Case Report

Hypomagnesemia Associated with Caroli's Disease

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Abstract

Caroli's disease is a hereditary disorder invariably associated with biochemical changes characteristic of cholestasis and/or chronic kidney disease (CKD). Two cases of Caroli's disease with CKD presented with hypomagnesemia. Urinary fractional excretion of magnesium was inappropriately high. Magnesium mal-absorption and inappropriate urinary wasting are potential explanations of hypomagnesemia.

These case reports raise physician awareness about hypomagnesemia as one of the potential biochemical abnormalities that complicates the rare disorder of Caroli's disease and the possible appropriate course of treatment. They also attract investigators' interest for more research to explore the exact cause of this abnormality in this condition.

INTRODUCTION

Caroli's disease is a rare disorder characterized by a combination of intrahepatic bile ducts dilatation and cystic renal disease and is diagnosed by imaging [1]. In cholestatic conditions as in Caroli's disease, fat soluble vitamin absorption including vitamin D is impaired [2]. This vitamin is commonly deficient in CKD patients [3,4]. Serum vitamin D level therefore is expected to be low in Caroli's disease. Hypomagnesemia may be one of the biochemical consequences of this deficiency. In these 2 case reports who were admitted with hypomagnesemia which improved partially with vitamin D level correction. Partial correction of serum magnesium raises the question of a possible other mechanism as urinary wasting that might explain this biochemical abnormality in this condition.

CASE PRESENTATION

Case 1

66 years old lady with a diagnosis of Caroli's disease, polycystic kidneys disease (PKD) referred to renal services for follow up of deteriorating kidney function. She developed symptoms of muscle weakness and numbness of extremities. Routine investigations revealed CKD4 with an eGFR of 18 ml/min. This was associated with hypokalemia, hypomagnesemia and hypocalcaemia as shown in Table 1. Patient regular medications included Lansoprazole, Alfacalcidol, Loop Diuretic and Ciprofloxacin. The latter was given daily as a prophylaxis of liver cysts infection. She was admitted for intravenous (IV) potassium, magnesium and calcium infusion. Loop diuretic stopped and Lansoprazole replaced by Ranitidine. Symptoms improved with correction of biochemical abnormalities. She was discharged on oral magnesium glycerophosphate which she could not tolerate because of diarrhoea. Few months later she was readmitted with similar symptoms and biochemical abnormalities. On this occasion 25 OH Vitamin D serum level was checked and was low as shown in Table 1. Urinary fractional excretion of magnesium (MFE) checked in two separate occasions and was inappropriately high at 8%. High doses of oral nutritional vitamin D, colecalciferol (10.000 units) was given on weekly basis. Vitamin D serum levels improved from 20 to 55 nmol/L. Ameloride tablets were tried to help improve both hypokalemia and hypomagnesemia but she could not tolerate it. She maintained serum magnesium below reference range at 0.6 mmol/L on recurrent occasions but remained symptom free. All other biochemical abnormalities known to potentiate hypomagnesemia as hypokalaemia and hypocalcaemia were normalized as shown in Table 1. Vitamin D level remained acceptable at 55 nmol/L. Of note serum magnesium has improved temporarily as shown in Table 1 with IV magnesium infusion despite suboptimal vitamin D serum levels at 20.7 in May 2012. This improvement did not last long except after correction of vitamin D serum levels at 55 in October 2012 when the patient did not require any more admissions for IV magnesium and remained symptom free. Throughout her illness she maintained an eGFR at around 20 ml/min. She was reviewed on many occasions by dietician to ensure adequate intake of deficient nutritional elements although she has lost a

Table 1: Biochemical results of Case 1

Date	Cr (umol/L)	Ur (mmol/L)	eGFR (ml/min)	K (mmol/L)	Ca (mmol/L)	P (mmol/L)	Mg (mmol/L)	PTH (pmol/L)	25OH-Vit D (nmol/L)	Alb (g/L)	ALP (IU/L)	Bil (umol/L)	AST (U/L)
11.201	243	12.6	18.2	3.9	1.79	1	0.33	31.5		39	249	3	23
5.201	216	19	21	3.5	2.12	1	0.55		20.7	22	142	7	
10.201	199	17	22	3.4	2.34	0.9	0.54	13.2	55.7	25	146	7	

Table 2: Biochemical results of Case 2

Date	Cr (umol/L)	Ur (mmol/L)	eGFR (ml/min)	K (mmol/L)	Ca (mmol/L)	P (mmol/L)	Mg (mmol/L)	PTH (pmol/L)	25OH-Vit D (nmol/L)	Alb (g/L)	ALP (IU/L)	Bil (umol/L)	AST (U/L)
5.201	247	12.2	19.2	3.8	2.04	1.1	0.55	76.3		31	1736	3	88
5.201	328	17.1	13.8	4.1	2.3	1.5	0.59	12.6	58.8	26	657	5	
6.201	420	15.3	10.3	4.5	2.58	1.9	0.69	10.3	51.3	29	921	9	

significant amount of weight within the 2 years follow up period.

Case 2

50 years old lady diagnosed with Adult polycystic kidney disease in 1982 with strong family history of PKD suggesting autosomal dominant inheritance (ADPKD). Genetic testing was not done to confirm the responsible gene mutation. In 2003, she underwent cholecystectomy and left hepatectomy because of common bile duct and intrahepatic biliary stones. She was found to have cystic changes in the biliary channels consistent with Caroli's disease. She was referred to the renal department because of worsening kidney function with CKD4. Her main complaint on referral was intense pruritus which failed to respond to most of the antihistamines, Ursodeoxycholic acid, Rifampicin, Naltrexone or Gabapentin. She did respond only to recurrent Molecular Adsorbents Recycling System (MARS). Liver function tests (LFTs) were deranged reflecting cholestatic picture. Synthetic liver functions were normal. In 2008 she was admitted with clinical picture, biochemical changes and imaging all consistent with the diagnosis of acute pancreatitis and commenced on pancreatic supplement. In one of the routine follow up visits she complained of pins and needles in her hands. Corrected calcium, magnesium and vitamin D serum levels were all low at 1.77 mmol/L, 0.56 mmol/L and 22 nmol/L respectively. She was given IV calcium and magnesium infusion and she was already receiving daily dose of the active vitamin D alfacalcidol. She received high doses of native vitamin D (colecalciferol) as a replacement therapy. Repeat check of vitamin D was 58.8 nmol/L. Serum magnesium level remained low despite of advanced CKD with an eGFR of 13.8 ml/min. It was difficult to replace Esomeprazole because of severe gastritis. Whilst haemodialysis (HD) treatment improved serum magnesium, it did not reach reference range (Table 2). Urinary magnesium studies were only done when patient maintained on regular HD. Clearly HD treatment would confuse the results of this investigation with intradialytic magnesium influx. A 24hour urinary magnesium was 1.23 mmol. MFE was 24% which is inappropriately high in the context of low serum magnesium at 0.69 mmol/L. Serial checks of biochemical variables are presented in Table 2.

DISCUSSION

Pathophysiology of Caroli's disease is unclear although mutation of polycystic kidney and hepatic disease 1 gene (PKHD1) is implicated in many cases with Caroli's disease associated with autosomal recessive PKD [5]. Fibrocystin function which is the protein product of this gene [6] is also unclear [7]. Rare cases of Caroli's disease are associated with ADPKD. The protein products of ADPKD genes polycystin 1 and 2 are unrelated to fibrocystin although there might be an interrelationship between both in the development of cystic kidney changes [8]. It's unknown that any of these proteins are involved in magnesium handling in the gastrointestinal tract or kidneys. Polycystin 1 and 2 proteins are known as cation-selective ion channels transient receptor potential (TRPP). This subfamily bears some structural similarity to a member of the TRP superfamily called TRPM6 [9]. Mutations of TRPM6 cause familial hypomagnesemia with secondary hypocalcaemia [10,11]. Whether mutation in any of these TRP genes is responsible for production of abnormal proteins that are involved in magnesium handling remains unknown. Unfortunately, genetic study of these cases was not performed which might have added more light on the pathophysiology of hypomagnesemia. Both patients presented with hypomagnesemia which is uncommon finding in patients with advanced renal failure. Surprisingly enough, serum magnesium level is generally elevated in chronic kidney disease (eGFR<30ml/min) and patients on HD [12-15]. Magnesium homeostasis in these cases will depend largely on increased fractional urinary magnesium excretion to compensate for reduced excretory function of the kidneys. The fine adjustment of magnesium loss takes place in the distal tubule where 5-10% of the filtered load is reabsorbed actively through a transcellular route via the TRPM6. Around 3-5% of the filtered load is excreted in the urine [16].

Urinary magnesium wasting is suggested when daily magnesium loss is in excess of 10 mg or MFE of more than 2% in the presence of normal kidney function and hypomagnesemia. Urinary magnesium in our cases is complicated by the advanced renal failure with the characteristic compensatory increase in MFE to maintain normal serum magnesium which makes reliability of this test in our cases would be questionable. Reasons are partly

due to reduced eGFR and partly due to inevitable magnesium gain from dialysis treatment. Therefore, the contribution of excessive urinary magnesium loss as a cause of hypomagnesemia in these cases in addition to gastrointestinal malabsorption would be very difficult to ascertain. Partial response to colecalciferol treatment is not unexpected. Of interest both patients were already receiving the active form of vitamin D alfacalcidol when they presented with hypomagnesemia. Nesibe and Sinasi have reported [17] a positive role of vitamin D in the treatment of familial hypomagnesemia. Calcitriol increases also gastrointestinal magnesium absorption [18,19]. Vitamin D deficiency is not uncommon in patients with CKD [20,21]. Moreover, fat soluble vitamins absorption may be impaired in Caroli's disease due to cholestasis, hence serum levels of this vitamin would be even worse. There is also a theoretical risk of reduced vitamin D hydroxylation in cases with cholestasis albeit denied by others [22]. Lack of hydroxylation in these cases may explain the poor response of hypomagnesemia to alfacalcidol but does not explain the partial response to native vitamin D replacement.

CONCLUSION

These case studies report for the first time unexplained hypomagenesemia in Caroli's disease. Of interest it did happen in the context of chronic kidney disease with or without haemodialysis treatment which is a confounding factor. The exact cause of hypomagnesemia remains unclear and would be a subject for further investigations. Correction of vitamin D deficiency could be one of the treatment options amongst others for this biochemical abnormality. The recommended preferred form of vitamin D replacement in these cases needs further investigations.

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DISCLOSURE

The author declares no conflicts of interest.

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