Reviewer's report

Title: Abnormal Auditory Pathways In PHOX-2B mutation positive Congenital Central Hypoventilation Syndrome

Version: 2  Date: 21 October 2014

Reviewer: Thomas Rossor

Reviewer's report:

This is a very interesting approach to brainstem dysfunction in CCHS, in which ABR is used to determine if the abnormalities in the autonomic nervous system commonly seen in CCHS extend to abnormalities in the auditory pathway. I feel there are two major limitations of this paper. The first is a failure to use meaningful normative values to determine which patients have abnormal ABR. It is quite possible (I have not had time to go through the age adjusted norms for all the patients, but I have referenced normative data for infants in the first few months of life) that these abnormalities disappear when corrected for age.

My second concern is that if when the ABR have been age adjusted abnormalities persist, consideration must be given to alternative explanations for any increased latency in the ABR of affected children. Given the increasing body of evidence for increased interpeak latency of infants who have suffered various insults (HIE/Severe prematurity/ hyperbilirubinaemia) the possibility should be addressed that any abnormality of ABR seen in these infants could be a result of the frequent hypoxic/hypercarbic episodes these infants may face early in life, rather than reflecting a process directly associated with PHOX2B mutation.

While I am not convinced that this paper has demonstrated any association between abnormal ABR and CCHS, I think it is an interesting study that has a place in the literature. I do feel strongly that further consideration of normal values is essential, and the addition of the number of alanine repeats for each patient would be useful.

Major compulsory revisions

1) I am concerned with regards to the methods by which the ABR was determined to be abnormal. As we know that ABR latencies change considerably during the first two years of life, I do not feel that it is justifiable to simply take extremes of the combined population of normals and consider these abnormal. In fact the V-I latencies certainly for patient 1 are within normal age adjusted limits (1). I think it essential to judge the individuals against age adjusted norms. It may be that there are abnormalities that would thus be unmasked. If on the other hand these values have somehow been age adjusted, this has not been made sufficiently clear in the text.

(1) ROSA, Luana Araujo Cruz; SUZUKI, Marcia Rumi; ANGRISANI, Rosanna

Minor essential revision

1) It is unclear looking at the data table why there is no value for the Left V-I interpeak latency for patient 2 - should this be 5.4? (which might actually be abnormal)

2) P5, Line 18 - I cannot see on the table any infants without a wave I latency, but the text states 'one patient showed.....an unidentified wave I'. It would be useful to clarify what is meant.

Discretionary revisions:

1) P1, Line 4 - "PHOX2B which is the major causing-disease gene" is poorly phrased - perhaps "The PHOX2B gene, mutations of which define the condition, is expressed...."

2) P1, Line 7 - should be 'to which extent'

3) P4 Line 16 - 'The table shows major clinical conditions associated with CCHS' is not true. Perhaps it shows clinical characteristics

4) P4, Line 5 - if this normal data is to be used, further details including age of normals would be very useful as a separate table

5) P4, Line 7 - I am not sure of the rationale for performing a statistical analysis of R v L

6) P6, Line 4 - I suggest removing 'as a matter of fact'

7) Table 1 - would it be possible to include number of alanine repeats?

8) Table 2 - The decimal points are inconsistent (Wave V left)

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests