Editorial on:

The familial co-aggregation of ADHD and intellectual disability: a register-based family study

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“The familial co-aggregation of ADHD and intellectual disability: a register-based family study” published in this issue of JAACAP is, in my view as a practicing clinician and researcher, one of the most interesting and important papers I have read this year. Individuals with Intellectual Disability (ID) are known to be at substantially elevated risk for psychopathology$^2$ so mental health clinicians will be involved in their assessment and treatment. ID spans a very broad range of IQ test scores and functioning, so affected individuals are not necessarily immediately recognizable. Previous research of those with ID already tells us that Attention Deficit Hyperactivity Disorder (ADHD) is one of the most commonly co-occurring conditions$^1$. Although that is also the case for Autism Spectrum Disorder (ASD), historically comorbidity between ID and ADHD has been dealt with very differently. The association between ASD and ID has long been accepted$^3$. However clinicians and researchers have been plagued by concerns that ADHD features are an epiphenomenon of ID. This has led not only to diagnostic over-shadowing and a failure to treat ADHD in those with ID in some instances$^1$ but also to research exclusions. For example, historically molecular genetic studies of schizophrenia and autism have not supported excluding participants on the basis of lower IQ or ID$^4$. In contrast, although ADHD shows a similar strong association with lower IQ as one might expect for a neurodevelopmental disorder, typically those with low IQ have been excluded$^5$ or separated in analysis$^6$ thereby diminishing the available research evidence base for these individuals as well as research applicability to daily practice. The findings from the paper by X et al. in this issue challenge this historical trend.

The authors took advantage of nationwide Swedish registry data on around 2 million people to examine diagnoses of ID and ADHD in tens of thousands of relatives who differ in their degree of biological relatedness. They included MZ and DZ twin pairs, parent-offspring, sibling half sibling and cousin pairs. They observed that ADHD and ID strongly share genetic risks. That is, ADHD rates were observed to be higher not only in individuals with ID (probands) but also in their biological relatives; ADHD risk was highest in those most closely related to the probands and not explained by probands who had both
phenotypes (i.e. ID and ADHD). Interestingly, findings were different for the most severe form of ID (profound ID) which did not show familial co-aggregation with ADHD. This finding is in keeping with the view that ID mainly lies at one end of a multi-factorial, polygenic continuum of intellectual ability whereas profound ID is etiologically distinct and qualitatively different from the rest of the IQ spectrum and mild-moderate ID. This discontinuity appears to apply to the familial co-aggregation with ADHD and might be explained by rare causes including genetic syndromes (e.g. de novo/non-inherited mutations) and environmental agents (e.g. intra-uterine exposure to infection) contributing to profound ID. The authors discuss the strengths and limitations of their study including the reliance on registry data and recorded diagnoses. Nevertheless it is of interest and relevance that directly assessed population-based twin studies (e.g. involving interviews and questionnaire measures) also have shown a strong genetic correlation between lower IQ test scores and ADHD (as well as with other neurodevelopmental traits such as ASD). The etiologies of ID and ADHD are mainly polygenic (explained by multiple, different gene variants) and multi-factorial (non-genetic risks also contribute). The findings in this paper should not detract from remembering that ID and ADHD, like most common medical conditions, have complex etiologies. The genetic correlation estimates also will include gene-environment correlation and interaction effects.

Why is this important? For clinicians, it is likely that we already appreciate the elevated rates of ADHD in those with ID when assessing and planning treatment. This paper serves as a reminder. However, as is the case for autism, we might be less surprised now if families report a family history of ID (amongst other neurodevelopmental disorders). In the future, this finding could have relevance to genetic counsellors. ADHD treatments are effective in those with ID so the presence of ID should not deter us from treating those affected. However there is a higher risk of side effects so careful monitoring is required.
For researchers, this paper conveys a very important message. There really are no good scientific (or of course ethical) reasons for excluding individuals with ID from our research studies including ones on ADHD. ADHD phenotype presentations and outcomes are similar or more severe in those with ID versus the rest of the population\textsuperscript{10} and this paper provides further evidence of a shared genetic etiology between ADHD and ID/IQ across most of the IQ spectrum. Indeed, this finding supports the DSM-5 approach to grouping child neurodevelopmental disorders whereby ADHD, ID, ASD, communication, learning and motor disorders are grouped together. The move away from unhelpful exclusion criteria is welcome as is the greater use of dimensional approaches. Whilst over-zealous diagnosis and over-treatment are to be guarded against in those with ID, appropriate, careful assessment and treatment are important as is scientific endeavor that includes the full spectrum of intellectual ability.

**References**


