Should the Frascati criteria for HIV-associated neurocognitive disorders be used in children?

Cognitive impairment is likely common in children and adolescents with HIV infection in low-resource settings. While early treatment with highly active antiretroviral therapy has greatly reduced the most severe form of cognitive impairment in children, milder forms of cognitive impairment may be increasing in prevalence due to longer survival. Before 2007, marked heterogeneity in definitions of HIV-associated neurocognitive disorders (HAND) made it challenging to interpret different rates of cognitive impairment among regions or populations. The Frascati criteria, developed in 2007, created a uniform approach to the diagnosis of HAND in adults and vastly improved the ability of researchers to understand these disorders and their consequences. Application of the Frascati criteria requires neuropsychological testing in at least 5 cognitive domains, assessment of impairment of activities of daily living, and exclusion of other causes of cognitive impairment. Recently, several analyses suggest that the Frascati criteria have a high false-positive rate for milder forms of HAND in adults, which may limit the utility of these criteria. False-positive rates may be affected by incomplete exclusion of confounding disorders such as subclinical depression, drug use, educational deprivation, and effects of socioeconomic status.

In this issue of Neurology®, Hoare et al have utilized the Frascati criteria in a cohort of perinatally infected children with HIV, and attempted to define the spectrum of HIV-associated neurocognitive impairment in children. This is a well-executed study of cognitive impairment in this population. The authors have carefully attempted to control for confounders, and provided a thoughtful analysis of their results. Not unexpectedly, the authors found high rates of neurocognitive impairment in children with HIV. However, they additionally found high rates of neurocognitive impairment in a group of HIV-uninfected children intended to serve as controls. Nearly a third of the uninfected controls recruited for this study met criteria for asymptomatic neurocognitive impairment or mild neurocognitive disorder. This “false-positive” rate in children is substantial and comparable to that observed in adults. In addition, nearly half of the children with a clinical diagnosis of HIV encephalopathy did not have impairment by Frascati criteria. As the authors point out, this was due to relative preservation of cognitive function in some patients with microcephaly or motor deficits due to HIV. However, this represents a problem with the criteria, as HIV encephalopathy is an important part of the spectrum of HIV-associated neurocognitive dysfunction in children. The issues with both false-positive and false-negative results seen in this study add to the growing body of evidence that the Frascati criteria may not have sufficient diagnostic accuracy to justify use in children with HIV.

Making it more challenging to sort out these issues is the fact that few locations in which pediatric HIV is common have validated neurocognitive tests in local languages with published norms. Thus, studies are left to either use published norms from high-resource settings or to attempt to calculate local norms, both of which have substantial problems. Utilizing norms from high-resource settings will almost always overestimate the rate of neurocognitive impairment in lower-resource settings. Determining local norms is preferable, but is challenging due to the necessity of recruiting large numbers of children in different age strata. Finally, developing local norms requires identifying an appropriate control population. If the norms are taken from healthy uninfected children from the same socioeconomic group, this will still overestimate the prevalence of HAND, as it will ignore the effects of chronic disease and maternal HIV on cognition. Calculating norms from HIV-exposed uninfected controls is another option, but may result in underestimation of the true rate of neurocognitive impairment. Complicating matters is the fact that neurocognitive impairment in children with HIV is probably not a single distinct disorder due to inflammatory brain injury, but may reflect multiple overlapping pathologies including effects of socioeconomic deprivation, in utero effects of maternal HIV, increased rates of maternal drug and alcohol use during pregnancy.
malnutrition, stigma, decreased access to educational opportunities, depression, antiviral drug side effects, and nonspecific effects of chronic illness.

So what should be done? Developing accurate diagnostic criteria for neurocognitive impairment in children with HIV in low-resource settings is a critical step to advance the field. The ideal criteria should have validated performance characteristics across multiple settings and low false-positive and false-negative rates. A consensus should be reached regarding a toolkit of appropriate tests to be included in a neuropsychological battery and for assessment of functional status. Cognitive domains that are most affected by HIV, such as memory and executive function, should be prioritized; tests that are strongly affected by education, literacy, or cultural/regional effects should be deprioritized. Potential approaches to improve accuracy of diagnostic criteria include increasing threshold scores for impairment, limiting test battery size to reduce false-positive tests, and incorporating longitudinal assessments to capture patients with cognitive decline. Finally, creating consensus around how to generate appropriate normative samples or incorporating novel statistical techniques, such as multivariate normative comparison, is essential.

Dr. Hoare et al. have done important work in highlighting the challenges in making the diagnosis of HIV-associated cognitive impairment in children. In addition, their work provides an impetus to critically reappraise existing criteria in adults. To move forward, we need to recognize that the assessment of cognition in children and adolescents with HIV will require new methods and a distinct approach from what is used in adults.

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DISCLOSURE

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REFERENCES