Reviewer's report

Title: Newborn screening for congenital adrenal hyperplasia in Tokyo, Japan from 1989 to 2013: epidemiology and efficiency of the screening: a retrospective population-based study

Version: 5  Date: 5 May 2015

Reviewer: Scott D Grosse

Reviewer's report:

Major compulsory revisions

1. The second paragraph of the Background section indicates that a primary purpose of the paper is to address a lack of knowledge about the incidence and epidemiology of CAH in Japan. However, the incidence of CAH in Japan is known to vary between 1 in 18,000 (Suwa 1994) and 1 in 21,000 (Morikawa et al. 2014), the same as in other countries. The authors should provide a context for their study in relation to the previous literature. They should indicate which aspects of their study are novel and which confirm previously published findings. In particular, it is the screening algorithm and its high positive predictive value (PPV) that appears novel. To explain why this is novel, it is necessary for the authors to summarize the relevant CAH screening literature and the lower PPV and higher rates of false positives that have been reported from other screening programs. Similarly, statements in the Discussion such as “This is the first large scale retrospective study of CAH newborn screening in East Asia” are incorrect.

2. The Methods section needs to explain the relationship of the newborn screening program in Tokyo to the screening program in other parts of Japan. Are the screening cutoffs or algorithms different in Tokyo? Who makes those decisions? Is there a designated screening laboratory for Tokyo hospitals? Has Tokyo always used gestational age cutoffs for CAH screening? Who made that decision? Was it influenced by the experience of other countries such as Switzerland that have long used gestational age-specific 17-OHP cutoffs?

3. The Results section should present information that can be compared with previously published CAH newborn screening results from Japan. In particular, it is important to report the recall rate for this study, which appears to be 0.02%. That is extremely low compared with other screening programs. In Sapporo City, which does not use gestational age or birth weight cutoffs, the recall rate is reported to be at least 10 times higher (Morikawa et al. 2014). Also, just 25% of the infants in Tokyo who were recalled were born prior to 37 weeks, compared with 75% in Sapporo.

4. The statement, “All but four (94.5%) of the SW patients were positive on the first test” requires further explanation. The Methods section states that only infants who have abnormal results on a first screen undergo a second screen.
How were these 4 infants detected if they were not positive on the first screening test? Was the screening algorithm different from that described in the Methods section?

Discretionary Revisions

5. This study notes in the Discussion that no fatalities were reported among 106 CAH cases identified by screening, which belongs in the Results section. However, the Discussion should indicate that does not rule out fatal adrenal crises in this population. Fatal cases occurring in at least 1 in 80 cases in Japanese infants with CAH detected by NBS (Ogawa et al. 2003). In other countries, about 1% of infants who have classical CAH detected by screening die in infancy (Grosse and Van Vliet 2007). The fact that no deaths were reported could be due to chance, with small numbers of cases, or to a possible lack of thorough reporting of deaths in the follow-up survey.

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

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