Reviewer's report

Title: Screening for inborn errors of metabolism in high risk children: a three-year study in Zhejiang Province, China

Version: 2 Date: 9 September 2011

Reviewer: Veronica WILEY

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This is a valuable addition to the literature on screening for inborn errors of metabolism. There are some suggestions which may improve the paper

Major Compulsory Revisions

1. The authors indicate in "Cut-off value" that cut-off values were set on full term newborns. What was the age of the baby for the cut off values. There are significant differences of cut-offs with age. The subjects ranged from 0.04 to 168.2 months, therefore the authors need to comment and discuss the likelihood that disorders could be missed with the cut-offs for newborns.

2. The authors need to detail the timing of collection in relation to symptoms. FAO defects may be missed depending on the timing of sample collection. This should be included in the discussion

3. The papers of Mohamed Rashed should be referenced in the discussion as this work was pivotal in the introduction of MSMS for screening

4. There needs to be rewriting of some sections for clarity
   a. Methods; MS instrument and analytes: Is citrulline included twice?
   b. the acylcarnitines could be moved ...and 20 acylcarnitines (C0, C2, C3 ....), were evaluated individually and in specific combinations. What combinations were used?

5. Methods are not detailed and authors state "All procedures of sample preparation and MS analysis were performed according to the protocol provided by the manufacturers". The manufacturers provide alternate procedures and therefore a brief description of the solvents used and sample preparation for example whether the samples are derivatised would enhance understanding. Most laboratories performing this testing use LC MSMS with ESI. Was API used?

6. Discussion: The discussion requires rewriting to avoid repetition and improve clarity. Especially paragraph 5 about organic acidaemia, and paragraph 6

7. Discussion, paragraph 4: The authors state "All the PCD patients had good outcome if detected at early age with timely life-long treatment." As this is a three year study, is this phrased correctly?
Minor Essential Revisions
1. Abstract; Methods: the authors indicate that diagnoses were further confirmed through ... and molecular studies. I was unable to find molecular results in the paper. Which disorders were confirmed with DNA analysis?
2. Abstract; Conclusions: Subjects are not "old age" the median was 28.8 months. Old age should be rephrased throughout the paper
3. Abstract; Conclusions: Suggested rephrasing: Poor medication compliance could reduce the efficacy of treatment
4. Background Para 1: morbidity in children with an IEM.
5. Methods; Cut-off value: should be: The borderline cut-off
6. There should be no space in the number of newborns ie 12,720
7. The patients were referred for confirmatory tests if the second analysis was above the cut-off value.
8. Confirmatory tests: there may be inappropriate spaces: between included and repeat; between biotin and,
9. .... test were performed to subgroup hyperphenylalaninaemia ...
10. Results: HMG shoud be HMG CoA lyase
11. Results; aminoacidaemias: the authors state "Ten PKU patients had persistent developmental delay after treatment. How long were they treated? Was there any improvement with treatment?
12. FAO disorders: typos: The one patient detected with MCAD ...
...her blood C6, C8 and C10 levets were elevated at screening.
13. Organic acidaemias; could be redrafted: Patients with MMA and PA presented with hypoglycemia, metabolic acidosis, convulsions and developmental delay. Two MMA patients died and the parents of the other two discontinued treatment. Two of the 4 PA patients died, one from metabolic acidosis and the other due to respiratory failure. The symptoms in individuals with GA I varied. Two presented with recurrent convulsions and motor development delay at 1 year of age, while the other had macrocephaly and hypotonia at 4 months of age. The cranial MRI showed extensive abnormal signals in the white matter and basal ganglia.... All three patients improved remarkably after treatment. (Comment: the authors could indicate how the improvement was determined)
14. Discussion; paragraph 3; line 4: median age
15. Discussion; paragraph 4: Is there a reference for the incidence of FAO in China?
16. Discussion; paragraph 4: I do not understand the sentence about MCAD
17. Discussion; paragraph 5: All 4 MCD patients recovered dramatically ... Motor development delay
Did the authors mean: The baby with HMG CoA lyase deteriorated rapidly and
died before diagnosis?
Our study indicated that if patients with an organic acidaemia were not diagnosed and treated at an early stage of disease, there is likely to be irreversible neurological sequelae?

18. Discussion; paragraph 6: About ten patients became asymptomatic... How many?
19. Table 1: Cut-off values for ratios should be included
20. Table 2,3 and 4: Spacing should be corrected for clarity

Discretionary Revisions
1. Results; line 1: A total of 11,060 symptomatic patients (6720 boys, 4340 girls) with a median age...

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I declare that I have no competing interests