初診時うつ状態の成人患者の中から自閉症スペクトラム障害患者を見出すために診断の参考となる臨床指標について

Autism spectrum disorder among first-visit depressed adult patients: Diagnostic clues from backgrounds and past history

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Abstract

Objective: The present study aimed to extract discriminating indicators for diagnosis of autism spectrum disorder (ASD) from personal backgrounds and past history among depressed adult outpatients.

Methods: Subjects were 430 depressed adults, consisting of patients with ASD (n=70) and those without ASD (n=360). Group comparison and discriminant analysis was conducted with regard to backgrounds (age, gender, education, marriage, living alone, physical diseases and family history of mood disorders) and past history (school non-attendance, bullied experience, psychotic-like experiences, conduct problems, suicide-related behaviors and interpersonal friction).

Results: Six discriminating indicators (interpersonal friction, bullied experience, psychotic-like experiences, age under 32 years, school non-attendance and university educational level) were identified by stepwise discriminant analysis ($P<0.001$). Absence of the first 4 indicators almost excluded ASD diagnosis with the highest negative predictive value (98%) and the least negative likelihood ratio (0.11) whereas one or more out of these 4 indicators showed low positive predictive value (32%) despite high sensitivity (93%).

Conclusions: Abovementioned 4 indicators may be useful clues to cover possible ASD subjects among depressed adults although further detailed ASD focused diagnostic procedure is absolutely necessary to specify true ASD subjects. Meanwhile, absence of these 4 indicators is probably helpful to rule out ASD diagnosis.

1. Introduction

Autism spectrum disorders (ASDs), known as pervasive developmental disorders in the DSM-Ⅳ-TR [1], are characterized by qualitative impairments in communication, reciprocal social interaction and the presence of restricted and repetitive behaviours or interests. ASDs include Autistic disorder, Asperger's disorder and pervasive developmental disorder not otherwise specified (PDD-NOS) according to the DSM-IV-TR. Autistic disorder is defined the presence of above symptoms and onset of symptoms prior to 3 years. Asperger's disorder is distinguished from Autistic disorder by the lack of delay or deviance in early language development, and does not have clinically significant delays in cognitive development. PDD-NOS does not meet full criteria for either Autistic disorder or Asperger's disorder, but with pervasive deficit in social interaction.

Recently, the prevalence of ASD in adults was estimated to be 0.98% [2], which is almost similar to that found in children [3]. Thus, ASD has nowadays become a more common disorder than previously recognized.

Strang et al. [4] indicated that children and adolescents suffering from ASD even with normal intelligence were at greater risk for depression than those in general population. In ASD adults with normal intelligence, Hofvander et al. [5] reported that the most common life-time comorbidity was mood disorder (53%) (median age of subjects was 29 years). Also, Lugnegård et al. [6] reported that the most common life-time comorbidity was major depression (70%) (mean age of subjects was 27 years). In contrast, the prevalence of life-time major depressive disorder from 18 to 29 years was 12.0% in the United States [7]. In the International Consortium of Psychiatric Epidemiology Surveys, lifetime prevalence of major depressive episodes was from

3.0% in Japan to 16.9% in the US [8]. For these reasons, general psychiatrists might encounter many depressed adult outpatients with ASD in usual clinical settings. Early diagnosis of ASD can help promoting non-pharmacological treatment strategies (psychoeducation, social skills training and environmental rearrangements) especially in workers suffering from ASD with comorbid depressive state. However, less attention to these supports may sometimes mislead to miserable consequences, e.g., prolonged depressive episodes, frequent relapse, development of further comorbidities like anxiety disorders, failed rehabilitation, job loss and social withdrawal. Therefore, it is important for clinicians to know some clues, always prompting them to interview for possible diagnosis of ASD when seeing depressed adult outpatients.

However, mild psychopathology of ASD tends to be easily missed or often masked by prominent depressive symptomatology. In particular, fatigue and psychomotor retardation associated with depression can mask such symptoms as social withdrawal and abnormal speech patterns of ASD [9]. Furthermore, ASD adults suffering from depressive symptoms rather showed higher cognitive ability and less social impairment than those without depressive symptoms [10]. Therefore, it is often difficult for clinicians to find out modest autistic traits in depressed ASD patients with high social functioning. In addition, it is also difficult for adult patients to precisely describe their childhood developmental history whereas clinicians cannot timely obtain such information from their parents who do not necessarily preserve old memory as accurate.

Accordingly, simple and useful discriminating indicators for potential ASD, based on the patient’s backgrounds and past history, are highly expected before initiating detailed diagnostic interview for ASD. It is more desirable that these indicators can be easily asked by clinicians. Thus, the objective of this study is to

clarify clinical indicators to pick up patients with ASD among the overall depressed adult outpatients in usual clinical settings.

2. Methods

2.1. Subjects

We conducted a case-control study in a retrospective manner to extract discriminating indicators for diagnosis of ASD. Subjects were depressed adult outpatients without apparent intellectual problems, i. e., receiving mainstream education, who newly visited our clinic from January 2009 to December 2012. Their age ranged from 18 to 87 years. Their final diagnosis was confirmed in January 2014. Among 483 depressed patients who were collected from the medical records, 53 patients (9% of total) did not have precise description of their backgrounds and personal history, and thereafter were excluded from the study as missing data. Ultimately, we extracted 430 depressed outpatients, whose mean age (±Standard Deviation) was 40.4 (±14.7) years and proportion of females was 60%. These depressed patients included the patients with adjustment disorder (n=89), major depressive disorder (n=215) and bipolar disorder (n=126).

2.2. Diagnostic procedure of ASD subjects

Axis-I psychiatric morbidity was assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [11]. Although psychotic symptoms such as hallucinations and delusions were noted separately during the SCID-I interview, there were no patients fulfilling the sufficient criteria for the diagnosis of schizophrenia and other psychotic disorder. DSM-IV-TR criteria was used for

diagnosis of ASD. Developmental history in ASD subjects was confirmed from their parents by the psychiatrists who were qualified as Certified Supervising Psychiatrist of the Japanese Board of Psychiatry, and were in charge of outpatient clinic for both child-adolescent and adult psychiatry. Parents were requested to bring suitable records (maternal and children health handbook, school reports in primary and middle school) as references. The criteria for the allocation to the ASD group were the Autism-Spectrum Quotient Score of at least 26, explained in the next section, and a confirmation of diagnosis in an expert interview. Among 430 depressed subjects, 70 subjects were diagnosed as ASD (ASD group).

2.3. Assessment the autistic traits of ASD subjects

We assessed the autistic traits of ASD subjects by the Japanese version of Autism-Spectrum Quotient (AQ-J) [12]. The original version of AQ is 50-item self-administered questionnaire for adults with normal intelligence to assess the presence of autistic traits, which consists of five domains such as social skill, attention switching, attention to detail, communication and imagination [13]. The AQ score ranges from 0 to 50, and the higher AQ score indicates higher autistic tendency. Although AQ is not a diagnostic tool, it is a useful screening tool [14]. For AQ-J, its most optimal cut-off score for distinguishing ASD from non-ASD subjects was 26 or more, with modest sensitivity (0.76)/specificity (0.71), low positive predictive value (0.24) and high negative predictive value (0.96) [12].

2.4. Backgrounds and past history for analyses

As the candidates for discriminating indicators of ASD, the following factors were selected from various studies. These were patients' backgrounds (age, gender,

education level, marital history, living alone, physical diseases [15,16] and family history of mood disorders [17]), age of onset for psychiatric comorbidity, and past history affecting social function and adjustment (school non-attendance [18-20], bullied experience [21-23], psychotic-like experiences [6,24,25], conduct problems [26,27], suicide-related behaviors [24,28] and interpersonal friction at work/school [29]). These variables can be easily asked by clinicians without information from parents of the patients. Presence or absence of these variables were confirmed by simply answering either 'yes' or 'no' by patients. For bullied experience, we asked such questions like "Have you ever been bullied during your school days? For example, being frequently targeted or routinely harassed in any way? ". For interpersonal friction at work/school, we asked questions like "Have you ever experienced interpersonal problems at work/school? For example, having a quarrel or an interpersonal conflict with colleague or your boss? ".

2.5. Statistical analyses

Abovementioned variables were compared between depressed subjects with ASD and those without ASD. Comparisons (Table 1) were made by using the Mann-Whitney U-test (for continuous variables), the Chi-squared test (for categorical variables) or Fischer's exact test (when one of the expected values in a 2×2 tables is less than 5). The step-wise discriminant analysis with Maha-lanobis' distance measure (Table 2) was performed to reveal possible contributing factors for ASD diagnosis among the overall depressed subjects. The best cut-off point for ASD diagnosis when using significant discriminators (Table 3) were examined by calculating the area under the curve (AUC) of the receiver operating characteristic (ROC) curve. An AUC > 0.7 is generally considered an acceptable test performance [30]. The optimal cut-off

point was calculated as the best balance in a trade-off between sensitivity and specificity, using maximal values derived from the Youden Index, i. e., sensitivity+specificity-1 [31].

SPSS 19.0 for Windows (SPSS Japan, Tokyo, Japan) and XLSTAT version 2014. 1 (Addinsoft, Tokyo, Japan) were used for the statistical analyses. A two-tailed *P* value less than 0.05 was regarded as statistically significant.

2.6. Ethics

We had informed the patients of anonymous inclusion of our ASD subjects in this retrospective study and the data analyses as coded and grouped on the website of our department, together with information that the study was approved by the Ethics Committee of the University of the Ryukyus. These also included the sentence that the participants could withdraw from this study without any penalty or loss of benefits for their treatments, although no patients refused to participate in this study.

3. **Results**

3.1. Diagnostic profiles of ASD subjects

Seventy (16%) out of 430 total depressed adults were diagnosed as ASD. Among these 70 subjects with ASD, the majority was 45 subjects diagnosed as PDD-NOS (64%) while 6 subjects were diagnosed as autistic disorder (9%) and 19 subjects as Asperger's disorder (27%). Incidentally, 6 subjects with Autistic disorder showed onset of symptoms prior 3 years old, although had not visited medical specialists until adulthood. Because their parents did not recognize the necessity of support.

Mean score of total AQ was 31.5±6.1 (range: 26-43).

Diagnoses of the comorbidity as adjustment disorder, major depressive disorder and bipolar disorder were 33 cases (47%), 21 cases (30%) and 16 cases (23%) in the 70 ASD subjects whereas respective values were 56 (15%), 194 (54%) and 110 (31%) in the 360 non-ASD subjects. Significant findings were greater comorbidity with adjustment disorder in the ASD group in contrast to greater comorbidity with major depressive disorder and bipolar disorders in the non-ASD group (Chi-square=36.1, df=2: $P<0.001$).

3.2. Comparison between ASD and non-ASD subjects

Clinical backgrounds (age of the first visit, gender, education level, marital history, living alone, physical diseases, family history of mood disorders), age of onset for psychiatric comorbidity, and past history affecting social function/adjustment (school non-attendance, bullied experience, psychotic-like experiences, conduct problems, suicide-related behaviors, interpersonal friction at work/school) were compared between ASD and non-ASD subjects (Table 1).

Age of the first visit in the ASD group (30.2±10.1) was younger (U=6207.0, $P<0.001$) than that of the non-ASD group (42.4±14.6). Also, the age of onset for psychiatric comorbidity (mood problems) in the ASD group (27.4±9.7) was younger (U=6377.0, $P<0.001$) than that of the non-ASD group (38.9±14.7). The ASD group had less marital history (36% vs. 71%: Chi-square=32.4, df=1, $P<0.001$) and less physical diseases (4% vs. 18%: $P=0.006$). Additionally, we calculated partial correlation between ASD and marital history or physical diseases after controlling age and gender factors. Marital history was negatively correlated with the presence of ASD, but the relation was weak (partial correlation coefficient r = -0.120, $P=0.013$).

Meanwhile, the presence of ASD was not related to physical diseases (r = -0.032, *P*=0.503).

Regarding past history of maladaptation and mental health problems, the ASD group was significantly characterized by more episodes of school non-attendance (23% vs. 4%: Chi-square=32.5, df=1, *P*<0.001), bullied experience (37% vs. 6%: Chi-square=59.0, df=1, *P*<0.001), psychotic-like experiences (24% vs. 3%: Chi-square=46.1, df=1, *P*<0.001), suicide-related behaviors (24% vs. 13%: Chi-square=5.8, df=1, *P*=0.019) and interpersonal friction at work/school (37% vs. 8%: Chi-square=46.0, df=1, *P*<0.001).

3.3. Discriminators for ASD diagnosis

Among abovementioned 13 variables, the following 6 significant discriminating indicators for diagnosis of ASD were identified by stepwise discriminant analysis (Table 2), i.e., interpersonal friction at work/school (standardized canonical discriminant function coefficient: 0.578), bullied experience (0.471), psychotic-like experiences (0.465), age of the first visit (-0.353), school non-attendance (0.253) and educational level (0.201). Canonical correlation was 0.594, and the obtained value of Wilks' lambda 0.642, which was significant at *P*<0.001 (Chi-square = 188.4, df = 6).

By calculating the AUC and the Youden Index for age of the first visit, we found that younger than 32 years was the optimal cut-off for ASD subjects (AUC=0.754, *P*<0.001; sensitivity=0.66, specificity=0.73, positive predictive value=0.32, negative predictive value=0.92). Accidentally, on the AUC and the Youden Index for onset age, we found that younger than 32 years was the optimal cut-off for ASD subjects (AUC=0.747, *P*<0.001; sensitivity=0.81, specificity=0.64, positive predictive value=0.31, negative predictive value=0.95).

3.4. Scoring using discriminators

Various scoring methods using aforementioned 6 discriminators and their combinations were analysed from aspects of their sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood and negative likelihood (Table 3).

Among all of the scoring systems, absence of the first 4 indicators (interpersonal friction at work/school, bullied experience, psychotic-like experiences and age under 32 years) almost excluded ASD diagnosis with the highest negative predictive value (98%) and the least negative likelihood ratio (0.11) whereas one or more out of the 4 indicators showed relatively low positive predictive value (32%) despite the highest sensitivity (93%), as shown in Table 3.

4. Discussion

4.1. Depressed ASD subjects in depressed adults

The present study revealed clinical reality that the rate of ASD subjects was 16% in the first-visit depressed adults, and that the majority (64%) was diagnosed as PDD-NOS in the ASD group. This fact suggests that one-sixth of depressed adults may have ASD and one-tenth may have PDD-NOS by a rough estimation. Depressed state in ASD subjects often seems situational or reactive rather than endogenous because nearly a half cases with ASD (47%) were comorbid with adjustment disorder in this study. These results were consist with a previous study by Kato et al. [32], which showed that 7.3% out of depressed suicide attempters were diagnosed as ASD, and that the diagnosis as adjustment disorder was more common in the ASD group than in non-ASD group (70.0% versus 41.5%).

More importantly, most of the first-visit ASD subjects as well as their surroundings have not been aware of their autistic traits, suggesting that clinicians should make sure of definite diagnosis for ASD and must cautiously inform them of ASD diagnosis. Furthermore, clinicians should prepare not only pharmacotherapy but also psychosocial intervention targeting ASD profiles. Fombonne [33] argued that the needs of treatment for the individuals even with PDD-NOS are as important as those with autistic disorder.

4.2. High rate of PDD-NOS in the ASD group

In the ASD group, majority (64%) was diagnosed as PDD-NOS in this study. In ASDs, the rate of PDD-NOS is approximately 57% [34]. Additionally, Kim et al. [35] showed that the ratio of autistic disorder to other ASD subtypes in the mainstream school sample was much lower than in the disability registry, special education school and regular school who had psychiatric service use (1:2.6 versus 2.6:1). Furthermore, Lugnegård et al. [6] argued that more subtle social impairment of autistic traits led to a delayed diagnosis, and resulted in lost opportunity of early intervention and increased risk of future depression or anxiety. Besides, PDD-NOS, which includes atypical autism [1], has heterogeneous features, i.e., social and communication impairment without repetitive and stereotyped behaviors [36]. Some studies have indicated that the patients with high-functioning variants of ASD often run unrecognized until late in adult life [37, 38]. For these reasons, high rate of PDD-NOS in the ASD group was as a clinical reality in the present study.

4.3. Backgrounds related to ASD (age, education, marital history and physical diseases)

Depressed subjects with ASD visited our clinic at younger age than those without ASD. Also, the onset of the depressive episodes was younger in the ASD group than in the non-ASD group, in the present study (Table 1). As mentioned above, this may be partly explained by the fact that late-onset endogenous depression was less frequently observed as comorbid depressed state in ASD subjects than in non-ASD subjects. Meanwhile, it is also suggested that patients with atypical or mild autistic traits without knowing the cause and coping strategy may have been suffering from interpersonal problems, experience of isolation and maladaptation to society for a long term since their childhood, which leading to lowered self-esteem and failure in accessing support from others after becoming adults [39]. Therefore, inherent vulnerability in individuals with ASD and unfavorable psycho-social consequences may result in an early onset of adjustment disorder with depressed mood in their young adulthood compared to individuals without ASD.

In the present study, depressed subjects without apparent intellectual problems were collected. Although there was no significant difference in the educational levels between ASD and non-ASD subjects (Table 1), high educational level (university or upper) was shown to be a weak discriminating indicator for ASD diagnosis (Table 2). For ASD individuals, intelligence may increase awareness of their own social difficulties [40,41]. In addition, it has been also reported that depressed group rather showed higher intelligence and fewer autistic traits than non-depressed group [10]. Therefore, subjects with high educational level and mild ASD may be at higher risk of depression probably because of stressful over-adaptation beyond their social/communication capability and anxiety from their lowered self-esteem and interpersonal hypersensitivity.

Fewer marital history may be at least partly associated with the presence of ASD, since the correlation was still significant after controlling age and gender. This can be explained by poor interpersonal communication, little interest in seeking close relationship and avoidance of social situations in ASD subjects. On the other hand, fewer physical diseases were regarded to be unrelated to the presence of ASD in the present study.

4.4. Past history related to ASD (school non-attendance, bullied experience, psychotic-like experiences, suicide-related behaviors and interpersonal friction)

Adaptation to school life is the first experience stepping forward to consecutive process of social adjustment. However, the rate of school non-attendance for children/adolescents with ASD was relatively high (13.8-27.3%) in Japan [19,20]. The present study also clearly showed that the rate of school non-attendance in subjects with ASD was higher than in those without ASD (23% vs. 4%: Table 1). Egger et al. [42] reported that school refusal was associated with depression and separation anxiety disorder, which may easily lead to lowered self-esteem and anxiety for social adaptation in the future. Therefore, it is suggested that an early failure in adjustment as school non-attendance is regarded as a potential risk for vulnerability to future development of depressive reaction even after becoming adults.

Bullied experience is closely related to and is often causative of school non-attendance in ASD children. The overall prevalence of peer victimization in children with Asperger's disorder ranged from 77% to 94% according to the reports from their mothers [21,22]. Also, the 95% of respondents with adolescents and adults with Asperger's disorder living in the community reported their past history of bullied experience [23]. In the present study, the rate of bullied experience was apparently

higher in ASD subjects than in non-ASD subjects (37% vs. 6%: Table 1), but was relatively lower than those in abovementioned previous studies [21-23]. Passivity and introversion in mild autistic traits with high intelligence and functioning may keep our ASD subjects away from serious victimization. However, it is surprising that symptomatology of ASD is rather negatively correlated with the victimization measures [43]. This fact may imply that bullied experience is not rare even among mild ASD. Zablotsky et al. [44] suggested that children with ASD attending public schools were at an increased risk of experiencing victimization. Therefore, past bullied experience seems to be an important discriminating indicator for ASD diagnosis irrespective of the severity of ASD.

It has been pointed out that children with early autistic traits had a greater risk of developing psychotic experiences [45]. De Bruin et al. [46] reported that 8.6% of PDD-NOS children, who did not fulfill the criteria for schizophrenia, had psychotic symptoms such as delusions or hallucinations. Also, Mouridsen et al. [47] reported that 28.1% of subjects with atypical autism were diagnosed as schizophrenia at least one time in the follow-up study period. In the present study, past history of psychotic-like experiences was more frequently observed in ASD subjects (24% vs. 3%: Table 1). It has been also suggested that autism and schizophrenia are referred to as early and late onset neurodevelopmental disorders with common pathophysiology in late years [48-50]. Therefore, the past history of psychotic-like experiences may be characteristic of ASD subjects, and these findings may justify usefulness of psychotic-like experiences in distinguishing depressed patients with mild ASD from those without non-ASD.

Suicide-related behavior cannot be overlooked in adults with high functioning ASD than is generally recognized. Balfe et al. [23] reported that 15% of adolescents

and adults with Asperger's disorder living in the community had attempted suicide. Also, Billstedt et al. [27] reported that a half of individuals with autism disorder or atypical autism had engaged in moderate or severe degrees of self-injurious behaviours at some point throughout their life in the follow-up study for 13–22 years. Therefore, the point and cumulative incidences of suicide-related behaviors seem relatively high from both cross-sectional and longitudinal aspects. The present study also proved higher incidence of past suicide-related behavior in ASD subjects than in non-ASD subjects (24% vs. 13%: Table 1). Low self-esteem, aloneness, interpersonal problems and social failure have been regarded as plausible promoters for such risky behaviors [24] as well as cognitive inflexibility and difficulty identifying feelings of distress in depressed ASD subjects [51,52]. It might be warned of that ASD subjects at suicidal risk may more easily tend to take action (attempting or committing) rather than to remain ideation (thinking or planning), compared with non-ASD subjects at similar risk.

The experiences of interpersonal friction at work/school as the social maladaptation were more often observed in ASD subjects than in non-ASD subjects in the present study (37% vs. 8%: Table 1). Employment consultants and service coordinators have pointed out the problems of the persons with ASD at work, such as communication difficulties, socially inappropriate behaviours, difficulties in adapting to changeable situations, poor hygiene, poor coping with multiple tasks and low productivity [53]. Holwerda et al. [54] have suggested that these behaviors in ASD subjects often cause conflicting relationship with their fellow employees, thereafter sometimes leading to job loss by firing. Although ASD subjects feel many difficulties at work or in school life [55], mainstream support like sympathetic response, general persuasion or encouragement is not necessarily suitable for ASD subjects while

surrounding supporters never know how to educate and instruct maladapted ASD subjects [56]. It should be emphasized that interpersonal friction at work/school is characteristic indicators for ASD, when considering its highest correlation coefficient determined by discriminant analysis in the present study (Table 2).

4.5. Screening of ASD by backgrounds and past history

Six discriminating indicators (interpersonal friction, bullied experience, psychotic-like experiences, age under 32 years, school non-attendance and university educational level) were identified by stepwise discriminant analysis in the present study (Table 2). These factors are suggested to be possible candidates for differential diagnosis of depression with ASD from that without ASD in usual clinical setting. However, scoring system using these indicators and their combinations revealed insufficient positive predictive values for prediction of ASD diagnosis (Table 3). We do not have any rational explanation for these negative results. It is also suggested that correct diagnosis of ASD cannot be obtained only from patient's backgrounds and past history, but needs detailed interview process to clarify characteristics of ASD by experts.

On the other hand, absence of the first 4 indicators (interpersonal friction, bullied experience, psychotic-like experiences and age under 32 years) can be used for exclusion diagnosis of ASD because of its highest negative predictive value (98%) and the least negative likelihood ratio (0.11), as shown in Table 3. In contrast, positive predictive value remained to be only 32 % using abovementioned factors although the presence of one or more factors out of these 4 indicators covered 93% of ASD subjects. Therefore, if clinicians find at least one of these characteristic factors from

personal backgrounds and past history, further detailed ASD-focused diagnostic procedure is highly recommended to specify true ASD subjects as the next step.

4.6. Limitations

The present study has some limitations as follows. First, we could not cover whole subjects because some defect data existed due to the retrospective study design. Second, there was imbalance in number of subjects between ASD and non-ASD subjects in this naturalistic study. Third, use of ADOS and ADI-R, which have not been yet fully available for any clinicians or researchers in Japan, may have been needed to guarantee further correctness of ASD diagnosis in the present study. Forth, we did not assess the severity of depression and intelligence by adequate assessment tools. Fifth, investigated variables from the past behavioral problems and maladjustment may not have been fully comprehensive. Sixth, positive predictive value for ASD diagnosis remaining insufficient level by using combined discriminating factors in the present study.

5. Conclusions

Among the first-visit depressed adults, 16% were diagnosed as ASD. From personal backgrounds and past history, ASD subjects were characterized by interpersonal friction at work/school, bullied experience, psychotic-like experiences, age under 32 years, school non-attendance and university educational level. Among these possible discriminating indicators, the first 4 factors (interpersonal friction at work/school, bullied experience, psychotic-like experiences and age under 32 years) cover most of ASD subjects among depressed adults although further detailed ASD-focused diagnostic procedure is absolutely necessary to specify true ASD subjects.

Meanwhile, absence of these 4 indicators is probably helpful to rule out ASD diagnosis.

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Table 1

Group comparisons of personal backgrounds and past history between subjects with ASD and those without disorder

Comorbidity		**Adjustment disorder** (n = 89)		**Major depressive disorder** (n = 215)		**Bipolar disorder** (n = 126)		**Total** (n = 430)		
		ASD (n = 33)	non-ASD (n = 56)	ASD (n = 21)	non-ASD (n = 194)	ASD (n = 16)	non-ASD (n = 110)	ASD (n = 70)	non-ASD (n = 360)	p
Age										
The first visit (years)	Mean	32.1	37.1	28.7	45.1	28.3	40.2	30.2	42.4	< 0.001
	SD	11.2	13.0	8.9	15.1	8.9	13.3	10.1	14.6	
	range	18-55	18-63	19-55	20-87	18-51	18-77	18-55	18-87	
Age of onset for psychiatric comorbidity (years)	Mean	31.0	36.6	25.3	42.3	22.6	34.1	27.4	38.9	< 0.001
	SD	11.0	12.8	8.0	15.3	6.1	13.0	9.7	14.7	
	range	17-54	17-62	15-55	17-87	13-31	15-71	13-55	15-87	
		n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	
Female gender		15 (45)	35 (63)	14 (67)	102 (64)	6 (38)	64 (64)	35 (50)	225 (63)	0.059
Educational level										
University or upper		13 (39)	23 (41)	10 (48)	81 (42)	12 (75)	43 (39)	35 (50)	147 (41)	0.156
High school or lower		20 (61)	33 (59)	11 (52)	113 (58)	4 (25)	67 (61)	35 (50)	213 (59)	
Marital history		14 (42)	42 (75)	7 (33)	144 (74)	4 (25)	70 (64)	25 (36)	256 (71)	< 0.001
Living alone		7 (21)	7 (13)	7 (33)	33 (17)	1 (6)	25 (23)	15 (21)	65 (18)	0.507
Physical diseases		2 (6)	9 (16)	0 (0)	43 (22)	1 (6)	11 (10)	3 (4)	63 (18)	0.006
Family history of mood disorders		6 (18)	6 (11)	3 (14)	31 (16)	2 (13)	16 (15)	11 (16)	53 (15)	0.831
School non-attendance		8 (24)	4 (8)	4 (19)	5 (3)	4 (25)	5 (5)	16 (23)	14 (4)	< 0.001
Bullied experience		12 (36)	5 (9)	7 (33)	11 (6)	7 (44)	5 (5)	26 (37)	21 (6)	< 0.001
Psychotic-like experiences		7 (21)	0 (0)	6 (29)	6 (3)	4 (25)	4 (4)	17 (24)	10 (3)	< 0.001
Conduct problems		1 (3)	3 (5)	1 (5)	0 (0)	0 (0)	3 (3)	2 (3)	6 (2)	0.622
Suicide-related behaviors		5 (15)	8 (14)	9 (43)	22 (11)	3 (19)	17 (15)	17 (24)	47 (13)	0.016
Interpersonal friction at work/school		17 (52)	4 (7)	6 (29)	10 (5)	3 (19)	14 (13)	26 (37)	28 (8)	< 0.001

Table 2

Discriminating indicators for ASD diagnosis from depressed adult subjects

Selected discriminating indicators by stepwise discriminant analysis	Standardized canonical discriminant function coefficients
Interpersonal friction at work/school	0.578
Bullied experience	0.471
Psychotic-like experiences	0.465
Age of the first visit	- 0.353
School non-attendance	0.253
High educational level (university or upper)	0.201

Above 6 significant discriminating indicators for ASD diagnosis were selected by stepwise discriminant analysis from 13 variables listed in Table 1. Canonical correlation was 0.598. Wilks' lambda (0.642) was significant at $P<0.001$ (Chi-square = 188.4, df = 6).

Table 3

Screening of ASD subjects from the overall depressed adults by the cut off scores for the 6 discriminators and their combinations

Indicators	The best cut-off	Sensitivity	Specificity	PPV	NPV	Youden Index	+LR	-LR
①Interpersonal friction at work/school	1	0.37	0.92	0.48	0.88	0.29	4.78	0.68
②Bullied experience	1	0.37	0.94	0.55	0.89	0.31	6.37	0.67
③Psychotic-like experiences	1	0.24	0.97	0.63	0.89	0.21	8.74	0.78
④Age of the first visit	< 32	0.66	0.73	0.32	0.92	0.39	2.41	0.47
⑤School non-attendance	1	0.23	0.96	0.53	0.87	0.19	5.89	0.80
⑥High educational level (university or upper)	1	0.50	0.59	0.19	0.86	0.09	1.22	0.85
①+②	≥1	0.66	0.87	0.49	0.93	0.53	5.03	0.39
①+②+③	≥1	0.74	0.84	0.48	0.94	0.58	4.78	0.30
①+②+③+④	**≥1**	**0.93**	**0.62**	**0.32**	**0.98**	**0.55**	**2.46**	**0.11**
①+②+③+④+⑤	≥2	0.63	0.92	0.61	0.93	0.55	8.08	0.40
①+②+③+④+⑤+⑥	≥2	0.80	0.79	0.43	0.95	0.59	3.89	0.25

PPV = positive predictive value; NPV = negative predictive value; +LR = positive likelihood ratio; -LR = negative likelihood ratio.

The best cut-off was determined by the maximal Youden index.