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EDITORIAL

Combining epidemiological and neurobiological perspectives to characterize the lifetime trajectories of ADHD

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Attention-deficit/hyperactivity disorder (ADHD) has been conceptualized by DSM-5 [1] as a neurodevelopmental disorder and included in the respective category grouped with autism spectrum disorder, intellectual disability, communication disorders, specific learning disorders, and motor disorders. Neurodevelopmental disorders are thought to be the result of deviations of normal brain developmental processes and are characterized by an early onset during childhood, usually accompanied by neurocognitive deficits, and a steady course over time [2].

The concept of ADHD as a neurodevelopmental disorder has emerged from a large number of studies from convergent perspectives pointing all to that direction. Recent studies published in the European Child and Adolescent Psychiatry support this notion. With regard to early risk factors and manifestations, preterm birth and low birth weight are consistent risk factors for the disorder, and even among those children born extremely preterm or with extremely low birth weight, those with minor neurodevelopmental impairments were found to be more likely to have ADHD symptoms in a dose–response relationship [3]. At 6 months of age, signs such as motor functioning and incessant crying, and at 18 months mothers' concerns such as difficulty to handle the child were found to be associated with an increased probability of childhood ADHD [4]. With regard to continuities and discontinuities across development, hyperactivity at age 3 years was found to be a strong predictive of poor adolescent and adult outcomes, specifically for males [5]. A follow-up of a clinical sample of children with ADHD revealed that 86.5% persisted with a DSM-5 ADHD diagnosis at late adolescence [6]. In this sample, ADHD severity and family history for the disorder revealed to be important risk factors [6]. On the other hand, a follow-up of a community sample of children revealed a general decrease of ADHD symptoms with age and only about 3% follow a course with a high level of symptoms [7]. A meta-analysis indicated that the severity of ADHD, treatment for ADHD, comorbid conduct disorder and major depressive disorder are childhood predictors for ADHD persistence into adulthood [8].

Despite the growing literature and the general consensus pointing to ADHD as a neurodevelopmental disorder, a recent finding challenged this notion. Three independent longitudinal studies following prospectively community samples from New Zealand, UK, and Brazil from childhood to early and middle adulthood consistently revealed that most cases of adult ADHD were not continuation of childhood ADHD [9–11]. Adult ADHD cases without a history of childhood ADHD were not fully explained by comorbidities, subthreshold symptoms, and information bias. Possible explanations for these findings are that subthreshold cases in childhood emerge as cases in adulthood when demands exceed capacities. Alternatively, child onset and adult onset may be distinct syndromes, meaning that ADHD is not always a neurodevelopmental disorder. How these possible explanations can be understood from a neurobiological perspective?

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If childhood- and adult-onset ADHD are distinct syndromes, then we would expect distinct etiologies and there is already some evidence of distinct genetic risk factors. Firstly, a measure of an individual's genetic risk for ADHD across the genome (the 'polygenic risk score') predicts childhood but not adult onset forms of the ADHD [9]. Secondly, the likelihood of adult-onset ADHD arising in a monozygotic twin is not increased when the co-twin has childhood-onset ADHD [10]. Such a lack of shared risk between MZ twins suggests distinct genetic contributions for adult and childhood onsets. Finally, there is growing evidence that the risk genes for the onset of ADHD are largely distinct from those determining its course, and that genetic risk factors for childhood ADHD often do not apply to the adult form [12, 13].

Epidemiological evidence can also inform the search for neurobiological causes. For example, while childhood-onset ADHD shows a male preponderance, adult-onset ADHD has a more equal gender balance. Such a shift points perhaps to brain regions where sexual dimorphism emerging in late adolescence could act as a risk factor for the late onset of ADHD. Additionally, while childhood-onset ADHD shows neurocognitive features repeatedly found to be associated with the disorder (such as a slightly lower IQ), the adult onset form has a more 'intact' neurocognitive profile. However, to test the hypothesis that childhood- and adult-onset ADHD have distinct neurobiology will ultimately require imaging and cognitive assessments within a prospective, population cohort study. Will we find that the adult onset of ADHD is tied to a break away from previously typical, childhood trajectories of brain structure and function?

Alternatively, it is possible that childhood- and adult-onset ADHD share very similar early onset neurobiology vulnerabilities, but among those with adult-onset ADHD, 'protective' factors in childhood—such as parental support—suppress early symptom expression. This is in keeping concepts of ADHD as a multifactorial entity, in which environmental factors can counteract neurogenetic risk, keeping symptom expression below a clinical threshold. Following this model, we might predict similar anomalies of brain structure and function in adults who have ADHD, regardless of whether symptoms had a childhood or adult onset. There is one pertinent finding, stemming from a prospective study of hyperactive boys, followed clinically from childhood into their late 30s and 40s [14]. At the final assessment when the cohort had neuroimaging, 30% of the original non-ADHD children met criteria for ADHD, that is, they had adult-onset ADHD. Interestingly, brain structure among those with the adult-onset ADHD lay closer to those who were never affected by ADHD than to those with childhood-onset ADHD. While this would not support a model of shared neural vulnerabilities between early and late onset ADHD, the study looked only at brain structure. Perhaps, the neural anomalies of late onset group may lie in brain function, neurochemistry or receptor profiles.

Epidemiological studies are providing strong evidence for the possibility of adult-onset ADHD. We now turn to neurobiology to determine whether adult onset represents the late expression of early onset neurogenetic risk factors or if it constitutes a novel diagnostic entity.

Compliance with ethical standards

Conflict of interest Dr. Shaw reports no conflicts of interest. Dr. Polanczyk has served as a consultant to Shire, Johnson & Johnson, and Teva. He has served on the speakers' bureau of Shire and has developed CME material for Shire and Janssen-Cilag. He has received royalties from Editora Manole.

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