CNS Spectrums (2014), **19**, 157–164.
doi:10.1017/S1092852913000941

REVIEW ARTICLE

Clinical features, developmental course, and psychiatric comorbidity of adult autism spectrum disorders

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Autism spectrum disorders (ASDs) include a heterogeneous group of neurodevelopmental disorders with early onset in childhood. ASDs should be considered lifelong clinical entities, although there is a certain variability in developmental trajectories, and therefore should be considered of great interest also for adulthood psychiatrists. A few studies have been carried out to explore the clinical picture and course development of these disorders during adulthood, or their relationship with other mental disorders. Indeed, ASDs often share overlapping features with other disorders, such as schizophrenia and obsessive-compulsive, mood, and personality disorders, and as a result misdiagnoses often occur. The aim of this review is to summarize the available literature on ASDs in adulthood with a specific focus on the clinical picture, course, and psychiatric comorbidity. It is proposed that a careful diagnostic screening for ASDs in adults would contribute to clarifying the relationship with comorbid psychiatric disorders, while improving the possibility of treatment and outcome of such conditions.

Received 6 September 2013; Accepted 1 November 2013; First published online 19 December 2013

Key words: Adult autistic spectrum disorders, mood disorders, personality disorders, psychiatric comorbidity, schizophrenia.

Clinical Implications

- ASDs are relatively common neurodevelopmental disorders and should be considered lifelong clinical entities, causing significant lifetime disabilities.
- Due to atypical clinical manifestations and the associated psychiatric comorbidity, ASDs are often misdiagnosed and mistreated in adults. The underestimation is particularly frequent in high functioning ASDs.
- A detailed cross-sectional and longitudinal clinical definition of ASDs and associated comorbid disorders may improve the recognition of specific and nonspecific features, and promote adequate management and therapeutic strategies.

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Introduction

The term "autism" was introduced by Bleuler in the attempt to define 1 of 4 primary features of the syndromal concept of schizophrenia: the "detachment from reality with the relative and absolute predominance of the inner life."[1] In the 1940s, Kanner resumed use of the Bleulerian term, while making it autonomous and closer to its current conceptualization. He described "early infantile autism" as characterized by an inborn "disorder of the affective contact."[2] Almost contemporaneously, Asperger, a pediatrician in Vienna, described a group of 4 socially awkward boys with the title of "autistic psychopathy."[3] These patients showed difficulties in understanding the emotions and feelings of others and presented multiple behavioral problems. In addition, they were focused on narrow areas of interests, albeit being of normal intelligence. Both Asperger and Kanner used the term "autism" to refer to their cases, but Kanner's contribution became widely known in the scientific community, while Asperger's

article remained largely unnoticed, partly because it was published in German. From the beginning, however, the term autism was applied to a broad spectrum of conditions in terms of both impairment and cognitive functioning.

In the *International Classification of Diseases*, 10th revision (ICD-10) and the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), autism and autism-like behavioral disorders have been included within the broader category of "pervasive developmental disorders" (PDD). The adjective "pervasive" emphasizes the derangement of different areas, while "developmental" refers not only to the early phases of life, but also to the "normative unfolding of multiple developmental competencies, including social relations and communication."[4] While key diagnostic features are similar to those of DSM-IV, other aspects of the diagnosis involve major changes in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5). The name of the broader category of autism is no longer PDD, but autism spectrum disorders (ASDs), as it encompasses a number of syndromes such as Asperger's disorder and PDD not otherwise specified, which previously were individually classified. Whereas DSM-IV included 3 sets of symptoms for autism (qualitative impairment in social interaction; qualitative impairment in communication; and restricted, repetitive, and stereotyped patterns of behavior, interests, and activities), in DSM-5, only 2 sets are proposed ("social/communication deficits" and "fixated interests and repetitive behaviors"), resulting from the unification of social and communication problems under the same label.

ASDs in Adulthood

The great heterogeneity of ASDs and their scarce diagnostic specificity are reflected in the variability of prevalence rates in the literature. Recent investigations report a prevalence of 60/10,000 children,[5] while viewing autism to be one of the most common causes of childhood disability.

The prevalence of an ASD tends to remain stable throughout a subject's lifetime, so those diagnosed with ASDs during childhood are likely to maintain the disorder when reaching adulthood.[6,7] Nevertheless, the clinical picture characteristics may vary over time. In this respect, Shattuck *et al*[8] observed that "autism is a lifelong disorder whose features change with development." The modifications seem to be gender-related, with different symptomatological profiles over time for males and females.[9]

A significant contribution to the progression of the clinical picture may be given by the so-called "setback" phenomenon, which refers to a massive regression after a period of regular development.[10] Severe episodes of regression may be triggered by concurrent physical illnesses, contextual tension, and periods of pressure on growth, such as puberty or school transition. From 2% to 15% of ASDs, depending on the severity and subtype of the disorder, seem to reach an adjustment and functioning level similar to that of the normal population.[11]

From the clinical point of view, in adults as well as in children, autism may be distinguished as "social" (difficulties with social interaction and communication) and "non-social" (restricted and repetitive behaviors and interests) subtypes. "Non-social" autism is characterized by a preference for sameness, repetitive body movements, and a strict limitation of interests. Stereotyped movements (stereotyped march, swinging movements, manipulation of objects, mannerisms) and language problems (stuttering), especially in subjects with a normal IQ, tend to reduce in severity and pervasiveness during growth. On the other hand, obsessive-compulsive features (complex rituals, repetitiveness, and compulsions) often become the prevalent aspect of the clinical picture. Impulsive behaviors, self-injuring, and peculiarity of interests remain stable over time.[12]

According to several studies, some non-social traits seem less severe in female adults: indeed, women show less eccentric and peculiar interests,[13] or less frequent and pervasive stereotyped activities than men. Nonetheless and independently from gender differences, the literature does provide some contradictory data. In a sample of 242 ASD subjects who were followed for 10 years from childhood to adulthood, a global improvement was found especially in the domains of repetitive behaviors, stereotyped interests, social reciprocity, and verbal communication.[11] A reduction of maladjusted behaviors, such as self-injuring, aggression, and defiance, was also reported.[8] Esbensen *et al*[14] examined age-related variations of repetitive and stereotyped behaviors and, in agreement with previous investigations,[8,13] they described a reduction of severity and frequency in repetitive behaviors.

With respect to social abilities, the literature quite uniformly reports that both expressive and receptive language tend to improve with aging, even if the intonation tends to be monotonous and dull. In addition, difficulties with fundamental social skills may decrease as children grow older; similarly, poor eye contact and reduced responsiveness and conflicts with peers mitigate in adults.[15,16] The most typical social manifestations of the autistic spectrum in adults include dull intonation, repetitiveness on limited topics with difficulties in shifting attention between different subjects, deficits in discrimination of emotional nuances and in communicating with others,[15,16] poor sympathetic abilities, and a high tendency in the systematization of relationships. In this area, gender differences are much more evident during adulthood. Women are endowed with more compensatory

https://doi.org/10.1017/S1092852913000941 Published online by Cambridge University Press

socio-communicative abilities than men.[17] An enduring effort in imitating the behaviors and habits of surrounding people and the adoption of a strict social role allows them to behave properly in social contexts. Because of this aptitude, autism in women is much harder to detect.[17,18]

An important symptomatological expression is related to "sensory issues," such as unusual sensory behaviors, generalized over-responsiveness to sensory stimuli, and abnormal or idiosyncratic responses to sensorial triggers.

In adulthood, high functioning ASDs maintain a distinct clinical profile and a less severe general impairment. While IQ and expressive language are not impaired, the ability to intuitively recognize nonverbal signals and, consequently, social interaction appears to be significantly limited. The language is polished and sophisticated, sometimes "baroque" and pompous. Attention is usually focused on few unusual, "special" interests, and behaviors are usually guided by a strict routine. Adults with high functioning ASDs show poor interest towards others, scarce emotional reciprocity and empathy, aversion to physical closeness, and sometimes excessive self-confidence; these can interfere in interpersonal and work functioning. On the other hand, their ability to develop an absolute devotion to limited fields of interests makes some of them highly competitive in certain areas of work.[19]

Psychiatric Comorbidity

Psychiatric comorbidity in adult ASDs is highly frequent and may represent the main reason for medical and psychiatric help request. The wide overlap between some symptomatological features of autism and those of other mental disorders may complicate the correct detection of psychiatric comorbidities in such a population.[20–22] Similarly, psychiatric comorbidity may hide ASD symptoms, preventing an appropriate diagnosis.[23] In addition, especially in ASD patients with low IQ, comorbid disorders tend to be characterized by atypical manifestations, such as self-injuring, irritability, aggression, bizarre movements, and behaviors.[24]

Schizophrenia and psychosis

Although comorbidity between ASDs and psychosis represents a crucial issue from the clinical and research points of view, just a few population studies investigated such comorbidity in adults. In particular, two population studies showed a high prevalence of psychotic disorders, ranging from 4.4%[25] to 18%.[26] Similar findings were reported also in clinical studies, with percentages between 7% and 16%.[24,27] In a case-series study that compared 14 autistic males with 14 schizophrenic males,[28] at least half of the autistic subjects met the criteria for schizophrenia. A high prevalence of schizophrenia was also observed in relatives of ASD patients.[29] On the other hand, schizophrenic patients seem to present autistic features more often than control subjects.[30,31]

In a 30-year follow-up study from childhood to adulthood, comorbid schizophrenic spectrum disorders resulted in 35% of the patients diagnosed with atypical autism versus 3% of the healthy control subjects.[27] ASDs and schizophrenic spectrum disorders have been interpreted as neurodevelopmental abnormalities, characterized by early and late onset, respectively,[32] with several overlapping interpersonal and cognitive deficits. In spite of distinct criteria and evolution, motor,[33] cognitive,[34] communication,[35] and social impairments[36] may be similar. Autistic features seem to be correlated with schizotypal traits that are predictive of schizophrenia in adulthood.[37] Moreover, the presence of autistic features during childhood and adolescence seems to be predictive of schizophrenia severity, in terms of positive and negative symptoms, disorganization, and long-term outcome.[38] On the other hand, auditory hallucinations, delusions, and paranoid ideation are quite frequent in ASDs, and some autistic features may be misconceived as premorbid symptoms.[23]

In conclusion, the relationship between ASDs and schizophrenic spectrum disorders is still unclear, and, while considering the high prevalence of psychotic symptoms in ASDs, the validity of the comorbidity concept remains questionable.

Mood disorders

Data on comorbidity between ASDs and mood disorders are meager and controversial. From the first descriptions of ASDs, depressive symptoms and mood episodes have been reported.[39] The comorbidity of mood disorders may worsen ASD evolution and prognosis, and provoke a further impairment of social and communication skills, while complicating the clinical picture with increased motor activation, obsessive behaviors, aggression, and sleep abnormalities.[40,41]

Unipolar depression is the most frequent disorder reported in the majority of the studies.[42,43] Only some authors[44] suggested that bipolar disorder (BD) might be the most frequent comorbid mood disorder in ASDs. This finding is consistent with family studies, showing high rates of BD among relatives of ASD probands.[45,46] An increased risk for comorbid depression and mood disorders has been reported in subjects with better cognitive and social skills, older age, and anxiety comorbidity, in particular with obsessive-compulsive disorder (OCD) and generalized anxiety disorder (GAD).[47,48]

The relationship between BD and ASD is still under debate. The studies conducted in this field are different from a methodological point of view and do not permit an appropriate comparison of the available data. In ASD

https://doi.org/10.1017/S1092852913000941 Published online by Cambridge University Press

samples, BD is often underestimated,[49] especially because of the communication difficulties and low IQ that may complicate the correct identification of the clinical picture. Most studies on BD comorbidity have been conducted in children and adolescents, where BD is often characterized by atypical characteristics, such as irritability, mood lability, behavioral disturbances, and psychotic features, which are frequently associated with attention deficit hyperactivity disorder (ADHD), conduct, and multiple anxiety disorders. In young populations, the presence of multiple comorbidities was suggested as a predictor of bipolarity, even in the absence of a clear manic episode.[50]

Among the few studies that have been conducted in adult ASD samples, only 1 reported a 7% prevalence of BD.[51] The comorbidity of ASD and BD would seem to be associated with a higher risk for Tourette syndrome (TS).[52] In a sample of 95 adult subjects suffering from high functioning ASDs,[53] a 21% prevalence of psychotic disorders was reported. Eight subjects reported also previous manic episodes. In a similar clinical population, the prevalence of BD was 9%.[54]

A relationship between BD and ASDs has been confirmed also by family investigations. BD was found in 4.2% of relatives of an ASD sample,[55] with even higher values in relatives of high functioning patients (6.1% vs 3.3%). In another study on ASDs, family loading for mood disorders was detected in 17% and 13% of relatives of patients with Asperger's and autistic syndromes, respectively.[56]

The presence of a positive family history for BD seems to influence the clinical picture of ASDs. This latter tend to be associated with severe mood swings, obsessive and neuro-vegetative features, the development of specific abilities, and a history of severe regression after periods of regular development.[57]

Anxiety disorders

Anxiety comorbidity has been extensively studied in children and adolescents with ASDs.[58] In a study of 54 adults suffering from high functioning ASD, 56% of them were affected by at least 1 anxiety disorder, while about 20% presented 2 or more anxiety disorders.[54] Social anxiety and GAD were the most frequent (22%), while panic disorder, agoraphobia, and OCD represented 13%, 15%, and 7%, respectively.

OCD comorbidity has been widely studied especially in children. Some symptomatological features of the 2 disorders are largely overlapping, in particular ritualistic behaviors and the full adherence to strict routine habits. If on one hand autistic children frequently show obsessive features,[59] on the other 6.2% of OCD children present autistic traits.[60] It is likely that this relationship persists in adulthood, as about 20% of adults suffering from OCD seem to be affected by autistic spectrum features.[61] The prevalence of obsessive-compulsive manifestations in ASD subjects is reported to range between 7% and 35%, depending on the type of diagnostic criteria utilized for the selection of the samples.[48,62] In an attempt to distinguish obsessive-compulsive–like manifestations in ASDs from true comorbid OCD, several studies have been conducted. In a comparison of 50 autistic with 50 OCD patients,[63] obsessive thoughts, ablutomania, checking, and counting behaviors where shown to be less frequent in autism. On the contrary, reiterations, hoarding, touching, tapping, and self-injuring appear to be highly frequent among autistic patients. In a similar study from the methodological point of view, no difference between ASD and OCD subjects was detected with respect to obsessions and compulsions.[62] According to these authors, somatic obsessions and checking compulsions prevail in OCD, while sexual obsessions are more frequent in autism.

The relationship between OCD features in relatives and repetitive behaviors in autistic probands was investigated in some studies. Relatives of autistic patients may show similar social and communicative difficulties, although at a low level of severity. The presence of family history for OCD and of obsessive traits in one or both parents seems to predict higher prevalence and severity of repetitive and stereotyped behaviors in patients with ASD.[64] These observations suggested the existence of a broadened ASD phenotype within the obsessive spectrum.[47] Abramson *et al*[65] showed that "insistence on sameness" in autistic subjects is related to high scores for obsessive-compulsive symptoms in parents and to family loading for OCD. These data, as well as findings from twin studies, might suggest that repetitive behaviors are sustained by a specific genetic liability.

Regarding the comorbidity of ASD with tics and TS, higher percentages have been reported as compared with the general population. The presence of TS and tics does not seem to influence the severity of the clinical picture. Tic prevalence appears elevated also in relatives of patients with ASD, while suggesting a familial predisposition.[66]

From the clinical point of view, complex motor tics can be difficult to distinguish from stereotypies in the absence of self-reported subjective experiential information, particularly regarding the volitional aspects of the behavior. Tics are short lasting, inappropriate to the contexts, and interrupt the course of actions or speech. Tics and stereotypies are subjectively perceived in a different way: tics are apparently started in order to alleviate inner tension, while stereotypies trigger preoccupation. Further, tics are worsened by stressors and anxiety and are reduced when the attention is focused on specific tasks, while stereotypies are less liable to external influences. Finally, tics may

https://doi.org/10.1017/S1092852913000941 Published online by Cambridge University Press

be drastically reduced by dopaminergic antagonists, which work poorly or are not at all effective against stereotypies.[67]

Personality disorders and broader autism phenotype

There is a considerable overlap in symptoms between high functioning ASDs and certain personality disorders (PDs).[68] Some of the basic characteristics of ASDs such as pervasive impairment, abnormal development, stable patterns and long duration, and childhood–adolescence–early adulthood onset are in fact superimposable to those indicated for PDs. Strictly applied, an exclusion criterion for PD in DSM-5 is that "the enduring pattern is not better accounted for as a manifestation or consequence of any other mental disorder," which implies that an ASD diagnosis is to be preferred over a PD. However, many trait features of ASD patients overlap with criteria for schizoid, schizotypal, avoidant, obsessive-compulsive, and narcissistic PD as defined by DSM-5.

Evidence on similarities and overlap between ASDs and PDs is limited, and most of the research has been focused on distinguishing between ASDs and schizoid/schizotypal PDs.[69] Children and adolescents diagnosed with schizotypal PD were found to have high rates of autistic features.[38] Another approach when investigating schizotypal personality traits was to compare them to autistic features in nonclinical samples, with results showing a substantial degree of overlap.[70]

In a recent report on 54 young adults with ASD diagnosis, about half of the participants also met criteria for a PD according to DSM-IV-TR criteria. Approximately two-thirds of the men and one-third of the women met criteria for only 4 PDs: schizoid, schizotypal (cluster A), avoidant, and obsessive-compulsive (cluster C).[71]

Personality traits similar to, but not as severe as the defining features of ASDs, seem to be common among family members of ASD patients. This group of "sub-threshold" social skills, communication traits, and unusual personality traits, which are believed to be milder manifestations of ASDs, have been indicated as the broader autism phenotype (BAP). The personality features more commonly described as components of BAP include "rigid," "impulsive," "aloof," "shy," "tactless," "reserved/schizoid," "irritable," "hypersensitive to criticism," "neurotic," "undemonstrative," and "anxious."[72] Other characteristics are different combinations of poor interest in others, mild social detachment, bizarre or atypical social behaviors, shyness and tendency to diffidence, and scarce emotive response and reciprocity in interpersonal relationships.[73] Abnormalities in communication patterns have also been described, such as difficulties in organizing and finalizing communication; poor ability in conducting a conversation; and difficulties in language, reading, and writing.[16] Finally, peculiar and circumscribed interests, repetitive behaviors, rituals, rigidity in thinking, insistence on routines, poor propensity or clear aversion, and fear of changes have also been reported.[74,75]

These observations would indicate that the expression of autistic traits extends beyond the diagnostic boundaries of ASDs. Several researchers conceptualized autism as a set of quantitative traits that might be variously combined and merged in the general population.[76,77] Further research is needed to elucidate the relationship between autistic traits, PD, and the possibility of an increased risk in developing other psychiatric conditions (eg, mood disorders, psychotic symptoms, and OCD).

Treatment Implications

Different classes of psychotropic drugs have been suggested for specific dimensions of ASDs. The majority of data are focused on second generation antipsychotics in children and adolescents, with a supposed efficacy on some core dimensions of ASDs as well as on the management of several comorbidities. Specific psychosocial and supportive interventions should be always considered as first line treatments.

Psychopharmacological treatment is essential for the management of some behavioral problems and comorbidities. For example, aggression, self-harm, or other abnormal behaviors might be sustained by different comorbid conditions such as stereotypic movement disorder and/or BD, or simply by a sudden rise in subjective anxiety.

Among antipsychotics, those showing high selectivity for the serotonin transporter 5-HTT and the 5-HT2A receptors seem to have a specific effectiveness in improving several aspects of ASDs.[78] Risperidone and aripiprazole are the most studied and have been shown to be effective in reducing psychotic symptoms; irritability; repetitive, aggressive, and impulsive behaviors; and in improving some aspects of sociality in controlled clinical trials.[79] They can also be useful in the management of the manic phases of BD.[79]

Mood stabilizers are preferable as maintenance treatment in comorbid ASD-BD, although there is a substantial lack of studies in this area. Several observations suggest the efficacy and safety of anticonvulsants, particularly valproate and lithium. Valproate should be preferred in the case of epilepsy and EEG abnormalities.[80] Instead, BD family history,[81] extreme hyperactivity unresponsive to stimulants, a cyclic pattern of behavioral changes, irritability, prolonged outbursts of laughter, subjective dizziness, and the presence of at least some BD diagnostic criteria[82] are considered favorable prognostic factors for positive response to lithium.

https://doi.org/10.1017/S1092852913000941 Published online by Cambridge University Press

The use of antidepressants, both tricyclics (TCAs) and selective serotonin reuptake inhibitors (SSRIs), should be considered in the presence of comorbid anxiety disorders.[83] Before their utilization, a bipolar diathesis should be excluded, given the high risk of (hypo)manic switches and development of suicidal ideation among ASDs subjects.[84]

Conclusion

ASDs represent one of the most common neurodevelopmental disorders and can cause significant lifetime disabilities. The category of ASDs includes heterogeneous entities, in terms of both specific clinical manifestations and psychiatric comorbidities. The evolution of ASDs from childhood to adulthood is influenced by the severity of the clinical picture, gender, onset of neurological disorders, such as epilepsy during adolescence, and by psychiatric comorbidity. Unfortunately, specific diagnostic criteria or clinical paradigms for adults are lacking. The available literature on ASDs in adults is limited, and mainly focuses on the role of age on clinical manifestations, abilities, and comorbidities.

Due to the heterogeneity of clinical manifestations and the poor knowledge of specific childhood disorders, adult psychiatrists too often underdiagnose ASDs, thus classifying these patients as affected by mental retardation, PDs, schizophrenia, or other psychotic disorders. This underestimation is particularly frequent in high functioning ASD subjects, especially when a comorbidity with other mental disorders is present. For this reason, the definition of specific diagnostic criteria for adults is clinically relevant. Current diagnostic criteria emphasize the history of the first years of life that adults do not often recall. Moreover, criteria for specific manifestations during adulthood are lacking.

Psychiatric comorbidity is the main reason for which the majority of ASD adults seek medical help. If on one hand psychiatric comorbidity may hide ASDs, then on the other hand mental disorders associated with ASDs are often characterized by atypical manifestations, with the possibility of diagnostic, prognostic, and therapeutic mistakes. This is particularly true for those disorders that present wide areas of symptomatological overlap with ASDs, such as mood disorders, schizophrenia, PDs, and OCD. Therefore, research should aim for a detailed cross-sectional and longitudinal delineation, not only of ASDs, but also of comorbid disorders. Long-term perspective investigations are needed in order to delineate ASD specific and non-specific features, and to improve management and therapeutic strategies.

Disclosures

The authors do not have anything to disclose.

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