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Research report

High prevalence of bipolar disorder comorbidity in adolescents and young adults with high-functioning autism spectrum disorder: A preliminary study of 44 outpatients

T. Munesue *, Y. Ono, K. Mutoh, K. Shimoda, H. Nakatani, M. Kikuchi

Department of Neuropsychiatry, Kanazawa University Hospital, Kanazawa, Japan

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Abstract

Background: Psychiatric comorbidity of autism spectrum disorder (ASD) has not been well examined.
Methods: Mood disorders in 44 consecutive outpatients with high-functioning ASD were examined at a university hospital according to DSM-IV. Inclusion criteria were an IQ of 70 or higher on the Wechsler Intelligence Scale and age of 12 years or over.
Results: Sixteen patients (36.4%) were diagnosed with mood disorder. Of these 16 patients, four were diagnosed as having major depressive disorder, two patients as bipolar I disorder, six patients as bipolar II disorder, and four patients as bipolar disorder not otherwise specified. Bipolar disorder accounted for 75% of cases. Twelve patients had Asperger disorder and four patients had pervasive developmental disorder not otherwise specified. None of the patients had autistic disorder.
Limitations: The sample size was small. We could not use Autism Diagnostic Interview – Revised. Referral bias could not be avoided in this study.
Conclusions: The major comorbid mood disorder in patients with high-functioning ASD is bipolar disorder and not major depressive disorder. The autistic spectrum may share common vulnerability genes with the bipolar spectrum.

Keywords: Adolescent; Autism spectrum disorder; Bipolar disorder; Comorbidity; Young adult

1. Introduction

Autism spectrum disorder (ASD) is a diagnostic continuum that comprises autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified. Autistic disorder is a prototypical syndrome and characterized by a clinical triad of symptoms that includes impairment of reciprocal communication, deviant development of language, and repetitive patterns of interests and activities. Asperger disorder is distinguished from autistic disorder by the absence of clinically significant impairment of speech development. Pervasive developmental disorder not otherwise specified is an atypical condition of autistic disorder with subthreshold symptoms or late age at onset according to DSM-IV (American Psychiatric Association, 1994).

Depression is the main psychiatric comorbidity reported in individuals with ASD (Ghaziuddin *et al.*,

* Corresponding author. 13-1, Takaramachi, Kanazawa, Ishikawa 920-8641, Japan. Tel.: +81 76 265 2304; fax: +81 76 234 4254.
E-mail address: munesue@med.kanazawa-u.ac.jp (T. Munesue).

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1992, 1998). According to a review of 17 published cases demonstrating depression (Lainhart and Folstein, 1994), half of the patients were female, the age of onset ranged from childhood to young adulthood, and almost all of the patients were mentally retarded. Although depression may be the most common comorbidity in ASD (Ghaziuddin *et al*., 2002), some cases of bipolar disorder (BP) have been reported (Frazier *et al*., 2002; Gutkovich *et al*., 2007; Komoto *et al*., 1984). For example, 14 of 66 consecutively referred children with ASD demonstrated mania as the comorbid condition (Wozniak *et al*., 1997).

As individuals with ASD, especially those with low intellectual abilities (IQ < 70), have limited verbal communication abilities and inappropriate facial expressions, it remains uncertain whether they are verbalizing their inner experiences, such as sadness or inflated self-esteem, and clinicians may observe depressive or (hypo)manic symptoms from facial expressions or behaviors. In the above studies, the researchers regarded a sad appearance, loss of interest in activities, frequent crying spells, insomnia, and loss of appetite as depressive symptoms, or a cheerful appearance, hyperactivity, pressure of speech, and increased appetite as (hypo)manic symptoms. However, it would be more appropriate to study individuals with ASD who have normal intelligence quotient, *i.e.*, high-functioning abilities (IQ ≥ 70). Such subjects could verbalize inner experiences more appropriately than low-functioning individuals.

From our daily practice at the outpatient clinic, our impressions regarding psychiatric comorbidity in patients with high-functioning ASD were as follows: 1) depressive symptoms were sometimes recognized; 2) hypomanic symptoms were often overlooked and undiagnosed; and 3) high-functioning ASD itself was sometimes unrecognized and undiagnosed in adolescent or young adult patients who sought care for other psychological complaints. The diagnosis of such patients sometimes puzzled clinicians and the patients were frequently diagnosed as having depression, adjustment disorder, and even personality disorder, while ASD was missed.

This study evaluated the comorbidity of mood disorder in adolescents and young adults with high-functioning ASD retrospectively.

2. Methods

2.1. Subjects

The study population was comprised of both patients who were referred to the outpatient clinic of Kanazawa University Hospital, Japan, for evaluation of ASD and patients who sought care at the clinic for psychological complaints, such as school refusal, self-injury, violence, or occupational maladaptation, but were later diagnosed as having ASD in our clinic. Inclusion criteria were as follows: 1) patients who were regularly consulting the outpatient clinic on 28 February 2007; 2) IQ of 70 or over on the Wechsler Intelligence Scale; and 3) an age of 12 years or over on the above day.

Our clinic functions not only as a tertiary care unit but also as a primary or secondary care unit. Individuals with any psychological complaints residing in Kanazawa city and the surrounding area often seek care at the clinic without a letter of referral (annual referral rates have been about only 30% for the last decade). This implies that many patients in our clinic have various complaints rather than complicated complaints. This study was performed in the daily practice at our clinic, and therefore we considered that informed consent was not necessary for the study.

2.2. Assessments

None of the authors was licensed to use the Autism Diagnostic Interview – Revised (Lord *et al*., 1994), recognized world-wide as an instrument to evaluate and diagnose ASD for research. Therefore, when we diagnosed a patient as having ASD in daily clinical setting, it was necessary to evaluate them using alternative means. One of the authors (T. M.) is a skilled child and adolescent psychiatrist, and screened patients suspected of ASD using the Tokyo Autistic Behavior Scale (TABS; Kurita and Miyake, 1990), the High-Functioning Autism Spectrum Screening Questionnaire (ASSQ; Ehlers *et al*., 1999), and the Autism-Spectrum Quotient (AQ; Baron-Cohen *et al*., 2001). All of these are self-rated or caregiver-rated questionnaires for screening ASD. At the initial intake and during subsequent sessions on other days, we analyzed and reassessed each of the answers on these questionnaires by asking patients and caregivers again, then confirmed whether the items of DSM-IV criteria were fulfilled. In Japan, all local public health centers perform health examinations for all children 3 years of age residing in the district served by that center. A diagnosis of Asperger disorder was made if the patients had acquired some communicative phrases at the time of this health examination within their caregiver's recollection.

After patients were diagnosed as having a particular disorder of ASD, they continued to attend our clinic alone or with their caregivers every two or four weeks to receive supportive psychotherapy, medication, or family guidance. If the patients showed mood symptoms during

these sessions, they were further assessed by asking all of the items of DSM-IV criteria of mood disorder. At the initial intake, if previous episodes of mood disorder were reported, we assessed these episodes retrospectively by interviewing the patients or their caregivers.

2.3. Statistics

The demographic and clinical variables were compared between the groups of patients with and without mood disorder. Continuous variables were analyzed using Student's *t*-test and categorical variables were analyzed using Fisher's exact test. Significance was set at a level of 0.05 (two-tailed).

3. Results

Forty-four patients were eligible for this study. Nineteen patients had been referred for evaluation of ASD, while the other 25 patients sought care at our clinic for other psychological complaints: eight of school maladjustment, seven of school refusal, four of occupational maladjustment, two of mood swing, and one each of tic, auditory hallucination, wasting money, and violence. They were thereafter diagnosed as having ASD. Nine patients had autistic disorder, 27 patients had Asperger disorder, and eight patients had pervasive developmental disorder not otherwise specified.

Sixteen patients (36.4%) had demonstrated mood disorder before the initial intake ($n=10$) or showed mood symptoms during the intake and subsequent sessions ($n=6$). Demographic and clinical features of patients with and without mood disorder (Table 1) showed that gender ratio, index age, age at intake, follow-up period, rate of mood disorder in first- and second-degree relatives, and IQs were not significantly different between the two groups. Mood disorder occurred during late adolescence in most patients. With regard to scores on three questionnaires for ASD, patients with mood disorder showed significantly lower scores on TABS than those without mood disorder, although scores on ASSQ and AQ were not significantly different between the two groups.

The distributions of the three diagnoses of ASD were significantly different between the two groups (Table 2). None of the patients with autistic disorder demonstrated mood disorder. In 16 patients with mood disorder, BP accounted for 75%.

4. Discussion

Psychiatric comorbidity of ASD is not a frequently referred medical condition. The results of our study suggested that BP was the major comorbidity for mood disorder in adolescents and young adults with high-functioning ASD. About one-third of the patients in this series had mood disorder and the prevalence of BP was three times that of major depressive disorder.

In our daily practice at the outpatient clinic, we carefully examine adolescent and young adult patients with depressive symptoms to avoid overlooking hypomania, since hypomanic symptoms are liable to be unrecognized and patients are misdiagnosed as having major depressive disorder (Benazzi and Akiskal, 2003).

Table 1
Demographic and clinical features of patients with and without mood disorder

	With mood disorder	Without mood disorder	*P*
	$n=16$	$n=28$	
Female gender, %	50.0	28.6	0.200
Index age, mean (S.D.; range), years	21.8 (4.6; 14–31)	19.4 (6.8; 13–39)	0.214
Age at intake, mean (S.D.; range), years	19.4 (5.3; 12–29)	16.6 (7.3; 8–38)	0.207
Follow-up period, mean (S.D.), months	32.0 (28.0)	34.1 (35.4)	0.843
Age at onset of mood disorder, mean (S.D.; range), years	18.0 (4.2; 14–27)	–	–
Family history of mood disorder in first- and second-degree relatives, %	37.5	10.7	0.053
Wechsler Intelligence Scale			
FIQ, mean (S.D.)	92.8 (12.4)	94.5 (15.3)	0.726
VIQ, mean (S.D)	99.2 (12.3)	97.7 (13.9)	0.750
PIQ, mean (S.D.)	85.8 (13.1)	91.7 (19.0)	0.329
Questionnaires for autism spectrum disorder			
TABS, mean (S.D.)	7.4 (3.3)	12.7 (6.3)	0.028
ASSQ, mean (S.D.)	14.7 (5.1)	16.6 (5.7)	0.400
AQ, mean (S.D.)	27.8 (6.1)	32.1 (5.6)	0.085

Abbreviations: FIQ, full intelligence quotient; VIQ, verbal intelligence quotient; PIQ, performance intelligence quotient; TABS, Tokyo Autistic Behavior Scale; ASSQ, High-Functioning Autism Spectrum Screening Questionnaire; AQ, Autism-Spectrum Quotient.

Table 2
Diagnoses of patients

	With mood disorder	Without mood disorder	P
	n=16	n=28	
Diagnoses in autism spectrum disorder			
Autistic disorder	0 (0)	9 (4)	0.029
Asperger disorder	12 (3)	15 (10)	
Pervasive developmental disorder not otherwise specified	4 (1)	4 (3)	
Diagnoses in mood disorder			
Major depressive disorder	4 (1)	–	–
Bipolar I disorder	2 (1)	–	–
Bipolar II disorder	6 (0)	–	–
Bipolar disorder not otherwise specified	4 (2)	–	–

Numbers in parentheses indicate numbers of subjects aged from 12 to 18.

The percentage of BP in depressed patients aged 29 years or younger was reported to be 63% in a private clinic (Parker *et al*., 2006). A comparative study showed that the rate of high-functioning ASD among 438 subjects (mean age±S. D., 12.7±3.2) with BP was 2.1% (Axelson *et al*., 2006). These findings imply that clinicians should pay attention to (hypo)manic symptoms in depressed adolescents and young adults with high-functioning ASD.

Ghaziuddin *et al*. found that 13 (37.1%) of 35 patients with Asperger disorder between 8 and 51 years old had mood disorder based on DSM-IV. Of these 13 patients, eight patients had major depressive disorder, four had dysthymia, and only one had BP (Ghaziuddin *et al*., 1998). The rates of mood disorder in the study by Ghaziuddin *et al*. and in our study were almost equal (37.1% and 36.4%, respectively), but the details of the diagnoses were different. This may be explained by the small sample size in both studies and the differences in clinical setting (a developmental disorders clinic in the study by Ghaziuddin *et al*. *vs*. a general clinic in our study). Wozniak *et al*. reported that 14 (21.2%) of 66 patients with ASD (including 57 patients with high-functioning ability) were diagnosed with mania based on DSM-III-R (Wozniak *et al*., 1997). As 13 of these 14 patients had major depressive episodes, they would be diagnosed as having bipolar I disorder if DSM-IV were applied. The rates of BP in both the study by Wozniak *et al*. and our study were roughly equal (21.2% and 27.3%, respectively), but in our study the rate of patients with bipolar I disorder was slightly lower. Although DSM-III-R did not yet define the criteria for hypomanic episodes, subjects in the study by Wozniak *et al*. adequately fulfilled the criteria for manic episodes. We consider that this may be explained by the difference in index age (the mean age was 10.6 years in the study by Wozniak *et al*. *vs*. 21.8 years in our study).

Subjects with mood disorder showed significantly lower scores on TABS than those without mood disorder. TABS contains eight questions concerning speech development in all 39 questions. None of the subjects with autistic disorder in this study had mood disorder. Autistic disorder is characterized by delayed and deviant speech development, so we suggest that the score on TABS was significantly higher in subjects without than in those with mood disorder.

It is difficult to explain why none of the subjects with autistic disorder had comorbid mood disorder in this study. Some case studies have reported that mood disorder is the main psychiatric comorbidity in individuals with autistic disorder (Lainhart and Folstein, 1994). This difference may be due to small sample size, or difficulties in diagnosing Asperger disorder (Volkmar *et al*., 2000). We set the differential diagnosis between autistic disorder and Asperger disorder as some communicative phrases at 3 years of age. This setting may have been somewhat nonrestrictive. If any deviant or delayed development of speech should prevent a diagnosis of Asperger disorder, some of our subjects with Asperger disorder may be re-diagnosed as autistic disorder (Miller and Ozonoff, 1997). However, our contention is that BP is the main comorbid disorder in the subjects with autism *spectrum* disorder.

This study has some limitations as follows. First, the small sample size may have induced type I error. Second, the Autism Diagnostic Interview – Revised was not used to evaluate the patients and establish the diagnosis of ASD. Finally, referral bias (sampling bias) may have resulted in overestimation of the prevalence of mood disorder. Referral bias is inevitable in studies performed in a tertiary care facility, such as a university hospital. However, the influence of referral bias may not have been so great in this study for several reasons. First, Kanazawa University Hospital functions as a primary

and secondary care facility rather than a tertiary care facility, based on the referral rate of 30%. Second, the prevalence of 27.3% of BP in subjects with ASD is much too high compared to the prevalence of 9.1% of major depressive disorder in subjects with ASD in this study. It is unlikely that patients with BP would visit the hospital more often than those with major depressive disorder. In this study, subjects with bipolar II disorder, in which hypomanic episodes are liable to be overlooked (Benazzi and Akiskal, 2003), were more common than those with bipolar I disorder. Therefore, it is not reasonable that more subjects with complicated BP tended to visit our hospital. However, controlled studies are needed using large population samples with ASD to avoid referral bias.

The significance of our study is to emphasize BP as comorbidity in high-functioning ASD. The significance can be considered from two perspectives: a therapeutic approach and genetic pleiotropy. The patient reported by Frazier *et al*. (2002) had received numerous diagnoses and had been prescribed a number of medications over a span of several years without improvement. Finally, he was diagnosed as having BP and Asperger disorder, and combination of lithium, risperidone, and clonazepam improved his behavioral symptoms. This case study indicates a strong likelihood that both disorders may be unrecognized. Clinicians should keep in mind that patients with high-functioning ASD may consult a general clinic or a general hospital with various psychological complaints or behavioral symptoms, and that hypomanic symptoms in patients with ASD are liable to be confused with the symptoms of ASD itself.

An association between two disorders may be explained by two models; a causal association or a common etiology (Gorwood, 2004; Merikangas, 1990). According to the former model, one disorder causes the second disorder. However, it is unlikely that ASD causes BP or *vice versa*. The latter model suggests that two disorders share common etiological factors. Both ASD and BP are highly heritable. Ninety percent of monozygotic twins are concordant for autistic disorder *vs*. 10% of dizygotic twins (Folstein and Rosen-Sheidley, 2001), and 40% of monozygotic twins are concordant for BP *vs*. 5.4% of dizygotic twins (McGuffin *et al*., 2003). There are some biological similarities between the two disorders: for example, decreased serum melatonin levels (Kennedy *et al*., 1996; Melke *et al*., 2008) and disturbances of sleep and circadian rhythms (Harvey *et al*., 2006; Limoges *et al*., 2005). Pleiotropic effects of the same genes could lead to a combination of these two disorders (Merikangas, 1990). Considerable research on the genetics of ASD has been performed in recent years (Gupta and State, 2007). Whether there are overlapping linkage regions between ASD and BP may warrant investigation as additional analyses of the genetics of both disorders. Therefore, controlled studies using large population samples are needed to clarify the comorbidity of BP in ASD.

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Conflict of interest

The authors declare that there is no conflict of interest.

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References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental disorders, Fourth ed. American Psychiatric Association, Washington D. C.

Axelson, D., Birmaher, B., Strober, M., Gill, M.K., Valeri, S., Chiappetta, L., Ryan, N., Leonard, H., Hunt, J., Iyengar, S., Bridge, J., Keller, M., 2006. Phenomenology of children and adolescents with bipolar spectrum disorders. Arch. Gen. Psychiatry 63, 1139–1148.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., Clubley, E., 2001. The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. J. Autism Dev. Disord. 31, 5–17.

Benazzi, F., Akiskal, H.S., 2003. Refining the evaluation of bipolar II: beyond the strict SCID-CV guidelines for hypomania. J. Affect. Disord. 73, 33–38.

Ehlers, S., Gillberg, C., Wing, L., 1999. A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. J. Autism Dev. Disord. 29, 129–141.

Folstein, S.E., Rosen-Sheidley, B., 2001. Genetics of autism: complex aetiology for a heterogenous disorder. Nat. Rev. Genet. 2, 943–955.

Frazier, J.A., Doyle, R., Chiu, S., Coyle, J.T., 2002. Treating a child with Asperger's disorder and comorbid bipolar disorder. Am. J. Psychiatry 159, 13–21.

Ghaziuddin, M., Weidmer-Mikhail, E., Ghaziuddin, N., 1998. Comorbidity of Asperger syndrome: a preliminary report. J. Intellect. Disabil. Res. 42, 279–283.

Ghaziuddin, M., Tsai, L., Ghaziuddin, N., 1992. Comorbidity of autistic disorder in children and adolescents. Eur. Child Adolesc. Psychiatry 1, 209–213.

Ghaziuddin, M., Ghaziuddin, N., Greden, J., 2002. Depression in persons with autism: implications for research and clinical care. J. Autism Dev. Disord. 32, 299–306.

Gorwood, P., 2004. Generalized anxiety disorder and major depressive disorder comorbidity: an example of genetic pleiotropy? Eur. Psychiatr. 19, 27–33.

Gupta, A.R., State, M.W., 2007. Recent advances in the genetics of autism. Biol. Psychiatry 61, 429–437.

Gutkovich, Z.A., Carlson, G.A., Carlson, H.E., Coffey, B., Wieland, N., 2007. Asperger's disorder and co-morbid bipolar disorder: diagnostic and treatment challenges. J. Child Adolesc. Psychopharmacol. 17, 247–255.

Harvey, A.G., Mullin, B.C., Hinshaw, S.P., 2006. Sleep and circadian rhythms in children and adolescents with bipolar disorder. Dev. Psychopathol. 18, 1147–1168.

Kennedy, S.H., Kutcher, S.P., Ralevski, E., Brown, G.M., 1996. Nocturnal melatonin and 24-hour 6-sulphatoxymelatonin levels in various phases of bipolar affective disorder. Psychiatry Res. 63, 219–222.

Komoto, J., Usui, S., Hirata, J., 1984. Infantile autism and affective disorder. J. Autism Dev. Disord. 14, 81–84.

Kurita, H., Miyake, Y., 1990. The reliability and validity of the Tokyo Autistic Behaviour Scale. Jpn. J. Psychiatry Neurol. 44, 25–32.

Lainhart, J.E., Folstein, S.E., 1994. Affective disorders in people with autism: a review of published cases. J. Autism Dev. Disord. 24, 587–601.

Limoges, E., Mottron, L., Bolduc, C., Berthiaume, C., Godbout, R., 2005. Atypical sleep architecture and the autism phenotype. Brain 128, 1049–1061.

Lord, C., Rutter, M., Le Conteur, A., 1994. Autism Diagnostic Interview – Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. J. Autism Dev. Disord. 24, 659–685.

McGuffin, P., Rijsdijk, F., Andrew, M., Sham, P., Katz, R., Cardno, A., 2003. The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. Arch. Gen. Psychiatry 60, 497–502.

Melke, J., Goubran Botros, H., Chaste, P., Betancur, C., Nygren, G., Anckarsäter, H., Rastam, M., Ståhlberg, O., Gillberg, I.C., Delorme, R., Chabane, N., Mouren-Simeoni, M.-C., Fauchereau, F., Durand, C.M., Chevalier, F., Drouot, X., Collet, C., Launay, J.-M., Leboyer, M., Gillberg, C., Bourgeron, T., the PARIS study, 2008. Abnormal melatonin synthesis in autism spectrum disorders. Mol. Psychiatry 13, 90–98.

Merikangas, K.R., 1990. Comorbidity for anxiety and depression: review of family and genetic studies. In: Maser, J.D., Cloninger, C.R. (Eds.), Comorbidity of Mood and Anxiety Disorders. American Psychiatric Press, Washington, D. C., pp. 331–348.

Miller, J.N., Ozonoff, S., 1997. Did Asperger's cases have Asperger disorder?: a research note. J. Child Psychol. Psychiatry 38, 247–251.

Parker, G., Brotchie, H., Fletcher, K., 2006. An increased proportional representation of bipolar disorder in younger depressed patients: analysis of two clinical databases. J. Affect. Disord. 95, 141–144.

Volkmar, F.R., Klin, A., Schultz, R.T., Rubin, E., Bronen, R., 2000. Asperger's disorder. Am. J. Psychiatry 157, 262–267.

Wozniak, J., Biederman, J., Faraone, S.V., Frazier, J., Kim, J., Millstein, R., Gershon, J., Thornell, A., Cha, K., Snyder, J.B., 1997. Mania in children with pervasive developmental disorder revisited. J. Am. Acad. Child Adolesc. Psych. 36, 1552–1560.