RESPONSE TO

NOTE TO DR.GROSS FOLLOWING EXPERTS' MEETING

EXPERTS'S MEETING 9.th MARCH 2012

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ISSUE 1 : INQUIRY WILL SEND HARD COPIES OF THE CHARTS AND OF ADAM's TIMELINE OF MAIN EVENTS 1991 – 1995

This material has not arrived yet .

ISSUE 2 : IDENTIFY ANY SPECIFIC PAPERS OF Dr.J.VERBALIS THAT YOU CONSIDER TO BE OF PARTICULAR RELEVANCE ESP. IN RELATION TO THE RATE OF FALL OF SERUM SODIUM

1) JG Verbalis , MD Drutarosky : Adaptation to chronic hypoosmolality in rats . Kidney Int. 34 : 351-360 , 1988

2) JG Verbalis et al. : Brain adaptation to hyponatremia : physiological mechanisms and clinical implications . 1995 Elsevier . Neurohypophysis : Recent progress of vasopressin and oxytocin research . T Saito , K Kurokawa , S Yoshida eds. , : 615-626

ISSUE 3 : SET OUT YOUR FINAL CALCULATION OF THE RATE OF FALL OF ADAM's SERUM SODIUM a) DURING THE FIRST HOUR OF HIS SURGERY , b) FROM THE START OF SURGERY UNTIL 9:32 a.m. ON NOV.27.th OF 1995

Because the terminology was used in a slightly different manner before (tables on Adam's perioperative fluid balance) I presume I am asked about the time periods a) 7 a.m. to 8 a.m. and b) 7 a.m. to 9:32 a.m. .

a)The fluid excess was 573 cc and the NaCl excess was 16.6 mmol . Assuming a serum sodium of 132 mmol/L at 7 a.m. this yields 448 cc of NaCl free water added to Adam . At an assumed 12 kg of total body water and at distribution equilibrium I calculated the serum sodium at 8 a.m. to have been 127.1 mmol/L . The rate of fall would have been 4.88 mmol/L/hr .

b)The rate of fall amounted to 3.6 mmol/L/hr .

ISSUE 4 : ARTICLES BY PAUT et al. AND SICOT et al. .

Thank you . (I had obtained and used the French version in my comments of March 19 , 2012).

ISSUE 5 : COPY OF ARTICLE BY ARIEFF et al. IN MEDICINE , 1976

I sent a copy of the article to your office on March 19 , 2012 in a previous communication .

ISSUE 6 : PROVIDE A COPY OF THE LITERATURE OF PROF. BRÜCK FROM GÖTTINGEN TO WHICH YOU REFERRED ON MARCH 9.th 2012 INDICATING HIS AGREEMENT WITH THE 1992 PAPER OF PROF. ARIEFF et al.

Arieff et al. wrote :" That transtentorial herniation was present in all nine patients ... correlates well with the observation that the human brain can expand by only about 5-7 % of its normal volume before herniation occurs". (B.M.J. 304 : 1218 , 1992).

I previously quoted Prof.Brück as follows :"According to Prof.Brück ... the extracerebral fluid spaces ... in a healthy 4 year old amount to approximately 125 cc of fluid , which is space that can be used to accommodate brain edema ". (201 – 004 – 106) . At an assumed weight of the brain in a 4 year old of 1300 gr , 125 cc would be equal to 9.6 % .

By my comment on March 9.th I meant to indicate the similarities of these figures . (In my opinion they are similar.) The information from Brück was obtained by personal communication . Brück did not mention or quote a publication .

ISSUE 7 : COMMENT ON PROFESSOR KIRKHAM's REPORT

I am not a neurologist and this is not my area . Prof.F.Kirkham's report is very detailed . I should first like to go through the report pointing out some remarks and I shall summarize (comment) at the end .

-ITEM 30(208-002-028) Prof.Kirkham's report says : "Dr.Squier ... pointed out that the majority of the swelling involves the posterior structures". However in (206-004-025,Dr. Squier's report) it says :"The autopsy findings ... reflect the changes at the time of death which occurred 24 hrs after surgery . During this 24 hrs ... I presume that (Adam) was receiving treatment for his brain swelling . A number of secondary effects may have taken place in the brain ; the swelling may have led to ischemia which exacerbated the already severe brain swelling ... . **These** progressive secondary **effects make the post-mortem assessment of brain swelling far less accurate than the CT scan ."** The full text of Dr.Squier's comment is more cautious than what was reported of it in Prof.Kirkham's statement and should have been documented accordingly .

ITEM 32(208-002-029) Prof.Kirkham's report says :"...I have not been able to ascertain from (Arieff's) paper or that of Moritz and Ayus (2005) ... which of the patients were administered glucose 280 mmol/L in water (similar to 5% dextrose as used in the U.K.) and which glucose 280 mmol/L / sodium chloride 38 mmol/L (similar to 0.18% saline/4% dextrose as used in the U.K.) " (sic). These statements can be understood to imply that there was an important difference between the 2 solutions . In the publication by Arieff et al. it says :" Most of the iv fluids were administered as 280 mmol/L glucose either in water or NaCl 38 mmol/L , but the plasma glucose concentration was only 7 mmol/L at the time hyponatremia was diagnosed ". (The normal range for plasma glucose is reported as 4.2 to 6.1 mmol/L .) Arieff's note of the plasma glucose being close to normal indicates that the glucose had been metabolized leaving the water behind . Hence it is not justified in this context to make a distinction between dextrose 5% and dextrose 4% . Furthermore Arieff et al. only speak of

"hypotonic infusions" . This I think is their comment on 0.18% saline being very hypotonic as compared to 0.9% saline (physiologically isotonic). In other words in the eyes of Arieff et al. there is no significant difference between the 2 types of infusion , which are equally labeled hypotonic by them . Also attention should not be diverted from Arieff's main point –which is hypoosmolality of infusions- to minor issues such as almost negligible differences between individual preparations of such hypotonic infusions .

ITEM 34(208-002-129) : Prof.Kirkham's report says :" Recent work from the research group which includes Arieff ... has emphasized ... hypoxia (in determining the severity of cerebral edema) ".
This can be understood to imply that since there was no documented hypoxia in Adam it was unlikely that he could have severe cerebral edema from hypotonicity . However the point of Arieff's paper in 1992 (B.M.J.) is that hypotonic brain edema may lead to severe sequelae including brain death in the absence of hypoxia . This is shown by the authors' statement :
"Immediately after respiratory arrest in the course of severe hyponatremia but before oxygen was administered the arterial oxygen tension ... was 6 kPa in 11/16 patients " (Normal range : 11-14) . In the full context of their paper this note serves to exclude a role of hypoxia in severe brain edema . I think this should have been said in Prof .Kirkham's report .

ITEM 35(208-002-030) Prof.Kirkham's report says :" ... Arieff noted that most of the infants and children reported previously had had central nervous system disorders ... ".
This can be understood to imply that central nervous system disorders are a requirement in hyponatremia with complications from the central nervous system . (In Adam , central nervous system disorders were not known.)
However in Arieff's publication (B.M.J. , 1992) , i.e. in his own report of 16 cases the main point is that all were previously healthy , i.e. free of central

nervous system disease . I think that Arieff's findings were not reported fully and adequately .

ITEM 35(208-002-030) Prof.Kirkham's report says ."...the (16) patients in Arieff's report had preexisting risk factors ... including orchidopexy (undescended testes are common in neurological disorders) ".
Reading Arieff's report reveals one child with undescended testicle . I believe this low number is more suggestive of a random association .

ITEM 35(208-002-030) Prof.Kirkham's report writes that the patients in Arieff's series had preexisting risk factors for hypoxia , e.g. in the context of tonsillitis . (Adam did not).
Reading the report shows that 7 of 16 children had tonsillitis . The authors point out that operations of nose/mouth/pharynx are the commonest operations in children in the U.S. and explain the high incidence in this way . Furthermore as I outlined earlier the article (B.M.J. , 1992) was written to show that hypoosmolality but not hypoxia was important in these 16 children . I think that observations from other articles should not be altered .

ITEM 37(208-002-030) Prof.Kirkham's report writes :" ... although CT was available from 1977 there was no neuroimaging reported for the cases in Arieff's series ". It also says that neuroimaging was of lesser sophistication in the 1990's .
However the report by Arieff et al. (B.M.J. , 1992) says :" ... all 16 children had radiological evidence -CT or MRI- of cerebral edema whereas at necropsy 9 of 10 evaluated had cerebral edema with herniation ." In other words , Arieff et al. did report neuroimaging (supplemented with autopsy findings). I suspect that the high incidence of brain autopsy may more than compensate for technical progress with scans as done presently . Importantly , neither the neuroimaging(MRI included) nor the autopsies uncovered cerebral comorbidities or sinus venosus thrombosis . Arieff et al. were not of the

opinion that sinus venosus thrombosis or cerebral comorbidities contributed to the hypotonic severe cerebral edema in their children (10 died of it). I think reporting of other scientists's work has to be done in a faithful manner .

ITEM 40(208-002-031) Prof.Kirkham's report says : "I have found 'only' (added by P.Gross) 4 cases of cerebral edema in children without preexisting cerebral nervous system disease where the fluid administered was 0.18% - 0.3% NaCl in 4 or 5% dextrose."
This statement suggests that cerebral edema in children without central nervous system disease and receiving hypotonic infusions (as in Adam) would be exceeding/rare . However in addition to Arieff's own 16 cases (B.M.J. , 1992) , who were previously healthy children , i.e. without central nervous system disease and who were all receiving hypotonic fluid I would like to quote from further down in the article by Arieff et al. (1992) . They say :"The estimated yearly incidence in the U.S. is 7448 cases of pediatric postoperative hyponatremia , with 626 such hyponatremic deaths in children " . (It might be noteworthy that A.Arieff was the leading authority on hyponatremic brain edema in the U.S. and beyond at the time of his publications). The 4 cases mentioned in Prof.Kirkham's report may be an understatement .

ITEM 43(208-002-032) : I take exception to Prof.Kirkham's report suggesting to divide between hyponatremias on the basis of purported risk factors . The implicit suggestion is that such risk factors frequently lead to the events that they (may) pose a risk for . In my opinion this is unknown . For instance many people smoke cigarettes but medicine is unable to predict which of them will get lung cancer . I have not seen a suggestion like Prof. Kirkham's in the literature before .

ITEM 43(208-002-032) : I take exception to making a distinction in terms of hyponatremia between the 3 categories i , ii , iii . They are all caused by

hypotonic infusions –to use Arieff's term- in a comparable manner . I have pointed this out before under ITEM 32 .

ITEM 48(208-002-034/035) Prof.Kirkham's report says :" I think that ... chronic venous sinus thrombosis is a likely cause of Adam's previous ... neurological problems . ... I think ... that further acute thrombosis in the venous sinuses was associated with acute posterior cerebral edema during the operation ."
I do not agree with these proposals which postulate both chronic and acute thrombosis , i.e. more than tiny subtle changes . There are two reasons :
-Neither Dr.Anslow , the radiolologist , nor Drs. Armour and Squier , the parthologists , were able to describe findings suggesting acute or chronic (or both) forms of sinus venosus thrombosis in Adam .
–I am of the opinion that it is impossible to establish a diagnosis on the basis of risk factors alone – as was done here . I would also point at the following : the majority of renal transplant recipients harbor a comparable set of supposed risk factors as listed under 208-002-034 . From the literature in kidney transplantation I am not aware of sinus venosus thrombosis as having been more than a rare problem in such patients . Likewise in over 600 kidney transplantations in my own experience I cannot remember a single such case .

ITEM 50(208-002-036/037) Prof.Kirkham's report says :" I consider it likely that ... PRES for which Adam had at least 3 risk factors ... contributed to the rapid development of mainly posterior cerebral edema in his case ."
I do not find this suggestion plausible .
A)On Nov 27 , 1995 Adam's surgery ended at 11:00 . At 11:55 Adam failed to wake . He did not breathe . His pupils were fixed and dilated . (Implying brain death). At 12:05 or shortly thereafter Adam was given mannitol on PICU . At 14:15 or 14:30 the CCT was taken . Thus there were more than 2 hrs and possibly as much as 4.5 hrs between Adam's supposed brain death and the CCT . In addition to the mannitol it is possible that the transfusions of red blood

cells or of HPPF (after 9:32 in the operating room) could have affected his brain , possibly after brain death and before the CCT . Therefore it is not certain that Adam's CCT , showing more marked posterior cerebral edema than anterior , is an accurate reflection of Adam's condition of the brain at the time of brain death .

B) The suggestion of PRES is also largely based on risk factors . I am doubtful about this approach .

C) I consulted 4 articles on PRES :

C) 1 . J Hinchey et al. , N Engl J Med 334 : 494-500 , 1996 . These authors describe 15 adults with PRES . Most had some degree of renal insufficiency .
-12/15 had hypertension,headache,vomiting (not present in Adam)
-the clinical signs of PRES were reversible in all 15 (not in Adam)
-the patients had focal seizures with secondary generalization (not in Adam)
-4/15 patients received cyclosporine A (in Adam only after brain death)
-their CCT reports speak of 'white matter hypodensities' or –in 1 case- of 'bilateral low density areas involving the white matter of the parieto-occipital lobe" (not described in Adam) .

C) 2 . H Gümüs et al. , Neurol Sci 13 : 125-131 , 2010 . The authors describe 9 children with PRES .
–The clinical features were headache and hypertension (not present in Adam)
-No patient died (as opposed to Adam)
-Patients had renal disease , immunosuppressants (Adam had these , too)
-A single patient had erythrocyte transfusion for severe iron deficiency anemia (Adam received red blood cell transfusions for intraoperative blood losses . As an underlying diagnosis he seems to have had iron deficiency but certainly not severe and it may have been largely replenished by his iron supplements at the time of the operation on Nov.27 , 1995).

C) 3 . K Ishikura et al. , Pediatr Nephrol 27 : 375-384 , 2012 . This is a review . It stresses hypertension , cyclosporine A and seizures as characteristic aspects of PRES . (None of them were present in Adam . Adam received cyclosporine A after his brain death had occurred). It says that of 44 pediatric patients with PRES described in the literature none died .

C) 4 . A Yamada et al. , Pediatr Nephrol 27 : 277-283 , 2012 . They describe 11 children with PRES .
–None died (as opposed to Adam)
-Seizures , hypertension , headache , vomiting were present in almost all (as opposed to Adam).

Together : as I read it there are many more discrepancies of these reports with Adam's description than there are similarities . Adam would have to be called a very unusual case of PRES . The major similarity may be the accentuation of changes in imaging studies in posterior parts of the brain . But even this feature is described in the above literature as "white matter hypodensities" or "leukoencephalopathy" whereas Dr.Anslow - not using these terms - spoke of "The CSF spaces have become obliterated , the ventricles are much smaller" . I wondered if these were necessarily the same phenomena or not .

To my understanding the evidence for a diagnosis of PRES in Adam is not sufficient . I think it is unlikely that Adam would have had PRES .(I am not a specialist in this area of medicine .)

ITEM 52(208-002-037) Possibility of Adam having had cerebral salt wasting . – I take exception to this suggestion of Prof.Kirkham's report on the grounds that Adam had end stage renal failure . Cerebral salt wasting has not been described in end stage renal failure . For pathophysiological reasons it probably cannot occur in end stage renal failure .

ITEM 54(208-002-038) Prof.Kirkham's report says :" The argument that Adam's acute cerebral edema and brain death was caused by dilutional hyponatremia is based on :
-The fall in sodium . Adam had experienced similar levels of hyponatremia on a number of previous occasions .
–The evidence for generalized edema in the lungs and the rest of the body .
–Dr.Armour's autopsy . There are discrepancies in brain weight which mean

that the cerebral edema may not have been as severe as previously assumed .

-The literature showing fatal cerebral edema in children ... when many ... appear to have received 5% dextrose ."

I disagree with all of these 4 remarks by Prof.Kirkham's report .
–A) According to the evidence presented Adam's cerebral edema was not primarily due to 'the fall in sodium' but to the pernicious velocity by which his serum sodium fell . Thus his rate of fall had been between 0.04 mmol/L/hr and 0.75 in previous episodes (between Oct 15 , 1991 and June 8 , 1995) but it was 3.6 mmol/L/hr from 7 a.m. to 9:32 a.m. on Nov. 27 , 1995 -it even reached 4.88 mmol/L/hr between 7 a.m. and 8 a.m.- when his fatal cerebral edema occurred . Thus it was at least 5 times larger on Nov. 27 than during previous episodes . This sets his hyponatremia on Nov. 27 apart from previous hyponatremias . His hyponatremia on Nov. 27 was definitely **not** similar to his previous hyponatremias .
–B) Adam's (possible evidence of) edema in the lungs or the rest of his body was irrelevant to Adam's cerebral edema . In my reports I have not described any such relationship . In the literature hyponatremic brain edema is not known to be associated with edema in the lungs or in the rest of the body . For example in severe hyponatremia of SIADH with cerebral edema patients do not show peripheral edema . On the other hand in the presence of peripheral edema (as may occur in cardiac failure or in NaCl overload) there is no brain edema . It is necessary to keep these different categories of edema separate , they do not have to do with each other - as implied by Prof. Kirkham's report .
–C) The issues related to Dr.Armour's autopsy : Be this as it may ; the best evidence we have available on the supposed degree of brain swelling is that from the CT scan on Nov. 27 , 14:15 . Dr.Anslow wrote :" The brain has become very swollen ." (206-005-111) . In view of this statement plus the fact that the brain swelling lead to herniation of the brain into the foramen magnum there can be no doubt about the severity of the cerebral edema .
–D) As I described before in the opinion of the scientists leading in this field (Dr.Arieff , Dr.Verbalis , Dr.Berl , Dr.Ayus and others) it is the 'hypotonicity' of an infused fluid –and not whether this hypotonicity is caused by 5% dextrose or 4% dextrose or 4%dextrose/0.18% NaCl- which matters . In his landmark

1992 publication (B.M.J.) Arieff et al. bluntly speak of 'hypotonic fluid administration' which caused hyponatremia and death or permanent brain damage in healthy children . The emphasis on 5%dextrose in Prof.Kirkham's report is therefore misguided .

IN SUMMARY

1) The report by Prof.Kirkham does not appreciate hypotonic acute brain edema as proposed in relevant literature . The landmark article by Arieff et al. (B.M.J. , 1992) is quoted by the report in a selective way and in other parts it is quoted inadequately . It thereby deviates significantly from the meaning of the contents of the article .

2) The report by Prof.Kirkham overstates the case for a suggested diagnosis of chronic and acute cerebral sinus venosus thrombosis . This diagnostic proposal rests on suggested risk factors only . There is no evidence in terms of any factual findings . In my opinion Adam is not likely to have had cerebral sinus venosus thrombosis .

3) The report by Prof.Kirkham overstates the case for PRES . I would call the resemblance between Adam and the cases in the 4 articles which I read 'vague' . I did not see convincing factual evidence in favor of PRES in Adam . I think it is not likely that Adam had PRES .

ISSUE 8 : YOU HAD COMMENTED ON Dr.LANDES' REPORT ON THE X-RAYS AND PULMONARY EDEMA . COMMENT ON THE FINDING OF Dr.ARMOUR ON AUTOPSY THAT THE LUNGS WERE EDEMATOUS (sic)

I do not recall having made specific comments on Adam's chest X-rays and pulmonary edema .

In the autopsy report of Dr. A.Armour (011-010-036) a historical note says :" ... a chest X-ray revealing pulmonary edema ..." . This comment is for the time on PICU on Nov.27 after 13:15 . In Dr.A.Armour's own description of the autopsy I failed to find a comment on Adam's lungs or pulmonary edema . However in the section 'microscopy' Dr.A.Armour says :"There was congestion of the capillaries and there were moderate numbers of alveolar macrophages . There was no evidence of embolism or infarction ." To my understanding Dr.A.Armour was not seeing any major degree of pulmonary edema because she did not describe free fluid in alveoli . (I failed to find the original report by Dr. Landes).

I do not know whether these reports contradict each other or whether they possibly describe the same phenomenon (pulmonary congestion bordering on pulmonary edema) . I also do not know whether in another autopsy report by Dr.A.Armour there is a description of pulmonary edema (as the wording of ISSUE 8 implies) .

Neither of the 2 possibilities (no pulmonary edema vs. pulmonary edema) are of particular relevance to my reports on Adam . Assuming Adam did have pulmonary edema after the end of his operation : patients even with severe dilutional hyponatremia , e.g. in SIADH are not known to get pulmonary edema . Hypotonic brain edema and pulmonary edema are usually separate entities , unrelated to each other . - Could any pulmonary edema during operation have caused oxygen desaturation of Adam's blood and hence cerebral hypoxia and brain swelling ? 1) We do not seem to know when any possibly present pulmonary edema first began ; for example it could have been a consequence of the mannitol Adam received on PICU ; 2) Dr.Taylor did not find any oxygen desaturation of Adam's blood throughout the operation .

ISSUE 9 : COMMENT ON Dr.COULTHARD's STATEMENTS IN RELATION TO CEREBRAL PERFUSION AND THE INCREASED VENOUS PRESSURE BEING COMPENSATED BY THE DECREASED (sic) ARTERIAL PRESSURE AND THAT IT WAS IRRELEVANT WHETHER ADAM's HEAD WAS UP OR DOWN

(These are issues outside my area of expertise although I tried to consider them and will repeat here).

Adam's measured CVP was 17 mm Hg at the begin of operation and increased to 20 mm Hg after 2 hrs (WS-008/1) . Dr.S.Haynes has voiced concern on March 9,2012 over the zeroing of the CVP . For the purposes of the present calculations I will take the 17 and 20 mm Hg as they were reported . The CVP showed respiratory and cardiac patterns . Therefore it was measuring from inside the lumen of the right internal jugular vein into which it had – inadvertantly- travelled , i.e. away from the heart and up towards the brain by maybe 2 or 3 cm as shown later by X-ray . The normal range of a CVP is 2-7 mm Hg . Thus in Adam the measured CVP was 10 mm Hg higher than normal at the begin and later 13 mm Hg . The left internal jugular vein was ligated . (I quote this as stated in Dr.A.Armour's autopsy report although it seems to have come into some question lateron).

The normal (intra)capillary pressure in the cardiovascular system is reported to be approximately 17 mm Hg . In brain capillaries in an upright healthy person it should be lower than this number ; I assume it could be 5-10 mm Hg or even lower (I failed to find a measurement in literature).

In Adam lying supine and being in head-down position –presumably lowering the head by 10 cm or 7.7 mm Hg compared with supine non-head-down- the minimal pressure at the venous end of posterior cerebral capillaries therefore would have been (17 + 7.7) 24.7 mm Hg initially and (20 + 7.7) 27.7 mm Hg after 2 hours . This is a minimal estimate for 2 or 3 reasons : a) the niveau of capillaries at Adam's posterior brain in the head-down position was probably >10 cm below the niveau of the tip of the CVP catheter due to the anterior-posterior dimension of the brain ; b)in order for blood to flow from the arterial to the venous end of a capillary the pressure has to be higher at the former ;

hence the mean (intra)capillary pressure will be higher than what one finds at the venous end . (Further , if –as Dr.Coulthard said on March 9.th- an orthostatic effect from the head-down position on the venous side was compensated by a commensurate increase of pressure on the arterial side then this will cause (intra)capillary pressure to rise even higher than what I considered so far .) In other words Adam's intracapillary pressure in posterior cerebral vessels is likely to have been significantly higher than the stated 24.7 and 27.7 mm Hg .

It can be seen that Adam's (intra)capillary pressure in posterior capillaries was much higher than under normal conditions , perhaps 2-5 fold higher . Such a change favors hydrostatic filtration of intravascular fluid into surrounding brain tissue and may cause additional edema formation . Oncotic pressure opposes this phenomenon . Normal oncotic pressure (retaining fluid inside capillaries) is reported to be 28 mm Hg . Oncotic pressure is determined by the concentrations of plasma proteins . At 13:00 on Nov.27 a measurement showed Adam's total protein in serum at 41 gm/L (normal range 58-85) (ref. 058-040-186). Assuming approximately 60% of total plasma protein to be made up of albumin I calculated Adam's oncotic pressure at this time to have been approximately 18 mm Hg . I assume that Adam's plasma protein concentration must have fallen during operation , since plasma albumin had been normal -40 gm/L (normal range 35-50)- on Nov.26 , 23:00 . I find this plausible because during operation Adam : lost approx. 900 cc of his blood serum ; received 1000 cc of HPPF (containing 88% albumin) ; received a total of 2000 cc of non-albumin-containing iv fluids – before a background of his supposed total blood volume being 2.2 L . I made the assumption that the reduced oncotic pressure may have been present in Adam throughout much of his operation on Nov. 27 . Together : Comparing the intracapillary pressure of 24.7 and 27.7 mm Hg (which are minimal estimates and probably were significantly higher) posteriorly in Adam's head-down position with his reduced oncotic pressure of 18 mm Hg fluid filtration would clearly be favored . (I omitted extravascular hydrostatic and oncotic pressures from this description because –at least initially- they should have been similar to each other.)

-Assuming an anterior-posterior distance of 16 cm of Adam's skull it can be calculated that the minimal pressure at the venous outflow end of anterior brain capillaries in the head-down position would have been (17-4.6) 12.4 mm Hg initially and (20-4.6) 15.4 mm Hg after 2 hrs . Again the pressures may have been higher for the same reasons pointed out earlier . The reduced oncotic pressure of supposedly 18 mm Hg would have applied here , too.
Together : Hydrostatic and oncotic forces in the head-down position in Adam in anterior parts of his cerebral vasculature favored fluid filtration less than what we calculated above for posterior parts . In fact the figures do not suggest fluid filtration for anterior parts at all whereas for posterior parts they do .

SUMMARY

In Adam calculations suggest that **it was not irrelevant** whether his head was up or down . The effects of the head-down position on hydrostatic pressures in his brain capillaries , the fact that his CVPs were significantly elevated and the measurement of subnormal total protein(indicating a markedly reduced oncotic pressure) appear to add up in such a way that fluid filtration from capillary lumen into surrounding brain tissue was favored in posterior parts of his brain but not in anterior ones . I am unable to suggest whether or not such forces can explain the differences in brain edema that were described in Adam by Dr.Anslow . Perhaps a neuroradiologist or a neurophysiologist could comment .

(P.S.: Whether Dr.Coulthard's suggestion about arterial compensation for orthostatic venous outflow inhibition would apply to Adam's head in the head-down position I am unable to answer . To my understanding the effects of orthostatic changes on the arterial side on capillaries would be influenced by (myogenic) autoregulation of arterioles supposedly dampening such influences . Due to time constraints I did not study literature on this point . Also –as I pointed out above- if Dr.Coulthard's suggestion applied it would make posterior fluid filtration only worse .)

ISSUE 10 : COMMENT ON THE CAUSE OF THE GREATER DEGREE OF CEREBRAL EDEMA WHICH WAS SEVERE IN THE POSTERIOR FOSSA , AND THE REASONS WHY THE CEREBRAL EDEMA WAS NOT UNIFORM

I am a nephrologist , not a neurologist . This question is not from my area of expertise .

1) The wording of the question in my mind is not quite accurate . Dr.Anslow wrote :"The brain has become very swollen . The changes are severe in the posterior fossa ." I interpret this as saying that there was marked generalized brain edema , which was more pronounced in the posterior fossa . I find it important that Dr.Anslow saw marked generalized brain edema .

2) It may be possible that the CT does not precisely reflect the condition of Adam's brain at the time when brain death occurred . The CT was taken at 14:15 or 14:30 of Nov. 27 , 1995 . Adam's brain death most likely occurred during his operation , perhaps as early as at 9:32 a.m. . There appears to have been an interval of between 2 hrs and 4 hrs 45 min between his brain death and the CT . Adam received treatments and they may have been given during this interval such as transfusion of red blood cells and infusion of 1 L of plasma protein fractions . It may be possible that they reached some parts of his brain more than other parts and hence caused different effects .

3) Adam was prescribed 50 cc of 20% mannitol at 12:00 on Nov.27 and I presume that he received it . Mannitol is often given to counteract brain edema . It may be possible that Adam's mannitol reached anterior parts of his brain better than other parts and hence caused differential effects .

4) Orthostatic factors due to Adam's head-down position in the setting of an increased CVP -as suggested previously- may have contributed to the marked generalized brain edema to manifest more severe changes posteriorly .

5) Possibly other events and factors causing regional changes and known to neuroradiologists and neurologists . (I am not knowledgable in this field).

ISSUE 11 : IN RELATION TO ADAM's BRAIN STEM TESTS , THESE WERE CARRIED OUT BY Dr.DAVID WEBB , CONSULTANT PEDIATRIC NEUROLOGIST , AT 19:35 ON 27.th NOV. 1995 AND 9:10 ON 28.th NOV . 1995 . THE RESULTS OF THESE TESTS ARE SEEN AT REF 058-004-009 . COMMENT ON THE FACT THAT ADAM WAS STILL HYPONATREMIC WHEN HIS BRAIN STEM TESTS WERE CARRIED OUT AND WHETHER THIS WAS APPROPRIATE , AND THE REASONS FOR YOUR ANSWER . PLEASE STATE WHAT YOU WOULD HAVE EXPECTED TO HAVE BEEN DONE IN 1995 , BY WHOM , WHEN , AND WHAT DIFFERENCE IF ANY THAT IT WOULD HAVE MADE TO THE OUTCOME OF ADAM'S CASE :

-Adam's serum sodium was 124 mmol/L at 16:30 and 120 at 22:00 on Nov.27 and it was 125 mmol/L on Nov.28 at 8:00 , the closest measurement I could find to the time of the second set of brain stem tests at 9:10 on Nov. 28.th . This degree of hyponatremia –while often causing general cerebral symptoms- is not known to suppress brain stem reflexes . Hence the testing was appropriate even without correction of the hyponatremia .

-According to the rules in Germany the brain stem tests in a 4 yr. old –if used as the only criterion for brain and brain stem death- should be done 24 hrs or more apart . I do not know whether this interval would have applied in Belfast , too .

- An alternative to the foregoing (in Germany) would have been to do one set of brain stem tests in combination with one technical test (EEG or evoked potentials or Duplex ultrasound of cerebral vessels). If each test (the physical test and one technical test) showed the characteristic changes of brain and brain stem death this would have sufficed to pronounce brain death . I am not sure whether the same rules would have applied in Belfast at the time or not .

-These tests are preferably done by knowledgable physicians in these fields of expertise (neurologists , angiologists , intensivists etc) .

-The testing for brain and brain stem death might have been done earlier than at 19:35 on Nov.27 of 1995 –e.g. after the CT- however there are sometimes psychological , organizational or medical problems(diazemuls) resulting in delay .

-To my understanding Adam's prognosis was grave once the descensus of parts of the cerebellum and brain stem through the foramen magnum had occurred and had been diagnosed by CT . This is an irreversible condition , always leading to brain death . Hence the different tests that were done and could have been done to diagnose brain and brain stem death in Adam would not have made a difference to his outcome (except permitting that organs of Adam could be used properly in potential organ donation).

ISSUE 12 : COMMENT ON THE FOLLOWING :

a) IT APPEARS THAT ADAM WAS GIVEN DIAZEMULS AT APPROXIMATELY 13:20 ON 27.th NOV. 1995 RESULTING IN NO EFFECT (058-005-011 ; 058-035-137 ; 058-035-138 ; 058-038-153).

b) THE NOTE OF Dr.WEBB IN ADAM'S MEDICAL NOTES AT 9:30 RECORDING "ON NO MUSCLE RELAXANTS OR SEDATION "(058-035-139).

To a) : a note under 058-035-138 says :" 1:20 pm (Nov. 27) diazemuls 6 mg iv given in case (increased) blood pressure (lead) to seizure – no effect ". This note suggests to me that the diazepam (diazemuls) was given in an attempt to rule out status epilepticus as a possible cause of Adam's changed mental status . (Although in the absence of spontaneous respirations between 11:30 and 13:20 status epilepticus would be unlikely .) At 13:20 the CT had not been done yet . In my experience giving diazepam to try and exclude seizure activity is accepted procedure amongst the specialists in this field , i.e. neurologists .

To b) : This note is the first line in Dr.Webb's description of Adam's brain stem test results at 9:30 p.m. on Nov. 27 of 1995 . In my opinion Dr.Webb meant to document his assessment that Adam was not under the influence of drugs at this time whose drug levels might interfere with Adam's brain stem reflexes , including the diazepam . (The Martindale textbook says :' Diazepam has a biphasic half life with an initial rapid distribution phase followed by a prolonged terminal elimination phase of 1 to 2 days'). We may conclude from this that 8 hrs after giving the diazepam (i.e. at 9:30 p.m. on Nov. 27) the initial rapid distribution phase would have been over and diazepam would have had a low or very low blood level , which is compatible with performing the brain stem tests .

Dresden , March 26 , 2012

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