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Later Paternal Age and Sex Differences in Schizophrenia Symptoms

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Abstract

Objective—Advanced paternal age is consistently associated with an increased risk for schizophrenia, accounting for up to a quarter of cases in some populations. If paternal age-related schizophrenia (PARS) involves a distinct etiopathology, then PARS cases may show specific characteristics, *vis-á-vis* other schizophrenia cases. This study examined if PARS exhibits the symptom profile and sex differences that are consistently observed for schizophrenia in general, wherein males have an earlier onset age and more severe negative symptoms than females.

Method—Symptoms were assessed at baseline (admission) and during medication-free and treatment phases for 153 inpatients on a schizophrenia research unit, 38 of whom fulfilled operationally defined criteria for PARS (sporadic cases with paternal age ≥ 35).

Results—Males and females with PARS had the same age at onset and a similar preponderance of negative symptoms, whereas the other (non-PARS) cases showed the typical earlier onset age and more severe negative symptoms in males. When medications were withdrawn, PARS cases showed significantly worse symptoms than non-PARS cases (higher total PANSS scores and positive, activation, and autistic preoccupation scores). However these symptoms globally improved with antipsychotic treatment, such that the differences between the PARS and other schizophrenia cases receded.

Conclusion—The lack of sex differences in the age at onset and the greater severity of medication-free symptoms bolster the hypothesis that PARS has a distinct etiopathology. It also suggests that female sex does not exert a protective effect on the course of PARS, as it may in other forms of schizophrenia.

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Conflict of Interest:
All authors declare no conflict of interest.

Keywords

genetics; heterogeneity; positive symptoms; negative symptoms

1. Introduction

Advanced paternal age is consistently associated with the risk for schizophrenia. We reported a near tripling of risk for the offspring of older (>45–55 years) compared with younger (<25 years) fathers (Malaspina et al., 2001) in our epidemiology study and there have been numerous similar reports (Sipos et al., 2004; El-Saadi et al., 2004; Zammit et al., 2003; Byrne et al., 2003; Dalman and Allebeck, 2002; Brown et al., 2002; Wohl and Gorwood, 2006). In a subsequent clinical study (Malaspina et al 2002), we found significantly older fathers in sporadic than familial cases, demonstrating that later paternal age was not associated with parental psychiatric illness. These findings support the hypothesis that de novo mutations contribute to the risk for sporadic schizophrenia.

In the current study we compared clinical phenomena between familial schizophrenia cases and sporadic cases with paternal age ≥ 35 years of age, as our data suggested, and subsequent analysis has shown that the odds ratio is consistently above 1 at this age threshold (Wohl and Gorwood, 2006). We studied the cases in sex-specific analyses, as sex differences contribute to substantial variability in age at onset and clinical symptoms

2. Methods

2.1. Participants

The sample included 153 inpatients (93 males and 60 females) from the New York State Psychiatric Institute (NYSPI) Schizophrenia Research Unit (SRU) and was approved by the IRB (Malaspina et al 2002).

Paternal age-related schizophrenia was operationally defined as those with no family history of schizophrenia or psychosis and whose fathers' age at birth was ≥ 35 years (based on Malaspina et al 2002); all other cases were considered "non-PARS". Symptoms were assessed with the 30-item Positive and Negative Syndrome Scale (Kay et al., 1989) using both conventional and pentagonal models. Diagnoses and ratings were conducted by Master's level clinicians. Raters achieved high reliability with each other (i.e. Kappa > .80 for individual symptom ratings and 95% agreement on diagnosis) before evaluating subjects

2.2. Procedures

We examined PANSS ratings from three specific in-hospital phases: *admission* (or baseline at entry into the study), *medication-free* (≥ 3 weeks, except lorazepam as needed), and *treatment* (on stable doses of antipsychotic medications for ≥ 4 weeks). For the treatment phase, both first- and second-generation antipsychotic medications and specific adjunctive medications were allowed for optimal treatment as clinically indicated.

2.3. Data Analysis

SPSS (version 15.0) was used for statistical analysis (1989–2006). For our primary analyses, we performed multivariate ANOVAs separately examining PANSS factors during each of the assessment phases. PARS grouping and sex served as main effects. An additional analysis examined PANSS factors across clinical phases from medication-free to treatment phases. A repeated measures ANOVA was performed with PARS group and sex as between factors, and

PANSS factors across clinical phases from medication-free to treatment phases as the within factors.

3. Results

3.1. Subject characteristics

Among the 153 subjects in the sample, 21 (22.6%) of the 93 males and 17 (28.3%) of the 60 females were categorized as PARS (chi-square=0.65, df=1, p=.421). Among the demographic variables, significant interactions of PARS status and sex were exhibited for current age (F = 4.37, p = .038), age at onset (F = 9.34, p = .003) and age at first treatment (F = 3.73, p = .055). PARS males were older than PARS females ($mean_{male}$ (SD) = 37.1 (11.4) vs. $mean_{female}$ (SD) = 31.1 (9.1)); however non-PARS males and females did not differ in current age ($mean_{male}$ (SD) = 30.5 (10.2) vs. $mean_{female}$ (SD) = 32.5 (9.1)). The non-PARS sample demonstrated expected sex differences in age at onset; males had 5.6 years earlier age at onset ($mean_{male}$ (SD) = 19.0 (4.1) vs. $mean_{female}$ (SD) = 24.6 (7.5), t = 22.20, df = 113, p = .001) and 5.6 years earlier age at first treatment ($mean_{male}$ (SD) = 18.7 (5.1) vs. $mean_{female}$ (SD) = 23.1 (9.8), t = 22.35, df = 11, p = .001). By contrast, PARS males and females showed equivalent ages at onset ($mean_{male}$ (SD) = 21.2 (4.3) vs. $mean_{female}$ (SD) = 20.0 (7.6)) and first treatment ($mean_{male}$ (SD) = 20.6 (6.5) vs. $mean_{female}$ (SD) = 19.7 (7.5)). Educational attainment did not differ by PARS status or by sex.

3.2. Clinical characteristics during phases of assessment (Table 1A-C)

The overall multivariate ANOVA analysis of PANSS symptoms at admission revealed a marginal interaction of PARS group and sex (Wilks' Lambda F = 1.98, df = 5/67, p = .093). We further examined the between subjects effects for significant PARS group and sex and interaction effects. The non-PARS males demonstrated significantly greater negative factor scores than non-PARS females (t=2.27, df=56, p=.027, post hoc analysis), whereas the PARS males and females did not differ. The non-PARS males and females exhibited equal levels of dysthymic mood factor while the PARS females had lower levels than PARS males (t=2.14, df=16, p=.048, post hoc analysis), thus indicating a significant interaction between PARS and sex (F=5.17, p=.026). Additionally, PARS females had lower dysthymic mood factor scores than non-PARS females (t=2.17, df=24, p=.040, post hoc analysis). Though there were no significant differences overall in positive factor scores between the PARS and non-PARS groups, post hoc analysis revealed that PARS males had significantly greater scores than non-PARS males (t=2.93, df=48, p=.021). No significant between-group differences were noted in activation and autistic preoccupation factors during these admission ratings. Total PANSS scores did not differ significantly among groups.

The overall multivariate ANOVA analysis of PANSS symptoms during the medication-free phase revealed a significant PARS group effect (Wilks' Lambda F = 2.49, df = 5/64, p = .040) and a marginal interaction of PARS group and sex (Wilks' Lambda F = 2.20, df = 5/64, p = .065). PARS subjects had significantly greater positive, activation, autistic preoccupation and total PANSS scores than non-PARS subjects. There was a significant interaction of PARS group and sex, manifested in the negative (F = 6.72, df = 1/68, p = .012) and dysthymic mood (F = 4.55, df = 1/68, p = .037) factors. Post hoc analyses revealed that most of the significant findings could be attributed to the PARS group exhibiting higher symptom levels, particularly PARS females. Post hoc analyses demonstrated that PARS females had greater symptoms than non-PARS females across most PANSS factors: positive (t=2.45, df=25, p=.022), negative (t=2.36, df=10 [separate error variance (sev)], p=.040), activation (t=1.90, df=9 (sev), p=.089), autistic preoccupation (t=2.31, df=11 (sev), p=.041), and PANSS totals (t=2.54, df=10 (sev), p=.030). PARS males also exhibited greater positive symptoms than non-PARS males (t=2.35, df=43, p=.024). Females as a whole had greater dysthymic mood factor scores than males; this

effect was driven largely by PARS females. In post hoc analysis of the PARS sample, females had a higher mean dysthymic mood factor score than males (t=2.15, df=16, p=.047). The non-PARS males exhibited higher negative factor scores than non-PARS females (t=2.56, df=54, p=.013), but PARS males' and females' scores did not differ significantly.

With treatment, the differences among the groups diminished. PARS males and females differed in autistic preoccupation scores, while non-PARS males and females did not. In post hoc analyses, PARS males exhibited a trend toward greater autistic preoccupation scores than non-PARS males (t=2.00, df=23 (sev), p=.058), and within the PARS sample, males had marginally greater autistic preoccupation scores than females (t=1.97, df=25 (sev), p=.059). Within the non-PARS sample, males continued to exhibit marginally greater negative symptoms than females (t=1.84, df=106, p=.068) and females continued to have marginally greater dysthymic mood symptoms (t=1.91, df=106, p=.058).

3.3. Comparison of clinical characteristics across phases of assessment (Table 2)

PANSS symptoms were compared across medication-free to treatment phases for cases with repeated assessments. The reduction in total PANSS score related to treatment was significantly greater for the PARS sample, as was the reduction in autistic preoccupation and negative factor scores. The negative factor scores improved for non-PARS males and PARS males and females from medication-free to treatment phases. Conversely, non-PARS females' negative factor scores increased by 2.4 points, accounting for a significant interaction. While the autistic preoccupation factor scores decreased from medication-free to treatment phases for all groups, variation in the amount of decrease accounted for the significant interaction. PARS females exhibited the greatest decrease and non-PARS females the least.

There was a significant PARS group effect for the PANSS positive and activation factors. Both the PARS and non-PARS samples experienced a reduction in these symptoms with treatment; however, the PARS sample continued to exhibit higher symptoms. The dysthymic mood factor exhibited a significant sex effect, with females consistently higher than males, independent of the assessment phase. The RM-ANOVA analysis of the PANSS total score revealed a significant 3-way interaction of assessment phase, PARS groups and sex. All four groups as defined by PARS and sex decreased from medication-free to treatment though the degree varied from group to group. PARS females exhibited the largest decrease in total PANSS (24.5 points) and non-PARS females exhibited the smallest decrease (1.9 points).

4. Discussion

The results showed that subjects without a family history and with older fathers did not show the expected sex differences in the age at onset and negative symptoms, and they had more severe symptoms off antipsychotic medications. The capacity to compare symptoms for subgroups of cases between both medication-free and treatment phases enhanced our ability to identify specific features of PARS. While off antipsychotic medications, the PARS cases demonstrated significantly greater positive, activation, and autistic preoccupation factor scores and total PANSS scores. The PARS females in the medication-free phase experienced particularly high symptoms across all domains. Nonetheless, the PARS cases had robust treatment effects, including significant reduction of negative symptoms. During clinical stabilization, the differences between PARS and non-PARS cases receded, although PARS males still had elevated autistic preoccupation. The response in the PARS sample may indicate this to be a more unitary and dopamine-dependent disorder. The lack of sex differences for cases in the PARS grouping is notable. Inasmuch as female sex did not ameliorate the manifestations of schizophrenia in the PARS subgroup, female sex, per se, may not explain the later onset and milder course of schizophrenia in many women, as is commonly believed.

In conclusion, the current study contrasted phenotypic features of cases with presumptive paternal age-related schizophrenia with those of other schizophrenia cases. PARS may represent a subtype of schizophrenia with similar symptoms and age at onset in males and females, more severe symptoms during medication-free periods, and more responsiveness to antipsychotic medications. Future studies should seek to replicate and expand on these findings by examining further the neurobiology, symptoms, course of illness, and treatment effects in PARS males and females as compared to other groups. Our results indicate PARS may be a clinically relevant subtype that could inform further progress in understanding and treating schizophrenia.

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Table 1

PANSS Scales for PARS and Non-PARS Subjects at Baseline/Admission, Medication-Free and Treatment Phases[a]

A. Baseline/Admission Data										
	Non-PARS		PARS		Statistics					
PANSS scales	Males (N = 38)	Females (N = 19)	Males (N = 11)	Females (N = 7)	PARS F	PARS p	Sex F	Sex p	PARS/Sex F	PARS/Sex p
Wilks' Lambda					1.56	.183	1.20	.321	1.98	.093
	mean (SD)	mean (SD)	mean (SD)	mean (SD)						
Negative	20.8 (8.9)	16.0 (5.5)	17.2 (5.3)	17.3 (6.7)	0.30	.586	1.23	.271	1.34	.250
Positive	10.9 (3.8)	12.5 (4.9)	15.0 (5.9)	13.1 (5.0)	3.42	.069	0.01	.913	1.85	.178
Dysthymia	10.7 (4.2)	11.2 (3.6)	12.7 (5.5)	7.9 (3.0)	0.34	.564	3.50	.065	5.17	.026*
Activation	9.5 (4.0)	10.4 (4.6)	11.3 (4.0)	9.4 (3.6)	0.12	.728	0.19	.666	1.35	.248
Autistic Preoccupation	12.3 (4.3)	12.3 (4.1)	13.1 (4.3)	11.3 (3.6)	0.01	.940	0.61	.436	0.58	.449
PANSS total	63.1 (15.7)	59.2 (15.0)	67.4 (21.2)	61.3 (8.1)	0.51	.479	1.24	.269	0.06	.805

B. Medication-free Data										
	Non-PARS		PARS		Statistics					
PANSS scales	Males (N = 38)	Females (N = 18)	Males (N = 9)	Females (N = 9)	PARS F	PARS p	Sex F	Sex p	PARS/Sex F	PARS/Sex p
Wilks' Lambda					2.49	.040*	1.84	.118	2.20	.065
	mean (SD)	mean (SD)	mean (SD)	mean (SD)						
Negative	22.3 (11.3)	14.8 (7.0)	19.6 (7.2)	27.1 (14.9)	2.76	.101	0.00	.989	6.72	.012*
Positive	11.6 (5.2)	12.4 (3.7)	16.7 (8.0)	17.2 (6.6)	10.76	.002*	0.20	.654	0.01	.934
Dysthymia	9.7 (4.0)	10.3 (3.3)	8.8 (4.1)	14.3 (6.6)	1.76	.189	6.80	.011*	4.55	.037*
Activation	11.7 (5.6)	9.4 (4.2)	12.4 (6.8)	16.2 (10.3)	4.82	.032*	0.19	.662	3.14	.081
Autistic Preoccupation	12.7 (6.0)	12.1 (4.9)	16.2 (8.4)	18.9 (8.1)	8.60	.005*	0.33	.568	0.88	.353
PANSS total	66.6 (23.4)	56.7 (17.0)	72.7 (30.7)	88.3 (35.4)	7.57	.008*	0.18	.674	3.49	.066

C. Treatment (Fixed Dose or Discharge) Data												
	Non-PARS		PARS		Statistics							
PANSS scales	Males (N = 71)	Females (N = 35)	Males (N = 18)	Females (N = 14)	PARS F	PARS p	Sex F	Sex p	PARS/Sex F	PARS/Sex p		
Wilks' Lambda					0.83	.529	1.66	.149	1.44	.214		
	mean (SD)	mean (SD)	mean (SD)	mean (SD)								
Negative	19.1 (7.8)	16.3 (6.4)	18.8 (8.2)	17.2 (6.1)	0.04	.846	2.22	.139	0.16	.692		
Positive	10.1 (4.9)	10.9 (4.2)	12.2 (5.4)	10.8 (4.6)	1.04	.309	0.09	.766	1.38	.243		
Dysthymia	8.6 (3.6)	10.1 (4.0)	9.8 (4.1)	9.8 (3.6)	0.35	.554	0.94	.334	0.94	.334		
Activation	8.8 (3.3)	9.0 (4.4)	9.8 (4.9)	10.1 (3.9)	1.68	.198	0.09	.761	0.00	.970		
Autistic Preoccupation	11.0 (4.0)	11.1 (4.1)	14.2 (6.9)	10.9 (2.6)	2.85	.094	3.21	.075	3.99	.048*		
PANSS total	56.4 (14.5)	55.4 (14.9)	63.7 (22.4)	57.9 (14.2)	2.42	.122	1.13	.289	0.58	.448		

*indicates statistical significance

[a]Test statistic is a multivariate ANOVA with PARS and sex as factors.

Table 2

PANSS Scales Repeated-Measures Statistics in PARS and Non-PARS Subjects from Medication-free to Treatment Assessments for PANSS Symptom Factors[a]

	Medication-Free Phase				Treatment Phase			
PANSS scales	**Non-PARS**	**Non-PARS**	**PARS**	**PARS**	**Non-PARS**	**Non-PARS**	**PARS**	**PARS**
	Males (n = 36)	**Females (n = 11)**	**Males (n = 8)**	**Females (n = 7)**	**Males (n = 36)**	**Females (n = 11)**	**Males (n = 8)**	**Females (n = 7)**
	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Negative	22.3(11.3)	12.6 (4.0)	20.6 (6.8)	24.3(12.9)	19.3 (8.2)	15.0 (5.1)	16.1 (3.2)	17.0 (7.4)
Positive	11.6 (5.2)	12.6 (4.3)	16.6 (8.6)	15.6 (6.6)	9.3 (4.3)	11.0 (3.2)	13.4 (4.9)	10.4 (5.6)
Dysthymia	9.7 (4.0)	10.2 (2.9)	9.3 (4.1)	12.3 (4.1)	7.9 (3.1)	10.1 (3.6)	9.1 (4.1)	11.0 (3.4)
Activation	11.7 (5.6)	8.4 (3.5)	13.0 (7.0)	15.6 (9.7)	8.6 (3.4)	7.1 (1.8)	10.5 (5.2)	10.4 (5.1)
Autistic preoccupation	12.7 (6.0)	10.9 (3.9)	17.0 (8.7)	18.4 (9.0)	10.2 (4.1)	10.5 (3.0)	12.4 (3.6)	11.4 (2.7)
PANSS total	66.6(23.4)	52.9(14.9)	75.6(31.4)	82.4(33.1)	54.2(15.6)	51.0(11.0)	61.4(16.9)	57.9(17.7)

	Repeated-measures Statistics											
PANSS scales	**Phase**		**Phase by PARS**		**Phase by P by S**		**PARS**		**Sex**		**PARS by Sex**	
	F	**p**	**F**	**p**	**F**	**p**	**F**	**p**	**F**	**p**	**F**	**p**
Negative	7.12	.010*	5.74	.020*	3.07	.085	0.81	.372	0.89	.350	3.46	.068
Positive	22.78	.001*	2.92	.093	1.00	.322	4.02	.050*	0.04	.836	1.40	.242
Dysthymia	1.95	.168	0.04	.846	1.47	.231	0.95	.334	3.87	.054*	0.36	.549
Activation	15.45	.001	1.14	.291	2.15	.148	6.45	.014*	0.19	.661	1.87	.177
Autistic Preoccupation	20.87	.001	7.55	.008*	2.04	.159	6.74	.012*	0.03	.873	0.11	.744

Phase = repeated measure (medication-free to treatment); P = PARS, S = sex, p = probability level

*indicates statistical significance

[a]Test statistic is a repeated measures ANOVA with Phase (medication-free to treatment) as the within-subject repeated measure, PARS and sex as between-subject factors.