Reviewer's report

Title: The bladder cooling reflex distinguishes clinical bladder hypersensitivity from overactivity disorders

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Reviewer: Mary P. FitzGerald

Reviewer's report:

General
The authors present interesting preliminary results concerning the use of the ice-water test in patients with PBS and IDO. The paper is well written and illustrated; the results are novel and add to the literature, and should be published. However this reviewer feels that the data is being over-interpreted and that the manuscript needs considerable editing before suitable for publication.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The authors are encouraged to consider revising their terminology throughout the paper. The BCR is either present or absent, not positive or negative (i.e. there is no such thing as a negative BCR). Alternatively, they could say that the ice-water test was either positive or negative. An analogy would be the Babinsky sign, which is referred to as being present when there is dorsiflexion etc of the toes. The current terminology is distracting because BCR negative doesn’t exist.

The title needs to be revised, since the findings of the study are NOT that ‘the BCR distinguishes clinical bladder hypersensitivity from overactivity disorders’, rather they found that ‘Pain during ice water test distinguishes clinical bladder hypersensitivity from overactivity disorders’ and this is a critical difference.

A final, major concern is the apparently premature rush to attribute the study’s findings to the involvement of TRPM8 receptors. The authors do concede near the end of the discussion that in fact TRPM8 may not be involved, but this concession does not balance the weight of earlier discussion of possible TRPM8 involvement, which really is not supported by the data from this study. The authors should consider de-emphasizing TRPM8, including removing that label from the figures. The conclusions of the authors regarding the importance of descending inhibition in PBS patients is not supported by this study.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Page 5: second paragraph – C-fiber afferent ‘activation’ in various ways ‘may be associated with functional changes such as increased urination frequency and urgency, as well as suprapubic pain’ – what evidence do the authors have for this statement? Please supply references.

Page 7: last paragraph – ‘cold sensation in the suprapubic region, presumably referred from the bladder’ – could this sensation actually be referred from the urethra?

Page 9: Discussion – ‘None of our PBS patients had a positive BCR, indicating that despite the increased TRPM8 nerve fibers, the inhibitory signals from higher centres being preserved, result in a negative BCR’ – another implication might be that in these patients, TRPM8 is not involved in the BCR.

Page 11: again, the pain of the ice water test does not evoke the BCR … one conclusion might be that the pain of the ice water test is just not due to involvement of TRPM8.

Please explain why the PBS patients in this study had such low levels of bladder pain at the start of urodynamics – levels of about 1/10 seem to be prevalent, and this seems to be too low for this group of patients. Perhaps this would be clarified by more clinical information about this group of patients?

Discretionary Revisions (which the author can choose to ignore)
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I declare that I have no competing interests.