

Hyporeninemic hypoaldosteronism in a patient with diabetes mellitus: an unforgettable case report

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Abstract: A 58-year-old man presented with a 3-year history of chronic and intermittent hyperkalemia requiring recurrent attendances to the emergency department for urgent treatment. His medical history included secondary diabetes mellitus following a bout of acute pancreatitis and a previous splenectomy for a spontaneous splenic rupture. He also had a history of prolonged use of non-steroidal anti-inflammatory drugs for back pain and painful neuropathy. He was not on any medication or diet that would cause a raised serum potassium level and his renal function was normal. He was on a basal-bolus insulin regimen but his diabetes control had been poor for several years. As the hyperkalemia had gone on for so long in the presence of normal renal function, he went on to have further tests. Adrenal insufficiency had been ruled out following a short Synacthen test. Further investigations revealed low serum aldosterone levels and inappropriately low serum renin levels in the presence of hyperkalemia. This was suggestive of hyporeninemic hypoaldosteronism (HH). He was then treated with fludrocortisone and furosemide and his serum potassium levels remained normal. Additionally, he did not require any more emergency admissions to treat hyperkalemia thereafter. It was concluded that the HH-induced hyperkalemia was caused by diabetes mellitus or due to a combination of diabetes and prolonged use of non-steroidal anti-inflammatory drugs. The absence of renal impairment may have contributed to the delay in diagnosis. HH is a commonly overlooked cause of hyperkalemia. This case highlights the fact that it should always be suspected when unexplained hyperkalemia is found in patients with only mild-moderately impaired renal function, especially in the presence of diabetes mellitus.

Keywords: hyperkalemia, diabetic nephropathy, juxtaglomerular cells, renin, aldosterone, fludrocortisone

Introduction

Hyporeninemic hypoaldosteronism (HH) is a type of renal tubular acidosis (RTA), also referred to as type-4 RTA. The aldosterone deficiency results in failure of hydrogen and potassium secretion in the collecting ducts, disorders in sodium reabsorption in distal tubules, and hyperkalemia-induced impaired ammoniogenesis in the proximal tubules.¹ The net effect is a reduction in potassium excretion, resultant hyperkalemia, and acidic urine due to loss of the ammoniogenesis-related buffering capacity of the urine.¹ There could also be a mild hyperchloremic metabolic acidosis. This is distinct from the other types of RTA where there is accompanying severe metabolic acidosis due to the inability to acidify the urine.² The commonest renal disease to produce HH is diabetic nephropathy, but other renal disorders may also produce it.³ In fact, most cases of HH are associated with mild to moderate renal impairment, where the renal

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impairment on its own is not enough to cause hyperkalemia.³ Despite this, the condition is still underdiagnosed in patients with diabetes mellitus. We report a case of a patient with secondary diabetes mellitus who had no obvious renal disease but developed chronic hyperkalemia requiring repeated treatment and was later found to have HH. Written informed consent was provided by the patient to have his case details published.

Case report

A 58-year-old Caucasian man presented to the endocrine clinic in 2008 with a 3-year history of chronic and intermittent hyperkalemia requiring recurrent attendances to the emergency department to receive urgent treatment with intravenous calcium–insulin–glucose therapy.

He had a long history of chronic back pain for which he had been using non-steroidal anti-inflammatory drugs (NSAIDs: indomethacin, diclofenac, and ibuprofen). In 1999, he had an urgent splenectomy for a spontaneous splenic rupture. A few months afterward while on holiday in Egypt in 2000, he was diagnosed with acute pancreatitis and secondary diabetes mellitus requiring urgent treatment with subcutaneous insulin. In 2008, he was seen by the neurologist for a 2-year history of symptoms of painful neuropathy and poor balance. Nerve conduction studies confirmed diabetic sensory-motor neuropathy secondary to poor diabetes control. Prior to being seen in the endocrine clinic, the patient had been advised to reduce the intake of potassium-containing foods and to avoid the use of NSAIDs as it was thought that these may be contributing to his continued hyperkalemia. Despite these interventions, the hyperkalemia and recurrent attendances to the emergency department persisted. His medication list at the time of presenting to the endocrine clinic included Humalog® insulin at meal times, human insulatard insulin at bed time, and calcium resonium powder to remove excess potassium.

On examination, he had no abnormal clinical findings apart from peripheral sensory loss affecting his feet. His serum creatinine and urinary albumin-creatinine ratio were normal, and an ultrasound scan revealed normal kidneys. Therefore, renal impairment and diabetic nephropathy were ruled out as a cause for his hyperkalemia. He also had a normal short Synacthen (adrenocorticotrophic hormone stimulation) test, which ruled out adrenal insufficiency. Further analysis of his serum renin and aldosterone levels revealed low serum aldosterone levels and inappropriately low serum renin levels consistent with a diagnosis of HH. He was not on any medication that would influence the renin–aldosterone analysis and he had

been seated for at least 15 minutes prior to venipuncture. The sample was obtained and taken to the laboratory within 15 minutes of venipuncture in accordance with stipulated standards to ensure proper and accurate results. Table 1 shows the results of investigations carried out, which excluded adrenal insufficiency and renal impairment but confirmed HH.

The patient was then started on fludrocortisone 100 µg daily and furosemide 40 mg daily for the hyperkalemia. His potassium levels remained in the normal range thereafter. He was also able to stop taking the calcium resonium powder.

Discussion

Hyperkalemia is defined as a serum potassium level above 5.0–5.5 mmol/L. It is usually asymptomatic but levels above 7 mmol/L can cause neurological and hemodynamic consequences, cardiac arrhythmias, cardiac arrest, and respiratory paralysis.⁴ Severe hyperkalemia is a medical emergency which requires a series of treatment steps (intravenous calcium to protect the heart, intravenous glucose and insulin to enhance cell uptake of potassium, beta-adrenergic agonist therapy, diuretics, or gastrointestinal cation-exchange medications to increase renal or gut excretion).⁵ Pseudohyperkalemia which is seen with difficult venipuncture, hemolysis and thrombocytosis should be ruled out by repeat careful venipuncture when possible.⁵

Over 90% of oral potassium intake is excreted through the distal-collecting tubules of the kidney and this is in exchange for sodium. This sodium–potassium exchange is dependent on sodium delivery, brisk urine flow, and an adequate response

Table 1 Results of the investigations

Biochemical test	Laboratory reference range	Results
Sodium, mmol/L	132–145	134
Potassium, mmol/L	3.4–5.1	5.9
Chloride, mmol/L	95–108	102
Creatinine, µmol/L	50–120	78
eGFR, mL/min	> 60	95
Bicarbonate, mmol/L	21–32	25
Post-ACTH cortisol, nmol/L ^a	> 550	617
Renin, mU/L	5.4–60	5
Aldosterone, pmol/L	100–450	< 75
Anion gap, mmol/L ^b	8–16	12.9
ACR, mg/mol ^c	< 3.5	0.5
Glycated hemoglobin (HbA1c), mmol/mol	20–44	96

Notes: ^aPost-ACTH cortisol is the cortisol level after the adrenocorticotrophic hormone (ACTH) stimulation test to rule out adrenal insufficiency. ^bAnion gap is calculated from serum [(sodium + potassium) – (chloride + bicarbonate)]. ^cACR, urinary albumin-creatinine ratio, a screening test for early diabetic nephropathy.

Abbreviation: eGFR, estimated glomerular filtration rate.

to aldosterone.^{6,7} Low plasma sodium or low renal blood flow, stimulates the conversion of prorenin to active renin in the juxtaglomerular (JG) cells in the kidneys. Renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by the angiotensin-converting enzyme (ACE) found in the endothelial cells of the capillaries throughout the body. Angiotensin II causes arterioles constriction resulting in increased arterial blood pressure. Angiotensin II also stimulates the secretion of aldosterone from the adrenal gland. Aldosterone stimulates renal tubular reabsorption of sodium, while at the same time causing potassium excretion into the urine. Therefore, aldosterone resistance or aldosterone deficiency due to impaired renin production from the JG cells, as seen in HH, will lead to impaired potassium excretion.^{6,7}

It is difficult to ascertain the prevalence of HH because patients are often on several medications in the presence of varying degrees of impaired renal function, and the condition has variable presentations. A previous case study has demonstrated that a large proportion of patients with unexplained hyperkalemia have biochemical features that suggest HH as a commonly overlooked cause of hyperkalemia and should always be suspected when unexplained hyperkalemia is found in patients with only mild-moderately impaired renal function.⁸ The diagnosis of HH is based on finding chronic hyperkalemia in a patient with no obvious cause (such as renal failure, use of potassium supplements, or potassium-sparing diuretics) with a low serum aldosterone level and a low or normal serum renin level on biochemical testing. Primary adrenal insufficiency should also be ruled out.⁹

There are various causes of hyperkalemia (glomerular disease, adrenal failure, potassium-sparing diuretics, potassium supplements, etc) as well as several causes of impaired renin production of which diabetes mellitus and NSAIDs are relevant to this case.¹⁰

Diabetes is thought to cause impaired renin secretion through 1) direct injury to the JG cells; 2) defects in the conversion of prorenin to active renin; 3) autonomic dysfunction with reduced beta-adrenergic stimulation; or 4) a primary increase in renal salt retention with volume expansion, which suppresses renin synthesis.^{9,10} A previous study revealed that about half of the patients with HH were found to have diabetes mellitus.¹¹ In addition, diabetes and hyperkalemia are commonly found together because of insulin deficiency, kidney disease, HH and use of medications such as angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-2 receptor blockers (ARBs).¹² Previous studies have found an association between HH and the microvascular complications of diabetes, namely autonomic neuropathy and diabetic nephropathy.¹³ However, most cases

of diabetes-related impaired renin production are associated with mild-moderate renal impairment.^{9,10} It is also important to remember that the presence of hyperkalemia in patients with type 1 diabetes may be due to concurrent adrenal insufficiency in the case of autoimmune polyglandular syndrome.¹⁴

NSAIDs cause raised serum potassium levels by decreasing renin secretion and impairing angiotensin II-induced aldosterone release. However, the hyperkalemia is usually mild and associated with NSAID-induced renal impairment or if there is concurrent use of other drugs that raise the plasma potassium level such as angiotensin inhibitors and potassium-sparing diuretics.^{15,16}

The treatment of HH usually involves the use of fludrocortisone (100–200 µg per day) which is a mineralocorticoid that promotes the reabsorption of sodium and loss of potassium in the renal tubules.¹⁷ Electrolytes must be monitored for the occurrence of hypokalemic alkalosis while on this medication. Alternatively or in addition, diuretics can be used to increase renal potassium loss if conditions such as hypertension, heart failure or edema are a concern.¹⁷

The patient in this case report had inadequately controlled secondary diabetes mellitus for several years before the onset of hyperkalemia. He also had a history of prolonged NSAID usage; however, the NSAID had been stopped a year before the diagnosis of HH. His renal function was completely normal. Painful diabetic neuropathy was the only diabetes complication he had at the time. He was not on any potassium supplements or potassium-sparing diuretics and he did not have biochemical evidence of adrenal insufficiency. In the presence of hyperkalemia, his serum aldosterone level and his serum renin level were below the normal range. Once started on oral fludrocortisone and furosemide tablets, his potassium level rapidly returned to the normal range. Every time he admittedly stopped taking his fludrocortisone for a few days, his potassium levels went up again and quickly returned to normal once he restarted the medication. This happened a few times when he occasionally felt fed up with taking his tablets in general. His serum potassium levels remained normal while on the fludrocortisone. We believe that poor diabetes control contributed to reduced renin production either by direct damage to the JG cells or impaired beta-adrenergic stimulation as part of diabetic neuropathy. It is possible that prolonged use of NSAIDs may have contributed to this. The fact that there was no evidence of renal impairment makes this case interesting and may have contributed to the delay in diagnosis. Since the diagnosis of HH, he has developed other diabetes-related complications, such as retinopathy, autonomic gastropathy, and very mild diabetic nephropathy.

Conclusion

We have presented a case of HH in a patient with secondary diabetes mellitus but no renal impairment. We believe the HH-induced hyperkalemia in this patient was caused by the poor diabetes control and possibly exacerbated by the prolonged use of NSAIDs. The delay in diagnosis gives credence to the notion that HH is an overlooked cause of hyperkalemia even in patients with no other obvious cause. We hope that this case report will not only add to the existing literature but also, most importantly, highlight the fact that HH is a commonly overlooked cause of chronic hyperkalemia and should not be forgotten.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Penny MD, Oleesky DA. Renal tubular acidosis. *Ann Clin Biochem.* 1999;36(Pt 4):408–422.
2. Batlle D, Kurtzman NA. Distal renal tubular acidosis: pathogenesis and classification. *Am J Kidney Dis.* 1982;1(6):328–344.
3. Batlle D, Haque SK. Genetic causes and mechanisms of distal renal tubular acidosis. *Nephrol Dial Transplant.* 2012;27(10):3691–3704.
4. Lederer E, Alsaukas ZC, Mackelaite L, Nayak V [webpage on the Internet]. Hyperkalemia. *Medscape* [updated May 18, 2017]. Available from: <https://emedicine.medscape.com/article/240903-overview>. Accessed October 17, 2017.
5. Ahee P, Crowe AV. The management of hyperkalaemia in the emergency department. *J Accid Emerg Med.* 2000;17(3):188–191.
6. Montani JP, Van Vliet BN. General physiology and pathophysiology of the renin-angiotensin system. In: Unger T, Schölkens BA, editors. *Angiotensin Vol. I.* Heidelberg: Springer-Verlag; 2004:3–29.
7. Kobori H, Nangaku M, Navar LG, Nishiyama A. The intrarenal renin-angiotensin system: from physiology to the pathology of hypertension and kidney disease. *Pharmacol Rev.* 2007;59(3):251–287.
8. Tan SY, Burton M. Hyporeninemic hypoaldosteronism. An overlooked cause of hyperkalemia. *Arch Intern Med.* 1981;141(1):30–33.
9. Sousa AGP, Cabral JVS, El-Feghaly WB, Sousa LS, Nunes AB. Hyporeninemic hypoaldosteronism and diabetes mellitus: pathophysiology assumptions, clinical aspects and implications for management. *World J Diabetes.* 2016;7(5):101–111.
10. Sondheimer JH [webpage on the Internet]. Hyporeninemic hypoaldosteronism. *Medscape* [updated March 12, 2017]. Available from: <https://emedicine.medscape.com/article/242494-overview>. Accessed October 17, 2017.
11. Phelps KR, Lieberman RL, Oh MS, Carroll HJ. Pathophysiology of the syndrome of hyporeninemic hypoaldosteronism. *Metabolism.* 1980;29(2):186–199.
12. Shaked Y, Blau A, Shpilberg O, Samra Y. Hyporeninemic hypoaldosteronism associated with multiple myeloma: 11 years of follow-up. *Clin Nephrol.* 1993;40(2):79–82.
13. Nakamura R, Saruta T, Yamagami K, Saito I, Kondo K, Matsuki S. Renin and the juxtaglomerular apparatus in diabetic nephropathy. *J Am Geriatr Soc.* 1978;26(1):17–21.
14. Liamis G, Liberopoulos E, Barkas F, Elisaf M. Diabetes mellitus and electrolyte disorders. *World J Clin Cases.* 2014;2(10):488–496.
15. Schlondorff D. Renal complications of nonsteroidal anti-inflammatory drugs. *Kidney Int.* 1993;44(3):643–653.
16. Campbell WB, Gomez-Sanchez CE, Adams BV, Schmitz JM, Itskovitz HD. Attenuation of angiotensin II- and III-induced aldosterone release by prostaglandin synthesis inhibitors. *J Clin Invest.* 1979;64(6):1552–1557.
17. DeFronzo RA. Hyperkalemia and hyporeninemic hypoaldosteronism. *Kidney Int.* 1980;17(1):118–134.

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