Risk factors for cerebral palsy: current knowledge and future causal inference

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This commentary is on the systematic review by McIntyre et al. on pages 499–508 of this issue.

McIntyre et al.[1] present a useful systematic review of studies of risk factors for cerebral palsy (CP) in term births. They correctly point out that CP is likely to be the result of a large number of complex causal pathways; many of these may be poorly understood or as yet unknown. The systematic review identified ten risk factors consistently associated with CP and the authors propose the development of a clearinghouse of observational and experimental data that may help researchers pinpoint causal pathways for CP. It is hoped that this may ultimately lead to more effective preventive strategies.

To have the best chance at prevention, a clear understanding of the causal pathways to CP will indeed be critical. Some important questions immediately arise. Which, if any, of the risk factors identified by McIntyre et al., or which may be discovered in the future, is truly a *cause* of CP? Does the presence or severity of any risk factor directly change the probability of a child developing CP? Or is a given risk factor part of a causal chain, influencing other causal factors but having no *direct* relationship to CP? Might some risk factors be causal in both senses?

Until relatively recently, there was simply no rigorous statistical framework for measuring the strength of evidence for causal relationships in medical research, much less for differentiating types of causal relationships. Today, however, a modern and rigorous theory of causality does exist, thanks to a growing body of research by Pearl et al. on the use of directed acyclic graphs, and related methods, in epidemiology.[2,3]

While our own experience with these methods is not vast, we appreciate the value they add in analyzing the impact of an exposure on an outcome. We also understand that if one wishes to measure the causal effect of a given exposure (e.g. neonatal infections) on an outcome (CP), then the following three points, taken from Pearl,[2] are critical: (1) strong predictors of exposure should be excluded from the analysis; (2) factors affecting outcome (or their proxies) are safer and more effective bias reducers than those affecting exposure; and (3) consideration of covariate selection should be grounded in structural assumptions (they cannot be left at the mercy of conventional wisdom, however entrenched). In item 2, one may ponder exactly what Pearl means by 'safer'. We will return to this.

In the modern theory of causality, a directed acyclic graph may be drawn to represent the researchers' best understanding of the causal relationships between exposures, confounders, and outcome, including possible intermediate causes and unmeasured confounders. From such a graph, and under certain assumptions, one can determine which variables ought to be included in a multivariate analysis in order to minimize the bias in the estimated effects of the exposures of interest.

For example, the theory would suggest that if we want to measure the causal effect of neonatal infection on CP, then controlling for birth asphyxia (a factor affecting the outcome, CP) is more likely to reduce bias (i.e. 'safer') than controlling for maternal infection (a factor affecting exposure, neonatal infection), which may well increase bias. That controlling for variables more closely associated with exposure than with outcome can amplify bias is a corollary of this causal theory, and is contrary to conventional wisdom. This may be one of the theory's most significant contributions to modern epidemiology.

The call for research into primary prevention in CP is timely. The review by McIntyre et al.[1] provides valuable information for researchers seeking to build a causal framework for CP. Tools (directed acyclic graphs and related methods) to more effectively characterize the causal relationships now exist and are quickly gaining ground in epidemiology. We are hopeful they will soon gain ground in the epidemiology of CP and other developmental disabilities, and that effective new preventive strategies will eventually result.

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