Reviewer’s report

Title: High frequencies of elevated alkaline phosphatase activity and rickets exist in extremely low birth weight infants despite current nutritional support

Version: 2 Date: 4 June 2009

Reviewer: Reginald Tsang

Reviewer’s report:

The authors are to be commended for an excellent point by point revision of the text which answers most of the original questions.

However, I feel uncomfortable about being the only reviewer for this paper, as I understand it. No one person can adequately cover all the bases and as I re-review the paper, I now find additional questions that could have been detected possibly by a second reviewer.

Abstract section.

Results: The sentence “32 patients had radiographic…” should be rephrased as “evaluation for evidence of rickets, based on p-APA greater than 800, parenteral nutrition greater than 3 to 4 weeks, and clinical suspicion”. This allows the reader to understand this approach clearly; this is a key feature of the study; otherwise it is quite unclear why radiographic evaluation for rickets occurred.

Infants with birth weight less than 600g were more likely to have radiologic rickets. This is to allow the reader an understanding that it is not biochemical or chemical rickets that the authors are talking about, since some authors use those as definitions of rickets.

The sentence “p-APA was significantly higher in infants with rickets compared to those not evaluated for rickets” is a circular argument, since the reason for diagnosis of rickets was based on a high p-APA to begin with. Also the authors should say radiologic rickets.

Conclusions

Radiologic rickets

The authors should be a bit more precise by what they mean with more aggressive mineral supplementation. Do they mean earlier mineral supplementation or actually higher dose?

Page 3 background

Metabolic bone disease may also theoretically worsen the respiratory problem....... a reference should be given for this concept.

Paragraph 2 last line. Medications…also appear to contribute to the development of metabolic bone disease

Page 5 First line During this period (delete time)……..

The authors have now defined very clearly the situation for doing a radiograph

Paragraph 2 what happened to the data on “early” rickets vs. “advanced” rickets? If these data are not available or of interest, then maybe they should not mention this. It leaves the reader dangling in suspense

Page 6 Results Paragraph 3 Normally we reverse the sequence of comparison, i.e. state that the infants less than 600 grams had significantly higher p-APA than the other groups etc. since that is the main point of concern. i.e. we compare the group with “disease” in contrast to the more “control like” groups.

Last Paragraph

Only infants with elevated p-APA greater than 800, total TPN greater than 3 weeks……..

The authors should be consistent in their criteria and I would assume that all three criteria are necessary for the evaluation of radiographic evidence of rickets

Page 7 Paragraph 2

Similarly 17 infants with p-APA greater than 800 units, is fine, but on page 9 the authors use greater than 1,000 units, so which one is correct?

Page 8 the authors present 55 patients with cholestasis and 58 without cholestasis. The main question is how many of the increases in p-APA had cholestasis, etc..

Discussion Line 2 radiographic rickets

Line 3 mean p-APA exceeded 600 IU /L in all birthweight (delete size) subgroups

Last line of paragraph: “There was no significant difference in p-APA in those in whom rickets was diagnosed compared to those who had osteopenia without rickets.” This is the first time osteopenia without rickets is commented upon. Where are the osteopenia data? Not sure what this means and why it is introduced at this point.

Last Paragraph the sentence might read better: The diagnosis of rickets generally remains dependant on clinical suspicion and on biochemical p-APA
data with the radiograph verifying the findings.

Page 9 Paragraph 2 here the authors talk about p-APA greater than 1,000 IU/L which could be confusing; it is best to say “including 5 patients with p-APA greater than 800 units” (is that correct?); in all these 5 infants, p-APA was actually greater than 1,000 units

Line 3 radiographic rickets

Last Paragraph line 3 “preterm formulas, fortified human milk and TPN…...typically should provide about 180 to 220 milligram per kilogram per day.” This is only true if it is given appropriately and successfully, which may not be the case in reality. This is a major consideration which should be emphasized unless the authors have data to the contrary. Another possibility is that p-APA is really non-specific for detection for rickets in any case, and is complicated by the presence of cholestasis?

The authors should say at least one sentence about the case report in reference 13, since it is not clear that a high mineral demand was “documented.”

Page 10 since rapid bone growth has not been documented, the authors should say we suggest that very high APA…… may be caused by rapid bone growth, rather than “suspect”; “suspect” implies that there is some evidence

Paragraph 2 …..predicted radiographic osteopenia…….(just to be sure that there are no other definitions of osteopenia)

Other studies have shown…… correlated with APA, with sustained elevated? levels of p-APA correlating with more severe disease. Was there a period of elevation that was significant?

Elevated APA….. is associated with decreased bone strength. Is this a general statement or is that related to infants? Or are we talking about animals?

Quoting the results of Faerk and their challenge to the utility of AP and serum P is ok, as long as the authors at least state in one sentence what the challenge consists of.

Page 11 the statement “birthweight alone may be a more sensitive indicator of rickets of patients with birthweight less than 600 grams” – This sentence is not very clear and should be rephrased to make it more understandable

Paragraph 2 the authors again use 1,000 units for the limit of APA, but previously used 800 units; is there some reason for this?

Further indications for radiographs…….. are the findings in an incidental radiograph