Psychiatria Danubina, 2010; Vol. 22, No. 4, pp 514-521 *Original paper*
© Medicinska naklada - Zagreb, Croatia

AUTISTIC SPECTRUM DISORDERS AND SCHIZOPHRENIA IN THE ADULT PSYCHIATRIC SETTING: DIAGNOSIS AND COMORBIDITY

Michele Raja & Antonella Azzoni

Servizio Psichiatrico di Diagnosi e Cura, Ospedale Santo Spirito, Rome, Italy

received: 03.04.2010; revised: 01.10.2010; accepted: 30.11.2010

SUMMARY

***Background**. The relationship between Autism Spectrum Disorders (ASDs) and schizophrenia is currently unclear. We aimed to (a) assess psychotic symptoms in a consecutive series of adult patients with ASDs, (b) evaluate the comorbidity diagnosed to account for the concurrent psychotic symptoms in patients with ASDs, and (c) compare the clinical features between the patients with schizophrenia and patients with comorbid schizophrenia and ASDs.*

***Subjects and methods**. We included patients with ASD that were seen in adult psychiatric clinical settings during a 15-year period. The sample was further grouped according to the existence of a comorbid diagnosis of schizophrenia. Clinical and epidemiological features were assesed in in the whole sample, and further compared between the two groups.*

***Results**. We identified 26 patients with first-time diagnosed ASDs. Among the 22 cases who manifested psychotic symptoms (84.6%), 16 had a concurrent diagnosis of schizophrenia (72.73%) and 6 of mood disorders (27.27%). Compared with patients with schizophrenia patients with comorbid ASDs and schizophrenia were more often men, of younger age, and more frequently developed motor side effects to antipsychotics.*

***Conclusions**. Adult psychiatric service users with ASDs are often misdiagnosed. This could be in part due to the fact that adult psychiatrists are not familiar with the diagnosis of ASDs. The high prevalence of psychotic symptoms in this sample is likely to depend on the specific setting of the study, i.e., that people with more severe forms of ASD than those typically followed-up in the national health service were reaching our public inpatient and private outpatient services. The high comorbidity rate between ASDs and schizophrenia could be related to shared neurobiology, but also to arbitrary restrictions imposed by current diagnostic systems.*

***Key words:** Asperger's syndrome – autism – comorbidity – diagnosis - pervasive development disorder - schizophrenia*

* * * * *

INTRODUCTION

Autism like other common terms in psychiatry, such as anxiety and depression, may refer to both a symptom and to a disorder or a group of disorders. The term was coined by Eugen Bleuler (1911) to describe a detachment (withdrawal) from reality associated with rich fantasy; he inserted autism in his lists of both secondary (today's negative) and fundamental symptoms of schizophrenia. About 30 years later, Leo Kanner (1943) borrowed the term to characterize a developmental disorder of childhood with "inability to relate… in the ordinary way to other people" and by "insistence on sameness", thus coining a group of disorders characteristic of childhood. However, despite the possibility that such symptomatological overlap may underlie common pathophysiological mechanisms, schizophrenia and autism are held wide apart through arbitrary restrictions in the Diagnostic and Statistical Manual nosography (American Psychiatric Association 2000). According to the DSM-IV-TR, to give a comorbid diagnosis of schizophrenia and autism, autism must appear first. If hallucinations and delusions are present at onset, a diagnosis of autism spectrum disorder (ASD) should not be made. Instead, a diagnosis of early or childhood onset schizophrenia (COS) should be given.

The ASDs are included in the Pervasive Developmental Disorders subgroup of Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence of the DSM-IV-TR (American Psychiatric Association 2000). In the ICD-10 (World Health Organization 1992), ASDs are classified under the heading of pervasive developmental disorders in the grouop of the disorders of psychological development.

ASD is an umbrella term comprising autistic disorder (or infantile autism, AD), Asperger's syndrome (or high-functioning autism, AS), and pervasive developmental disorder (PDD) not otherwise specified (NOS). Some investigators also include Rett's syndrome, childhood disintegrative disorder and atypical forms of autism in the same group. While the majority of investigations focus on the ASDs in infancy and adolescence, long-term outcome of autism and its course in adulthood are seldom investigated. Roughly, the odds of having a poor outcome when ASD is developed in early adulthood is 50%, while the outcome for about 20% of patients diagnosed with ASD during their childhood or adolescence is fair or very good, depending on the patients' IQ (Eaves and Ho 2008). However, the transition of people with autism from children's to adult services is often poorly managed and needing a higher degree of communication between services (House of Commons, 2009). Furthermore,

patients with ASD often receive late or erroneous diagnoses, like schizophrenia (Dossetor 2007). Several clinical features of ASDs, especially those of AS, overlap with those of schizophrenia; these include impaired social interactions, communication disorder, restricted interests, and bizarre or illogical thinking.

Clinical presentation of symptoms in patients with PDD consist of heterogeneous symptoms and the categorical boundaries among the most common PDD – AS, AD, PDD-Not Otherwise Specified (NOS) – lack diagnostic validity. These disorders lie on an autism spectrum (Miller & Ozonoff 2000, Frith 2004, Macintosh & Dissanayake 2004). Walker et al. (2004) found that even the residual class of PDD-NOS is highly heterogeneous. Sharpening the differential diagnosis between ASD and schizophrenia could improve treatment approaches (Da Fonseca et al. 2008). However, an accurate distinction is sometimes difficult, especially in adult patients, in whom the expression of disorders of reciprocal social interaction, communication, imagination and repetitive stereotyped thinking and actions changes during progression to adulthood (Hengeveld et al. 2008), while the phenotype of ASD undergoes modification. Official diagnostic criteria reflect current uncertainty. According to the DSM-IV-TR (American Psychiatric Association 2000), a diagnosis of COS is an exclusion criterion for the diagnosis of AS or AD. However, the DSM-IV-TR acknowledges that (a) schizophrenia may develop in individuals with AS or AD; (b) the additional diagnosis of schizophrenia is warranted only if prominent hallucinations or delusions have been present for at least one month (or less, if successfully treated) and if the onset of AS or AD clearly preceded the onset of schizophrenia; and (c) the relation between AS and Schizoid Personality Disorder is unclear. In other words, according to the DSM-IV-TR, the diagnosis of AS depends on the time of onset of the hallucinations or delusions, while major diagnostic criteria for AS *per se* are not always sufficient to justify a diagnosis of AS. Implicitly, the DSM-IV-TR assumes that diagnostic criteria for schizophrenia, other than delusions and hallucinations, may be already met by patients with AS. Consistently, Deprey and Ozonoff (2009) suggested that differential diagnosis between ASD and schizophrenia should be based on the presence/absence of positive symptoms; if these symptoms preexisted to the diagnosis of ASD, the diagnosis of COS should be posed. If their onset followed the diagnosis of ASD, a comorbid diagnosis of COS and ASD may be made. If one thinks about the implications of the impending introduction of attenuated psychotic syndrome in the DSM-5 (Woods et al. 2010), the picture is expected to become really fuzzy.

DSM-IV-TR considers ASD to be distinct from schizophrenia. However, recent data increasingly point to an intermediate clinical area that deserves investigation. Data of comorbidity and family occurrence provide a rejoinder between ASD and schizophrenia. A study of 101 children and adolescents with COS found comorbid ASD in 28% of cases. In these cases, ASD was a persisting and stable diagnosis with onset in the first five years of life, while the onset of psychotic symptoms occurred typically 3-5 years later (evidence reviewed in Rapoport et al. 2009). In a study of 58 DSM-IV AS patients (48 males; mean age 13.34; mean full scale IQ 104.87), three had first degree relatives with AS, nine (15%) had a family history of schizophrenia, and 35 (60%) had a family history of depression.

Recent data from genetic studies show overlap between ASDs and schizophrenia. The velo-cardio-facial or 22q11.2 deletion syndrome, a syndrome with multiple congenital abnormalities involving various tissues deriving mainly from the neural crest, is characterized by intellectual impairment and is often comorbid with ASDs (Antschel et al. 2007) and schizophrenia (Murphy 2002); in a substantial number of patients with this syndrome, high rates of childhood ASD (20-50%) and psychotic symptoms (26.7%) were found. Microdeletion and microduplication in the 16p11.2 region has been observed in 1% of cases of autism and 2% of cases of COS. Deletions, disruptions, and missense mutations in Neurexin 1 have been reported in several cases with autism and schizophrenia (reviewed in Rapoport et al. 2009). Disrupted-in-Schizophrenia-1 (DISC1) gene is a risk factor for schizophrenia and other major mental illnesses. DISC1 single nucleotide polymorphisms (SNPs) were found to be overtransmitted in schizophrenia and to be associated with its negative dimension (Lepagnol-Bestel et al. 2010). One study found an association between autism and a DISC1 intragenic microsatellite (D1S2709; P=0.004) and evidence for association with AS of an intragenic single nucleotide polymorphism (SNP) of DISC1 (rs1322784; P=0.0058), as well as with a three-SNP haplotype (P=0.0013) overlapping with the HEP3 haplotype, that was previously observed to associate with schizophrenia in a Finnish population (Kilpinen et al. 2008). Another author showed a 2 Mb deletion of chromosome 1q42 in a child with ASD (Williams et al. 2009). The AS susceptibility loci on 1q21-22 and 13q31-33 overlap with the reported schizophrenia susceptibility loci (Ylisaukko-oja et al. 2004).

These genetic studies cast doubt on the validity of current diagnostic criteria that tend to diagnose schizophrenia in people presenting with ASD symptoms, but also with delusions and hallucinations.

The aims of this study were: (a) to investigate psychotic symptoms in a relatively large series of adult psychiatric patients with ASD; (b) to evaluate the comorbidity diagnosed to account for the concurrent psychotic symptoms in patients with ASDs, and (c) compare the clinical features between the patients with schizophrenia and patients with comorbid schizophrenia and ASDs. Since the purpose of this study was descriptive in its nature, we did not specify hypotheses related to study objectives in advance.

METHODS

We have included in this study all patients manifesting symptoms of ASDs that were followed-up at the Psychiatric Intensive Care Unit (PICU) of a general hospital and in our private practice since 1994. Symptoms and signs suggestive of PDD were considered. We screened for communication problems, language difficulties, impaired social interaction, difficulty relating to people, unusual play, slowness in adapting to changes, and repetitive body movements and other behavior, along with other accessory signs like strange, inappropriate or bizarre behavior, impaired cognitive and learning abilities, as well as enhanced abilities in particular areas, periods of mutism, circumscribed interests, facial abnormalities, clumsy and uncoordinated movements, atypical obsessions or compulsions, stereotypies, enhanced sense of humor and ability to imitate, and history of several inconsistent psychiatric diagnoses, especially schizoid or schizotypical personality disorder, schizophrenia, social phobia, alexithymia, and obsessive-compulsive disorder (OCD). We reassesed patients who screened positive of at least for one of these clinical features, and diagnosed taking into accpunt also the past medical chart review and interview with patient's relatives. DSM-IV-TR diagnoses were consensually made by the authors. Due to the reasons we explained above, we lumped diagnoses of all PDDs we diagnosed according to the DSM-IV-TR into one generic diagnosis of ASD, as it is becoming increasingly common in current research (Klin 2009).

To compare patients with ASD and comorbid schizophrenia with patients with schizophrenia without ASD only ASD patients admitted to the PICU were considered due to the low number of patients with schizophrenia seen in our private outpatient practice. We compared these groups for socio-demographic features (age, gender, marital status, and parenthood) and clinical features (assesment scales: Brief Psychiatric Rating Scale (BPRS), the Scale for the Assessment of Positive Symptoms (SAPS), the Scale for the Assessment of Negative Symptoms (SANS), the Mini Mental State Examination (MMSE), the Unified Parkinson's Disease Rating Scale (UPDRS), the Barnes Akathisia Scale) and the daily dose of antipsychotic treatment expressed in chlorpromazine-equivalents (Baldessarini 1985) at admission and at discharge). Regarding relative oral potency of 2nd generation antipsychotics, we considered chlorpromazine 100 mg equivalent to clozapine 50 mg, risperidone 1.6 mg, sertindole 3.2 mg, olanzapine 5 mg, quetiapine 200 mg, amisulpride 200 mg, aripiprazole 7.5 mg; these values, based on clinical experience, are slightly different from those commonly accepted (Woods 2003). We used the χ^2 test to analyze categorical variables and Student's *t*-test to analyze continuous variables. All tests were two-tailed; statistical significance was set at $p < 0.05$.

RESULTS

In a period from 1994 to 2009 we diagnosed ASD in 26 subjects (25 men, 1 woman; mean age, 30.2 years; standard deviation [SD]=9.8; years of education, 11.7 years; SD=7.1; full-scale IQ, mean, 83.5; SD=18.2; verbal IQ, mean, 92.0; SD=19.4; performance IQ, mean, 75.9; SD=19.2). We diagnosed DSM-IV-TR AS in 16 patients, AD in 5, and PDD-NOS in another 5.

In the Table 1 are shown diagnosis, presence of delusions, hallucinations, and disorganized thinking in patients, psychiatric comorbidity, patients' previous diagnoses, and psychiatric symptoms in their relatives.

Twenty-one of 26 patients (80.8%) manifested delusions and 19 of 26 (73%) reported hallucinations during their lifetime. Among the 22 cases (84.6%) manifesting hallucinations or delusions, 16 received a concurrent diagnosis of schizophrenia and six of mood disorder. Other concurrent diagnoses were obsessive-compulsive disorder (OCD, N=2), and substance-related disorder (N= 4). Relatives of 5 (19.2%) patients reported positive psychotic symptoms and in relatives of 8 patients (30.8%) a mood disorder was diagnosed. Schizophrenia had been diagnosed in a relative of one patient (3.8%). Ten patients (38.5%) received a diagnosis of psychosis in previous assessments, seven (26.9%) were diagnosed with schizophrenia. In table 2 we report the comparison of sociodemographic and clinical features between inpatients with schizophrenia with and without ASD.

Compared to the patients affected by schizophrenia only, patients with comorbid ASD and schizophrenia were mostly men, of younger age and more frequently developed motor side effects of antipsychotic treatment. The two groups did not differ for other clinical measures.

Mood disorder diagnoses were based on the presence of prominent mood symptoms; the diagnosis of schizophrenia required the presence of hallucinations and delusions, according to the DSM-IV-TR. If delusions or hallucinations had been considered as possible ASD features, no case of schizophrenia would have been diagnosed, since an ASD diagnosis would be accounted for by all other symptoms.

DISCUSSION

In this study we found that people who use adult psychiatric services and satisfy criteria for ASDs are more often diagnosed with a major psychosis based on to the presence of specific symptoms like delusions and hallucinations. If these symptoms had been considered compatible with an ASD diagnosis, these people would have been diagnosed as plain ASD not comorbid with schizophrenia. The mere presence of these symptoms in otherwise ASD-compatible patients biases diagnosis towards other DSM-IV-TR mental disorder diagnoses and contributes to the general underestimation of the occurrence of ASD among adult psychiatric service users. This has negative implications for their treatment and outcome.

Table 1. Clinical features of the 26 cases with a diagnosis of ASD

Age, gender, diagnosis	Previous diagnosis	Psychiatric comorbidity	Family history (psychiatric)	Delusions	Halluci-nations	Conceptual disorgani-zation
33 ♂ AD	Early onset psychosis	Schizophrenia; OCD; alcohol abuse		Persecution, horror, sexual		
20 ♂ AS	Paranoid disorder; OCD	Schizophrenia		Persecution, reference	Auditory	Circum-stantiality
42 ♂ AS	Schizophrenia	Schizophrenia	Grandmother: depression	Religiosity; thought reading and withdrawal	Auditory, Visual	Echolalia
18 ♂ PDD-NOS	Schizophrenia; StPD; anorexia nervosa	Schizophrenia	Father: SAD; sister: cyclothymia	Persecution, religious	Auditory	Derailment, illogicality, incoherence
31 ♂ AS	Schizophrenia	Schizophrenia	Mother: personality disorder NOS	Persecution	Auditory, visual	Illogicality
31 ♂ AS		Schizophrenia; substance abuse	Uncle: AS persecutory delusions Aunt: persecutory delusions	Persecution	Auditory	Illogicality, incoherence, tangentiality
23 ♂ AS		Schizophrenia	Uncle: mental retardation; Grandmother: alcoholism	Reference	Auditory, olfactory	
36 ♂ AS	OCD, SdPD, Schizophrenia	Schizophrenia	Sister: anxiety Father: PD-NOS	Reference	Auditory, olfactory, somatic, visual	Illogicality, incoherence, tangentiality
34 ♂ AD		Schizophrenia		Persecution	Auditory	
42 ♂ AS	Obsessive psychosis; Schizophrenia	Schizophrenia	Mother: cold and strange; OCD Father: depression 2 sisters: eating disorder	Persecution, reference, guilt, religious	Olfactory, somatic	Circum-stantiality, tangentiality
28 ♂ PDD-NOS		Schizophrenia, alcohol abuse	Unknown	Persecution, reference, religious, grandiose		Illogicality, incoherence, tangentiality
19 ♀ AS	Bipolar disorder, BPD	Mania with psychotic signs	Father and grandfather: anxiety, depression, hypochondriasis; Uncle: paranoid delusions, SA	Sex, somatization		
25 ♂ AS	Infantile psychosis, OCD, depression	Depression		Persecution and reference	Auditory	
30♂ AD		Depression	Sister of grandmother complete isolation	Magic, esoteric content	Auditory, olfactory, visual	
31 ♂ AS	Schizophrenia; StPD	Depression, agitation, hostility	Brother: PD-NOS; Two cousins, son of a mother's cousin: suicides			
19 ♂ AS	BPD		Grandfather: SA			
35 ♂ AS		Schizophrenia	Father: depression Mother: StPD; autistic behavior		Olfactory	
30 ♂ AS		MDps		Persecution	Olfactory	
48 ♂ AS	Schizophrenia	Schizophrenia	Aunt: PD-NOS; Uncle: suicide by fall	Reference	Auditory	Illogicality
16 ♂ AD			Grandmother: depression Mother: hyperthymic			
32 ♂ AD	OCD	MDps; OCD	Aunt: chronic psychosis; Uncle: OCD	Persecution	Auditory	
20 ♂ AS		Schizophrenia		Persecution, reference, somatization	Auditory, thought echo	Circum-stantiality, logorrhea,
22 ♂ AS		Schizophrenia	Two cousins: depression	Persecution, reference, magic	Auditory, visual	
56 ♂ PDD-NOS		Alcohol abuse				

Table 1. Clinical features of the 26 cases with a diagnosis of ASD

Age, gender, diagnosis	Previous diagnosis	Psychiatric comorbidity	Family history (psychiatric)	Delusions	Halluci-nations	Conceptual disorgani-zation
39 ♂ PDD-NOS		Schizophrenia	Grandmother: depression with somatic delusions; Grandfather: alcoholism; Father: irritable, choleric, violent; Sister: AS	Persecution, reference, guilt	Auditory, visual	
25 ♂ PDD-NOS		MDps	Grandfather: OCD Brother of grandfather: Schizophrenia Brother: SAD; Mother: anxiety; Uncle: PD-NOS; Aunt: complete isolation	Persecution, reference, magic-esoteric	Auditory	

AD=Autistic disorder; AS=Asperger's disorder; ASD=Autism spectrum disorder; BPD=Borderline personality disorder; MDps=Mood disorder with psychotic symptoms; PD-NOS=Psychiatric disorder not otherwise specified; PDD-NOS=Pervasive developmental disorder not otherwise specified; SAD=Schizoaffective disorder; SdPD=Schizoid personality disorder; OCD=Obsessive-compulsive disorder; StPD=Schizotypal personality disorder

Table 2. Comparison between the groups of patients with a comorbid diagnosis of ASD and Schizophrenia and with a single diagnosis of Schizophrenia

	ASD and schizophrenia: 9	Schizophrenia: 175	$\chi 2$	df	P
Male gender	9 (100%)	104 (59.4%)	4.357	1	0.037*
Single marital status	9 (100%)	137 (78.3%)	1.316	1	0.251
Children	0	23 (13.1%)	0.417	1	0.518
Commitment	1 (11.1%)	39 (22.3%)	0.143	1	0.705
CGI score (on admission)	4: n.0; 5: n.0; 6: n.7; 7: n.2; NA: n.0	4:n.2; 5:n.6; 6:n.118; 7:n.19 NA: n.30	3.058	4	0.548
CGI score (improvement)	1:n.1; 2:n.3; 3:n.3; 4:n.2; NA:n.0	1:n.31; 2:n.72; 3:n.29; 4:n.13; NA:n.30	5.566	4	0.234
Suicidal risk	Yes:n.0; No: n.7; NA: n.2	Yes: 21; No: n. 104; NA: n.50	1.680	2	0.432
	t-test	t-test	t	df	P
Age (years)	31.7±8.3	39.5±11.7	-1.972	181	0.049*
Current GAF score	(n.8) 21.6±7.9	(n. 136) 21.4±6.6	0.082	142	0.934
Best GAF score in the last year	(n.8) 39.1±11.9	(n. 133) 37.6±11.3	0.364	139	0.717
BPRS total score:	(n.8) 61.9±13.9	(n. 129) 62.5±11.9	-0.137	135	0.891
BPRS th score	(n.8) 11.6±3.9	(n. 129) 12.9±4.6	-0.781	135	0.436
BPRS rr score	(n.8) 12.5±3.3	(n. 129) 9.7±4.2	1.848	135	0.067
BPRS hos score	(n.8) 6.6±3.9	(n. 129) 9.0±3.6	-1.822	135	0.071
BPRS ad score	(n.8) 7.5±5.6	(n. 129) 7.7±3.8	-0.140	135	0.889
SAPS score	(n.8) 34.1±13.8	(n. 129) 46.9±21.9	-1.630	135	0.105
SANS score	(n.8) 73.9±12.6	(n. 129) 65.3±19.9	1.205	135	0.230
MMSE score	(n.8) 28.4±1.8	(n. 129) 26.4±3.5	1.205	130	0.112
UPDRS total score	(n.8) 11.8±6.8	(n. 129) 6.4±5.5	2.652	128	0.009*
UPDRS rigidity score	(n.8) 0.4±0.5	(n. 129) 0.4±0.7	0.000	128	1
UPDRS tremor score	(n.8) 1.6±1.2	(n. 129) 1.2±1.4	0.789	128	0.432
UPDRS akinesia score	(n.8) 1.6±1.4	(n. 129) 0.9±1.1	1.715	128	0.089
BAS score	(n.8) 1.0±1.2	(n. 129) 0.6±1.0	1.083	127	0.281
CPZ-eq dose on admission(mg)	(n.8) 366.7±172.4	(n. 153) 390.2±433.9	-0.152	159	0.879
CPZ-eq dose on discharge(mg)	(n.8) 462.5±321.8	(n. 160) 618.2±401.5	-1.079	166	0.287

ASD=Autism spectrum disorder; BPRS=Brief Psychiatric Rating Scale; BPRS th=BPRS thought disorder cluster; BPRS rr=BPRS retardation-withdrawal cluster; BPRS hos=BPRS hostility cluster; BPRS ad=BPRS anxiety-depression cluster; CGI=Clinical Global Impression; CPZ-eq=Chlorpromazine equivalents; GAF=Global Assessment of Functioning; MMSE=Mini Mental State Examination; n.=number; NA=Not assessed; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; UPDRS=Unified Parkinson's Disease Rating Scale; BAS=Barnes Akathisia Scale; *=statistically significant

Our sample has a relatively large proportion of patients with ASDs attending adult psychiatric services and probably suffer from more severe symptoms than those with ASDs attending specific centers for autism and developmental disorders. The ASD tend to be underdiagnosed and poorly studied in those patients, possibly because adult psychiatrists are unfamiliar with ASDs (Raja 2006). Usually, only professionals involved specifically in ASD care and research are more aware of the ASD symptomatology. In fact, none of our patients had received a diagnosis of ASD previous to our study and all of them received it for the first time in their life during the study. Most of them had been visited by several psychiatrists and treated in qualified psychiatric centers receiving alternative diagnoses. Interestingly, when specific ASD symptoms were described and explained to the patient relatives, they were able to identify their presence in the patient.

The prevalence of delusions, hallucinations, and thought disorder in this sample is surprisingly high for ASDs. This may depend on the specific clinical settings where this study was performed, as it is more likely that more severely impaired patients with ASDs were admitted to this setting, compared to those attending centers for autism and developmental disorders. Regarding this aspect, one important caveat should be discussed. Diagnosing delusions in patients with ASD is difficult, because the often reported bizarre, absurd, repetitive and narrowly focused, ideas resemble, but are not qualitatively identical, to the typical delusions of psychotic disorders (Raja & Azzoni 2007). Furthermore, patients' poor social judgment and theory-of-mind skills may suggest paranoid delusions (Deprey & Ozonoff 2009). Imagination and originality are common in AS (Frith 2004). Some patients with AS are able to coin original verbal expressions and to create imaginary worlds in words and pictures. They may also engage in extensive and wide-ranging imaginary activities or be particularly able to produce creative narratives (Frith 2004). To an inexperienced clinician's eyes, those symptoms could be misdiagnosed as delusions. Similarly, the presence of disorganized thought in patients with ASDs is sometimes erroneously inferred due to the lack of reciprocity, presence of poor ability to maintain the main conversations topic, pedantic, idiosyncratic, and bizarre speech, which are quite different from the disorganized speech of patients with schizophrenia, but may be so inadequate to resemble tangentiality, incoherence, illogicality, and circumstantiality, therefore prompting for being detected as disorganized thoughts. However, in our experience, the detection of hallucinations is much easier and reliable since there is less ambiguity in patients' report. Therefore, we are confident that "true" psychotic symptoms were present in our patients.

It is interesting that among the 22 patients who reported psychotic symptoms, 72.7% (N=16) received a comorbid diagnosis of schizophrenia, while only 27.2% (N=6) received a diagnosis of mood disorders. The percentage of patients without ASD seen in the same clinical setting who received a diagnosis of schizophrenia is much lower. Among the 2930 patients admitted to our PICU over a twelve-year period, only 5.3% (N=156) received a diagnosis of schizophrenia. The difference is disproportionate (χ^2=168.772; degrees of freedom=1; $p<0.0001$). This means that if positive psychotic symptoms are not considered as possible features of ASD, comorbid diagnosis with schizophrenia will be higher than what would have been expected by chance, i.e., a casual co-occurrence of two independent disorders.

Our results are compatible with three viable possibilities that may coexist and contribute to what we observed. First, ASD and schizophrenia share possible etiological and/or pathogenetic factors, which is compatible with the existing literature (Antschel et al. 2007, Murphy 2002, Rapoport et al. 2009, Lepagnol-Bestel et al. 2010, Ylisaukko-oja et al. 2004). Second, psychotic symptoms belong to the symptomatic spectrum of ASD *per se* and there is no need to add the diagnosis of schizophrenia when hallucinations or delusions are present in patients with ASD. Actually, the frequent absence of significant mood alterations in people with ASD with psychotic symptoms leads to the diagnosis of schizophrenia for lack of alternatives. Third, the presence of psychotic symptoms in patients with AS could be related with early onset. Adolescence and early adulthood are developmental stages that favor the clinical expression of psychotic symptoms (Volkmar 1996, Altman et al. 1997). In fact, age-related decrease in the likelihood to report delusional ideas were found among 444 primary care patients with no lifetime history of psychiatric disorder, with younger people scoring higher on most dimensions of delusional ideation (Verdoux et al. 1998), suggesting that there may be a physiological neurodevelopmental stage favoring psychosis proneness in healthy people. Hence, the frequent presence of psychotic thought disorder in neuropsychiatric disorders of adolescence, irrespective of any specific diagnosis, could be due to an interaction between normal brain maturational processes and cerebral abnormalities involved in the etiology of the disorders.

Of the 16 patients who were co-morbid with schizophrenia, two had comorbid alcohol abuse (25%); of the 10 patients without diagnosis of schizophrenia, one (10%) had alcohol abuse and this was the only psychiatric comorbidity of this PDD-NOS patient. These figures are by no means surprising, given the high association of alcohol abuse with both autism (Miles et al. 2003) and schizophrenia (McMillan et al. 2009).

There are limitations in the study that deserve mentioning. We did not use standardized diagnostic instruments because we chose to enlarge the spectrum of symptoms suggesting ASD and not to set rigid inclusion/exclusion criteria; we did this to increase diagnostic assessment sensitivity. Similar reasons prompted other authors to modify DSM- IV or ICD-10

criteria, to deal with AS and high-functioning autism as if they were interchangeable, or to use investigator-defined criteria, in spite of the decrease of study comparability (Klin et al. 2005). In our sample, the detection of any symptom suggesting ASD resulted in intensive clinical assessment that allowed a reliable DSM-IV-TR diagnosis of ASD.

In adult psychiatric services, psychotic symptoms are very frequent in patients with ASD. This suggests that patients with ASD and without psychotic symptoms seldom seek assistance to adult psychiatry services. Since hallucinations and delusions are considered neither diagnostic nor associated features of PDD both in DSM-IV-TR and ICD-10, most patients with such symptoms receive a comorbid diagnosis of schizophrenia, if they show no significant mood alterations. However, the very high rate of comorbidity between ASD and schizophrenia in the adult psychiatric setting could be only an artifact due to the inappropriate exclusion of hallucinations and delusions from the list of characteristic or associated symptoms of ASDs. Besides referral and screening/surveillance biases, artifacts in the detection of comorbidity may also arise from the use of categories where dimensions might be more appropriate. It would reduce errors due to overlapping diagnostic criteria, artificial subdivision of syndromes, one disorder representing an early manifestation of the other, and one disorder being part of the other (Caron & Rutter 1991). Currently, on the basis of available evidence, we find it difficult to solve the problem. However, the two alternatives are not heuristically equivalent. We suspect that the exclusion of psychotic symptoms from the diagnostic and associated features of PDDs encourages over-diagnosing schizophrenia and underestimating PDD in adult psychiatric services.

CONCLUSIONS

Current nosographic classifications do not allow the inclusion of delusions and hallucinations among the symptoms of ASDs. Furthermore, there is a split between child and adolescent services and adult psychiatric services that does not allow the patient to be followed up consistently. Current training in psychiatry which does not emphasis these issues enough, tends not to train psychiatrist to adequately diagnose ASDs. The overall result is that the most severe ASD cases remain underdiagnosed in adult psychiatric settings. A conjoint effort in all abovementioned areas is needed to improve the healthcare service for this population of users.

REFERENCES

1. *Altman H, Collins M & Mundy P: Subclinical hallucinations and delusions in non psychotic adolescents. Journal of Child Psychology and Psychiatry, and Allied Disciplines 1997; 38:413-20.*
2. *American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington DC: American Psychiatric Publishing, Inc., 2000.*
3. *Antshel KM, Aneja A, Strunge L, Peebles J, Fremont WP, Stallone K, et al.: Autistic spectrum disorders in velo-cardio facial syndrome (22q11.2 deletion). J Autism Dev Disord 2007; 37:1776-86.*
4. *Baldessarini RJ: Chemotherapy in Psychiatry: Principles and Practice. Cambridge, Mass: Harvard University Press, 1985.*
5. *Bleuler E: Dementia praecox oder Gruppe der Schizophrenien. Leipzig und Wien: Franz Deuticke, 1911.*
6. *Caron C & Rutter M: Comorbidity in child psycho-pathology: concepts, issues and research strategies. Journal of Child Psychology and Psychiatry, and Allied Disciplines 1991; 32:1063-80.*
7. *Da Fonseca D, Viellard M, Fakra E, Bastard-Rosset D, Deruelle C & Poinso F: Schizophrénie ou syndrome d'Asperger ? [Schizophrenia or Asperger syndrome?] Presse Médicale 2008; 37:1268-73.*
8. *Deprey L & Ozonoff S: Assessment of comorbid psychiatric conditions in Autism spectrum disorders. In Goldstein S, Naglieri JA & Ozonoff S (eds.): Assessment of Autism Spectrum Disorders, 290-317. New York, NY: The Guilford Press, 2009.*
9. *Dossetor DR: 'All that glitters is not gold': misdiagnosis of psychosis in pervasive developmental disorders – A case series. Clinical Child Psychology and Psychiatry 2007; 12:537-48.*
10. *Eaves LC & Ho HH: Young adult outcome of autism spectrum disorders. Journal of Autism and Developmental Disorders 2008; 38:739-47.*
11. *Engström I, Ekström L & Emilsson B: Psychosocial functioning in a group of Swedish adults with Asperger syndrome or high-functioning autism. Autism 2003; 7:99-110.*
12. *Frith U: Emanuel Miller lecture: confusions and controversies about Asperger syndrome. Journal of Child Psychology and Psychiatry, and Allied Disciplines 2004; 45:672-686.*
13. *Hengeveld MW, van Londen L & van der Gaag RJ: Herkenning van autismespectrumstoornissen bij volwassenen [Recognition of autism spectrum disorders in adults]. Nederlands Tijdschrift voor Geneeskunde 2008; 152:1365-9.*
14. *House of Commons, Public Accounts Committee: Supporting people with autism through adulthood. Fiftieth Report of Session 2008–09. Stationery Office, London, 15 July 2009.*
15. *Kanner L: Autistic disturbances of affective contact. Nervous Child 1943; 2:217-50.*
16. *Kilpinen H, Ylisaukko-oja T, Hennah W, Palo OM, Varilo T, Vanhala R, et al: Association of DISC1 with autism and Asperger syndrome. Molecular Psychiatry 2008; 13:187-196.*
17. *Klin A. Subtyping the autism spectrum disorder. Theoretical, research, and clinical considerations. In Goldstein S, Naglieri JA & Ozonoff S (eds.): Assessment Of Autism Spectrum Disorders, 91-116. New York, NY: The Guilford Press, 2009.*
18. *Klin A, Pauls D, Schultz R & Volkmar F: Three diagnostic approaches to Asperger syndrome: implications for*

research. Journal of Autism and Developmental Disorders 2005; 35:221-34.

19. *Lepagnol-Bestel AM, Dubertret C, Benmessaoud D, Simonneau M, Adès J, Kacha F, et al.: Association of DISC1 gene with schizophrenia in families from two distinct French and Algerian populations. Psychiatr Genet 2010 May 25; [Epub ahead of print; doi:10.1097/YPG.0b013e32833aa5c4]*
20. *Macintosh KE & Dissanayake C: Annotation: the similarities and differences between autistic disorder and Asperger's disorder. A review of the empirical evidence. Journal of Child Psychology and Psychiatry, and Allied Disciplines 2004; 45:421-34.*
21. *McMillan KA, Enns MW, Cox BJ, Sareen J. Comorbidity of Axis I and II mental disorders with schizophrenia and psychotic disorders: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Canadian Journal of Psychiatry 2009; 54:477-486.*
22. *Miles JH, Takahashi TN, Haber A, Hadden L: Autism families with a high incidence of alcoholism. Journal of Autism and Developmental Disorders 2003; 33:403-415.*
23. *Miller JN & Ozonoff S: The external validity of Asperger disorder: lack of evidence from the domain of neuropsychology. Journal of Abnormal Psychology 2000; 109:227-38.*
24. *Murphy KC: Schizophrenia and velo-cardio-facial syndrome. Lancet 2002; 359:426-30.*
25. *Raja M: The Diagnosis of Asperger's Syndrome. Directions in Psychiatry 2006; 26:89-103.*
26. *Raja M & Azzoni A: Thought disorder in Asperger syndrome and schizophrenia: Issues in the differential diagnosis. A series of case reports. World Journal of Biological Psychiatry 2007; 26:1-9.*
27. *Rapoport J, Chavez A, Greenstein D, Addington A & Gogtay N: Autism spectrum disorders and childhood-onset schizophrenia: clinical and biological contributions to a relation revisited. Journal of the American Academy of Child and Adolescent Psychiatry 2009; 48:10-8.*
28. *Verdoux H, Van Os J, Maurice-Tison S, Gay B, Salamon R & Bourgeois M: Is early adulthood a critical developmental stage for psychosis proneness? A survey of delusional ideation in normal subjects. Schizophrenia Research 1998; 29:247-54.*
29. *Volkmar FR: Childhood and adolescent psychosis: a review of the past 10 years. Journal of the American Academy of Child and Adolescent Psychiatry 1996; 37:843-51.*
30. *Walker DR, Thompson A, Zwaigenbaum L, Goldberg J, Bryson SE, Mahoney W, et al: Specifying PDD-NOS: a comparison of PDD-NOS, Asperger syndrome, and autism. Journal of the American Academy of Child and Adolescent Psychiatry 2004; 43:172-80.*
31. *Williams JM, Beck TF, Pearson DM, Proud MB, Cheung SW & Scott DA: A 1q42 deletion involving DISC1, DISC2, and TSNAX in an autism spectrum disorder. American Journal of Medical Genetics Section A 2009; 149A:1758-62.*
32. *Woods SW: Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003; 64:663-667.*
33. *Woods SW, Walsh BC, Saksa JR & McGlashan TH: The case for including Attenuated Psychotic Symptoms Syndrome in DSM-5 as a psychosis risk syndrome. Schizophrenia Research 2010 September 8. doi:10.1016/j.schres.2010.08.012.*
34. *World Health Organization: The ICD-10 Classification of Mental and Behavioural Disorders. Clinical descriptions and diagnostic guidelines. Geneva: WHO, 1992.*
35. *Ylisaukko-oja T, Nieminen-von Wendt T, Kempas E, Sarenius S, Varilo T, von Wendt, et al: Genome-wide scan for loci of Asperger syndrome. Molecular Psychiatry 2004; 9:161-168.*

Correspondence:

Michele Raja, M.D.
Servizio Psichiatrico di Diagnosi e Cura, Ospedale Santo Spirito
via Prisciano 26, 00136 - Rome, Italy
E-mail: michele.raja@libero.it; michele.raja@fastwebnet.it