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Attention deficit hyperactivity disorder and comorbidity: A review of literature

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Abstract

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder with onset in early childhood. It is a clinically heterogeneous condition with comorbidity posing a distinct challenge to diagnosing and managing these children and adolescents. This review aims to provide an overview of comorbidity with ADHD including other neurodevelopmental disorders, learning disorders, externalising and internalising disorders. Challenges in screening for, diagnosing and managing comorbidity with ADHD are summarised. Also, methodological challenges and future directions in research in this interesting field are highlighted.

Key words: Attention deficit hyperactivity disorder; Comorbidity; Review

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Core tip: Attention deficit hyperactivity disorder (ADHD) is a clinically heterogeneous condition that is typically complicated by extensive comorbid conditions. Screening for comorbidity is imperative for appropriately managing these children and adolescents presenting with complex difficulties. Further research is required for elucidating the implications of comorbidity in terms of diagnosing and managing children with ADHD.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is characterized by pervasive and impairing symptoms of inattention, hyperactivity, and impulsivity according to Diagnostic and Statistical Manual of Mental Diseases (DSM-V)^[1]. It is a common childhood onset mental disorders with reported prevalence rates of 5%-8% in school children^[2]. ADHD has been identified as an extremely clinically heterogeneous disorder with one of the reasons being high rates of comorbidity with other childhood onset disorders. It is estimated that around 60%-100% of children with ADHD also exhibit one or more comorbid disorders that often continue into adulthood^[3,4]. This narrative review aims to provide an overview of current research (including recent research findings) on comorbidity with ADHD, methodological issues with such studies and implications for nosological systems, clinical management as well as future research. The scope of this review includes comorbid mental health disorders but not physical illnesses. The review also highlights the need for a dimensional construct, particularly after release of DSM V diagnostic criteria^[1].

ADHD AND COMORBIDITY

Autism spectrum and other neurodevelopmental disorders

Autism spectrum disorder: While DSM IV precluded a dual diagnosis of ADHD and autism spectrum disorder (ASD), DSM V allows for the dual diagnosis if appropriate diagnostic criteria are met. In a recent nationally representative sample from United States, in children diagnosed with ASD, the rate of comorbidity with ADHD was 42% and the rate of comorbidity with ADHD and learning disability (LD) was 17%, resulting in a 59% total comorbidity rate of ADHD and ASD^[5]. In terms of symptomatology, it is widely believed that there is good degree of overlap between symptoms of ADHD and ASD. However, a recent study demonstrated that it was possible to discriminate symptom profiles of ASD and ADHD in children^[6]. Another study demonstrated that children and adolescents with combined ADHD and ASD have more severe symptoms across all domains and an additive severity of sleep-related difficulties in this group^[7].

Novel neuroimaging techniques including diffusion tensor imaging (DTI) have been utilised to demonstrate neurobiological changes that correspond with clinical severity in neurodevelopmental disorders and this might be a future tool to assess for additive severity of comorbid conditions in this regard^[8].

Learning disorders: There is a wide variation in reports of comorbidity between ADHD and learning disorders, ranging from 10%-92%^[9]. This is possibly due to differences in diagnosis and discriminating between both the conditions in individual studies^[8]. A recent study demonstrated the relationship between learning difficulties and ADHD symptoms, predominantly in the inattentive type^[10]. In an earlier study, a LD was present in 70% of the children with ADHD. A LD in writing was two times more common (65%) than a LD in reading, math, or spelling^[11].

Tic disorders: In an international study on tic disorders and ADHD, the reported prevalence of ADHD in Tourette's syndrome (TS) was 55%^[12]. Previous studies have cited similar numbers as well^[13]. The other salient findings from the study were ADHD was associated with earlier diagnosis of TS and a much higher rate of other difficulties including anger management, insomnia, learning difficulties, Obsessive compulsive disorder (OCD), Oppositional defiant disorder (ODD), mood disorder, and self-injurious behaviour^[14].

ADHD and internalizing disorders

Depressive disorder: The rate of major depression in youth with ADHD ranges from 12% to 50% which is more than five times higher than in youth without ADHD^[15]. It is also shown that this comorbidity is higher in clinical sample than in the community sample^[14]. Depressive disorders with ADHD typically occur several years after the onset of ADHD and is independent of other comorbidities^[15]. Co-morbid depression is regarded as an outcome of ADHD-related impairments and negative environmental circumstances also called as ADHD-related demoralization by many authors^[15-17].

However, ADHD and depression have independent and distinct courses. This proves that ADHD-associated depression reflects a depressive disorder and not merely demoralization^[17].

Bipolar disorder: The rates of comorbidity between pediatric bipolar disorder and ADHD have been greater than the chance findings but are dramatically different across studies^[18-20]. Evidence suggests some mechanisms for comorbidity including shared risk factors, distinct subtypes and weak causal relationships^[21]. However, the clinical diagnosis of ADHD is not a reliable antecedent in the developmental trajectory toward bipolar disorder^[22]. The association between these disorders appears more co-incidental than a causal relationship / predictive association. But when these two disorders co-occur the patient will have poorer global functioning, greater symptom severity, and more additional comorbidity than for either of these disorders^[23].

Anxiety disorders: The prevalence of anxiety symptoms in ADHD patients range from 15% to 35%^[24,25]. The rates of comorbidity may be affected by the symptom overlap and the diagnostic systems^[13]. The relationship between ADHD and anxiety appears to be robust, existing in all populations and in children seen by primary care pediatricians as well^[24,25]. This co-existence has been described by different psychological as well as biological models^[26,27]. In terms of neurophysiology, anxiety in ADHD may partially inhibit the impulsivity and response inhibition deficits, make working memory deficits worse, and may be qualitatively different from pure anxiety. The co-morbid condition has more negative affectivity and disruptive social behaviour and less fearful/phobic behaviour. The anxiety in ADHD may substantially change the presentation and course of the disorder^[17]. The co-morbid condition is associated with more attentional problems, school phobia and mood disorders and lower levels of social competence than either ADHD or anxiety alone^[14]. However, when the moderation effect of ADHD in anxiety was studied it was seen that ADHD had a limited impact on the manifestation of anxiety disorder giving an evidence that ADHD and anxiety disorders are independently expressed in children^[28]. It is widely suggested that due importance be given to assessment of anxiety symptoms while assessing and treating ADHD^[29,30].

ADHD and externalizing disorders: Common externalizing disorders comorbid with ADHD include ODD and Conduct disorder (CD). Newer diagnostic categories like Disruptive Mood Dysregulation Disorder (DMDD) and Intermittent Explosive Disorder (IED) have also been shown to exist comorbidly with ADHD^[31,32]. It is demonstrated that 30%-50% children with ADHD also fulfill criteria for CD or ODD. Population-based studies usually identify occurrence of comorbidity more in boys than girls^[33].

The strikingly high rates of comorbidity could at least be partially attributed to shared genetic origin^[34]. Longitudinal studies suggest that the correlation between ADHD-like and externalizing traits increases across age (from childhood to adulthood) and ADHD-like traits may exacerbate externalizing tendencies in the transition from adolescence into adult life^[35]. With regard to predictive environmental factors, researchers have found that children with ADHD suffering from neuropsychological dysfunction, early aggressive behaviour, and adverse family circumstances are at increased risk for comorbid externalizing disorders^[36].

CD and oppositional defiant disorder: The combined impact of ADHD with other externalizing disorders on functioning can be profound. Higher rate of academic problems in children with above comorbidity like reading disorder, impaired verbal skills, visual motor integration and visuospatial skills on neuropsychological measures is well documented when compared with children without such comorbidity^[36]. Furthermore, ADHD/CD children are more likely to abuse drugs, engage in criminal behaviour, have driving-related outcomes and are more likely to adult antisocial personality disorder than children with ADHD alone^[37-39]. ADHD/CD has also been found to be associated with higher expulsion and dropout rates in school than in children with ADHD alone^[40] (Table 1).

Apart from impact on clinical course and symptomatology, such comorbidities also pose a diagnostic challenge for clinicians. With several overlapping clinical features, distinction between ADHD and CD can sometimes be unclear. Thus, a hybrid disorder hyperactive CD with an earlier onset and an outcome worse than of either disorder alone is now recognized^[41]. Similarly, most of the patients who have been diagnosed as DMDD also fulfilled the diagnostic criteria for ODD/CD with ADHD and it becomes difficult to diagnose them as comorbid disorders^[41].

Disruptive mood dysregulation disorder and IED: Sagar-Ouriaghli *et al*^[31] thus

Table 1 Summary of some key studies on comorbidity with attention deficit hyperactivity disorder in children and adolescents

Comorbidity with attention deficit hyperactivity disorder	Incidence (%)	Ref.
Autism spectrum disorder	59	Stevens <i>et al</i> ^[5]
Learning disorders	10-92 70	Biederman <i>et al</i> ^[9] Mayes <i>et al</i> ^[11]
Tic disorders	55	Freeman <i>et al</i> ^[12]
Depressive disorder	12-50	Angold <i>et al</i> ^[13]
Bipolar disorder	5-47	Galanter <i>et al</i> ^[18]
Anxiety disorders	15-35	Jensen <i>et al</i> ^[25]
Conduct disorder	3.5-10	Barkley <i>et al</i> ^[40]
Oppositional defiant disorder	30-50	August <i>et al</i> ^[37]

postulated that DMDD appears to be an alternative way of describing the presence of ODD/CD with either anxiety or ADHD. Symptoms of aggression, anger and impulsivity are also seen in IED and high rate of comorbidity are reported in literature. An early onset and common core clinical features of both these disorders suggest a strong association between these disorders^[42].

IMPLICATIONS

Phenotypes and endophenotypes of ADHD

Genetic studies on ADHD and comorbid disorders is one of the key methods to investigate the putative ADHD phenotypes based on comorbidities. For example, the study addressed the question of how the association between ADHD and reading disability (RD) might arise. The clear conclusion from subsequent studies investigating their co-occurrence is that there is a common genetic aetiology^[43-49]. This raises two possibilities: either that RD and ADHD in general are influenced by the same genes or when they co-occur this comorbid group have a distinct genetic origin from those acting on RD and ADHD in isolation^[50].

Studies focusing on dimensional constructs of ADHD like executive dysfunction in "pure" cases *vs* comorbid cases is another method to disentangle the association. For example, in a recent study comorbid problems including autistic traits, motor coordination problems and reading problems were just associated phenotypically, were also related to the executive function (EF) and motor ADHD-endophenotypes after correction for ADHD^[51]. These findings may point towards a shared underlying neuropsychological dysfunction that may give rise to both ADHD and comorbid disorders. These familial and shared neuropsychological endophenotypes appear to have multiple behavioural consequences (pleiotropy)^[52].

This gives rise to the question whether ADHD with comorbidity is viewed as a distinct phenotype or simply accentuates the severity of ADHD symptoms. A number of studies suggest that the combination of ADHD with a comorbid problem may not be best conceptualized as a distinct phenotype since the interaction between ADHD and the comorbid condition did not have predictive value on the core deficits (*e.g.*, EF) over and beyond the independent effects of ADHD and the comorbid condition^[13,53-56].

Response to treatment

Comorbid conditions with ADHD have a definite bearing on selection of treatment modality as well as treatment response. For example, the landmark Multimodal treatment of ADHD study demonstrated that subjects with both ADHD and anxiety disorders are particularly responsive to behavioural therapy, compared with subjects in other comorbidity groups including those with ODD/CD^[25,52]. Patients with ADHD, anxiety disorders and ODD/CD subjects were preferentially responsive to combination interventions with both medication and behavioural therapy. In children with only ADHD, and ADHD with ODD/CD behavioural intervention in isolation didn't appear beneficial^[25,54].

Nosological systems

Evaluating the presence of comorbidity between different psychiatric conditions offers a method of both correcting and validating psychiatric nosology^[13]. The co-occurrence of ADHD and comorbidity is partly due to shared familial/heritable neuropsychological deficits and motor dysfunction^[56]. This implies that these symptoms cannot be diagnosed or treated independently of one another. This has

definite theoretical implications in future nosological systems, particularly when we consider this in the framework of RDoC (research domain criteria) of NIMH (National institute of mental health) that postulates linking basic dimensions of functioning to behaviour^[57].

Methodological issues in research on ADHD and comorbidity

For an accurate interpretation of studies on ADHD and comorbidity in relation to implications in clinical management as well as future research, it is important that we consider the results in light of certain methodological limitations. The choice of information sources (*e.g.*, clinician, parent, teachers self-report, behavioural observation) as well as method of arriving at a diagnosis (*e.g.*, Standardized scales or clinical interview) were heterogenous across different studies^[58]. A combination of information from different sources might sometimes lead to overdiagnosis of comorbidity and vice versa. There is also a possibility of Berkesonian bias in referred clinical population with typically more severe symptomatology, more comorbid disorders or more severe comorbid disorders^[14]. In addition to this, use of different classificatory systems may lead to differences as well *e.g.*, ASD can be co-diagnosed with ADHD in DSM V but not in DSM IV^[1,59].

CONCLUSION

Cross-disciplinary research combining genetics, symptom dimensions, core deficits, choice of treatment and treatment response on a large sample size is likely to shed more light on this complex but exciting area^[60]. This would aid in more personalized and precise matching of patients to treatment modality using patients' comorbidity profiles and result in much better treatment gains for individual patients. A comprehensive screening for comorbidity in cases diagnosed with ADHD should be mandatory to achieve the above objectives.

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