Peer Reviewer Comments on Expert Advisors Report on Claire Roberts

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Background

This report has been prepared at the request of the Northern Ireland Inquiry into Hyponatraemia-Related Deaths as a peer review of the Consolidated Report of the Expert Advisors' Report dated 14th August 2012. As well as this I have reviewed the reports provided by the following experts: Dr. Robert Scott-Jupp, Professor Brian Neville, Dr. Waney Squier, Professor Brian Harding, Dr. Keith Cartwright, Sally Ramsay, Dr. Caren Landes, Dr. Jeffery Aronson and Dr. Roderick MacFaul.

The Expert Advisors' report is very comprehensive and has identified a long list of issues for the inquiry to investigate, some of which they have labeled as key issues. I will attempt to distil these down further into what I think are the five key issues. I am also very conscious of the fact that one of the biggest challenges the inquiry faces is to review the evidence in the light of what was accepted practice and state of knowledge in 1996 rather than what is known or acceptable practice today.

Diagnosis and Management of Claire's Illness During her Hospitalisation.

Claire was obviously a child with some significant underlying medical problems. Her presentation was certainly in keeping with an acute neurological illness and the admitting list of differential diagnosis was appropriate. However, her previous history of epilepsy may have had led her care givers to focus on seizures as the cause of her neurological findings leading to the use of first, second and third line anticonvulsant therapies without the appropriate investigations. All these therapies have sedating effects and probably affected her level of consciousness. The use of a midazolam infusion in a ward setting is certainly a high risk strategy and in my opinion should not be used outside a PICU setting. Certainly the Glasgow Coma Score of 6 to 8 in the afternoon/evening of 22nd October indicates a depth of coma which would require the attention of a paediatric intensive care specialist. It is highly likely that this level of coma was due to a combination of a rising intracranial pressure as the serum sodium fell as well as the effect of the iv midazolam.

Hyponatraemia, Cerebral Oedema and SIADH

I continue to be concerned that there is lack of clarity around these issues. Whatever was the underlying medical illness that precipitated Claire's admission to hospital on 21st October, it is clear that the immediate cause of her death was cerebral oedema secondary to ***acute*** hyponatraemia. This is commonly defined in the literature as a fall in serum sodium to <130 mmol/L over a 24 hr period and is associated with seizures and cerebral oedema when the level falls below 125mmol/l (symptomatic hyponatraemia). There are two reasons why serum sodium falls acutely, either by salt loss (vomiting) or water gain from hypotonic saline or oral fluid intake. The most common cause in hospitalized patients is the use of hypotonic saline.

I think we must accept that there is no laboratory or pathological evidence to support a diagnosis of acute encephalitis in Claire's case. The cell count in the CSF is a spurious result as the sample was taken during the autopsy and would have been contaminated with post mortem blood while the dissection was being performed. Additionally, there are no standards for post mortem cell levels in the CSF. The normal values we use are from samples taken by lumbar puncture during life. I do not think we will ever get any closer to the underlying diagnosis that precipitated her admission to hospital than we are now and have to accept that she had some form of acute encephalopathy. However, that does not mean that her original clinical diagnosis was not a reasonable one.

I would like to try to add some additional clarity to the issues of acute hyponatraemia and SIADH because there seems to be some misconceptions about what role they played in Claire's terminal events. We all continually produce anti-diuretic hormone (ADH) regardless of whether we are sick or well. When we are well the amount of ADH released depends on the amount of oral fluids we ingest and is tightly controlled to produce a concentrated urine. Large amounts of fluid ingested leads to the production of increaing amounts a dilute urine while through suppression of ADH release while fluid deprivation results in the sensation of thirst, increased ADH release and a more concentrated low volume urine output. The end result is that the serum sodium and serum osmolarity remain constant. The control mechanism for this is the serum osmolarity regulation is located in sensors in the brain.

This normal physiological feedback mechanism frequently becomes deranged in hospitalized patients who, for various reasons fail to inhibit ADH secretion. In these patients fluid intake is not driven by thirst but by obligatory fluid intake, namely administration of iv fluids. Children are particularly at risk because of the widespread use of iv fluids that contain only small amounts of sodium and large amounts of free water (hypotonic saline). The normal physiological response in this situation should be to shut down ADH secretion and produce a dilute urine. When this feedback mechanism fails water is retained, serum sodium falls and acute hyponatraemia develops. Children with CNS disorders are particularly vulnerable to this but whether this was widely known in 1996 is debatable. What is not a subject for debate is that cause of Claire's death was that her acute cerebral oedema was caused by the administration of hypotonic saline in a situation where ADH secretion was not inhibited.

I am concerned when I read that some experts have ascribed Claire's death to SIADH. This is incorrect. Oversecretion of ADH in of itself cannot cause acute hyponatraemia and cerebral oedema in the absence of fluid intake, either orally or iv. As supporting evidence for this statement I refer to many of the published

studies in intensive care medicine published in the past 10 years where Vasopressin (ADH) has been infused in large doses as a vasopressor agent to support low blood pressure in shock. In none of these was there any fall in serum sodium. I am attaching a published paper on a multi-centre paediatric study which our group participated in (Choong Am J Respir CritCare Med 2009; 180:632) where there was no fall in serum sodium because hypotonic saline was not used. We all secrete large amounts of ADH during periods of fluid deprivation but the serum sodium rises rather than falls. The distinction is important otherwise the focus moves away from the choice of the type and amount of iv fluid used in these cases, which is the fundamental issue.

It is clear that there was little understanding of these issues in 1996 when Claire had acute, symptomatic hyponatraemia. I am concerned to read in Dr. MacFaul's opinion the statement that 0.18 NaCl is contra-indicated in acute encephalopathy citing a paediatric textbook available in 1996 (P10 #11). He then goes on to state that that its use was consistent with or within the range of current practice at that time (P18 #85, P34 # 165). While I agree with his view about 0.18 NaCl my concern is that we are applying current standards and knowledge to 1996. Most of the publications in this area have appeared since 2000. I am attaching the copy of a letter to the *New England Journal of Medicine* published in 2001 by Moritz (Moritz N Engl J Med 2001: 345:148) which was of the first publications to highlight the dangers of using hypotonic fluid in patients with encephalitis. This was written in response to a publication of a case series of children with La Crosse encephalitis where they found hyponatraemia was a common feature. I have highlighted the author's response in which they state that "there is no clear consensus in the medical literature that isotonic saline should be used in children with CNS infections."

The clinicians in 1996 didn't realize the significance and gravity of a serum sodium of 121 mmol/l and that it had fallen rapidly from the previous days level. Acute, symptomatic hyponatraemia is a medical emergency which requires urgent intervention to raise the serum sodium to >130 mmol/l to reduce cerebral oedema and prevent brain stem coning. There is still some lack of clarity in understanding the mechanisms and treatment priorities that persists to this day. Fluid restriction or the use of 0.45 NaCl, as mentioned in various experts reports, would be insufficient to prevent coning. There is no downside, as has been suggested, to taking measures to rapidly increase the serum sodium in acute symptomatic hyponatraemia, as has been suggested. Indeed these may be life saving and include the use of mannitol or hypertonic saline.

Roles and Responsibilities for Claire's Care

This has been identified as a key issue by both experts and advisors. I fully agree with this and hopefully things have improved significantly since Claire's death. There was no clear understanding of who was directing her investigations and treatment. This applies to both nursing and medical staff. The consultant paediatrician under whose care she was admitted had little or no involvement in her care until after the coning event. The various members of the junior medical staff did not seem to know that they should have sought advice and, if so, from whom. Much has been made of the fact that no EEG or CT scan was obtained. I understand that there were potential barriers to this happening but to overcome these requires leverage applied at consultant level.

Case Review and Family Communication

Any unexpected death of a child, particularly when it involves errors in clinical management, provides an opportunity for clinicians to learn and for the institution to identify problems in system management. In many instances the lessons learned are of some source of consolation to parents. This clearly didn't happen in Claire's case until some considerable time after her death and then prompted by the media. This is particularly disappointing in light of the fact that Adam Strain had died from acute hyponatraemia in the same hospital a year earlier. The communication with Claire's family both during her acute illness and after her death was poor. The information given to them after her death was incorrect due to a combination of lack of understanding about the causes and affects of acute hyponatraemia as well as errors in autopsy findings. The decision not to notify the coroner immediately following the death was also an error.

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