Anxiety in Autism Spectrum Disorder: clinical characteristics and the role of the family.

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Abstract

Background: Anxiety Disorder (AD) is among the most common psychiatric comorbidities in children and adolescents with Autism Spectrum Disorder (ASD). However, findings regarding the characterization of anxiety symptoms and the use of validated measures for children with ASD and AD are inconsistent. Parental psychological distress (PPD) has been linked to anxiety symptoms in children with ASD. This study aims to identify and to explore clinical characteristics of anxiety symptoms in ASD. Furthermore we shed light on the possible presence of PPD involving families of children and adolescents with ASD and AD.

Methods: The final sample consisted of 75 children and adolescents (Mean age: 11.8 ± 2.3 years; Range age: 8-16 years) and their parents. Participants were divided into three groups based on the diagnosis: children and adolescents with a diagnosis of Autism Spectrum Disorder and Anxiety Disorders in comorbidity, children and adolescents with a diagnosis of Anxiety Disorders but without a diagnosis of Autism Spectrum Disorder, children and adolescents with a diagnosis of Autism Spectrum Disorder but without a diagnosis of Anxiety Disorders.

Results: Results show the presence of clinical phenotype ASD+AD with specific features than AD group (p = 0.00003). A major functional impairment is reported for ASD+AD group compared the other groups. Finally, parents of the ASD+AD group reveal higher levels of PPD than AD (p = 0.005).

Conclusions: Understanding clinical characteristics of anxiety disorder and the role of PPD could define individualized treatments and a better prognosis in children and adolescents with ASD and AD

1. Background

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction, as well as restrictive and repetitive patterns of behavior, interests, or activities that cause clinically significant impairment in several areas of functioning [1]. ASD is a significant cause of morbidity deriving from early-onset, lifelong persistence, a high level of associated impairments, and an absence of effective treatment for communication, social and cognitive deficits. The clinical expression of ASD varies wildly, depending on the severity of autistic symptoms and on the developmental level. In 2016, about 1 in 54 children (age: 8 years old) received a diagnosis of ASD, according to CDC's Autism and Developmental Disabilities Monitoring (ADDN) Network.

In children and adolescents with ASD, psychiatric comorbidity is expected, with rates of 70% – 75% [2, 3, 4], or even 83% [5, 6]. Recently, Hossain and colleagues [7] confirmed the high prevalence variability in different studies (54.8% up 94%). Psychiatric comorbidity increases the possibility of worse long-term outcomes, risk of mortality, and impaired quality of life [2, 5]. Previous studies showed that Anxiety Disorder (AD), Oppositional Defiant Disorder (ODD), and Attention Deficit Hyperactivity Disorder (ADHD) are among the most common psychiatric comorbidities in children and adolescents with ASD. Simonoff et al. [3] examined 112 ASD children (10–14 years) and proposed that at least a third of the participants
reported three or more psychiatric disorders in comorbidity. Specifically, 29.2% of the total sample reported AD with symptoms of social anxiety.

Interestingly, the severity of autism was not a significant predictor of other disorders. Brookman-Frazee et al. [6] investigated psychiatric comorbidities in a group of 201 children with ASD (9–13 years). The most frequent pattern of comorbidity was Anxiety with ADHD and ODD (17%), followed by Anxiety with Mood + ADHD + ODD (16%). Lecavalier et al. [8], in a sample of 658 children with ASD (mean age: 7.2 years) observed that 42% of the total sample reported AD, 81% ADHD, 46% ODD, and 12% Conduct Disorder in comorbidity. In particular, 46% of children with ASD + ADHD met the criteria for anxiety disorders.

According to recent literature, the clinical significance of concomitant psychiatric disorders in children and adolescents with ASD must be thoroughly studied [8]. Concerning anxiety disorders in ASD, it is necessary to understand which anxiety disorders are most frequently observed and clarify their clinical characteristics in ASD. Furthermore, it is important to explore the presence of impairment in quality of life and impact on the functioning in social, scholastic, and family contexts of children and adolescents with ASD and AD to identify specific interventions [3].

To our knowledge, a growing body of research investigated general psychological symptoms and Parental Psychological Distress (PPD) in families of ASD children. Increased PPD has also been showed in family of children with ASD [10]. PPD is defined as family members’ distress, resulting in high levels of family conflict, and increased expressed emotions, defined as criticism, hostility, and emotional over-involvement [9]. Yorke and colleagues [10] showed the relationships between the child’s emotional and behavioral problems and PPD in a group of ASD children, finding a moderate association between parenting stress, parental mental health problems, and ASD child’s emotional and behavioral problems.

Concerning the possible correlation between PPD and ASD, parents of children with ASD have higher parental stress levels and lower quality of life than parents of normotypical children [11, 12, 13, 14], similarly to parents with disabilities’ children (e.g., Down syndrome, cerebral palsy, and intellectual disability) [15, 16].

Based on the literature, the study aims to investigate anxiety symptoms in children and adolescents with ASD, and to explore the presence of specific clinical characteristics which marked a comorbid phenotype ASD + AD. Moreover, the present study aims to clarify the presence and the role of PPD in ASD + AD children and adolescents' families.

2. Methods

2.1 Participants

75 children and adolescents (Mean age: 11.8 ± 2.3 years; Range age: 8–16 years) and their parents were recruited between May 2020 and March 2021 at the Child Neuropsychiatric Unit of the Bambino Gesù
Children's Hospital, Rome, Italy. All children and adolescents were outpatients attending our Unit for clinical assessments.

The inclusion criteria included a diagnosis of Autism Spectrum Disorder (ASD) and/or a diagnosis of Anxiety Disorders (AD), based on the DSM-5 criteria [1], and Intellectual Quotient (IQ) higher than 70.

Participants were divided into three groups based on the diagnosis:

- **Group 1 (ASD + AD):** children and adolescents with a diagnosis of Autism Spectrum Disorder and Anxiety Disorders in comorbidity;
- **Group 2 (AD):** children and adolescents with a diagnosis of Anxiety Disorders, but without a diagnosis of Autism Spectrum Disorder;
- **Group 3 (ASD):** children and adolescents with a diagnosis of Autism Spectrum Disorder but without a diagnosis of Anxiety Disorders.

Written informed consent was obtained from parents or legal guardians of each participant included in the study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

### 2.2 Procedures

Trained developmental psychiatrists and neuropsychologists conducted neuropsychological and psychopathological evaluations.

#### 2.2.1 Children and adolescent assessment

Social Communication Questionnaire (SCQ) [19] was used as a screening instrument to confirm or exclude the presence of ASD in all participants. SCQ is a caregiver-report, derived from Autism Diagnostic Interview-Revised (ADI-R) [20] used to assess social communication impairment, the presence of repetitive and restrictive behaviors and screen ASD symptoms.

The presence of ASD was evaluated by ADOS-2 [21], a semi-structured observation of communication and social interaction, considered the “gold standard” in the assessment of ASD symptomatology. ADOS was administered and scored by licensed clinicians who have reached clinical reliability on the instrument. The calibrated severity score of each domain was also calculated [22, 23].

Wechsler Intelligence Scale for Children (WISC-IV) assessed cognitive functioning (IQ) [24]. The WISC-IV provides a measure of global intelligence quotient (IQ), obtained through four different indexes: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and
Processing Speed Index (PSI). In cases of failures in completing the WISC-IV for the inadequacy of the language, we administered Leiter-3 [25] or Raven Matrix [26].

Leiter-3 [25] provides a measure of nonverbal intelligence based on four subtests: Figure Ground, Form Completion, Classification and Analogies, and Sequential Order. Raven Matrix [26], provides a measure of non-verbal intelligence, through matrix reasoning test to complete.

The presence of anxiety disorders and other psychopathological disorders was assessed by the K-SADS-PL DSM-5 [27], a semi-structured interview based on DSM-5 criteria [1]. Functional impairment was assessed by the Children's Global Assessment Scale (CGAS) [28] on a scale from 0 to 100 (from severe impairment to superior functioning).

Furthermore, all participants and caregivers completed self and parent report to assess anxiety and depressive symptoms through the Multidimensional Anxiety Scale for Children-Second Edition (MASC – 2) [29] and the Children's Depression Inventory-2 (CDI – 2) [30], respectively.

### 2.2.2 Parents’ psychopathological distress clinical assessment

Each caregiver completed the Parenting Stress Index-Short Form (PSI-SF) [31] a self-report questionnaire to investigate parenting distress perceived, examining personal factors, parent-child interaction, and behavioral characteristics of the child.

Moreover, caregivers completed the Symptom Checklist 90-Revised (SCL-90-R)[32], a self-report questionnaire to assess psychopathological distress (GSI - Global Severity Index), examining various symptoms dimensions (somatization, obsessive-compulsive behavior, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism).

### 2.2.3 Statistical Analysis

Data were analyzed using SPSS IBM Statistics version 20 statistical software (IBM Corp, Armonk, NY, USA). Three groups’ comparisons based on one-way ANOVA were performed on demographic and psychiatric variables to confirm that groups are comparable for age, IQ and autistic symptomatology, and analyzed differences between groups in clinical variables (self-report and parent-report). Post-hoc analyses were performed to determine Bonferroni confidence intervals (95%) to establish differences between means. Chi-Square tests were performed on frequency data.

The two groups were unequal in size, but Levene's test confirmed the homogeneity of variance and, the Shapiro–Wilk test confirmed the normal distribution of the variables based on continuous data.

### 3. Results

#### 3.1 Sample Characteristics
The total sample of 75 children and adolescents (Mean age: 11.8 ± 2.3 years; Range age: 8–16 years) was divided into three groups:

- **Group 1 (ASD + AD)** was composed of 21 participants diagnosed with Autism Spectrum Disorder with Anxiety Disorders in comorbidity (18 males, 3 females; Mean age: 11.9 ± 2.4 years);
- **Group 2 (AD)** was composed of 31 participants diagnosed with only Anxiety Disorders (23 males, 8 females; Mean age: 11.9 ± 2.2 years);
- **Group 3 (ASD)** was composed of 23 participants diagnosed with only Autism Spectrum Disorder (23 males, 0 females; Mean age: 11.6 ± 2.3 years).

The three groups did not differ significantly in terms of chronological age (F 2,72 = 0.41; p = .6637) and IQ (F 2,72 = 2.06; p = .1353).

SCQ results confirmed significant differences between the three groups (F (2,72) = 14.92; p = .000). In particular, Group 2 reported lower scores compared to Group 1 and Group 3 (Gr1 vs Gr 2: p = 0.000; Gr2 vs Gr3: p = 0.000). Other comparison was not significant (Gr1 vs Gr3: p = 1.000).

Group 1 and Group 3 were assessed also with ADOS-2. Not significant differences were found between the two groups in ADOS-2 total score (F (2,72) = 0.78; p = .3822), ADOS-2 Social Affect Score (F (2,72) = 0.03; p = .8569), and ADOS-2 Restricted and Repetitive Behavior score (F (2,72) = 0.05; p = .8254).

Specific means and SD data were reported in Table 1, separate for each group.

### 3.2 Differences between groups

Regarding psychopathological variables, we found significant group differences in functional impairment (F (2,72) = 49.204; p = .000). Specifically, Group 1 reported major functional impairment compared to Group 2 and Group 3 (Gr1 vs Gr 2: p = 0.000; Gr1 vs Gr3: p = 0.000; Gr2 vs Gr3: p = 0.000).

Regarding MASC − 2 self-report Total score, not significant differences between groups were found (F (2,72) = 1.425; p = .247). Instead, significant differences between groups were found in MASC − 2 parent report Total score (F (2,72) = 10.609; p = .000), with Group 1 reported major total score compared to Group 2 and Group 3 (Gr1 vs Gr 2: p = 0.015; Gr1 vs Gr3: p = 0.000). Other comparison was not significant (Gr2 vs Gr3: p = 0.128).

Regarding CDI − 2 self-report Total score, significant differences were found between three groups (F (2,72) = 103.745; p = .000), with Group 1 reported major total score compared to Group 2 and Group 3 (Gr1 vs Gr 2: p = 0.000; Gr1 vs Gr3: p = 0.000; Gr2 vs Gr3: p = 0.000). Also, in CDI − 2 parent report Total score were found significant differences between groups (F (2,72) = 8.624; p = .000), with Group 1 reported major total score compared to Group 2 and Group 3 (Gr1 vs Gr 2: p = 0.003; Gr1 vs Gr3: p = 0.001). Other comparison was not significant (Gr2 vs Gr3: p = 1.000).

Specific means and SD data were reported in Table 1, separate for each group.
Regarding parent assessment, analyzing PSI-SF results, significant differences between groups were found in mothers results ($F(2,72) = 5.455; p = .006$). In particular, Group 1 mothers reported major score compared to Group 2 mothers ($Gr1$ vs $Gr2$: $p = 0.005$), while other comparisons were not significant ($Gr1$ vs $Gr3$: $p = 0.145$; $Gr2$ vs $Gr3$: $p = 0.723$). Father results in PSI-FS total score were not significant ($F(2,72) = 2.371; p = .101$).

Regarding SCL-90 GSI score, mothers reported significant group differences between groups ($F(2,72) = 6.655; p = .002$). In particular, Group 1 mothers reported major score compared to Group 2 mothers ($Gr1$ vs $Gr2$: $p = 0.002$), while other comparisons were not significant ($Gr1$ vs $Gr3$: $p = 0.492$; $Gr2$ vs $Gr3$: $p = 0.109$). Also, in fathers SCL-90 GSI score were found significant differences between groups ($F(2,72) = 7.999; p = .001$). In particular, Group 1 reported major total score compared to Group 2 and Group 3 ($Gr1$ vs $Gr2$: $p = 0.001$; $Gr1$ vs $Gr3$: $p = 0.008$). Other comparison was not significant ($Gr2$ vs $Gr3$: $p = 17.389$).

Specific means and SD data were reported in Table 2, separate for each group.

### 3.2.1 Comparison between Group 1 and Group 2 in Anxiety Clinical Profile

According to K-SADS-PL DSM-5, there were significant differences between Group 1 and Group 2 in percentage presence of Anxiety Disorders ($\chi^2 = 23.4236; p = 0.00003$). Even if both groups reported elevated percentage frequencies of Generalized Anxiety Disorder ($Gr1$: 86%; $Gr2$: 87%), Group 1 reported major percentage frequencies of diagnosis of Separation Anxiety Disorder ($Gr1$: 38%; $Gr2$: 10%) and Specific Phobia ($Gr1$: 38%; $Gr2$: 10%). While Group 2 reported major percentage frequencies of diagnosis of Social Anxiety Disorder ($Gr1$: 9%; $Gr2$: 10%). No participant received a diagnosis of Selective Mutism, Panic Disorder or, Agoraphobia.

For details, intragroup analyses were conducted to analyze if, in within confronted groups (Group 1: ASD + AD and Group 2: AD), there were significant differences in the frequency distribution of different Anxiety Disorders based on chronological age.

Considering Group 1 (ASD + AD), significant differences were found compared by age ($\chi^2 = 23.0153; p = 0.00004$). In particular, the $\leq 11$ years participants reported a major perceptual frequency of Separation Anxiety Disorder compared with the $> 11$ years participants. On the contrary, Specific Phobia was majorly reported in the $> 11$ years participants compared to the $\leq 11$ years participants. There were no significant differences for Generalized Anxiety Disorder and Social Anxiety Disorder.

Also in Group 2 (AD) significant differences were found compared by age ($\chi^2 = 34.1926; p = 0.00001$). In particular, in this group, a major perceptual frequency of Separation Anxiety Disorder was found in the $\leq 11$ years participants compared to the $> 11$ years participants. In contrast, the $> 11$ years participants reported major perceptual frequency of Social Anxiety Disorder and Specific Phobia compared to the $\leq 11$ years participants. No significant differences were found for Generalized Anxiety Disorder.
4. Discussion

The first aim of our study was to investigate anxiety symptoms in children and adolescents with ASD and to understand whether anxiety symptoms in youth with ASD are the same as anxiety disorders in the typical development (TD) pediatric population. Frequently, children with ASD can manifest compulsions, strange specific phobias, and social withdrawal, in addition to the common symptoms of anxiety [33]. We compared three groups of children and adolescents (Group 1: ASD + AD, Group 2: AD, Group 3: ASD) matched by age, IQ and severity symptoms of ASD (Group 1: ASD + AD, Group 3: ASD).

The first result revealed the presence of a significant global functional impairment in ASD + AD, compared to AD and ASD groups. This result implements the idea that anxiety symptoms in ASD can be considered a separate and distinct construct from ASD that affects children's global functioning. Moreover this result is in line with literature that shows that CGAS scores decreased significantly secondarily to the increment of the number of psychiatric comorbidities [36].

The second aim of this study was to characterize anxiety symptoms in three groups of children and adolescents (Group 1: ASD + AD, Group 2: AD, Group 3: ASD).

The literature has already been reported a significant discrepancy between child and parents' ratings on the anxiety measures for children with ASD [40]. In the absence of psychometrically sound assessments for anxiety symptoms in ASD [37], in this study, we used “the best-established and widely used measures” for typical children and adolescents with AD [38, 39], keeping in mind the different symptom presentations in individuals with ASD: self and parent-report of MASC-2. Our results showed significant differences in MASC-2 parent report Total score, with the group ASD + AD reporting a major total score compared to the Group AD and the Group ASD, but we found no difference in MASC-2 self-report. Furthermore, confirming the results of Russell E. & Sofronoff K. [40], our group ASD + AD reported anxiety symptoms similar to the other groups. Our findings could show a poor match between children and parents regarding diagnoses [41]; the possible hypothesis is that autism symptoms without impairment of IQ may have reduced insight into difficulties of these children, as suggested by other studies [42, 43].

On the other hand, high vulnerability towards depression among children and adolescents with ASD, frequently with anxiety symptoms [44], generated our interest in exploring depressive symptoms through parent and child versions of CDI-2. The use of self-reports has been validated in providing information on the prevalence of depressive symptoms, especially during adolescence in ASD [45]. Our findings showed higher depressive symptoms in Group ASD + AD than AD and ASD groups, both in the child and parents' report. These results are in line with existing literature [5, 46].

Moreover, following a systematic process of assessment proposed by Vasa et al. [39], we have evaluated symptoms of anxiety in ASD using a clinician behavioral observation (K-SADS-PL DSM-5), in addition to child and parent-report information. The aim was to obtain an objective evaluation of clinical symptoms of anxiety, considering the diagnostic utility of the DSM-5 categories [38]. As a matter of fact, similar to studies of Weems and Costa [47], Weems et al. [48], and Varela et al. [49], we tried to understand the
possible variability of anxiety symptoms relative to the age in ASD. Our results showed higher symptoms of generalized anxiety disorder in both groups, ASD + AD, and AD. We found higher prevalence of symptoms of separation anxiety and specific phobias in group ASD + AD. Whereas, for group AD, prevalent social anxiety symptoms emerged. These results are in line with the most common comorbid anxiety disorders found in the ASD population, including specific phobias, generalized anxiety disorder, and separation anxiety disorder [38]. Gjevik E. and colleagues [50] revealed the prevalence of specific phobias, such as reported by other authors [51, 52, 53], but differently from our results, no symptoms of generalized and separation anxiety disorders were evidenced. In opposition, Esther Ben-Itzchak and colleagues [54], in a group of adolescents with ASD, reported a significant prevalence of separation anxiety followed by social and generalized anxiety.

It is possible that rate differences could reflect samples variability and different ways of evaluating and performing symptoms of anxiety [50]. In addition, intra-group analysis evidenced separation anxiety symptoms in children under 11 years of age in both groups, ASD + AD and AD, and high specific phobia symptoms in children aged 11 and over for the ASD + AD group. Prevalent social anxiety was found only in group AD in older children. No significant differences were found for Generalized Anxiety Disorder in both groups ASD + AD and AD. Research examining the influence of the child's age on anxiety symptoms in ASD has produced mixed results. In a cross-sectional study of toddlers, children, young adults, and older adults with ASD, Davis, Hess, et al. [55] suggested that the trajectory of anxiety symptoms in ASD is similar to that of young people with typical development. Our results confirm the presence of separation anxiety in younger children of both groups, rather than a subsequent prevalence in older children of specific phobia and social anxiety in ASD + AD and AD groups, respectively.

In opposition, others studies reported no age differences in individuals with ASD [56, 57, 58, 35, 59]. The characteristics of the group studied and assessment methods used may be important conditions to consider to define anxiety symptoms in ASD [60]. For symptoms of generalized anxiety, it is not clear why younger groups may exhibit similar symptoms to their older age counterparts. It is possible that children with ASD, like children with TD, are more vulnerable to worry in general and maybe more easily submitted to ambiental factors or stimuli anxiety-provoking at that young age, as suggested by Varela et al. [49].

Concerning the third aim, in line with other findings of reduced parental acceptance and greater use of psychological control among parents of children with ASD compared to parents of TD children [64, 65], we found that mothers of the group ASD + AD reported higher PSI-SF scores than the AD group. Together with mothers and fathers, the ASD + AD group showed higher significantly GSI scores than the AD group, and only for fathers also compared to the ASD group. Similar to this result, a longitudinal study demonstrated that mothers of adolescents with ASD experienced levels of depression, anger, and anxiety well above mothers of adolescents with TD [66]. In addition, Bolte and collaborators [67] reported higher GSI scores of ASD parents regarding schizoid traits and depressive symptoms than GSI scores parents of subjects with other psychiatric disorders.
According to the results and in line with current evidence, we believe that mental health practitioners should evaluate the complex psychopathological relation between ASD and other co-occurring disorders, the impairment of quality of life in terms of functioning in social, scholastic, and family contexts of children and adolescents with ASD as well as their families. Future studies should focus on researching comorbid psychiatric features present in ASD children and adolescents, investigating general psychopathology, and exploring possible forms of PPD.

4.1 Strengths and limitations

One of the strengths of this study is to have examined anxiety symptoms in children and adolescents with ASD, identifying the presence of specific clinical features characterizing a comorbid phenotype ASD + AD, using a 'gold standard' instrument for the assessment of psychiatric disorders (K-SADS-PL DSM-5). Moreover, we examined the level of global functioning using tools based on the clinician's judgment (C-GAS).

Moreover, to our knowledge, this is first study that investigates the clinical characteristics of a comorbid phenotype ASD + AD and also analyzes the presence of PPD. As suggested by Yorke et al. the heightened rates of psychopathology in children with ASD in addition to the increase in PPD rates in their families identifies the need to investigate their association. Moreover heightened levels of PPD seem to minimize the effectiveness of early interventions in ASD [16, 17]. Investigating these aspects is essential to define a global care scheme, with the cooperation of anyone who is engaged in, or involved with ASD children and adolescents, as recommended by the Guidelines (LG21 ISS) [68].

This study also has several limitations. Firstly, the sample studied comprises a small number of participants. Therefore, we believe that expanding the study population is necessary to confirm the present data, which can be interpreted as preliminary results.

Secondly, the study participants recruited have average IQ. If this choice allowed us to exclude characteristics dependent on other comorbidities, on the other hand, it does not represent a significant percentage of ASD children and adolescents. Therefore, specific studies on IQ-impaired samples are necessary.

Finally, we used child and parent-report questionnaires to examine social communication impairment, parental stress, anxiety, and depressive symptoms. To straight the results, we associate the use of K-SADS-PL DSM-5, based on clinical judgment.

5. Conclusion

According to the current literature evidence and the results of our study, we believe that the assessment of ASD in children and adolescents should focus on the early recognition of ASD symptoms, the investigation of psychiatric comorbidities and global functional impairment, in addition to searching of
parental psychopathological distress. In this way, it could be possible to plan a tailored-made intervention based on the child's characteristics and involving parents and caregivers.

Moreover, based on our findings that anxiety disorders similarly manifested in ASD children and adolescents compared to TD children and adolescents, we believe that a specific treatment based on cognitive-behavioral therapy (CBT) with exposure and response prevention (ERP) paradigm could be an effective intervention strategy to reduce functional impairment [69].

**Abbreviations**

AD  
Anxiety Disorder  
ADDM  
Autism and Developmental Disabilities Monitoring  
ADHD  
Attention Deficit Hyperactivity Disorder  
ADI-R  
Autism Diagnostic Interview-Revised  
ASD  
Autismo Spectrum Disorder  
ATN  
Health Anxiety Workgroup  
BASC-2  
Behavioral Assessment System for Children—Second Edition  
CBT  
Cognitive Behavioral Therapy  
CDI – 2  
Children's Depression Inventory-2  
C-GAS  
Children's Global Assessment Scale  
DSM-5  
Diagnostic and Statistical Manual of Mental Disorders. 5th edition  
CAPA  
Child and Adolescent Psychiatric Assessment-Parent Version  
PS  
Parenting Stress  
EBP  
Emotional and Behavioral Problems  
EOS  
Early Onset Schizophrenia  
GSI
Global Severity Index
ID
Intellectual Disability
IQ
Intellectual Quotient
K-SADS-PL DSM-5
Schedule for Affective Disorders and Schizophrenia for School Aged Children Present and Lifetime Version DSM – 5
LG21 ISS
Superior Health Institute Guidelines
MASC – 2
Multidimensional Anxiety Scale for Children-Second Edition
OCD
Obsessive–Compulsive Disorder
ODD
Oppositional Defiant Disorder
PPD
Parental Psychological Distress
PRI
Perceptual Reasoning Index
PSI
Processing Speed Index
PSI-SF
Parenting Stress Index-Short Form
SCL-90-R
Symptom Checklist 90-Revised
SCQ
Social Communication Questionnaire
SPSS IBM
Statistical Package for Social Science IBM
TD
Typical Development
VCI
Verbal Comprehension Index
WISC-IV
Wechsler Intelligence Scale for Children
WMI
Working Memory Index

Declarations
Ethics approval and consent to participate: The study was approved by Ethics Committee of the Children's Hospital. All participants and their parents/legal guardians provided written informed assent and consent.

Consent for publication: Not applicable

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Authors' contributions: SG and MP have made substantial contributions to the conception and design of the work. MCT, CDV, DB, EN and GV contributed to the acquisition, analysis and interpretation of data. SG and MP wrote the manuscript. SG, MP, GV and SV contributed to the revision of the final version of the manuscript and supervised the project. All listed Authors have approved the submitted version of the manuscript.

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Tables

Table 1. Socio-demographic and Psychiatry assessment data score separately for three groups
| Variable                        | Group 1                        | Group 2                        | Group 3                        | p-Value   |
|--------------------------------|-------------------------------|-------------------------------|-------------------------------|-----------|
| **Group 1**                    | ASD+AD                        | AD                            | ASD                           |           |
| N = 21                         | N = 31                         | N = 23                        |                               |           |
| **Mean (SD)**                  | Mean (SD)                     | Mean (SD)                     | Mean (SD)                     |           |
| Age (years)                    | 11.9 (2.4)                     | 11.9 (2.2)                     | 11.6 (2.3)                    | .6637     |
| IQ level                       | 96.7 (15.0)                    | 104.6 (12.5)                   | 98.7 (17.4)                   | .1353     |
| SCQ total                      | 12.9 (6.6)                     | 4.2 (2.8)                      | 12.1 (9.3)                    | **.0000***|
| ADOS 2 total                   | 5.1 (1.5)                      | 5.5 (1.7)                      |                               | .3822     |
| *ADOS 2: social affect*        | 5.4 (1.6)                      | 5.5 (1.9)                      |                               | .8569     |
| *ADOS 2: restricted/ repetitive behaviors* | 5.7 (2.1) | 5.8 (2.6) | .8254 |
| C-GAS                          | 41.7 (3.6)                     | 56.6 (4.0)                     | 48.7 (7.7)                    | **.0000***|
| MASC 2-self total             | 60.6 (13.7)                    | 58.1 (12.7)                    | 54.5 (9.6)                    | .247      |
| MASC 2-parent total           | 78.7 (17.6)                    | 66.2 (14.7)                    | 57.2 (14.6)                   | **.0000***|
| CDI 2-self total              | 72.9 (5.3)                     | 52.8 (7.9)                     | 45.2 (5.4)                    | **.0000***|
| CDI 2-parent total            | 67.8 (13.4)                    | 57.1 (11.1)                    | 54.7 (8.8)                    | **.0000***|

*< .05

IQ: intelligence quotient; SCQ: Social Communication Questionnaire; ADOS 2: Autism Diagnostic Observation Schedule-Second Edition; C-GAS: Children’s Global Assessment Scale; MASC 2: Multidimensional Anxiety Scale for Children-Second Edition, self-report and parent version; CDI 2: Children's Depression Inventory-Second Edition, self-report and parent version.*< .05

Table 2. Comparison between the three groups in parent assessment score separately for mothers and fathers.
| Variable | MOTHERS | | | MOTHERS | | | FATHERS | | | FATHERS |
|----------|---------|---|---|---------|---|---|---------|---|---|---------|---|---|
|          | Group 1 | Group 2 | Group 3 | p-Value | Group 1 | Group 2 | Group 3 | p-Value |
| ASD+AD   | N = 21  | N = 31  | N = 23  |         | N = 21  | N = 31  | N = 23  |         |
| Mean (SD)| Mean (SD) | Mean (SD) |         | Mean (SD) | Mean (SD) | Mean (SD) |         |
| PSI-FS Total | 85.57 (24.19) | 62.58 (23.76) | 70.61 (26.27) | .006* | 65.95 (24.47) | 63.06 (21.20) | 51.52 (26.30) | .101 |
| SCL-90 GSI | 59.34 (13.23) | 46.93 (7.40) | 54.13 (16.06) | .002* | 60.29 (17.64) | 47.55 (7.94) | 46.35 (9.12) | .001* |

* < .05

PSI-SF: Parenting Stress Index-Short Form; SCL-90-R: Symptom Checklist 90-Revised.

**Supplementary Files**

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