Hypertriglyceridemia in Infants and Children with Hypernatremia

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Abstract:

Background: Hypertriglyceridemia in association with hypernatremia was reported in a few children; however, studies exploring this association are limited.

Objective: To determine the pattern of change in serum triglycerides levels in hypernatremia patients.

Design and setting: A prospective case-control study done at North West Armed Forces Hospital, Tabuk, Saudi Arabia from April 2008 to March 2011

Patients and method: serum triglycerides and sodium were measured in 16 patients with hypernatremic dehydration as a study group and 14 patients with isonatremic dehydration as a control group. The trend of serum sodium and triglycerides was followed during treatment in the study group.

Results: There were 6 boys and 8 girls in the control group (isonatremic dehydration). Their age ranged between 4 months and five years (M±SD = 1.7±1.3 years). In the study group (hypernatremic dehydration), there were 6 boys and 10 girls. The age range was 2-14 months (M±SD = 0.6±0.4 years). The serum sodium and triglycerides (M±SD = 165.8±9.1 mmol/l, 5.1±8.1 mmol/l respectively) were significantly higher compared with the control group (M±SD = 137.5±3.9 mmol/l, 0.7±0.3 mmol/l and $P < 0.001$, $P < 0.05$ respectively). Duration of symptoms in patients with hypernatremic dehydration (M±SD = 2.9±2.4 days) were comparable to control group (M±SD = 2.0±0.9 days, P = 0.18). Four patients from the study group had normal serum triglycerides (M±SD = 1.1±0.1 mmol/l). With treatment, serum sodium was normalized in all patients followed by serum triglycerides.

Conclusion: Hypertriglyceridemia is present in most children with hypernatremia and it disappears when serum sodium returns to normal.

Keywords: Dehydration, Hypernatremia, Hypertriglyceridemia.

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Introduction

Hypertriglyceridemia is defined on the basis of the 95th centile as a fasting triglycerides concentration of 1.15 mmol/L in the first decade of life and 1.5 mmol/L in the second decade. [1] The primary form is due to various genetic defects leading to abnormal triglyceride metabolism. The secondary forms are acquired such as diabetes mellitus, glycogen storage disease type1, cholestasis, nephrotic syndrome and certain drugs. [2]

Hypernatremia is defined as a serum sodium concentration more than145 mmol/L. [3] Chronic hypernatremia is a hypernatremia of more than 2 days. [40] It is generally due excessive water loss, as in diabetes insipidus, or inadequate water intake, as in essential hypernatremia. [5, 6] Essential hypernatremia was reported in a number of Pediatric patients as idiopathic [7-17] or secondary to hypothalamic inflammation, tumors and cerebral malformations. [18-27]

Serum lipids are rarely measured in patients with hypernatremia. Hypertriglyceredemia in association with hypernatremia was reported in few children. [8, 12, 14, 18-20, 25] Interestingly, a similar association was reported in a dog. [28] In some of these reports the association was discovered when the plasma was observed to be lipemic. [18, 29]

We report 16 patients with hypertriglyceridemia and hypernatremia secondary to various causes. A possible explanation for the association was discussed.

Case

An 11-months-old Saudi boy was admitted with vomiting and fever for two weeks. He was febrile, severely dehydrated, obese, and microcephalic with right-sided hemiparesis. The scrotum was small with small testes. Blood drawn for work-up was milky. Funduscopy showed lipemia retinalis. His plasma sodium was 180 mmol/L, non-fasting serum triglycerides 74.8 mmol/L, serum cholesterol 14.2 mmol/L, HDL-C 0.6 mmol/L, serum glucose 5.6 mmol/L, serum creatinine 55 mmol/L, and BUN 13 mmol/L. Liver enzymes levels were normal. Hematocrit was 31%. The blood layered into a frothy supernatant and white thick curdy deposits when it was allowed to stand an overnight at 4°C. Serum lipoprotein electrophoresis showed an increased preβ-lipoprotein. No chylomicron was detected. The parents' lipid profile was normal. He was treated with adequate intravenous fluid for 3 days. Despite that, he remained hypernatremic. He showed no desire to drink and was noticed to be polyuric. When serum sodium was 158 mmol/L, serum vasopressin level was 1.4 ng/ml and urine osmolality was 62 mOsm/kg. MRI brain showed a cyst involving the right temporal lobe and most of the frontal lobe consistent with an arachnoid cyst. The right anterior hypothalamus appeared thinned. The posterior pituitary lobe high signal was missing. Treatment with a vasopressin analogue, Desamino-8-D-arginine vasopressin (DDAVP), and forced hydration restored plasma sodium to normal. Serum triglycerides also returned to normal. Further attacks of hypernatremia were associated with hypertriglyceridemia. All returned to normal with treatment (table 1).

Table 1. Serum sodium and triglyceride level in the case

Day	Serum [Na^+] mmol/L	Serum Triglyceride mmol/L	Comment
1	180	74.8	Severely dehydrated
2	160	74.0	
3	158	62.2	
4	155	58.1	DDAVP started
5	155	57.0	
6	151	47.0	
7	148	11.1	
9	144	4.8	
14	137	2.3	
15,16, 17	138	1.5	Treatment stopped
18	192	6.5	Readmitted
19	169	13.2	
21	154	9.2	
22	143	7.8	
23	138	3.8	
24	140	1.6	

Material and Methods

After we have encountered the above-mentioned case, we prospectively measured serum triglycerides, in sixteen patients

admitted with hypernatremic dehydration and compared them to fourteen patients admitted with isonatremic dehydration as a control. Serum triglycerides were measured in the studied patients, who were receiving intravenous fluids only at the time of blood sample collection, using Kodak Ektachem 700 analyzer. Serum glucose and hematocrit were also measured.

Statistical evaluation was performed using SPSS (SPSS for windows 19.0). Studied variables were described in means (M), standard deviations (SD) and bar charts. Unpaired T-test and used to assess significant difference in the means of sodium and triglycerides levels in the different groups. $P < 0.05$ was considered significant.

Results

There were 6 boys and 8 girls in the control group (isonatremic dehydration). Their age ranged between 4 months and five years (M±SD = 1.7±1.3 years). All had gastroenteritis and were symptomatic for 1-4 days (M±SD = 2.0±0.9 days). The serum sodium concentrations of the control group ranged between 132 and 144 mmol/l (M±SD = 137.5±3.9 mmol/l) (Figure 1); while serum triglycerides concentrations range was 0.2 to 0 .9 mmol/l (M±SD = 0.7±0.3 mmol/l) (Figure 2).

In the study group (hypernatremic dehydration), there were 6 boys and 10 girls. The age range was 2-14 months (M±SD = 0.6±0.4 years). The serum sodium ranged between 154 and 183 mmol/l (M±SD = 165.8±9.1 mmol/l) and was significantly higher compared with the control group ($P < 0.001$). Serum triglycerides range was 0.90 mmol/l to 31.9 mmol/l. Serum triglycerides of the study group (M±SD = 5.1±8.1 mmol/l) was significantly higher compared with the control group (M±SD = 0.7±0.3 mmol/l, $P = 0.04$). The cause of dehydration in most hypernatremic patients was due gastroenteritis (N =10) followed by diabetes insipidus (N = 4), glucose-galactose malabsorption (N =1) and disaccharidase deficiency (N =1). Duration of symptoms in patients with hypernatremic dehydration (M±SD = 2.9±2.4 days) were comparable to control group (M±SD = 2.0±0.9 days, $P = 0.18$). Four patients from the study group had normal serum triglycerides (M±SD = 1.1±0.1 mmol/l). With treatment, serum sodium was normalized in all patients followed by serum triglycerides. (Figure 3)

Figure 1: Serum sodium concentrations among studied groups

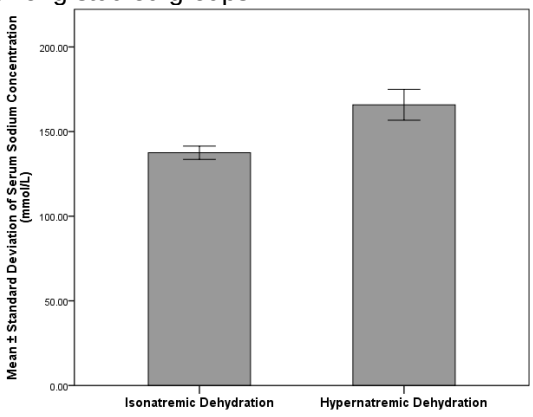


Figure 2: Serum triglyceride concentrations among studied groups

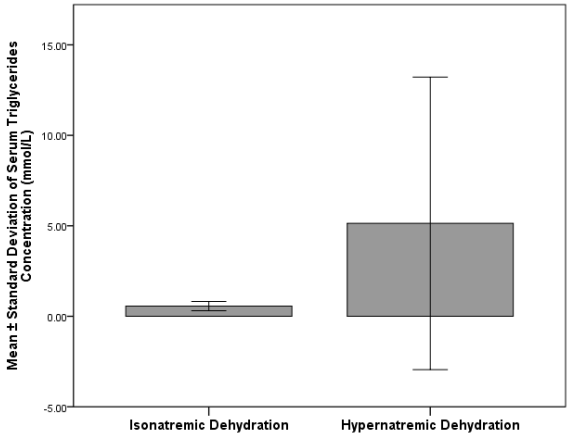
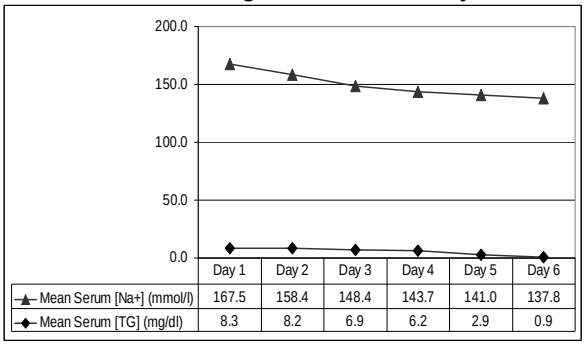


Figure 3: Serum sodium and triglycerides concentrations during treatment of dehydration



	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Mean Serum [Na+] (mmol/l)	167.5	158.4	148.4	143.7	141.0	137.8
Mean Serum [TG] (mg/dl)	8.3	8.2	6.9	6.2	2.9	0.9

Discussion

Several explanations have been suggested to interpret the association between hypernatremia and hyperlipidemia. One explanation is the enhanced hepatic triglyceride formation, as a direct action of hypernatremia; [30] or indirectly, through hormonal mediators released in response to hyperosmolar state, [31] stress [32, 33] or lesions of ventromedial hypothalamus (VMH). [34, 35] Hypertriglyceridemia has been attributed, both in human [19] and laboratory animals, [31, 36, 37] to the destructive lesions of (VMH). An alteration in dietary habits as well as hypothyroidism, secondary to VMH destruction, was suggested as additional contributory factors. [20] Central diabetes insipidus was diagnosed in only one patient of the study group and therefore above-mentioned explanations do not give solid clarification of the cause(s) of hypertriglyceridemia in most of currently studied patients. This suggestion is further supported by the fact that most of studied patients were infants who had no control on their food intake.

In the cases reported in the literature (summarized in table 2), as well as ours, the hyperlipidemia resolved with the correction of hypernatremia and recurred in association with recurrent hypernatremic crisis. Hayek at al [8] characterized these hyperlipidemic episodes as secondary effect of hypernatremia and they have proven that in experimental animals. [38] The duration and the severity of hypernatremia were suggested to be an important factor in the causation of hyperlipidemia. [18] Our first patient was symptomatic for 2 weeks when he presented with serum sodium of 180 mmol/L and serum triglyceride of 74.8 mmol/L. When the same patient was symptomatic for 2 days, his serum sodium was 192 mmol/L but serum triglycerides was 6.5 mmol/L. This had increased next day to 13.2 mmol/L despite a fall in serum sodium to 169 mmol/. Seven patients with gastroenteritis for 2 days or less were hypernatremic (159-171 mmol/L), but their serum triglycerides were either normal or mildly elevated. All of these indicate that the mere presence of hypernatremia is not enough; it has to be chronic to cause hyperlipidemia.

Table 2. Children and animals with hypernatremia and hyperlipidemia reported in the literature

Reference	Age	Sex	Diagnosis	Serum $[Na^+]$ (mmol/l)	Serum triglyceride (mg/dl)
8	9 years	Male	Idiopathic essential hypernatremia	191	786
14	4 months	Female	Idiopathic hypodipsic hypernatremia	140-170	370-2640
18	11 years	Female	Hypothalamic-astrocytoma adipsia and central diabetes insipidus	183	65.4
19	7-11 months	Female	CNS germinoma	160	448
19	8-12 months	Male	CNS germinoma	170	2640
20	12 years	Male	Histiocytosis	164	239

Inhibition of lipoprotein lipase (LPL) by hypernatremia was suggested by Crook and colleagues to be the causative factor [18]. LPL, which helps in clearing chylomicrons and very low density lipoprotein from circulation, is inhibited almost instantaneously by 500 mmol/l of NaCl in vitro. (39) However, the inhibition is fully reversible by dilution with salt-free medium. (39) In Hayek *et al* report, (38) hypertriglyceridemia developed when the mean serum sodium concentration exceeded 159 mmol/L in rats. Therefore, it seems that there are two mechanisms of inhibitions of LPL: instantaneous inhibition that occurs in vitro, when the enzyme is exposed to very high level of sodium chloride; and a gradual inhibition that occurs in vivo when the enzyme is exposed to high level of sodium chloride over longer period. This latter mechanism is probably the one that operates in patients with chronic hypernatremia.

Based on the above-mentioned explanations, the hypertriglyceridemia associated with hypernatremia is probably caused by two sequential mechanisms: The initial rise is due to a short-lived increased hepatic secretion of triglycerides. This elevation is maintained by LPL inhibition. These mechanisms are analogous to the sepsis-related hypertriglyceridemia. (40) Fatty liver, a well known clinical manifestation of sepsis, (40) was also documented in the hypertriglyceridemia of hypernatremia. (38) In both, the fatty liver is a result of disordered fat metabolism and not the cause. Mentioning these striking similarities, it needs to be determined if the hypertriglyceridemia of hypernatremia has a protective function as suggested in the hypertriglyceridemia of sepsis. (41)

Chronic hypernatremia is associated with increased concentration of organic osmolytes in the brain as a protective mechanism. (6, 42) The most important of these osmolytes can be quantified with proton nuclear magnetic resonance (NMR) spectroscopy in the brain of humans in vivo. (43, 44) This was suggested to be valuable in guiding the therapy of hypernatremic patients. (44) As chronic hypernatremia is also associated with hypertriglyceridemia, we can assume that the rise of serum triglycerides parallels the accumulation of organic osmolytes in the brain of these patients. If this association is confirmed, then serum triglycerides can be used as a simple method to guide therapy in hypernatremic patients.

In conclusion, the hypertriglyceridemia that accompanies chronic hypernatremia is probably caused by an increased hepatic secretion and maintained by the inhibition of lipoprotein lipase. It might be of help to guide therapy in these patients.

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