Reviewer’s report

Title: Case Report: Extreme coronary calcifications and hypomagnesemia in a patient with a 17q12 deletion involving HNF1B

Version: 0 Date: 19 May 2019

Reviewer: Gema Ariceta

Reviewer's report:

Dear Dr Howard and coauthors:

Your manuscript entitled "Case Report: Extreme coronary calcifications and hypomagnesemia in a patient with a 17q12 deletion involving HNF1B, describes a patient with hypomagnesemia of renal origin and bilateral renal cysts associated with MODY type diabetes, and severe coronary artery calcification, who was discovered to be caused by 17q12 deletion involving HNF1b gene and other 15 genes. The patient was diagnosed at 62 years of age, and presented with neurologic symptoms as well.

The case report is well described and is of interest, and further, demonstrates that even in senior patients monogenic diseases can be discovered. In this patient, systemic involvement of different systems could raise an alert of a unique cause, whereas a large 17q12 deletion could explain the complex phenotype and mainly the neurologic picture.

I support this manuscript for publication, however before that, I recommend some changes and comments, detailed below:

* Lines 87-90 authors missed to comment about the presence of hypokalemia and hypocalcemia at baseline. Further, it would be important to remark if the presence of hypercalciuria was observed before starting treatment with furosemide, of it could be secondary to diuretic use. That concept is key as disorders at the ascending thick segment of loop of Henle cause hypermagnesiuria and hypercalciuria, whereas disorders at the distal convoluted tubule cause loss of magnesium in urine and not increase loss of calcium in urine.

* Family history: could other members of the family be tested for 17q12del? Authors said there were not history of consanguinity. Please state that HNF1beta deletions are very frequently "de novo mutations" and they are inherited as dominant trait,… therefore lack of consanguinity had not a major impact on the diagnosis suspicion.
Discussion

* Please add that other causes of urinary calcium and magnesium loss could be related to CaSR and lack of action of HNF1b on claudin 19 and 14 among others

* Lines 156-160. The explanation that permanent Mg wasting could be attributed to subclinical acute nephrotoxic episodes and parallelism with cisplatin toxicity is not convincing in this patient. Please introduce other ideas at the discussion such as:
  
i) Hypomagnesemia linked to HNF1b mutation has been described to very more frequent and severe over time, with age, and thus, it is expected in a 62 y, old patient

ii) HNF1b deletion causes more severe phenotype, and this patient had a large deletion involving 15 genes,... could be the clinical picture the resulting effect of other gene?

iii) Discuss the rol of CKD in this patient with bilateral cysts,... and chronic tubulointerstitial disorder too. Consider the potential consequences of chronic untreated kypokalemia on cysts formation, CKD and tubulointerstitial disease

iv) Was patient diabetes well controlled? Often hypoMg is associated with bad controlled diabetes

* Associated family cardiovascular risk factors: did other family members have a genetic diagnosis?

* Hypomagnesemia has been observed to produce HTN, could be another CV factor in this patient?

* Please make a comment on patient treatment. How could you justify the continuous use of furosemide? Could that diuretic be the cause of moderate hypercalciuria and worsening urinary magnesium loss?

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