Reviewer’s report

Title: Neurodevelopmental profile of Fetal Alcohol Spectrum Disorder: A systematic review

Version: 1 Date: 17 Apr 2017

Reviewer: Larry Burd

Reviewer's report:

PSY-D-17-00010R1

The manuscript examines existing data to determine if FASD has a signature neurocognitive presentation.

This is an interesting idea since neurobehavioral impairments are the unifying criterion across all FASD categorical diagnoses. I exclude ARBD since it is almost never diagnosed.

Page 5 36-46 this is commonly stated but it's unclear to me what this means. Dubowitz Syndrome is mistaken for FASD? This must be exceptionally rare since the conditions the authors list are uncommon. In my experience the opposite is much more common. FASD is rarely diagnosed and is misdiagnosed in about 85% of cases. ARND is the most frequently misdiagnosed of the FASD. Lastly, why would a diagnosis of Cornelia de Lange exclude prenatal alcohol exposure and the neurocognitive effects of PAE supporting a diagnosis of FASD? So would not the most common diagnosis be both?

PAE and FASD present similar problems for ADHD, ODD and CD. It seems likely the PAE/FASD are the most common causes of ADHD, ODD, psychosis etc in childhood. So it seems to me that again the issue is that FASD is the diagnosis that is most often missed. ADHD and ODD may be diagnosed but FASD is almost never diagnosed. As above it seems to me that it is not FASD or ADHD but very likely both. This is true for intellectual disability and several other common diagnoses as well.

I am curious about the author's thoughts on these issues.

Methods

The search expertise of this research group is state of the art. The inclusion and exclusion criteria are clear.
Results

The breakdown of behavioral observations is very useful. We do not currently have biomarkers for most of these entities or diagnoses. So observational data is the best we have. We also utilize neuropsychological testing. This is an area with multiple problems:

1. Many of the measures were developed for another purpose and have no norms relates to PAE or FASD.

2. The differences between head injury and FASD etc often have significant overlap.

3. The population norms for many of these tools are inadequate. Caucasians in the normative sample are very often part Hispanic, African American or American Indian.

4. Similarly, the ethnic racial populations are also often mixed. This is one of the overlooked features of normative data for facial features lip/philtrum palpebral fissure length etc. If the child is 40% Caucasian and 50% African American and 10% Hispanic why do we suggest using a 100% norm for African Americans to determine the correct facial feature measures for a child.

5. The rating scales often do not result in a diagnosis.

When calculating sensitivity and specificity we might want to begin with what we know. First PAE is underreported by 25 to 50%. Thus we classify these cases as unexposed. This dramatically effects calculations of sensitivity, specificity accuracy and positive and negative likelihood ratios. So it may be that PAE and FASD have much more robust adverse effects than we currently appreciate. Secondly, on page 14 heavy exposure to alcohol in one study is defined as 4 or more drinks per occasion etc. This seems to me to be very modest levels of exposure. If one looks at the minimum levels of cumulative exposure these criteria produce PAE is very toxic. I think most FASD clinics see mostly children with exposure levels many times higher than this.

Page 16 lines 36-41. Is FASD a cause of ADHD? If somewhere around 50% of people with FASD have ADHD, it seems it must be a very common cause of ADHD. How does this analysis work if that is correct?

Discussion

I think the authors have an admirable goal here. What do we know about the expression of FASD? Does FASD have a phenotype(s) that are detectable?

Three studies might help. The first is by Burd et al. in 2003 in Neurotoxicology and Teratology, followed by a related study in 2010 in Alcohol also by Burd et al., and a third by Berg et al.
These studies examined comparisons across FASD diagnostic schema. The results suggest very modest rates of agreement even for FAS and Partial FAS. The ARND numbers are very low so comparisons are difficult. However, what this suggests is that a narrow or distinctive phenotype for FASD has yet to be achieved.

Two relevant points for the authors to consider. In previous publications by this group they demonstrated that prenatal alcohol exposure is associated with extremely broad phenotypic presentation comprised of several hundred comorbid conditions. Some might be due to chance alone. Some are almost certainly due to PAE (ADHD, intellectual disability, vision disorders etc). The key is if PAE is present these conditions are likely due to PAE. If no PAE is reported the conditions could be due to other causes. Even then misclassification of PAE is likely very common. What is the potential phenotypic signature from PAE or the presence of FASD? It's difficult to imagine how this could be identified since the outcomes from PAE depend on maternal (genetics, health, alcohol metabolism, polysubstance exposure) and the fetal risk is from (generational effects of exposure, epigenetic factors from either the father or mother, fetal exposure(s), fetal susceptibility or protective factors, timing of exposure) and our ability to appreciate (detect and or diagnose) the consequences of exposure. It could be that if the brain can do it or suffer from it PAE might cause it, make it worse or lower the threshold for expression of the condition. If this is the case then FASD is a pleotropic phenotype (one cause (PAE) = many outcomes (growth impairment, abnormal facial features, visual impairments, ADHD, intellectual disability) etc. Conversely, if FASD is a canalized disorder every feature of FASD has many causes (ADHD is caused by genetics, PAE, smoking, postnatal environmental adversity) then the phenomic presentation is complex and a useful behavioral signature is less likely.

Currently the data suggests that FASD has a mostly a pleotropic phenotype. Where PAE or FASD is present they are likely to be an important element of an epidemiological causal chain. And if they are removed from the causal chain the disorder is much less likely to be present.

I have provided a several discussion items the authors should feel free to include any that they feel are relevant and also to ignore any that are not relevant.

This work is currently identifying strengths and limitations and importantly offering guidance and methods to improve future research in this area. This is emerging science for a common condition as a result its important.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.
Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests.

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report
including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal