Prof. em. Dr. Dietz Rating

Ehem. ärztlicher Direktor der
Kinderheilkunde V
(Schwerpunkt: Kinderneurologie,
Epilepsie-Zentrum und Sozialpädiatrisches Zentrum)
Zentrum für Kinder- und
Jugendmedizin
Universität Heidelberg

Heidelberg, den 23.11.2012

Privat:
[redacted]

Prof. em. Dr. Dietz Rating

Prof. Dr. D. Rating
[redacted]

To
Inquiry into Hyponatraemia Related Deaths
Arthur House
41 Arthur Street
Belfast BT1 4GB

UNITED KINGDOM

Reg.: Strain, Adam
born on 14 August 1991

On behalf of the "*The Inquiry into Hyponatraemia Related Deaths*" I have been asked to comment on some new information I received in October 2012 in a folder named "Supporting Documents for Brief Vol 1 and Vol 2" (paper copy and disc), which included

- the first (208-002-017 to 049) and the second (208-007-0068 to 129) expert reports of Prof. Kirkham as well as the expert reports of
- Dr. Anslow (206-005-109 to 112 and 208-004-051)
- Dr. Coulthard (200-019-226 to 231; 200-018-222 to 225; 200-021-254 to 259; 200-013-177 to 204; 200-020-232 to 253; 200-022-260 to273)
- Prof. Gross (201-015-215 to 282; 201-016-284 to 304)
- Dr. Haynes (204-008-353 to 360; 204-009-361 to 372; 300-077-141 to 148; 204-012-379 to 388; 204-013-389 to 400)
- Dr. Squier (206-006-113 to 114; 206-010-120 to 127)
- and the transcript of meetings at the Inquiry on 22 February and 9 March 2012.

As a paediatric neurologist I considered it my duty within this inquiry to deal especially with the reports of Prof. Kirkham, the expert in paediatric neurology.

In respect to the reports of Dr. Coulthard and Prof. Gross (adult and paediatric nephrologist) and Dr. Haynes (consultant paediatric cardiothoracic anaesthesia and intensive care) I agree on most topics. They gave very sophisticated and detailed information on the calculation of fluid intake and output from 26 to 27 November 1995, and I am pleased to learn that my calculations, although I am not a nephrologist and not so used to making such calculations, are in the range of the experts in nephrology. Where I do have remarks in these regards, I will include them in my remarks on the paragraphs of Prof. Kirkham.

.

After having read the new material and especially the protocol of both meetings of the Inquiry I realise the problem of the Court.

I wish to submit my position in two ways - first I would like to give some sort of a summary of my understanding of the new material, discussing especially the view of Prof. Kirkham (Section A); secondly, I will go through the paragraphs of Prof. Kirkham's expert report (Section B) step by step, giving some remarks along the way.

Section A

To my understanding the main difficulty and where I disagree is that Prof. Kirkham simply denied that there is any such entity as an osmotic encephalopathy, although she stated this in a much more diplomatic way: *"I haven't said that I am absolutely sure .. What I have said is that I can't find a case of a patient given Solution 18 in whom brain death has occurred secondary to this ... Well no, I am not saying it couldn't happen, I am saying, you know, I tend to go on evidence and literature evidence counts very favourably in developing an argument. If I have got literature evidence then it is much easier to say this is likely to have happened in this case, there is no other case previously, then this is the first case described. I am not saying that it couldn't be, I am just being very sceptical when there are no cases like this"* (all Prof. Kirkham from page 57ff – protocol of the meeting 9 March 2012) and *"However, I think the cases that are in the literature have not been exactly the same as Adam's case and there a number of anxieties I have about simply saying that because there is a 7% increase in water and that will have crossed into the astrocytes that necessarily cause Adam's death"* (page 82 – ibid.) and *"What I'm saying is that I don't think that the oedema caused by the increase in free water on its own killed Adam Strain"* (page 85 - ibid.).

Towards the end of her report as well as and much more clearly in the meeting on 9 March 2012 she stated that to her understanding the osmotic mechanism alone would not have killed Adam - *"then I think he would have survived"* (page 85 – ibid.).

Prof. Kirkham therefore had to look for other, additional factors / reasons to explain Adam's death. She came up with three different arguments:

1. Pre-existing neurological symptoms/deficits/disorders as a predisposition acting together with others so that posterior reversible encephalopathy syndrome (PRES) and/or an acute sinus venous thrombosis (SVT) will become manifest (or manifest itself easier), ending in Adam's death.
2. Sinus venous thrombosis (SVT)
    a. Chronic SVT, perhaps acquired in the past, allows development either to an acute SVT or PRES on 27 November.
    b. Acute SVT developing on the 27 November
3. Posterior reversible encephalopathy syndrome (PRES) which developed on its own or together with the predisposition of 1 and/or 2 on 27 November.

ad 1. Pre-existing neurological symptoms / deficits / disorders

I refer here to my remarks in the second part of my first report, especially to paragraphs 3, 4, 10, 62, and especially 63.

In this context I would like to pinpoint the remarks made by Dr. Coulthard at the meeting of 22 February 2012 regarding the feeding difficulties in children on peritoneal dialysis (page 61-64). I can accept the experience of Dr. Coulthard . I am surprised that Prof. Kirkham in her final expert report of 28 March 2012 did not made any remarks on that witness.

To my understanding there are no clear-cut indicators in the files that point to a neurological lesion in Adam's case. Prof. Kirkham´s expert report contains numerous considerations but no proven event, nor a proven neurological defect – a lot of hypothesis but no proof.

ad 2. Sinus venous thrombosis

Chronic SVT:

Here too, Prof. Kirkham brought forward only hypothetical considerations. Nothing was proven or very likely or only likely, while in some way only playing around with arguments, avoiding having to clarify her position.

Whether she is really convinced that Adam was suffering from a chronic SVT did not became clear (for me at least); she only hypothesized and asked for dehydrating events which – hypothetically – might have provoked an SVT, which – again hypothetically – did not spontaneously clear afterwards. I can give her a further event, which to my reading was not discussed at the meetings in February and March 2012 - in 1991 Adam had had a phase of hypernatraemia that persisted for some days: on 12 December 1991 a hypernatraemia of 146 mmol/l was noticed the first time. The sodium concentration increased slowly over the next days – on13 Dec 149

mmol/l (049-029-128), on 14 Dec 151 mmol/l (049-029-126), on 16 Dec 156 (049-030-162), on 19 Dec 153 mmol/l (049-029-106), and on 19 Dec 156 mmol/l (049-030-179).

However, besides all these events in the files no other hints can be found indicating that an SVT occurred at any time. The SVT argument is easy to bring forward but very difficult - if not impossible - to reject. To be a bit unfair – according to Prof. Kirkham's list of probable events at which time Adam could have developed a SVT – I am really astonished that I have not suffered an SVT in my life so far.

A further difficult aspect is that Prof. Kirkham did not clarify whether in her opinion the chronic or the acute SVT was more likely or more important in Adam's case and whether it was her view that because of chronic SVT a new, acute SVT was engrafted.

As I have seen many cases of acute / subacute sinus venous thrombosis I have difficulty in accepting that subtle neurological symptoms such as feeding difficulties, expressive language deficits, and pathological movements of the jaw are the prominent symptoms of SVT in Adam´s case. If an acute und proven SVT in a previously totally normal child have happened in the past, one can start to discuss whether symptoms such as feeding difficulties or speech problems could be the residuum of acute SVT. However, since such a clear-cut neurological event apparently had not taken place, Prof. Kirkham asked (that was my understanding of her remarks) whether these symptoms were due to an ongoing primary chronic SVT (Prof. Kirkham *"not cleared spontaneously").* I have great difficulty in accepting, and even disagree with this series of "arguments", which are not arguments at all but merely hypotheses, none of which is proven.

For example – given a patient with such minimal neurological features claimed by Prof. Kirkham - if I speculate in such a patient that the features were due to

- a minor insult of the brain intraunterinally between the 25th and 33th weeks of fetal life, leading only to periventricular leucomalacia which was so tiny that it could not be detected by CT (only by MRI, and then thin-sliced MRI), or
- intermittent CSWS (continuous spike and waves during slow sleep) in which an electrical status epilepticus provokes maldevelopment of children, or
- an unidentified mitochondrial disorder or another slow going metabolic disease

all these diagnoses would be at the same level of argumentation: I do not have a good argument for any of these speculative disorders, but again none could be excluded by anyone postmortally without having done the correct investigations during the patient's life time.

My hypothesis brought forward in the hypothetical patient is "made out of thin air" just as much as is Prof. Kirkham's hypothesis of a chronic sinus venous thrombosis.

Acute SVT:

Prof. Kirkham is well-known in Europe because of her interest in all the problems surrounding CNS bleeding, stroke or coagulopathies leading to CNS lesions. Prof. Kirkham knows everything in this field.

Prof. Kirkham introduced her very important paper in Brain (Sebire et al. 2005), which is of extreme significance for all paediatric neurologists worldwide since the field of stroke, infarcts, CNS embolism, and acute SVT is an ever-growing topic in child neurology. While in adult neurology good concepts have been developed to handle patients with an acute apoplexy, these are nearly totally lacking for the paediatric age group, while unchanged children will come too late to specialised hospitals for any active drug / interventional therapy.

In the paper Sebire et al., dealing in most cases in acute SVT, 42 children with SVT with or without stroke and haemorrhages were reported. Four of the 42 experienced their SVT after surgical procedures - Fontan operation (very risky regarding postsurgery coagulopathic problems), shunt operation, brain tumour resection, and colectomy for ulcerative colitis. Although the authors stated that they found a 100% trigger event - I suppose because of the lack of space provided by the publisher - we have only little information, only that the SVT was "diagnosed immediately after surgical procedures", with no further details provided. For instance, did the anaesthesiologist already notice the problems intraoperatively, at which time after operation did the first symptoms occur, did those patients have a partial or a full-blown SVT?

I have had difficulties to find papers on the time when first symptoms occurred after an operation which provoked the acute SVT. In a very old paper, also in Brain (Barnett et al, 1953), the authors reported the neuropathological findings in acute SVT in elder patients. In five of there 39 patients SVT was triggered by an operation and only for those authors gave the time-lag between triggering factor (operation) and first symptom: the time-lag was between 24 hours and 7 days. From my other reading – e.g. SVT in craniotomies with setting operative lesions to the dural sinus – the only information this yielded was that SVT did not occur as quickly as it would have been in Adam's case (here only 3-4 hours).

Sebire et al. reported that a CT was made in all patients - perhaps Prof. Kirkham can provide some more details on these CTs: for example, how many of them were sufficiently conclusive to make the diagnosis of SVT on the basis of the CT alone, and how often an MRI was required; in addition, I would be especially interested to hear how often the CT - in which lag of time to the presumed time of SVT - showed a global brain swelling without any other aspects. This information cannot be gleaned from the paper.

I can instantly accept that acute SVT is a differential diagnosis in Adam's case. I even can accept that an intraoperative SVT, which however - according to the concepts of triggers she listed - could not start before 9:30 to 10:00 and could lead to coning in 1 to 2 hours and death at 11:30.

I am, however, very sceptical that if such a peracute and fulminant SVT leading to death in such a short time had indeed happened, it is not seen in neuropathology. One cannot argue that SVT on the one side was so

insidious or lingering that the pathologist had not seen it and on the other side it was so peracute that the child died. A fulminant SVT leading to death in such a short time would have produced some cortical bleedings.

I have still not found a comprehensive neuropathological report of Adam´s brain in the files. To my knowledge, any neuropathological investigation of a brain involves the preparation of some sectional cuts of the brain. When these sectional cuts lack any indication of SVT, then a fulminant acute SVT leading to death can be excluded.

I am aware of the statement of Dr. Squier that, as it was not intensively looked for, the diagnosis of a SVT cannot been excluded – to my understanding in Adam's case of an acute death after an insinuated SVT one does not have to look "intensively". But perhaps all these statements from Dr. Squier were made only in respect to a chronic SVT as predisposition for PRES.

I suggest that Dr. Squier should address a somewhat different question: to her experience and knowledge, how likely is it that a peracute, severe SVT leading to death within the space of 1 - 2 hours was not seen during brain section. To my understanding - it can be excluded that in 1995 a brain section will not make the diagnosis of a SVT severe enough to bring the boy to death; this cannot be "overseen".

In the statement paper "Diagnosis and management of cerebral venous thrombosis" done by Saposnnik et al. (2011) the American Academy of Neurology / the American Association of Neurological Surgeons / the Ibero-American Stroke Society, a meta-analysis of papers dealing with SVT was performed. In this paper one cannot find any clear-cut answer to the question as to how quick a fulminant SVT will lead to death; no case of a patient dying intraoperatively from SVT is mentioned, while one finds statements such as "mortality rates were low, typically < 10%, often due to the underlying disease ... rather than SVT and rarely due to intracranial hypertension. The majority of patients fully recovered neurological function, and few became disabled". The group of "early death" included the first 30 days after acutes SVT; a peracute death is not mentioned. In this paper authors stated that seizures were "3.7 fold increase in SVT with parenchymal lesions in CT/MRI" i.e. bleedings / haemorrhages that must have been seen upon neuropathological investigation.

According to all these data, on the balance of probabilities acute, fulminant SVT, leading to death within the space of 1-2 hours, cannot be diagnosed in Adam's case.

ad 3. Posterior reversible encephalopathy syndrome (PRES)

PRES is an interesting hypothesis even in Adam's case.

The clinical picture of *hypertonic encephalopathy* seen in hypertonic patients and in women suffering an eclampsia has been well known for a long time. In 1996 Hinchey et al. described similar clinical and MRI patterns - and that was new - in patient with normal blood pressure suffering from renal disorders, autoimmunological diseases, and on/after an immune modulating therapy. Posterior reversible encephalopathy syndrome

(PRES) still is an ill-defined syndrome, characterised as a "clinico-radiological" entity with numerous predispositions. The MR findings were said in all papers to be principally localised, not generalized and predominantly in "posterior" parts of cerebrum – i.e. the occipital and parietal lobes - but were also seen in the frontal or temporal regions, in other words that the predisposed areas within the brain are mainly supratentorial , while - at least in children - "less commonly, the brainstem, basal ganglia, thalami and cerebellum are afflicted" (Iyer et al. 2011); according to Roth et al. (2011) "lesions .. in basal ganglia, cerebellum or brainstem can be found in about one-third of cases".

PRES is described in a great variety of very different diseases, and in the moment it is difficult to name the common link of all these various diseases. When the headword *PRES* is given in the PubMed machine, in the first 40 papers that appear,and published in 2011 and 2012 PRES was associated with:

Acute leucemia, AIDS, acute nephrotic syndrome, chronic renal insufficiency, Guillain-Barré syndrome, systemic lupus erythematosus,	various rheumatological diseases, Crohn's disease, after severe infections/sepsis, in children with / after aplastic anaemia, Schonlein-Henoch purpura acute poststreptococcal glomerulonephritis,	after drug therapy with gemcitabine, after chemotherpy including oxaliplatin after fluoropyrimidine, after deoxycoformycin and alemtuzumab, after organtransplantation, after therapy with anti-vascular-endothelial-growth factor (VEGF)

and, and, and....

Clinical findings include headaches, altered mental status, seizures, cortical visual disturbances, and loss of consciousness (Ugurel 2005, Hefrzy 2009, Incecik 2009). Because of the very nonspecific clinical picture CNS imagings became very important for diagnosis and while the PRES changes were hard to see in CT scans MRI scans are the best-suited diagnostic tool.

PRES can manifest itself as an acute encephalopathy with epileptic seizures, reduced consciousness all the way to deep coma, vomiting, as well as with focal neurological signs. Mostly a fluctuating vigilance with headaches, phases of lethargy replaced by agitation were seen in patients in whom the syndrome started slowly over days. Highly elevated blood pressure is seen in 70-80% of adults at PRES manifestation, while in the rest the blood pressure is normal or only slightly increased.

In children PRES is quite often seen in various oncological diseases and especially in acute childhood leukaemia (Iyer et al. 2011), as that is the most frequent paediatric oncological disease.

Regarding the pathophysiology, there are two mechanisms currently under discussion:

a) Breakdown of the cerebral autoregulation in cases of an acute hypertonic crisis, leading to a breakdown/disruption of the blood-brain-CSF barrier and changes in endothelial cells with extravasation of blood and macromolecules resulting in cortical and subcortical oedema, while fluid and organic macromolecules leave the vessels and cross into the interstitium. In this context the question of a hyperperfusions is discussed by some authors.

b) At the beginning there is a primary - probably sympathetically induced - arteriolar vasoconstriction (Ugurel 2005) and hypoperfusion with secondarily provoked ischemic lesions by which the oedema starts to built up. The localisation of MRI changes in the posterior parts of cerebrum in PRES is said to reflect the gradient of sympathetic innervation of the brain (McKinney et al. 2007).

When re-reading papers on MRI changes in PRES, I was puzzled by the fact that in the overwhelming majority of papers local oedemas were presented by neuroradiologists as a "vasogenic oedemas" and only few pictures were published showing small ventricles, with a generalised brain oedema; i.e. most pictures did not follow the description of a highly increased intracranial pressure (although I am aware that MRI / CT scans cannot tell you the true degree of the rise in (intracranial / intraparenchymal pressure in the brain) (see attached pictures, taken from the papers of Staykov 2012, Iyer et al. 2011, as well as the images of Petrovic et al. 2011, which paper was cited by Prof. Kirkham, from which paper I cannot make a copy in

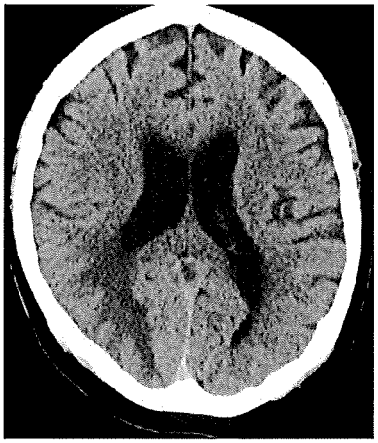

Fig. 1: From - Stayko et al. Nervenarzt (2012)

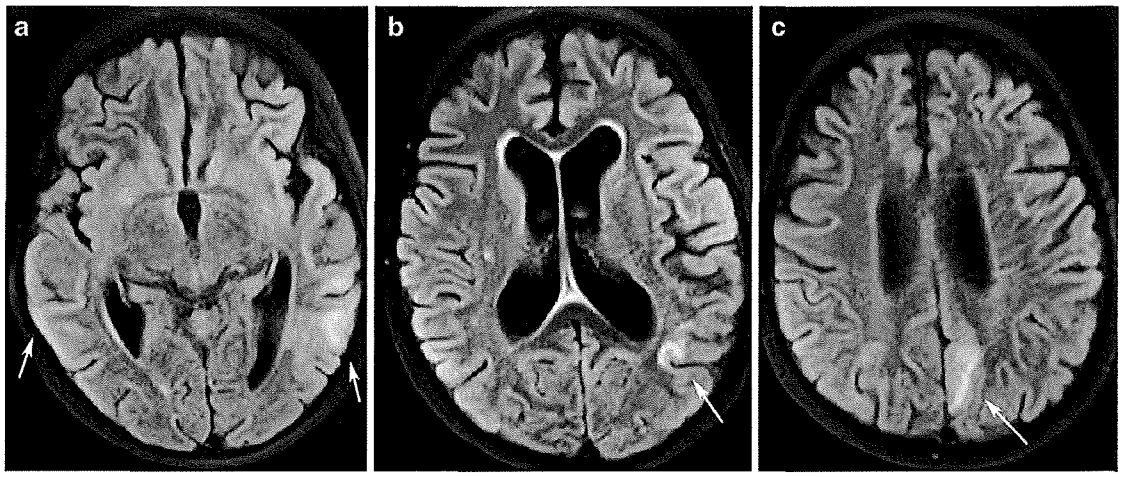

Fig. 2: From - Iyer et al. (2011)

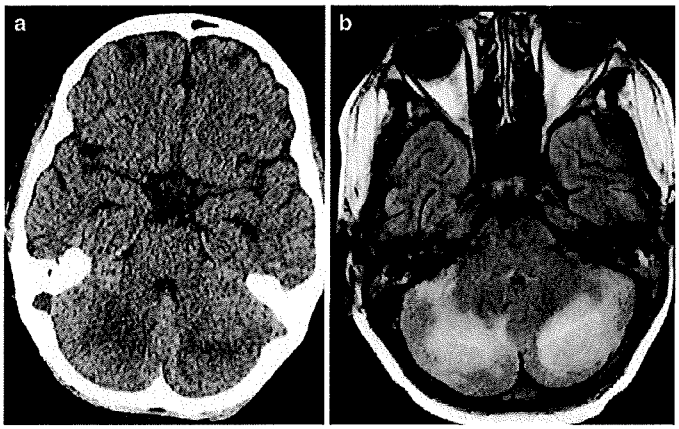

Fig. 3: From - Iyer et al. (2011)

this as I was unable to get it in a digital version and I have to refer to the printout from Prof. Kirkham's report (2008-007- fig 1 (-138), fig 2 (-140), fig 5 (-142) or the paper of Fugate et al. (2010)).

There are some scans which show nicely corresponding areas in both the CT as well as the MRI scans (Iyer et al. 2011, Fig. 3) although MRI provides much more information on the involvement of cortical and subcortical regions of the brain, while in Adam's case only a severe supratentorial and more distinct infratentorial brain oedema was seen.

I accept that CT can miss some signs of PRES; nevertheless I got the impression that in those cases not seen in CT it was always on only local distribution of small vasogenic oedema that were not depicted in CT. I have not found any image published in connection with PRES comparable with what is seen in Adam's CT .

I learned from Dr. Coulthard's witness at Court on 22 February (page 74) and on 9 March 2012 (page 124) that the increase in blood pressure starting at 9:30 is a normal increase, intended by anaesthesiologists in any

renal transplantation to ensure and provide the function of donated adult kidneys, which during their adult life are/were used to higher blood pressures. I accept this explanation and I want to withdraw my interpretation that this blood pressure increase is a counteraction of the brain to increasing intracranial pressure.

Osmotic oedema in Adam's case

Having read all remarks made by Prof. Kirkham I got the impression - maybe I am mistaken - that Prof. Kirkham is not convinced that there at all exists a clinical or neuroradiological or neuropathological picture of a massive brain oedema following an acute overload with free water in a short time. leading to what is called dilutional hyponatraemia, brain oedema and death. Therefore she had to look for other explanations / factors of Adam's death, such as e.g. PRES and SVT, accompanied by other factors which might have exerted an influence.

Prof. Kirkham did not pay any consideration in her argumentations and citations to what is the most important aspect in differentiating between acute and chronic dilutional hyponatraemia (for example in paragraph 71a. (208-007-099) writing *"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"* (my emphasis: DR), while in acute dilutional hyponatraemia the ion pumping could not withstand the transfer of water, which takes place easily when hyponatraemia develops over a longer time of many hours or even days.

Furthermore, she did not consider the fact that, while in a normal person all the mechanisms leading to the elimination of water from the body are present, these mechanisms are not available in end-stage renal failure.

When Prof. Kirkham raised the question (paragraph 69 - 208-007-??) *"if Adam developed any primary cerebral problem such as PRES and/or CVST, during 26-27th November, he would have been at risk so hyponatraemia secondary to compromise of the cellular sodium pumping mechanism, which requires energy, as well as antidiuretic hormones secretion"* – it is my opinion **that this argumentation turns the pathophysiological mechanisms upside down**. Adam's kidney - energy supply missing or not - could not react to any antidiuretic hormone secretion which is indispensible for eliminating free water from the body.

The brain oedema after an acute overload with water starts with a diffusion of water in the cell and - as Prof. Kirkham correctly stated - immediately an energy-supplying pumping of sodium out of the cells started. Prof. Kirkham declared *"I think that there will have been astrocytic and therefore brain swelling, but I don't think ... that will necessarily have caused Adam's death ... because there are compensatory mechanisms ... sodium potassium pump .... extra CSF shunts into the ventricles and then down to the CSF spaces and is reabsorbed in the arachnoid granulations"*.

However, while water influx is a passive diffusion following gradients of concentration, the ion-pumping process is an active transport mechanism, which like all other active transport mechanisms it has a maximum

transport capacity that can run out. Furthermore, the easy transfer to the ventricles, to CSF subarachnoidal space will also be hindered by any swelling of the brain.

My interpretation is hence that there is the situation that these compensatory mechanisms are overwhelmed and the circulus vitiosus turns a further rotation; only at that stage, when brain perfusion is hindered by high intracranial pressure, does an inadequate energy supply for the pumping machine come into the picture. There is no evidence at all – and to the physiological rules of osmotic diffusion there should not be any - that pre-existing static cerebral lesions, an infarct or a gliotic scar or a chronic SVT, will have any influence on the osmotic diffusion of water, neither on the transport capacity of ion pumps, as claimed by Prof. Kirkham.

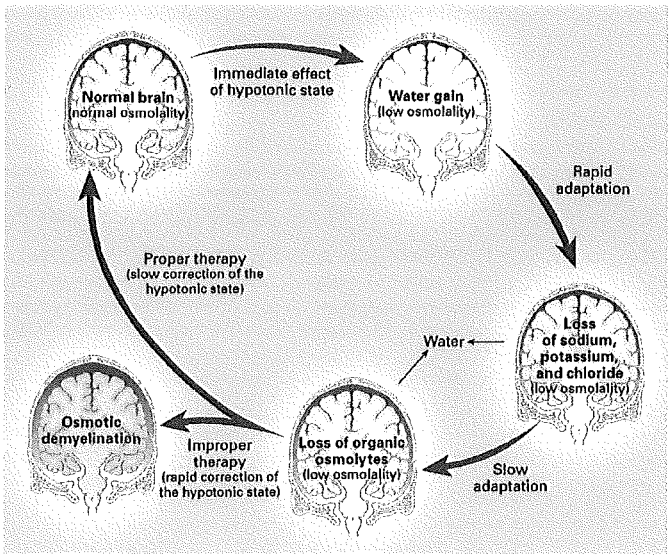

Fig. 4: From - Nathan BR (2007)

Nathan (2007) presented a comprehensive paper on "Cerebral Correlates of Hyponatremia". He stated: "hyponatraemia also activates a regulatory volume decrease. ... Regulatory volume decrease begins with the immediate displacement of water from the brain into the cerebrospinal fluid and then to the systemic circulation, a compensatory event that is driven by hydrostatic pressure. Another early adaptive response is the rapid extrusion of electrolytes, ... and the concomitant loss of somatically driven water from the brain cells. Electrolyte loss begins within minutes of the onset of hyponatraemia and continues for approximately 3 hours. ... In patients with acute hyponatraemia, **the rapid decline in the serum Na+ may overwhelm the adaptive mechanisms** (my emphasis: DR). Thus, acute hyponatraemia is more likely to be symptomatic, even when the decrease in serum Na+ is relatively modest."

In the draft of my first report to the Inquiry I originally wrote (but later on omitted, as I thought it would not fit in the context):

In the early 1970s - and I remember well the furious discussion on that topic - at the Children's Hospital of the Free University Berlin we had some cases that infants after a severe diarrhoea leading to a hypertonic dehydration died in hospital. At that time in our hospital there was no established infusion therapy, what sort of infusion one should give to infants (< 12 months of age) who came to the hospital with an acute loss of about 10 - 15% of body weight or even more and Na+-concentrations of in some cases well above 160 - 165 mmol/l.

I remember well the argument in this discussion that because of the high Na+ concentration one should not give the infants any Na+-containing fluids at all.

The three cases I remember all took the same course: because of the dehydration all children were immediately given an albumin infusion and because of high sodium concentrations an infusion of free water. The clinical status of the children improved substantially during the first 3 - 4 hours. But then they started to go into seizure, went into coma and died. In the neuropathological investigations severe oedema and central myelinolysis were found.

At my hospital a very hard discussion started and it took a lot of time and a lot of calculation to realise that the children had not only a dehydration (loss of 10% of body weight over the last 24 to 48 hours because of the diarrhoea) but although the Na+ concentrations were extremely high they had a severe loss of Na+ too and that they needed a great amount of Na+ intake.

At that time we learned that the problems occur because free water given passed easily and very quickly in cells while there was an active, controlled transport system for the Na+ ions, which needed time. Because of the rapid passive water influx along the gradient in cells, neurons were overinflated, blown up and lost their function.

As a young member of the staff I never will forget this serious and furious discussion when listening to my clinical teachers. We learned some major lessons from the cases at that time:

1. One must strictly and carefully calculate all substrates involved: water, Na+, K+, Cl-, and Na+ bicarbonate, omitting different infusions with various electrolyte and dextroxe concentrations;
2. One must pay attention to the time schedule - one should try to get the high Na+ concentration down, but one has to allow time for this to take place and that the equilibrium should not be achieved within the first 24 hours, but within 48 hours or even longer. As a rough rule of thumb one could only make the mistake of lowering the Na+-concentrations too rapidly, but a child will never come into a critical situation if the Na+ concentrations were not in normal range after 48 hours.
3. Hypotonic dehydration follows the same rules. This was not so difficult to understand as for everyone it was clear and reasonable that the child with a very low Na+ concentration and a loss of 10% of body weight needs a lot of Na-intake too.

Exactly this aspect of what to do in patients with hypernatraemia was touched upon in the discussion on 9 March 2012 (page 39/40).

Since the rapid fall in the sodium concentration of 165 to 145 is osmotically the same as from 135 to 115, the same mechanisms are at work, explaining the same clinical picture in false treatment of osmotic brain oedema in cases of hypernatraemic dehydration and dilutional hyponatraemia.

I think it very unlikely that Adam's case fits the diagnosis of PRES. In my interpretation, the CT scan performed on 26 November - although it cannot exclude PRES - is very untypical for PRES, showing as it does too much generalised brain swelling while in PRES there is most often a localised/focal brain oedema, and very often ventricles are even large and not so small as in Adam's case.

Dr. Anslow, consultant neuroradiologist, described (in comparison to the first CT): *"There has been a dramatic change. The brain has become very swollen. The CSF spaces have become obliterated and the ventricles are much smaller. These changes are severe in the posterior fossa. The cerebellar tonsils have descended through the foramen magnum"* (206-005-111).

The paper by Petrovic et al. (2011) was introduced by Prof. Kirkham. The paper is an overview of the neuroradiological findings in PRES and is designed to give inexperienced people with not much knowledge about PRES a visual impression of the image of PRES in CT and MRI scans. All images given in this article (and in others - see above) are not scans of an acute severe brain swelling as in Adam's case, but rather images of localised oedema with quite of lot of space.

One should be aware of a neat linguistic trick: While Dr. Anslow and Dr. Armour described - neutrally - that the changes in Adam's case were a bit more pronounced in the posterior fossa i.e. in the cerebellum and hence infratentorially - in further statements it shifted from posterior fossa to posterior, which naming smoothly led over to posterior encephalopathy syndrome.

One should bear in mind the fact that the naming came from the distribution of MRI findings in the posterior parts of cerebrum, i.e. the occipital and parietal lobe, localised supratentorially, and not of the involvement of the cerebellum, localised infratentorially. According to the paper by Iyer et al. (2011), at least in children the cerebellum is even less involved in PRES compared to the cerebrum; the same was found by Fungate et al. (2010) in 120 cases of PRES at the Mayo clinic.

I have not found robust data on the velocity of PRES manifestation. Considering the list of underlying diseases I have the feeling, but not the evidence, that it takes some time for PRES to emerge and not the short time that we are discussing in Adam's case. Roth et al. (2011): "The symptoms usually develop quite quickly over a few hours, reaching their worst in 12 – 48 h".

Regarding the prognosis authors stated: "Although PRES can be a severe neurological disease, recovery is the rule" and "As the name PRES implies, brain lesions are reversible. Nonetheless, occasionally poor neurological outcome has been mentioned again and again as being due to conversion from primary vasogenic into cytotoxic oedema. In our prospective follow-up of 25 PRES patients, poor outcome in three patients was due to multimorbidity". The remark of Petrovic et al. (2011) goes in the same direction: "The prognosis in patients

with PRES is variable but is typically considered to be favourable. ... However, in some patients, PRES progresses to ischemia, infarction or death".

I have not found a single case in the literature reporting death in the very first hours after the onset of disease. When pooling the data of Fugate et al. (2010), who described 120 patients with PRES and of Kim et al. (2012) describing 19 cases of PRES in acute childhood leukaemia, no child died, neither it was reported that the patients became life-threateningly ill.

In my first report I was a bit vague about the time at which brain death occurred. After reading the discussions on 22 February and 9 March 2012 and learning that as an expert one is asked to answer to the best of his own understanding of the case, which is a mixture of proven facts and unproven material you extrapolate, I would say that brain swelling set in at around 8 - 9 o'clock, when the great amount of free water was infused. It is much more difficult to judge the time of coning. As the processes of water diffusion start swiftly and the ion-pumping system restarts immediately when the water content in the cells rises, the time will be rather 9:30 to 10 o'clock than 11:30 when he was found to be brain-stem-dead.

I have the impression that this time schedule fits in well with the process of osmotic oedema, and it does not fit in with the assumption that first some other effect will provoke SVT or PRES, leading secondarily to severe brain oedema.

Although exact data are lacking, in my interpretation I have gained the impression that in most cases PRES - not provoked by hypertonic crisis - will not manifest itself within such a short time as one had to concede in Adam's case. On the other hand, the evidence provided by Dr. Coulthard regarding blood pressure during renal operation is convincing. Following this statement

- I have difficulty in accepting that a hypertonic crisis triggered PRES in Adam's case and
- as the given drugs, the blood transfusion, and the anaemia are unlikely to fit in with the time schedule, these explanations brought forward by Prof. Kirkham neither do support the diagnosis of PRES in Adam´s case.

After my reading I will not exclude that even the field of hyponatraemic brain oedema medicine can learn something from the discussion going on regarding the pathomechanisms involved in PRES. Perhaps these discussions will provide a better understanding in finding the point up to which the velocity of the fall of sodium in water or the increase of the volume of free water is / can be compensated, and perhaps they will disclose other, as yet unknown pathophysiological processes in the future.

Nevertheless – we have to remember which are the primary aspects and which the secondary ones. And although Prof. Kirkham brought forward some interesting hypotheses, one has to accept that the very first was far too great a load with free water. This is what provoked the brain cell oedema and triggered the circulus vitiosus.

For me – and in this respect I totally disagree with Prof. Kirkham – Adam would not have died from SVT or PRES if the mistake in the infusion regime had not taken place.

Let's for a moment take the position that Prof. Kirkham might be right with her thesis that it was ultimately PRES or SVT that killed Adam. In that case we have to answer the question – what effect did the overload have that resulted in triggering PRES or SVT??

If Prof. Kirkham is right with PRES, we should remember that the "R" in PRES stands for "reversible" and that the incidence of death in acute SVT is not high – which means that Adam would have stood a good chance of coming out of the operation with PRES or SVT and of still being treated effectively afterwards and surviving.

Section B

Comments on some paragraphs of Prof. Kirkham's expert report.

I think it is the best to go through her statement paragraph by paragraph, giving comments along the way. I refer to her second expert report (208-007-068 to 128), which is an expanded version of the report given before (2008-002-019 to 049).

ad 1. - 2.

No comments.

ad 3.

I could not find any information on "speech therapy" in the folders, but it is reasonable to assume that Adam was seen by a person qualified in feeding, as the feeding problem including swallowing was a important symptom. I got the impression, however, that his feeding difficulties did not reflect any clear-cut neurological dysfunction.

In the reports of nurses on the ward regarding Adam's development, it is said in October and November 1992 - i.e. at the age of 14 to 15 months - that Adam "talks quite well" (055-027-050, 054-045-101, page 17 of my report); this would be impossible in a boy who has neurological dysfunctions leading to the fact that he was unable to suck, drink, or eat.

Furthermore I refer to the witness evidence supplied by Dr. Coulthard, given at the discussions in February / March 2012.

ad 4.

To my reading there is no evidence of epilepsy or epileptic seizures in Adam's file. Prof. Kirkham did not state that Adam suffered from epilepsy; "subcutaneously", however, she expounded a problem of epilepsy without giving facts on it. The same applies to her mention of "rigor". Rigor is an extrapyramidal symptom pointing to

basal ganglia dysfunction - however, the files contain no mention of any basal ganglia symptoms or dysfunction.

ad 5. - 9.

No comments.

ad 10.

Prof. Kirkham stated that *"Adam .. walked at exactly 18 according to the developmental checklist from his general practice notes"* - this note was missing in the papers send to me.
However, in October 1992, i.e. when Adam was at the age of 14, nurses again give the information "walks when supported" (054-045-101), and in November 1992 at the age of 15 months the information "walks well" (055-027-050) is written down. I interpreted this as "walks unsupported", but that perhaps could be a misinterpretation of the files.
As in paragraph 3, Prof. Kirkham's statement of *"limping on his left leg"* on only one occasion in the context of a febrile illness - while Prof. Kirkham is dealing with gross motor development! - is irritating. If this is an attempt to construct an underlying neurological disease, it should be said that this cannot be proven by the data in the files.

ad 11.

I was not able to read these documents. I accept the fact of some speech problems in this child.

ad 12. to 18.

No comments.

ad 19. - 20.

Regarding CVP:

Dr. Coulthard claimed that all the problems were probably due to the fact that the zero calibration was not done sufficiently (200-022-265 and 200-019-228). I disagree with the statement of Dr. Coulthard that the head-down position would not be of any harm. He is right in his statement that *"cerebral "oedema" differs in its pathophysiology from generalised oedema in that it consists of an accumulation of water within cells, and not an excess of extra-cellular interstitial water. This means that, unlike generalised somatic oedema, it is not affected by gravity, and will not "pool" in dependent tissues"* (200-020-243). However, intracranial pressure is a summary of the pressure built up by the volume of brain cells **and** the volume in arterial / venous vessels as well as in the subdural space. These volumes are altered by position. The same view is expressed in the paper of Brosnan et al. (2008) (204-012-387), which was introduced at the Inquiry by Dr. Haynes.

I agree with the statement of Dr. Haynes that *"Numerous central venous lines had been placed in Adam ... it is my opinion ... that there was some narrowing of the great veins draining his head and neck (but) I am abso-*

lutely certain that the CVP reading obtained during Adam's operation could not be relied on either as an absolute number or as a trend monitor ... I do believe it likely, purely because Adam because of the number of venous drainages inserted during his life, that Adam had some vulnerability of the venous drainage of his brain - which might have only become significant once cerebral oedema ... begun to develop. I do not believe that obstruction to venous drainage of the brain was the primary event initiating the cerebral oedema." (204-013-395). And regarding the "head-down position during operation - "Head-down positioning will cause an increase in intracranial pressure and result in a decrease in cerebral perfusion pressure" (204-013-396) – this statement coincides exactly with my opinion and which I tried to express in my first report. In weighing the impairment of brain perfusion by head-down position against the impairment by hyponatraemically driven oedema, the head-down position is merely a minor factor and of little importance

ad 22.

No comments.

ad 23 - 24.

I refer to the extensive calculations of Dr. Coulthard, Dr. Haynes, and Prof. Gross. For me it is beyond all doubt that the boy got too much free water in too short a time.

ad 25 - 27.

No comments.

ad 28.

It was the interpretation in my first report that the slow increase of blood pressure starting at about 9:30 was probably a reaction to compensate the reduced perfusion of the brain due to developing intracranial pressure.

Prof. Kirkham's interpretation is that first the blood pressure increased and afterwards, due to high blood pressure, PRES (in this case - as hypertonic encephalopathy) occurred.

Dr. Coulthard stated that the time and magnitude of blood pressure in Adam's case was typical seen and is especially wanted during renal transplantation, as the adult-donated kidney is not used to the low blood pressure in children.

I can accept this statement and withdraw my original statement.

In my view, the time course is difficult to match with the assumption of provoking PRES - as Prof. Kirkham stated - by

- rising blood pressure ~ 9:35
- blood transfusion - starting ~ 9:30 first 250 ml; 10:30 second 250 ml
- methylprednisolone - given at 10:30 (protocol 22.02.12 - page 52)

It was agreed that Adam was found to be coned at 11:30 at the end of operation (protocol 22.02.12 - page 52).

If blood transfusion to PRES or SVT is mediated by pressure and increase in corpuscles, then the risk of provoking PRES / SVT will lay at the end of the transfusion time, i.e. about 11 o'clock. The same would be true regarding the administration of methylprednisolone - I have not found any data, but to my understanding again the time is too short to find Adam coned at 11:30. For all immunologically triggered cases of PRES, from my reading I gained the impression that it takes days and not hours for the manifestation of PRES, although data are weak / missing.

I have not found any evidence to discuss the possibility of seizure during operation - this is a mere hypothetical question, however much it is needed by Prof. Kirkham to come to the diagnosis of SVT or PRES. I can only accept the statement that seizures in anaesthesia are hard to recognise.

ad 29.

To my reading of the files, Adam did not suffer from any cardiac problems. Dr. Haynes, who works in the field of paediatric cardiology, did not mention any cardiac problems in Adam.

Maybe it is my English, but I did not understand the sentence that some cardiac dysfunction - although I think that were none present in Adam - will reduce "the ability to compensate by increasing blood pressure acutely in response to seizure or intracranial pressure waves".

If this line of argument goes in the direction that

- there was a seizure / seizures during operation,
- seizures in an anaesthetised patient, however, can only be detected by an increase of blood pressure,
- but Adam's blood pressure could not rise because of a poor cardiac function,
- and hence that seizures could not be detected

one should bear in mind that this is mere speculation.

Up to the time of the operation, nobody claimed that Adam was not capable of bearing physical strain. The line of argument of a lack of pressure increase (due to cardiac problems) for the detection of seizures is furthermore strange, since Prof. Kirkham reported an increase in blood pressure at that time and afterwards; ultimately blood pressure drugs had to be given to control hypertonic blood pressure because of the increase.

ad 30. - 35.

No comments.

ad 36.

While Prof. Kirkham correctly described that *"Dr. Anslow has noted that the changes were particularly severe in the posterior fossa"* there is a shift to *"The keeping with the development of acute cerebral oedema particularly involving* ***posterior*** (my emphasis: DR) *cerebral structures .... but posterior reversible encephalopathy syndrome .. cannot be determined without further neuroimaging"*.

I only want to pinpoint the fact that Dr. Anslow did not made the diagnosis of a PRES – he only described the impression that it was most prominent in the posterior fossa !! – i.e. cerebellum (see my remarks to imaging in Section A - PRES). In PRES the supratentorial involvement of the posterior parts of cerebrum, i.e the supratentorial location of occipital and parietal lobes, is much more often to be seen as an infratentorial involvement of cerebellum or brainstem.

ad 37. - 41.

No comments

ad 42.

Prof. Kirkham cited the paper of Chawla et al. (2011): "*Chawla et al. found that mortality was higher in those with moderate compared to profound hyponatraemia 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*" (–italics by Prof. Kirkham).

Alhough the title of this paper is very suggestive, it did not make any new impact on the discussion of Adam's case, since the authors did not deal - and because of the design indeed could not deal - with the most important parameter, i.e. the time course of the development of hyponatraemia due to the lack of data. Most of their patients have had chronic diseases, even disease in end stages, therefore chronic hyponatraemia is very likely in most cases. The authors only once used the phrase "acute hyponatraemia" when they wrote "It is well accepted that acute hyponatraemia itself can be lethal if it is not treated promptly". They did, however, add "and that overcorrection of hyponatraemia can cause potentially fatal neurological sequelae" – again, as in many other papers cited by Prof. Kirkham or in others (e.g. Stiefel et al. 2007 under the heading of "Perspectives in Acute Hyponatraemia" reported a case of chronic hyponatraemia, as the girl described drunk 5 – 7 l of free water for several days before she became symptomatic), the fault lies the failure to differentiate between acute and chronic hyponatraemia.

In my interpretation, the paper of Chawla et al. did not add any real information to Adam's case; in particular, the paper is not at all an argument against the hypothesis of a critical brain oedema due to too rapid infusion of too much free water.

The two cases in the paper by Boetzkes et al. (2010) mentioned by Kirkham deserve consideration: the first case - although authors spoke of "an acute dilutional hyponatraemia" - is a classic case of chronic hypona-

traemia as it was provoked by adding a new drug in the treatment of enuresis (oxybutynin) to an ongoing treatment with desmopressin, provoking hyponatraemia over days.

The other case is that of a 12-year-old boy who was "forced" to drink 4 l of water in about one hour; the boy developed headache, nausea, and vomiting; his consciousness deteriorated leading to switching of phases of agitation with lethargy. His sodium was determined at 120 mmol/l. A "computed tomography scan of the brain .. did not reveal abnormalities". This case is quite different from Adam since this boy - although it is not written down in the paper, but it can justifiably be assumed - had had normal renal function and therefore could react to water overload. The time at which the scan was performed is not given; therefore no further speculations are possible in this case.

ad 43. - 44.

The group of D. Bohn (Hospital Sick Children Toronto/Canada) published two papers (Halberthal et al. 2001 and Hoorn et al. 2004) which deal with the problem of iatrogenic hyponatraemia in children's hospitals. Only in their second paper did the authors report the fact that 30% of those children from the 2001 paper were seen with "an acute hyponatraemia (occurring) within 48 hours ... there was a 30% adverse outcome rate death or neurologic injury". Both papers are not very informative for Adam's case, as due to the retrospective design the authors could not give exact details on the time course of hyponatraemia, focussing instead on the problem of how often the hyponatraemia was induced inside hospitals and by which mechanisms.

I again got the impression of a biased reception of papers when Prof Kirkham reported on frustrated attempts to contact authors to get information on the *"precise nature of the hypotonic fluid given"* but did not report the details that "the second patient (fall in PNa of 13 mmol/L from 142 to 128 mmol/L within 1.5 hours) had a cardiac arrest. Although she was resuscitated initially, she ultimately died. Post-mortem examination revealed brain cell swelling" (Hoorn et al. 2004).

ad 45.

No comments

ad 46.

I cannot agree to Prof. Kirkham's summary of the paper of Arieff et al. (1992) "*the patients in Arieff's series had pre-existing risk factors for central nervous system disorders, including apparently minor trauma and orchidopexia (undescended testes are common in neurological disorders) or risk factors for pre- and /or post-operative hypoxia (tonsillitis, adenotonsillectomy, pneumonia)*" - this is mere speculation.

Furthermore I would like to clarify at this point that most of Prof. Kirkham's arguments describe only **associations.** Arieff et al. listed the diagnoses, operations etc., which were known resp. performed in these patients, to provide some background information on the cases. This list, however, does **not prove any causal relationship.**

Prof. Kirkham's line of argument suggests a causal relationship of pre-existing chronic neurological problems or of accidental brain trauma/lesion by accident or of intraoperative hypoxia in all the patients who developed hyponatraemia and came to death inter alia by respiratory arrest due to coning. However, it should be clear that this is only a speculation, some sort of an initial suspicion, nothing more.

ad 47.

I again got the impression of a biased citation when Prof. Kirkham reported case 2 of Boetzkes (2010) patient when writing *"In Boetzkes' second case, a boy who drank 4 liters of tap water in an hour* (Boeztkes et al. wrote - "in approximately 1-hour time - DR) *and in who dilutional anaemia was diagnosed, the haematocrit was 33% , .. when lower limit of normal at this age is 35%"* (Prof. Kirkham). Boetzkes et al. reported their "reference range 37% - 49%)".

ad 48. - 51.

No comments.

ad 52.

Maybe my comment is not fair - but for the overwhelming majority of clinical papers Prof. Kirkham's statement will be true that patients are reported *".. in whom the diagnosis of venous sinus thrombosis was not considered"*.

ad 54.

No comments.

ad 55.

Maybe this paragraph most clearly demonstrated the totally opposing views of Prof. Kirkham on the one side and Dr. Coulthard, Dr. Hayes, Prof. Gross and myself on the other – when Prof. Kirkham suggested that *"a simple way of reviewing the reported cases of hyponatraemia associated with hypotonic fluids is to dive in those with*

a. Pre-existing central nervous system disease
b. Risk factors for hypoxia
c. Risk factors for venous thrombo-embolism 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 sinus thrombosis and posterior reversible encephalopathy syndrome."

This classification lacks the very first and most important criterion for the time course of the fluid overload, which marks the first and principal split. It is senseless to compare the outcome in a case in which dilutional hyponatraemia to, say, 120 mmol/l was provoked in one hour or 24 hours. To my view Prof. Kirkham missed the central point in Adam's case, ignoring the time factor throughout her entire statement.

This classification (dated 28 March 2012) is insofar most impressive as the timing of the fall of sodium was a prominent feature in all discussions in which Prof. Kirkham was involved at the Inquiry on 22 February and 9 March 2012.

ad 56.

Again - it is not a fact of whether 4% or 5% dextrose or 0.18% saline was used - it is a matter of the calculation of free water and electrolytes to be given in time, irrespective of any mixing up different sorts of infusion solutions.

ad 57. - 61.

No comments.

ad 62.

As I do not have the report of the speech therapist in Adam's case, I cannot make any comment in this regard. I am, however, very sceptical as to whether the difference between "verbal abstraction difficulties" and "expressive language delay" is so specific to distinguish the groups prone to sinus venous thrombosis or not - or why did Prof. Kirkham make this point??

ad 63.

Again, as I do not have the report of the speech therapist I cannot argue on this point.

I have not, however, found any report in the files that Adam was drooling - a very obvious symptom in children having difficulties with swallowing on a neurological basis, especially when it is classified as a "bulbar dysfunction". As these children have difficulties in swallowing own saliva, they drool all the time, often wearing nice but always wet ties. This is not reported in the files for Adam, therefore I question the neurological basis of poor drinking. It should be mentioned that there were no reports in the files of other symptoms of a *"neurological disorder affecting bulbar function"* as assumed by Prof. Kirkham.

The most important remark comes perhaps from Dr. Coulthard reporting on his experience of feeding difficulties in the end stage of renal failure on peritoneal dialyses (page 61-64); this is a further major point against the assumption of a pre-existing neurological disorder.

ad 64. to 65.

I refer here to my remarks in Section A on PRES and SVT.

ad 66.

Prof. Kirkham summarised the paper of Moritz and Ayus (2005): *"while retinal haemorrhages do not appear to have been documented in fatal cerebral oedema associated with hyponatriaemia"*. However, no such statement was made by Moritz and Ayus. Authors listed "Papilledema" in their "Tabl. 3 Clinical symptoms of hyponatremic encephalopathy". The occurrence of retinal bleeding is a question of the time and degree of intracranial pressure. To my understanding of neurology, it is a misinterpretation of the paper of Moritz and Ayus when retinal bleeding (seen in Adam) was said to be *"characteristic"* (Prof. Kirkham) for hypertensive encephalopathy, but not for "fatal cerebral oedema associated with hyponatraemia" (Prof. Kirkham).

ad 67. to 68.

I refer here to my remarks in Section A on PRES and SVT.

ad 69.

When Prof. Kirkham raised the question: *"if Adam developed any primary cerebral problem such as PRES and/or CVST, during 26-27 November, he would have been at risk to hyponatraemia secondary to compromise of the cellular sodium pumping mechanism, which requires energy, as well as antidiuretic hormones secretion"* - one has to state that this line of argument turns the pathophysiological mechanisms as well as the events which took place in the operation theatre upside down (see Section A). The primary event and mechanism was a heavy overload with free water. This was first.

ad 70.

I am very astonished that Prof. Kirkham did not deal at all with the pathomechanisms of an acute overload with free water and the mechanisms at brain cell levels, but discussed in a very sophisticated manner the impact of not-assured seizures on cerebral blood flow, brain perfusion and/or intracranial pressure.

ad 71.

With this paragraph and stating that she was *"not able to find any literature supporting the notion that the rate of fall of sodium is critical in causing cerebral oedema"* Prof. Kirkham demonstrated that she is not willing to deal with the rules and pathomechanisms of osmotic diffusion in the human body; furthermore she merely ignored the witness evidence supplied by Prof. Gross, Dr. Coulthard and Dr. Haynes and the impact of their work to understand cerebral oedema in Adam's case.

ad 72.

I disagree with the statement that *"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"*.

The false argumentation is due to the fact that Prof. Kirkham denied the most important influence of the time course of the fall of sodium (208-007-099). Prof. Kirkham is correct in stating that ion pumps need energy,

and when energy supply is missing ion pumps will become ineffective or indeed will cease to function. However, if the water overload is high enough ion pumps in brain cells are not able to prevent swelling of brain cells. While in other organs the swelling of cells after the water overload does not lead to major problems, due to the rigidity of the skull the intracranial pressure on the brain will increase markedly.

ad 73 to 75.

No further comments.

ad 76.

I suggest that Dr. Squier be asked whether the neuropathology in Adam's case

- is in line with an increased intracranial pressure and furthermore
- whether she can exclude with certainty that Adam died as a result of increased intracranial pressure.

I ask this so specifically since all of Dr. Squier's statements were the other way round - she was always asked to comment on the likelihood of SVT and PRES. To my reading of Adam's files - although I have not found a comprehensive neuropathological report - what is seen in Adam's brain is brain oedema and not PRES (or hypertonic encephalopathy) and not peracute SVT.

ad 77.

I refer here to page 38/39 of my first report.

ad 78. to 81.

No further comments.

ad 82.

According to the principal mechanism of Adam's fatal course on the basis of osmotic oedema, the administration of cyclosporin at 11:55 does not add anything. The brain at this time was already coned.

ad 83. to 87.

No further comments.

To summarise:

1. The suggestion of chronic SVT is mere hypothesis.
2. It is not proven at all that a seizure occurred during surgery. The event of a seizure in an anaesthetised patient is a rare - but to be fair, not fully - investigated situation. However, the assumption of a seizure during surgery is mere hypothesis brought forward only to support the thesis of PRES and / or acute SVT.
3. CT and neuropathology for my reading fit in much better with an osmotic oedema than with PRES.

4. Under the premises that published data

   a. speak against such a severe progression that patients come to death within the space of two to three hours;

   b. prognosis is reportedly excellent in most cases, favourable in the majority, and in most patients who died this was because of the underlying disease;

   c. CT in Adam's case is not typical at all for PRES (although with CT one cannot exclude the possibility of localised vasogenic oedema);

   PRES can be excluded as the cause / reason in Adam's case.

5. The suggestion of an acute VST is mere hypothesis, although I can admit that an acute SVT can kill a child during an operation within a short time. All the same, I have my doubts that pathologists / neuropathologists performing brain section in an autopsy can overlook the fact that the death of a person is due to an acute, fulminant SVT, severe enough to kill him/her within the space of two to three hours.

6. For these reasons and on the probabilities of balance it is my view that the brain death of Adam was due to the overload of the body with free water in too short a space of time, provoking an osmotic oedema according to normal physiological rules and ultimately leading to brain death.

7. The CVP, perhaps higher as normal, and the head-down position might have had some influence on intracranial pressure; this influence is, however, much lower-ranking than the rise in intracranial pressure provoked by osmotic oedema. The minor effect of these factors would not have brought Adam into any critical and life-threatening situation.

8. Given that there was no false infusion regime or no overload with free water the child would have not died due to

   a. a fall in hemoglobin or of anaemia at least partly provoked by the wrong infusion or
   b. blood transfusion or
   c. medication with methylprednisolone or
   d. medication with cyclosporine or
   e. a combination of those factors.

   Although all these drugs and transfusions were given and the fall of hemoglobin occurred, the boy would have survived.

Sincerely yours

D. Rating

Prof. Dr. D. Rating

References:

1. Barnett HJ, Hyland HH (1953) Noninfective intracranial venous thrombosis. Brain 76: 36-49
2. Boetzkes S, et al (2010) Two Unusual Pediatric Cases of Dilutional Hyponatremia. Pediatr Emer Care 26: 503 -505
3. Brosnan et al (2008) Effects of head-down positioning on regional central nervous system perfusion in isoflurane-anaesthetized horses. Am J Vet Res 69: 737-43
4. Coulthard MG, Crosier J et al. (2002) Outcome of reaching end stage renal failure in children under 2 years of age. Arch Dis Child 87: 511–517
5. Chawla A et al. (2011) Mortality and serum sodium: do patients die from or with hyponatraemia? Clin J Am Soc Nephrol 6: 960-965
6. Fugate JE, Claassen DO, Cloft HJ et al. (201O) Posterior Reversible Encephalopathy Syndrome: Associated Clinical and Radiologic Findings. Mayo Clin Proc 85: 427-432
7. Halberthal M, Halperin ML, Bohn D (2001) Acute hyponatraemia in children admitted to hospital: retrospective analysis of factors contributing to its development and resolution. BMJ 322: 780-782
8. Hefzy HM, Bartynski WS, Boardman JF et al. (2009) Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. AJNR 30: 1371–1379
9. Hinchey J, Chaves C, Appignani B et al. (1996) A reversible posterior leukoencephalopathy syndrome. N Engl J Med 334: 494– 500
10. Hoorn EJ, Geary D, et al. (2004) Acute Hyponatremia Related to Intravenous Fluid Administration in Hospitalized Children: An Observational Study Pediatrics: 113: 1279-84
11. Incecik F, Hergüner MO, Altunbasak S et al. (2009) Evaluation of nine children with reversible posterior encephalopathy syndrome. Neurol India 57: 475–478
12. Iyer RS, et al. (2011) Medication neurotoxicity in children: Pediatr Radiol 41: 1455–1464
13. Kim SJ, Im SA et al (2012) Predisponing factors of peosterior reversible encephalopythy sancrome in acute childhood heukemia Pediat Neurol 47: 436-442
14. McKinney AM, Short J, Truwit CL et al. (2007) Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJR 189: 904–912
15. Nathan BR (2007) Cerebral Correlates of Hyponatremia: Neurocrit. Care 06: 72–78

16. Petrovic et al. (2011) Posterior reversible encephalopathy syndrome and venous thrombosis. Radiol Clin N Am 49: 63-80

17. Roth C, Ferbert A (2011) The posterior reversible encephalopathy syndrome: what's certain, what's new? Pract Neurol 11: 136-144

18. Staykov D, Schwab S (2012) Posteriores reversibles Enzephalopathiesyndrom: Nervenarzt 83: 1013-1020

19. Stiefel D, Petzold A H2O Coma (2007) Neurocrit Care 6: 67-71

20. Ugurel MS, Hayakawa M (2005) Implications of post-gadolinium MRI results in 13 cases with posterior reversible encephalopathy syndrome. Eur J Radiol 53: 441–449

Prof. em. Dr. Dietz Rating

Ehem. ärztlicher Direktor der
Kinderheilkunde V
(Schwerpunkt: Kinderneurologie,
Epilepsie-Zentrum und Sozialpädiatrisches Zentrum)
Zentrum für Kinder- und
Jugendmedizin
Universität Heidelberg

Heidelberg, den 25.11.2012

Prof. Dr. D. Rating

[redacted]

To
Inquiry into Hyponatraemia Related Deaths
Arthur House
41 Arthur Street

Belfast BT1 4GB Zeiten Frei 6; Sams 8, Sonn 6, Mon 2 Donne 2, Frei 6, Sa 6, So 6

UNITED KINGDOM

Reg.: Strain, Adam
born on 14 August 1991

I read the reports of Dr. Squier regarding Adam´s case.

1. To my reading the reports do exclude a severe and acute SVT leading to death within the space of 1 to 2 hours time.
2. In PRES (as PRES stands for reversible and patients recover) only few information are available on the neuropathology. Therefore the report could neither prove nor reject the diagnosis PRES. I would like to ask Dr. Squier while there are quite substantial neuropathological changes whether these findings are more in favourite or against the diagnosis of PRES.
3. Dr. Squier could not prove the diagnosis of an osmotic oedema. I would like to ask Dr. Squier which influence time schedule will have on the neuropathological findings in a case
    a. when oedema developed so quickly that death occurred in 2 - 3 hours time
    b. when a child after 8 to 10 hours came to death.

    This is the question which time is needed to see the characteristics of myelinolysis. It should be taken in mind that these changes where most pronounced in the pons.

    To my reading and understanding the report is consistent with an acute osmotic oedema.

Prof. Dr. D. Rating