Table 3. Summary of Demographic Data of Patients With High Pentosidine and/or Low Pyridoxal Levels

Characteristic	Patient No. MZ65	TZ5	MZ70	TZ77	NP50	TZ72	MZ192	TZ40	TZ16	TZ41	SF114	SF136	TZ20
Sex	M	F	M	F	F	F	M	M	M	M	M	M	M
Age, y	66	53	60	46	60	59	57	41	60	41	63	60	41
Age at onset, y	17	18	17	16	21	17	18	25	22	19	48	20	19
High pentosidine level	Yes[a]	Yes[b]	Yes[c]										
Very low pyridoxal level, <3.0 ng/mL			Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GLO1 genotype	Ala/Ala	Glu/Glu	T27NfsX15	Glu/Glu	P122LfsX27	Glu/Glu	Glu/Ala	Glu/Glu	Glu/Ala	Glu/Glu	Ala/Ala	Ala/Ala	Glu/Ala
Enzymatic activity, mU/10^6 RBC	4	5.5	2.8	5.7	3	6.6	5.9	6.6	5.5	6.1	5.5	4.9	5.5
Pentosidine, ng/mL	276.6	172.6	137	106.6	74.7	55.8	49	47.8	46.7	43.3	42.9	40.6	40.6
Pyridoxal, ng/mL	7.3	3.4	2.8	2.4	<2.0	2.3	2.4	<2.0	2.4	2.1	2.8	<2.0	<2.0
Antipsychotics, haloperidol equivalent, mg/d	34.6	54	38	18	7	8	16	20.5	13	9	8	12.3	10.1
Minor tranquilizer, diazepam equivalent, mg/d				10				6.7		6.3			18.8
Benzodiazepine hypnotics, nitrazepam equivalent, mg/d	5	25	20	10	10		10	10	10	10	10	20	7.5
Other medications		CBZ		PB, CBZ, GBP	VPA, CLN	CBZ	VPA	CBZ	Li_2CO_3, CBZ		CLN		
Smoking	No	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Past smoker	Yes	Yes
Duration of hospitalization, y	33	10.6	21.4	25.3	14.2	2.7	3.4	0.8	35.8	0	12	35	15
Educational background	HS	College, 2 y	HS dropout	HS	JHS	JHS	U, 8 y	JHS	JHS	JHS	JHS	JHS	College dropout
Case type			Familial	Familial				Familial	Familial	Familial			
Criminal record			Yes			Yes							

Abbreviations: CBZ, carbamazepine; CLN, clonazepam; GBP, gabapentin; HS, high school; JHS, junior high school; Li_2CO_3, lithium carbonate; PB, phenobarbital; RBC, red blood cell; U, university; VPA, sodium valproate.

[a] Patient 1 in Figure 1A.

[b] Patient 2 in Figure 1A.

[c] Patient 3 in Figure 1A.

treatment-resistant schizophrenia (with doses of antipsychotics in haloperidol equivalents of 34.8-54.0 mg/d), with more than a 20-year disease history and more than 10 years of hospitalization each (range, 10.6-33 years) (**Table 3**). Patient 3 (Figure 1A) has an elder brother who committed suicide and 2 maternal uncles, all of whom had schizophrenia; patient 3 killed his mother and exhibited violent behavior against hospital staff.

Most of the patients had been taking multiple medications; we did not control for smoking by subjects. The daily dose of medication in haloperidol equivalents was significantly correlated with plasma pentosidine level ($r=0.513$, $P=.001$) but not with serum vitamin B_6 level ($r=-0.087$, $P=.61$). The significance of correlation between pentosidine and medication dose disappeared when the data for patients 1, 2, and 3 were excluded ($r=0.186$, $P=.29$). The mean value of medication dose in the high-pentosidine group was not significantly different from that in the normal pentosidine group (17.0 mg/day [SD, 12.4 mg/day] vs 12.4 mg/day [SD, 9.1 mg/day], respectively; $P=.495$). No significant correlation was found between pentosidine and dose of medication (high-pentosidine group, $r=0.027$, $P=.93$; normal group, $r=-0.067$, $P=.78$). Pentosidine level in smokers was not significantly different from that in nonsmokers (smokers, 65.6 ng/mL [SD, 29.7 ng/mL]; nonsmokers, 80.3 ng/mL [SD, 60.9 ng/mL]; $P=.69$), nor did vitamin B_6 level differ between these groups (smokers, 5.5 ng/mL [SD, 6.4 ng/mL]; nonsmokers, 7.3 ng/mL [SD, 5.4 ng/mL]; $P=.08$). Plasma pentosidine and vitamin B_6 levels did not appear to be affected by confounding factors such as duration of hospitalization, since there were no correlations between biochemical data and duration of hospitalization (pentosidine, $r=0.295$, $P=.07$; vitamin B_6, $r=-0.072$, $P=.67$).

COMMENT

This study revealed that some patients with schizophrenia are predisposed to enhanced carbonyl stress. Pyridoxal is 1 of the 3 forms of vitamin B_6, ie, pyridoxine, pyridoxal, and pyridoxamine. In vivo, pyridoxamine is biosynthesized from both pyridoxal and pyridoxine. Marked decreases in serum pyridoxal levels were found in 11 schizophrenic patients, but not in the control subjects (Table 1 and Table 3). Two schizophrenic patients with heterozygous frameshift mutations displayed markedly lowered pyridoxal levels (Table 3). Depletion of pyridoxal might thus reflect elevated carbonyl stress induced by *GLO1* defects and other unknown factors in these patients. Carbonyl stress and AGEs are known to interfere with cellular functions in various fashions. First, carbonyl compounds are biologically active and initiate a variety of cellular responses.[47] Second, AGEs induce not only structural alterations in proteins, but also influence cellular functions on interaction with receptors for

AGEs.[48] Agents able to inhibit AGE formation or entrap carbonyl compounds may also prove to be of therapeutic value, if carbonyl stress is directly linked to schizophrenic signs and symptoms. Some AGE inhibitory compounds are already clinically available (eg, angiotensin receptor blockers).[49] Others, including pyridoxamine[50] and TM2002,[51] have potent abilities to entrap toxic carbonyl compounds and prevent toxicity. In particular, the markedly lower vitamin B_6 levels in schizophrenic patients with high pentosidine levels suggest that pyridoxamine, a nontoxic, water-soluble vitamin B_6, may prove clinically useful.

To examine the molecular mechanisms underlying the carbonyl stress we observed and determine whether elevated carbonyl stress plays a causative role in schizophrenia, we performed a deep resequencing analysis of one of the target genes, *GLO1*. We focused on *GLO1*, because it is ubiquitous and because a highly active defense against glycation appears to be associated with the risk of development of various disorders,[8] though several enzymes are capable of reduction of α-dicarbonyls, eg, aldose reductase, betaine-aldehyde dehydrogenase, and 2-oxoaldehyde dehydrogenase.[52] We identified rare but drastic genetic variants, 2 different heterozygous frameshift mutations, and a functional Glu111Ala polymorphism. Biochemical analyses revealed that all of these resulted in a 10% to 50% reduction in GLO1 activity in RBC and were linked to attendant biochemical abnormalities, ie, increased plasma pentosidine and decreased serum vitamin B_6. These *GLO1* genetic defects/alterations were also identified in a fraction of control subjects; though in contrast to schizophrenic patients, these controls exhibited normal pentosidine and vitamin B_6 levels, implying the existence of compensatory mechanisms, such as upregulation of other relevant enzymes. Such compensatory mechanisms might not function in schizophrenia owing to additional unknown defects. The mechanisms through which healthy subjects with *GLO1* genetic defects/alterations escape carbonyl stress are of special interest. Elucidation of such mechanisms might clarify not only the sequential events involved in the development of schizophrenia, but also provide clues to novel therapeutic approaches in patients with carbonyl stress. Collectively, our findings suggest a cross-sectional link, albeit incomplete, between *GLO1* defect–elicited carbonyl stress and a subgroup of patients with schizophrenia.

We detected 13 Ala111/Ala111 genotype carriers among 3271 Japanese subjects. The frequency of the Ala111 allele exhibits high population diversity: 0.354 to 0.475 in Europeans, 0.239 to 0.395 in African Americans, 0.267 in sub-Saharan Africans, and 0.033 to 0.125 in Asian populations. The allelic frequency of Ala111 determined in the present study is identical to that described by Thornally.[11] The high prevalence of the Ala111 allele in European and African American populations suggests the existence of a mechanism maintaining normal plasma pentosidine and serum vitamin B_6 levels, despite diminished GLO1 activity, in individuals from these populations.

We estimate that approximately 20% of patients exhibited enhanced carbonyl stress–related schizophrenia based on our biochemical analyses using as criteria both high accumulation of pentosidine (>55.2 ng/mL) and depletion of vitamin B_6 (male, <6 ng/mL; female, <4 ng/mL), as shown in eTable 4. The frequency of such individuals was estimated to be approximately 1% when the criterion was carriage of a heterozygous frameshift mutation or homozygote for Ala111.

There are possible limitations of our study. First, all patients in our study had taken medication. We could not exclude the possibility of an increase of carbonyl stress through antipsychotic medicines. We hope to clarify whether carbonyl stress is involved in psychiatric illnesses using drug-naive patients in the near future. Second, the sample size of biochemical analyses was modest. Further investigations of reciprocal relationships between pentosidine accumulation/vitamin B_6 depletion and genetic defects using large Japanese samples and individuals from different ancestral populations are needed. Third, for biochemical analyses, we arbitrarily selected molecules and cofactors affecting glyoxalase detoxification systems in vivo, as shown in eFigure 1. We thus may have missed important molecules involved in the metabolic cascades maintaining homeostasis by compensating for *GLO1* genetic defects. Fourth, we could not exclude effects of exercise on our biochemical findings, as we were unable to quantify the physical activity of patients in a systematic fashion. In future work, we plan to focus on profiling the metabolomics, genomics, and clinical manifestations of carbonyl stress–related schizophrenia with or without *GLO1* defects. Fifth, the reason why low GLO1 protein expression was observed only in patients with the Ala111/Ala111 genotype in vivo remains unclear.

In summary, our study revealed the pivotal role of carbonyl stress in some patients with schizophrenia, and subsequent intensive resequencing analysis of *GLO1* detected 2 novel frameshift mutations with loss of function and moderate-effect Glu111/Ala111 polymorphism in Japanese cohorts. Additional studies of carbonyl stress in schizophrenia may well pave the way toward novel therapeutic/preventive measures for this devastating disease.

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Author Affiliations: Project for Schizophrenia Research, Tokyo Institute of Psychiatry, Tokyo, Japan (Drs Makoto Arai, Haga, Ichikawa, Nishida, Tanaka, Furukawa, and Itokawa; and Mss Nohara, Obata, and Mayumi Arai); Institute of Medical Sciences, Tokai University, Bohseidai, Isehara, Kanagawa, Japan (Ms Yuzawa and Dr Miyata); Laboratory for Molecular Psychiatry, RIKEN Brain Science Institute, Saitama, Japan (Drs Ohnishi, Toyota, Yoshikawa, and Itokawa; and Ms Iwayama); Department of Neuropsychiatry, Okayama University Graduate School of Medicine and Dentistry, Okayama, Japan (Dr Ujike); Department of Psychiatry, Tokyo Metropolitan Matsuzawa Hospital, Tokyo (Drs Aikawa, Kuroda, Niizato, Izawa, Matsushita, Okazaki, and Itokawa); Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, Hamamatsu, Japan (Drs Nakamura and Mori); Department of Integrative Neurophysiology, Chiba University Graduate School of Medicine (Dr Matsuzawa), Division of Clinical Neuroscience, Chiba University Center for Forensic

Mental Health (Dr Hashimoto), and Department of Psychiatry, Chiba University Graduate School of Medicine (Dr Iyo), Chiba, Japan; Department of Neuroscience, Division of Psychobiology, Tohoku University Graduate School of Medicine, Miyagi, Japan (Dr Sora); Core Research of Evolutional Science & Technology, Japan Science and Technology Agency, Tokyo (Drs Yoshikawa and Itokawa); and Center for Translational and Advanced Research on Human Disease, Tohoku University Graduate School of Medicine, Miyagi (Dr Miyata).
Correspondence: Masanari Itokawa, MD, PhD, Project for Schizophrenia Research, Tokyo Institute of Psychiatry, 2-1-8 Kamikitazawa, Setagaya, Tokyo 156-8585, Japan (itokawa-ms@igakuken.or.jp); Toshio Miyata, MD, PhD, Center for Translational and Advanced Research on Human Disease, Tohoku University Graduate School of Medicine, Miyagi 980-8575, Japan (t-miyata@mail.tains.tohoku.ac.jp).
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REFERENCES

1. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry.* 2003;60(12):1187-1192.
2. Sullivan PF. The genetics of schizophrenia. *PLoS Med.* 2005;2(7):e212.
3. Schulz JB, Lindenau J, Seyfried J, Dichgans J. Glutathione, oxidative stress and neurodegeneration. *Eur J Biochem.* 2000;267(16):4904-4911.
4. Tosic M, Ott J, Barral S, Bovet P, Deppen P, Gheorghita F, Matthey ML, Parnas J, Preisig M, Saraga M, Solida A, Timm S, Wang AG, Werge T, Cuénod M, Do KQ. Schizophrenia and oxidative stress: glutamate cysteine ligase modifier as a susceptibility gene. *Am J Hum Genet.* 2006;79(3):586-592.
5. Young J, McKinney SB, Ross BM, Wahle KW, Boyle SP. Biomarkers of oxidative stress in schizophrenic and control subjects. *Prostaglandins Leukot Essent Fatty Acids.* 2007;76(2):73-85.
6. Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. *Int J Neuropsychopharmacol.* 2008;11(6):851-876.
7. Kikuchi S, Shinpo K, Takeuchi M, Yamagishi S, Makita Z, Sasaki N, Tashiro K. Glycation: a sweet tempter for neuronal death. *Brain Res Brain Res Rev.* 2003;41(2-3):306-323.
8. Thornalley PJ. The glyoxalase system: new developments towards functional characterization of a metabolic pathway fundamental to biological life. *Biochem J.* 1990;269(1):1-11.
9. Thornalley PJ. Glyoxalase I: structure, function and a critical role in the enzymatic defence against glycation. *Biochem Soc Trans.* 2003;31(Pt 6):1343-1348.
10. Miyata T, van Ypersele de Strihou C, Kurokawa K, Baynes JW. Alterations in nonenzymatic biochemistry in uremia: origin and significance of "carbonyl stress" in long-term uremic complications. *Kidney Int.* 1999;55(2):389-399.
11. Thornalley PJ. The glyoxalase system in health and disease. *Mol Aspects Med.* 1993;14(4):287-371.
12. Brown AS, Bottiglieri T, Schaefer CA, Quesenberry CP Jr, Liu L, Bresnahan M, Susser ES. Elevated prenatal homocysteine levels as a risk factor for schizophrenia. *Arch Gen Psychiatry.* 2007;64(1):31-39.
13. Frankenburg FR. The role of one-carbon metabolism in schizophrenia and depression. *Harv Rev Psychiatry.* 2007;15(4):146-160.
14. Gilbody S, Lewis S, Lightfoot T. Methylenetetrahydrofolate reductase (MTHFR) genetic polymorphisms and psychiatric disorders: a HuGE review. *Am J Epidemiol.* 2007;165(1):1-13.
15. Gysin R, Kraftsik R, Sandell J, Bovet P, Chappuis C, Conus P, Deppen P, Preisig M, Ruiz V, Steullet P, Tosic M, Werge T, Cuénod M, Do KQ. Impaired glutathione synthesis in schizophrenia: convergent genetic and functional evidence. *Proc Natl Acad Sci U S A.* 2007;104(42):16621-16626.
16. Haidemenos A, Kontis D, Gazi A, Kallai E, Allin M, Lucia B. Plasma homocysteine, folate and B12 in chronic schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry.* 2007;31(6):1289-1296.
17. Levine J, Stahl Z, Sela BA, Ruderman V, Shumaico O, Babushkin I, Osher Y, Bersudsky Y, Belmaker RH. Homocysteine-reducing strategies improve symptoms in chronic schizophrenic patients with hyperhomocysteinemia. *Biol Psychiatry.* 2006;60(3):265-269.
18. Saadat M, Mobayen F, Farrashbandi H. Genetic polymorphism of glutathione S-transferase T1: a candidate genetic modifier of individual susceptibility to schizophrenia. *Psychiatry Res.* 2007;153(1):87-91.
19. Yao JK, Leonard S, Reddy R. Altered glutathione redox state in schizophrenia. *Dis Markers.* 2006;22(1-2):83-93.
20. Kirk RL, Theophilus J, Whitehouse S, Court J, Zimmet P. Genetic susceptibility to diabetes mellitus: the distribution of properdin factor B (Bf) and glyoxalase (GLO) phenotypes. *Diabetes.* 1979;28(10):949-951.
21. Miyata T, van Ypersele de Strihou C, Imasawa T, Yoshino A, Ueda Y, Ogura H, Kominami K, Onogi H, Inagi R, Nangaku M, Kurokawa K. Glyoxalase I deficiency is associated with an unusual level of advanced glycation end products in a hemodialysis patient. *Kidney Int.* 2001;60(6):2351-2359.
22. Fujimoto M, Uchida S, Watanuki T, Wakabayashi Y, Otsuki K, Matsubara T, Suetsugi M, Funato H, Watanabe Y. Reduced expression of glyoxalase-1 mRNA in mood disorder patients. *Neurosci Lett.* 2008;438(2):196-199.
23. Junaid MA, Kowal D, Barua M, Pullarkat PS, Sklower Brooks S, Pullarkat RK. Proteomic studies identified a single nucleotide polymorphism in glyoxalase I as autism susceptibility factor. *Am J Med Genet A.* 2004;131(1):11-17.
24. Sacco R, Papaleo V, Hager J, Rousseau F, Moessner R, Militerni R, Bravaccio C, Trillo S, Schneider C, Melmed R, Elia M, Curatolo P, Manzi B, Pascucci T, Puglisi-Allegra S, Reichelt KL, Persico AM. Case-control and family-based association studies of candidate genes in autistic disorder and its endophenotypes: TPH2 and GLO1. *BMC Med Genet.* 2007;8:11.
25. Politi P, Minoretti P, Falcone C, Martinelli V, Emanuele E. Association analysis of the functional Ala111Glu polymorphism of the glyoxalase I gene in panic disorder. *Neurosci Lett.* 2006;396(2):163-166.
26. Ledig M, Doffoel M, Ziessel M, Kopp P, Charrault A, Tongio MM, Mayer S, Bockel R, Mandel P. Frequencies of glyoxalase I phenotypes as biological markers in chronic alcoholism. *Alcohol.* 1986;3(1):11-14.
27. Ditzen C, Jastorff AM, Kessler MS, Bunck M, Teplytska L, Erhardt A, Krömer SA, Varadarajulu J, Targosz BS, Sayan-Ayata EF, Holsboer F, Landgraf R, Turck CW. Protein biomarkers in a mouse model of extremes in trait anxiety. *Mol Cell Proteomics.* 2006;5(10):1914-1920.
28. Hovatta I, Tennant RS, Helton R, Marr RA, Singer O, Redwine JM, Ellison JA, Schadt EE, Verma IM, Lockhart DJ, Barlow C. Glyoxalase 1 and glutathione reductase 1 regulate anxiety in mice. *Nature.* 2005;438(7068):662-666.
29. Krömer SA, Kessler MS, Milfay D, Birg IN, Bunck M, Czibere L, Panhuysen M, Pütz B, Deussing JM, Holsboer F, Landgraf R, Turck CW. Identification of glyoxalase-I as a protein marker in a mouse model of extremes in trait anxiety. *J Neurosci.* 2005;25(17):4375-4384.
30. Arolt V, Lencer R, Nolte A, Müller-Myhsok B, Purmann S, Schürmann M, Leutelt J, Pinnow M, Schwinger E. Eye tracking dysfunction is a putative phenotypic susceptibility marker of schizophrenia and maps to a locus on chromosome 6p in

families with multiple occurrence of the disease. *Am J Med Genet.* 1996;67 (6):564-579.
31. Brzustowicz LM, Honer WG, Chow EW, Hogan J, Hodgkinson K, Bassett AS. Use of a quantitative trait to map a locus associated with severity of positive symptoms in familial schizophrenia to chromosome 6p. *Am J Hum Genet.* 1997; 61(6):1388-1396.
32. Nurnberger JI Jr, Foroud T. Chromosome 6 workshop report. *Am J Med Genet.* 1999;88(3):233-238.
33. Turner WJ. Genetic markers for schizotaxia. *Biol Psychiatry.* 1979;14(1):177-206.
34. Arai M, Yamada K, Toyota T, Obata N, Haga S, Yoshida Y, Nakamura K, Minabe Y, Ujike H, Sora I, Ikeda K, Mori N, Yoshikawa T, Itokawa M. Association between polymorphisms in the promoter region of the sialyltransferase 8B (SIAT8B) gene and schizophrenia. *Biol Psychiatry.* 2006;59(7):652-659.
35. Hattori E, Nakajima M, Yamada K, Iwayama Y, Toyota T, Saitou N, Yoshikawa T. Variable number of tandem repeat polymorphisms of DRD4: re-evaluation of selection hypothesis and analysis of association with schizophrenia. *Eur J Hum Genet.* 2009;17(6):793-801.
36. Ide M, Muratake T, Yamada K, Iwayama-Shigeno Y, Iwamoto K, Takao H, Toyota T, Kaneko N, Minabe Y, Nakamura K, Kato T, Mori N, Asada T, Someya T, Yoshikawa T. Genetic and expression analyses of FZD3 in schizophrenia. *Biol Psychiatry.* 2004;56(6):462-465.
37. Toyota T, Yoshitsugu K, Ebihara M, Yamada K, Ohba H, Fukasawa M, Minabe Y, Nakamura K, Sekine Y, Takei N, Suzuki K, Itokawa M, Meerabux JM, Iwayama-Shigeno Y, Tomaru Y, Shimizu H, Hattori E, Mori N, Yoshikawa T. Association between schizophrenia with ocular misalignment and polyalanine length variation in PMX2B. *Hum Mol Genet.* 2004;13(5):551-561.
38. Yamada K, Gerber DJ, Iwayama Y, Ohnishi T, Ohba H, Toyota T, Aruga J, Minabe Y, Tonegawa S, Yoshikawa T. Genetic analysis of the calcineurin pathway identifies members of the EGR gene family, specifically EGR3, as potential susceptibility candidates in schizophrenia. *Proc Natl Acad Sci U S A.* 2007;104 (8):2815-2820.
39. Arinami T, Ohtsuki T, Ishiguro H, Ujike H, Tanaka Y, Morita Y, Mineta M, Takeichi M, Yamada S, Imamura A, Ohara K, Shibuya H, Ohara K, Suzuki Y, Muratake T, Kaneko N, Someya T, Inada T, Yoshikawa T, Toyota T, Yamada K, Kojima T, Takahashi S, Osamu O, Shinkai T, Nakamura M, Fukuzako H, Hashiguchi T, Niwa SI, Ueno T, Tachikawa H, Hori T, Asada T, Nanko S, Kunugi H, Hashimoto R, Ozaki N, Iwata N, Harano M, Arai H, Ohnuma T, Kusumi I, Koyama T, Yoneda H, Fukumaki Y, Shibata H, Kaneko S, Higuchi H, Yasui-Furukori N, Numachi Y, Itokawa M, Okazaki Y; Japanese Schizophrenia Sib-Pair Linkage Group. Genomewide high-density SNP linkage analysis of 236 Japanese families supports the existence of schizophrenia susceptibility loci on chromosomes 1p, 14q, and 20p. *Am J Hum Genet.* 2005;77(6):937-944.
40. McLellan AC, Thornalley PJ. Glyoxalase activity in human red blood cells fractioned by age. *Mech Ageing Dev.* 1989;48(1):63-71.
41. Miyata T, Taneda S, Kawai R, Ueda Y, Horiuchi S, Hara M, Maeda K, Monnier VM. Identification of pentosidine as a native structure for advanced glycation end products in beta-2-microglobulin-containing amyloid fibrils in patients with dialysis-related amyloidosis. *Proc Natl Acad Sci U S A.* 1996;93(6):2353-2358.
42. Bisp MR, Bor MV, Heinsvig EM, Kall MA, Nexø E. Determination of vitamin B6 vitamers and pyridoxic acid in plasma: development and evaluation of a high-performance liquid chromatographic assay. *Anal Biochem.* 2002;305(1): 82-89.
43. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function–measured and estimated glomerular filtration rate. *N Engl J Med.* 2006;354 (23):2473-2483.
44. Sugiyama S, Miyata T, Ueda Y, Tanaka H, Maeda K, Kawashima S, Van Ypersele de Strihou C, Kurokawa K. Plasma levels of pentosidine in diabetic patients: an advanced glycation end product. *J Am Soc Nephrol.* 1998;9(9):1681-1688.
45. Miyata T, Ueda Y, Shinzato T, Iida Y, Tanaka S, Kurokawa K, van Ypersele de Strihou C, Maeda K. Accumulation of albumin-linked and free-form pentosidine in the circulation of uremic patients with end-stage renal failure: renal implications in the pathophysiology of pentosidine. *J Am Soc Nephrol.* 1996;7(8): 1198-1206.
46. Koyama K, Usami T, Takeuchi O, Morozumi K, Kimura G. Efficacy of methylcobalamin on lowering total homocysteine plasma concentrations in haemodialysis patients receiving high-dose folic acid supplementation. *Nephrol Dial Transplant.* 2002;17(5):916-922.
47. Rhodes J. Covalent chemical events in immune induction: fundamental and therapeutic aspects. *Immunol Today.* 1996;17(9):436-441.
48. Yan SD, Schmidt AM, Anderson GM, Zhang J, Brett J, Zou YS, Pinsky D, Stern D. Enhanced cellular oxidant stress by the interaction of advanced glycation end products with their receptors/binding proteins. *J Biol Chem.* 1994;269(13): 9889-9897.
49. Miyata T, van Ypersele de Strihou C, Ueda Y, Ichimori K, Inagi R, Onogi H, Ishikawa N, Nangaku M, Kurokawa K. Angiotensin II receptor antagonists and angiotensin-converting enzyme inhibitors lower in vitro the formation of advanced glycation end products: biochemical mechanisms. *J Am Soc Nephrol.* 2002; 13(10):2478-2487.
50. Booth AA, Khalifah RG, Hudson BG. Thiamine pyrophosphate and pyridoxamine inhibit the formation of antigenic advanced glycation end-products: comparison with aminoguanidine. *Biochem Biophys Res Commun.* 1996;220(1):113-119.
51. Izuhara Y, Nangaku M, Takizawa S, Takahashi S, Shao J, Oishi H, Kobayashi H, van Ypersele de Strihou C, Miyata T. A novel class of advanced glycation inhibitors ameliorates renal and cardiovascular damage in experimental rat models. *Nephrol Dial Transplant.* 2008;23(2):497-509.
52. Vander Jagt DL, Hunsaker LA. Methylglyoxal metabolism and diabetic complications: roles of aldose reductase, glyoxalase-I, betaine aldehyde dehydrogenase and 2-oxoaldehyde dehydrogenase. *Chem Biol Interact.* 2003;143-144: 341-351.

5 Gau SSF, Shang CY, Liu SK *et al.* Psychometric properties of the Chinese version of the Swanson, Nolan and Pelham, version IV scale-Parent form. *Int. J. Methods Psychiatr. Res.* 2008; 17: 35–44.

Hsueh-Ling Chang, MD[1], Nai-Chi Ko, BS[2] and Hsin-Yi Liang, MD[1]
[1]*Department of Child Psychiatry, Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, TaoYuan and* [2]*Dun Nan Attention Facilitation Center, Taipei, Taiwan*
Email: chang0687@adm.cgmh.org.tw
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Effects of cellular phone email use on the mental health of junior high school students in Japan

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IN RECENT YEARS, cellular phone (CP) email has become a major communication method among young people in Japan. Furthermore, 'cyberbullying' via email, chat and message board postings on the Internet and CP is becoming an important issue.[1] In the present study we conducted a large-scale survey of junior high school students in Japan to investigate the effects of CP email on emotional status.

The subjects consisted of a total of 10 709 junior high school students in grades 7–9 from Tsu City (5335 students) and Nagasaki City (5374 students). An anonymous 50-item self-completed questionnaire survey was conducted in July 2006 (Tsu)[2] and January 2008 (Nagasaki). Students absent on the day of the survey and those whose questionnaires were left blank were excluded; 4894 and 4864 valid responses were obtained for Tsu and Nagasaki, respectively (total, 9758; boys, 4952; girls, 4806).

Overall, 49.9% of students possessed a CP. The rate of possession increased with year in school; 39.6% of 7th graders, 50.2% of 8th graders and 59.3% of 9th graders possessed CP.

In response to the question 'Have you experienced stress during email exchange using your CP in the past week?', 8.4% of students reported 'once', 2.6% reported 'twice', 5.5% reported 'three times or more' (≥3 times), and the remainder reported 'never'. Logistic regression analysis was conducted controlling for grade and sex; odds ratios (OR) of the 12-item General Health Questionnaire (GHQ-12) poor mental health status (GHQ-12 score ≥ 4) were 1.83 (95% confidence interval [CI]: 1.57–2.12; once), 2.36 (95%CI: 1.81–3.07; twice), and 3.97 (95%CI: 3.25–4.85; ≥3 times) as compared to 'never'. Thus, the number of occurrences of email-related stress was associated with poor mental health status.

A significant association was also observed between subjects who answered 'yes' to the item 'Have you been the victim of bullying within the past year?' and those who reported '≥3 times' to the email question (OR, 2.02; 95%CI: 1.65–2.49). The OR of the GHQ-12 poor mental health status for subjects who met the two aforementioned criteria was markedly high (19.30; 95%CI: 10.60–35.15) compared to those who answered 'no' to the bullying question and 'never' to the email question.

Thus, a marked decline in mental health was observed in subjects who were experiencing both stress due to CP email use and bullying. These findings suggest that problems with CP email may have a considerable effect on the emotional status of young teens. CP email stress should be a new focus of mental health intervention in young people in Japan.

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REFERENCES

1 Slonje R, Smith PK. Cyberbullying: Another main type of bullying? *Scand. J. Psychol.* 2008; 49: 147–154.
2 Nishida A, Tanii H, Nishimura Y *et al.* Associations between psychotic-like experiences and mental health status and other psychopathologies among Japanese early teens. *Schizophr. Res.* 2008; 99: 125–133.

Akira Imamura, MD, PhD,[1] Atsushi Nishida, PhD,[2]* Noriko Nakazawa, MA,[1] Shinji Shimodera, MD, PhD,[3] Goro Tanaka, PhD,[1] Hirohisa Kinoshita, MD, PhD[1] Hiroki Ozawa, MD, PhD[1] and Yuji Okazaki, MD[2]
[1]*Department of Neuropsychiatry, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki,* [2]*Tokyo Institute of Psychiatry, Tokyo and* [3]*Department of Neuropsychiatry, Kochi Medical School, Kochi, Japan*
**Email: nishidaa@prit.go.jp*
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Original Article

Application of the Comprehensive Assessment of At-Risk Mental States (CAARMS) to the Japanese population: reliability and validity of the Japanese version of the CAARMS

Tetsuo Miyakoshi,[1] Kazunori Matsumoto,[2] Fumiaki Ito,[2] Noriyuki Ohmuro[1] and Hiroo Matsuoka[1]

Abstract

Aim: The putative prodromal state of schizophrenia has been conceptualized as an at-risk mental state (ARMS), which is identified on the basis of ultra-high-risk (UHR) criteria, and the Comprehensive Assessment of At-Risk Mental States (CAARMS) has been developed as a specific instrument. However, the generalizability of CAARMS and the concept of ARMS have not been established. In this study, we tested the reliability and validity of the Japanese version of CAARMS (CAARMS-J).

Methods: The participants were recruited from a specialized clinic for ARMS. The inter-rater reliability of CAARMS-J was examined. The Positive and Negative Syndrome Scale (PANSS) subscale scores and the basic symptoms of the CAARMS-J-defined UHR-positive group were compared with those of first-episode psychosis (FEP) and UHR-negative groups. The predictive validity was examined by following up the UHR-positive individuals. The 12-month transition rate to psychosis and the antipsychotics prescription rate were calculated.

Results: The CAARMS-J showed good inter-rater reliability. The PANSS-positive symptoms subscale scores of the UHR-positive group were intermediate between the FEP and the UHR-negative groups, and the UHR-positive group scored higher than the UHR-negative group in some basic symptoms. The positive and negative symptoms scores of the CAARMS-J significantly correlated with the corresponding scores of the PANSS. After 12 months, 3 out of 28 (10.7%) UHR-positive cases had transitioned to psychosis and 11 (39.2%) individuals were prescribed antipsychotics.

Conclusions: The CAARMS-J is a reliable and valid tool for assessing and detecting ARMS in Japanese clinical settings, suggesting that the concept of ARMS is applicable in Japan.

[1]Department of Psychiatry, Tohoku University Graduate School of Medicine, and [2]Department of Psychiatry, Tohoku University Hospital, Sendai, Japan

Corresponding author: Dr Tetsuo Miyakoshi, Department of Psychiatry, Tohoku University Graduate School of Medicine, Seiryo-machi 1-1, Aoba-ku, Sendai, Miyagi, 980-8574, Japan. Email: xt5t-myks@asahi-net.or.jp

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Key words: at-risk mental state, prodrome, psychosis, schizophrenia, ultra-high risk.

INTRODUCTION

It is well known that many people experience a prodromal phase prior to the onset of full-blown psychosis or schizophrenia.[1] Therefore, accurate identification of people at this stage and prediction of the future development of psychosis have been a matter of great interest in psychiatry. The putative prodromal state has been conceptualized as an at-risk mental state (ARMS), and attempts have been made to provide early intervention to young people with ARMS.[2–4]

ARMS indicates a prospectively high but not inevitable risk of developing psychosis, and it is usually determined on the basis of ultra-high risk (UHR) criteria,[2,5] composed of three UHR groups: attenuated psychotic symptoms (APS), which represent subthreshold psychotic positive symptoms;

brief limited intermittent psychotic symptoms (BLIPS), which are apparent psychotic symptoms that spontaneously remit within 1 week; and trait- and state-risk groups, in which the patient has a family history of psychosis (psychosis in first-degree relatives) or manifests schizotypal personality disorder along with low functioning that is sustained for at least 1 month. The transition rate of ARMS to full-blown psychosis has been reported to be approximately 10–50%, and this rate is considered to be influenced by the follow-up interval, type of intervention, settings of the service system and characteristics of the samples.[3,6]

People with ARMS exhibit a variety of symptoms, including non-specific psychiatric symptoms and attenuated positive symptoms, and most of them are diagnosed with comorbid axis-I disorders.[4,7] Therefore, it is essential to use a specific instrument for accurate identification and elaborate assessment of ARMS individuals. The Comprehensive Assessment of At-Risk Mental States (CAARMS)[8] and the Structured Interview for Prodromal Syndromes[9] are the two major instruments that have been developed to meet this need.

The CAARMS, which was developed at the PACE clinic in Melbourne, is a semi-structured interview designed to measure a wide variety of symptoms. It is thought to be useful for identifying and assessing symptoms, including attenuated positive symptoms, negative symptoms, general psychopathologies, behavioural changes and Huber's basic symptoms in people with ARMS. The reliability and validity of this instrument were confirmed by Yung *et al.*,[8] who conducted joint interviews of 34 UHR individuals to assess the inter-rater reliability of the instrument. The predictive validity was examined by comparing the 6-month transition rates of the CAARMS-defined UHR group ($n = 43$) and the non-UHR group ($n = 107$). The discriminant validity was assessed by comparing the CAARMS scores of UHR individuals ($n = 48$) and the control group ($n = 48$), and the concurrent validity was examined by testing the accordance between the CAARMS-defined UHR criteria and the Brief Psychiatric Rating Scale (BPRS)/Comprehensive Assessment of Symptoms and History (CASH)-defined UHR criteria in 49 participants. The CAARMS has been adopted in many countries/regions outside Australia, including the UK,[10] Korea[11] and Hong Kong.[12] However, only the original version has been assessed for reliability and validity.[8]

We assessed the generalizability of CAARMS by examining its applicability in Japan – a country with cultural and medical systems different from those of the other countries where the concepts of ARMS and early intervention service have already been developed. We developed the Japanese version of the CAARMS (CAARMS-J), applied the instrument for the assessment of the Japanese population and evaluated its reliability and validity. The inter-rater reliability was examined by using the data from joint interviews of 40 ARMS individuals who met the CAARMS-J-defined UHR criteria (UHR+). The construct validity was assessed by comparing the Positive and Negative Syndrome Scale (PANSS) subscale scores and the basic symptoms of the UHR+ group with those of the first-episode psychosis (FEP) and UHR– (individuals who did not meet the CAARMS-J-defined UHR criteria) groups. The concurrent validity was examined by assessing the correlations of the positive and negative symptoms scores between CAARMS-J and PANSS. The predictive validity was assessed on the basis of the 12-month transition rate and the antipsychotics prescription rate in 28 UHR+ individuals.

METHOD

Participants

The participants were recruited from the Sendai at-risk mental state and first episode (SAFE) clinic at the Department of Psychiatry, Tohoku University Hospital; this clinic is an outpatient clinic for people with ARMS. The individuals who fulfilled the following inclusion criteria were defined as ARMS cases in this study: (i) those aged between 14 and 35 years; (ii) those seeking psychiatric help; and (iii) those fulfilling the UHR criteria defined by CAARMS-J. The exclusion criteria were: (i) a history of psychotic episodes, or a history of manic episodes that fulfilled the diagnostic criteria of bipolar I disorder specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (bipolar I disorder being often as severe as psychotic disorders); (ii) history of treatment with antipsychotics; (iii) serious risk of suicide or violence due to a personality disorder; (iv) current substance dependence; (v) known intellectual disability (IQ < 70); and (vi) neurological disorders, head injury or any other significant medical condition associated with psychiatric symptoms. The study was carried out with the authorization of the Ethics Committee of Tohoku University Graduate School of Medicine and Tohoku University Hospital, and all the participants gave their written informed consent.

Instruments

The CAARMS instrument encompasses different aspects of psychopathology and functioning in

TABLE 1. Demographic variables, and the scores of GAF, the PANSS and the CAARMS-J in three diagnostic groups†

	ARMS (n = 31)	FEP (n = 10)	Others (n = 20)	Test statistic	P	Post hoc test
Age Mean (SD)	20.3 (4.6)	19.3 (4.9)	20.8 (4.2)	X^2 = 1.32	0.516	–
Sex (M : F)	11:20	3:7	9:11	–	–	–
GAF Mean (SD)	47.7 (6.6)	36.4 (8.7)	49.6 (9.0)	X^2 = 12.98	0.002	others = ARMS > FEP
PANSS subscale scores						
Positive symptoms	15.5 (3.8)	18.5 (3.8)	10.8 (2.5)	X^2 = 25.55	<0.001	FEP = ARMS > others
Negative symptoms	14.5 (4.6)	19.0 (3.2)	13.8 (4.4)	X^2 = 10.53	0.005	FEP > ARMS = others
General psychopathology	38.8 (9.2)	37.5 (7.3)	30.8 (5.1)	X^2 = 11.89	0.003	FEP = ARMS > others
CAARMS-J						
Positive symptoms						
Thought content	3.8 (1.3)	4.9 (1.1)	1.3 (0.8)	X^2 = 37.56	<0.001	FEP = ARMS > others
Perceptual abnormalities	2.8 (1.7)	4.8 (1.5)	1.2 (1.0)	X^2 = 24.80	<0.001	FEP > ARMS > others
Disorganized speech	2.2 (1.2)	3.3 (1.3)	1.1 (1.0)	X^2 = 18.64	<0.001	FEP = ARMS > others
Huber's basic symptoms						
Subjective experience of cognitive change	2.7 (1.3)	3.5 (0.5)	2.0 (0.8)	X^2 = 14.80	0.001	FEP > others
Subjective complaints of impaired motor functioning	1.0 (1.2)	1.0 (1.2)	0.4 (0.7)	X^2 = 5.33	0.070	–
Subjective complaints of impaired bodily sensation	1.2 (1.7)	1.9 (2.1)	0.1 (0.4)	X^2 = 11.40	0.003	FEP = ARMS > others
Subjective complaints of impaired autonomic functioning	2.8 (1.0)	2.1 (1.7)	2.5 (1.1)	X^2 = 2.29	0.318	–
Subjective emotional disturbance	2.4 (1.1)	2.2 (1.4)	1.9 (1.3)	X^2 = 1.53	0.464	–
Avolition/apathy	3.0 (1.3)	3.1 (1.5)	2.6 (1.3)	X^2 = 1.73	0.422	–
Impaired tolerance to normal stress	3.1 (1.5)	3.2 (1.5)	2.4 (1.6)1	X^2 = 2.92	0.232	–

†Data are given as mean (standard deviation (SD)) except where indicated otherwise.
GAF, The Global Assessment of Functioning; PANSS, The Positive and Negative Syndrome Scale; CAARMS-J, The Japanese version of the Comprehensive Assessment of At-Risk Mental States; ARMS, At-risk mental state group; FEP, First episode of psychosis group; Others, Other disorder group.

order to enable comprehensive assessment of individuals with ARMS. The CAARMS contains seven categories consisting of 28 subscales,[8] including some of Huber's basic symptoms[13,14] (Table 1). Each subscale is rated in terms of the dimensions of intensity (0–6) and frequency/duration (0–6). The positive symptoms category is used to determine the UHR criteria. The threshold of psychotic disorder is defined by operationalized clear-cut levels of positive symptoms occurring for at least 1 week, either on a daily basis or for more than three times a week with each symptom continuing for more than 1 hour on each occasion, according to the psychosis criteria defined by CAARMS-J.

The CAARMS was translated into Japanese by two Japanese psychiatrists (KM and TM) after obtaining permission from the original authors. As some colloquial English phrases were difficult to translate, we carefully selected words and phrases so that the translation would be in natural Japanese. This Japanese version of the CAARMS (the CAARMS-J instrument is available from the second author upon request) was back translated into English by professional translators who had not perused the original English text. The results of the back-translation were examined and judged as satisfactory by a staff member of PACE who was familiar with the usage of the CAARMS.

The PANSS[15] is a 30-item scale designed to include three subscales for different types of symptoms: positive syndrome, negative syndrome and general psychopathology. The inter-rater reliability and the criterion-related and construct validities of PANSS were evaluated by Kay *et al.*,[15] and the inter-rater reliability and internal consistency of the Japanese version have been evaluated by Igarashi *et al.*[16]

Procedures

Inter-rater reliability

The inter-rater reliability of CAARMS-J was examined by using the data from consecutive joint interviews of 40 UHR+ individuals (10 males and 30 females; mean age ± standard deviation (SD), 20.0 ± 4.5 years) at intake. Initially, three psychiatrists trained each other on the usage of CAARMS-J, with help from the CAARMS training DVD. Preliminary administration of the instrument to suspected ARMS individuals was conducted before the study.

Two of the three raters were paired for each interview. We also assessed the inter-rater agreement for the UHR criteria.

Construct validity

Sixty-one individuals (23 males and 38 females; age, 14–35 years; mean age ± SD, 20.3 ± 4.5 years) who consecutively attended an intake interview at the SAFE clinic participated in this study. All the participants were interviewed using CAARMS-J and PANSS. We used CAARMS-J to determine whether these individuals met the UHR criteria, and the axis-I diagnosis was made according to DSM-IV-TR on the basis of the agreement between two trained psychiatrists (KM and TM). After the interview, the participants were divided into three groups on the basis of the UHR criteria assessment: UHR+ group, FEP group and UHR– group (Table 1). The FEP group consisted of patients with schizophrenia ($n = 2$), schizophreniform disorder ($n = 2$), brief psychotic disorder ($n = 3$) and psychotic disorder not otherwise specified ($n = 3$). The UHR– group consisted of individuals who visited the SAFE clinic for risk assessment but did not meet the criteria of UHR or psychosis. They were diagnosed with anxiety disorders ($n = 10$), depressive disorders ($n = 6$), adjustment disorders ($n = 4$), somatoform disorders ($n = 2$) and no axis-I disorders ($n = 1$); there were three individuals with dual diagnosis.

We assessed the construct validity of CAARMS-J by determing the presence of the characteristic features of ARMS in the CAARMS-J-defined ARMS individuals. We compared the UHR+, FEP and UHR– groups in terms of the PANSS positive-, negative- and general psychopathology-symptoms subscale scores and Huber's basic symptoms measured by CAARMS-J. We hypothesized that the positive-symptoms scores of the UHR+ group would be intermediate between those of the FEP and UHR– groups. Further, we predicted that the scores of some of Huber's basic symptoms in the UHR+ and FEP groups would be higher than those in the UHR– group, because the basic symptoms are self-experienced deficit symptoms which are thought to be observed through the entire course of schizophrenia, including the prodromal state.[13] It has also been reported that some of the basic symptoms predict the onset of psychosis.[17]

Concurrent validity

The abovementioned 61 individuals participated in this study. The concurrent validity of CAARMS-J for evaluating psychotic symptoms was tested by examining the correlations between the positive symptoms of CAARMS-J and the corresponding scales of PANSS. We verified the ability of CAARMS-J to measure negative symptoms by examining the correlation between the emotional disturbances and negative-symptoms category scores of CAARMS and the negative-symptoms subscale scores of PANSS.

Predictive validity

The predictive validity of the CAARMS-J-defined UHR criteria was tested by consecutively identifying young people with ARMS according to the CAARMS-J-defined UHR criteria. Twenty-eight individuals with ARMS were followed up at the SAFE clinic. Twenty-three individuals met the APS criteria, one individual met the risk-factor criteria, three individuals met the APS and risk-factor criteria, and one individual met the APS and BLIPS criteria. The participants were treated by one of the three psychiatrists according to the treatment guidelines of the SAFE clinic. A summary of the guidelines is as follows. Eclectic psychological intervention combining supportive therapy and cognitive therapy was provided to all the participants. The prescription of antipsychotics was avoided unless the individuals (i) had an imminent risk of suicide or severe violence; (ii) were overwhelmed by psychotic symptoms; (iii) were rapidly deteriorating; or (iv) did not respond to any other treatment. Low-dose atypical antipsychotics were used, if necessary. Selective serotonin reuptake inhibitor or benzodiazepines were used to treat depression, anxiety and insomnia. The participants were usually followed up weekly or after every 2 weeks, in accordance with their clinical needs. We calculated the rate of transition to psychosis at 12 months and the rate of prescription of antipsychotic medication during the 12-month follow-up period. Psychosis was defined according to the CAARMS-J criteria. We predicted that the transition rate at 12 months would be comparable to that in other studies in which putatively effective treatments were provided.

Data analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) 16.0 J for Windows (SPSS; Chicago, IL, USA). Intraclass correlations (ICCs) were calculated to assess inter-rater reliability, and the kappa coefficient was used to evaluate the inter-rater agreement on the diagnosis. Statistical comparisons across the three groups were examined by using the Kruskal–Wallis test, and post hoc comparisons were conducted by using the

Mann–Whitney U test with Bonferroni correction; the application of Bonferroni correction was found to reduce the level of significance from $P < 0.05$ to $P < 0.017$. Spearman correlations were adopted to determine the correlation between the PANSS and CAARMS-J scores.

RESULTS

Inter-rater reliability of the CAARMS-J

The ICC coefficients of the seven categories and the three positive-symptoms subscales of CAARMS-J are shown in Table 2. We found very good to excellent agreement in all the categories and positive-symptoms subscales. The kappa coefficient for the agreement on the UHR criteria between the three raters was 0.82 ($P < 0.001$).

Construct validity

The PANSS positive-symptoms subscale scores were different among the three groups (Table 1). The PANSS positive-symptoms subscale scores of the UHR+ group were significantly higher than those of the UHR– group ($P < 0.001$). The positive symptoms were more severe in the FEP group than in the UHR+ group, but the differences were not significant ($P = 0.033$).

There were significant differences among the three groups in the PANSS negative-symptoms subscale scores and the PANSS general psychopathology subscale scores. The PANSS negative-symptoms subscale scores of the FEP group were significantly higher than those in the UHR+ ($P = 0.002$) and the UHR– ($P = 0.002$) groups; however, there was no difference between the scores of the UHR+ and the UHR– groups ($P = 0.698$). The PANSS general psychopathology scores for the UHR+ and FEP groups were significantly higher than those for the UHR– group ($P = 0.001$ and $P = 0.015$, respectively), although there was no significant difference between the scores of the UHR+ and FEP groups ($P = 0.879$).

In the assessment of Huber's basic symptoms, two of the seven subscales adopted in CAARMS (i.e. the subscales relating to subjective experience of cognitive change and impaired bodily sensation) showed a significant difference among the three groups (Table 1). The score for subjectively experienced cognitive change in the FEP group was significantly higher than that in the UHR– group ($P < 0.001$). The individuals in the UHR+ group experienced subjectively higher cognitive change than those in the UHR– group ($P = 0.030$), and the patients in the FEP group experienced subjectively higher cognitive change than those in the UHR+ group ($P = 0.039$); however, the differences were not significant. The individuals in the FEP and UHR+ groups experienced higher impairment of body sensations than those in the UHR– group ($P = 0.013$ and $P = 0.004$, respectively). There were no significant differences between the groups in the assessment of the other five Huber's basic symptoms.

TABLE 2. Intra-class correlation coefficients (ICCs) of eight main subscales of the CAARMS-J ($n = 40$)

CAARMS-J subscale	ICC
Positive symptoms	0.94
Disorder of thought content	0.91
Perceptual abnormalities	0.97
Conceptual disorganization	0.87
Cognitive change concentration/attention	0.76
Emotional disturbance	0.74
Negative symptoms	0.87
Behavioural change	0.76
Motor/physical changes	0.84
General psychopathology	0.92
Overall	0.92

CAARMS-J, The Japanese version of the Comprehensive Assessment of At-Risk Mental States.

Concurrent validity

Table 3 shows the results of the Spearman correlation coefficient analysis between the CAARMS-J and PANSS subscales. Each subscale of the positive symptom scale of CAARMS-J correlated with the corresponding positive symptoms subscale of PANSS. Moreover, the emotional disturbance and negative symptoms category scores of CAARMS-J correlated with the negative symptom subscale score of PANSS.

Predictive validity

Five of the 28 participants did not complete the 12-month follow-up period. Four of these participants moved out of the clinic catchment area and we ascertained the absence of psychosis in two participants by telephone interview; however, we could not complete the follow-up for the other two participants. The fifth participant stopped visiting our clinic at 4 months, and he could not be contacted.

After 12 months of follow-up, 3 of the 28 participants (10.7%) had transitioned to psychosis, and all three had been prescribed antipsychotics during the follow-up period; the prescription periods for the

TABLE 3. Spearman correlations of the CAARMS-J scores with PANSS scores (n = 61)

CAARMS	PANSS	r (95% CI)
Positive symptoms	Positive symptoms	0.72* (0.57–0.82)
Thought content	delusion	0.85* (0.76–0.91)
Perceptual abnormalities	hallucinatory behaviour	0.90* (0.84–0.94)
Disorganized speech	conceptual disorganization	0.73* (0.58–0.83)
Emotional disturbance	Negative symptoms	0.64* (0.47–0.77)
Negative symptoms	Negative symptoms	0.53* (0.32–0.69)

*$P < 0.01$.
CAARMS-J, The Japanese version of the Comprehensive Assessment of At-Risk Mental States; CI, confidence interval; PANSS, The Positive and Negative Syndrome Scale.

three participants were 2, 10 and 22 weeks before the onset of psychosis, respectively. Antipsychotics were prescribed to 11 (39.2%) participants during the follow-up period. The average prescription period in the eight participants that did not progress to psychosis was 20.4 ± 18.5 weeks (range: 2–48 weeks); three of these participants were still being prescribed antipsychotics at 12 months. One participant developed psychosis at 13 months. This participant had fulfilled the criteria for APS and BLIPS at intake, and she had been refusing to take the prescribed antipsychotics.

DISCUSSION

This is the first study on the application of CAARMS and UHR criteria to the Japanese population and on the reliability and validity testing of CAARMS-J. The results indicate that CAARMS-J is a reliable and valid instrument for evaluating ARMS in the Japanese population. CAARMS and the concept of ARMS seem to exhibit generalizability across different cultures.

The ICC of each subscale of CAARMS-J showed good to excellent reliability, which was comparable to that reported by Yung *et al.*[8] The result demonstrated that CAARMS-J could be used for the reliable assessment of the comprehensive symptoms of ARMS. The inter-rater reliability of the UHR criteria defined by CAARMS-J was also confirmed to be satisfactory, as observed in the original study.[8]

The positive-symptoms subscale scores of the UHR+ group were intermediate between those of the FEP and UHR– groups. A similar pattern was observed in a study showing the intermediate severity of positive symptoms measured by the Scale of Prodromal Symptoms in ARMS individuals.[18] Miller *et al.* reported that the PANSS positive-symptoms subscales in the ARMS individuals were less severe than those in untreated patients with first-episode schizophrenia, but comparable to those in treated first-episode patients.[19] Most of the psychotic patients in our study were referred for apparently mild positive symptoms, and five of them already had been treated with antipsychotics; therefore, these patients were relatively stable. This could have been the reason for the absence of significant differences between the positive symptoms in the FEP and UHR+ groups.

The FEP group was determined on the basis of the positive symptom scores of CAARMS-J; however, the severity of the PANSS negative-symptoms subscales in the FEP group was significantly more than that in the UHR– group. It has been reported that the severity of negative symptoms in first-episode patients is usually greater than that in ARMS individuals.[20–22] The ARMS individuals who develop psychosis may exhibit more severe negative symptoms.[8]

The UHR+ and FEP groups had a higher general psychopathology score than the UHR– group. However, there was no significant difference between the UHR+ and FEP groups. This finding proves that the ARMS individuals in our study were not just a group of individuals undergoing incidental psychotic-like experiences with a relatively low risk of developing psychosis, but they were suffering from a general psychopathology that was as severe as that found in the FEP patients. Furthermore, the majority of ARMS individuals in our study were referred from psychiatrists who may have recognized the patients' risk of developing psychosis and their needs for specific psychiatric treatment.

The CAARMS contains several items that assess Huber's basic symptoms, which are thought to be prominent in ARMS individuals and patients with schizophrenia.[17,23] In the present study, the severity of two of the seven basic symptoms – subjective experience of cognitive change and subjective complaints of impaired bodily sensation – were different among the three groups; the scores of these symptoms in the UHR+ and FEP groups were higher than those in the UHR– group. These findings may be

indicative of the sensitivity of the cognitive change and impaired body sensation items in signalling the imminent risk of psychosis, and the indistinguishability of the other five items from non-specific psychiatric symptoms. Specialized instruments for measuring basic symptoms in ARMS individuals such as Schizophrenia Proneness Instrument, Adult-version,[24] could prove useful for reinforcement of the UHR criteria.

We expected that the positive and negative symptoms measured by CAARMS-J would correlate with those assessed by PANSS. The present results demonstrated that this expectation was justified. The present study demonstrated that CAARMS-J has good concurrent validity with PANSS in measuring the positive and negative symptoms of ARMS.

The methodological limitations of our study must be considered when comparing the results after the 12-month follow-up in our UHR-positive group with those of other studies. In the present study, we provided interventions that were expected to be effective for ARMS individuals, because optimal treatment for the patients was ethically required in our clinical setting. In addition, our interventions were not controlled and not uniformly delivered. However, in light of these limitations, the overview of transition rates in other studies in which active interventions were implemented may provide interesting insights. McGorry *et al.*[25] performed a randomized control study in which they compared the transition rate of ARMS individuals who were treated with specific prevention intervention (SPI), which combined cognitive-behavioural therapy and low-dose antipsychotic medication with that of ARMS individuals who were treated with need-based intervention (NBI). The transition rate of the SPI group was 10% at the end of the treatment phase and 19% at the 12-month follow-up; however, the transition rate of the NBI group was 36% at the end of the 6-month treatment phase and the 12-month follow-up. Morrison *et al.* conducted a randomized control study and reported that the transition rate at the 12-month follow-up was 6% for the ARMS individuals who received cognitive therapy for 6 months and 26% for those who did not receive the therapy.[26] In a North American longitudinal study that was conducted across eight clinical research centres, 291 subjects were longitudinally followed up with treatment that was administered according to the clinical judgment of the treating physicians, and the transition rate was $12.7 \pm 1.9\%$ at 6 months, $21.7 \pm 2.5\%$ at 12 months and $32.6 \pm 3.3\%$ at 24 months.[27] Considering these results, it can be assumed that CAARMS-J can reliably detect ARMS individuals.

The antipsychotic prescription rate in our study (39.2%) was almost similar to that in the abovementioned North American longitudinal study (35.1%).[27] In our study, 8 of the 11 participants who received antipsychotic medications did not progress to psychosis during the follow-up period; however, the other three participants developed psychosis in spite of receiving the treatment. The antipsychotic medication could have delayed or avoided the conversion to psychosis in some of the cases that did not progress to psychosis;[25,28] however, the use of this treatment method in these circumstances is still open to debate.[29] Out of the 20 individuals who completed the follow-up period without developing psychosis, only three participants were being prescribed antipsychotics at 12 months, which implies that the continuous prescription of antipsychotics to ARMS individuals is not always necessary. Considering the active treatment provided to the ARMS individuals and the relatively short period of follow-up in this study, it can be assumed that more than 10.7% participants may actually develop psychosis. In fact, one participant progressed to psychosis after the 12-month follow-up period (onset at 13 months) despite undergoing continuous treatment, which implies that at least 14.3% of the participants in our UHR+ group were at risk of developing psychosis after a longer follow-up period. However, the transition rate in our study seems to be low, and it supports the recent advocation of more benign forms of treatment for ARMS individuals.[29]

There were certain other limitations in this study. Firstly, the results were obtained by a small group of raters who had considerable clinical experience of assessing individuals with prodromal symptoms and were familiar with CAARMS-J. The generalizability of the results should be studied in the future. Secondly, the sample size was small and the number of female participants was almost double that of the male participants. This might be attributed to the fact that more female individuals visited our ARMS clinic. Finally, first-episode psychosis patients were not represented in this diagnostic population because they visited our clinic for suspected diagnosis of prodrome. This fact indicates that our ARMS clinic can also act as a gateway in the identification of FEP patients. The development of ARMS clinics is proving to be of great benefit for the advancement of early intervention in psychosis.

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REFERENCES

1. Yung AR, McGorry PD. The prodromal phase of first-episode psychosis: past and current conceptualizations. *Schizophr Bull* 1996; **22**: 353–70.
2. McGorry PD, Yung AR, Phillips LJ. The 'close-in' or ultra high-risk model: a safe and effective strategy for research and clinical intervention in prepsychotic mental disorder. *Schizophr Bull* 2003; **29**: 771–90.
3. Olsen KA, Rosenbaum B. Prospective investigations of the prodromal state of schizophrenia: assessment instruments. *Acta Psychiatr Scand* 2006; **113**: 273–82.
4. Yung AR, Phillips LJ, McGorry PD. *Treating Schizophrenia in the Prodromal Phase*. London: Taylor and Francis, 2004.
5. Yung AR, Phillips LJ, Yuen HP *et al.* Psychosis prediction: 12-month follow up of a high-risk ('prodromal') group. *Schizophr Res* 2003; **60**: 21–32.
6. Yung AR, Yuen HP, Berger G *et al.* Declining transition rate in ultra high risk (prodromal) services: dilution or reduction of risk? *Schizophr Bull* 2007; **33**: 673–81.
7. Rosen JL, Miller TJ, D'Andrea JT, McGlashan TH, Woods SW. Comorbid diagnoses in patients meeting criteria for the schizophrenia prodrome. *Schizophr Res* 2006; **85**: 124–31.
8. Yung AR, Yuen HP, McGorry PD *et al.* Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. *Aust N Z J Psychiatry* 2005; **39**: 964–71.
9. Miller TJ, McGlashan TH, Rosen JL *et al.* Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. *Schizophr Bull* 2003; **29**: 703–15.
10. Broome MR, Woolley JB, Johns LC *et al.* Outreach and support in south London (OASIS): implementation of a clinical service for prodromal psychosis and the at risk mental state. *Eur Psychiatry* 2005; **20**: 372–8.
11. Chung YS, Kang DH, Shin NY, Yoo SY, Kwon JS. Deficit of theory of mind in individuals at ultra-high-risk for schizophrenia. *Schizophr Res* 2008; **99**: 111–18.
12. Lam MM, Hung SF, Chen EY. Transition to psychosis: 6-month follow-up of a Chinese high-risk group in Hong Kong. *Aust N Z J Psychiatry* 2006; **40**: 414–20.
13. Huber G. Das Konzept substratnaher Basissymptome und seine Bedeutung fuer Theorie und Therapie schizophrener Erkrankungen. *Nevenarzt* 1983; **54**: 23–32.
14. Suellwold L, Huber G. *Schizophrene Basisstoerungen*. Berlin, Heidelberg: Springer-Verlag, 1986.
15. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res* 1998; **23**: 99–110.
16. Igarashi Y, Hayashi N, Yamashina M *et al.* Interrater reliability of the Japanese version of the Positive and Negative Syndrome Scale and the appraisal of its training effect. *Psychiatry Clin Neurosci* 1998; **52**: 467–70.
17. Klosterkoetter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F. Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 2001; **58**: 158–64.
18. Simon AE, Cattapan-Ludewig K, Zmilacher S *et al.* Cognitive functioning in the schizophrenia prodrome. *Schizophr Bull* 2007; **33**: 761–71.
19. Miller TJ, Zipursky RB, Perkins D *et al.* The PRIME North America randomized double-blind clinical trial of olanzapine versus placebo in patients at risk of being prodromally symptomatic for psychosis. II. Baseline characteristics of the 'prodromal' sample. *Schizophr Res* 2003; **61**: 19–30.
20. Bechdolf A, Pukrop R, Kohn D *et al.* Subjective quality of life in subjects at risk for a first episode of psychosis: a comparison with first episode schizophrenia patients and healthy controls. *Schizophr Res* 2005; **79**: 137–43.
21. Francey SM, Jackson HJ, Phillips LJ, Wood SJ, Yung AR, McGorry PD. Sustained attention in young people at high risk of psychosis does not predict transition to psychosis. *Schizophr Res* 2005; **79**: 127–36.
22. Haefner H, Maurer K, Ruhrmann S *et al.* Early detection and secondary prevention of psychosis: facts and visions. *Eur Arch Psychiatry Clin Neurosci* 2004; **254**: 117–28.
23. Schultze-Lutter F, Ruhrmann S, Picker H, von Reventlow HG, Brockhaus-Dumke A, Klosterkotter J. Basic symptoms in early psychotic and depressive disorders. *Br J Psychiatry* 2007; **51** (Suppl.): s31–7.
24. Schultze-Lutter F, Addington J, Ruhrmann S, Klosterkotter J. *Schizophrenia Proneness Instrument, Adult version (SPI-A)*. Roma: Giovanni Fioriti Editore s.r.l., 2007.
25. McGorry PD, Yung AR, Phillips LJ *et al.* Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. *Arch Gen Psychiatry* 2002; **59**: 921–8.
26. Morrison AP, French P, Walford L *et al.* Cognitive therapy for the prevention of psychosis in people at ultra-high risk: randomised controlled trial. *Br J Psychiatry* 2004; **185**: 291–7.
27. Cannon TD, Cadenhead K, Cornblatt B *et al.* Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. *Arch Gen Psychiatry* 2008; **65**: 28–37.
28. McGlashan TH, Zipursky RB, Perkins D *et al.* Randomized, double-blind trial of olanzapine versus placebo in patients prodromally symptomatic for psychosis. *Am J Psychiatry* 2006; **163**: 790–9.
29. Yung AR, Nelson B, Stanford C *et al.* Validation of 'prodromal' criteria to detect individuals at ultra high risk of psychosis: 2 year follow-up. *Schizophr Res* 2008; **105**: 10–17.

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Perspectives in Early Intervention

Clinical practice and research activities for early psychiatric intervention at Japanese leading centres

Masafumi Mizuno,[1] Michio Suzuki,[2] Kazunori Matsumoto,[3] Masaaki Murakami,[4,5] Kiyoaki Takeshi,[1] Tetsuo Miyakoshi,[3] Fumiaki Ito,[3] Ryoko Yamazawa,[5] Hiroyuki Kobayashi,[5] Takahiro Nemoto[5] and Masayoshi Kurachi[6]

[1]Il Bosco, Toho University Omori Medical Center, [4]Department of Social Welfare, Faculty of Sociology, Meiji Gakuin University, [5]Non Profit Organization, Minato net 21, Tokyo, Departments of [2]Neuropsychiatry and [6]Psychiatric Early Intervention, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, and [3]Department of Psychiatry, Tohoku University Hospital, Sendai, Japan

Corresponding author: Dr Masafumi Mizuno, Department of Neuropsychiatry, Toho University School of Medicine, 6-11-1, Omori-Nishi, Ota-ku, Tokyo 143-8541, Japan. Email: mizuno@med.toho-u.ac.jp

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Abstract

Aim: To describe clinical practice and research activities for early psychiatric intervention in Japan, a country with a huge number of psychiatric beds and a history of long-stay, hospital-based psychiatry.

Methods: The characteristics, methods and activities of early intervention studies and implementation at four leading institutions in Japan are described.

Results: The Tokyo Youth Club (Tokyo), the Department of Neuropsychiatry of Toyama University Hospital (Toyama), the Sendai At-risk Mental State and First Episode (SAFE) service (Sendai), and the Il Bosco of Toho University Omori Medical Center (Tokyo) have unique and active psychiatric programmes. Each centre has its own clinical research programme and treatment strategies. The Japanese Society for the Prevention of Psychiatric Disorders, founded in 1996, has made a steady contribution to psychiatric care by providing a forum for members to promote best practices for early intervention and by hosting annual meetings to discuss research and treatment.

Conclusions: The Japanese psychiatry service is continuing its transition from hospital-based psychiatry to community-based psychiatry. Despite these difficult circumstances, the publication of data on the duration of untreated psychosis in Japan along with evidence that early detection determines outcome has encouraged new attempts to promote early psychiatric intervention.

Key words: ARMS, early intervention, Japan, prevention, schizophrenia.

INTRODUCTION

For many years, the Japanese psychiatric service has struggled against conservative hospital-based psychiatry to realize a transition to community-based psychiatry.[1] Despite these efforts, the psychiatric service in Japan remains predominantly hospital-based, involving huge numbers of psychiatric beds and long-term stays. A decline in hospital beds has been observed since 1994, but the total number of inpatient beds is still 2.9 per 1000 persons, compared with 0.9 in the UK and 0.5 in the USA. Such reliance on hospital-based psychiatry is a barrier to the development of community-based psychiatry. The Japanese government first mentioned the term 'community psychiatry' in 1965 and acknowledged the need for a transition to community-based psychiatry. According to several surveys conducted by different agencies, approximately 30% of the patients in psychiatric hospitals would be capable of living in the community if appropriate community support programmes were available. The background of this situation lies mainly in the historical structure of the Japanese psychiatric system itself.

In 1950, the Japanese government declared that mental hospitals should be constructed within each of the 47 prefectures in Japan and that the construction of these hospitals was the responsibility of the public sector; however, the government never provided any funding for this endeavour. Thereafter, the government abandoned all responsibility for giving psychiatric services to the public, instead providing subsidies to the private sector to build mental hospitals. Even persons who were not involved in the medical profession became interested in this field, as managing psychiatric hospitals is a lucrative undertaking. Consequently, nearly 90% of all the psychiatric beds in Japan are operated by the private sector. Drastic changes to the Japanese psychiatric system are now impossible to make without considering the intention of the Japanese Association of Psychiatric Hospitals. Even in this adverse situation, some innovative hospitals have attempted to make the transition to community-based psychiatry through their own endeavours.

The reason for the adverse situation being faced by these hospitals lies in the characteristics of the financial system for Japanese health care. In Japan, all citizens are covered by a national health plan and have access to all sorts of medical resources, paying only 10–30% of the medical fees personally; the remainder of the health costs are covered by public expenditure and national insurance. A fee is paid for each service. These fees are regulated by a nationally uniform reimbursement schedule that does not favour community-based psychiatry, although it has made gradual changes towards this goal over the last 10 years, such as the creation of a new category for nurse visits to patients' homes (outreach activities) and decreasing the administration fees for inpatients as the length of the hospital stay increases. At present, no category for early intervention exists in the national reimbursement schedule. This slow and incomplete transition to community-based psychiatry is still a long way from an 'inclusive society' and remains a source of stigma against patients with schizophrenia.

TOKYO YOUTH CLUB (http://www.tokyo-yc.org/)

Minato net 21 is the Tokyo centre of the Optimal Treatment Project, an international project advocated by the late Ian R.H. Falloon that collects data to develop effective evidence-based treatment strategies for persons with mental illness.[2]

Minato net 21 has a home page for the 'Tokyo Youth Club', a site intended for teenagers and young adults that provides the latest information on mental health and consultations concerning mental health. Its aim is early detection and intervention to prevent the onset of psychosis, as part of the strategies included in the Optimal Treatment Project. The site contains general information on schizophrenia, including its prodromal signs, pathology, latest biopsychosocial treatment and the duration of untreated psychosis (DUP) data for Tokyo (approximately 14 months).[3] The site stresses the importance of early intervention for a good prognosis.[4] This undertaking has been named 'project DUP zero', reflecting its goal of shortening the DUP. A revised version of the self-check 'Yale University PRIME Screening Test' has been translated into Japanese, with some improvements, so that persons visiting the website can take the screening test and, if they match the criteria and feel that they are in need of help, can select one of the collaborating medical facilities where they can receive an initial consultation. Also, any consultation emails sent to the site are answered directly and, if needed, a referral to an appropriate clinic or hospital is given. Information for family members is also available on the site because older generations continue to have a strong stigma against psychiatric care and they might be unsupportive of their child's wish to consult a psychiatrist.

The homepage contains animations and friendly logos targeted at teenagers and young adults who might be at risk. The goal of the website is to promote mental health literacy among young persons and to help create pathways to professional consultation, either preventing the onset of psychosis or reducing the DUP to improve the prognosis.

EARLY DETECTION AND INTERVENTION PROJECT IN TOYAMA (http://www.med.u-toyama.ac.jp/neuropsychiatry/index-kokoro.html)

Intervention during the prodromal phase of schizophrenia might prevent or delay the onset of psychosis, reduce the severity of illness or improve the long-term outcome. Promoting efficacious intervention requires the implementation of optimal services, as well as the development of better diagnosis methods and treatments for at-risk individuals.

Over the past decade, the Department of Neuropsychiatry of Toyama University Hospital has been active as a clinical and research centre for early detection and intervention for schizophrenia in Toyama prefecture. It has provided opportunities for assessment and treatment to patients with early-phase schizophrenia, as well as prepsychotic individuals who visit the hospital. Research has focused

on the biological aspects of early-phase schizophrenia. Analyses of data have shown the morphological basis of the brain for the schizophrenia spectrum,[5] the effect of the DUP on brain morphology,[6] the applicability of structural brain imaging for the objective diagnosis of schizophrenia[7] etc.

The Consultation and Support Service in Toyama (CAST) for at-risk mental state (ARMS) is a newly established, specialized clinical setting to study and treat young persons (aged 15–30 years) at risk for developing psychosis. The CAST service was launched in October 2006 by the Toyama University Hospital in cooperation with the Toyama Prefectural Mental Health Centre. The specific aims of the service are: (i) to provide young persons suspected to be at risk with opportunities to be assessed by specialists and to receive specific intervention; (ii) to reduce the delay in access to evidence-based treatment for persons who already have psychosis; (iii) to contribute to the elucidation of the biological basis for risk of schizophrenia; and (iv) to develop innovative and optimized approaches for diagnosing and treating persons at risk for psychosis.

The consultation service is offered free of charge at the Mental Health Centre by psychiatrists or psychologists to persons referred because of a suspicion that they might be at risk for psychosis. It accepts self-referrals, as well as referrals made by surrounding persons. An initial non-psychiatric setting for consultation is intended to promote access. Individuals who are thought to fulfil the criteria for ARMS are then referred to the monitoring and support service at the University Hospital for further evaluation.

The specialized clinic at the University Hospital provides a detailed assessment of clinical symptoms using the Comprehensive Assessment of At-Risk Mental States (CAARMS) and other instruments, supplying information about the risk of psychosis, clinical case management, and treatments using cognitive behaviour therapy and/or need-based low-dose medication regimens. Individuals who provide their informed consent undergo evaluations by neuropsychological tests, magnetic resonance imaging, electroencephalography, exploratory eye movement etc. The neurobiological characterization of the prodromal state will not only add to knowledge regarding the pathogenesis of schizophrenia, but will also lead to innovative early diagnosis and treatments.

The number of referrals to CAST in the first year (between October 2006 and October 2007) was 28 (16 women, 12 men; mean age: 23.1 ± 6.1 years). They included 13 individuals with ARMS and four individuals who had already satisfied the criteria for schizophrenia. CAST has just made its first steps. Nevertheless, the preliminary results suggest that this specialized service can promote early intervention in patients with schizophrenia.

SENDAI AT-RISK MENTAL STATE AND FIRST EPISODE SERVICE (SAFE) (http://safe-youthcentre.jp/)

At Tohoku University Hospital in Sendai, Japan, a clinical service for persons with prodromal symptoms was launched in November 2004. Initially, the service was restricted to only the patients of the hospital; currently, however, referrals from nearby areas are also accepted. A Japanese website was recently established for the benefit of young persons with ARMS. The criteria used to identify ARMS individuals are similar to those developed by the Personal Assessment and Crisis Evaluation (PACE) clinic in Melbourne, and the Japanese version of the CAARMS[8] is used as an assessment tool. All clinical assessments and treatments are conducted by psychiatrists in accordance with international clinical practice guidelines.[9] Eclectic psychological therapy, including cognitive and/or supportive therapy, is applied based on information provided in a textbook on cognitive therapy for ARMS that was authored by French and Morrison.[10] Second-generation antipsychotics, antidepressants and benzodiazepines are prescribed, if required.

Thus far, they have interviewed 81 patients: 43 were referred from within the hospital; 24 were referred from other psychiatric hospitals or clinics; and 7 were referred from mental health services at universities/colleges. Of the 81 patients, 48 met the ARMS criteria, whereas 11 met the criteria for psychosis. The mean age of the ARMS patients was 20.0 ± 4.6 years, and two-thirds of the patients were students. Among these 48 patients, 38 met the attenuated psychotic symptoms (APS) criteria, 2 met the Trait plus State criteria, 6 met both the APS and Trait plus State criteria, and 2 met the APS and Brief Limited Intermittent Psychotic Symptoms criteria. Most of the patients experienced comorbid anxiety and mood disorders. Of the 81 patients, 29 ARMS patients completed the follow-up examinations, spanning a period of 6 months, and 4 patients (13.5%) were found to be transitioning to a state of psychosis despite previous antipsychotic treatment. Most of the remaining 25 non-psychotic ARMS patients exhibited an improvement during the 6-month follow-up period, and 8 patients did not meet the ARMS criteria after 6 months. Of the 29 patients, 10 received antipsychotic treatment for more than 2 months.

TABLE 1. The details and staff members of 'Il Bosco'

Floor space 132 m^2
Open from 9.00 to 17.00 hours
Professional staff† 5.5 (psychiatrist 1, resident 1, occupationaltherapist 1, nurse 1, social worker 1, clinical psychologist 0.5)
Non-professional staff 1.5 (administrator 0.5, educator 1)

†Full-time member (5 days work weekly) is counted as one.

In Japan, the ARMS approach is a feasible strategy for offering clinical services to persons with prodromal symptoms. Because the medical service system in Japan is different from those in other countries such as Australia, the UK, Germany or the USA, where most ARMS research has been conducted, accurate guidelines for care and the establishment of a care system for ARMS patients under the existing public medical service system are needed. In our study sample, more than 85% of the patients with ARMS did not develop psychosis within the 6-month follow-up period. A longer follow-up period is necessary to determine the long-term transition rate of ARMS patients. The significance of early intervention to individuals with ARMS should be considered from the viewpoint not only of preventing psychosis, but also of improving youth mental health in general.

IL BOSCO (http://www.lab.toho-u.ac.jp/med/omori/mentalhealth/)

The Toho University Omori Medical Center in Tokyo established a new early psychosis unit named 'Il Bosco' in May 2007. The DUP of the hospital catchment area is longer (mean DUP: 30 months) than that of other areas in Tokyo. The unit is run by a strategy of Optimal Treatment Program (OTP). This OTP is a multidisciplinary team that uses the cognitive-remediation-oriented approach advocated by Ian R.H. Falloon.[11] The service model includes early detection and intervention, repeated assessment and psychoeducation. Treatment strategies consist of optimal pharmacotherapy by atypical neuroleptics, cognitive function trainings, cognitive behavioural therapy and job coaching as a final treatment programme. The cognitive function training is aimed at stimulating divergent thinking using mainly computers. Details are shown in Table 1. The number of staff members is larger than that at other typical day-care services for chronic patients restricted by the health insurance system, which defines three professionals (one nurse, one occupational therapist and one social worker or clinical psychologist) are always in attendance. This large staff number in 'Il Bosco' was made possible through the hospital's independent efforts and a research grant from the government.

The participants are restricted to ARMS patients or first-episode schizophrenia patients between the ages of 15 and 30 years. One year has passed since its opening, and so far 20 outpatients (13 women and 6 men; mean age: 23.1 years) are registered. Several patients have recovered through the rehabilitation programme, which focuses on social cognition to enable them to return to their former workplaces and schools. Some patients have shown a drastic recovery in their negative symptoms and global functioning, as assessed by the global assessment of functioning. The percentage of attendance was better than the former day care, which had no age limitation. We are developing some new programmes for cognitive rehabilitation and remediation[12] and a psychoeducation website for early psychosis. In February 2008, three members had returned to school and three members were planning to return to school, whereas eight members were able to get new jobs.

THE JAPANESE SOCIETY FOR THE PREVENTION OF PSYCHIATRIC DISORDERS (http://square.umin.ac.jp/JSPD/)

The Japanese Society for the Prevention of Psychiatric Disorders (JSPD) was officially funded in March 1996 by Professor Tsutomu Ogura, Professor Yuji Okazaki and their colleagues. The JSPD is an organization for persons conducting research on the prevention of psychiatric disorders in Japan. To promote treatment and research for prevention and early intervention for psychiatric disorders, the JSPD provides a forum for members to promote best practice in early intervention and has hosted an annual meeting to present research and treatment findings. In 2007, the 10th annual academic conference was held in Yokohama, and a multicentre research project on early psychosis in Japan was proposed.

CONCLUSION

The development of early psychosis services is expected to be a breakthrough for many issues in Japan, such as the antistigmatization movement, the prevention of suicide in younger generations,

and the development of early interventions for psychosis itself and the promotion of mental health literacy in general.

Professor McGorry was invited as a keynote speaker to the 104th Japanese Society of Psychiatric Association in 2008. We hope that the message he delivered will become an epoch-making event for future early intervention movements in our country.

REFERENCES

1. Mizuno M, Murakami M. Differences in strategies for implementing community-based psychiatry in Japan. In: Lefley HP, Johnson DL, eds. *Family Interventions in Mental Illness: International Perspectives*. Westport, CT: Praeger Publishers, 2002; 185–192.
2. Falloon IRH, Montero I, Sungur M *et al.* Implementation of evidence-based treatment for schizophrenic disorders: two-year outcome of an international field trial of optimal treatment. *World Psychiatry* 2004; **3**: 104–9.
3. Yamazawa R, Mizuno M, Nemoto T *et al.* Duration of untreated psychosis and pathways to psychiatric services in first-episode schizophrenia. *Psychiatry Clin Neurosci* 2004; **58**: 76–81.
4. Yamazawa R, Nemoto T, Kobayashi H, Chino B, Kashima H, Mizuno M. Association between duration of untreated psychosis, premorbid functioning, and cognitive performance and the outcome of first-episode schizophrenia in Japanese patients: prospective study. *Aust N Z J Psychiatry* 2008; **42**: 159–65.
5. Suzuki M, Zhou S-Y, Takahashi T *et al.* Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. *Brain* 2005; **128**: 2109–22.
6. Takahashi T, Suzuki M, Tanino R *et al.* Volume reduction of the left planum temporale gray matter associated with long duration of untreated psychosis: a preliminary report. *Psychiatr Res Neuroimaging* 2007; **154**: 209–19.
7. Kawasaki Y, Suzuki M, Kherif F *et al.* Multivariate voxel-based morphometry successfully differentiates schizophrenia patients from healthy controls. *Neuroimage* 2007; **34**: 235–42.
8. Yung AR, Yuen HP, McGorry PD *et al.* Mapping the onset of psychosis: the Comprehensive Assessment of At-Risk Mental States. *Aust N Z J Psychiatry* 2005; **39**: 964–71.
9. International early psychosis association writing group. International clinical practice guidelines for early psychosis. *Br J Psychiatry Suppl* 2005; **48**: s120–4.
10. French P, Morrison AP. *Early Detection and Cognitive Therapy for People at High Risk of Developing Psychosis – A Treatment Approach*. Chichester: John Wiley & Sons, 2004.
11. Falloon IRH, Coverdale JH, Laidlaw TM, Merry S, Kydd RR, Morosini P. Early intervention for schizophrenia disorders. *Br J Psychiatry* 1998; **177** (Suppl. 48): 33–8.
12. Nemoto T, Kashima H, Mizuno M. Contribution of divergent thinking to community functioning in schizophrenia. *Prog Neuropsychopharmacol* 2007; **31**: 517–24.

連載 マインドマターズ オーストラリアの学校精神保健増進プロジェクト 8

喪失と悲嘆（最終回）

松沢病院マインドマターズチーム
代表 針間博彦 Harima Hirohiko

今回はオーストラリアの学校精神保健増進プロジェクト「マインドマターズ（MindMatters）」のうち、各論テキストの最後の一冊である「喪失と悲嘆（Loss & Grief）」を取り上げる。このテキストは中等教育六年間（日本の中学一年生〜高校三年生に相当）を通じて使用されるものである。ここでいう喪失には、家族別居、疎外、死別、身体（の一部）などが含まれ、それにともなう正常の反応としての悲嘆が紹介されている。

喪失と悲嘆は、抑うつとの関連が指摘されているが、従来、学校ではこうした問題が十分に取り上げられていない。このテキストは学校で死と喪失を取り扱う際に重要となる実際的問題について概説しており、中等学校での具体的な授業内容が紹介されている。

喪失と悲嘆に対する学校全体の取り組み

若者にとって悲嘆の転帰に影響する大きな要因は、大人と仲間から受ける支援であることが研究によって示されている。また、喪失体験は、教師にとっても、職場での遂行能力に影響を及ぼしかねない。とくに問題となるのは、生徒や同僚の死、あるいは学校での人的、物的損害を生じるような大きな事故や災害のように、職場環境に直接かかわる「職業上の喪失」の場合である。

悲嘆に対する現在のアプローチは、個人の対処への援助に重点を置いたものが多い。喪失と悲嘆を正常な生活上の体験として受容するうえで、学校の役割は、それぞれに対して支持的環境を提供することであり、そのことを確認する必要がある。

親からの自立という思春期の発達上の変化もあって、若者が喪失体験を理解し対処するには、仲間と親以外の大人の助けが重要な役割を果たす。喪失体験は社会的相互作用を通じて解釈されるものである。若者は喪失という現実を明確化し、喪失にともなう感情を表現し、支援と情報を得て、その体験を自身の人生の中に統合する必要がある。そのために学校の仲間と教師からの援助を求めている。

学校は、生徒にとっては社会的な場所、職員にとっては職場であり、その全員が長時間過ごすところだ。学校ができることは、（方針、プログラ

ム、実践といったかたちで）支持的な環境を提供することである。また公式および非公式の方法で援助してくれる人へのアクセス経路を確保することである。

若者を支援するのは、主に家族である。喪失と悲嘆に際しても、学校は、親の役割に取って代わることを考えるのではなく、別の役割を提供するべきだ。

教師は生徒にどのように感じるべきか教えるのではなく、喪失と悲嘆を感じるのは正常なことであると伝えるのである。生徒が他の人の話を聞くという代理体験によって、こうした生活上の出来事に対する自信を多少ともつける機会を与えるのである。正常な悲嘆反応がどのようなものか、正確な情報が伝われば、生徒は自分の体験を「正常化」することができる。思春期は自分が人と違う、人と感じ方が違うと強く意識する時期であるだけに、このことはきわめて重要である。

喪失と悲嘆について教え、悲嘆している生徒を支援することは、教師の役割の一部である。それは、生徒が自信をもち、学業上の目標を達成するうえでも必要なことだ。

喪失と悲嘆に学校全体で取り組むことは、危機的インシデントに介入しマネジメントを行うのにも、悲嘆する生徒を支援するのにも役立つ。情報を交換し、援助を求めて受けるという積極的態度を形成し、他者を支援することを通じて、予防的な作用も及ぼしうる。喪失が学校コミュニティのメンバーに与える影響を認めることは、安全な、思いやりのある、支持的な環境を提供するという学校の目標を示すものである。

カリキュラム教材

マインドマターズに示された「喪失と悲嘆」の授業カリキュラムは、年齢に適した情報を生徒に提示することを目的としており、生徒は次のことを学習する。

- 死という現実、そして死と生との関係を理解する
- 生徒が抱く死や離婚に関する疑問に答えることができ、悲嘆に対処するのを支援してくれる大事な大人がいることを理解する
- いつ助けが必要であるのかわかり、どんな援助と支援が得られるのか、またそれにアクセスする方法を知ったうえで、何がアクセスへの障壁となるのかを考える
- 支持的な友人になるための技能を育て、自分が他の人に対して負う責任の限界を知る

生徒は次の四つの重要なメッセージを学ぶことができる。

すなわち、人は喪失体験に対してさまざまな反応を示すこと、自分あるいは友人の喪失体験に対処するのを助ける方策が存在すること、すべての人がどこで援助が得られるか知っておく必要があること、文化的／民族的／宗教的背景が異なれば喪失に対処する方法も異なること、の四つである。

授業カリキュラムは一二のセッションからなり、セッション1から6までは中等学校一、二年（日本の中学一、二年）向け、セッション7から10は中等学校三年（日本の中学三年）以上向け、セッション11と12は中等学校五年（日本の高校二年）以上向けである。

以下、これらの内容を順次紹介する。

セッション1
生活上の変化は喪失と悲嘆をもたらす

ここでは、生徒が生活の変化がいかにして喪失と関係しているかを理解し、マイナスの反応が悲嘆反応であることを知る。

活動例1　変化

黒板に四列の表を描き、各列に「過去三年間の学校生活の変化」「失ったもの」「感情と行動」「対処」という見出しをつける。生徒に転校など生活上の変化を挙げさせる。次いでそのときに何を失ったか、またどんな気持ちが生じ、どんな行動をとったのかを挙げさせて、板書する。さらに、そうした状況に対処するためにどんなことをするか生徒に問い、板書する。この表をもとに、生徒はそれぞれの対処方法がプラスのものかマイナスのものかについて話し合う。