Author’s response to reviews

Title: Renal manifestations of Tuberous Sclerosis Complex: patients' and parents' knowledge and routines for renal follow-up - A questionnaire study

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Author’s response to reviews:

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Editor in Chief
Dr Hayley Henderson

Dear editor and reviewers,

Thank you for finding our manuscript of interest. Please find enclosed a revised version of the manuscript BNEP-D-17-00270:

Renal manifestations of Tuberous Sclerosis Complex: patients' and parents' knowledge and routines for renal follow-up - A questionnaire study

We found the comments from the reviewer very helpful and have tried to accommodate to the suggestions made, as described below:
Comments from the Editor:

-Please submit the French questionnaire or translation as an appendix.

Response: A translation of the French questionnaire is submitted as an appendix.

Reviewers’ comments:

- Reviewer #2.1 Methods report only informed consent was obtained for Norwegian participants. Either report the same practice was followed for French participants or include a statement in the methodology that requirement for informed consent was waived by the ethics board or regulatory body providing oversight for the study in France.

Response:

The following section has been included on page 7 paragraphs 4, lines 48-55, and under consent to participate on page 16 paragraph 4, lines 43-50:

In France, the questionnaire was anonymous and the study design was classified as ‘non-interventional’ by the Ethics Committee. As a result, the need for an informed consent was waived.

Letter from the French ethics board is submitted on request.

- Reviewer #2.2

Prior to international consensus recommendations published in 2013 in which renal surveillance imaging was recommended to be done every 1-3 years, recommendation for surveillance imaging in TSC had not been emphasized in published literature for the most part since 1998-1999. As this study was conducted in France prior to 2013 and the bulk of Norway surveys done afterward, could this have contributed to the lower utilization of surveillance imaging in France compared to Norway (in addition to differences in health care systems, etc.)?

Response:

Thank you for your comment. The study was conducted in France prior to the international recommendations and prior to the French guidelines recommending renal imaging every 1-3 years. The French recommendations were published before the Norwegian study was conducted, but more than half of the Norwegian patients were included before the international recommendations were published. It is believable that recommendations need a longer time period to be implemented.

The following section has been included on page 14 paragraph 2 lines 46-54:

Although the follow-up guidelines were probably not implemented in 2013-2014, when the study was conducted in Norway, awareness regarding kidney changes and the need for regular
investigations may have been greater at that time than in 2009-2011 when the study was conducted in France [6, 12].

- Reviewer #2.3

3) 2nd to last paragraph on page 10 in results section has obvious typo. At first I thought on line 37 a simple omission of "three" before years was the problem. But then in continuing to discuss the details of the observation that some patients receive no imaging at all, adding up the different subgroups indicates that the authors are describing those without any imaging (N=24) rather than those who were not getting imaging at least every 3 years but at least had some imaging in the past (N=76). This needs to be fixed/clarified.

Response:

Thank you for your correction. We have clarified according to your suggestion.

I found a further mistake in the data and have corrected it accordingly. The percentage of patients that did not receive renal imaging at least every three years has been changed from 28 % to 30 %; appropriate corrections have been made in the abstract, the manuscript, and in Table 2).

The following change has been made in the abstract: Among 30% of patients, renal imaging was not received at all, or not conducted every 1-3 years as recommended by current guidelines.

The following changes have been made on page 9 paragraph 3 lines 39-57 in the manuscript: Imaging at least every three years had not been performed for 30 % of the patients (83/276) and, among these, 24 had never undergone any renal imaging. Among those who had not undergone any imaging, seven were under 15 years, three were between 15 and 29 years, eight were between 30 and 44 years, and five were over 45 years. In one case the patient’s age was not provided. The proportion of patients who did not receive imaging at least every three years was significantly higher among patients in France (36 % [65/182]) than in Norway (19 % [18/94]; p= 0.004).

The proportion of patients who did not receive imaging at least every three years in France is changed in the discussion on page 13 paragraph 2 line 32 from 33 to 36%.

- Reviewer #2.4

4) In the discussion, the authors stress the importance for clinicians and other sources of information to parents/patients provide education/awareness of angiomyolipoma and associated bleeding risk at least by age 15y (and thereafter). It would be helpful and important for the current discussion regarding angiomyolipoma bleeding risk in TSC therefore to include in addition to age risk (that they do discuss) what is known about risk of bleeding overall from prior epidemiology/natural history studies as well as the current literature (albeit limited) that suggest that angiomyolipoma size >4cm (Ewalt 1998) is also an important risk factor.

Response:
Knowledge of the natural history of AMLs is limited [20], but it is well known that the risk of bleeding increases when the diameter is > 4 cm [10, 16]. Presence of micro-aneurysms may also predispose to bleeding [21-23]. Unfortunately, the presence of micro-aneurysms can only be assessed by intra-arterial angiography and this criterion cannot be used on a routine basis [24].

Lack of knowledge about the risk of bleeding was found to occur more frequently in the group of patients without AML (54 %) than in patients with AML (24 %, Table 2). Information provided to patients should be sufficient to ensure that they have adequate knowledge, but without causing unnecessary anxiety. This balance can be difficult to achieve.

Whether patients without AML or those considered to have a low risk of bleeding should be informed about this risk is debatable. In our opinion, those patients that do not have AML, or only small AMLs, should be informed that their risk is minimal; this provides information but should not provoke unnecessary worry.

Risk factors other than age are also included on page 11 paragraph 2 lines 53-56:

All should be provided with information about potential renal complications of TSC by the risk age for bleeding (15 years) or earlier if they are considered to be at risk.

And on page 12 paragraph 1 lines 14-17:

The medical community needs to improve their dissemination of information to patients and their families, and to adapt this information to patients’ ages and individual risk factors for bleeding.

And on page 15 paragraph 2 lines 46-52:

In addition, it is important that provision of advice is based upon the extent of renal manifestations in the individual patients.

Further changes in the manuscript:

A slight change has been done on page 8 paragraph 3 lines 41-45:

This percentage was significantly higher in Norway than in France, in patients who completed the questionnaire themselves, in patients in whom renal imaging was not performed at least every three years, and when the patients were < 15 years of age (Table 2).

A slight change has been done in the legend of figure 1.

A reference has been added on page 3 paragraph 2 lines 21-27:
Patients with TSC are at risk of suboptimal medical management for several reasons. First, it is a relatively rare disease affecting 1/6000 to 1/10000 live births [4, 5].

Two references has been removed and replaced with another on page 4 paragraph 1 lines 17-22:

Spontaneous bleeding of an AML is one of the most serious renal complications [14], and, at worst, may be life-threatening, potentially necessitating emergency nephrectomy [16, 17].

A reference has been removed and replaced with another on page 4 paragraph 1 lines 22-32:

Although the causes of AML bleeding are not well understood, the risk increases with AML size [18], and several guidelines recommend renal imaging every one to three years to monitor AML growth and to trigger prophylactic treatment for those AML considered to be at risk of bleeding [7, 13, 18].

A reference has been removed on page 11 paragraph 2 lines 56-59 to page 12 paragraph 1 lines 1-2:

Information should also be provided about the symptoms of renal bleeding: flank pain, haematuria, and shock [13, 16, 20, 28], and patients and their care givers should know what they should do if these symptoms occur.

A reference has been removed on page 13 paragraph 2 lines 36-41:

In addition, although the risk of developing symptomatic AML increases with age [10, 19] and increased monitoring are recommended in adulthood [7, 13, 26],

A reference has been added on page 14 paragraph 1 lines 10-13:

CT and MRI are more accurate, but more expensive and time consuming [32, 33].

The word mean has been included on page 11 paragraph 2 line 17-22:

The mean/median age of first detection of a renal abnormality (cyst or AML) in TSC ranges from 7.2 to 11.3 years [11, 23-26].

The following section has been included on page 17 paragraph 2 lines 19-23:

MB have received speaker honoraria from Novartis and is the national coordinator (Norway) of the EXIST-3 trial and an international disease registry collecting data on manifestation and outcomes in patients with tuberous sclerosis complex – TOSCA, funded by Novartis.

We hope you’ll find the revised manuscript acceptable for publication.
On behalf of the authors:

Yours sincerely,

Ine Cockerell