Second Supplementary Medico-legal report 15.03.12

Adam Strain

Dob: 4th August 1991
Dod: 28th November 1995

Prepared on behalf of:

THE INQUIRY INTO HYPONATRAEMIA RELATED DEATHS
Chairman Mr John O'Hara QC

By:

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This addendum is prepared following two experts' meetings and review of further evidence and published scientific papers. The aim of this addendum is to draw together the aspects of the case relevant to my expertise as a Neuropathologist.

There are certain pieces of objective evidence which are relevant and will be considered:-

i. During preparation for and during surgery on November 27th 1995 between 7am and 11.45 am Adam experienced an effective water overload of 500ml [1]
ii. At completion of surgery Adam did not start breathing and was considered brainstem dead.
iii. CT scan at 2 ½ hours after surgery showed brain swelling.
iv. At autopsy brain swelling was identified.
v. Both radiology and autopsy examination indicate that brain swelling was more severe in the posterior part of the brain, sparing the cerebral cortex.

1. The mechanisms for the development of brainstem death and brain swelling are considered as well as additional factors which may have contributed to the pathology.
2. The steps which may have been taken to prevent the outcome are discussed.

3. **i Water overload of 500ml**
   The causes of this fluid imbalance are not within my expertise. Water overload will cause water to enter the cells of the body by osmosis. The brain has mechanisms to resist swelling following osmotic water entry; these mechanisms may be altered by pre-existing metabolic alterations and electrolyte imbalance. Brain swelling also depends on the speed of osmotic disturbance. These subjects are not within my own expertise.
   Water will enter cells of the brain, of which the astrocytes tend to manifest swelling. These are the supporting cells of the brain and occupy a position between the blood vessels and the nerve cells and are thus in a position to protect the nerve cells from harmful blood-borne agents including osmotic, metabolic, toxic and infectious agents. Neuropathology demonstrated astrocytic swelling which is not specific for osmotic damage but is consistent with it. I am unaware of any factors which would predispose one part of the brain to swell more than any other due to osmotic disturbance.

4. **ii At completion of surgery Adam was considered brainstem dead.**
   The most likely mechanism is brainstem compression due to brain swelling.

[1] Evidence presented by Dr Coulthard at experts' meeting March 9th 2012

Alternative mechanisms of local brainstem damage such as stroke or a ruptured blood vessel during surgery are excluded by neuropathology.

5. **iii.CT scan 2 ½ hours after surgery showed brain swelling and iv. brain swelling at autopsy**

Types and mechanisms of brain swelling:

6. Brain swelling is usually categorised as vasogenic or cytotoxic oedema. In vasogenic oedema fluid leaks across the walls of the small blood vessels of the brain into the spaces between the cells of the brain. In cytotoxic oedema the individual cells of the brain, predominantly astrocytes, swell. In most conditions these types of oedema co-exist in various proportions; osmotic oedema is predominantly cytotoxic. Other causes of cytotoxic oedema are impaired blood or oxygen supply to the brain (hypoxic-ischaemic injury HII) and metabolic cell damage (Marmarou 2007).
7. Impaired venous outflow from the brain can lead to both vasogenic oedema and cytotoxic oedema. The venous pressure rises, interfering with normal fluid dynamics, including the normal transfer of interstitial fluid into the capillary and venous system. If the venous obstruction is severe enough to compromise blood flow out of the brain, cytotoxic oedema and/or infarction can occur.
8. Hyperdynamic circulation or excessively high flow through the blood vessels may also lead to brain swelling. In this case there may be a component of vasogenic oedema but in addition the blood vessels dilate and the blood volume within the brain increases.

Effects of chronic renal failure on brain weight

9. Several studies have indicated that children with chronic renal failure have smaller brains than normal children. Valanne described children post transplant of whom over 50% had infarction, some preceding transplantation (Valanne, Qvist et al. 2004). Laakkonen described 21 infants on peritoneal dialysis of whom one third had infarcts or ischaemic lesions.(Laakkonen, Lonnqvist et al. 2011)
10. Coulthard described a population of young children with renal failure which included infants who had brain pathology which contributed to reduced brain size in addition to their renal problems.(Coulthard and Crosier 2002)
11. I have found no reports in which autopsy brain weights are available.
12. No pre-existing brain pathology which may have altered brain weight was observed in Adam.

Hypoxic-ischaemic injury (HII)

13. This has been suggested as a cause of Adam's brain swelling. Two lines of evidence suggest that this is unlikely.
I-There was no pathological evidence of nerve cell death predominating in those regions of the brain most likely to show HII- the hippocampus, the depths of cortical sulci, the cerebellar dentate nucleus or the inferior olivary nuclei of the brainstem.
ii-The anaesthetic record indicates that oxygen levels were normally maintained throughout surgery.[2]

Seizures

Seizures may increase cerebral blood flow and intracranial pressure. Whether seizures occurred is a matter for clinical opinion. Examination of the brain showed no specific damage to the hippocampus, a part of the brain susceptible to damage in seizures. Indeed the hippocampus was noted to appear less oedematous with less neuronal damage than elsewhere.

Anaemia

Anaemia may exacerbate metabolic stress in the brain and if uncorrected would exacerbate the effects of hypoxia and oedema.

Anaesthetics and drugs

Halothane, dopamine and other drugs given as well as raised CO2 levels, may have effects on the cerebral circulation. Alterations of flow induced by these agents may exacerbate oedema but it is not within my expertise to comment. The circulatory changes induced by these agents are dynamic and would not result in changes in the blood vessels of the brain visible at autopsy or by microscopy.

Impaired venous outflow

Impaired venous outflow may contribute to brain swelling as noted above. Outflow may be impaired if there is venous obstruction by thrombosis. In this case there remains a further question concerning obstruction of the internal jugular veins, the left by a suture and the right by central venous pressure line[3]

14. There was no evidence of venous thrombosis at autopsy, but this cannot be excluded as the sinuses were not described. The evidence regarding jugular vein obstruction is unclear. The paravertebral plexus is a potential site for venous thrombosis but was not described. It is not routine to examine this plexus at autopsy. I am unaware of any autopsy protocol where this would be expected.

[2] Evidence of Dr Haynes; Experts' meeting 9.3.12
[3] Autopsy report Dr Armour; conclusion

15. There is no pathological evidence of longstanding venous outflow obstruction. In this condition the superficial veins of the brain would be expected to be dilated and tortuous. This is not seen on the available autopsy photographs.
16. Further, significant venous obstruction leads to infarction of the subcortical white matter. This was not seen in the tissue examined.
17. It is not possible to exclude venous obstruction of relatively recent origin; perhaps several days or hours before death.
18. There are two venous systems in the brain. The superficial system drains the cortex and underlying white matter. This blood leaves the brain through bridging veins which enter the dural sinuses. The sinuses unite in the posterior part of the cranial compartment. After leaving the dural sinuses the route for venous return to the heart is posture dependent, via the jugular veins in the supine, or the paravertebral plexus in the upright position. (San Millan Ruiz, Gailloud et al. 2002)
19. The existence of two return pathways may have minimised the effect of chronic obstruction of the jugular veins.

20. **v. Brain swelling was more severe in the posterior part of the brain, sparing the cerebral cortex.**
21. The relative severity of swelling of the brainstem and cerebellum as compared to the cerebral hemispheres was noted by Dr Anslow on the brain scans. Reference to the photographs of the brain at autopsy confirms this and shows that the gyri of the cerebral cortex maintained their normal rounded appearance and the sulci remain open with some residual space in the cerebral ventricles.
22. The factors influencing the specific distribution of brain swelling are not commonly addressed. It can be difficult to identify subtle differences in distribution of swelling pathologically. The usual means of identifying brain swelling is by brain weight, usually comparing the forebrain (cerebral hemispheres) and hindbrain (brainstem and cerebellum).
23. The ratio of forebrain and hindbrain weights was normal, but the inaccuracies of this comparison have been discussed.[4]

24. Posterior Reversible Encephalopathy Syndrome (PRES)

25. This syndrome has been suggested by Professor Kirkham as a cause for the observed pattern of posteriorly prominent cerebral swelling seen in Adam's brain.
26. This syndrome is diagnosed on the basis of clinical and radiological features. I am aware of only a single description of neuropathological features in which vascular changes similar to those seen in hypertension were described (Kheir, Lawlor et al. 2010). No vascular abnormalities were seen in the sections of Adam's brain.
27. PRES is a relatively recently described condition and new studies are constantly expanding the phenotype so swelling may not be purely posterior and may not be

[4] Report W Squier 15.10.11 page 6

reversible. The range of conditions associated with PRES is also growing and include infection, sepsis and shock (Bartynski, Boardman et al. 2006) venous thrombosis and following surgery (Kummer, Schaper et al. 2010; Petrovic, Nemeth et al. 2011).

28. The reason for selective distribution of brain swelling is unclear. It seems likely that the innervation of the cerebral blood vessels may be significant. There is a distinct difference between the nature and density of the innervation of anterior and posterior cerebral circulations. Both sympathetic and parasympathetic nerves supply the cerebral vessels. In addition the trigeminal nerve supplies the anterior circulation (including the cortex of the cerebral hemispheres), while the posterior circulation is supplied by the ninth and tenth cranial nerves and the upper three cervical nerves Innervation density is greater in the anterior than the posterior circulation (Fricke, Andres et al. 2001).
29. The causes of selective activation of the perivascular nerves are unknown. However, selective activation/changes in perfusion likely play a role in certain conditions. For instance, differential perfusion between the anterior and posterior circulation is thought to contribute to the radiographic "reversal sign" of supratentorial edema (Kavanagh 2007), and focally increased flow is seen beneath areas of subdural bleeding (Deibler, Pollock et al. 2008).
30. The trigeminal nerve mediates cerebral blood flow adaptations via peripheral axon-reflex mechanisms during severe hypertension and seizures (Sakas, Moskowitz et al. 1989). Neuropeptides released from the sensory fibres of the trigeminal nerve may lead to altered vascular permeability (Goadsby and Sercombe 1996).
31. Selective activation of the cerebro-vascular innervation may lead to redistribution of the cerebral circulation and may contribute to regional brain swelling.
32. These phenomena may contribute to the unusual patterns of insult in PRES.

33. **Conclusions**
34. It appears that fluid imbalance during surgery is the most likely cause of Adam's brain swelling. No other obvious cause has been identified. There is no pathological support for ischaemic brain damage.
35. The unusual distribution of swelling is unexplained, but is consistent with regionally determined activation of the cerebrovascular innervation.
36. There is no evidence of long-standing venous outflow obstruction to explain the distribution of swelling but acute obstruction of venous outflow cannot be excluded.

37. What could have been done to prevent Adam's death?

I am unable to comment on the management of Adam's clinical care.

38. Determining the precise cause of death depends on detailed and thorough autopsy examination. In this case this may have been improved by:
    - Full review of case history and brain scans prior to autopsy
    - Better documentation of the findings.

- A formal Neuropathological examination and report.

39. Response to specific Questions:

1. *Please explain how the anatomy of the hind brain might explain the differences in degree of Adam's brain swelling.*

   This is addressed at paras 21-23 and 28-32 above

2. *You previously stated that you wished to consider whether the pattern of swelling in Adam's brain corresponded to compromised/diminished venous outflow of the brain. We would be grateful if you could now provide same.*

   See paras 14-19

3. *Please comment on the possibility and likelihood of venous thrombosis in the paravertebral plexus in Adam's case.*

   The paravertebral plexus might present a likely site for venous thrombosis due to its complex anatomy of small and branching vessels. However this is a hypothetical consideration and I am not aware that venous thrombosis has been described here in clinical practice. The plexus is not routinely examined at autopsy. I cannot offer a likelihood for thrombosis here.

4. *Please comment on the likely effect of the administration of 50ml Mannitol at approximately noon and thereafter (Ref: 057-018-026 and 027) on the degree and distribution of cerebral oedema as shown on the CT scan at approximately 14.15, and in particular whether it could have accounted for the different degree of swelling in the posterior fossa and elsewhere.*

   The effects of therapy are not within my expertise. I understand that this drug may act to reduce brain swelling but I cannot explain why it should have had a differential effect on the forebrain.

Waney Squier

15 March 2012

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