This is a report by

Dr Malcolm Coulthard

requested by the *Inquiry into Hyponatraemia-Related Deaths*

in response to the document by Professor Kirkham, 16/02/2012

20/02/2012

What is PRES?

First, you need to understand what hypertensive encephalopathy is ...

Children with kidney disease are at serious risk of suffering from raised blood pressure (hypertension) for a number of reasons, including producing an excess of the kidney hormone renin, and being liable to becoming overloaded with fluid as they lose control of regulating their body's water balance. This has been known for some decades; as it happens, Dr Savage was the first author on an important paper which drew attention to this in a common kidney scarring condition nearly 40 years ago.[1] Unlike adult patients, where hypertension is relatively common due to a range of causes, hypertension in children is due to a kidney cause in approximately 90%; severe hypertension in childhood is rarely due to any other causes.[2]

For this reason, children presenting with symptoms of hypertension are almost universally referred to paediatric nephrologists for diagnosis and management. Sometimes the drugs used by paediatric nephrologists can compound the risks of children developing hypertensive encephalopathy too, such as the immunosuppressive drugs in the calcineurin inhibitor class (cyclosporin and tacrolimus), high doses of steroids including methyl prednisolone, and the over-use of the hormone erythropoietin such that it causes polycythaemia (the opposite of anaemia). These risk factors are well understood by paediatric nephrologists, and their use is generally highly judicious.

... and its signs and symptoms ...

Severe hypertension may appear suddenly in at-risk children, whether or not they have had suffered from milder hypertension. It then has a high risk of leading to an alteration of the brain functioning (hypertensive encephalopathy). The signs and symptoms of this are well known to paediatric nephrologists – managing such cases is one of their areas of special expertise. The symptoms and signs of children with a severe onset or exacerbation of hypertension include the following[2] –

- Severe headache (almost universal).
- Nausea and vomiting (very common).
- Visual disturbances (less common, but of major concern as it may result in sudden blindness[3] associated with haemorrhages and exudative changes to the retinas).
- Impaired conscious level or coma.
- Fits.

... and its treatment ...

The most important element of treatment is to promptly and accurately recognition the hypertension, and to control it appropriately. Recognition frequently presents a major difficulty for a number of reasons. Blood pressure is not always easy to measure precisely in children, and is often not carried out in situations where it would routinely be done in adults.[4] Just as importantly, the normal range of readings is much lower in small children than in adults, so severe hypertension sufficient to cause an encephalopathy in a child can occur at pressures that are seen commonly among well older people. Due consideration must always be given to the possibility that another cause of encephalopathy may occur in parallel in a child with a renal condition: these are discussed in a chapter I co-authored.[5]

The method of controlling the blood pressure is also vitally important. This is because if high blood pressure is sustained for a long period, changes occur in the small blood vessels in the brain which take a day or two to reverse. Thus, children who have a known background of a normal blood pressure, and who then present with any of the above symptoms and are found to be hypertensive, will tolerate their blood pressure being rapidly reversed, and this is the ideal treatment. By contrast, children whose prior blood pressure status is not known (for example, children who are first seen with the above symptoms due to hypertensive encephalopathy) could have had sustained hypertension, and there would be a high risk to the blood supply to the brain if the blood pressure was lowered quickly, before the tiny blood vessels in the brain tissues were able to open up sufficiently. Thus, particular regimens are used to gently lower the blood pressure in a tightly regulated way over about 4 days.

... and why acute brain scanning is not useful when children suffer from it ...

When all of these management protocols were being worked out, the immediate and intensively informative methods of imaging (scanning) the brain were not available for urgent paediatric clinical use. That is, paediatricians in general, and paediatric nephrologists in particular, did not include CT or later MRI imaging of the brain as a useful diagnostic test to use in children presenting with hypertensive encephalopathy.[2]

Brain scans are still used very infrequently in the acute clinical setting because the diagnosis is usually obvious without doing so, and the extremely careful management required to control the blood pressure is not aided by having to move the child to an imaging suite for no obvious benefit. Most paediatric nephrologists would only consider undertaking a brain scan at a later date in children who sustain permanent sequelae of their encephalopathy, to establish a plan for further management. Though permanent damage (and even death) may occur as a result of hypertensive encephalopathy, acute episodes of severe acute hypertension are very commonly seen by paediatric nephrologists, and most children have their encephalopathy prevented, or if it occurs most make a full recovery, and do not receive brain imaging at all.

And how does PRES fit into this?

The initial recognition of PRES Dr Hinchey and colleagues in the Department of Neurology in the New England Medical Centre in Boston were interested in identifying different brain imaging patterns that they were beginning to recognise on clinical CT and MRI scans during the years 1988 to 1994. In 1996 they published a report of 15 patients they had identified in a retrospective trawl who had had a particular pattern of change to the white matter of their brains while suffering from functional brain disturbances (encephalopathy). They noticed that these patients had feature in common and defined the condition as a reversible posterior leukoencephalopathy syndrome.[6] This term has been changed by subsequent authors to the posterior reversible encephalopathy syndrome, or PRES.[7]

All of their patients were adult apart from a 15 year old girl who developed puerperal eclampsia, a complication of pregnancy associated with severe hypertension. About half had underlying kidney conditions associated with high blood pressure. All were hypertensive, typically with sharp rises in blood pressure at the time, and all were encephalopathic. They described exactly the same range of symptoms, and in similar proportions, to those I have listed above for hypertensive encephalopathy. All were successfully treated by having their blood pressures reduced, either with hypotensive (blood pressure reducing) medication alone, or this combined with the withdrawal or reduction in dose of their calcineurin inhibitors which are known to increase the blood pressure, and which may also increase the impact of hypertension on the brain. All the patients made a full recovery, and in all of those who had their brain scans repeated at follow up, it was normal.

It seems very clear that these authors were in fact identifying the imaging abnormalities that are associated with acute hypertensive encephalopathy. They themselves appear to say as much in the final paragraph of their paper –

> *The cause of the reversible posterior leukoencephalopathy syndrome is multifactorial. The syndrome should be promptly recognized, since it is reversible and readily treated by controlling blood pressure and discontinuing the offending immunosuppressive agent or decreasing the dose. The mechanism of the syndrome is probably a brain-capillary leak syndrome related to hypertension, fluid retention, and possibly the cytotoxic effects of immunosuppressive agents on the vascular endothelium.*

However, instead of calling their paper a description of the acute brain scan changes seen in hypertensive encephalopathy, they defined PRES as a separate syndrome.

It is interesting to speculate why these authors took this decision. One important clue may come from comparing the blood pressure readings of some of the individual patients they describe, and in particular from the fact that the levels from the 4 they label as having hypertensive encephalopathy overlap with the other cases who they give other diagnoses to. It is certain from this, and the fact that

they do not give any diagnostic thresholds for categories of hypertension, that they are not defining whether patients have hypertensive encephalopathy by their blood pressure levels, but are presumably merely reporting the clinical diagnosis that had been made at the time, in this retrospective study of imaging and case-notes.

For example, the 4 patients labelled as having hypertensive nephropathy all had primary renal diagnoses (2 with SLE, 1 with acute nephritis, 1 with hepatorenal syndrome), and had are therefore likely to have been under the care of nephrologists, who are very familiar with this label. However (and particularly relevant to this report), a 36 year old woman who developed seizures and confusion at the time of her kidney transplant had an extremely high blood pressure at 210/110 mmHg, but is not labelled as having hypertensive encephalopathy. And this is despite the fact that her blood pressure was higher than those that were labelled this way.

... or to summarise ...

I argue that the first description of PRES was made by a team of neurologists who identified what the acute scanning pictures of patients' brains looked like while they were experiencing hypertensive encephalopathy, but who presented their findings as if they had described a new clinical syndrome. It was as if they had discovered a new illness rather than describing what the brain looked like in a well known one.

Subsequent publications about PRES ... have confirmed the fact that it is a benign[7-9] 'clinicoradiological entity',[7-9] by which they mean that it is a diagnosis based upon typical CT or MRI brain scan images in a patient with an acute rise in blood pressure,[7-9] who also has the spectrum of symptoms associated with hypertensive encephalopathy. They agree its mechanism or common pathway is a surge of blood pressure, and its management is the rigorous control of that blood pressure.[7-9]

It is interesting that these authors continue to talk about PRES as if it is a definite syndrome or entity, rather than what they have actually shown it to be, which is the imaging associated with those cases of hypertensive encephalopathy where the clinicians have considered it helpful to undertake a brain scan. It is also interesting to note that the authors of one of these papers lament the fact that "paediatricians seem to be less familiar with this condition". It appears that these authors have not realised that paediatricians (and paediatric nephrologists in particular) are all too familiar with managing hypertensive nephropathy, but have not engaged with making the diagnosis of PRED because it is little more than an academic exercise which does not benefit the children or add to their management in any way. They already know that their role is to manage children's blood pressure meticulously – seeing a picture of the brain does not help.

Did Adam Strong have PRES?

The simple answer to this is no. He did not have a headache, fits, altered consciousness or any visual disturbances before he went to theatre. His blood pressure was meticulously maintained throughout, without any peaks or sudden increases. It is not possible to diagnose if a child might have 'potentially' had any of the symptoms of headache, fits or visual disturbance while he was maintained therapeutically asleep, pain free, and paralysed. To suggest that 'he may have done' is entirely speculative.

To focus a little closer on his blood pressure management, the ideal for a child receiving a transplant is complicated because normally it is ideal to keep their levels normal for their age, but at the end of the operation it is theoretically ideal for it to also be as high as the donor's levels so that the new kidney is provided with the pressures it has been used to, before allowing it to adapt to the child's blood pressure over a few days. For that reason, it is common to support the blood pressure artificially a little early on in the anaesthetic, and then to try to keep it somewhere between the child's normal levels and the level that the donor was likely to have had, but not high enough to risk inducing an encephalopathy in the child. The trace on 058-008-023 demonstrates a very good example of exactly this, and is therefore typical of the blood pressure changes that young transplant recipients are normally exposed to.

Did Adam have cerebral venous sinus thrombosis?

What is cerebral venous thrombosis?

Some of the blood that drains from the brain flows into relatively large vessels, the dural venous sinuses. There is a risk that the venous blood within them may thrombose (clot) and lead to cerebral venous thrombosis. This may then lead to headaches and malaise which may be acute or chronic, and also to symptoms that are similar to a stroke (which is usually due to a problem with the arteries supplying the brain, rather than the veins draining them).

How common is it, and how does it present?

Cerebral venous thrombosis is rare in childhood. It is seen most commonly in babies as a consequence of problems around the time of birth, and when it is seen in older children it may be caused by them having an inherited disorder of their blood clotting mechanisms, or of them having an infection of a part of the head close by which drains its blood into the sinus system (such as a severe infection around the eyes).

Another potential risk factor for cerebral venous thrombosis which may occur in children with kidney disease is the presence of very severe dehydration (when the blood flow through the sinus may become extremely sluggish). This is probably relatively common world-wide; severe dehydration is a common terminal event in malnourished children who develop diarrhoea in the absence of medical facilities. However, in the UK it is exceptionally rare, and is more often described in severely nephrotic children (who have a major propensity to develop thromboses through losing clotting factors into their urine) who are allowed to remain in a state of prolonged, severe intravascular hypovolaemia (acute shortage of circulating blood) due to the rapid loss of albumin into the urine. I have personally treated literally hundreds of episodes of acute hypovolaemia in nephrotic children during my career, and have seen just 1 child who was probably developing cerebral venous thrombosis (but who, happily, recovered fully after treatment with intravenous heparin).

Was Adam at special risk?

In my opinion, it would be an exaggeration to consider a child to be at significant risk of cerebral venous thrombosis simply on the grounds that s/he had some theoretic risk factors present. When Professor Kirkham suggests that Adam was such a child, the evidence she cites is as follows:

I. Adam had some “rather subtle neurological problems” which she feels are otherwise explained, and for which she feels that “on the balance of probabilities , chronic venous sinus thrombosis is a likely cause”.

II. He was on erythropoietin (though still anaemic).

III. His polyuria put him at risk of dehydration.

IV. He was given a bolus of methyl prednisolone during the transplant operation.

V. The venous drainage from his neck was obstructed by the combination of previous venous access to his neck, and the presence of a central venous catheter during the transplant operation.

VI. The fact that he had iron-deficiency anaemic at the time of his transplant surgery.

I will consider each of these in turn for Adam:

Point I: his “rather subtle neurological problems”
Professor Kirkham lists some background neurological problems which she does not feel are explained by some of the common and well recognised causes, such as birth difficulties, etc. These are essentially the facts that he “had severe feeding difficulties and expressive language delay” but

no “neuroimaging or post mortem evidence of an underlying cerebral abnormality”. She also indicates that at the age of 4 he was noted to “need input to improve his attention”.

What Professor Kirkham appears to have completely ignored is the fact that Adam had renal failure all of his life, which had become end-stage in his pre-school years. These are more than theoretical risk factors for subtle (and sometimes not so subtle) alterations to developmental delay; they are the real, clinically and socially important everyday experience of doctors, nurses and psychologists that work in paediatric kidney units. This is extensively documented. Children with chronic renal failure have long been known to have significant developmental delay, and that this worsens as they reach the point of requiring renal support.[10] Having chronic renal failure and requiring dialysis both lead to delay, whereas successful transplantation tends to reverse this, though not completely.[11] There is evidence that we are getting better at looking after small children on dialysis in that their cognitive and psychological outcomes are improving, but they are still far from being normalised.[12] It is a normal part of counselling parents of young children with renal failure that such difficulties can be anticipated.

It may be of interest to the inquiry that our department in Newcastle undertook a study of children reaching end-stage renal failure at a young age in the UK and Ireland during the decade 1988 to 1997 inclusive, which of course included the children in Professor Savage’s department, and which illustrates the ranges of developmental outcome that might be expected for them.[13] Of 105 surviving children that were old enough to assess in this regard, 91 did or were expected to attend a normal school, but 16 of these required the support an individual extra classroom helper. Fourteen children attended special schools, 11 for their developmental and emotional needs, and three for physical reasons.

In summary, Adam’s developmental status was entirely to be expected for a child of his age with renal failure, and probably milder than average. To suggest that these “rather subtle neurological problems” were remotely likely to be evidence of chronic cerebral venous thrombosis would have been unfounded in his circumstances, and they were certainly not the most likely explanation “on the balance of probability”.

Points II and VI: being on erythropoietin and having iron-deficiency anaemia
Professor Kirkham lists these 2 points as separate and apparently independent risk factors for Adam developing cerebral venous thrombosis.

I will deal with point VI first. Adam did not have any evidence of iron deficiency anaemia. His markers of the body’s iron stores were normal (including the ferritin at 433 µg/l, which is reliable in renal failure, and his serum iron and total iron-binding capacity which are less so[14]). Neither did his blood counts indicate this. In particular, none of his mean red cell volume measurements were low (a low MCV is the most sensitive and reliable index of iron deficiency), but instead were all in the high-normal range of about 85-100 fentilitres.

Although erythropoietin use is a known risk factor for thrombosis in adults with renal failure, this is not due to the administration of the drug as such, but is mediated by its excessive use such that the haemoglobin is pushed abnormally high (polycythaemia, the opposite of anaemia), or is driven up to high-normal levels very rapidly. Though there have been very few randomised cross-over controlled trials of erythropoietin in children, we did undertake one in Newcastle, and confirmed its safety if it is handled in children as it should be in adults, avoiding its excessive effects.[15]

In summary, Adam had neither iron-deficiency anaemia, nor polycythaemia due to excessive erythropoietin usage; these risk factors therefore do not apply to him.

Point III: his polyuria put him at risk of dehydration
Although uncontrolled polyuria in children can lead to dehydration severe enough to induce intravascular hypovolaemia, which is a risk factor for thrombosis in general, Adam did not suffer from any serious episodes of this in his life, and was certainly not in this state prior to his transplant. In other words, it is dehydration that is the risk, not being polyuric, and Adam wasn’t.

Point IV: methyl prednisolone
All children that undergo renal transplants are given a bolus of methyl prednisolone as an immunosuppressive agent at the time that the vascular clamps are released, when the child's blood begins to circulate through the new kidney. If Professor Kirkham is correct that this is an important risk factor for children suffering a fatal cerebral venous thrombosis, then you would expect to find this complication reported previously as a complication of paediatric transplantation. I have conducted a thorough Medline search to look for reports of children in whom the combination of 'cerebral venous thrombosis' and 'renal transplantation' (and variations around these) have been reported, and cannot find a single case.

In any case, given the timing of Adam's case, it is extremely likely that he had already suffered his irreversible consequences of cerebral oedema by the time he was administered it towards the end of surgery, as he was found to be unrousable just 1 hour later.

Summary of point IV: a single routine dose of methyl prednisolone during paediatric kidney transplant surgery does not appear to actually pose a risk of cerebral venous thrombosis, and in Adam's case the timing of the events rules this out anyway.

Point V: venous drainage from his neck
I have dealt elsewhere in previous reports about Adam's central venous line (especially in my report of 10/02/2012 which I wrote in response to the document by Dr L Dyer, dated 24/01/2012). In summary, it is clear to me that Adam's central venous line was not obstructed, as evidenced by the fact that the respiratory and cardiac pressure traces were recorded on it. Therefore, the whole premise of Professor Kirkham's point V is invalid.

As a matter of interest to the inquiry, the situation of a child undergoing a transplant following a series of previous internal jugular and subclavian (neck) lines is common, almost routine among the children who have had renal failure from birth. Central vein access is almost the universal method of performing haemodialysis, many babies require lines for albumin or total peripheral nutrition, or to support their management during various urological and other operations on their journey to being transplanted. The clinical fact is that their veins do re-canalise extremely effectively, and it is rare for the anaesthetists to have to use an alternative, such as the femoral vein.

A second point for the interest of the inquiry is to note that Dr Taylor's assertion that his finding difficulty in managing to insert a central line into one of Adam's central vein was a marker of him being dehydrated should not be taken as being an evidence-based fact. I mention this now because Professor Kirkham appears to accept his view. While being dry is a theoretical risk factor, the fact is that it is never easy to cannulate the central veins of small children, and even the most experienced operators will fail on occasions in any child, however well hydrated they are.

Summary of Adam's risk of cerebral venous thrombosis
Adam was at no greater risk of having had chronic venous thrombosis, nor of suffering an acute thrombosis, than any other pre-school child on dialysis who is undergoing a kidney transplant, and the fact is that such a risk must be extremely rare since it has not been reported in the medical literature to my knowledge.

What is the evidence that Adam sustained a cerebral venous thrombosis?

Above I have considered if Adam had particular risk factors for developing cerebral thrombosis. Here I will ask what the evidence is to support the notion that he may have actually have sustained such an event, despite not being at especial risk. Presumably a diagnosis would require positive evidence, either in the form of clinical features, or imaging, or at post-mortem examination.

There are no specific clinical features for the presence of cerebral venous thrombosis – rather it is a condition that should be considered in the differential diagnostic list of possible causes of a range of neurological symptoms. It should then be sought by imaging tests.

As far as I am aware, Adam's imaging reports described appearances typically seen in cerebral oedema, and did not mention any positive evidence of venous thrombosis.

My reading of Dr Squires' report of 16/02/12 is that she cannot find any evidence to support the diagnosis of cortical venous thrombosis. Prof Kirkham's doubts about his brain weight seem to assume that a child with his history would be known to have the same weight brain as a previously completely healthy child, which I do not think has been established.

Summary on cerebral thrombosis hypothesis ... this would appear to have no positive supportive evidence at all, but to be mere speculation.

Adam's fluid management

I do not propose to discuss Adam's fluid management in any depth here, as this is a complex issue that has been the subject of previous reports from me.

However, I do wish to comment on Professor Kirkham's dismissal of this being at all likely to be relevant in Adam's case, based upon her interpretation of the literature on infusing hypotonic fluids into children. She concludes that using such fluids has never been shown to lead to a child's death; it simply has not been reported before. This is summed up in this sentence from her paragraph 44:

> "I have not been able to find any other case of documented cerebral oedema or brain death in a child without a central nervous system condition given 0.18% saline 4% Dextrose intra-operatively *as Adam was*."

The underlining and italics are mine, and are intended to draw attention to a vital point. Nobody has tested or reported in the literature what the effect would be of giving an excess of about 1 litre of excess free water that is retained by the body, by any means whatsoever.

What the papers of Arieff and others have looked at is the impact of giving the correct volume of fluid to a child using a hypotonic versus less hypotonic fluid – nobody would ever suggest overloading a child with 5% of his body weight of free water, as happened to Adam, to see what would happen! A basic understanding of physiology can answer that without the need for a clinical study. It would inevitably cause brain swelling, and that might be sufficient to cause a rise in intra-cerebral pressure and brain death.

Final summary of my response to the report by Professor Kirkham

I do not find any of Professor Kirkham's speculations about Adam Strain's death to be proven.

Adam did not have hypertensive encephalopathy, and therefore did not have the posterior reversible encephalopathy syndrome which is hypertensive encephalopathy accompanied by head scanning pictures of it.

Adam was at no greater risk of cerebral venous thrombosis than any other pre-school child on dialysis and undergoing a renal transplant, and there does not seem to be any clinical, radiological or pathological evidence to support this speculation.

I disagree with Professor Kirkham's interpretation of the literature on the risks of infusing hypotonic fluids into children.

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Expert Witness Declaration

I Malcolm Coulthard DECLARE THAT:

1) I understand that my duty in providing written reports and giving evidence is to help the Court, and that this duty overrides any obligation to the party by whom I am engaged or the person who has paid or is liable to pay me. I confirm that I have complied and will continue to comply with my duty.
2) I confirm that I have not entered into any arrangement where the amount or payment of my fees is in any way dependent on the outcome of the case.
3) I know of no conflict of interest of any kind, other than any which I have disclosed in my report.
4) I do not consider that any interest which I have disclosed affects my suitability as an expert witness on any issues on which I have given evidence.
5) I will advise the party by whom I am instructed if, between the date of my report and the trial, there is any change in circumstances which affect my answers to points 3 and 4 above.
6) I have shown the sources of all information I have used.
7) I have exercised reasonable care and skill in order to be accurate and complete in preparing this report.
8) I have endeavoured to include in my report those matt ers, of which I have knowledge or of which I have been made aware, that might adversely affect the validity of my opinion. I have clearly stated any qualifications to my opinion.
9) I have not, without forming an independent view, included or excluded anything which has been suggested to me by others, including my instructing lawyers.
10) I will notify those instructing me immediately and confirm in writing if, for any reason, my existing report requires any correction or qualification.
11) I understand that;
    11.1) my report will form the evidence to be given under oath or affirmation;
    11.2) questions may be put to me in writing for the purposes of clarifying my report and that my answers shall be treated as part of my report and covered by my statement of truth;
    11.3) the court may at any stage direct a discussion to take place between experts for the purpose of identifying and discussing the expert issues in the proceedings, where possible reaching an agreed opinion on those issues and identifying what action, if any, may be taken to resolve any of the outstanding issues between the parties;
    11.4) the court may direct that following a discussion between the experts that a statement should be prepared showing those issues which are agreed, and those issues which are not agreed, together with a summary of the reasons for disagreeing;
    11.5) I may be required to attend court to be cross-examined on my report by a cross-examiner assisted by an expert;
    11.6) I am likely to be the subject of public adverse criticism by the judge if the Court concludes that I have not taken reasonable care in trying to meet the standards set out above.
12) I have read Part 35 of the Civil Procedure Rules and the accompanying practice direction including the “Protocol for Instruction of Experts to give Evidence in Civil Claims” and I have complied with their requirements.
13) I am aware of the practice direction on pre-action conduct. I have acted in accordance with the Code of Practice for Experts.

Statement of Truth

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

Signed _____ Dr Malcolm Coulthard

Dated _____ 20/02/2012

Dr Malcolm Coulthard, BSc, MB BS, DCH, FRCP, FRCPCH, PhD