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24 October 2001

Dear Dr Herron

Re: Rachel Ferguson DOB 4/2/92
Ref: NPPM 61/2001

Thank you for asking me to look at the Altnagelvin records of this girl who had a major seizure approximately 28 hrs after an apparently uncomplicated appendicectomy. Significant hyponatraemia was noted after the seizure and she subsequently died, cerebral oedema being your major finding at autopsy. I have summarised relevant sections of the notes available to me, the page of origin identified by the title in italics:

This 9-year-old girl was admitted via A&E on the evening of 7/6/01 with abdominal pain (*"Accident & Emergency" sheet:* not legible due to photocopy quality).

Admission and pre-operative period
"Clinical notes" Pg. 1: patient was examined on the Children's ward (ward 6?) by the surgical SHO, who documented periumbilical pain, which had shifted to the right iliac fossa (McBurney's point); she had RIF tenderness, guarding and mild rebound tenderness. Absence of urinary symptoms was recorded. She was felt to have acute appendicitis and consent was obtained for appendicectomy. Intravenous fluids were prescribed.
"Observation sheet" (nursing) Pg. 1(7/6/01) documented abdominal pain and pain on urination.
"TPR chart": on admission, patient was afebrile, BP was 103/61, weight was 25kg. An (undated, time 23:19) urinalysis printout indicated proteinuria++.
"Parenteral nutrition fluids prescription sheet" (Pg.1): Intravenous fluids ("No. 18 solution") were erected at 80mls/hr at 10.15pm.
(FBP/U&E checked: see table of biochemistry results below.)

Intra-operative / peri-operative period
"Theatre nursing care plan": arrived at 11.20pm. Alert, not premedicated, IV infusion site right arm.
"Surgeon's report": mildly congested appendix. Peritoneum clean. Flagyl prescribed.
"Intra-operative nursing care": received rectal Voltarol 12.5mg and paracetamol 500mg at 11.40pm.
"Anaesthetic record" Pg1/2: received ondansetron 2mg, fentanyl 50mg total, propofol 100mg, scoline 30mg, cyclimorph 5mg, mivacurium 2mg, metronidazole 250mg. Peri-operative event: "prolonged sedation due to opioids".
Hartmann's fluid 1L?: anaethetist's intention indicated, but administration not confirmed by fluid balance chart.

"Parenteral nutrition fluids prescription sheet"(Pg.1) (same document as for pre-op): Hartmann's fluid prescribed at 80mls/hr, signed by anaethetist, but deleted (unsigned).

Post-operative period prior to seizure

"Fluid balance for IV fluids" (Pg. 1: 7/6/01): Received total 540 mls No. 18 solution between 22.15 on 7/6/01 and 07.00 hrs on 8/6/01. No record of urine output.

"Clinical notes" (Pg. 2:8/6/01): "Free of pain. Apyrexial. Continue observation."

"Paediatric unit"sheet (7-8/6/01) (Apparently a nursing record chart.)
Temperature/respiratory rate/pulse/blood pressure recorded on return from theatre 01.55am, half-hourly until 4am, then 5am, 7am. BP range 78-96/41-57. Temp, resp rate and pulse only recorded 4 hourly from 9am until 21.15 on 8/6/01. Afebrile throughout. No problems documented until 21.15pm: "colour flushed→pale. Vomiting++. C/o headache."
[NB: No *"Observation sheet"* for 8/6/01 is present in copy of notes I received (7/6/01 and 9/6/01 both present: see above and below).]

"Parenteral nutrition fluids prescription sheet"(Pg.2): 1L No.18 solution prescribed at 80mls/hr and erected at 12.15pm. [A second litre of 0.9% NaCl was apparently prescribed early on 9/6/01: from subsequent nursing notes.]

"Fluid balance for IV fluids" (Pg. 2: 8/6/01): Received 1520mls No.18 solution between 08.00 on 8/6/01 and 04.00 on 9/6/01. No record of urine output. No record of oral intake, if any. Seven episodes of vomiting documented between 08.00 on 8/6/01and 01.00 am on 9/6/01, with "coffee-grounds" mentioned latterly, but no measure of volume ("large vomit", "vomit++").

"Observation sheet" (nursing) 9/6/01: 03.05am: major seizure. Bloods taken at 3.30am for electrolytes: see table.

Likely pathogenesis of cerebral oedema

I have little doubt that the cerebral oedema which you noted at autopsy was caused by an intracellular fluid shift as a result of rapid fall in tonicity of the extracellular fluid (ECF). As you can see from the table of biochemistry results, I have estimated a fall of 37mOsm/L (293 to 256 mOsm/L) over approximately 30 hrs. Sodium is the predominant extracellular cation and as such is the major determinant of extracellular tonicity. The cell membrane is relatively impermeable to sodium due to an active sodium pump mechanism, and rapid changes in the concentration of sodium in the ECF (in either direction) result in significant fluid shifts to maintain osmotic equilibrium between the intracellular and extracellular compartments. The brain is particularly susceptible to the effects of such fluid shifts and profound neurological damage such as occurred in this case has been well-described in association with rapid increases and decreases in plasma sodium concentrations. Cerebral oedema with its attendant acute neurological features is characteristic of rapidly-developing hyponatraemia.

I believe that in this case the fall in plasma sodium concentration and thus ECF tonicity was caused by a combination of 3 main factors:

1. infusion of hypotonic parenteral fluids (No. 18 solution contains 31mmol Na in 1 litre 4% glucose solution, one-fifth the concentration of plasma);

2. profuse vomiting in the post-operative period. Although vomitus contains 70-100mmol of sodium /L, which is relatively less than plasma (at 140mmol/L), if the ECF volume is replaced as in this case with fluids containing very little sodium, the net effect is a significant salt loss, with little or no water deficit;
3. Anti-diuretic hormone (ADH) secretion, known to be associated with stress (e.g. surgery), vomiting and pain, is likely to have been a major contributor to the overall picture by inhibiting excretion of excess free water.

The relative contributions of these factors will remain unknown. Normally administration of generous volumes of hypotonic fluids will result in a brisk diuresis, and certainly this will be noted by most healthy people who can tolerate drinking large amounts of dilute fluids without consequence. However in this case excess ADH secretion for the reasons mentioned above might have resulted in a net positive fluid balance and an inappropriately concentrated urine. Urine osmolarity was indeed inappropriately high in the sample taken after the seizure (measured last week on the sample obtained by you from Altnagelvin laboratory), and the low urea notable in the post-seizure serum samples, relative to that on admission, might indicate relative water excess as a consequence of ADH action. However whether this was a cause or effect of the cerebral oedema cannot be judged and no plasma or urine samples are available from the post-operative but pre-seizure period. Unfortunately no record of fluid balance was apparent. A low urinary output might have given an early sign of evolving problems.

(I also measured cortisol in the post-seizure blood sample and this was appropriately elevated, excluding adrenal insufficiency as a cause of the hyponatraemia.)

In summary, I believe that the cerebral oedema which you noted at autopsy was caused by a rapid fall in plasma sodium concentration as a result of a net sodium loss coupled with hypotonic fluid administration in a situation (i.e. post-operative state ± vomiting) where a normal physiological response inhibited the effective excretion of the excess free water.

I hope this has been of some help. Please do not hesitate to contact me if further clarification is required.

Best wishes.

Yours sincerely,

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289

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Table of relevant laboratory results: Rachel Ferguson (DOB 4/2/92)
(*tests performed *post-mortem*)

Serum					
	Pre-operatively	Post-seizure			
Date	7/6/01	9/6/01	9/6/01	9/6/01	9/6/01
Time received in lab	9pm approx.	4.06am	4.40am	9.22 am	3pm
Lab. No.	01633	01742	01747	5380	(RBHSC)
Na (mmol/L)	137	119	118	119	130
K (mmol/L)	3.6	3.0	3.0	3.4	
Cl (mmol/L)	107	90	90	90	
CO2 (mmol/L)	22	16	15	22	
Urea (mmol/L)	4.8	2.3	2.1	2.5	
Creat (mmol/L)	47	44	43	22	
Glucose(mmol/L)	7.2	9.9	11	7.1	
T prot (mmol/L)	69	71	72	68	
Osmol (mOsm/L) (calc)	293*	256*		255*	
Urine					
Date				9/6/01	
Time				9am	
Lab. No.				5425	
Na (mmol/L)				90	13
Osmol (mOsm/L)				382*	73