Reviewer’s report

Title: Congenital emphysematous lung disease associated with a novel Filamin A mutation. Case report and literature review

Version: 0 Date: 02 Dec 2018

Reviewer: Nadia Nathan

Reviewer's report:

The manuscript is a case report on FLNA mutation with lung involvement. These presentations are rare enough to be of great interest for clinicians in the field of rare lung diseases. The authors report a new mutation, and a largely documented review of the literature.

Despite needed modifications, the manuscript is very interesting and well written.

Major comments:
The case report is nicely described.

1/Some precisions would be appreciated in the case description:
- "After stabilization of the subject's respiratory condition..." how? Spontaneously? With medications?
- "the patient shows general muscular hypotonia": is it really muscular hypotonia, were the muscles tested, or neurological hypotonia, or hypotonia due to respiratory failure and fatigue? This sentence is in opposition with a following sentence: "the patient was not suffering from any neurological symptoms at this stage". Please precise.

2/The molecular finding needs some precisions:
- How important is the mosaic?
- What are the molecular arguments for the pathogenicity of the identified variant?
- Did you performed a FLNA staining on the lung biopsy?

3/The illustration (Figure 1) needs to be improved:
- Add the first CT-scan so the reader could appreciate the child's evolution (panels Bc and Bd could be removed as they don't add substantial info to panels Ba and Bb).
- Panel C: it may be my PDF version's problem but the resolution is low and I can't see lung fibrosis on panel Ca. Could you improve the figure's resolution and add arrows? To me, on the proposed slide, alveolar simplification is not clearly seen neither. Panel Cb: the tenascin is a extracellular matrix staining that is unfrequently used. A control panel would be useful. Here again, the resolution is low and the histology seem very different from Panel Ca. Do the 2 panels show different parts of the lung biopsy (heterogeneity of the lesions?). It's unclear.
- Panel D: add arrows to point out PVNH

4/ Discussion
- Table 1 and a large part of the discussion (lines 12 to 46) are redundant. An abstract of the number of described cases, median age at onset, number of cases with PVNH, male/female severity, discussion of PDA association, etc … would be much more interesting.
- Table 1: what was the ordering criteria of the Table? Pick-up one (date of publication, number of the amino-acid involved, age at onset or whatever that could be logical for the reader). Precise when the patients are from the same family. And precise the [REF] of the listed articles.
- Table 1 and text: Gerard-Blanluet (not Blaunluet). As I understand, in this manuscript, the male twins present a severe disease. Could it be related to premature birth (precise term of birth) and BPD? The mother and the sisters carry the mutation (and PVNH) but have no lung disorder: there is an offset in the Table (also for follow-up). Age at onset is birth? 24-26 weeks are the term of gestation? Unclear and I have no access to this manuscript to better understand.

5/ Conclusion
Early recognition with chest imaging … this is too much fuzzy. Please precise what the reader should look for on chest imaging that should make him think about FLNA? Same remark in the abstract.

Minor comments:

Case presentation
- remove () "on the basis of radiological findings"
- "the patient shows general muscular (and not muscolar) hypotonia"
- 3,140 grams or 3.140 kg
- surfactant (the "t" is missing)
- Was TBX4 mutations excluded (hips and lung alveolar simplification)?

Discussion
- line 5: multiple organs ("s")
- One says that male FLNA mutations are more severe than in females. This has been discussed and controverted by other reports involving females. This could be better resumed in the discussion section.
- MSC: explicit

Table 1
- PDA: explicit under the Table. When PDA, precise if the patients are prematurely born?
- p.(…) or (p….). Une the same layout
- Precise the type of mutation (frameshift, nonsense, splice etc…)
- 5th column: chest CT scan, and avoid ";" with nothing after
- Line 3: dysplasia ("a" is missing), and precise the lung status at follow-up
- Line 8: Focal hyperinflation with minimal patchy atelectasis: move to CT findings
- Line 9: death at what age?
- Line 10: meconium (no "h")
- Line 11: hyperinflation and hyperluency: is it a mosaicism aspect? Central PA enlargement: where there clinical or echographic signs of PAH?
- Line 12: your case: add tracheostomy in the surgery column?

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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Not relevant to this manuscript

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Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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