Author’s response to reviews

Title: A case report of adult-onset COQ8B nephropathy presenting focal segmental glomerulosclerosis with granular swollen podocytes

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Version: 1 Date: 23 Jul 2020

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July 23, 2020

Dear Maria Jose Soler:

Thank you for your comments on our manuscript (BNEP-D-20-00213) entitled “A case report of adult-onset COQ8B nephropathy presenting focal segmental glomerulosclerosis with granular swollen podocytes”, which was submitted for publication in the BMC Nephrology. We wish to express our appreciation to the editor and Reviewer #1 for his or her insightful comments, which have helped us significantly improve the manuscript. Our responses follow the Reviewer’s comments.
Comment 1: First of all, it is striking that this patient has exclusively kidney involvement. As the authors will know, in a large percentage of cases there are extrarenal manifestations, mainly neurological. How could the exclusive renal involvement be explained in this clinical case?

Response 1: Thank you for this comment. According to your suggestion, we added this explanation to the “Discussion and Conclusions” section of the revised manuscript as follows:

“This patient had no neurological or myopathic features, which are common in mitochondrial diseases. Consistent with these observations, COQ8B mutations cause selective glomerular phenotypes, mostly without neurological and myopathic deficits [11,12,19–24]. Although the mechanism of this selectivity remains unclear, a potential explanation may be the difference in distribution patterns between COQ8B and COQ8A with high sequence similarity [11,12]. COQ8B is highly expressed in podocytes, whereas COQ8A is expressed in most body tissues but not podocytes [11]. Neurologic abnormalities were reported in only 14%–24% of patients with COQ8B nephropathy [12,19]. Although we cannot completely exclude the possibility of extrarenal involvement, the patient was clinically considered to have presented a selective glomerular phenotype.”

Comment 2: The main question refers to the findings of the renal histology. Are these types of population abnormalities specific to this entity? Is there other scientific evidence that can corroborate these findings? These podocytic findings could not correspond to those found in the FSGS podocytes? It is essential to clarify these issues to give greater scientific relevance to this clinical case.

Response 2: We thank you for this important comment. According to your suggestion, we performed COX-IV staining to clarify the possibility that light microscopy can detect accumulation of mitochondria. This clearly showed increased segmental staining of COX-IV in this patient compared to the control. This finding is consistent with the results of Masson’s trichrome staining. On the other hand, we cannot refer to scientific relevance, such as the sensitivity or specificity of this podocyte finding because it is difficult to obtain enough patients for rare diseases.

Therefore, we have made the following revisions to the manuscript. First, we have included Figure 1H and its relevant legend as follows.

“H Immunochemistry staining for COX IV showing increased segmental staining of COX-IV in the glomeruli of this patient (left panel), but not those of control patient with no mitochondrial diseases (right panel). COX IV-positive podocytes and normal podocytes are indicated by white and black arrowheads, respectively. Scale bars: 20 μm.”

Second, we have added upon the results shown in Figure 1H in the “Discussion and Conclusions” section of the revised manuscript as follows:

“is the best way to detect these cells because it stains mitochondria red [27]. Therefore, our light microscopic findings of podocytes due to COQ8B nephropathy appear to be similar to those of GSECs in tubules due to mitochondrial diseases [27], which suggests that this is the first report to
detect GSECs in podocytes due to mitochondrial diseases under light microscopy. Moreover, increased podocyte expression of a mitochondrial-specific protein COX IV in this patient supports the observation that light microscopy can detect accumulation of mitochondria in podocytes (Fig. 1H). It might be difficult to clearly detect red-stained granules in all abnormal podocytes because their cells are smaller than tubular cells.”

Third, we have added several sentences in the “Discussion and Conclusions” section of the revised manuscript as follows:

“We cannot refer to the sensitivity or specificity of these podocyte findings because it is extremely difficult to obtain sufficient numbers of patients for rare diseases. Because Masson’s trichrome staining was not demonstrated in previous report of COQ8B nephropathy [11,12,19–24], further studies may be necessary to carefully evaluate and determine the scientific relevance of this staining.”

In addition, we have changed sentences in the “Discussion and Conclusions” section of the revised manuscript as follows:

“who presented with granular swollen podocytes in segmental and global sclerotic glomeruli under light microscope. When GSECs are found in podocytes, suspecting mitochondrial disease may lead to a faster and more accurate diagnosis. Therefore, we propose that this finding can be the clue for the diagnosis of mitochondrial nephropathy. As few patients develop COQ8B nephropathy aged 20 or older, it is important to carefully suspect CoQ10 deficiencies.”

Finally, we have changed the Abstract as follows:

“This is the first report of granular swollen podocytes due to mitochondrial diseases detected under light microscopy. We propose that this finding can be the clue for the diagnosis of both COQ8B nephropathy and the other CoQ10 deficiencies.”

We appreciate the reviewers’ helpful suggestions. We believe the revised manuscript is significantly improved over the initial submission. We hope that it meets the standards and will be now accepted for publication in the BMC Nephrology.

Sincerely,

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