage	
500–1,000 mg/day for 5 days i.v.	6
i.v. treatment followed by 1–1.5 mg/kg/day orally for at least 10 days	4
Latency between CS Tx	
During treatment	4
CVT	
<3 days	2
Lumbar puncture	
Optic neuritis	2[2]
Multiple sclerosis	1[3]
Other risk factors	
Oral contraceptives	3
Smoking	4
Coagulopathies	0
Symptoms	
Persistent headaches	5
Seizures	4
Focal neurological deficits	3

Unless otherwise stated, data are actual number with percentages in parentheses. Tx = treatment.

[1] Only 67 patients (56%) had uniform screenig for coagulopathies (Factor V Leiden, prothrombin polymorphism, antithrombin III, protein C and S, plasminogen deficiencies, lupus anticoagulant).

[2] Six and 26 days prior to CVT.

[3] Nineteen days prior to CVT.

between preceding lumbar puncture and the development of CVT has been discussed in the past [4]; however, the temporal relationship between lumbar puncture and CVT is at best weak in our patients. Only 1 MS patient received a lumbar puncture 19 days prior to CVT. Hence, suggesting an association between CS treatment and CVT seems justifiable. Table 1 summarizes demographic and clinical data of the CVT patients.

Based on recent prevalence data of MS in Germany (100 per 100,000 inhabitants) [5], a rough estimate of the expected frequency of MS cases in the CVT cohort would be one case at maximum. This results in a crude odds ratio for the development of CVT in MS patients treated with high-dose CS of 34.4 (95% CI 12.5–95.2, $p < 0.001$), a risk higher than that attributed to heterozygous protein C deficiency [3]. However, this odds ratio has to remain crude because of the obvious difficulties to recruit a suitably matched control group. Furthermore, a potentiation of the CS effect by acquired and inherited risk factors is conceivable. In 67 of the 120 CVT patients, who had a uniform work-up for coagulopathies specified in table 1, we found an incidence of more than 30%. More than 50% of patients had one or more acquired risk factors. None of the 5 patients who developed CVT during CS treatment and had received uniform screening for coagulopathies had a thrombophilic factor. One of the patients with presumed CS-related CVT was screened for protein C and S as well as for an AT III deficiency, without pathological result. The latter patient died of brain herniation. Other laboratory test systems for screening were not routinely available at this time. However, at least 3 of these patients had accepted acquired risk factors for CVT.

Our data imply that high-dose CS treatment is associated with an increased risk of developing venous thrombosis when other risk factors are present, and that prophylactic low-dose heparin treatment may be warranted in these patients. Severe headaches, seizures or new focal neurological signs in such patients should lead to the exclusion of acute CVT.

References

1 Aidi S, Chaunu MP, Biousse V, Bousser MG: Changing pattern of headache pointing to cerebral venous thrombosis after lumbar puncture and intravenous high-dose corticosteroids. Headache 1999;39:559–564.

2 Albucher JF, Vuillemin-Azaïs C, Manelfe C, Clanet M, Guiraud-Chaumeil B, Chollet F: Cerebral thrombophlebitis in three patients with probable multiple sclerosis. Cerebrovasc Dis 1999;9:298–303.

3 Lane DA, Mannucci PM, Bauer KA, Bertina RM, Bochkov NP, Boulyjenov V, Chandy M, Dahlbäck B, Ginter EK, Miletich JP, Rosendaal FR, Seligson U: Inherited thrombophilia: Part 1. Thromb Haemost 1996;76:651–662.

4 Wilder-Smith E, Kothbauer-Margreiter I, Lämmle B, Sturzenegger M, Ozdoba C, Hauser SP: Dural puncture and activated protein C resistance: Risk factors for cerebral venous sinus thrombosis. J Neurol Neurosurg Psychiatry 1997;63:351–356.

5 Hein T, Hopfenmüller W: Hochrechnung der Zahl an multipler Sklerose erkrankten Patienten in Deutschland. Nervenarzt 2000;71:288–294.

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Cerebral venous sinus thrombosis in children: risk factors, presentation, diagnosis and outcome

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Summary

Neuroimaging and management advances require review of indications for excluding cerebral venous sinus (sinovenous) thrombosis (CSVT) in children. Our goals were to examine (i) clinical presentations of CSVT, (ii) prothrombotic risk factors and other predisposing events, (iii) clinical and radiological features of brain lesions in CSVT compared with arterial stroke, and (iv) predictors of outcome. We studied 42 children with CSVT from five European paediatric neurology stroke registries. Patients aged from 3 weeks to 13 (median 5.75) years (27 boys; 64%) presented with lethargy, anorexia, headache, vomiting, seizures, focal signs or coma and with CSVT on neuroimaging. Seventeen had prior chronic conditions; of the 25 previously well patients, 23 had recent infections, eight became dehydrated and six had both. Two children had a history compatible with prior CSVT. Anaemia and/or microcytosis (21 probable iron deficiency, five haemolytic, including two with sickle cell disease and one with β-thalassaemia) was as common (62%) as prothrombotic disorder (13/21 screened). High factor VIII and homozygosity for the thermolabile methylene tetrahydrofolate reductase polymorphism were the commonest prothrombotic disorders. The superficial venous system was involved in 32 patients, the deep in six, and both in four. Data on the 13 children with bland infarction and the 12 with haemorrhage in the context of CSVT were compared with those from 88 children with ischaemic (AIS) and 24 with haemorrhagic (AHS) arterial stroke. In multiple logistic regression, iron deficiency, parietal infarction and lack of caudate involvement independently predicted CSVT rather than arterial disease. Five patients died, three acutely, one after recurrence and one after 6 months being quadriparetic and blind. Follow-up ranged from 0.5 to 10 (median 1) years. Twenty-six patients (62%) had sequelae: pseudotumour cerebri in 12 and cognitive and/or behavioural disabilities in 14, associated with epilepsy in three, hemiparesis in two and visual problems in two. Eighteen patients, including six with haemorrhage, were anticoagulated. Older age [odds ratio (OR) 1.54, 95% confidence limits (CI) 1.12, 2.13, P = 0.008], lack of parenchymal abnormality (OR 0.17, 95% CI 0.02, 1.56, P = 0.1), anticoagulation (OR 24.2, 95% CI 1.96, 299) and lateral and/or sigmoid sinus involvement (OR 16.2, 95% CI 1.62, 161, P = 0.02) were independent predictors of good cognitive outcome, although the last predicted pseudotumour cerebri. Death was associated with coma at presentation. Of 19 patients with follow-up magnetic resonance (MR) venography, three had persistent occlusion, associated with anaemia and longer prodrome. A low threshold for CT or MR venography in children with acute neurological symptoms is essential. Nutritional deficiencies may be modifiable risk factors. A paediatric anticoagulation trial may be required, after the natural history has been further established from registries of cases with and without treatment.

Keywords: venous sinus thrombosis; anaemia; magnetic resonance; anticoagulation

Abbreviations: CSVT = cerebral venous sinus (sinovenous) thrombosis; MRV = magnetic resonance venography; SCD = sickle cell disease; tMTHFR = thermolabile variant of the methylene tetrahydrofolate reductase gene; SLE = systemic lupus erythematosus

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Introduction

The incidence of cerebral venous sinus (sinovenous) thrombosis (CSVT) is at least 0.67 per 100 000 children per year (de Veber *et al.*, 2001), although there is concern that cases of this potentially treatable condition are missed. The clinical manifestations can be life-threatening and cause long-term neurological deficits (Barron *et al.*, 1992; Carvalho *et al.*, 2000). However, as the symptoms and signs are non-specific, diagnosis is often delayed and may be missed altogether. Although the incidence may be declining, as some of the conditions historically associated with CSVT in children are now rare or treatable, e.g. cyanotic congenital heart disease or mastoiditis, the diagnosis is made more commonly in life because of advances in neuroimaging. The onus is on the clinician to request the appropriate investigations but many have never diagnosed a case. CT may not be adequate to exclude CSVT and indications for MRI and magnetic resonance (MR) venography in acute neurological presentations have not been established, as there are few data from which evidence-based guidelines for investigation could be developed.

The importance of genetic and acquired prothrombotic disorders has been emphasized in recent series of paediatric CSVT (de Veber *et al.*, 1998*a*; Bonduel *et al.*, 1999; Heller *et al.*, 2003). However, although single cases of homocystinuria (Buoni *et al.*, 2001; Vorstman *et al.*, 2002) and severe anaemia (Belman *et al.*, 1990; Hartfield *et al.*, 1997; Meena *et al.*, 2000; Swann and Kendra, 2000; Keane *et al.*, 2002) have been reported as associations, there are few data on the relative importance of milder anaemia or genetic determinants of hyperhomocysteinaemia (Martinelli *et al.*, 2003; Boncoraglio *et al.*, 2004), both of which might be modified with low risk by nutritional supplementation. High factor VIII levels appear to be associated with CSVT in adults (Cakmak *et al.*, 2003), but factor VIII is not commonly performed in children (Kurecki *et al.*, 2003).

In order to explore the variety of clinical and neuroradiological presentation and the frequency of associated haematological risk factors, as well as to determine predictors of outcome, we describe our experience with consecutive children with CSVT in five centres. In addition, we compare the clinical presentation of children with infarction or haemorrhage secondary to CSVT with those with arterial ischaemic (Ganesan *et al.*, 2003) or haemorrhagic stroke. We emphasize the need for increased awareness of this entity in children.

Methods

Data review was conducted of consecutive patients personally known to three of the authors (G.S., A.N.W. and F.J.K.) and investigated prospectively at one of five European paediatric neurology centres with a paediatric stroke registry: Hôpital Kremlin-Bicêtre, France (1997); Cliniques Universitaires Saint-Luc, Belgium (1997–2002); The Princess of Wales Children's Hospital, Birmingham (1993–1998); Great Ormond Street Hospital, London (1990–2000); and Southampton General Hospital (1999–2001). Appropriate ethical permission was obtained. Patients were included if a diagnosis of definite CSVT had been made by a neuroradiologist either on CT after contrast enhancement showing the dense-triangle sign, or MR based on classical neuroradiological features (Sébire *et al.*, 2004). Patients presenting to neonatal paediatricians were not included. Patients underwent the following laboratory investigations, which increased in number over the study period as possible prothrombotic associations were reported: blood count, cholesterol, triglycerides, lipoprotein (a), fibrinogen, protein C, protein S, antithrombin, plasminogen, heparin cofactor II, prothrombin 20210, factor V Leiden, homozygosity for the thermolabile variant of the methylene tetrahydrofolate reductase gene (tMTHFR), factor VIII, factor XII, anticardiolipin IgG and lupus anticoagulant. Details of the clinical presentation, laboratory and radiological investigations and long term clinical and radiological follow-up were obtained from the databases and were supplemented by return to the medical notes. All patients were seen at least once for a follow-up with a paediatric neurologist and an interview with the parents about function in nursery or school, ongoing headache and epilepsy was conducted, as well as a neurological examination. Outcome was classified as death, cognitive sequelae, motor sequelae, visual sequelae, pseudotumour cerebri or none of these. Pseudotumour cerebri was diagnosed using classical criteria, including cerebrospinal fluid pressure measurement (Balcer *et al.*, 1999). 'Cognitive sequelae' refers to children being placed at least one school grade below their expected class for age or requiring a statement of special educational needs or—for preschool children—formal testing suggesting that the developmental speed was less than 75% of normal. Follow-up neuroimaging was undertaken at the discretion of the paediatric neurologist. Parenchymal changes were compared with the previous imaging and were classified as normal, improved or persistent. Venous sinus patency was assessed as normal, improved or persistent. We looked for distinctive features between venous and arterial strokes, in order to examine whether there were clues to the differential diagnosis. Comparison of the clinical, radiological and laboratory features of the patients with bland and haemorrhagic CSVT were made with a consecutive cohort of children with arterial stroke prospectively studied at Great Ormond Street Hospital between January 1994 and April 2000.

Statistical analysis was performed using χ^2 (statxact version 4.0.1), Kruskall–Wallis analysis of variance, Fisher's exact test and logistic regression (SPSS version 11.0).

Results

Forty-two children were included, one from Paris, four from Brussels, nine from Birmingham, nine from Southampton,

Table 1 *Previous medical history in 42 children with CSVT*

	Frequency (%)
Male	24/42 (57%)
Underlying illness	17/42 (40%)
Cardiac disease	2/42 (4%)
Inflammatory bowel disease	1/42 (2%)
Nephrotic syndrome	3/42 (6%)
Systemic lupus erythematosus	2/42 (4%)
Sickle cell disease	2/42 (4%)
Thalassaemia	1/42 (2%)
Hydrocephalus (recent shunt)	2/42 (4%)
Brain tumour	2/42 (4%)
Leukaemia	2/42 (4%)
Previously well	25/42 (59%)
Previous CSVT history	2/42 (4%)
Recent triggering event	42/42 (100%)
Ear infection (mastoiditis)	20/42 (47%)
Sinusitis	1/42 (2%)
Other infection	10/42 (24%)
Diarrhoea	5/42 (12%)
Other dehydration	9/42 (21%)
Recent head trauma	2/42 (4%)
Recent surgery	4/42 (9%)

Table 2 *Clinical features of CSVT in 42 children*

	Frequency (%)
Onset	
Acute	35/42 (83%)
Subacute	7/42 (17%)
Symptoms	
Seizures (generalized tonic-clonic)	17/42 (40%)
Headache	25/37 (68%)
Vomiting	12/42 (28%)
Drowsiness	18/42 (43%)
Anorexia/poor feeding	5/42 (12%)
Lethargy	19/42 (45%)
Irritability	5/42 (12%)
Confusion	5/37 (13%)
Numbness	1/37 (3%)
Signs	
Fever	19/42 (45%)
Coma	12/42 (28%)
Hemiparesis	14/42 (33%)
Ataxia	1/37 (3%)
Cranial nerve abnormality	14/42 (33%)
Visual deficit	4/37 (11%)

and the remainder from Great Ormond Street. Age ranged from 3 weeks to 13 years (median 5.75 years); 27 (64%) of the patients were boys.

Pre-existing diagnosis and triggers (Table 1)

Patients with previous chronic illness

Seventeen patients were known to have chronic illness (Table 1), including four who had CSVT diagnosed immediately after surgical procedures, namely modified Fontan for hypoplastic left heart syndrome, ventriculoperitoneal shunt, brain tumour resection, and colectomy for ulcerative colitis. Eight of the patients with chronic illness had recent infections (three involving the ear, none with mastoiditis) and four were dehydrated. Comparison using Fisher's exact test of the occurrence of underlying illnesses and of triggering events between the three different age groups (<1 year, $n = 5$; 1–6 years, $n = 17$; >6 years, $n = 20$) did not show any significant differences (Table 1).

Previously well children

Twenty-five patients were previously well, all of whom had triggers: 23 had recent infections (17 involving the ear, 11 with mastoiditis), eight became dehydrated and six were both infected and dehydrated.

There were no significant associations between age group and pre-existing diagnosis or any of the triggers (Table 1). Patients without pre-existing chronic illness were more likely to have had a recent infection, an ear infection or mastoiditis (Fisher's exact test, $P = 0.003$, $P = 0.002$, $P = 0.006$ respectively) but were not more likely to be dehydrated (Fisher's exact test, $P = 0.73$).

Clinical presentation (Table 2)

All patients had symptomatic CSVT (Table 2). The median duration of symptoms was 5 days (range 12 h to 120 days). The majority of children presented acutely with seizures, focal signs and symptoms of raised intracranial pressure, such as headache and decreased level of consciousness (Table 2). Subacute presentation, with chronic headache, vomiting, lethargy, anorexia or drowsiness for 3 weeks or more, occurred in six children. Nineteen children were febrile at presentation. Using Fisher's exact test, there was no significant difference in the type of clinical manifestations between the three different age groups (<1 year, $n = 5$; 1–6 years, $n = 17$; >6 years, $n = 20$).

Previous neurological history

Two children had a prior neurological history compatible with previous CSVT. One child with haemoglobin SC disease born at 36 weeks gestation had presented at the age of 2 weeks with a left-sided focal seizure in the context of a chest infection. Head ultrasound revealed bilateral intraventricular haemorrhage and lumbar cerebrospinal fluid was uniformly bloodstained but cerebral venous sinus thrombosis was not excluded. He required a shunt for communicating hydrocephalus and represented at the age of 9 years with severe headache secondary to venous sinus thrombosis (Fig. 1). Another patient, who was chronically iron-deficient, had developed a transient hemiparesis at the age of 18 months.

Laboratory findings

Routine haematology

Twenty-two children (52%) were anaemic (Z score for haemoglobin <2 SDs below the mean for age), two secondary

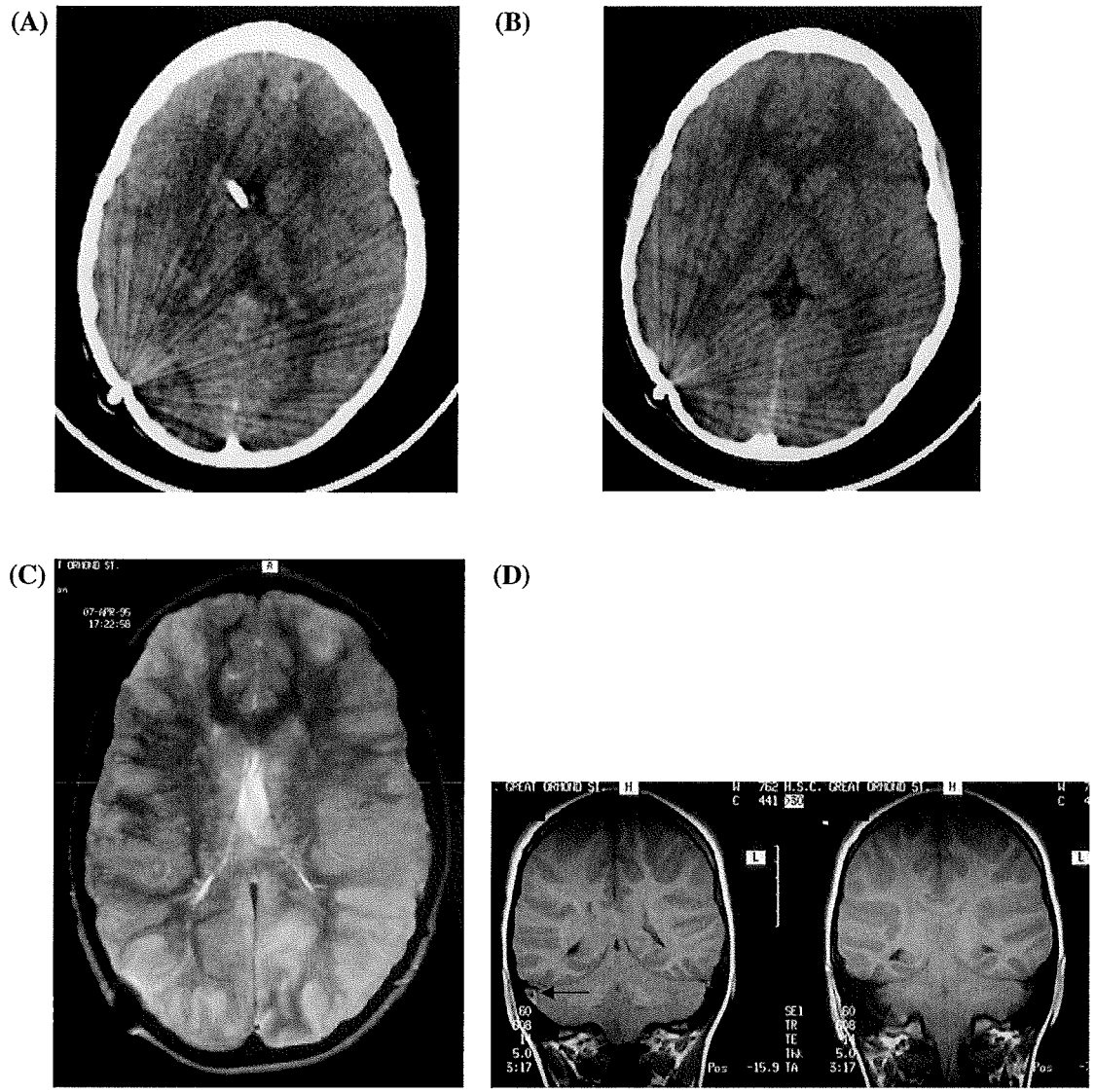

Fig. 1 (**A**) This child with haemoglobin SC disease had presented in infancy with seizures and had required a shunt for hydrocephalus. He represented at the age of 9 with severe chronic headache and 3 weeks later developed generalized seizures. There are no visible sulci and the ventricles are small on the initial CT scan, indicative of cerebral oedema. A right-sided shunt and intracranial pressure monitor are noted. (**B**) The CT scan at 10 days shows definite cerebral oedema and the dense straight sinus raises the possibility of CSVT, but is not diagnostic. (**C**) Two days later there is widespread cortical and basal ganglia high signal on T2-weighted axial MRI. (**D**) Marked swelling of the cerebral hemispheres and posterior fossa, which has led to tonsillar descent, is seen on the T1-weighted coronal images High signal is seen in the right transverse sinus (delta sign) due to either slow flow or thrombus (arrow).

to SC disease (one haemoglobin SC, one homozygous SS), one with β-thalassaemia and two others with haemolytic anaemia in the context of systemic lupus erythematosus (SLE) and non-Hodgkin's lymphoma. Seventeen anaemic children, including one treated for acute lymphoblastic leukaemia, and an additional four children with haemoglobin within the normal range, had microcytosis (haematocrit and/or mean cell volume <2 SDs below the mean for age) compatible with iron deficiency. Anaemia and/or microcytosis were seen in all age groups (60, 53, 75% amongst children aged <1 year, 1–6 years and >6 years respectively, χ^2, P = 0.15). There was a trend for microcytosis to be commoner in previously well children (Fisher's exact test, P = 0.07).

Screening for thrombophilia

A risk factor for thrombophilia was found in 18 of the 29 (62%) screened (Table 3). Although only 13 patients were tested, more than half had high factor VIII. Of 14 patients tested, four (29%) were homozygous for the thermolabile

variant of the methylene tetrahydrofolate reductase (tMTHFR) gene; comparison with 78 unselected controls admitted to Great Ormond Street hospital (Prengler *et al.*, 2001), nine (12%) of whom were homozygous for the tMTHFR mutation, shows a trend for an excess of homozygotes for the tMTHFR mutation in children with CSVT (Fisher's exact test, $P = 0.1$). Low protein C, factor V Leiden and prothrombin 20210 mutations were not found in this series.

Table 3 *Laboratory features of 42 children with CSVT*

Laboratory features (normal values)	Tested	Abnormal	%
Anaemia	42	23	55
Microcytosis	42	22	52
High cholesterol	6	1	
High triglycerides	6	1	
High lipoprotein (a)	2	0	
High fibrinogen (1.7–4 g/l)	13	3	23
Low protein S (72–130 IU/l)	22	4	18
Low free protein S (70–140 IU/dl)	5	1	20
Low protein C (37–130 IU/dl)	22	0	0
Low antithrombin (79–131 IU/dl)	20	3	15
Low plasminogen (39–83 IU/dl)	9	0	0
Low heparin cofactor II (50–150 IU/dl)	5	0	0
High factor VIII (50–150 IU/dl)	13	7	54
Low factor XII (50–150 IU/dl)	9	2	22
Factor V Leiden mutation	20	0	0
Prothrombin 20210 mutation	15	0	0
tMTHFR homozygosity	14	4	29
High anticardiolipin IgG (>12 IU/dl)	15	3	20
Lupus anticoagulant	9	1	11
One prothrombotic abnormality	29	13	45
Two prothrombotic abnormalities	29	2	7
Three prothrombotic abnormalities	29	1	3
Four prothrombotic abnormalities	29	2	7

Of two patients with nephrotic syndrome who were tested, one had low protein S and another had slightly low antithrombin and high fibrinogen acutely; the antithrombin was normal on repeat testing but the fibrinogen remained high. Raised IgM anticardiolipin antibodies were found in one of the patients with SLE and IgG anticardiolipin was raised in two other patients, both with familial history of SLE; the other 11 children tested were normal.

Radiological findings

Parenchymal imaging (Table 4)

All 42 children had CT and the diagnosis was made using parenchymal images with contrast enhancement in nine. MRI was performed in addition in 33, of whom 31 had MR venography. Of the 25 patients with parenchymal abnormalities, 24 had cortical involvement. Four children had bilateral haemorrhagic infarcts, seven had bilateral bland infarcts (Fig. 2) and 13 had unilateral infarcts (Fig. 3), eight of which were haemorrhagic. The anatomical regions involved were cortex of the frontal ($n = 8$), temporal ($n = 4$), parietal ($n = 15$) and occipital ($n = 5$) regions, thalamus ($n = 3$), putamen ($n = 2$), caudate ($n = 1$), internal capsule ($n = 1$), hippocampus ($n = 2$), deep white matter ($n = 2$) and cerebellum ($n = 1$). Clinical signs were related to the location of parenchymal lesions as classically expected in strokes. Seventeen patients had no visible infarction but one of these had a temporal abscess in association with mastoiditis and another had an arteriovenous fistula in the middle temporal fossa.

Patients with parenchymal lesions (haemorrhage or infarction) were more likely to present with hemiplegia (Fisher's exact test, $P = 0.01$) but not with seizures ($P = 0.2$) or Glasgow

Table 4 *Comparison of radiological and haematological features of venous and arterial stroke*

	Infarct and haemorrhage				Infarct only			
	Venous ($n = 25$)	Arterial ($n = 112$)	Odds ratio (95% confidence limits)	P	Venous ($n = 13$)	Arterial ($n = 88$)	Odds ratio (95% confidence limits)	P
Site								
Frontal	32%	48%	0.51 (0.2, 1.27)	0.15	38%	52%	0.57 (0.17, 1.88)	0.36
Temporal	16%	16%	1.0 (0.31, 3.24)	0.99	23%	18%	1.35 (0.33, 5.47)	0.67
Parietal	60%	21%	5.8 (2.31, 15.6)	0.0001	46%	24%	2.74 (0.83, 9.04)	0.10
Occipital	20%	10%	2.3 (0.72, 7.33)	0.16	31%	11%	3.47 (0.90, 13.4)	0.07
Thalamus	12%	6%	2.05 (0.49, 8.53)	0.33	15%	3%	5.15 (0.77, 34.3)	0.09
Putamen	8%	26%	0.25 (0.06, 1.12)	0.07	15%	33%	0.37 (0.08, 1.78)	0.22
Caudate	4%	38%	0.07 (0.009, 0.51)	0.009	8%	49%	0.08 (0.01, 0.70)	0.02
Insula	0%	13%	–	0.76	0%	16%	–	0.78
Internal capsule	4%	14%	0.25 (0.03, 1.98)	0.19	8%	18%	0.38 (0.05, 3.10)	0.36
Corpus striatum	0%	4%	–	0.75	0%	3%	–	0.86
Deep white matter	8%	19%	0.38 (0.08, 1.72)	0.21	0%	24%	–	0.81
Cerebellum	4%	6%	0.63 (0.07, 5.32)	0.67	0%	6%	–	0.81
Pons	0%	4%	–	0.75	0%	2%	–	0.84
Z score for haemoglobin	−3.07 (−6.8, 0.27)	−1.73 (−11.4, 3.87)	0.87 (0.74, 1.03)	0.1	−3.6 (−6.8, 0.13)	−1.87 (−11.4, 3.87)	0.86 (0.71, 1.05)	0.14
Microcytosis	56%	21%	4.93 (1.98, 12.3)	0.001	69%	18%	10.1 (2.77, 37)	0.0001
Platelet count	423 (36, 777)	290 (38, 637)	1.005 (1.001, 1.008)	0.014	475 (272, 717)	290 (38, 637)	1.007 (1.002, 1.012)	0.009

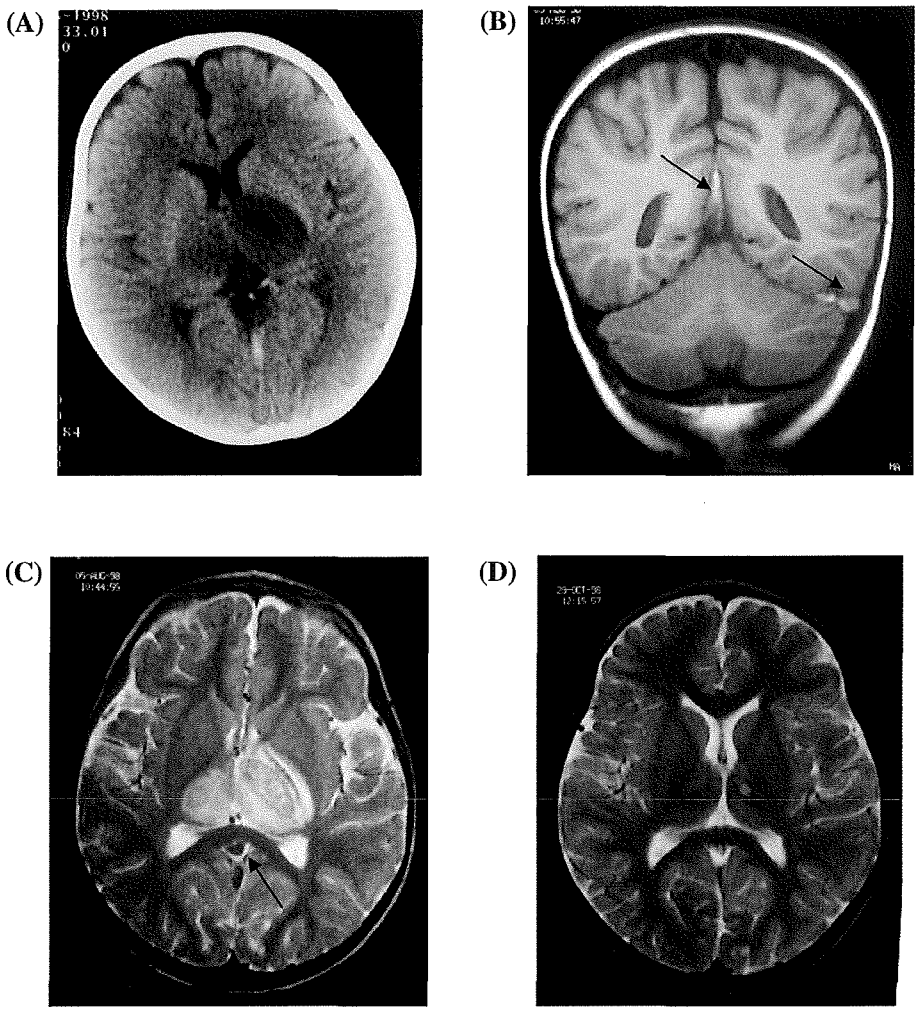

Fig. 2 Neuroimaging from a 20-month-old girl with iron deficiency anaemia. **(A)** Bilateral thalamic hypodensity and thrombus in the straight sinus and deep cerebral veins are demonstrated on the CT scan. **(B)** Thrombus in the straight and left transverse sinuses is seen as high signal on the coronal T1-weighted MRI (arrows). **(C)** The axial T2-weighted MRI shows bilateral thalamic high signal involving the posterior limb of the internal capsule and the posterior putamen. The vein of Galen and straight sinus are dark due to the iron products of haemoglobin (arrow). **(D)** Follow-up T2-weighted MRI 3 months later demonstrates almost complete reversal of the thalamic infarction, with only a small residual scar, and restored flow in the vein of Galen and straight sinus.

coma score <12 ($P = 0.5$). Patients with normal parenchymal imaging were more likely to present with cranial nerve signs ($P = 0.01$) but not with headache ($P = 0.3$).

Venous sinuses involved

The superficial (sagittal, transverse or sigmoid sinuses) and deep venous systems (deep cerebral veins and straight sinus) were involved in 32 and six patients respectively, with both involved in four. Sinuses involved were sagittal ($n = 16$), sigmoid ($n = 11$), transverse or lateral ($n = 20$), cavernous ($n = 4$) and straight ($n = 4$). The jugular vein was involved in three patients. In two patients there was cortical venous sinus thrombosis alone and in another thrombosis of the cortical veins was seen extending into the occluded superior sagittal sinus. Two and three vessels were involved in 14 and three patients respectively.

Comparison with arterial stroke (Table 4)

The data on the 25 children with infarction in the context of CSVT were compared with those from a consecutive cohort of 112 children with clinical stroke and cerebral arterial disease prospectively recruited at Great Ormond Street hospital between 1993 and 2000 and also imaged acutely. There were 82 children with ischaemic stroke and arteriopathy on conventional or MR angiography (11 dissection, 17 occlusion, 42 stenosis, four vasculitis, eight moyamoya) and 24 with haemorrhagic stroke and definite arterial pathology (13 arteriovenous malformation, five cavernomas and six aneurysms).

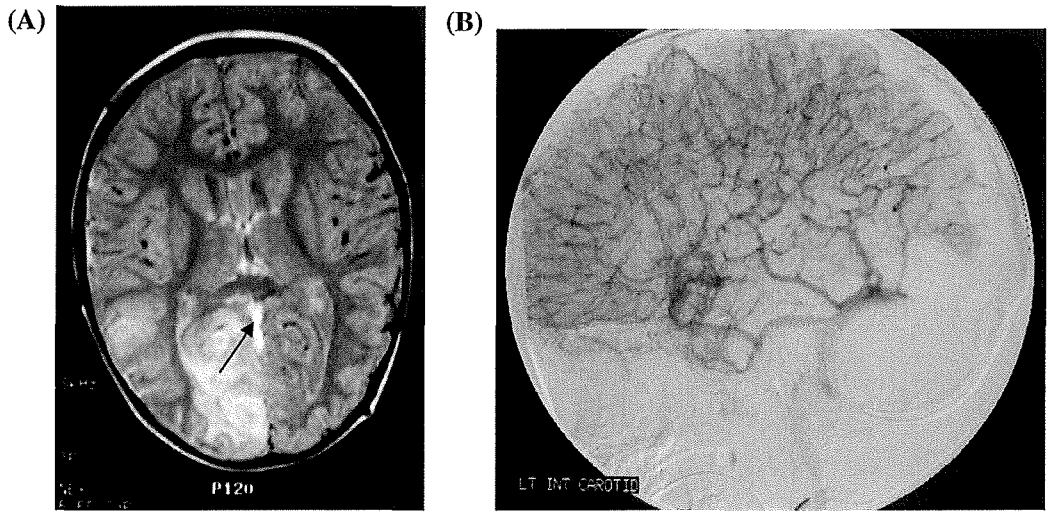

Fig. 3 Neuroimaging from a 22-month-old boy with iron deficiency anaemia. **(A)** MRI showing that the abnormal high signal involves predominantly the right occipital lobe. The straight sinus is occluded; subacute thrombus is seen as high signal on proton density images (arrow). **(B)** Five months later the venous phase of the cerebral angiogram demonstrates absence of flow in the occluded superior sagittal and straight sinus. Multiple collateral vessels drain the hemisphere towards the cavernous sinus.

In univariate analysis, CSVT was significantly commoner in those with parenchymal abnormality in a parietal distribution, and less common in those with involvement of the caudate nucleus. There was a trend for anaemia to be commoner in CSVT, microcytosis was commoner and platelet count was higher (Table 4). In multiple logistic regression, microcytosis [adjusted odds ratio (OR) 7.15, 95% confidence interval (CI) 2.31, 22.1, $P = 0.01$], parietal involvement (adjusted OR 6.8, 95% CV 2.25, 20.6, $P = 0.001$) and lack of caudate involvement (adjusted OR 0.05, 95% CV 0.006, 0.42, $P = 0.006$) independently predicted CSVT rather than arterial disease. Results were similar when infarcts were considered alone; in addition there were trends for occipital and thalamic infarction to be commoner in CSVT.

Outcome

Five patients died, three acutely and two later; one during a recurrent episode of CSVT and one with severe neurological sequelae, respectively 3 and 6 months after the initial event. For the 37 survivors, follow-up ranged from 6 months to 10 years (median 1 year). Eleven children had no neurological or cognitive difficulties at follow-up. Twelve had symptoms and signs compatible with chronic pseudotumour cerebri and 14 had cognitive difficulties (of whom two had a permanent hemiparesis, three had reduced visual acuity and two developed epilepsy). None of the patients with cognitive difficulties was diagnosed with pseudotumour cerebri.

Acute management and relationship with outcome

All of the children with sepsis were treated with antibiotics and three also had a mastoidectomy. Iron supplementation was given to those in whom severe iron deficiency was diagnosed. Three children required ventilatory support and four (including the two with sickle cell disease and one with β-thalassaemia) were transfused. The patient with SLE was immunosuppressed.

Eighteen of the patients in whom the diagnosis was made acutely were anticoagulated immediately with heparin (unfractionated in 15 and low molecular weight in three) and then warfarin or low molecular weight heparin for up to 6 months. Two children were treated with aspirin and one with haemoglobin SC disease was given tissue plasminogen activator but not until after he became deeply unconscious with an MRI showing widespread oedema (Fig. 1C). He died soon after without imaging evidence of haemorrhage.

Six of the anticoagulated patients had haemorrhage at presentation; none had an extension of the haemorrhage and all survived the index episode, although one with congenital nephrotic syndrome died after recurrent haemorrhagic CSVT treated with heparin. Of the six children who were not anticoagulated because of haemorrhage on neuroimaging, one died 16 h after presentation, three had cognitive difficulties (one with seizures, Fig. 3B) and only one had no sequelae.

Anticoagulated patients were more likely to have good cognitive outcome, with a statistical trend of borderline significance, and a reduction in mortality which was not statistically significant (Table 5). In some cases, a therapeutic dose of heparin appeared to have an immediately beneficial effect. One boy with haemorrhage, in whom activated partial thromboplastin time (APTT) was less than 2.5 for the first 24 h, remained unconscious (minimum Glasgow coma score 10) and continued to seize. Repeat CT showed no extension of the haemorrhage and he improved within an hour when the heparin dose was increased to achieve an activated partial

Table 5 *Associations with outcome*

	Odds ratio for death (5/42)	*P*	Odds ratio for good cognitive outcome (19/42)	*P*
Age	0.95 (0.74, 1.22)	0.7	1.26 (1.04, 1.52)	0.02
Duration of prodrome (days)	0.99 (0.94, 1.06)	0.8	1.01 (0.96, 1.04)	0.7
Pre-existing illness	0.98 (0.15, 6.58)	0.9	0.59 (0.17, 2.06)	0.4
Infective trigger	0.48 (0.07, 3.36)	0.5	1.64 (0.40, 6.76)	0.5
Seizures at presentation	2.42 (0.34, 17.0)	0.4	0.59 (0.17, 2.06)	0.4
Glasgow coma score <12 on admission	14.5 (1.42, 149)	0.02	0.29 (0.07, 1.19)	0.08
Parenchymal abnormality	1.14 (0.17, 7.67)	0.9	0.17 (0.04, 0.69)	0.01
Haemorrhage	1.80 (0.26, 12.4)	0.6	0.29 (0.07, 1.19)	0.09
Multiple sinus involvement	0.33 (0.03, 3.23)	0.3	3.06 (0.83, 11.3)	0.09
Involvement of lateral and/or straight sinuses	0.57 (0.09, 3.80)	0.6	0.20 (0.05, 0.75)	0.01
Involvement of deep sinuses	2.42 (0.34, 17.0)	0.4	0.46 (0.11, 1.94)	0.3
Involvement of straight sinus	0.35 (0.03, 4.25)	0.4	0.24 (0.02, 2.55)	0.2
Anticoagulation	0.29 (0.03, 2.89)	0.3	3.64 (0.98, 13.5)	0.05
Persistent occlusion (n = 20)			0.15 (0.01, 2.18)	0.2
Anaemia acutely	3.79 (0.39, 37.2)	0.2	1.73 (0.51, 5.91)	0.4
Microcytosis acutely	2.59 (0.26, 26.3)	0.4	1.16 (0.27, 4.93)	0.8

thromboplastin time (APTT) of 2.5, although he had pseudotumour cerebri at follow-up. Another child with confusion and personality change in the context of SLE and sagittal sinus thrombosis improved within 12 h of starting unfractionated heparin and remained well 1 year later on steroids and low molecular weight heparin. Of the 12 patients with chronic pseudotumour cerebri, six had been anticoagulated acutely (Fisher's exact test for comparison with those without pseudotumour cerebri, $P = 0.4$).

Treatment of chronic intracranial hypertension

Pseudotumour cerebri was treated with steroids and/or acetazolamide. Shunts for hydrocephalus were performed in infancy in two children with confirmed CSVT (one before and one after the diagnosis) and the child with haemoglobin SC disease, who may have had unrecognized CSVT in infancy. One child required a lumboperitoneal shunt.

Follow-up MRI

Of the 21 patients for whom follow-up MRI was available, complete reversal of the parenchymal change and CSVT were seen in three patients with haemorrhage. One patient had only a small residual lesion associated with complete clinical recovery (Fig. 2), although the acute imaging showed bilateral ischaemic changes in the thalami, subthalamic nuclei, left internal capsule and left temporal lobe. Mature infarcts developed in the remaining nine children who had parenchymal defects (two haemorrhagic) at the time of diagnosis, while the other eight MRIs remained normal.

Follow-up MRV showed complete ($n = 8$) or partial ($n = 8$) restoration of flow except in three patients who had persistent occlusion, two with a subacute presentation (Fig. 3). One of these cases had both sagittal and straight sinus thrombosis, one had sagittal and one had lateral sinus thrombosis. Multiple collateral veins were seen in all three patients, in one at the time of the diagnostic angiogram (Fig. 3) and in two on follow-up imaging. The prodrome was significantly longer in those with persistent occlusion than in those with complete or partial restoration of flow (Kruskal–Wallis test, $P = 0.04$). Haemoglobin was significantly higher at original presentation in those with recanalization at follow-up than in those with improvement or persistent occlusion (Kruskal–Wallis test, $P = 0.02$). There was no evidence that multiple vessel involvement (χ^2, $P = 0.2$), involvement of the deep sinuses (χ^2, $P = 0.6$) or anticoagulation (χ^2, $P = 0.4$) had an effect on recanalization. However, the numbers were small and some of the percentage differences quite large. For example, anticoagulation was given in 78% of those with complete restoration compared with only 33% of those with persistent thrombosis. There was no association between persistent thrombosis and death, cognitive sequelae or pseudotumour cerebri, but two of the three patients with epilepsy as an outcome had persistent occlusion.

Recurrence and systemic thrombosis

One child with congenital Finnish-type nephrotic syndrome had radiologically confirmed recurrent sagittal sinus thrombosis and died of raised intracranial pressure secondary to haemorrhage and oedema. Another child with thrombosis of the sagittal sinus and right internal jugular vein in the context of acute lymphoblastic leukaemia (not anticoagulated) had further transient episodes, one of dysarthria and ataxia and one of hemiplegia, hemisensory loss and hemianopia soon after her leukaemia relapsed. MRI and MRV were reported as normal and she has remained symptom-free 8 years after a

bone marrow transplant. Three children developed systemic venous thrombosis.

Predictors of outcome

The only statistically significant association with death was an admission Glasgow coma score <12 (Table 5). Mortality, cognitive outcome and pseudotumour cerebri were not related to anaemia or microcytosis (Fisher's exact test, Table 5). Good cognitive outcome was commoner in older children, those without parenchymal abnormality and those with lateral and/or sigmoid sinus involvement (Table 5), although chronic pseudotumour cerebri was commoner in the latter group (χ^2, $P = 0.01$). In multiple logistic regression, older age (OR 1.54, 95% CI 1.12, 2.13, $P = 0.008$), involvement of the lateral and/or sigmoid sinus (OR 16.2, 95% CI 1.62, 161, $P = 0.02$), lack of parenchymal abnormality (OR 0.17, 95% CI 0.02, 1.56, $P = 0.1$) and anticoagulation (OR 24.2, 95% CI 1.96, 299) were all independent predictors of good cognitive outcome.

Discussion

It is apparent from our study and review of the literature that the clinical manifestations of CSVT are non-specific and may be subtle (Bousser and Ross-Russell, 1997). Most of the clinical scenarios occur at all ages and the clinician should consider this diagnosis in a wide range of acute neurological presentations in childhood, including seizures, coma, stroke, headache and raised intracranial pressure. Common illnesses, including ear infections, meningitis (Kastenbauer and Pfister, 2003), anaemia (Belman *et al.*, 1990), diabetes (Keane *et al.*, 2002) and head injury (Stiefel *et al.*, 2000), may be complicated by CSVT, but as there is difficulty in making the diagnosis, data for incidence remain a minimum estimate (de Veber *et al.*, 2001). Although presentation with pseudotumour cerebri has been well documented (Biousse *et al.*, 1999), there are few data on the prevalence of CSVT in otherwise unexplained hydrocephalus (Norrell *et al.*, 1969) or in convulsive and non-convulsive seizures and status epilepticus (Wang *et al.*, 1997). CSVT may also be an important determinant of outcome in non-traumatic coma (Krishnan *et al.*, 2004).

Anatomically, the spectrum of venous infarcts includes unilateral and bilateral infarcts and haemorrhages of the deep grey structures (secondary to thrombosis of the deep cerebral veins and straight sinus) or of the cortex and subjacent white matter (secondary to thrombosis of the sagittal, transverse or sigmoid sinuses). Diffusion-weighted imaging has demonstrated that venous infarcts have restricted diffusion (cytotoxic oedema) in the early stages (Forbes *et al.*, 2001), supporting the theory that retrograde venous pressure decreases cerebral blood flow causing tissue damage, akin to arterial infarction (Rother *et al.*, 1996). However, follow-up imaging of both the venous sinuses and any parenchymal damage is usually reported as normal. If emergency imaging of the venous sinuses is not undertaken, the diagnosis is very likely to be missed in children presenting with acute symptomatology and in otherwise unexplained hydrocephalus, as well as those with pseudotumour cerebri and cavernous sinus syndrome (Bousser and Ross-Russell, 1997).

In childhood, CSVT is relatively equally distributed according to the different age groups, except for a high incidence in neonates (de Veber *et al.*, 2001). We excluded those presenting to neonatal paediatricians, as the clinical dilemmas are different (Shevell *et al.*, 1989; Rivkin *et al.*, 1992), but suspect that our patient with haemoglobin SC disease had CSVT as the cause of his neonatal seizures, intraventricular haemorrhage and communicating hydrocephalus, especially as he presented at the age of 2 weeks rather than at birth (Ramenghi *et al.*, 2002; Wu *et al.*, 2003).

There are few data on the clinical presentation in older children and it is likely that the diagnosis is often delayed or missed altogether in this group as well. It has been suggested that toddlers frequently present with seizures and focal signs, mainly hemiparesis, whereas older children present with headache and changes in mental status and seizures may be less common (Carvalho *et al.*, 2000). In our series, there was no pattern relating symptomatology to age, perhaps reflecting the recent trend to emergency imaging of the venous sinuses in children with acute coma, seizures or stroke as well as those presenting with pseudotumour cerebri. The manifestations of deep cerebral venous thrombosis are typically characterized by altered consciousness, decerebrate posturing, changes in extrapyramidal tone and psychiatric symptoms such as confusion as a result of infarction in the thalami and basal ganglia and white matter structures (Kothare *et al.*, 1998; de Veber *et al.*, 2001). Thus, as we observed in our series, the clinical presentation of CSVT is highly variable, extending from discrete symptoms, such as isolated headache, to severe and often multifocal neurological deficits.

The evaluation of children with suspected CSVT has been made considerably easier by modern neuroimaging techniques. In the largest studies, around half of infants and children had multiple sinuses and/or veins involved and 40% had associated parenchymal infarcts (Barron *et al.*, 1992; Carvalho *et al.*, 2000; de Veber *et al.*, 2001). In our series, 41% had more than one sinus involved whereas 57% had parenchymal changes, probably reflecting our interest in childhood stroke and the associated support for vascular imaging. Superior sagittal and lateral sinus thrombosis is diagnosed more frequently in most series (Heller *et al.*, 2003; Johnson *et al.*, 2003). However, this may reflect the current difficulties in diagnosing thrombosis in the deep system (Di Roio *et al.*, 1999) or cortical veins (Garcia, 1990; Jacobs *et al.*, 1996), which may require conventional angiography, which is difficult to justify after late presentation in coma and/or status epilepticus. Unenhanced CT scans may detect deep venous thrombosis as linear densities in the expected locations of the deep and cortical veins. As the thrombus becomes less dense, contrast may demonstrate the 'empty delta' sign, a filling defect, in the posterior part

of the sagittal sinus (de Veber *et al.*, 2001). However CT scan with contrast misses the diagnosis of CSVT in up to 40% of patients (Barron *et al.*, 1992; de Veber *et al.*, 2001). Diffusion and perfusion MRI may play a role in detecting venous congestion in cerebral venous thrombosis and in the differentiation of cytotoxic and vasogenic oedema (Forbes *et al.*, 2001) but does not differentiate venous from arterial infarction. CT venography or MRI with venous MR (MRV) are now the methods of choice for investigation of CSVT (Medlock *et al.*, 1992). The diagnosis is established by demonstrating a lack of flow in the cerebral veins with or without typical images of brain infarcts. Parenchymal MR and MRV are important in the demonstration of both the infarct and the clot within the vessels. On MRI, the thrombus is readily recognizable in the subacute phase, when it is of high signal on a T1-weighted scan and MRV is often not required. In the acute phase, the thrombus is isosignal on T1-weighted imaging and of low signal on T2-weighted imaging. This can be mistaken for flowing blood but MRV will demonstrate an absence of flow in the thrombosed sinus. However, MRI and MRV are techniques prone to flow artefacts and in equivocal cases an endoluminal technique such as high-resolution CT venography or digital subtraction angiography may be required as a final arbiter.

CSVT occurs in various clinical settings, including infection, dehydration, renal failure, trauma, cancer and haematological disorder (Barron *et al.*, 1992; Carvalho *et al.*, 2000; de Veber *et al.*, 2001; Heller *et al.*, 2003). Many children have multiple risk factors (Heller *et al.*, 2003). In our series, clinical risk factors (pre-existing diagnoses and/or infection and/or dehydration) were found in all patients. Although the frequency of septic thrombosis is decreasing, due to antibiotic development, recent studies have shown that it was still responsible for a substantial proportion of thrombosis in older children (Barron *et al.*, 1992; Carvalho *et al.*, 2000) and in our series there was an infectious trigger in nearly three quarters, in contrast to the much lower proportion in adults (de Bruijn *et al.*, 2001). Infection appears to be a particularly common trigger in previously well children, as is microcytosis suggestive of iron deficiency. Before the widespread use of early corrective surgery, CSVT used to be a common complication of congenital cyanotic heart disease, in which it occurred predominantly in patients over 2–3 years of age, usually with iron deficiency (Cottrill and Kaplan, 1973; Phornphutkul *et al.*, 1973). Anaemia as an association with CSVT has received little attention in the adult literature (Nagpal, 1983), but iron deficiency anaemia has been described in other children with CSVT (Belman *et al.*, 1990; Hartfield *et al.*, 1997; Meena *et al.*, 2000; Keane *et al.*, 2002), sometimes in association with thrombocytosis, and was found in half of this series. In addition, four of our patients had microcytosis without frank anaemia. Anaemia is commonly obscured by relative haemoconcentration in the acute phase and ferritin may be an acute-phase protein, so the diagnosis of iron deficiency should be comprehensively excluded or treated.

In five patients, CSVT occurred in the context of chronic haemolytic anaemia, as has been occasionally described previously (Shiozawa *et al.*, 1985). In a recent series of patients with focal neurological deficits in the context of β-thalassaemia major, it was suggested that chronic anaemia might predispose to CSVT (Incorpora *et al.*, 1999). Although the diagnosis was not made definitively in that series, the distribution of lesions in those who were imaged would certainly be compatible with CSVT and our series contains one patient with β-thalassaemia and lateral sinus thrombosis. Proven venous sinus thrombosis appears to be relatively uncommon in sickle cell anaemia (Garcia 1990; Oğuz *et al.*, 1994; Di Roio *et al.*, 1999; van Mierlo *et al.*, 2003), although this may be because neuroimaging is delayed because of the priority for emergency exchange transfusion. The radiological diagnosis was not obvious in either of our cases and it is possible that CSVT is missed in sickle cell disease and other chronic anaemias. High erythropoietin levels and the accompanying increase in adhesive reticulocytes might predispose to CSVT in recovering iron deficiency, haemolytic and aplastic anaemias and paroxysmal nocturnal haemoglobinuria, and it is of interest that CSVT has been reported in a patient treated with epoetin alfa (Finelli and Carley, 2000).

Prothrombotic disorders were found in between one-third and half the cases in recent series of paediatric CSVT (Bonduel *et al.*, 1999; de Veber *et al.*, 2001) and in 62% of our screened patients. Some of these are acquired prothrombotic states, such as acute protein C and S and antithrombin deficiency secondary to infection or protein loss, e.g. in nephrotic syndrome, or antiphospholipid antibodies, and are often normal on repeated investigation. In our series, high factor VIII levels, which may be determined by genetic and acquired factors (Cakmak *et al.*, 2003), were common but there were only three cases of acquired antithrombin and one of free protein S deficiency and three patients with anticardiolipin antibodies. Genetic polymorphisms appear to be important as risk factors in adults (Lüdemann *et al.*, 1998; Hiller *et al.*, 1998; Reuner *et al.*, 1998; Cakmak *et al.*, 2003) but although there is evidence for an excess of prothrombotic risk factors in paediatric CSVT (Heller *et al.*, 2003), the relative importance of the factor V Leiden or prothrombin 20210 mutations is less clear (Bonduel *et al.*, 2003; Johnson *et al.*, 2003) and none were diagnosed in out series. However, there was a trend for an excess of homozygotes for the thermolabile variant of the methylene tetrahydrofolate reductase gene compared to our control population, as in an adult series of CSVT (Hiller *et al.*, 1998). Hyperhomocysteinaemia and its genetic determinants may worth excluding or treating with folic acid, B_6 and B_{12} vitamin supplementation, as this has few risks, but further studies will be important. There are no data on whether longer-term treatment for any of the other prothrombotic disorders reduces the significant recurrence risk (de Veber *et al.*, 2001) and international collaboration will be required to address that issue (Heller *et al.*, 2003).

Treatment of CSVT has historically involved general supportive or symptomatic measures, such as hydration,

antibiotics for septic cases, control of seizure activity with anticonvulsants, and measures aimed at decreasing intracranial pressure. Antithrombotic therapy of CSVT in childhood has been influenced by clinical trials in adults (Einhaupl *et al.*, 1991; de Bruijn and Stam, 1999). De Veber and colleagues initiated a prospective cohort study of anticoagulant therapy in 30 children with CSVT from 1992 to 1996 and reported a mortality rate of 3/8 in untreated compared with 0/22 in treated children (de Veber *et al.*, 1998*b*). Anticoagulant treatment was well tolerated, with no extensions of the CSVT. Johnson *et al.* (2003) and Barnes *et al.* (2004) have also reported encouraging data on the safety of anticoagulation in children with CSVT. Our data confirm these observations, with very similar results on safety and likely better cognitive outcome. The development of pseudotumour cerebri may not be influenced by anticoagulation (Higgins *et al.*, 2003) but more data are needed for children. Although we observed one fatal haemorrhage in a child with intractable nephrotic syndrome and recurrent CSVT, the other children who died were not anticoagulated and there was no evidence of a detrimental effect. The options for treatment of infants and children include standard or low molecular weight heparin for 7–10 days followed by oral anticoagulants for 3–6 months. Thrombolytic therapy and mechanical thrombectomy are sometimes used for extensive thrombosis of superficial and deep venous structures (Griesemer *et al.*, 1994; Soleau *et al.*, 2003), but our experience and data from other studies suggest that in the current state of knowledge early anticoagulation would be a better strategy except perhaps in unconscious patients, in whom the mortality is higher, possibly justifying trials of chemical and mechanical thrombolysis (Soleau *et al.*, 2003).

CSVT has a variable and sometimes a poor prognosis in adults (Preter *et al.*, 1996; de Bruijn *et al.*, 2000, 2001; Buccino *et al.*, 2003) and children (de Veber *et al.*, 2000, 2001). In our series, the positive associations with death in our series were similar to those seen in adults who died or were dependent (de Bruijn *et al.*, 2001), although numbers were very small and only coma was statistically related. It is possible that pseudotumour cerebri was underdiagnosed as it is difficult to diagnose in young children, particularly those with learning difficulties; fundoscopy and visual acuity should be checked routinely at follow-up whether or not the child is irritable or complains of headache. Older age, involvement of the lateral and/or sigmoid sinuses and lack of parenchymal abnormality were associated with good cognitive outcome. Further studies documenting long-term neuropsychological evolution (de Schryver *et al.*, 2004) are justified.

The proportion of patients with complete and partial recanalization in our series is similar to that reported by the German collaborative group (Heller *et al.*, 2003). Our data suggest that some children with chronic conditions, e.g. anaemia or congenital nephrotic syndrome, are at risk of CSVT recurrence over very long periods of time. There have been few studies of the natural history of the thrombosed veins in relation to treatment or clinical outcome, but our data suggest that the venous system may be altered in a way which may predispose to further neurological events in some children, perhaps specifically those with chronic anaemia. It is of interest that iron deficiency may be associated with pseudotumour cerebri in adults (Biousse *et al.*, 2003); although there is no evidence for an association in our series, microcytosis was very common and further studies, including the effect of treatment, are required. In adults, there is no evidence that recanalization improves overall outcome (Baumgartner *et al.*, 2003; Stolz *et al.*, 2004); in this small paediatric series there was no evidence that those with persistent occlusion had worse outcome. However, the effect of permanent occlusion of portions of the venous drainage of the brain, with or without collateral formation, may be different in the developing brain and studies with detailed long-term follow-up are required. In addition, the aetiology of the discontinuity on venography of the lateral and sigmoid sinuses seen in association with intracranial hypertension (Farb *et al.*, 2003; Higgins *et al.*, 2004) remains to be established and could have its origin in childhood, perhaps in association with relative nutritional deficiency and local infection. As many patients receive antibiotics and perhaps a better diet in the context of the acute illness accompanying CSVT whether or not the vascular diagnosis is made, it may be difficult to prove a link but treatable problems such as iron deficiency, hyperhomocysteinaemia and chronic infection should be looked for in patients with chronic symptoms. The evolution may depend on the extent and location of parenchymal damage, haemoglobin, age and perhaps the rapidity of diagnosis and treatment in the acute phase. Multicentre collaborative studies will be needed to understand the risk factors for death, cognitive sequelae, pseudotumour cerebri and recurrent CSVT and the effects of treatment before acute and long-term management is evidence-based.

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References

Balcer LJ, Liu GT, Forman S, Pun K, Volpe NJ, Galetta SL, Maguire MG. Idiopathic intracranial hypertension: relation of age and obesity in children. Neurology 1999; 52: 870–2.

Barnes C, Newall F, Furmedge J, Mackay M, Monagle P. Cerebral sinus venous thrombosis in children. J Paediatr Child Health 2004; 40: 53–5.

Barron TF, Gusnard DA, Zimmerman RA, Clancy RR. Cerebral venous thrombosis in neonates and children. Pediatr Neurol 1992; 8: 112–6.

Baumgartner RW, Studer A, Arnold M, Georgiadis D. Recanalisation of cerebral venous thrombosis. J Neurol Neurosurg Psychiatry 2003; 74: 459–61.

Belman AL, Roque CT, Ancona R, Anand AK, Davis RP. Cerebral venous thrombosis in a child with iron deficiency anemia and thrombocytosis. Stroke 1990; 21: 488–93.

Biousse V, Ameri A, Bousser MG. Isolated intracranial hypertension as the only sign of cerebral venous thrombosis. Neurology 1999; 53: 1537–42.

Biousse V, Rucker JC, Vignal C, Crassard I, Katz BJ, Newman NJ. Anemia and papilledema. Am J Ophthalmol 2003; 135: 437–46.

Boncoraglio G, Carriero MR, Chiapparini L, Ciceri E, Ciusani E, Erbetta A, Parati EA. Hyperhomocysteinemia and other thrombophilic risk factors in 26 patients with cerebral venous thrombosis. Eur J Neurol 2004; 11: 405–9.

Bonduel M, Sciuccati G, Hepner M, Torres AF, Pieroni G, Frontroth JP. Prethrombotic disorders in children with arterial ischemic stroke and sinovenous thrombosis. Arch Neurol 1999; 56: 967–71.

Bonduel M, Sciuccati G, Hepner M, Pieroni G, Torres AF, Mardaraz C, Frontroth JP. Factor V Leiden and prothrombin gene G20210A mutation in children with cerebral thromboembolism. Am J Hematol 2003; 73: 81–6.

Bousser M-G, Ross Russell R. Cerebral venous thrombosis. W.B. Saunders; Philadelphia 1997.

Buccino G, Scoditti U, Patteri I, Bertolino C, Mancia D. Neurological and cognitive long-term outcome in patients with cerebral venous sinus thrombosis. Acta Neurol Scand 2003; 107: 330–5.

Buoni S, Molinelli M, Mariottini A, Rango C, Medaglini S, Pieri S, Strambi M, Fois A. Homocystinuria with transverse sinus thrombosis. J Child Neurol 2001; 16: 688–90.

Cakmak S, Derex L, Berruyer M, Nighoghossian N, Philippeau F, Adeleine P, et al. Cerebral venous thrombosis: clinical outcome and systematic screening of prothrombotic factors. Neurology 2003; 60: 1175–8.

Carvalho KS, Bodensteiner JB, Connolly PJ, Garg BP. Cerebral venous thrombosis in children. J Child Neurol 2000; 16: 574–80.

Cottrill CM, Kaplan S. Cerebral vascular accidents in cyanotic congenital heart disease. Am J Dis Child 1973; 125: 484–7.

de Bruijn SFTM, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low molecular weight heparin for cerebral sinus thrombosis. Stroke 1999; 30: 484–8.

de Bruijn SF, Budde M, Teunisse S, de Haan RJ, Stam J. Long-term outcome of cognition and functional health after cerebral venous sinus thrombosis. Neurology 2000; 54: 1687–9.

de Bruijn SF, de Haan RJ, Stam J for the Cerebral Venous Sinus Thrombosis Study. Clinical features and prognostic factors of cerebral venous sinus thrombosis in a prospective series of 59 patients. J Neurol Neurosurg Psychiatr 2001; 70: 105–8.

De Schryver EL, Blom I, Braun KP, Kappelle LJ, Rinkel GJ, Peters AC, et al. Long-term prognosis of cerebral venous sinus thrombosis in childhood. Dev Med Child Neurol 2004; 46: 514–9.

de Veber G, Monagle, Chan A, MacGregor D, Curtis R, Lee S, Vegh P, Adams M, Marzinotto V, Leaker M, Massicotte MP, Lillicrap D, Andrew M. Prothrombotic disorders in infants and children with cerebral thromboembolism. Arch Neurol 1998a; 55: 1539–43.

de Veber G, Chan A, Monagle P, Marzinotto V, Armstrong D, Massicotte P, Leaker M, Andrew M. Anticoagulation therapy in pediatric patients with sinovenous thrombosis. Arch Neurol 1998b; 55: 1533–7.

de Veber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol 2000; 15: 316–24.

de Veber G, Andrew M and the Canadian Pediatric Ischemic Stroke Study Group. The epidemiology and outcome of sinovenous thrombosis in pediatric patients. N Engl J Med 2001; 345: 417–23.

Di Roio C, Jourdan C, Yilmaz H, Artru F. Cerebral deep vein thrombosis: three cases. Rev Neurol 1999; 155: 583–7.

Einhaupl KM, Villringer A, Meister W, Mehraein S, Garner C, Pellkofer M, Haberl RL, Pfister HW, Schmiedek P. Heparin treatment in sinus venous thrombosis. Lancet 1991; 338: 597–600.

Farb RI, Vanek I, Scott JN, Mikulis DJ, Willinsky RA, Tomlinson G, terBrugge KG. Idiopathic intracranial hypertension: the prevalence and morphology of sinovenous stenosis. Neurology 2003; 60: 1418–24.

Finelli PF, Carley MD. Cerebral venous thrombosis associated with epoetin alfa therapy. Arch Neurol 2000; 57: 260–2.

Forbes KPN, Pipe JG, Heiserman JE. Evidence for cytotoxic edema in the pathogenesis of cerebral venous infarction. AJNR 2001; 22: 450–5.

Ganesan V, Prengler M, McShane MA, Wade A, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. Ann Neurol 2003; 53: 167–73.

Garcia JH. Thromosis of cranial veins and sinuses: brain parenchymal effects. In: Einhäupl K, Kempski O, Baethmann A, editors. Cerebral sinus thrombosis: experimental and clinical aspects. Plenum Press; New York 1990.

Griesemer DA, Theodorou AA, Berg RR, Spera TD. Local fibrinolysis in cerebral venous thrombosis. Pediatr Neurol 1994; 10: 78–80.

Hartfield DS, Lowry NJ, Keene DL, Yager JY. Iron deficiency: a cause of stroke in infants and children. Pediatr Neurol 1997; 16: 50–3.

Heller C, Heinecke A, Junker R, Knofler R, Kosch A, Kurnik K, et al., Childhood Stroke Study Group. Cerebral venous thrombosis in children: a multifactorial origin. Circulation 2003; 108: 1362–7.

Higgins JN, Cousins C, Owler BK, Sarkies N, Pickard JD. Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting. J Neurol Neurosurg Psychiatry 2003; 74: 1662–6.

Higgins JN, Gillard JH, Owler BK, Harkness K, Pickard JD. MR venography in idiopathic intracranial hypertension: unappreciated and misunderstood. J Neurol Neurosurg Psychiatry 2004; 75: 621–5.

Hiller CEM, Collins PW, Bowen DJ, Bowley S, Wiles CM. Inherited prothrombotic risk factors and cerebral venous thrombosis. Q J Med 1998; 91: 677–80.

Incorpora G, Di Gregorio F, Romeo MA, Pavone R, Trifiletti RR, Parano E. Focal neurological deficits in children with β-thalassemia major. Neuropediatrics 1999; 30: 45–8.

Jacobs K, Moulin T, Bogousslavsky J, Woimant F, Dehaene I, Tatu L, et al. The stroke syndrome of cortical vein thrombosis. Neurology 1996; 47: 376–82.

Johnson MC, Parkerson N, Ward S, de Alarcon PA. Pediatric sinovenous thrombosis. J Pediatr Hematol Oncol 2003; 25: 312–5.

Kastenbauer S, Pfister HW. Pneumococcal meningitis in adults: spectrum of complications and prognostic factors in a series of 87 cases. Brain 2003; 126: 1015–25.

Keane S, Gallagher A, Ackroyd S, McShane MA, Edge JA. Cerebral venous thrombosis during diabetic ketoacidosis. Arch Dis Child 2002; 86: 204–5.

Kothare SV, Ebb DH, Rosenberg PB, Buonamo F, Schaefer PW, Krishnamoorthy KS. Acute confusion and mutism as a presentation of thalamic stroke secondary to deep cerebral venous thrombosis. J Child Neurol 1998; 13: 300–3.

Krishnan A, Karnad DR, Limaye U, Siddharth W. Cerebral venous and dural sinus thrombosis in severe falciparum malaria. J Infect 2004; 48: 86–90.

Kurecki AE, Gokce H, Akar N. Factor VIII levels in children with thrombosis. Pediatr Int 2003; 45: 159–62.

Lüdemann P, Nabavi DG, Junker R, Wolff E, Papke K, Buchner H, et al. Factor V Leiden mutation is a risk factor for cerebral venous thrombosis: a case-control study of 55 patients. Stroke 1998; 29: 2507–10.

Martinelli I, Battaglioli T, Pedotti P, Cattaneo M, Mannucci PM. Hyperhomocysteinemia in cerebral vein thrombosis. Blood 2003; 102: 1363–6.

Medlock M, Olivero W, Hanigan W, Wright RM, Winek SJ. Children with cerebral venous thrombosis diagnosed with magnetic resonance imaging and magnetic resonance angiography. Neurosurgery 1992; 31: 870–6.

Meena AK, Naidu KS, Murthy JM. Cortical sinovenous thrombosis in a child with nephrotic syndrome and iron deficiency anaemia. Neurol India 2000; 48: 292–4.

Nagpal RD. Dural sinus and cerebral venous thrombosis. Neurosurg Rev 1983; 6: 155–60.

Norrell H, Wilson C, Howieson J, Megison L, Bertan V. Venous factors in infantile hydrocephalus. J Neurosurg 1969; 31: 561–9.

Oğuz M, Aksungur EH, Soyupak SK, Yildirim AU. Vein of Galen and sinus thrombosis with bilateral thalamic infarcts in sickle cell anaemia: CT follow-up and angiographic demonstration. Neuroradiology 1994; 36: 155–6.

Phornphutkul C, Rosenthal A, Nadas A, Berenberg W. Cerebrovascular accidents in infants and children with cyanotic congenital heart disease. Am J Cardiol 1973; 32: 329–34.

Preter M, Tzourio C, Ameri A, Bousser M-G. Long-term prognosis in cerebral venous thrombosis: follow-up of 77 patients. Stroke 1996; 27: 243–6.

Prengler M, Sturt N, Krywawych S, Surtees R, Kirkham F. The homozygous thermolabile variant of the methylenetetrahydrofolate reductase gene: a risk factor for recurrent stroke in childhood. Dev Med Child Neurol 2001; 43: 220–5.

Ramenghi LA, Gill BJ, Tanner SF, Martinez D, Arthur R, Levene MI. Cerebral venous thrombosis, intraventricular haemorrhage and white matter lesions in a preterm newborn with factor V (Leiden) mutation. Neuropediatrics 2002, 33: 97–9.

Reuner KH, Ruf A, Grau A, Rickmann H, Stolz E, Juttler E, et al. Prothrombin gene G20210→A transition is a risk factor for cerebral venous thrombosis. Stroke 1998; 29: 1765–9.

Rivkin M, Anderson M, Kaye E. Neonatal idiopathic cerebral venous thrombosis: an unrecognized cause of transient seizures or lethargy. Ann Neurol 1992; 32: 51–6.

Rother J, Waggie K, van Bruggen N, de Crespigny AJ, Moseley ME. Experimental venous sinus thrombosis: evaluation using magnetic resonance imaging. J Cereb Blood Flow Metab 1996; 16: 1353–61.

Sébire G, Fullerton H, Riou E, de Veber G. Toward the definition of cerebral arteriopathies of childhood. Curr Opin Pediatr 2004; 16: 617–22.

Shevell MI, Silver K, O'Gorman AM, Watters GV, Montes JL. Neonatal dural sinus thrombosis. Pediatr Neurol 1989; 5: 161–5.

Shiozawa Z, Ueda R, Mano T, Tsugane R, Kageyama N. Superior sagittal sinus thrombosis associated with Evans' syndrome of haemolytic anaemia. J Neurol 1985; 232: 280–2.

Soleau SW, Schmidt R, Stevens S, Osborn A, MacDonald JD. Extensive experience with dural sinus thrombosis. Neurosurgery 2003; 52: 534–44.

Stiefel D, Eich G, Sacher P. Posttraumatic dural sinus thrombosis in children. Eur J Pediatr Surg 2000; 10: 41–4.

Stolz E, Trittmacher S, Rahimi A, Gerriets T, Rottger C, Siekmann R, Kaps M. Influence of recanalization on outcome in dural sinus thrombosis: a prospective study. Stroke 2004; 35: 544–7.

Swann IL, Kendra JR. Severe iron deficiency and stroke. Clin Lab Haematol 2000; 22: 221–3.

Van Mierlo TD, Van den Berg HM, Nievelstein RAJ, Braun KPJ. An unconscious girl with sickle-cell disease. Lancet 2003; 361: 136.

Vorstman E, Keeling D, Leonard J, Pike M. Sagittal sinus thrombosis in a teenager: homocystinuria associated with reversible antithrombin deficiency. Dev Med Child Neurol 2002; 44: 498.

Wang PJ, Liu HM, Fan PC, Lee WT, Young C, Tseng CL, et al. Magnetic resonance imaging in symptomatic/cryptogenic partial epilepsies of infants and children. Acta Paediatr Sin 1997; 38: 127–36.

Wu YW, Hamrick SE, Miller SP, Haward MF, Lai MC, Callen PW, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. Ann Neurol 2003; 54: 123–6.

CASE REPORTS

Successful Management of Severe Intracranial Hypertension by Surgical Decompression

F. J. Kirkham
B. G. R. Neville

Surgical decompression has been very little used for the management of severe intracranial hypertension because of the rather disappointing results in acute head-injury in adults. This paper reports the successful use of this technique in the management of a child with encephalitis in whom cerebral perfusion was compromised.

Case report

The patient was a seven-year-old child with no previous medical history. She attended a normal school but her reading and mathematical abilities were considered to be in the low-average range.

She presented with a three-day history of pain in her right hip, mild abdominal discomfort and an ascending weakness. On admission to hospital she had a flaccid quadriplegia, mild meningism and was confused. 24 hours later there were no responses to command or pain, but brainstem reflexes were preserved. Ventilation was instituted because of poor respiratory effort. She had several seizures with biting, facial twitching and deviation of the eyes, which responded to intravenous phenytoin.

Cerebrospinal fluid pressure was 14cm of water (10mmHg) with a protein of 0·6g, white cell count of 34, 94 per cent lymphocytes, glucose 4, cultures including TB all negative. Serum ammonia was normal. Viral cultures and antibody titres were all negative. Mantoux was negative. CT scan was normal. EEG showed diffuse slow-wave activity but no focal abnormality. Initial nerve-conduction studies showed no definite abnormality but F waves were absent in a repeat study at 10 days which would be consistent with a radiculopathy. She received acyclovir and antituberculous therapy, although a viral encephalomyelitis was considered to be the most likely diagnosis.

A right frontal subarachnoid bolt (Edinburgh pattern) was inserted on day 4. The opening intracranial pressure was 45mmHg (A) with a cerebral perfusion pressure (mean arterial pressure minus intracranial pressure) of 50mmHg (Fig. 1). Control of intracranial pressure was attempted with hyperventilation, fluid restriction and bolus doses of mannitol (B) (Fig. 1). As the baseline intracranial pressure remained high, barbiturate coma using thiopentone was instituted as an additional measure to maintain cerebral perfusion pressure. An EEG pattern of burst suppression was achieved and the barbiturate appeared to have an effect for 12 hours by reducing intracranial pressure to <30mmHg but also reduced mean arterial pressure so that inotropic support was required. Cerebral perfusion pressure fell to about 40mmHg (C) (Fig. 1).

By day 6 the baseline intracranial pressure was 30mmHg. Three further brief increases (spikes) of intracranial pressure (D, E, F) were accompanied by increases in arterial pressure (Cushing responses), but on one occasion (E) the cerebral perfusion pressure fell to below 40mmHg (Fig. 2). In view of the risk of future compromise of cerebral blood flow the patient underwent a bifrontal surgical decompression that day.

Post-operatively she remained deeply unconscious for five days and then began a slow process of recovery, commencing with a lightening of conscious level followed by gradual improvement in motor function. Six weeks after presentation she was able to go home apparently recovered apart from a marked but transient torticollis. The skull flap was replaced two months after the acute illness.

Eight months later psychological assessment gave the following results using the WISC: full-scale IQ=83, verbal scale IQ=84, performance scale IQ=85. At 8 years 6 months her reading age was 6

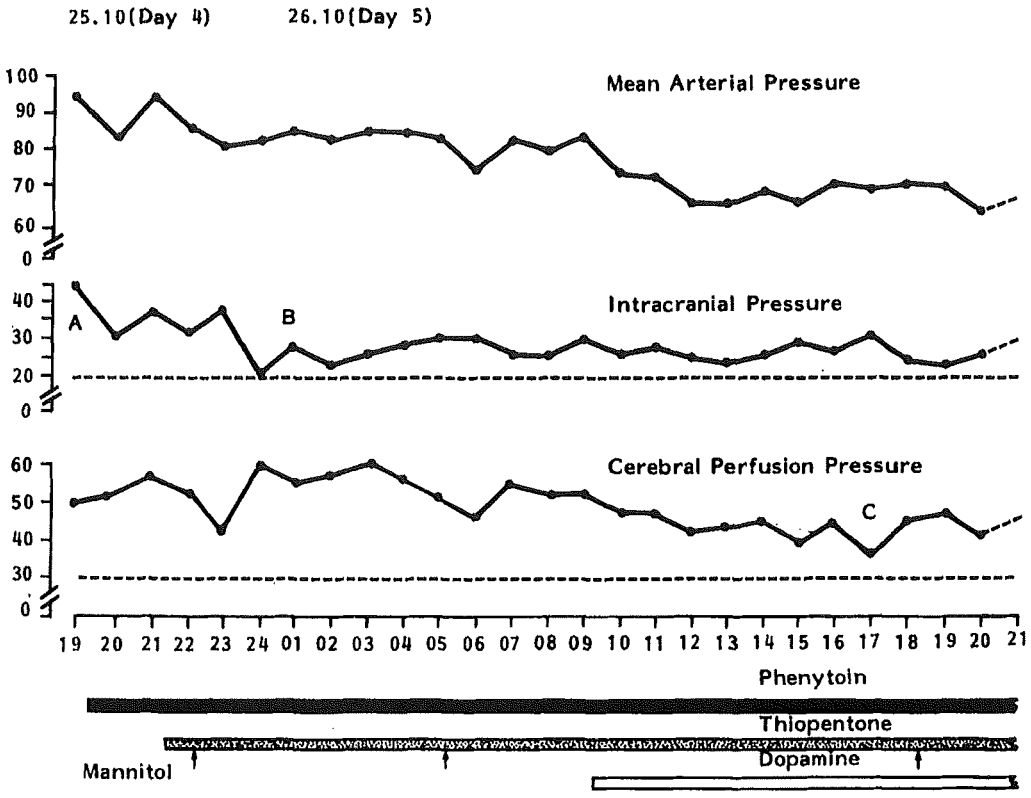

Fig. 1. Data from intensive-care charts, taken hourly over the 25 hours following insertion of the intracranial pressure monitor (days 4 & 5).

years 8 months assessed on the Neale Analysis of Reading Ability. Her class teacher does not feel that her reading skills have deteriorated since her illness. Her parents have noticed no change in her behaviour.

Discussion

The use of surgical decompression for uncontrollable raised intracranial pressure is controversial. Initial enthusiasm for radical craniectomy in the management of severe head injury (Kerr 1968, Kjellberg and Prieto 1971, Ransohoff *et al.* 1971) has been tempered by disappointing results (Venes and Collins 1975, Cooper *et al.* 1976). There is animal evidence that craniectomy may actually increase cerebral oedema (Cooper *et al.* 1979). Upward herniation of the human brain after circumferential craniectomy has been demonstrated at post-mortem (Clark *et al.* 1968). The procedure may be more worthwhile in children than adults with head trauma (Britt and Hamilton 1978, Sorensen *et al.* 1982) but no controlled trials have been conducted. There have been isolated reports of good outcome following surgical decompression in children with lead encephalopathy and Reye's syndrome (McLaurin and Nichols 1957, Ausman *et al.* 1976).

Neuro-intensive care has advanced in recent years and it is now possible to monitor continuously intracranial pressure and mean arterial blood pressure so that the cerebral perfusion pressure is always known. Previous studies have usually not had such measurements available and therefore the timing of surgical intervention may have been inappropriately late. The minimum perfusion pressure required to maintain cerebral function is not definitely established, but in a recent study of children with central nervous system infection there was 100 per cent mortality

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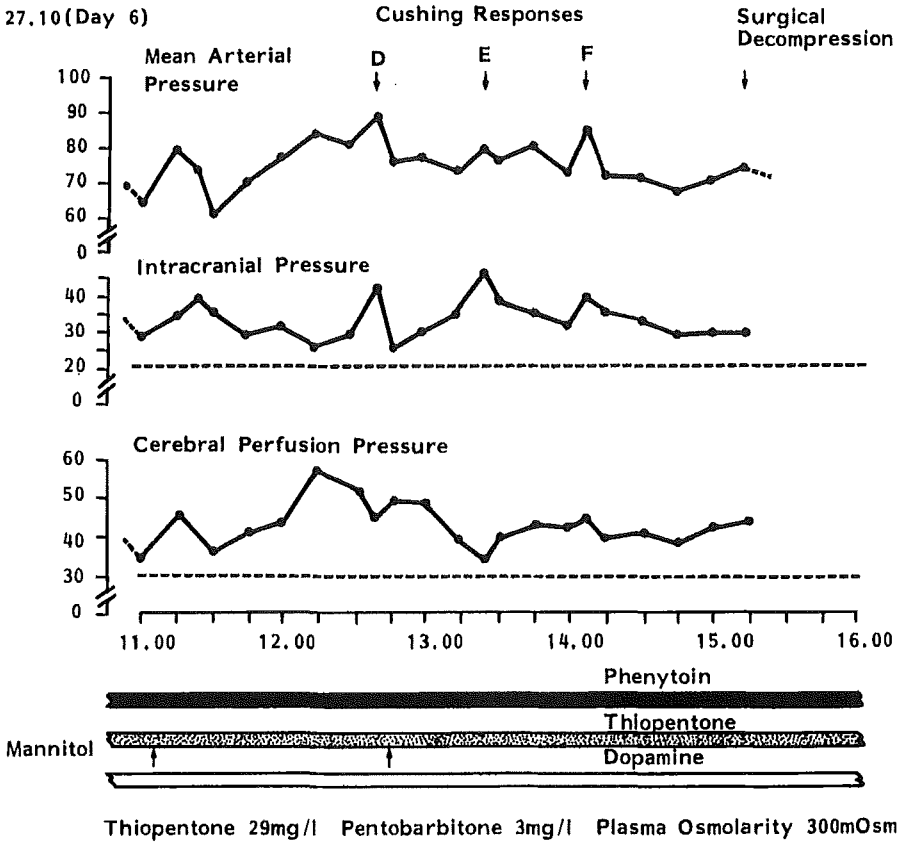

Fig. 2. Data from intensive-care charts taken quarter-hourly in the 4 hours before surgical decompression was undertaken.

in those with a pressure of less than 30mmHg and survival of those with a pressure above this figure (Goitein and Tamir 1983). Current evidence suggests that the aim of intracranial pressure management should be to keep cerebral perfusion pressure above 40mmHg.

Although it has been our experience that barbiturate coma has had an effect on reducing intracranial pressure, there are distinct problems in its use. First, the reduction in mean arterial pressure may cause a reduction in cerebral perfusion pressure. Second, brainstem signs and EEG are impaired or lost, and once a child is loaded with thiopentone it may take several days for the effects to wear off. It seems likely that the outcome for an acute encephalopathic illness will be proportionately better where the primary pathology looks to be relatively pure cerebral oedema as in Reye's syndrome, some forms of encephalitis, particularly rubella, and lead poisoning, than when the primary pathology also causes widespread cell death, for example hypoxic ischaemic damage and severe head injury. In the group with primary cerebral oedema there is a case for the use of surgical decompression in selected patients who have been fully monitored. This should be performed before decompensation occurs (Miller *et al.* 1972) so that additional ischaemic insults and acute herniation may be avoided.

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SUMMARY
Because of the rather disappointing results in the treatment of acute head-injury in adults, surgical decompression has been little used in the management of severe intracranial hypertension. The authors report the successful use of the technique for a child with encephalitis in whom cerebral perfusion was compromised.

RÉSUMÉ
Traitement efficace de l'hypertension intracranienne majeure par décompression chirurgicale
En raison des résultats décevants dans le traitement des traumatismes céphaliques aigus chez l'adulte, la décompression chirurgicale a été peu utilisée dans le traitement de l'hypertension intracranienne majeure. Les auteurs rapportent l'utilisation efficace de la technique chez un enfant porteur d'encéphalite dont l'irrigation cérébrale était compromise.

ZUSAMMENFASSUNG
Erfolgreiche Behandlung eines schweren intrakraniellen Hochdrucks durch chirurgische Dekompression
Wegen der relativ enttäuschenden Ergebnisse bei der Behandlung akuter Kopfverletzungen bei Erwachsenen ist die chirurgische Dekompression bei schwerem intrakraniellem Hochdruck selten durchgeführt worden. Die Autoren berichten über die erfolgreiche Anwendung dieser Methode bei einem Kind mit Enzephalitis, bei dem die cerebrale Perfusion gefährdet war.

RESUMEN
Tratamiento con éxito de la hipertensión endocraneana severa por descompresión quirúrgica
Debido a los resultados más bien decepcionantes obtenidos en la lesión craneal aguda en adultos, la descompresión quirúrgica se ha usado poco en el tratamiento de la hipertensión intracraneal aguda grave. Los autorea aportan la utilización con éxito de la técnica en un niño con encefalitis en que la perfusión cerebral estaba comprometida.

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References
Ausman, J. I., Rogers, C., Sharp, H. L. (1976) 'Decompressive craniectomy for the encephalopathy of Reye's syndrome.' *Surgical Neurology,* **6,** 97–99.
Britt, R. H., Hamilton, R. D. (1978) 'Large decompressive craniotomy in the treatment of acute subdural hematoma.' *Neurosurgery,* **2,** 195–200.
Clark, K., Nash, T. M., Hutchison, G. C. (1968) 'The failure of circumferential craniotomy in acute traumatic cerebral swelling.' *Journal of Neurosurgery,* **29,** 367–371.
Cooper, P. R., Hagler, H., Clark, W. K., Barnett, P. (1979) 'Enhancement of experimental cerebral edema after decompressive craniectomy: implications for the management of severe head injuries.' *Neurosurgery,* **4,** 296–300.
Cooper, P. R., Rovit, R. L., Ransohoff, J. (1976) 'Hemicraniectomy in the treatment of acute subdural hematoma: a re-appraisal.' *Surgical Neurology,* **5,** 25–28.
Goitein, K. J., Tamir, I. (1983) 'Cerebral perfusion pressure in central nervous system infections of infancy and childhood.' *Journal of Pediatrics,* **103,** 40–43.
Kerr, F. W. L. (1968) 'Radical decompression and dural grafting in severe cerebral edema.' *Mayo Clinic Proceedings,* **43,** 852–864.
Kjellberg, R. N., Prieto, A. (1971) 'Bifrontal decompressive craniotomy for massive cerebral edema.' *Journal of Neurosurgery,* **34,** 488–493.
McLaurin, R. L., Nichols, J. B. (1957) 'Extensive cranial decompression in the treatment of severe lead encephalopathy.' *Pediatrics,* **20,** 653–667.
Miller, J. D., Stanek, A., Langfitt, T. W. (1972) 'Concepts of cerebral perfusion pressure and vascular compression during intracranial hypertension.' *Progress in Brain Research,* **35,** 411–432.
Ransohoff, J., Benjamin, M. V., Gage, E. L. Jr., Epstein, F. (1971) 'Hemicraniectomy in the management of acute subdural hematoma.' *Journal of Neurosurgery,* **34,** 70–76.
Sorensen, M., Gaab, M., Gruss, P., Halves, E., Miltner, F. O. (1982) 'Decompressive craniectomy, an ultimate therapy in craniocerebral trauma.' *Monographs in Paediatrics,* **15,** 96–99.
Venes, J. L., Collins, W. F. (1975) 'Bifrontal decompressive craniectomy in the management of head trauma.' *Journal of Neurosurgery,* **42,** 429–433.

Traumatic Trochlear-nerve Palsy due to Haematoma

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Isolated acquired fourth-nerve palsy most frequently follows trauma (Rucker 1966, Burger *et al.* 1970, Younge 1977). We describe an unusual case of traumatic trochlear-nerve palsy due to documented haematoma in the region of the superior cerebellar cistern.

Case report

A 10-year-old boy fell from a swing, had a blow to his head and lost consciousness for five minutes. He woke with a headache and complained of double vision. Soon afterwards his parents noticed that his