Psychopathology and clinical outcomes of first-visit outpatients under 20 years old exhibiting a psychotic state

Psychopathology and clinical outcomes of first-visit outpatients under 20 years old exhibiting a psychotic state

Takao Ishibashi, Hotaka Shinzato, Yu Zamami, Morihiro Shimabukuro,Tsuyoshi Kondo

Department of Neuropsychiatry, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

(Received on February 3, 2020, accepted on March 27, 2020)

ABSTRACT

Aim: This study aimed to clarify the psychopathology, global functioning and clinical outcome of patients under 20 years old exhibiting a psychotic state. **Methods:** Forty-five patients (15 males and 30 females) under 20 years old with a diagnostic description of psychosis, schizophrenia, at-risk mental state (ARMS) or psychotic-like experiences, who had first visited our clinic between January 2012 and December 2017 were retrospectively extracted from medical records. Their age at the onset of symptoms; psychiatric diagnoses, including comorbidities; insight of disease; symptomatology (early, positive, negative, catatonic and anxiety-depression symptoms); course of illness; prescribed medication; and final treatment outcome were investigated from various aspects. **Results:** Prodromal stages of schizophrenia (ARMS and early schizophrenia) were observed in about one-third of the overall patients. Patients with insight of disease had a higher baseline global assessment of functioning and greater number of early schizophrenic symptoms and anxiety-depression symptoms than those without insight of disease. In particular, early schizophrenic symptoms appear to be a discriminating factor for insight of disease. A total of 36.4% of ARMS patients converted to schizophrenia, while 25% of early schizophrenia patients converted to frank schizophrenia. Doses of antipsychotics (chlorpromazine equivalence: mg/day) were lower in ARMS non-converters (100±63) than in ARMS converters (364±44) or schizophrenics (477±337). Among overall patients, 62.3% showed improvement as the final treatment outcome. The global assessment of functioning values were higher at 6 (54.2%±17.2%) and 12 months (55.1%±18.9%) than that at baseline (34.1%±10.3%).
Conclusion: The present study suggests that clinicians need to actively ask about early symptoms or attenuated positive symptoms in patients under 20 years old with a psychotic state who may still have insight of disease and encourage voluntary help-seeking. The first six months might be a critical period for achieving symptomatological remission and functional recovery in these patients. *Ryukyu Med. J., 39* (*1~4*) *29~40, 2020*

Key words: under 20, schizophrenia, at risk mental state, early symptoms, insight

INTRODUCTION

Schizophrenia has been regarded as a non-organic psychotic disorder with a poor functional outcome due to the irreversible and slowly progressive course of the illness[1]. The point and lifetime prevalence have been reported to be 0.45% and 0.7%, respectively[2]. Around 40% of adults with schizophrenia are retrospectively reported to show a

Corresponding Author: Takao Ishibashi, M.D., Department of Neuropsychiatry,Graduate School of Medicine,University of the Ryukyus, 207 Uehara,Nishihara,Okinawa 903-0125, Japan, Tel: +81-98-895-1157; Fax: +81-98-895-1419, E-mail: k188732@eve.u-ryukyu.ac.jp

symptom onset prior to 20 years old[3]. In general, younger-onset schizophrenia has been traditionally considered to have a poorer outcome and more severe symptom profile than adult-onset schizophrenia[4]. However, recent findings from an early psychosis prevention study[5] have shown relatively promising vocational and illness outcomes after long-term follow-up of younger individuals with schizophrenia, suggesting that early therapeutic intervention, especially at the prodromal stage of schizophrenia, may result in a better prognosis.

Schizophrenic prodrome, before the florid manifestation of the disease, consists of many non-specific psychiatric symptoms, such as anxiety, depression, and subthreshold psychosis-like experiences (PLEs)[6]. It lasts two to five years on average before showing an insidious decline in social functioning, usually during adolescence[7]. Since the need for early intervention in this vulnerable period has been intensively discussed, the terminology has shifted from the retrospective term "prodrome" (meaning "before illness") to the prospective concept "at risk mental state (ARMS)" for early psychosis[8].

The following three operational definitions have been proposed for this ultra-high-risk state: 1) attenuated psychosis syndrome (APS) with insufficient intense or frequency of symptoms; 2) brief limited intermittent psychotic symptoms (BLIPS), resolving within a week without any specific treatment; and 3) genetic risk and deterioration syndrome (GRD) with decreased psychosocial functioning in individuals with a genetic risk of schizophrenia[9]. Among these categories, APS has been reported to be the most prevalent manifestation of ARMS (83%)[10] and has been included in section III "under conditions for further study (not intended for clinical use)" of the latest 5th edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-5)[11]. Unlike patients with full-blown schizophrenia, individuals with APS usually have a preserved insight of disease, experience psychosis as an ego-alien phenomena, and sometimes try to voluntarily seek support from medical health professionals[11].

Long before the abovementioned international consensus of the ARMS for pre-psychotic stage of schizophrenia was launched, another concept of "early schizophrenia" had already been proposed by Nakayasu, a Japanese psychiatrist[12]. According to his profound observation and consideration from aspects of clinical psychopathology, early schizophrenia is cross-sectionally characterized by specific symptoms different from those of frank schizophrenia and longitudinally corresponds to the transitional state as an early but true onset of schizophrenia. In contrast to the symptoms list for typical schizophrenia, which meets the standard operational diagnostic criteria[11], early symptoms consist of four unique manifestations: autochthonous thoughts/visual images, heightened awareness (to auditory stimuli), a vague sense of being watched, and a tense and perplexed mood, as an independent clinical entity[13]. Nakayasu[12, 13] further emphasized that more sensitive psychosocial approaches should be applied to cases of early schizophrenia, since these patients often experience early symptoms with ego-alien and uncomfortable feelings and show voluntary help-seeking attitudes, as in the case with ARMS.

Adolescence is generally recognized as a vulnerable age period for emotional/behavioral problems due to a lack of maturity in impulse control and insufficient tolerance to anxiety/frustration, which sometimes promotes the onset of various psychiatric disorders, such as anxiety disorders, depression, bipolar disorders, and schizophrenia[3]. Among these disorders, schizophrenia spectrum disorders are of the greatest concern due to their association with more cognitive decline and longer-term impairment in psychosocial functioning than other psychiatric disorders[14, 15]. However, there is little information on the detailed profiles of schizophrenic spectrum disorders during the adolescent period, i.e. detailed psychopathology, prevalence of schizophrenic prodrome, response to treatments, and functional outcome.

Meanwhile, patients with ARMS also showed high prevalence of anxiety and depressive disorders, which may impact global functioning and longitudinal outcome as well as ongoing psychopathology[16]. Especially, depressive psychopathology was significantly associated with cognitive deficits[17] and quality of life[18] in individuals with ARMS, which may greatly affect their daily life functioning and social outcome despite its non-specific manifestations. Since anxiety and depression symptoms are more easily perceived in ARMS patients, it is assumed that such patients are more willing to seek and accept clinical help than those with apparent psychosis. Moreover, ARMS subjects showed greater insight

about illness and were more likely to interpret their psychotic symptoms as anomalous experiences than patients with first-episode psychosis[19]. However, the relationship between insight of disease and composition of symptoms is still unknown in individuals with ARMS or early psychosis.

Therefore, the present study investigated the psychopathology, including such non-specific psychopathology as anxiety and depression, and clinical outcome of first-visit outpatients under 20 years old who exhibited a psychotic state in a real-world clinical setting. In particular, this study aimed to focus on schizophrenic prodrome and its relationship with disease insight during this age period.

METHODS

Subjects

Forty-five patients (15 males and 30 females) under 20 years old with a diagnostic description of schizophrenia, psychosis, ARMS, or PLEs who first visited our clinic between January 2012 and December 2017 were retrospectively extracted from medical records.

The values for the mean (± standard deviation [SD]) and median (range) age at the first visit to our clinic were 14.9 (±2.6) and 15 (9-19) years old, whereas those at the disease onset were 13.5 (±2.5) and 13 (6-17) years old, respectively. The values for the mean (±SD) and median (range) duration of untreated psychosis were 11.3 (±11.6) and 8 (1-48) months, whereas the periods between the disease onset and first visit to our clinic were 14.7 (±12.0) and 12 (1-48) months, respectively.

Analyzed variables

The age at the onset of symptoms, psychiatric diagnoses (including comorbidities), insight of disease, symptomatology (early, positive, negative, catatonic and anxiety-depression symptoms), course of the illness, prescribed medication, and final treatment outcome were investigated from various aspects.

Psychopharmacology for schizophrenia-related symptoms focused on the following: hallucinations, suspiciousness/persecution, thought propagation, delusion of control and hostility (as positive symptoms), blunted affect, emotional withdrawal, incoherence, reduced tolerability, poor interpersonal relationships and lack of conversation flow (as negative symptoms), stupor, mutism, excitement and negativism (as catatonic symptoms), and anxiety/tension, increased interpersonal sensitivity, irritability, depressed mood, and suicidal ideation (as anxiety-depression symptoms), according to the symptomatological lists from the Positive and Negative Syndrome Scale (PANSS)[20] and Brief Psychiatric Rating Scale (BPRS)[21] along with a subsyndromal model of schizophrenic symptoms[22].

Early or attenuated positive symptoms were selected from the listed symptoms of early schizophrenia[12] and the Scale of Psychosis-risk Symptoms (SOPS)[23], including a sense of being watched, idea of reference, heightened auditory awareness, autochthonous experiences, elementary hallucinations, a tense and perplexed mood, nightmares, impaired immediate understanding, and depersonalization/derealization.

Assessments

Psychiatric diagnoses for schizophrenia spectrum disorders and other psychiatric comorbidities were made according to DSM-5 criteria[11]. The SOPS[23] was used for the specific detection of ARMS, while the independent clinical entity "early schizophrenia" distinct from frank schizophrenia was determined according to the specific psychopathology and early symptoms of schizophrenia proposed by Nakayasu (1990)[12].

Degrees of adjustment were assessed by the Global Assessment of Functioning (GAF) scale[24]. The efficacy of treatments as the final outcome was assessed according to the Global Impression Improvement (CGI-I) score[25]. The total daily doses of prescribed antipsychotic drugs were expressed according to the criteria of chlorpromazine-equivalence[26, 27].

Ethics and statistical analyses

All data were anonymously treated as grouped data during the study. Only coded and grouped data were used for analyses. The explanation of the purpose of the study, measures for the protection of personal information, and the right to opt out from the study were described in the research and reporting section of our homepage (http://www.psy.med.u-ryukyu.ac.jp). The study protocol was approved by the Ethics Committee of the University

of the Ryukyus (#1308).

The Mann-Whitney U test, Fisher's exact test, and logistic regression analysis were performed to test the effects of clinical background characteristics (age at the onset, gender, duration of illness, and global functioning) and symptomatology (number of positive, negative, catatonic, anxiety-depression, and early symptoms of schizophrenia-related psychopathology) on insight of disease. A repeated measures analysis of variance followed by Holm's test as a post-hoc analysis was performed to determine longitudinal changes in the GAF during 12 months of treatment. The Kruskal-Wallis test followed by the Steel-Dwass test as a post-hoc analysis was conducted for the comparison of daily antipsychotic doses among ARMS non-converters, ARMS converters, and schizophrenics.

A two-tailed P value <0.05 was regarded as statistically significant. All statistical analyses were performed using the EZR software program, version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan)[28].

RESULTS

Psychiatric diagnosis

The psychiatric diagnoses of 45 patients were schizophrenia (39%), ARMS (24%), early schizophrenia (9%), PLEs with autism spectrum disorder (ASD)(7%), schizoaffective disorder (7%), bipolar disorder (4%), brief psychotic disorder (4%), delusional disorder (2%), adjustment disorder (2%), and substance-induced psychotic disorder (2%) (Fig. 1). Prodromal stages of schizophrenia (ARMS and early schizophrenia) were observed in about one-third of the overall patients.

The initial diagnoses of 15 patients with ARMS or early schizophrenia from other clinics or hospitals that referred the patients to us varied, including schizophrenia (20%), adjustment disorder (20%), ASD (20%), ARMS (6%), major depressive disorder (6%), social anxiety disorder (7%), dissociative disorder (7%), delayed sleep phase syndrome (7%), and psychosomatic disease (7%). The concordance rate for the correct diagnosis of ARMS or early schizophrenia was only 6%.

Other psychiatric comorbidities were ASD including social communication disorder (39.1%), intellectual disability (13.0%), social anxiety disorder (13.0%), dissociative disorder (10.9%), selective mutism (6.5%), obsessive compulsive disorder (2.2%), panic disorder (2.2%), premenstrual dysphoric disorder (2.2%), reactive attachment disorder (2.2%), gender dysphoria (2.2%), epilepsy (2.2%), and narcolepsy (2.2%).

Cross-sectional psychopathology

The incidences of apparently psychotic symptoms that are mainly observed in frank schizophrenia were

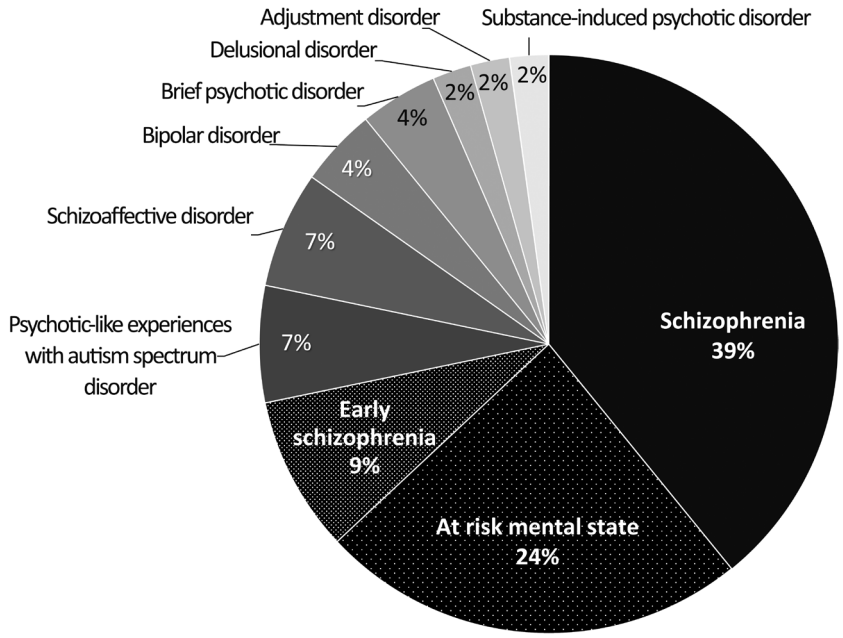

Fig.1 **Definite diagnoses of under 20 first-visit patients with psychotic symptoms (n = 45)**

hallucinations (65.2%), suspiciousness/persecution (54.3%), thought propagation (19.6%), delusion of control (19.6%), and hostility (8.7%) for positive symptoms; blunted affect (41.3%), lack of conversation flow (41.3%), emotional withdrawal (30.4%), incoherence (17.4%), poor interpersonal relationship (10.9%), and a reduced tolerability (6.5%) for negative symptoms; mutism (15.2%), stupor (10.9%), excitement (10.9%), and negativism (8.7%) for catatonic symptoms. Nonspecific anxiety-depression symptoms were mainly characterized by a depressed mood (39.1%), increased interpersonal sensitivity (28.3%), suicidal ideation (23.9%), anxiety/tension (17.4%), and irritability (17.4%).

Early and attenuated positive symptoms were also observed with non-negligible incidences, including a sense of being watched (34.8%), idea of reference (26.1%), heightened auditory awareness (23.9%), autochthonous experiences (19.6%), elementary hallucinations (17.4%), tense and perplexed mood (13.0%), nightmare (13.0%), impaired immediate understanding (10.9%), and depersonalization/derealization (10.9%) (Fig. 2). The psychiatric diagnoses of patients possessing these symptoms mainly consisted of ARMS (42%) and early schizophrenia (15%), while the prevalence of frank schizophrenia remained only 12%.

Insight of disease

Nine (20%) out of 45 patients preserved their insight of disease by voluntarily seeking help themselves. Their diagnoses were ARMS (n=4), early schizophrenia (n=3), schizoaffective disorder (n=1), and bipolar disorder (n=1); no diagnosis of frank schizophrenia was included.

Patients with insight of disease had a higher baseline GAF (P=0.004) and greater number of early (P=0.001) and anxiety-depression (P=0.004) symptoms than those without insight of disease (Table 1). Among these three factors, a logistic regression analysis revealed that only the number of early symptoms was a significant discriminator for insight of disease (adjusted odds ratio 2.29, 95% confidence interval 1.15-5.38, P=0.021) (Table 2).

Adjustment/Functioning

The following adjustment problems were observed at baseline: school non-attendance (60.9%), bullied experiences (26.1%), isolation from classmates (19.6%), social withdrawal (17.4%), and domestic violence (10.9%). The pre-treatment global functioning assessed by the GAF was only 34.1 (±10.3) on average (Fig. 3). However, the GAF scores after 6 and 12 months of treatment had significantly increased to 54.2±17.2 (P=0.000004) and 55.1±18.9 (P=0.000005), respectively, although further improvement was no longer found after 6 months of treatment (Fig. 3).

Treatment outcome

Prescribed antipsychotics and their prevalence

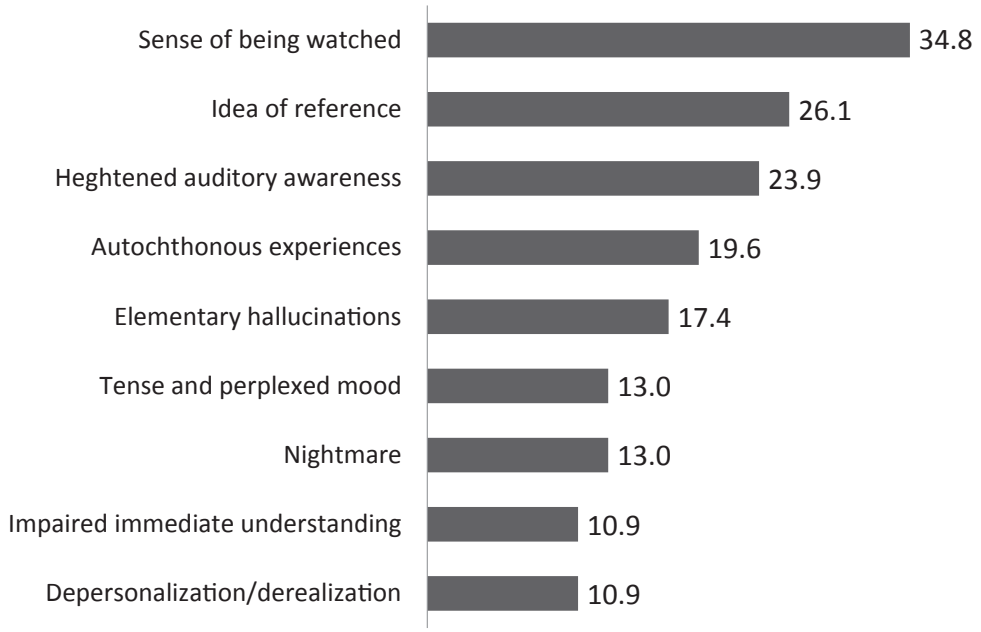

Fig. 2 **Incidences (%) of attenuated positive symptoms or early schizophrenic symptoms (n = 45)**

Table 1 **Differences in backgrounds and symptoms between patients with and without insight of disease**

	Age at onset (years)	Gender (% female)	Duration of illness (months)	Baseline GAF	Number of symptoms				
					Early	Positive	Negative	Catatonic	Anxiety-depression
Insight (−) (n=36)	13.5±2.7	66.7	12.5±12.3	31.0±10.1	1.1±1.4	1.8±1.2	1.4±1.6	0.6±1.0	1.6±1.3
Insight (+) (n=9)	13.2±1.6	66.7	6.6±6.3	40.7± 6.6	4.6±2.6	1.4±1.3	1.3±1.2	0.0±0.0	2.1±0.8
P value	.530	1.000	0.306	0.004	0.001	0.548	0.9	0.163	0.004

GAF: global assessment of functioning

Table 2 **Logistic regression analysis of contributing factors for insight of disease**

	β (S.E.)	Wald	Adjusted odds ratio	95% confidence interval	*P* value
Early symptoms	.91 (.39)	5.35	2.49	1.15 – 5.38	0.021
Anxiety-depression symptoms	1.36 (.79)	2.9	3.88	.82 – 18.50	0.089
Baseline GAF	.00 (.07)	0	1	1.00 -1.00	0.99

GAF: global assessment of functioning

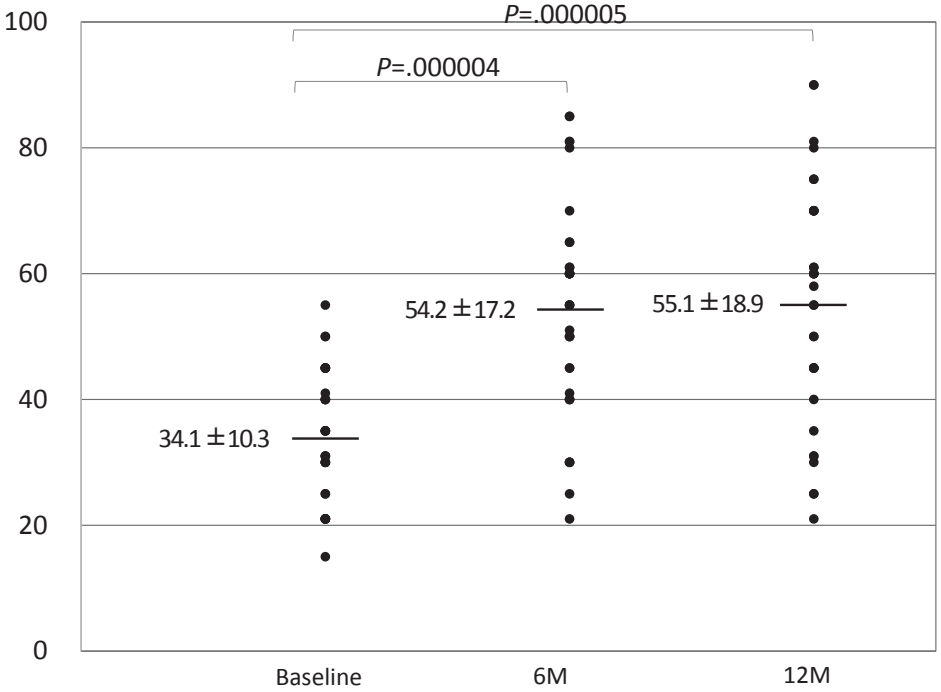

Fig.3 **Chronological changes in global assessment of functioning before and after treatments up to 12 months (n=33)**

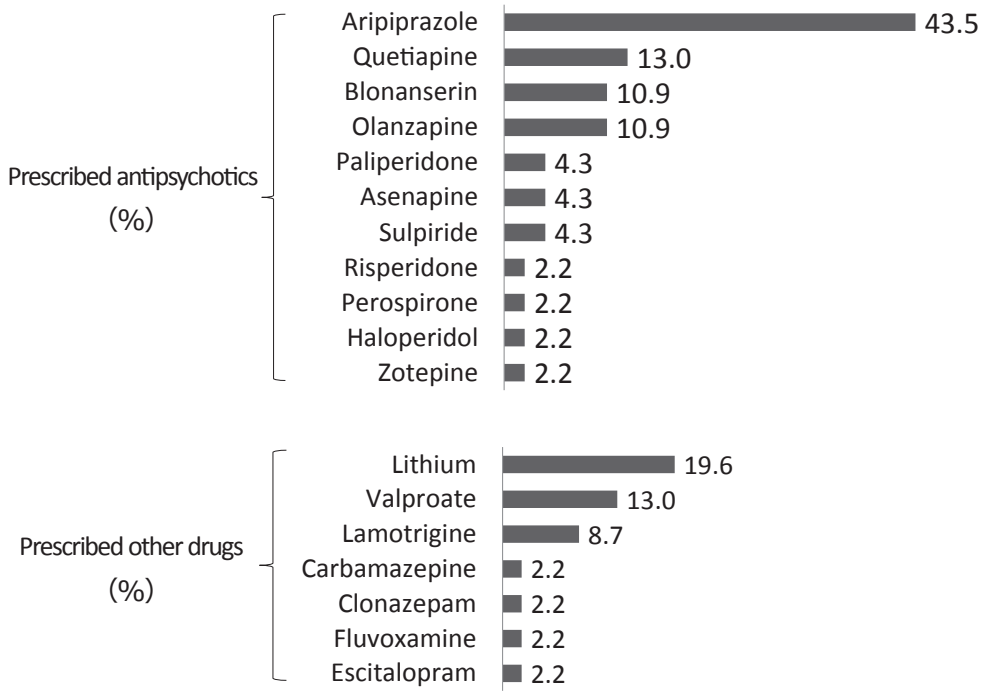

Fig. 4 **Definite diagnoses of under 20 first-visit patients with psychotic symptoms (n = 45)**

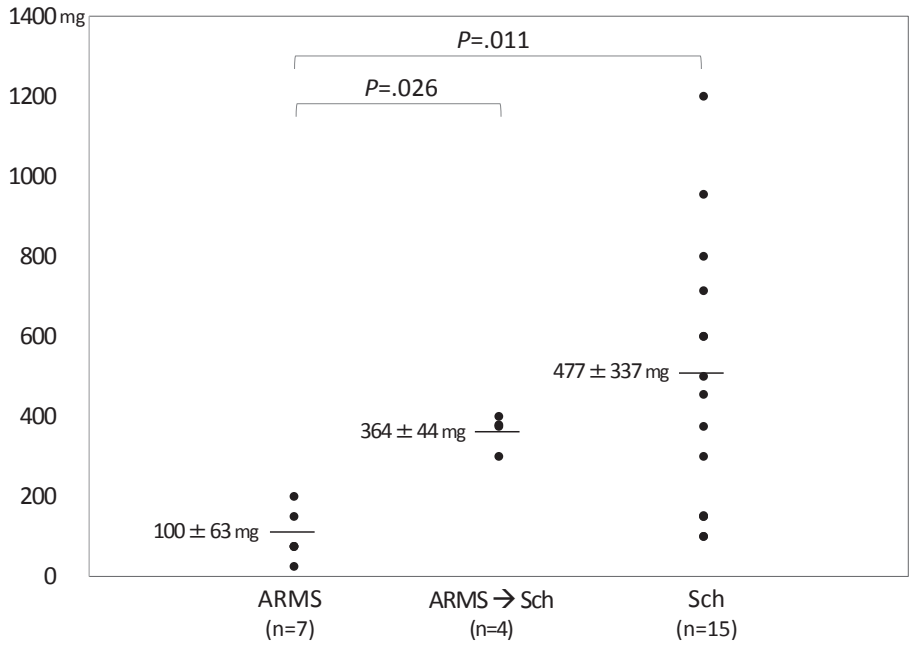

Fig. 5 **Maintained daily doses of antipsychotics (chlorpromazine equivalence) in at risk mental state (ARMS) non-converters, ARMS converters and schizophrenics (Sch)**

are summarized in Fig. 4. The most frequently used drugs were second-generation antipsychotics, e.g. aripiprazole (43.5%), quetiapine (13.0%), blonanserin (10.9%), and olanzapine (10.9%). Mood stabilizers were also used, including lithium (19.6%), valproate (13.0%), and lamotrigine (8.7%).

Despite intensive and flexible pharmacological treatments, 36.4% of ARMS patients converted to schizophrenia, while 25% of early schizophrenia patients converted to frank schizophrenia. Doses of antipsychotics (chlorpromazine equivalence: mg/day) were lower in ARMS non-converters (100±63) than in ARMS converters (364±44; P=0.026) and schizophrenics (477±337; P=0.011) (Fig. 5).

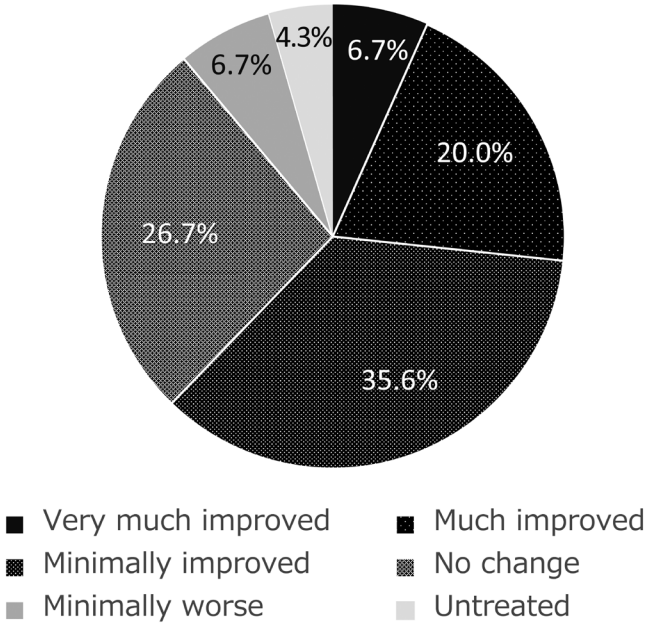

Fig. 6 **Final outcome assessed by clinical global impression of the improvement (CGI-I) (n = 45)**

Of the overall patients, 62.3% showed improvement as the final treatment outcome, as assessed by CGI-I, although more than half of treatment responders showed minimal improvement (Fig. 6).

DISCUSSION

Adolescents with underdeveloped psychological maturity may have a high affinity for psychotic symptoms, since the teenage years are generally believed to be a risky period for new-onset of schizophrenia[3]. Alternatively, traits of potential autism spectrum prevailingly found in younger patients may also induce the development of transient psychosis in stressful situations, as a close linkage has been repeatedly pointed out in the symptomatology and genetic backgrounds between ASD and schizophrenia patients[29-32]. The contribution of the autism spectrum in younger patients to the risk of psychosis was at least partly supported by our finding showing that a considerable number (nearly 40%) of patients with psychotic symptoms possessed autism spectrum disorder as their psychiatric comorbidity, compared to the prevalence of ASD in the general population (0.98% in adults[33] and 1.16% in children[34]).

However, various psychiatric diagnoses were made for first-visit outpatients under 20 years old who exhibited a psychotic state, although only 39% were definitely diagnosed with frank schizophrenia in the present study (Fig. 1). The diagnosis of schizophrenia may not be difficult if full-blown symptoms are apparent, even in patients under 20 years old. In contrast, the correct diagnosis of ARMS or early schizophrenia, which does not meet the diagnostic criteria of schizophrenia 11, 12), is relatively difficult unless clinicians are aware of what constitute early symptoms and sensitive to such symptoms[12, 23]. In fact, a non-negligible proportion (33%) of studied subjects were ultimately diagnosed with either ARMS or early schizophrenia in the present study (Fig. 1). Furthermore, the incidences of attenuated positive symptoms or early schizophrenic symptoms were also non-negligible among our adolescent patients (Fig. 2). These symptoms are schizophrenia-specific and are also found in patients with frank schizophrenia, although such attenuate manifestations are likely to be easily masked by apparently psychotic symptoms of schizophrenia, like hallucinations and delusion[35]. Nevertheless, the rate of the correct diagnosis of ARMS or early schizophrenia was extremely low (6%) when patients were referred to us. These findings suggest the high importance of actively interviewing patients for early symptoms based on an understanding of the psychopathology of ARMS

or early schizophrenia[12, 23] by clinicians who often treat adolescent patients exhibiting weak or doubtful psychosis-like symptoms but obviously impaired functioning, such as school non-attendance, in their daily clinical practice.

In addition, it is also important to understand that such patients with ARMS or early schizophrenia usually possess an insight of disease, in contrast to frank schizophrenics, who typically lack insight of disease[11]. In fact, insight of disease was better preserved in patients with a greater number of early and anxiety-depression symptoms and less severely impaired global functioning than in others (Table 1). In particular, psychopathology predominated by early schizophrenic symptoms is regarded as a determinant factor for insight of disease, according to our results. The early specific symptoms listed in Fig. 2 are usually recognized as ego-alien experiences in patients with ARMS or early schizophrenia, while anxiety-depression symptoms (depressed mood, interpersonal hypersensitivity, suicidal ideation, anxiety/tension and irritability) are relatively easy to verbalize and spontaneously expressed as subjective ailments. Clinicians may therefore need to be alert for an inclination toward voluntary help-seeking in patients with insight of disease and should reinforce reality testing of these patients by enhancing their ego-alien attitudes toward early symptoms and inducing psychological catharsis by verbalization of their anxious and depressed feelings. Such a narrative approach with empathy and cognitive-behavioral intervention for preserved insight of disease is extremely important in a stepped-care approach to treating young people with ARMS[36].

Even in younger patients with ARMS and early schizophrenia, the social and daily functioning was greatly reduced at baseline in the present study (GAF 34.1 on average, comparable to the previous finding of a low baseline functioning in early-onset schizophrenia [GAF 35.5 on average])[37]. This implies that poor functioning rather than symptomatological manifestations may be easily noticed by the people around patients with mild psychosis, like ARMS or early schizophrenia, leading to increased opportunities to receive psychosocial and medical support from medical care professionals. Treatment intervention resulted in the significant improvement of functioning at six months, although no further improvement was subsequently observed within one year (Fig. 3). This finding suggests that the first six months might be a critical period for achieving symptomatological remission and functional recovery in these patients.

In the present study, modest pharmacotherapy was administered, mainly with aripiprazole as a partial dopamine agonist and quetiapine for loose dopamine receptor binding along with mood-stabilizing agents, such as lithium, valproate, and lamotrigine, in order to treat comorbid mood instability (Fig. 4). Our selection of these two antipsychotics (aripiprazole and quetiapine) is supported by a recent network meta-analysis of acute antipsychotic treatments for children and adolescents with schizophrenia-spectrum disorders[38]. In our patients with ARMS in particular, minimal antipsychotic doses (100 mg/day on average) were carefully used in addition to psychosocial treatments (Fig. 5). Such selective and cautious intervention with modest pharmacotherapy is reasonable[36], since adolescent ARMS patients have been suggested to have a higher risk of adverse effects and lower chance of beneficial effects than adult schizophrenia patients[39].

However, unavoidably, 36.4% of ARMS patients converted to schizophrenia, and 25% of early schizophrenia patients converted to frank schizophrenia within the study period, rates that were similar to the previously reported transition risk from ARMS to schizophrenia (29%-36%)[40]. Our findings indicate that patients who convert from ARMS to schizophrenia require much higher antipsychotic doses than ARMS non-converters, with doses similar to those needed for frank schizophrenia (Fig. 5). This may be further supported by our finding that the final treatment outcome as a whole was only modest improvement (Fig. 6), which has been supported by a recent systematic review suggesting that the long-term outcome (>1 year) of early-onset schizophrenia (good 15.4% < moderate 24.5% < poor 60.1%) or schizophrenia spectrum disorders (good 19.6% < moderate 33.6% < poor 46.8%) is not optimistic compared with adult cases with psychosis[41].

Therefore, the present and previous findings suggest that adolescent patients with psychosis may show partial remission with improved functioning within a year but require continuous follow-up even after achieving remission or functional improvement, regardless of the severity of the psychotic state.

Limitations

The present study has several limitations. First, this study is based on a retrospective review of medical records, so the obtained findings need to be confirmed by a prospective study. Second, the main results were obtained from a relatively small number of subjects in a single institution. Third, the follow-up period was too limited to clarify more reliable outcomes of vulnerable patients during adolescence. Therefore, a collaborative study with a larger number of subjects and longer-term follow-up in a prospective design will be required in the future.

Conclusion

The present study suggests that clinicians need to actively ask about early symptoms or attenuated positive symptoms in patients under 20 years old exhibiting a psychotic state who may still have insight of disease and a willingness to seek help voluntarily. The first six months might be a critical period for achieving symptomatological remission and functional recovery in these patients.

ACKNOWLEDGMENTS

We appreciate the collaboration of many clinicians at local clinics and hospitals who referred patients under 20 years old with psychosis to our child-adolescent psychiatry clinic. This study was voluntarily conducted by the authors and was not tied to a grant or fund. The authors declare no conflicts of interest.

REFERENCES

1) Tandon R., Nasrallah H.A. and Keshavan M.S.: Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res. 110(1-3): 1-23, 2009.
2) Tandon R, Keshavan M.S. and Nasrallah H.A.: Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophr Res. 102(1-3): 1-18, 2008.
3) Madaan V., Dvir Y. and Wilson D.R.: Child and adolescent schizophrenia: Pharmacological approaches. Expert Opinion on Pharmacotherapy. 9: 2053-2068, 2008.
4) Fleischhaker C., Schulz E., Tepper K., Martin M., Hennighausen K. and Remschmidt H.: Long-term course of adolescent schizophrenia. Schizophr Bull. 31: 769-780, 2005.
5) Amminger G.P., Henry L.P., Harrigan S.M., Harris M.G., Alvarez-Jimenez M., Herrman H., Jackson H.J. and McGorry P.D.: Outcome in early-onset schizophrenia revisited: findings from the Early Psychosis Prevention and Intervention Centre long-term follow-up study. Schizophr Res. 131(1-3): 112-119, 2011.
6) Yung A.R. and McGorry P.D.: The initial prodrome in psychosis: Descriptive and quantitative aspects. Aust N Z J Psychiatry. 30: 587-599, 1996.
7) Beiser M., Erickson D., Fleming J.A.E. and Lacono W.G.: Establishing the onset of psychotic illness. Am J Psychiatry. 150: 1349-1354, 1993.
8) McGorry P.D., Yung A.R. and Phillips L.J.: The "close-in" or ultra high-risk model: A safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. Schizophr Bull. 29: 771-790, 2003.
9) Yung A.R., Phillips L.J., Yuen H.P., Francey S.M., McFarlane C.A., Hallgren M. and McGorry P.D.: Psychosis prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Bull. 60: 21-32, 2003.
10) Nelson B., Yuen K. and Yung A.R.: Ultra high risk (UHR) for psychosis criteria: Are there different levels of risk for transition to psychosis? Schizophr Res. 125: 62-68, 2011.
11) American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th edn. American Psychiatric Association, Washington, DC, 2013.
12) Nakayasu N.: Early schizophrenia. Seiwa Shoten, Tokyo, 1990 (in Japanese).
13) Nakayasu N., Seki Y. and Harima H.: Early schizophrenia: a revised version. Seiwa Shoten, Tokyo, 2017 (in Japanese).
14) Chen C.K., Lee C.Y., Lee Y., Hung C.F., Huang Y.C., Lee S.Y., Huang M.C., Chong M.Y., Chen Y.C. and Wang L.J.: Could schizoaffective disorder, schizophrenia and bipolar I disorder be distinguishable using cognitive profiles?

Psychiatry Res. 266: 79-84, 2018.
15) Terachi S., Yamada T., Pu S., Yokoyama K., Matsumura H. and Kaneko K.: Comparison of neurocognitive function in major depressive disorder, bipolar disorder, and schizophrenia in later life: A cross-sectional study of euthymic or remitted, non-demented patients using the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J). Psychiatry Res. 254: 205-210, 2017.
16) Fusar-Poli P., Nelson B., Valmaggia L., Yung A.R. and McGuire P.K.: Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. Schizophr Bull. 40: 120-131, 2014.
17) Ohmuro N., Matsumoto K., Katsura M., Obara C., Kikuchi T., Hamaie Y., Sakuma A., Iizuka K., Ito F. and Matsuoka H.: The association between cognitive deficits and depressive symptoms in at-risk mental state: a comparison with first-episode psychosis. Schizophr Res. 162: 67-73, 2015.
18) Ohmuro N., Matsumoto K., Ishii Y., Katsura M., Obara C., Kikuchi T., Hamaie Y., Ito F. and Matsuoka H.: The associations between quality of life and clinical symptoms in individuals with an at-risk mental state and first-episode psychosis. Psychiatry Res. 254: 54-59, 2017.
19) Lappin J.M., Morgan K.D., Valmaggia L.R., Broome M.R., Woolley J.B., Johns L.C., Tabraham P., Bramon E. and McGuire P.K.: Insight in individuals with an At Risk Mental State. Schizophr Res. 90: 238-244, 2007.
20) Kay S.R., Fiszbein A. and Opler L.A.: The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 13: 261-276, 1987.
21) Bech P., Kastrup M. and Rafaelsen O.J.: Mini-compendium of rating scales for states of anxiety, depression, mania, schizophrenia with corresponding DSM-III syndromes. Acta Psychiatr Scand. 73: 1-37, 1986.
22) Lindenmayer J.P., Bernstein-Hyman R., Grochowski S. and Bark N.: Psychopathology of schizophrenia: initial validation of a 5-factor model. Psychopathology. 28: 22-31, 1995.
23) McGlashan T., Walsh B. and Woods S.: The Psychosis-Risk Syndrome: Handbook for Diagnosis and Follow-Up. Oxford University Press; New York: 2010.
24) Endicott J., Spitzer R.L., Fleiss J.L. and Cohen J.: The global assessment scale: A procedure for measuring overall severity of psychiatric disturbance. Arch Gen Psychiatry. 33: 766-771, 1976.
25) Guy W.: ECDEU assessment manual for psychopharmacology. U.S. Department of Health, Education and Welfare; Rockville: 1976.
26) Leucht S., Samara M., Heres S. and Davis J.M.: Dose equivalents for antipsychotic drugs: The DDD method. Schizophr Bull. 42: 90-94, 2016.
27) Woods S.W.: Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry. 64: 663-667, 2003.
28) Kanda Y.: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 48: 452-458, 2013.
29) Barneveld P.S., Pieterse J., de Sonneville L., van Rijn S., Lahuis B., van Engeland H. and Swaab H.: Overlap of autistic and schizotypal traits in adolescents with Autism Spectrum Disorders. Schizophr Res. 126: 231-236, 2011.
30) Cross-Disorder Group of the Psychiatric Genomics Consortium.: Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. Nat Genet. 45: 984-994, 2013.
31) Sheitman B.B., Kraus J.E., Bodfish J.W. and Carmel H.: Are the negative symptoms of schizophrenia consistent with an autistic spectrum illness? Schizophr Res. 69: 119-120, 2004.
32) Waris P., Lindberg N., Kettunen K. and Tani P.: The relationship between Asperger's syndrome and schizophrenia in adolescence. Eur Child Adolesc Psychiatry. 22: 217-223, 2013.
33) Brugha T.S., McManus S., Bankart J., Scott F., Purdon S., Smith J., Bebbington P., Jenkins R. and Meltzer H.: Epidemiology of autism spectrum disorders in adults in the community in England. Arch Gen Psychiatry. 68: 459-465, 2011.
34) Baird G., Simonoff E., Pickles A., Chandler S., Loucas T., Meldrum D. and Charman T.: Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet. 368: 210-215, 2006.
35) Honda T., Suzuki H., Iwai K., Fujiwara Y.,

Kawahara H. and Kuroda S.: Autochthonous experience, heightened awareness, and perception distortion in patients with schizophrenia: a symptomatological study. Psychiatry Clin Neurosci. 58: 473-479, 2004.
36) Tiffin P.A. and Welsh P.: Practitioner review: schizophrenia spectrum disorders and the at-risk mental state for psychosis in children and adolescents--evidence-based management approaches. J Child Psychol Psychiatry. 54: 1155-1175, 2013.
37) Stentebjerg-Olesen M., Pagsberg A.K., Fink-Jensen A., Correll C.U. and Jeppesen P.: Clinical characteristics and predictors of outcome of schizophrenia-spectrum psychosis in children and adolescents: a systematic review. J Child Adolesc Psychopharmacol. 26: 410-427, 2016.
38) Pagsberg A.K., Tarp S., Glintborg D., Stenstrøm A.D., Fink-Jensen A., Correll C.U. and Christensen R.: Acute antipsychotic treatment of children and adolescents With schizophrenia-spectrum disorders: a systematic review and network meta-analysis. J Am Acad Child Adolesc Psychiatry. 56: 191-202, 2017.
39) Kruszewski S.P. and Paczynski R.P.: Atypical antipsychotic agents for the schizophrenia prodrome: Not a clear first choice.: International Journal of Risk and Safety in Medicine. 20: 37-44, 2008.
40) Fusar-Poli P., Bonoldi I., Yung A.R., Borgwardt S., Kempton M.J., Valmaggia L., Barale F., Caverzasi E. and McGuire P.: Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry. 69: 220-229, 2012.
41) Clemmensen L., Vernal D.L. and Steinhausen H.C.: A systematic review of the long-term outcome of early onset schizophrenia. BMC Psychiatry. 12: 150, 2012.