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Advanced paternal age associated with an elevated risk for schizophrenia in offspring in a Japanese population

Kenji J. Tsuchiya[a], Shu Takagai[a], Masayoshi Kawai[a], Hideo Matsumoto[b], Kazuhiko Nakamura[a], Yoshio Minabe[a], Norio Mori[a], Nori Takei[a,c,*]

[a]*Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, Hamamatsu, Japan*
[b]*Department of Psychiatry, Tokai University School of Medicine, Isehara, Japan*
[c]*Division of Psychological Medicine, Institute of Psychiatry, London, UK*

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Abstract

Objective: Advanced paternal age at birth as a risk for schizophrenia in the adult offspring has been reported in previous studies exclusively conducted in Western countries and Israel. The question has arisen whether this finding could be replicated in countries with socially and culturally different attitudes toward marriage, including factors such as age at marriage. To address this question, we conducted a case-control study of a Japanese population.
Methods: The subjects were representative inpatients with a DSM-IV diagnosis of schizophrenia. Unrelated healthy volunteers were recruited as control subjects. This study was conducted as one of a series of the projects by use of "The Mother and Child Health Handbooks (MCHHs)," from which information on parental characteristics around the time of birth, including parental ages at birth, had been extracted and recorded on computer.
Results: Ninety-nine subjects with schizophrenia and 381 healthy control subjects enrolled for the study. Advanced paternal, but not maternal, age was associated with an elevated risk for schizophrenia. Reproducibility of the association across different cultures is suggestive of a causal link.

Keywords: Schizophrenia; Paternal age; Risk factor; Case-control study; Japan

1. Introduction

Recent studies have consistently reported that advanced paternal age at birth is a risk factor for schizophrenia in the offspring (Brown et al., 2002; Byrne et al., 2003; Dalman and Allebeck, 2002; El Saadi et al., 2004; Malaspina et al., 2001; Zammit et al., 2003). Paternal germ line mutation may be a likely

* Corresponding author. Department of Psychiatry and Neurology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu 431-3192, Japan. Tel.: +81 53 435 2295; fax: +81 53 435 3621.
E-mail address: ntakei@hama-med.ac.jp (N. Takei).

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explanation (Malaspina, 2001), but the mechanism underlying this association is not yet fully understood.

Previous studies examining this association have been conducted exclusively in European countries, Israel, USA, and Australia. Attitudes toward marriage, in particular, age at the time of marriage, may vary according to cultural backgrounds. If the association between advanced paternal age and the risk for schizophrenia were reproduced among populations of different ethnic origin, the relationship addressed here would be more indicative of causal significance, and genetic explanations including de novo mutation on schizophrenia-susceptible genes would become realistic (Malaspina, 2001).

Therefore, we investigated whether or not the claimed association between advanced paternal age at birth and the risk for schizophrenia among offspring would be reproducible in a Japanese population.

2. Methods

This study was conducted as a series of our projects which were launched to investigate pregnancy- and birth-related events as risk factors for schizophrenia in Japan. The projects were set out to exclusively utilize the Mother and Child Health Handbook (MCHH), a set of notes covering a wide range of information, including pregnancy and delivery events, as well as newborns' characteristics and parental data. In Japan, every woman receives the MCHH from the local municipal office when pregnant and, in general, keeps it long after the birth of the offspring as a memorial. Ample information derived from the MCHHs has been systematically recorded on computer and, thus far, used for a series of studies (Kawai et al., 2004; Matsumoto et al., 1999, 2001).

We sought the participation of subjects with schizophrenia who were admitted to the University Hospital of the Hamamatsu University School of Medicine during the period extending from January 1, 1999 to December 31, 2002. A structured interview was conducted by trained psychiatrists (K.J.T., K.M., N.M. and N.T.) using the Schedule for Clinical Interview for Axis-I Diagnosis of DSM-IV (SCID-I) (First et al., 1996). Those individuals, who met the criteria for a DSM-IV diagnosis of schizophrenia (295.xx) and whose biological mothers were identified, were recruited. We also included unrelated healthy volunteers who were residents in the community from which the patient group was derived, and who were confirmed to have had no psychiatric history.

As regards the parental age and parity, we relied upon computerized MCHH data. As these data have become available since the year 1967, only individuals born in and after 1968 were included in the present study. Maternal and paternal ages were divided into tertiles according to the distribution of age (see Table 1). The family history of psychiatric diagnoses was examined via interviews with each subject and one close relative, most often the mother; subjects were designated as "positive" for a psychiatric family history if they had at least one first-degree relative with psychosis. Odds ratios (ORs) and

Table 1
Odds ratios for schizophrenia among offspring in relation to parental age

	Cases ($n=99$)	Controls ($n=381$)	Crude estimates		Adjusted estimates[a]	
			ORs	95% CI	ORs	95% CI
Maternal age (year)						
≦25 (reference)	31	128	1		1	
26–28	40	118	1.40	(0.82, 2.38)	1.08	(0.60, 1.93)
≧29	28	135	0.86	(0.49, 1.51)	0.59	(0.29, 1.20)
Test for trend			$p=0.60$		$p=0.14$	
Paternal age (year)						
≦28 (reference)	22	138	1		1	
29–31	36	120	1.88	(1.05, 3.37)	2.08	(1.12, 3.86)
≧32	41	123	2.09	(1.18, 3.71)	3.00	(1.49, 6.04)
Test for trend			$p=0.013$		$p=0.002$	

[a] Adjusted for age and gender of the subject, parity, family history, and age of the other parent.