PEER REVIEWER COMMENTS

ON THE MEMO FROM DR. HARVEY MARCOVICH DATED 11th JANUARY 2013

CONCERNING THE CASE OF ADAM STRAIN

Prepared by

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I have read the memo prepared by Dr. Harvey Marcovich dated 11th January 2013. In it he makes reference to the expert reports of Professor Rating and Professor Kirkham as well as responses to comments made by Professor Rating from Dr. Waney Squier and Professor Kirkham. I have previously reviewed both the expert reports provided to the inquiry by them. I have also reviewed Professor Rating's report and I concur with his analysis and conclusions.

I will summarise the points of concern raised by Dr. Malcovich, all of which are relevant and valid, as follows:

(a) Hypotonic saline has been used as the standard iv solution for children for over 50 years with only occasion alarms being raised. The incidence of symptomatic hyponatraemia is very low and most expert witnesses to the inquiry have never seen a case.
(b) Given the fact that there is extensive evidence from well conducted clinical trials that the use of hypotonic in the perioperative period will result in the development of some degree of hyponatraemia without symptoms, is there a biological rationale for an underlying predisposition for the development of cerebral oedema.
(c) The cause of death in Adam Strain. Is there any evidence to support Professor Kirkham's contention that Adam had either sinus venous thrombosis or PRES?
(d) The issue of cerebral oedema in children with diabetic ketoacidosis (DKA) and what role iv fluid administration may play in the development of that complication and has that any relevance in terms of mechanism to the development of cerebral oedema in acute hyponatraemia.

Hypotonic saline has been used as the standard iv solution for children for over 50 years with only occasion alarms being raised. The incidence of symptomatic hyponatraemia is very low and most expert witnesses to the inquiry have never seen a case.

I have heard this observation made many times over the years that I have given talks on this topic in various parts of the world. Unlike the experts, I am in the unfortunate position of having personal experience of at least 10 cases of death or severe neurological injury in children who developed acute hyponatraemia in association with the use of hypotonic saline. None of these children had any underlying CNS abnormality. All had neuro-imaging and autopsies, including detailed neuropathological examination, which did not show any other brain pathology apart from cerebral oedema. The fact that I have seen these cases whereas other experts, who have provided evidence to the inquiry, have not can be explained by the nature of my medical practice. People such as myself who have many years of paediatric intensive care practice will encounter these cases because when the catastrophe occurs the child is transferred to ICU.

In addition, there is the problem of failure to recognize and diagnose acute symptomatic hyponatraemia. A review of the published literature might suggest that the disease did not exist prior to 1986 when Arieff published his landmark series in the New England Journal of Medicine *(N Engl J Med 1986; 314:1529) Appendix A.* He reported on death or severe neurological injury in 15 otherwise healthy women who had undergone elective surgery. Hypotonic saline was administered throughout the perioperative period and patients developed seizures, coma and apneoa with a median serum sodium measured at 109 mmol/l. In only 33% of the patients in this series was the correct diagnosis made. The delay in making a diagnosis of acute hyponatraemia was 16±7 hours. The interval between the presentation and diagnosis was spent in obtaining diagnostic investigations which included CT scans, cerebral angiography, EEGs and, in two

instances, brain biopsies looking for brain pathology to account for the seizures. These diagnostic studies were done despite the fact that in 80% of cases the low serum sodium level was known. In his commentary Dr. Arieff made the observation that *"this suggests that many of the managing and consulting physicians were not aware that hyponatraemia could lead to the observed symptoms."*

This reflects my own experience in the cases I have either managed in my own ICU or reviewed for the Office of the Chief Coroner in Ontario. In these cases the first reaction of the treating physicians faced with a seizing child with a serum sodium of less than 125mmol/l was to order a repeat measurement because they don't believe the initial value. They would then order a CT scan looking for CNS pathology rather than administering urgent treatment to bring up the serum sodium. One of the cases I reviewed had two episodes on different hospital admissions of acute symptomatic hyponatraemia with seizures when receiving iv hypotonic saline and a measured serum sodium of <125 mmol/l. On the first admission the child recovered and an erroneous clinical diagnosis of viral encephalitis was made rather than acute hyponatraemia. He was admitted on a subsequent occasion, again received iv hypotonic saline, had a second episode of seizures with a serum sodium of <125mmol/l and on this occasion coned and died.

I have reviewed all of the published medical literature of acute hyponatraemia in children resulting in the development of seizures, death or neurological injury. The total number of cases I have found, including the case series I have collected, comes to over 100 patients. Many of these are summarized by Moritz *(Moritz Pediatr Nephrol 2005) Appendix B.* We can be sure that this significantly under represents the true number because care givers would be reluctant to report or publish cases because of the implications of medical error. I was surprised to see that Professor Kirkham's report showed that she had reviewed only a small number of the published case reports. A more extensive review of the published case reports would show that there is no evidence to support her statements about the majority of patients having underlying CNS abnormalities *(Kirkham Expert Report P15 #38-44).*

Finally, several comments have been made in various expert's reports that our publication on this topic in the BMJ *(Halberthal Brit Med J 2001)* lacked data on the amount and type of fluids infused. This was because we were limited to 1200 words. In order to remedy this I have attached timeline charts on five cases I have dealt with where children died from acute hyponatraemia. Full details on the amount of hypotonic saline used and the symptoms are provided *(Appendix C).* All received either 0.2 NaCl or 0.3 NaCl. One of the common findings in all these cases was the rapidity of the fall in serum sodium. In each case the child became symptomatic in less than 24 hrs and I think that this explains why some children develop complications while others do not.

Given the fact that there is extensive evidence from well conducted clinical trials that the use of hypotonic in the perioperative period will result in the development of some degree of hyponatraemia without symptoms, is there a biological rationale for an underlying predisposition for the development of cerebral oedema.

This is a very interesting and relevant question. There is certainly a considerable amount of evidence to suggest that women and children are more susceptible to the development of cerebral oedema in association with hyponatraemia. There may be an as yet unexplained mechanism that would explain why ADH is over expressed in these patient groups. This awaits further investigation. I would emphasise again that the common mechanism is a failure to suppress ADH secretion in the face of water retention and a falling serum sodium rather than the suggestion that there is an increase in ADH levels.

The cause of death in Adam Strain and is there any evidence to support Professor

Kirkham's contention that Adam had either underlying sinus venous thrombosis or PRES?

I would state unequivocally that the cause of death in Adam Strain was acute cerebral oedema secondary to acute hyponatraemia based on the clinico-pathological correlation. The CT scans and autopsy findings are unequivocal in supporting the diagnosis of cerebral oedema. Dr. Kirkham, perhaps because she has not seen cases of deaths from acute hyponatraemia, is seeking alternative explanations for this finding. There is nothing on either the CT scan or post mortem findings, both of which have been reviewed by experts, to support these alternative diagnoses. There are no specific findings in the brain that relate to a diagnosis of cerebral oedema from hyponatraemia which has perhaps led to some uncertainty. Professor Rating's question to Dr. Squier about myelinolyis is not relevant to this discussion *(240-004-028).* Myelinolysis, or osmotic demyelination as it is commonly know, is found in adults with chronic hyponatraemia where attempts have been made to increase the serum sodium rapidly. It has only rarely been reported in children and not in acute hyponatraemia.

I agree with Dr. Marcovitch's point about the difficulties in explaining the underlying aetiology Claire's case. There clearly was some background of CNS abnormality which may have increased the risk of the development of complications from hyponatraemia which is why hypotonic saline is never used in children with head injury or meningitis. Raychel's case was more straightforward as it was caused by a combination of salt loss from vomitus and water gain from hypotonic saline.

The issue of cerebral oedema in children with diabetic ketoacidosis (DKA) and what role iv fluid administration may play in the development of that complication and has that any relevance in terms of mechanism to the development of cerebral oedema in acute hyponatraemia.

Children with DKA are another group at risk for the development of cerebral oedema while receiving iv fluids. Myself and my colleagues in Toronto have also developed a research interest in this topic. The pathophysiology of this complication has been a source of some debate over the years. We feel that the most important physiological mechanism at play, similar to acute hyponatraemia, is an osmolar shift as water enters brain cells during rehydration. In DKA there are major fluid losses from the extracellular fluid compartment. The intracellular space becomes very hyperosmolar. When the fluid is infused into the extracellular space it rapidly crosses into brain cells because of the high osmotic gradient for water transfer and these swell. We have demonstrated that that a slower rehydration regime using normal saline prevents the development of cerebral oedema *(Hoorn J Pediatr 2007; 150:467) Carlotti Arch Dis Child 2003; 80:170 Appendix D.*

Appendices

A. Arieff. A Hyponatremia, convulsions, respiratory arrest and permanent brain damage after elective surgery in healthy women *N Engl J Med 1986; 314:1529*
B. Moritz M. Preventing neurological complications following dysnatremias in children. *Pediatr Nephrol 2005; 20:1687*
C. Timeline of cases of acute hyponatraemia reviewed by D.Bohn
D. Hoorn E. Preventing a drop in effective osmolality to minimize the likelihood of cerebral edema during the treatment of children with diabetic ketoacidosis *J Pediatr 2007; 150:467* Carlotti A. The importance of timing of risk factors for the development of cerebral oedema during therapy for diabetic ketoacidosis. *Arch Dis Child 2003; 80:170*