Author’s response to reviews

Title: Haemolytic uraemic syndrome associated with non shiga toxin-producing Escherichia coli bacteraemia: a case report

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Author’s response to reviews:

Dear Editor and Reviewers,

We would like to thank you for all your comments.

We have asked a colleague who is a native English speaker to read and correct our manuscript.

We now submit our responses to your questions and comments.

Response to Reviewer 1:

- Corrections to the English have now been made.

- Schistocytes did not appear on the blood smear on the first day, however they were subsequently observed in a significant quantity (3%). We are aware that this test is not always positive and needs to be repeated. However, we removed this sentence, as interpretation could lead to confusion.

- In our opinion, this somewhat unusual description essentially raises the question of the importance of exploring the complement alternative pathway in cases of what is known as « infection associated HUS ».

Response to Reviewer 2:

Thank you for your positive comments. Corrections to the English have been made.
Response to Reviewer 3:

- The objective was not made clear (although I wonder if that is necessary for this type of article) Defining an objective did not seem necessary for this type of article.

Execution

- The Abstract (mainly the conclusion) and the Background sections are not so well written. For example, "Infections play a central role in the development of HUS" (Introduction) as a single sentence is not appropriate, I would consider leaving it out of the intro and discussing this more in-depth in the discussion section. This point is also partly due to the language which should be improved throughout (suggest to consult a native speaker to carefully go through the work).

The manuscript has now been read and modified by a native speaker.

We have removed this sentence from the “background” section. We discuss the point more fully in the last paragraph of our discussion.

- I suggest to display the most important lab results, along with the reference values, perhaps for some key time points in a table.

We do not present a table of lab results; however, we believe that our Figure 1 is more ‘eloquent’. We can, of course, provide a Table if this is deemed necessary (although a Table featuring all the results of the complement biochemical analysis already appears with the article).

Interpretation

- The suggestion that the CFH mutation (p.Val215Ile ; c.643 G>A) could be pathogenic based on the region (SCR4) seems a bit premature (no functional studies have been performed by the authors or others); the authors should be a bit more careful in their interpretation.

Indeed, we cannot make any formal affirmation concerning the pathogenic nature of this rare CFH variant. We remain prudent, and do specify that ‘the functional implications of this variant warrant further investigation’.

- Haptoglobin was in the normal range, could the authors comment?
Haptoglobin had not fallen to the level expected for a case of hemolysis. However, it may have shown a ‘false normal’ because of the acute inflammatory syndrome (CRP and procalcitonin were both very high). The haptoglobin/orosomucoid ratio would probably have been in favour of hemolysis, supported by raised LDH and schistocyte level.

Furthermore, quite extensive complement analysis was performed, but all came back negative. Does this make the diagnosis less likely? The authors should discuss these findings in detail in the Discussion.

Quite extensive biochemical analysis came back normal, demonstrating the importance of a genetic screening. This has been described in a number of aHUS cohorts. In the French Cohort, C3 level is lower in only 40% of cases. Almost half of pathogenic variants have functional consequences, which have no impact on antigenic levels.

So this does not exclude the diagnosis. We have added this point in the ‘Discussion’ section.

I would like to see a more extensive discussion on previous studies suggesting the possibility of genetic predisposition to HUS that was "triggered" by an (infectious or other type of) event. Please also add references to support this.

We have included additional references supporting the hypothesis that the development of an aHUS requires factors of predisposition plus a trigger. This latter can be an infection or even pregnancy.

We have added Catherine Dal Molin to the ‘Acknowledgements’ section for her valuable help with reading the manuscript and advice on the writing.

We hope that the modifications made to the manuscript mean that publication will be possible in BMC Nephrology.

Yours sincerely,

Stéphane Bally, Jacques Fourcade et Véronique Frémeaux-Bacchi