Combo effect of hypomagnesemia and hypokalaemia inducing nephrogenic diabetes insipidus in a patient with type 1 diabetes mellitus

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March 25, 2021

Abstract

NDI is rarely considered versus diabetes mellitus in the situation of polyuria. It is well known that hypokalaemia and hypercalcemia induce NDI through decreased activity of arginine vasopressin and downregulation of Aquaporin-2 water channels in the collecting ducts. However, not much is known whether hypomagnesemia can directly induce NDI.

Introduction

Nephrogenic Diabetes Insipidus (NDI) is a rare condition when compared to diabetes mellitus (DM). Both forms of diabetes (DI and DM) can be difficult to distinguish if both occur in the same patient. They both present clinically similar in terms of polydipsia and polyuria. NDI results from the failure of the kidney to concentrate urine due to the insensitivity of the distal nephron to respond to antidiuretic hormone (ADH); also referred to as arginine vasopressin (AVP). The later leads to polyuria of more than 3L in 24 hours with urinary osmolality less than 300 mOsm/kg H_2O and specific gravity of less than 1.005, causing an increase in plasma osmolality in response to raised serum sodium and urea.(1,2) NDI can be hereditary or acquired disorder. Acquired NDI is the most commonly observed due to drugs such as lithium or metabolic imbalances, such as hypokalaemia and hypercalcemia.(3) Refractory hypokalaemia management has been attributed to hypomagnesaemia. The co-administration of magnesium and potassium is essential for correcting persistent hypokalaemia.(4) However, little is known about hypomagnesemia as one of the cause leading to NDI. Here we describe a case of type 1 diabetic young man acquired NDI due to hypokalaemia and hypomagnesemia.

Case Report

A 27 year old male, newly diagnosed type 1 diabetic not on an insulin regime, was referred to our emergency department (ED) from a nearby peripheral center 3 hours post appendectomy with altered mental status (barely conscious) responsive to pain and laboured breathing. He had a 2 week prior history of recurrent abdominal pain, diarrhoea and vomiting. He was treated in several hospitals with IV fluids and antibiotics with no relief. About 12 hours prior to our ED admission, he was diagnosed to have appendicitis and thereafter appendectomy was done. Post-surgery the patient had developed laboured breathing with altered mental status, and electrolyte imbalance with severe hypokalaemia of 1.6mmol/L and an elevated blood glucose.

On arrival to our ED, physical examination revealed a well-nourished albeit severely dehydrated male weighing about 53 kg. He was febrile, stuporous and had deep laboured breathing. His vitals were: BP = 151/69 mmHg; HR = 132 bpm, RR = 32 breaths/min, SPO_2 = 96% on room air, Temp = 38.9°C, random blood glucose = 16.6mmol/L. Bedside ultrasound revealed collapsed inferior vena cava (IVC). His initial point-of-care venous blood gas showed metabolic acidosis (pH = 7.20, PCO2 = 21.5 mmHg, HCO_3 = 10.1 mmol/L) with

severe hypokalaemia of 2.2 mmol/L (3.5-5.0 mmol/L), hypernatremia of 167 mmol/L (135-145 mmol/L) and hyperchloremia of 125 mmol/L (98-109 mmol/L). Serial venous blood gases and electrolytes were done at every 3 to 6 h interval (Table 1). Urine analysis was unremarkable including the absence of urinary ketones.

Central line at right subclavian vein was placed whereby he received IV Ringers lactate boluses of about 4L and later maintained on IV 5% Dextrose water 500mls (free water deficit) admixed with potassium chloride 40 - 80 mmol ran at 125ml/h (KCl rate at 10 – 20 mmol/h) and fast acting insulin infusion at 0.05 U/kg/h (2.5 U/h). Post-operative broad-spectrum parenteral antibiotics were initiated, and the patient was then admitted to the ICU.

After 24 h of his admission, we noted the patient had a urinary output of 9L of dilute urine with negative fluid balance of 3L. His serum potassium levels were persistently low despite being on KCl infusion for over 24 h. At this point, his serum K level was 1.94 mmol/L. Serum magnesium levels were ordered to rule out probable cause of refractory hypokalaemia, which revealed hypomagnesemia of 0.50 mmol/L (0.66 -1.25 mmol/L). All other blood investigations including Brain CT scan were unremarkable except for the ECG which showed diffuse U-wave morphology (Fig.1) correlating with hypokalaemia and/or hypomagnesemia. Test for plasma levels of antidiuretic hormone (ADH) and urine osmolality were not available at our center. The reliable test used was urinary specific gravity which was low at 1.005.

Table 1: Blood gas and electrolytes from admission to the following 3 days

	Initial	**3hrs**	**6hrs**	**12hrs**	**24hrs**	**48hrs**	**72hrs**
pH	7.20	7.26	7.38	7.37	7.52	7.50	7.44
PCO_2	21.5	36.3	29.4	46	41.6	45.1	38.8
HCO_3^-	10.1	15.7	17.6	26.4	33.4	34.9	26
Na^+	167	164	160	159	155	151	146
K^+	2.2	1.69	2.2	1.8	1.94	3.17	3.01
Cl^-	125	117	119	115	115	108	105

Based on these updated findings, a diagnosis of nephrogenic diabetes insipidus (NDI) was made secondary to severe hypokalaemia and hypomagnesemia. Henceforth, his treatment was modified by adding 4g of magnesium sulphate along with 40mmol of KCL in 5% Dextrose water 500ml bottle ran at 125ml/h and along with the same insulin rate of 0.05 U/kg/h (2.5 U/h). This treatment plan continued for about 48 h since initiation till all serum electrolytes parameters normalized. In addition, oral Bendroflumethiazide 5mg twice a day, Indomethacin 50mg thrice a day, Eplerenone 25mg twice a day and Magnesium trisilicate 250mg thrice a day were added to his treatment.

Improvement in potassium and magnesium levels were seen on the 3rd day post admission with significant ECG improvement with the disappearance of U waves (Fig.2). Since admission the urinary negative balance over every 24 h was persistent for up to 7 days but was steadily declining over the days as the treatment continued. On the 8^{th}day in the ICU, the patient had significant clinical improvement with normal serum electrolytes and adequate positive fluid balance (input of 3.5L and output of 2.9L in 24 h). Thereafter, he was transferred from ICU to the general ward to continue with the management and follow-up.

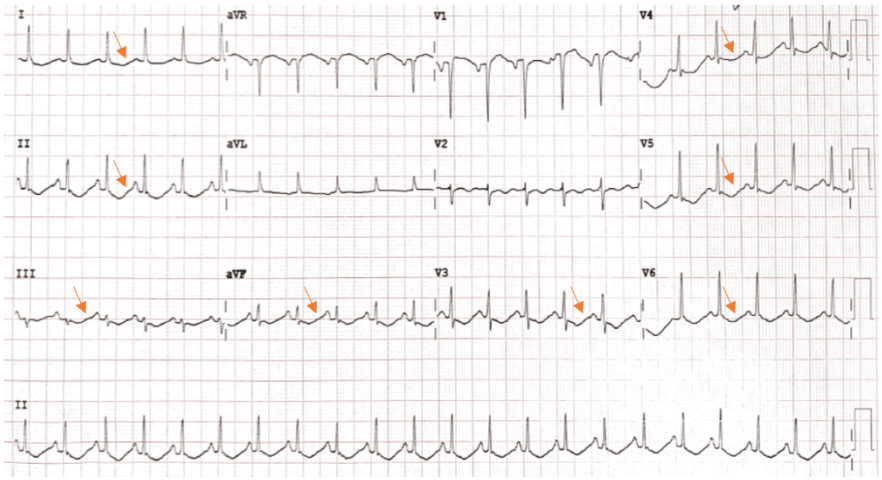

Fig 1. Diffuse U-waves on ECG correlating with hypokalaemia and hypomagnesemia.

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Fig 2. Two days on potassium chloride with magnesium sulphate infusion.

Discussion

Diagnosis of whether central or nephrogenic diabetes insipidus is challenging in resource limited set-ups especially if a patient has pre-existing diabetes mellitus. We were able to diagnose NDI and start the management on the second day with the resources available to us. Confirmatory tests like urine osmolality and plasma levels of arginine vasopressin (AVP) were not available, hence the diagnosis was made based on the available diagnostic tools and clinical judgment.

The ability of kidneys to concentrate urine is regulated through water balancing activities mediated via a complex AVP/AVP V2 receptor/Aquaporin-2 axis. Aquaporin-2 (AQP2) are the principal water channel cells that regulate water permeability at the collecting duct epithelium mediated chiefly via AVP effects.(5) Both hereditary and acquired causes of NDI lead to decreased in the AQP2 expressions and AVP action, thus causing similar consequences of free urinary water loss and increased plasma osmolality. Acquired NDI causes are more frequently encountered than the hereditary form, the culprit being drug induced or electrolyte disturbances. Lithium is not the only culprit but there are other several identified drugs (antibiotics, antifungals and antineoplastic) responsible in decreasing AQP2 expression and targeting, hence causing acquired NDI.(6)

In respect to metabolic cause, so far hypokalaemia and hypercalcemia have been identified from animal studies to induce NDI. It has been observed that hypokalaemia and hypercalcemia lead to autophagic degradation of AQP2 protein abundance in the inner medullary collecting ducts that impair urine concentrating ability. Henceforth, within their studies it was observed that correcting hypokalaemia and hypercalcemia ameliorates autophagic activities on AQP2 reversing NDI within 24 – 48 hours.(7,8) In our patient, hypokalaemia induced NDI was refractory to therapy despite high doses of parenteral potassium supplementation until a thought of coexistence of hypomagnesemia was sought. We corrected hypokalaemia and hypomagnesemia concurrently which had significant clinical improvement in correlation with ECG U-wave disappearance. (Fig.2)

Magnesium and potassium cations are predominantly intracellularly distributed which maintain stabilization

of membrane potential and decreasing cell excitability.(9) Deficiency of magnesium usually goes unrecognized exacerbating potassium wasting through impairment of Na-K-ATPase activity.(4) To our knowledge, no studies have been done to identify whether hypomagnesemia has any obvious physiological impact in directly causing NDI.

Conclusion

This was a rare clinical occurrence that we observed and treated in our practice. It is unknown whether similar occurrences have been taking place in our setting that are going unnoticed and being mismanaged due to its rarity and a delay in establishing diagnoses. Our emphasis is to always maintain a high level of suspicion in similar clinical presentations to ensure NDI does not go unrecognized.

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