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Beyond imagination: Sorting out and treating psychosis in the context of autism spectrum disorder

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ABSTRACT

In the last decades, growing caseness for Autism Spectrum Disorder (ASD) has been observed, owing to the diagnostic accretion of low-impairment forms, over and above other possible causes. Unrecognized ASD is likely to be mislabeled as a psychotic disorder (PD), as people in the spectrum may show 'pseudopsychotic' symptoms, resembling both negative and positive symptoms. On the other hand, PDs are likely to be overlooked when they arise in people with ASD, due to the 'diagnostic overshadowing' of new-onset conditions by lifelong core autistic symptoms. The three available metanalyses on the occurrence of psychosis in adults with ASD convergently reported a rate of PDs that is at least ten times higher than in the general population. Therefore, the lack of literature addressing risk factors, outcomes, and treatment options for psychosis in the context of ASD is utterly concerning. The present review aims to summarize up-to-date knowledge of PDs with comorbid ASD in terms of clinical features, course, and treatment.

1. Case vignette 1

PD is a 22 year-old, caucasian man, living in an urban area with his parents and a younger sister, diagnosed during middle childhood with Autism Spectrum Disorder (ASD) with no cognitive or language impairment. As a child, he was quiet and calm, with occasional tantrums. He always showed difficulties with peers and poor communication skills, and never built significant relationships. He has no friends and never had, his most significant social interaction being talking to some people at the park. He is very fond of technological devices, photography, and local public transport system, and often wears earplugs due to high sound reactivity. After graduating from high school, he entered an occupational program for people with ASD but struggled to find something working for him. At the age of 20, he begun to use social networks intensively: he started to spend hours checking the Instagram profile of a girl who had 'rejected' him several years before, convinced that some contents she posted were meant at him. Still, he would agree that his beliefs were unlikely upon discussing them with his therapist. An emerging psychosis was hypothesized by the treating psychiatrist, who thought, on the other hand, that symptoms could still be explained in the context of ASD, so that antipsychotic therapy was not prescribed. Over the following weeks, however, PD progressively lost the ability of adjusting his beliefs when confronted with evidence, and gained certainty about the girl wanting to harm him and his family. He thus developed a persecutory delusion that rapidly involved the neighbors, the parkgoers and the police force and started to show aggressive behaviors towards his parents. He was compulsory hospitalized and antipsychotic treatment was initiated. In light of limited efficacy and poor tolerability, several different antipsychotic agents were used, and recurrent inpatient treatments were needed over an eight-month period.

2. Case vignette 2

VI is an 18-year old, Caucasian woman, who lives with her parents. Since primary school, she has always been a good student and earned high grades, while showing difficulties in making friends. When she was 11, she developed nervous anorexia and started to see a therapist. At 13, she suffered from recurrent panic attacks with atypical features (mainly depersonalization and derealization). Shortly after starting

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SSRI treatment, she exhibited a hypomanic episode and was prescribed mood stabilizers. At 17 years of age, she developed the belief of being from another world, that she wanted to come back to. Upon showing suicidal thoughts and self-harm behaviors in order to reconnect to her world, she was referred for inpatient psychiatric treatment. During hospital stay, a peculiar behavioral and communication pattern was observed, leading to autism assessment and to a formal diagnosis of ASD and concurrent schizoaffective disorder. Despite several different antipsychotics, the delusional thought showed no improvement and recurring acute inpatient treatment was needed across a six-month period; hence, she entered a long-term mental health care facility.

PD and VI are two youngsters with ASD, featuring mild impairment and normal IQ, who developed a severe form of treatment-resistant psychosis. Despite being referred to a tertiary care specializing in the treatment of mental disorders during the course of ASD, their diagnosis and management was quite challenging. Yet, as the autism spectrum continues to expand, we must expect that similar clinical cases will be not unique to highly specialized mental health care.

3. Introduction

In the last decades, growing caseness for ASD has been reported, owing to the overall diagnostic accretion and to better case finding of mild forms, over and above other possible environmental and biological causes (Brugha et al., 2011). This is reflected in the sharp increase of prevalence starting from mid 90s, that is to say in the aftermath of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) release that featured for the very first time the diagnosis of Asperger Disorder (Fombonne and Psych, 2005). However, prevalence estimates from epidemiological studies have been failing to find correspondence in mental health services for adulthood, where only a few patients are diagnosed with ASD. One hypothesis might be that subjects with ASD are seldom referred to mental health services. However, there is also the chance that some of them - especially those with mild forms - seek for mental care while not being aware they have ASD, that is to say they are diagnosed and treated for some comorbid conditions or mis-diagnosed due to autistic core and associated symptoms drifting away the diagnostic process.

4. Misdiagnosis of ASD as psychosis

Unrecognized ASD is likely to be mislabeled as a psychotic disorder (PD), as people in the spectrum may show psychotic-like features, resembling both negative and positive symptoms (Van Schalkwyk et al., 2015). The overlap between communication challenges in ASD and negative symptoms in psychosis reflects the complex interplay between these two conditions (Abu-Akel et al., 2022), both having, at their core, the withdrawal from social relationships and the impairment in expressing oneself. While offering a better insight into both conditions and better understanding of known shared risk factors and genetic underpinnings, the broad overlap between ASD Criterion A and negative symptoms make it necessary to rely on ASD Criterion B (e.g., repetitive behaviors and restricted interests) and positive symptoms of psychosis to distinguish one disorder from the other. Yet, untangling autistic positive psychotic-like symptoms from true psychosis might still be challenging (Larsen and Mouridsen, 1997; Dratcu et al., 2007). People in the spectrum may often talk to themselves as a form of echolalia, as a way of thinking out loud or anticipating a conversation. However, this has nothing to do with psychotic symptoms and does not depend on hallucinations or delusion. They may create very elaborated fantasies and spend a great amount of time engaging in fantastic scenarios, running images and conversations repeatedly (Larsen and Mouridsen, 1997). Normal to high Intelligence Quotient (IQ) subjects usually have good grasp of reality, while those with cognitive disability may display a very immersive daydreaming, quite similar to delusion. A broad range of fixated and bizarre interests may as well resemble delusion (Isaac et al., 2022). They may have increased interpersonal sensitivity and become suspicious in social contexts. This may develop in frank delusional disorder, but more often it resembles a stable trait, occasionally clearing the way to transient psychotic symptoms (Lai and Baron-Cohen, 2015; Yamada et al., 2023). Many subjects with ASD have dissociative-like phenomena, termed “shutdowns”, and usually caused by emotional or sensory overload (Belek, 2019). During such episodes, the subject withdraws from their surroundings to different degrees, showing partial or complete unresponsiveness to external stimuli, inability to communicate and to move. Impairment of functioning during a shutdown ranges from mild (e.g., being able to walk around and talk) to severe (e.g., feeling detached from oneself body, going into a fetal position) (Belek, 2019; Phung et al., 2021). While lasting for a long time or causing wandering behaviors, shutdowns may be interpreted as dissociations of a psychotic nature.

Further, ASD patients often show sensory hypersensitivity, (i.e., heightened awareness of and over-reactivity to external stimuli, such as textures, smells, ambient light, loud noises, touch) that might be mistaken for hallucinations and lead to behaviors that resemble those observed in psychotic patients (e.g., being distressed by and avoiding loud places or certain clothes, avoiding being touched, covering oneself ears, seemingly listening to something else).

5. Psychosis in the context of ASD

On the other hand, psychotic symptoms are likely to be overlooked when they first arise in people with ASD. The term ‘diagnostic overshadowing’ has been used to indicate new-onset disorders going unrecognized while their symptoms and behaviors are instead attributed to a known mental disease. Growing literature has been claiming diagnostic overshadowing among people with ASD, which is quite concerning considering the high rate of comorbid disorders shown in this patient group (Buck et al., 2014). Patients with ASD present a greater risk of having psychotic-like experiences (Jutla et al., 2022) and developing psychosis than the general population (Ribolsi et al., 2022; Zheng et al., 2018). The two available metanalyses on the occurrence of PDs in adults with autism convergently provided prevalence estimates at least ten times higher than those available for the general population (Lugo Marín et al., 2018; Varcin et al., 2022). Interestingly, results from a national register-based study indicate that up to 50% of subjects with concurrent autism and PD or bipolar disorder received the diagnosis of autism only after they developed the PD (Schalbroeck et al., 2019), as it happened to the patient described in our second case vignette. This may obviously depend on the under-recognition of ASD especially in its low-impairment forms, but also may prompt clinicians to carefully consider ASD when dealing with a new onset psychosis in their daily practice. The majority of studies consistently indicate that male sex may increase the risk of PDs during the course of ASD (Larson et al., 2017; Hsu et al., 2019). This appears to differentiate the ASD from the general population, where males and females have a similar prevalence of PDs. However, the higher risk of psychosis within the ASD male population might be affected by the great under-recognition of ASD among females (Bargiela et al., 2016; Gesi et al., 2021).

6. Risk of psychosis across ages among ASD people

A recent meta-analysis focused on the few studies (n = 4) that included subjects with autism in their high risk for psychosis cohorts (CHR-P), reporting a pooled prevalence of ASD as high as 11% (range between 2.5 and 40%, Vaquerizo-Serrano et al., 2022). Somehow expectedly, ASD + CHR-P subjects were significantly younger than CHR-P only (mean age, 11 years vs 18 years). We may argue that autistic psychotic-like symptoms and bizarre interests of ASD people as well as their earlier contact with mental health professionals may lead to referral to CHR-P services at a younger age. However, the study also

showed that the two-year conversion rate did not differ between ASD and non-ASD subjects. This suggests that despite the earlier referral and the possible enhancing effect of autistic psychotic-like symptoms, ASD subjects who enter the CHR-P have an actual high risk for psychosis, that is not inferior to non-ASD counterparts, and starting at a younger age. A noteworthy difference between ASD and non-ASD psychotic people has been also found for the age of onset of actual psychosis. A large study, based on Dutch national registers, compared the risk of non-affective psychosis and bipolar disorder across ages between people with or without ASD. Results showed a three-fold increase in the prevalence of the two conditions between the 15–20 and the 25–29 age range in the general population, after which the curve flattens. In individuals with ASD, on the other hand, the prevalence was shown to keep on rising, with an increase of almost 50% from the 25–29 to the 30–34 age range (Schalbroeck et al., 2019). Although this finding may be due to several factors, it may also suggest that ASD subjects are at high risk of psychosis and bipolar disorder for a prolonged time compared to non-ASD counterparts.

7. Characteristics of the psychotic illness in the ASD group

Comparing data of previous literature, Vaquerizo-Serrano et al. (2022) argued that ASD patients with CHR-P might have higher rates of Attention Deficit Hyperactivity Disorder (ADHD) and anxiety disorders than those without. More severe core autistic symptoms, such as social cognition deficit, were also suggested to be associated with CHR-P status. This may be used to plan further investigations and/or a closer monitoring in patients with these clinical features. Larson et al. (2017) gathered the larger sample of ASD + PD known so far (n = 116), which was compared with a group of subjects with ASD and no comorbid psychosis, and a group with psychosis only. ASD + PD patients showed significantly fewer lifetime stereotyped, repetitive or restrictive interests/behaviors than those with ASD only. On the other hand, the co-occurrence between ASD and psychosis, was associated with lower rates of schizophrenia and higher rates of psychosis-NOS compared with patients with PD only. Another study based on a Sweden nation-wide cohort of people with a first hospitalization for psychosis (n = 2091), showed that among cases with concurrent ASD a larger proportion presented with delusional disorder compared to the rest of the cohort without ASD (Strålin and Hetta, 2019).

8. Treatment of psychosis with concurrent ASD

Given the high rates of PDs among people with ASD and the recent diagnostic accretion of this patient group, the lack of literature addressing the treatment of PDs in the context of autism is striking, especially in light of some data suggesting unique treatment response and tolerability in ASD subjects (Strålin and Hetta, 2019). A recent study (Downs et al., 2017) investigated factors associated with Multiple Treatment Failure (MTF, defined as the initiation of a third trial of novel antipsychotic due to nonadherence, adverse effects, or insufficient response) in youngsters aged 10–17 years with first episode of psychosis referred to a mental health services in South London, UK, between 2014 and 2018. Out of a total of 638 patients, 20% were reporting MTF, and 17% showed a comorbidity with ASD. Importantly, the proportion of ASD subjects in the MTF group was significantly higher than that of subjects without comorbid ASD (28% *vs* 17%). Moreover, ASD was a significant predictor of MTF in the multivariate analysis, over and above the effect of other demographic and clinical variables. The above referenced study from a Sweden nation-wide cohort of 2091 subjects with a first hospitalization for PD, showed that a larger proportion of cases with ASD were using antipsychotic (AP) medication one year before and one to two years after hospitalization and with higher doses compared to the rest of the cohort. Somehow consistently, in their revision and metanalysis of studies conducted on CHR-P populations, Vaquerizo-Serrano et al. (2022) found higher rates of AP users among CHR-P + ASD subjects compared to CHR-P without ASD, irrespectively of their transition to actual psychosis. Altogether, the few available data point toward the need of more intensive care for the ASD group due to poorer response/more severe symptoms or concurrent behavioral issues or both (Strålin and Hetta, 2019). Intriguingly, recent published data suggest that patients with treatment-resistant schizophrenia show a pattern of neurocognition and social cognition closer to that of ASD subjects than to that of treatment-respondent schizophrenic patients (Nakata et al., 2020). To the best of our knowledge, no intervention studies addressing the treatment of PDs in autistic people have been conducted so far. Among the few case reports, some showed satisfactory improvement of psychotic symptoms with AP treatment (Baykal and Mutlu, 2023), while others described cases in which several APs were sequentially attempted due to lack of efficacy and/or poor tolerability (Alamy et al., 2004; Bell et al., 2017; Garel and Joober, 2019; Traverso et al., 2021), similarly to the two case vignettes presented earlier in this paper. Another few clinical cases and one clinical series (n = 7) reported on the efficacy of clozapine (Yalcin et al., 2016; Sahoo et al., 2017). However, conflicting outcomes were found with respect to tolerability, with some reports showing good tolerability (Yalcin et al., 2016) and two cases reporting a clozapine-induced myocarditis (Beebani et al., 2022), developed as well by the first of the two cases presented in this paper. Adjunctive treatment with mood stabilizers were also individually attempted in several reports, as they were in both patients described in the two case vignettes (Alamy et al., 2004).

No studies provide information about the tolerability of single APs in ASD populations with PDs; however, a piece of information can be drawn from the literature on the use of AP for clinical target other than psychosis. Alfageh et al. (2019) conducted a systematic review meta-analysis focusing on the risk of adverse events among ASD subjects administered APs for behavioral abnormalities. The vast majority of studies was conducted on Risperidone, followed by Aripiprazole, and most frequent adverse events (AEs) were similar to those commonly reported in other patient group (weight gain, somnolence, increased appetite and extrapyramidal symptoms), with the exception of enuresis. In the meta-analysis (including 8 RCT and 7 open label studies) pooled risk of AEs was 22%. A pooled risk for single AEs was obtained only for Risperidone that showed a significant association with weight gain and hyperprolactinaemia. Again, despite providing some hints, these data may not be generalizable to ASD patients who are administered AP for treating PDs.

9. Conclusive remarks

Individuals with ASD have higher rates of PDs than the general population and represent a significant share of CHR-P cohorts, with similar rates of conversion to actual psychosis compared to non-autistic counterparts. Moreover, the age span of onset of psychosis might be larger in ASD people than in the general population. The literature on treatment of PDs during the course of ASD is scarce. Extant data point toward a great likelihood of treatment-resistant psychosis, despite they may be biased by a challenging differential diagnosis and concurrent problematic behaviors of this patient group. Clinicians should be aware of the frequent co-occurrence between psychosis and ASD and bear in mind a possible ASD in patients with late-onset or treatment-resistant psychosis, despite further data are needed to corroborate and explore several aspects of this comorbidity. As a way forward, research addressing PDs in people with ASD should be encouraged. On the other hand, researchers working in the field of psychosis should carefully consider the exclusion criteria for their clinical trials as the underrepresentation of participants with ASD may create gaps in our understanding of PDs and prevent ASD communities from benefit from scientific advances in the treatment of psychosis.

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Camilla Gesi: Writing – review & editing, Writing – original draft, Conceptualization. **Luca Giacovelli:** Writing – review & editing, Writing – original draft, Conceptualization. **Yacob Levin Reibman:** Writing – review & editing, Supervision. **Bernardo Dell'Osso:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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