ADHD and Early Experience: Revisiting the Case of Low Birth Weight

Joel T. Nigg, PhD,[a] Minkyoung Song, PhD[b]

The improving survival rates of extremely low, very low, and low birth weight (LBW) and premature (PM) infants are good news. Scientifically, they raise complex questions about trends in the incidence of neurodevelopmental conditions,[1] from severe injuries like cerebral palsy, now declining after earlier increases in incidence,[2] to subtler yet also disabling and costly conditions like attention-deficit/hyperactivity disorder (ADHD), whose true incidence likewise may not have increased in the past 15 years.[3]

In the accompanying meta-analysis by Franz et al,[4] the magnitude of the association of LBW/PM with ADHD is striking; at a risk increase of ∼300%, it is perhaps the strongest single risk factor for ADHD of any type (biological or environmental) now known. At this effect size, LBW/PM would characterize a substantial portion of ADHD cases. Researchers of ADHD populations who can clarify how many patients had LBW/PM, and who can include more in-depth characterization of ADHD than was possible in many of the studies included by Franz et al,[4] will help to determine how well these findings generalize across different sampling approaches.

LBW is multiply determined, but it also has modest heritability.[5] The authors of studies of LBW have rarely if ever considered causally informative designs[6] to take into account genotype-environment correlation or other unmeasured third causes of both LBW/PM and ADHD. For example, a study of surrogate mothers revealed that much of maternal smoking's association with offspring ADHD is accounted for by genotype-environment correlation.[7] Thus, causal inferences should be made cautiously here. However, the modest heritability of LBW compared with ADHD could suggest that the direct effect of LBW/PM on ADHD cannot be accounted for entirely by genotype-environment correlation. Thus, with their findings, Franz et al[4] underscore the commonplace understanding that ADHD is not determined simply by heredity, but more likely by the interplay of genetic and environmental dynamics, and that the disorder may ultimately be understood as an epigenetic condition.[8,9]

It is possible that many informative studies were excluded from the meta-analysis, and the authors note other limitations (heterogeneity of effect sizes, pooling across time and nation). We also note that the many important contributors to LBW/PM, such as maternal smoking, were, perhaps necessarily, beyond the scope of the current report. Yet, it is unlikely that these concerns would overturn the present findings. For example, LBW is associated with ADHD even when maternal smoking is considered in a comparison of LBW and children with normal birth weight.[10]

The magnitude of the observed association raises several additional questions. First, how specific is this linkage to ADHD? As the authors document, other conditions besides ADHD can arise from LBW/PM, but, apparently, few study authors have looked at ADHD and other conditions together in the same cohort. It may be that the effect size is similar for ADHD as for anxiety or other conditions, but

[a]*Department of Psychiatry, Doernbecher Children's Hospital, and* [b]*School of Nursing, Oregon Health & Science University, Portland, Oregon*

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Address correspondence to Joel T. Nigg, PhD, Department of Psychiatry, Doernbecher Children's Hospital, Oregon Health & Science University, Portland, OR 97238. E-mail: niggj@ohsu.edu

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this is unclear when one considers their frequent overlap. If the association with ADHD is reliably larger than with other developmental conditions, why would this be? Does LBW/PM primarily confer greater susceptibility to whatever follows, and if so then how is what follows ultimately determined? Crucially, how do some children at risk because of LBW/PM avoid neurodevelopmental harm? Again, of course, genetic susceptibility is likely 1 important moderator. But early risk further interacts with postnatal experiences, such as caregiver attunement or breastfeeding,[11] that may be able to rescue children at risk from LBW/PM, perhaps by epigenetic alterations.[12] It will be important to identify such actionable protective mechanisms.

This raises another key question: what are the key mediators in this association? Potentially traceable biological injury is of particular interest. The authors mention some of the many possible biological mechanisms that might mediate this effect but did not attempt to address that question in the current study, probably because of a shortage of comparable studies. In particular, along with the expected influence of genetic susceptibilities, do variable outcomes depend on the particular nature of the injury (eg, germinal matrix/intraventricular hemorrhage versus parenchymal lesions)?[13] Ongoing progress in brain imaging of fetal and neonatal brain structure and function holds considerable promise here.

Of particular interest is understanding the association between LBW/PM and ADHD-related comorbid conditions. For example, how does this association parse in relation to comorbid features of ADHD (besides inattention or hyperactivity as examined here), such as motor development[14] or emotional irritability? As the authors note, the authors of several studies have suggested potential features of ADHD with LBW/PM, including more neurologic problems but less psychiatric comorbidity. It was unfortunate that study variation prevented the authors from being able to pool such effects. This point now warrants much more focused investigation in light of emerging ideas about heterogeneity in ADHD and other disorders.

Overall, the increasing evidence of early-life influences on ADHD requires explanation. It also raises new opportunities for understanding ADHD etiology at the level both of mechanisms and of individual clinical variation. In addition, these types of findings reveal the need for new prospective studies of early development, in which scientists can consider genetic and environmental effects together. In particular, an approach in which epigenetic change in relation to early experience is examined and in which, when possible, causally informative designs are used[6] could dramatically improve current understanding of ADHD etiology. The coming generation of research on ADHD is likely to include more sophisticated, integrative accounts of how subtle neurodevelopmental injury is involved in child psychiatric conditions such as ADHD.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
LBW: low birth weight
PM: premature

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