Co-occurrence of Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD)

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Abstract

The current diagnostic manuals, DSM-IV-TR and ICD-10, do not allow the diagnosis of ADHD to be made separately in the presence of autism (pervasive developmental disorder). However, the characteristics of ADHD are very common in autism, occurring in around 30 to 70%. Surveys of children with ADHD also reveal a high proportion of features of Autism Spectrum Disorder (ASD). Furthermore, treatment of ADHD in the presence of autism is of benefit in a large proportion. The inconsistency in the diagnostic manuals should be resolved in the forthcoming DSM-5 and ICD-11. The results of twin studies have been consistent with the sharing of genetic influences between autism and ADHD symptoms. Genome-wide studies have also shown shared chromosomal regions of interest for susceptibility sites for both conditions. There is an overlap between the executive function deficits in both conditions, although the details of the dysfunction may be different. There is evidence that all the standard treatments for ADHD can be effective in the presence of autism (though to a lesser extent than in pure ADHD): methylphenidate, amphetamines, atomoxetine, clonidine and guanfacine. Atypical antipsychotics such as risperidone and aripiprazole may be of specific importance in managing ASD with irritability, aggression and hyperactivity. The idea that ADHD cannot be diagnosed or treated successfully in those with ASD is a myth that should be dispelled; many of those who have both autism spectrum disorder and ADHD can benefit greatly from the treatment of the ADHD.

Introduction

Pervasive Developmental Disorders (PDD) or Autism Spectrum Disorders (ASD), are early-onset developmental disorders with severe lifelong impact on social functioning, communication and behaviour. Children with ASD often present with interfering symptoms of Hyperkinetic Disorder (HKD) or Attention Deficit Hyperactivity Disorder (ADHD), i.e. symptoms of motor hyperactivity, impulsiveness and inattention requiring treatment (1). There is widespread clinical agreement that severe levels of hyperactivity in a pre-school age child should prompt suspicion that the 'underlying' disorder might be autism. It is not unheard of for a child suspected of suffering from severe ADHD (because of extremes of early onset hyperactivity and impulsivity) to be treated with a stimulant,

and for there to emerge autism features in the course of such treatment. In the past, this was often believed to be a side-effect of the treatment per se. While that is a real possibility, a more common link might be the suppression of severe hyperactivity leading to the 'unmasking' or 'surfacing' of the ASD which was always present but hidden under the more conspicuous symptoms associated with extreme hyperactivity (2) .

Concept of Developmental Co-morbidity

The term 'co-morbidity', coined by Feinstein, is now widely used to refer to the greater than coincidental association of two conditions in the same individual (3). The concept of "developmental comorbidity" looks at the possible influence of age and development on the occurrence of comorbidity in psychiatric conditions such as ADHD and autism, to outline distinct trajectories of symptom progression with possible impact on course and outcome. The occurrence of co-morbid symptoms, for example ASD symptoms, could temporally (i) arise before the appearance of first definite ADHD symptoms ("pre-comorbidity"); (ii) coincide with ADHD symptoms when they reach a clinical significance ("simultaneous comorbidity"); (iii) or rarely appear or be identified after the onset of ADHD ("post-comorbidity") (4).

Co-morbidity between HKD/ADHD and PDD/ASD

The diagnostic nomenclatures do not allow for the concurrent diagnosis of autism and HKD/ADHD. Both ICD and DSM classification systems assume a hierarchical standpoint when dealing with PDD/ASD and HKD/ADHD: the diagnosis of PDD/ASD automatically trumps the diagnosis of HKD/ADHD. The Diagnostic and Statistical Manual of Mental Disorders, 4th- text revision (DSM-IV-TR) (5) does not allow ADHD to be diagnosed if the ADHD symptoms occur only during the course of a Pervasive Developmental Disorder (American Psychiatric Association, 1994). A similar approach is taken by the International Classification of Diseases – 10th Revision (ICD-10) (World Health Organisation, 1992) (6), with the diagnosis of Hyperkinetic Disorders not being allowed if symptoms occur in the context of a PDD (synonymous to ASD). This reluctance to make co-morbid diagnosis of ASD and HKD/ADHD has treatment implications because ASD subjects with HKD/ADHD symptoms may not be identified or diagnosed, resulting in delayed treatment or even denial of treatment for the HKD/ADHD (2). This hierarchical diagnostic framework for ADHD and ASD is very likely to be removed from DSM-5 and ICD-11.

Clinic-based Studies of ADHD and ASD

Historically, Clark and colleagues estimated the rate of autism features within a sample of 49 DSM-IV ADHD children, using a retrospective, case-note-based extraction of symptoms as reported on the Autism Criteria Checklist (a 12-item parent-rated questionnaire): 65-85% of these children were reported as having significant difficulties in social interaction (particularly in empathy and peer relationships), and communication (particularly in imaginative ability, nonverbal communication and maintaining conversation) (7). Another review of 309 child & adolescent patients with ICD-10 Hyperkinetic Disorder (HKD) found that 40% of the HKD group had "social reciprocity problems," 24% had "speech and language difficulties" and 9% had "repetitive behavior" (8). Interestingly, substance use and alcohol use was only present in ASD adolescents if they had concurrent ADHD (9).

When ASD children were evaluated for ADHD, between 30 and 70% met symptom criteria for ADHD (10,11,12).

Population-based Studies of ADHD and ASD

Due to the obvious referral biases, the clinical samples described above will show increased psychiatric comorbidity, and hence it is important to investigate the association between ADHD and ASD in population-based samples. Reiersen and colleagues showed that children with ADHD selected from a general twin population have elevated levels of autism traits. DSM-IV combined subtype and the

population-derived severe combined subtype had the highest mean scores for each of the three autism symptom domains, with a substantial proportion of individuals scoring in the clinically significant range (13).

The Twins Early Development Study (TEDS), a study on a community sample born in England and Wales has also reported on the association between ADHD and ASD. They found significant correlations between autism and ADHD traits in the general population (0.54 for parent data, 0.51 for teacher data). They concluded that there are some common genetic influences operating across autism traits and ADHD behaviours throughout normal variation and at the extreme, and that it is relevant for molecular genetic research, as well as for psychiatrists and psychologists, who may have assumed these two sets of behaviours are independent (14).

Motor problems and high levels of autism traits are common in individuals with combined-type ADHD. Individuals with the combination of motor problems and ADHD were more likely to have high levels of autism traits than those with ADHD alone (15).

Another population-based study confirmed the association between autism and ADHD symptoms in a young adult twin sample assessed by self-report, and showed that in young adults, a substantial proportion of the genetic influences on self-reported autism and ADHD symptoms may be shared between the two disorders (16).

Biopsychosocial Risk Factors in ADHD and ASD

Genetic factors

Some studies in the early 1990s did suggest a strong familial overlap of the conditions (17,18). There is, perhaps unexpectedly, rather more to suggest a biological link between the two diagnosed conditions at the molecular genetic level. It has been suggested that the serotonin transporter gene is down-regulated in both ADHD and ASDs (19). Genome scan studies of autism have suggested certain chromosomal regions of interest for autism susceptibility genes, and genome scan studies of ADHD have demonstrated that some of these regions, e.g. on chromosomes 2q, 15q, and 16p, are also susceptibility sites for ADHD (20, 21).

Neuroanatomy and neurophysiology

At the brain biological level, the evidence linking the two conditions is highly contradictory. On the one hand there are many studies suggesting brainstem, cerebellar, basal ganglia, and frontal dysfunction in both conditions, even though it is not clear that the types of dysfunction are shared across them. On the other hand, some studies do suggest markedly different brain pathologies in the two disorders. For instance, in systematic studies, autism is quite often associated with macrocephaly (in about 20% of the cases) (22), whereas ADHD is often reported to be linked to smaller overall brain size (23).

Neuropsychological Findings in ADHD and ASD

To date, there are few studies that have compared executive functions (EF) in ASD and ADHD. Ozonoff and Jensen (24) compared children with ADHD, ASD or Tourette syndrome, as well as controls with typical development (TD) and reported that the ASD group showed more perseveration and poorer planning than any other group, while the ADHD group was poorer than TD controls on tasks of inhibition (25).

Geurts et al. conducted a study attempting to map distinct profiles of EF in ASD and ADHD. They compared 6-12 year olds (mean age 9) with ADHD, high-functioning autism, or TD (whose IQ was higher than the clinical groups) on a large battery of EF tasks. The ASD group showed deficits on all

EF tasks except interference control and working memory, and greater impairments than the ADHD group on planning and cognitive flexibility. The ADHD group, by contrast, was most impaired on inhibition of pre-potent response and verbal fluency. The authors conclude that EF problems are more severe in ASD, although poor performance in this group on non-EF control tasks was also noted (26). Another study concluded that spatial working memory is impaired in both ADHD and High Functioning Autism (HFA), and more severely in ASD. No differences were found between ADHD and ASD children on response inhibition, planning and flexibility tasks (27).

When the age and IQ matched groups with ASD, ADHD, or typically developing children were compared on tasks tapping planning, working memory and response inhibition, both clinical groups showed significant EF impairments compared with the typically developing group. At older (but not younger) ages, the ASD group outperformed the ADHD group, performing as well as the typically developing group on many EF measures. EF scores were related to specific aspects of communicative and social adaptation, and negatively correlated with hyperactivity in ASD and typically developing children. The overall findings suggested less severe and persistent EF deficits in ASD than in ADHD (28).

Learning, attention, graphomotor, and processing speed scores were analyzed in 149 typical control children and 886 clinical children with normal intelligence. Control children performed better than children with ADHD and autism in all areas. Children with ADHD and autism did not differ, except that children with ADHD had greater learning problems. Attention, graphomotor, and speed weaknesses were likely to coexist; the majority of children with autism and ADHD had weaknesses in all three areas and these scores contributed significantly to the prediction of academic achievement (29).

A community-representative sample of Swedish children with late developing language at 2.5 years of age had persisting difficulties with oral narrative skills at age 7-8 years (30). Compared to Normal Control (NC), children with HFA and with ADHD showed generalised pragmatic deficits and impairments in pragmatic language use, which did not vary with age (26).

In contrast to the well-established literature on the behavioural and cognitive deficits of children with ADHD, much less is known about the social deficits of this population. Wheeler et al. suggested that the social deficits of the ADHD subtypes could be best explained as social skills deficit, social performance deficit, self-control skill deficits and self-control performance deficit (31). Another concept considering social skills deficiencies of children with ADHD is that self-regulation of affect, motivation and arousal represents an important area of impairment in ADHD, beneath working memory, utilization of speech and reconstitution (32). Moreover, it has been reported that some socially inappropriate behaviours (eg. blurting out answers to questions, interrupting or intruding on the conversations of others, handling frustration in an impulsive, aggressive manner, etc.) seem directly related to the core features of ADHD (33). On the other hand, other social deficits in ADHD children, such as failing to comprehend the impact of one's actions on others, misinterpreting social information and possessing a limited repertoire of social responses, may be closer to the autism type of social difficulties. This is rarely discussed in the literature and it may be an important link to autism (34). The same hypothesis might be a plausible explanation for the research revealing that children with ADHD have difficulties in responding appropriately to the continuous changes in demands and cues that characterizes the flow of social interaction (35; 36).

Reasons why Symptoms Overlap

Over the past few years, in our Developmental Neuropsychiatry Clinic, we have seen a significant number of children with high functioning autism being referred who have been previously diagnosed as having only ADHD. Various reasons for the hyperactivity can be put forward. The inability of the child to switch attention from one task (overcircumscribed interest) to another may lead the child to return constantly to the original task, thus preventing sustained attention in other tasks. Apart from this, stimulant treatment in itself may lead to increased perseveration and over-focused attention, leading to inability to pay attention to routine tasks. Motor mannerisms can be mistaken for hyperactivity. Poor social skills and reciprocity can lead to inappropriate questioning and comments,

which are impulsive. Cognitive rigidity and language and communication impairment lead to oppositional and challenging behaviours.

Treatment of ADHD co-morbid with ASD

Methylphenidate has been considered the first-line treatment for children with ADHD without significant co-morbidity (other than co-morbid conduct disorder). A recent large open-label study found no statistically significant difference between children with ASD plus ADHD symptoms and children with ADHD alone, in the degree of improvements or rate of adverse effects (37). The most frequently reported adverse effect was decrease in appetite. The randomised, controlled, crossover trial of methylphenidate in ASD with hyperactivity showed that about half of these children responded to methylphenidate, although this treatment was less effective than that seen in typically developing children with ADHD. Moreover, methylphenidate was frequently associated with adverse effects leading to discontinuation (38). Similar results were found in the randomised, placebo-controlled, crossover study of methylphenidate for ADHD symptoms in pre-school children with developmental disorders, including ASD and intellectual disability (39).

Amphetamines have been used but recent studies in ASD are lacking. Two studies conducted in the early seventies did not show any significant improvement. In a placebo-controlled crossover study of 16 children (40), dextroamphetamine yielded no significant improvement. Another study, with levoamphetamine, a double-blind crossover trial of 12 children, showed only minimal positive effect (41).

Atomoxetine has been used to treat inattention and hyperactivity in ASD, with three open-label studies suggesting that it may be effective in children and adolescents with ASD for symptomatic treatment of hyperactivity, impulsivity and oppositionality (42, 43, 44). If methylphenidate has been ineffective, atomoxetine can be considered as another option. A placebo-controlled crossover pilot trial showed that atomoxetine appeared to be safe and effective for treating hyperactivity and the effect appeared as large as in a multisite methylphenidate trial in the same population, with fewer intolerable adverse effects (45). Other authors studied the efficacy and tolerability of atomoxetine in high-functioning boys with ASD and comorbid ADHD, showing significant reductions in ADHD symptoms rated by parents and by teachers, with half of the participants classified as clinical responders. In addition, most children tolerated the drug well (46).

Risperidone

Risperidone is licensed for use in autism to manage marked irritability and challenging behaviour. The Research Units of Paediatric Psychopharmacology (RUPP), Autism Network, conducted a double-blind placebo-controlled study in children and adolescents with autism and reported improvements in tantrums, aggression or self-injurious behaviour in children, and also of hyperactivity (47). Improvement in irritability and hyperactivity has been replicated in another Canadian multi-centre trial (48).

Aripiprazole

Aripiprazole is an atypical antipsychotic and is a 5-HT1a agonist, partial dopamine D2 agonist and serotonin 5-HT2A antagonist. Two recent double-blind randomised, placebo-controlled studies concluded that aripiprazole was effective in children and adolescents with irritability associated with autism disorder and was generally safe and well tolerated (49, 50). Hyperactivity was reported to have improved in both studies (49, 50).
Monitoring to rule out hyperprolactinaemia and emergence of metabolic syndrome is important when using atypical antipsychotics.

Clonidine

Clonidine is an alpha-2-adrenergic agonist that is useful in ASD with ADHD/Tourette syndrome.

Two double-blind, placebo-controlled crossover trials in the early nineties reported some benefits with clonidine in treating overactivity in children with autism, although the sample size was small. Fankhauser reported that patients on transdermal clonidine experienced fewer sensory responses, less affectual reactions and improvement in social relationships (51). Another study reported a decrease in irritability, stereotypy, hyperactivity, inappropriate speech and oppositional behaviour during patient treatment (52). Both studies reported sedation and fatigue as major adverse effects, along with decreased activity (53). Clonidine was effective in reducing sleep initiation latency and night awakening, and to a lesser degree in improving attention deficit and hyperactivity, mood instability and aggressiveness (54).

Guanfacine is another alpha-2-adrenergic agonist that has been shown to reduce hyperactivity in ASD. A retrospective case-note analysis of 80 patients with ASD on guanfacine showed that most patients tolerated it well (55). In a more recent eight-week prospective open trial of guanfacine in children with ASD, a significant decrease in hyperactivity was reported (56). Sedation, constipation, headache, increased irritability, aggressiveness, sleep disruption and decreased appetite are adverse effects reported in studies (55,56).

Conclusion

It is timely and important to examine the diagnostic approaches critically with regard to ADHD and ASD, with the goal of translating research evidence into treatments. Although it is unclear whether there are shared underlying causes producing both ADHD and ASD symptoms, it is clinically clear that a combination of these symptom domains can cause severe impairment, deserving special attention. Diagnosing ADHD in ASD is important as the ADHD can be pharmacologically treated and non-pharmacological interventions may need appropriate modifications. Parents, carers, and professionals need appropriate psychoeducation about developmental comorbidity to achieve optimal outcomes.

GP comment.

What have I learned from this paper?

1. The previous idea that ADHD could not be diagnosed in the presence of autism was misleading.

2. Children with both autism and ADHD can benefit from treatment of the ADHD with the usual medications, including methylphenidate, dexamfetamine, atomoxetine, risperidone and aripiprazole.

3. There is debate about why the two conditions overlap but there is some evidence for a common genetic susceptibility.

4. As a GP, this paper has made me more aware of the possibility of ADHD in a child with autism. As a result, I shall have a low threshold for referring children with autism spectrum disorder for specialist assessment and treatment of the ADHD.

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