ZEBRAS OF MEDICINE:
EQUITABLE DIAGNOSIS FOR THE "LOST GENERATION" OF ADULTS WITH ATTENTION-DEFICIT HYPERACTIVITY DISORDERS AND AUTISM SPECTRUM DISORDERS

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Abstract

Attention-deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are major neurodevelopmental disorders affecting both men and women throughout life. They both have male-predominant prevalence ratios and are usually diagnosed during early childhood. Though when comparing diagnostic descriptions of ADHD and ASD, few commonalities are found. Additionally, the release of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) allowed simultaneous ADHD and ASD diagnoses and the introduction to the concept of a "spectrum" of ASD. The DSM-5 now supports to firstly confer diagnosis of ADHD and/or ASD in adulthood with diagnostic behavioural descriptions that apply to all ages. Still, making a first-time diagnosis of ADHD and/or ASD in adults is a practical, developmental and clinical challenge. This article delineates the overlap and differences between ADHD and ASD, with a focus on misdiagnosis, late, or missed diagnosis while shedding light on the "lost generation" of adults with ASD and/or ADHD.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that was first described in 1775 [1]. It is found to be more common in men than in women [2]. This is supported by a meta-analysis of parent and teacher ratings which found a 2:1 male-to-female ratio in teens [2]. Other meta-analyses found that 5.9% of teenagers and 2.8% of adults meet the ADHD diagnostic criteria [2, 3]. It is important to note that adults do not necessarily 'lose' their diagnosis. These numbers show that prevalence rates tend to not be reflected in adult populations over time, as it is suggested in practice. The prevalence of ADHD in children and adolescents has not increased over the last 30 years [4]. Much less is known about ADHD, specifically in adults, but evidence demonstrates a more even male-to-female ratio of diagnoses in adulthood [5, 6].

Autism spectrum disorder (ASD) is also a neurodevelopmental disorder, with a constantly growing prevalence ever since it was first described by Leo Kanner [7]. Around 1% of the population in western countries across all ages are diagnosed with ASD [8]. Because ASD is still mainly characterised by early-onset difficulties, adults with ASD tend to be unrecognised [9]. Therefore, in the UK, a study estimated a weighted prevalence of ASD at 1.5% [9]. ASD also has a male-predominant prevalence ratio, reported by a meta-analysis as 3:1 (male-to-female) [10]. The age in which individuals get diagnosed with ASD diagnosis is broad, but tends to be greater for females than for males [11].

Based on current literature, genetic and environmental factors play substantial roles in aetiologies of both ADHD and ASD [12, 13]. So far, twin studies have documented high heritability for ADHD and have also confirmed the molecular polygenic background of ADHD [14-16]. For ASD, high heritability has been reported in twin studies as well [17, 18]. Studies have reported shared genetic liability of polygenic risk in ASD and psychiatric disorders, educational attainment, and academic achievement [19, 20].

What individuals with ADHD and/or ASD have in common, is that disorders are plagued with a male-biased understanding in clinical practice. This is due to longstanding underrepresentation of females in research [21-23]. Another commonality is the large body of literature concluding similarities of ADHD and ASD in genetic factors, cognitive profiles, functional, and structural brain characteristics [24, 25]. Nevertheless, extrapolation of these conclusions to all individuals with ADHD and ASD seems highly biased as studies on neurodevelopmental disorders continue to be strongly focused on childhood [24, 26, 27]. The previously mentioned points will be elaborated as this article aims to delineate the overlap and differences between ADHD and ASD, with a focus on misdiagnosis, late, or missed diagnosis while shedding light on the "lost generation" of adults with ASD and/or ADHD.

Clinical presentation

From the age of approximately 12 and older, differential rates of decline in clinical presentation of ADHD are seen [24]. Inattention remains relatively stable with a much more modest rate of decline in contrast to hyperactivity or impulsivity [28]. Hyperactivity or impulsivity tends to wane more strongly and remits more abruptly [29, 30]. Gender-specific differences are seen such as that female individuals are more likely to display a more 'life-persistent' form of ADHD [31]. This can be explained by the bigger likelihood of inattentiveness as a predominant symptom compared to males that persists through adulthood [32, 33]. Males tend to express typical overactivity [21], whereas females express more subtle hyperactivity-impulsivity behaviours along with compensation and masking [34]. This statement is also supported by a large Danish nationwide study where the female sex was more often associated with internalising disorders and the male sex was associated with an increased risk for neuropsychiatric disorders [35].

ASD has been thought of as an even more life-long persistent disorder than ADHD [24]. Clinical presentation of ASD is characterised by social and communication problems, restricted, repetitive

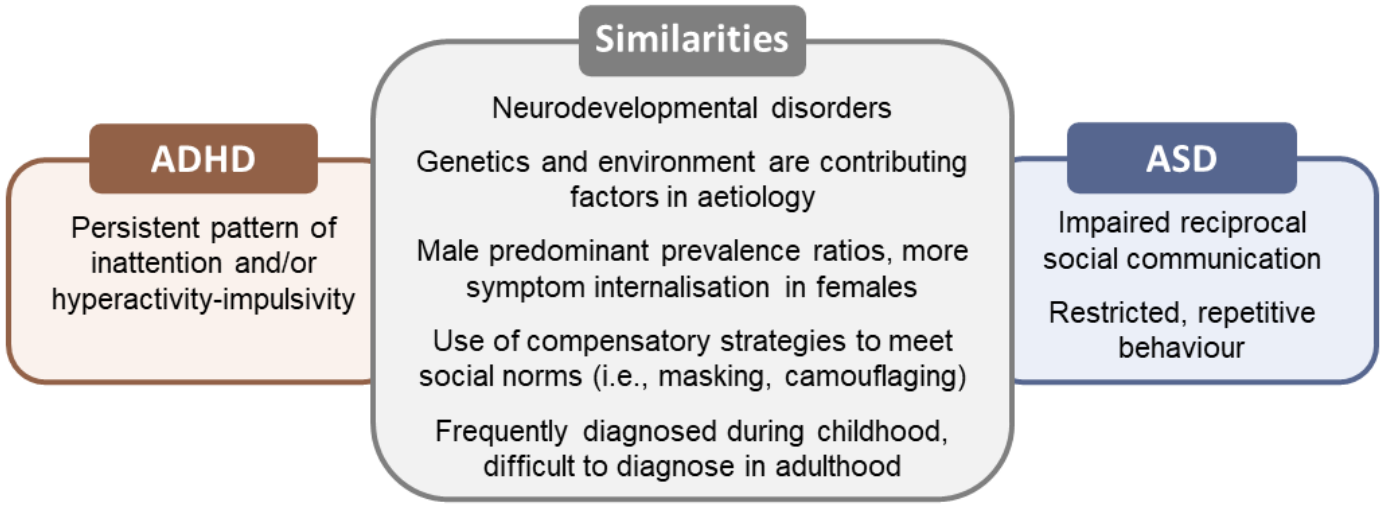

Figure 1: *A summary of the similarities and differences between clinical presentation for ADHD and ASD.*

behaviours, sensory abnormalities, and very specific interests [36, 37]. Although ASD shows stronger stability in clinical presentation than ADHD, social problems seem the most persistent in adolescence and adulthood [38, 39]. For example, the well-known social problems in adolescents were presented by them spending their free time with very few engagements or activities with peers [24, 40]. A similar internalising behaviour pattern (i.e., masking and compensation) of females with ADHD is also found in females with ASD [41-43]. Surveys and qualitative studies highlight the 'partly different' clinical presentation in females, presenting the previously mentioned greater internalisation alongside higher social motivation and masking of ASD characteristics than in males [41-45].

During late adolescence, the co-occurrence of symptoms as suggested by previous studies is highest for both ADHD and ASD [24]. Correlations between ADHD and ASD in adolescence can be explained, as the strength of the relationship is driven by adolescent individuals who still have symptoms [46, 47]. The individuals in this developmental stage are influenced by impairments in social and executive functions, which were found to be particularly prevailing in this stage for both disorders [48, 49]. There are also common co-occurring disorders in adults suffering from ASD and ADHD (e.g., anxiety, depression, obsessive compulsive disorder, sleep disorders, and gastrointestinal problems) [36]. These common co-occurring disorders can be explained by shared pathophysiology and symptom dimensions of both disorders, and the consequences of living with either disorder [45, 50]. These co-occurring disorders and their impact on diagnosis and in the progression of adulthood will be further described.

Diagnosis

This section highlights difficulties in adult and/or female diagnosis (i.e., diagnostic bias, misdiagnosis, and late diagnosis) by reviewing the diagnostic criteria of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [51]. The gold standard for diagnosing neurodevelopmental disorders is symptom-based categorical systems. DSM-5 allowed a first-time ever simultaneous diagnosis of ADHD and ASD [51, 52]. The diagnostic criteria of previous editions prohibited simultaneous ADHD and ASD diagnosis regardless of co-occurrences [13]. However, individuals with ASD and ADHD often do not completely fit within the diagnostic boundaries of a single disorder but show a mixed clinical presentation [51, 53, 54]. Hence why previously mentioned overlap of ADHD and ASD symptoms in individuals is seen in practice [13, 55].

ADHD diagnostics are done by licensed clinicians who interview the patients and/or caregivers to document possible symptoms that may fit the criteria of an ADHD diagnosis [51]. ADHD cannot be diagnosed by one single test (i.e., by rating scale, a neuropsychological test, or brain imaging alone) [1]. Although the subjectiveness of the diagnosis has been criticised, ADHD meets the validity criteria of a mental disorder [56].

There are currently no clear existing biomarkers for ASD, hence, the diagnostic process of ASD consists of referral, screening, interviews with the patient and family members, and assessments based on the DSM-5 criteria [36, 51, 57]. It is important to note that the DSM-5 diagnostic criteria were designed for men, resulting in clinicians reporting reduced confidence in diagnosing ASD in non-male individuals [44, 58]. This practice may have, in part, led to misdiagnosis or late diagnosis of female individuals with ASD and ADHD [23]. For ASD specifically, there is a disproportionate probability of not receiving a clinical diagnosis for females who meet the criteria for ASD [10].

When comparing diagnostic descriptions of ADHD and ASD, few commonalities are found. While individuals with ADHD are characterised by severe inattentiveness, hyperactivity, and impulsivity, ASD is contrastingly characterised by impaired social interaction and communication, along with restricted, repetitive behaviour and interests [51]. Additionally, the severity of ADHD/ASD symptoms correlates to receiving an earlier diagnosis for both disorders [8, 50].

The challenges of specifically adulthood ADHD/ASD diagnosis can be classified into three groups. Firstly, in terms of practicality, the adult's childhood caregivers might no longer be alive or in contact. Even in the case where the caregiver can be interviewed, there is a great probability of the caregiver's recall bias due to decades being passed since the adult's childhood, hindering the diagnostic procedure [21, 22, 50]. Secondly, so-called development of camouflaging as a compensatory strategy causes under-recognition by caregivers,

family, teachers, and clinicians [22, 36]. Camouflaging is masking and/or developing compensatory difficulties to fit more into social norms [45]. Lastly, clinical challenges can be explained as overshadowing ADHD or ASD symptoms by the widely reported high frequency of co-occurring disorders [24, 59].

In conclusion, lifespan development-based research can help bring awareness to the challenges of adult ADHD/ASD diagnosis due to bias in sex differences and extrapolation of conclusions from childhood research [24, 45].

Management of core symptoms

This section highlights only pharmacological and behavioural interventions since most non-medication treatments are less effective in reducing ADHD and ASD symptoms [28, 37]. Additionally, evidence for medication use in adults with ADHD and/or ASD is limited and, as previously mentioned, largely based on extrapolations containing mostly childhood studies [12]. Therefore, a brief overview is given on current treatment guidelines for both disorders for all ages where appropriate.

Attention-deficit hyperactivity disorder management

The National Institute for Health and Care Excellence recommends methylphenidate in children aged 5 years and older, and lisdexamfetamine or methylphenidate for adults as first-line pharmacotherapy [60]. Psychological approaches are listed as the second option, with cognitive behavioural therapy for individuals with ADHD whose symptoms still cause significant impairment despite beneficial effects from medication [60].

Autism spectrum disorder management

Approximately two-thirds of adolescents with ASD have used psychotropic medication (i.e., neuroleptic drugs, antidepressants, and stimulants) as a form of pharmacotherapy [61]. Mandell *et al*. reported that 56% of individuals with ASD were prescribed at least one psychotropic medication, and 20% of individuals had a prescription of three or more, mostly to manage comorbid disorders [62]. In terms of psychological approaches, behavioural evidence-based interventions have been classified into two groups: comprehensive treatment models and focused interventions [61]. Comprehensive treatment is long-term, intensive, and focused on multiple core symptoms [63]. Focused interventions address one skill or goal for a shorter time period than comprehensive treatment [64].

Treatment of co-occurring ADHD and ASD

In current research, it is commonly believed that both disorders can co-occur, but less is known about the nature of the co-occurrence of ADHD and ASD. One scenario that was disputed is that one disorder leads to the other as the cause. This would mean that treatment of ADHD might improve symptoms of ASD as well. However, it appears to not be the case: noradrenergic reuptake inhibitors and psychostimulants appear to be effective in treating ADHD symptoms for individuals with a combined diagnosis but have no substantial effect on ASD symptoms [65-67].

In conclusion, treatment of ADHD and ASD is applied in the form of first-line pharmacological symptom management with eventually occasional simultaneous psychological approaches [60, 61].

Conclusion

Despite large bodies of evidence for both ADHD and ASD, there is a lot more to learn about the disorders, specifically about diagnosis and management in adulthood ADHD/ASD. Lifespan development-based research can help bring awareness to the challenges of adulthood diagnosis due to bias in sex differences and extrapolation of conclusions from childhood research. Future neurodevelopmental research should consider greater delineation between sex-related and gender-related effects in pursuit of more equitable clinical care. This will result in improved population representation and reduction of contextual bias and cases of under-recognition.

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Note from the author

As previously acknowledged, the author was notified on the use of ableist language in some sections. The author apologises for being uneducated in this matter and will be taking action on educating themselves to avoid use of ableist language in the long term, rather than superficial modifications for just this publication.

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
A. 4% of the colposcopies performed are unnecessary.

A false positive test result indicates that a person has a specific condition even though the person does not have it. A positive test that suggests the need for further examination while there is no condition present results in performing unnecessary diagnostic tests. For the HPV test for cervical cancer, 4% of the positive tests are women that do not have cervical cancer and, therefore, undergo an unnecessary colposcopy.

For further reading:
Bouter, L. M., Van Dongen, M.C.J.M., Zielhuis, G.A., Zeegers, M.P.A. Chapter 9: Diagnostiek en prognostiek in Kernboek - Leerboek epidemiologie, 7th edition (Bohn Stafleu van Loghum, 2016).

Answer question 2:
B. hypokalemia.

K^+ is lost in small amounts through sweating, resulting in noticeable loss during heavy sweating caused by intense physical activity. After exercising, K^+ released into plasma is quickly reaccumulated by skeletal muscles, resulting in an evident decrease in K^+ during the start of recovery. Therefore, a hypokalemia is often seen after exercise.

For further reading:
Stehouwer, C.D.A., & Koopmans, R.P. Chapter 12: Zuur-basenevenwicht en kaliumhuishouding in Leerboek interne geneeskunde, 15th edition (Bohn Stafleu van Loghum, 2017).

The exam questions can be found back on page 11 in this journal.