Research article
Ερευνητική εργασία

Evidence of advanced parental age linked to sporadic schizophrenia*

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Novel emergence of schizophrenia (SCZ) in its sporadic type has been linked, among many candidate epigenetic factors, with advanced paternal age (PA) and advanced maternal age (MA). The most common hypothesis to the paternal age effect is the increased "*de novo* mutations" during spermatogenesis, while the maternal age hypothesis, though controversial, is at most based on studies that support higher frequency of perinatal complications. Our sample consisted of 462 subjects with DSM-IV-TR SCZ spectrum disorders from the outpatient unit of Eginition Hospital in Athens, Greece, who were further screened for heritability and were divided in a group of sporadic cases (no reported family history for SCZ related disorders up to 2nd degree relatives) and a group of familial SCZ-spectrum disorder cases (positive reported history for SCZ spectrum). These two groups of patients were compared regarding either paternal or maternal age, while the familial type band was used as a control group. The aim of this retrospective file study was to examine whether advanced parental age may contribute in novel appearance of non-affective psychosis in offspring. Using logistic regression analysis, we found that the risk for the sporadic type, as compared to familial type, showed a significant increase for both advanced MA (OR=4.39, p=0.001) and PA (OR=1.92, p=0.012). After adjusting for confounding effects for the other parent's age and gender, the risk effect for the sporadic type of SCZ remained statistically significant for both advanced MA (OR=4.04, p=0.002) and advanced PA, but with a loss of statistical power (OR=1.72, p=0.049). Few studies have been conducted in Greece concerning the role of parental age in SCZ. Our study is consistent with current literature which indicates that both advanced MA and PA may contribute to an increased risk for emergence of sporadic type of SCZ. Furthermore, it is implied that this risk for the sporadic type as compared to the familial type could be higher for advanced MA than advanced PA. Patients with the sporadic type of SCZ, though clinically indistinguishable from the patients with the familial type of the disorder, may share other pathophysiological underlying mechanisms in which parental age, especially advanced MA, may be a candidate mediator. However, future studies could help clarify the role of both PA and MA in the pathophysiology of the disorder.

Key words: Schizophrenia, sporadic/familial type, parental age, paternal age, maternal age.

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Introduction

The heterogeneity in what psychiatrists define as Schizophrenia (SCZ) has led many researches to try to identify clinical or biological subtypes of the disorder. Classification between sporadic and familial type has been the focus of attention for many years.[1,2] The present consensus suggests that SCZ is a result of gene-environment interplay between multiple genes, epigenetic factors, environmental exposures.[3] In many genetic diseases the appearance of a sporadic case, in a previous unaffected family, signals a possible de novo mutation. In SCZ it is not clear whether novel disease emergence (in an individual without any family history) originates from genetic mutations or environmental factors that act independently or through interaction with susceptibility genes.

It has been suggested that, amongst many other risk factors, the paternal age at birth of patients with schizophrenia-spectrum disorders plays a role in the development of the disorder.[4] There have been reports of later paternal age in SCZ patients since the 1950s. Book[5] was the first to suggest that new mutations might contribute to a higher risk by reintroducing genetic abnormalities to the population. More recent studies seem to confirm that advanced paternal age (PA) is linked with increased risk of SCZ in offspring[6,7] and it has been suggested that the accumulation of de novo mutations in paternal sperm contributes to the increased risk of schizophrenia.[8,9] The hypothesis of delayed childbearing in fathers who themselves have genetic schizophrenia vulnerability offers an alternative explanation,[10] but there are opposite evidence indicating that later childbirth may not be attributable to parental psychiatric illness.[11] It has also been supported that the risk due to PA may be different between genders and higher for males.[12] On the other hand, the role of maternal age (MA) has also been documented in studies supporting its association with SCZ onset. Higher risk has been reported in children of younger and older mothers.[13,14] However, other studies dispute MA as a risk factor supporting that paternal derived mutation drive this association,[15] while others argue for the higher importance of mother's age at time of birth compared to age of the father.[16] Nevertheless, this positive correlation of advanced parental (paternal and maternal) age with SCZ has not always been confirmed.[17,18]

The aim of this retrospective file study is to examine the possible association of paternal age and/or maternal age with the appearance of non-affective psychosis in offspring. In order to do that, two groups of patients with SCZ spectrum disorder were compared regarding both paternal or maternal age, one group with the sporadic type of psychosis and one with the familial type of psychosis, which was used as a control group. We assume that, if either PA or MA is correlated with a novel appearance of non-affective psychosis, then it would be expected that this association would appear more often in the group with the sporadic type of psychosis rather than in the group with the familial type.

Material and method

This file study was based on the outpatient register data unit of Eginition Hospital in Athens, Greece. Data for 2974 medical files was collected. Our sample included 462 patients with a DSM-IV-TR diagnosis of SCZ-spectrum disorder (SCZ, schizoaffective disorder, schizophreniform disorder, delusional disorder, atypical psychosis) which were assessed by the outpatient unit of our hospital from 2008 to 2012. Other diagnoses such as affective psychotic disorder (bipolar or depressive disorder with psychotic features), developmental disorder, psychotic disorder due to medical condition or substance-related psychotic disorder were excluded from our analysis.

Patients in our sample were further screened for heritability and were divided in a group of sporadic cases (no reported family history of SCZ related disorders up to 2nd degree relatives) and a control group of familial cases (positive family record for schizophrenia related disorders up to 2nd degree relatives). PA and MA were defined as the age of the parent at the proband's birthday and was estimated from information provided by the patient or their relatives. Sociodemographic data concerning marital status, professional status, years of education and place of residence were also available from patients and/or their relatives.

Data analysis

The final sample consisted of 462 individuals (285 males and 177 females). Differences between study groups were examined using chi-square test for categorical variables and independent sample t test for continuous variables. Probability values of $p<0.05$ were considered statistically significant. Familial type was used as a reference category. Due to the small sample size of fathers and mothers aged below 20 or over 40 in both groups, we set the lowest and highest parental age category at <25 and ≥35 years old respectively. PA and MA were divided into four bands: <25, 25–29, 30–34, and ≥35. Logistic regression was used to estimate the odds for each parental age group of having the sporadic type versus the familial type of the disorder. We set the 30–34 category as reference, since this one shared the lowest risk. At first, we conducted the analysis for each parental age separately and then re-ran the analysis adjusting for the participant's gender and the other parent's age at birth. All analyses were conducted using SPSS (version 22.0).

Results

Sociodemographic data

Sociodemographic data of our sample is indicated in table 1. The mean PA at subjects' birth was 34.3 (SD=±6.3) years and the mean MA was 28.4 (SD=±5.9) years. MA at subjects' birth was available for 87.9% of the cases (n=406) and the paternal date of birth for 86.4 % (n=399). The male individuals with the sporadic type of psychosis (n=192, p=66%) were more than the female (n=99, p=34%), while in the familial type the ratio between male (n=70, p=55.6%) and female (n=56, p=44.4%) patients was more balanced. Gender was not associated with neither MA (p=0.48) nor PA (p=0.86). The majority of individuals lived (n=389, p=85.5%) in the capital or another big city rather than small

Table 1. Distribution of 417 patients with schizophrenia spectrum disorders by sociodemographic variables and their relevance with familial or sporadic type of psychosis.

	Sporadic type		Familial type		p
Paternal Age (n=399)					
Years (SD)	34.78 (±6.43)		33.23 (±6.17)		0.028[b]
Maternal Age (n=406)					
Years (SD)	28.83 (±6.26)		27.50 (±5.05)		0.044[b]
Gender (n=417)		(%)		(%)	
Male (n=262)	192	73.3	70	26.7	0.043[a]
Female (n=155)	99	63.8	56	36.2	
Education (n=405)					
Mean years (SD)	12.67 (±3.17)		12.44 (±3.10)		0.512
Family status (n=414)					
Unmarried (n=351)	248	70.7	103	29.3	0.298
Married (n=63)	40	63.5	23	36.5	
Occupational status (n=416)					
Employed (n=121)	91	75.2	30	24.8	0.158
Unemployed (n=295)	200	67.8	95	32.2	
Residence (n=414)					
Big city	246	69.9	106	30.1	0.933
Small town or village	43	69.4	19	30.6	

(a) Statistically significant difference, Chi-square test, (b) Statistically significant difference, Independent Samples Test

towns or rural areas. Only 15.2% out of 414 patients were married (74% unmarried, 10.8% divorced or widowed) and 28.3% out of 416 patients were employed during assessment time. The mean years of education were 12.58 (SD=±3.17) of a total of 405 patients.

The sporadic cases of psychosis (n=291, p=69.8%) outnumbered the familial cases (n=126, p=30.2%). The distribution of the patients by age group (maternal/paternal) and type of heritability is shown in figure 1.

Paternal age

Logistic regression analysis of PA and sporadic type of SCZ is demonstrated in table 2. Using the third group as a reference category, we found that the group with the older PA had a greater risk of having a relative with novel psychotic disorder as compared to the familial type of the disorder (OR=1.92, p=0.012). Adjusting for confounding effects of MA and gender, the risk effect of this group on sporadic type remained statistically significant, but with loss of power (OR=1.72, p=0.049).

Maternal age

Logistic regression analysis of MA and sporadic type of SCZ is demonstrated in table 3. Using again the third group band as a reference category, we found that the group with the older MA (≥35 years old) had a greater risk of having a relative with sporadic SCZ, as compared to the familial type of the disorder (OR=4.39, p=0.001). Adjusting for confounding effects of PA and gender, the risk effect of this group on sporadic type remained highly statistically significant (OR=4.04, p=0.002). Moreover, the 25–29 age group showed a higher risk (in both adjusted and unadjusted analysis) for the sporadic type as compared to familial type.

Discussion

The present study focused on the investigation of sporadic schizophrenia and its possible association with parental age at the time of birth. This association is examined indirectly by comparing two groups of patients with schizophrenia spectrum disorder diagnosis, one belonging to the sporadic

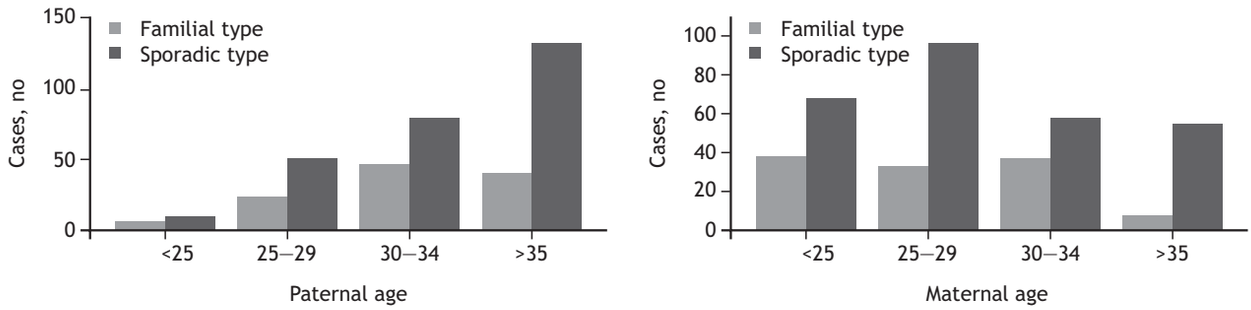

Figure 1. Distribution of schizophrenia spectrum cases by type of heritability by parental age group.

Table 2. Effects of Paternal age groups on heritability Type of Schizophrenia Spectrum Disorders, unadjusted and adjusted for maternal age and gender.

Age Group	Familial Type(n)	Sporadic Type (n)	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI) for Gender and Paternal Age	p
<25	6	10	0.98 (0.33–2.87)	0.969	1.13 (0.37–3.46)	0.834
25–29	24	51	1.24 (0.68–2.28)	0.472	1.39 (0.74–2.61)	0.309
30–34	47	80	1	–	1	–
≥35	41	133	1.92 (1.15–3.15)	0.012	1.72 (1.00–2.97)	0.049

Table 3. Effects of Maternal age groups on heritability Type of Schizophrenia Spectrum Disorders, unadjusted and adjusted for paternal age and gender.

Age Group	Familial Type(n)	Sporadic Type (n)	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI) for Gender and Paternal Age	p
<25	38	68	1.142 (0.64–2.02)	0.650	1.28 (0.68–2.43)	0.443
25–29	33	96	1.86 (1.05–3.29)	0.034	2.07 (1.14–3.78)	0.017
30–34	37	58	1	–	1	–
≥35	8	55	4.39 (1.88–10.25)	0.001	4.04 (1.69–9.66)	0.002

type of schizophrenia and one, which is used as a control group, belonging to the familial type of schizophrenia with PA and MA at birth time. Our findings indicate that both advanced PA and MA increase the risk for sporadic SCZ-spectrum disorder onset, but the robustness of the effect is more evident for advanced MA (OR=4.04, p=0.002) than PA (OR=1.72, p=0.049).

Our findings of advanced PA seem to confirm the hypothesis of Malaspina,[11] namely that patients without a family history of schizophrenia had significantly older fathers than probands with a positive family history of schizophrenia. Older fathers seem to increase the risk for sporadic SCZ in their children and moreover as this risk is differentiated for the sporadic versus the familial type, this may imply different underlying pathophysiological mechanisms for each subtype. The most common hypothesis to the PA effect is the increased "de novo mutations" in the paternal germ line,[4,8] due to the fact that point mutations can accumulate in the clones of spermatogonia as men age. Advanced father's age in the population may result in an accumulation of rare "de-novo" mutations in the paternal sperm and contribute to a significant proportion of SZ risk.[19] Other potential mechanisms seem to be related to delayed fatherhood rather than the advancing PA per se, which could be due to environmental (e.g. urban culture) and/or genetic (e.g. impaired social functioning traits) factors.[10,20] Still more assumptions such as dysregulation of epigenetic regulation (e.g. imprinting or DNA methylation),[21] or the impact of specific stressful events on children with older fathers (e.g. father's death)[22] warrant further investigation. Few studies found an association between younger PA (<25) and the risk of schizophrenia in the offspring, yet they need adjustment for potential confounders.[12,23] In our study, the effect of PA was reduced in terms of statistical significance, when adjusted for gender and MA. Besides statistical-related reasons, it could be supported that MA could be more important in mediating the advanced parental age effect on sporadic SCZ, as the opposite, i.e. adjusting PA in MA effect on SCZ subgroup is not met.

On the other hand, it remains controversial whether MA plays such an implicating role,[16] since there are studies reporting that the association of advanced MA and schizophrenia becomes non-significant when adjusted for paternal age.[24,25] However, it is assumed that advanced MA may have an independent effect on an increased risk of schizophrenia.[14,26] Recently, a case-control study in a greek sample found that MA, as a risk factor, characterises SCZ specifically compared to other mental disorders,[27] while we found that advanced MA (and PA) may furthermore specify the risk for its sporadic type. The late MA hypothesis is further reinforced in studies that support higher frequency of perinatal complications in older mothers and their association with increased risk of psychotic disorders.[28] Finally, younger MA (<25) has also been related to schizotypy[29] and schizophrenia spectrum disorders,[13,30] which might be associated with psychosocial, cultural or resource mediated factors.[18,31] In our study, results have been consistent with recent reports on the role of advanced MA and schizophrenia in offspring[14,16] and the hypothesis that SCZ risk associated with increased MA is explained by the age of the father may need to be reconsidered. The significant finding of the 25–29 age group, which showed higher risk compared to <25 subgroup, cannot be adequately

interpreted in this study, but it may imply a different pathophysiological effect of mother's age on novel psychosis compared to familial type. On the other hand, no replication of studies concerning increased risk of psychosis in the offspring of younger mothers[14] was confirmed.

The present study also suggests a small variation of increased frequency for males compared to females in the sporadic form of SCZ. Current literature provides evidence of greater incidence risk ratios for men to develop SCZ relative to women.[32,33] Our findings do not associate gender with advanced MA or PA arguing that older parental age does not possibly have an X-linked etiopathological role in an increased risk of SCZ.

Our study has to be considered in light of its limitations. First, we used SCZ cases (familial type) only and not healthy subjects as a control group. However, this study model has been used both in genetic[34] and psychiatric epidemiology.[11] Second, selection or information bias that should be expected, as register-based diagnoses may be biased towards more severe cases. Third, secondary diagnoses were not considered. Fourth, there is no evidence from the literature for a clear cut-off threshold beyond which PA or MA should be considered "advanced"[35] and thus determining age subgroups may not reflect precise risk for each age. Fifth, other potential confounders (psychological factors related to increased PA and MA, psychiatric diagnosis of fathers and mothers, obstetric events, psychological abuse and trauma, cannabis, migration) that are known risk factors for psychosis, could not be addressed in this study.

Conclusion

The sporadic versus familial cases in SCZ spectrum disorders raise a prominent scientific interest, as it could provide answers to possible etiopathological mechanisms underlying these perplexing psychiatric disorders. Patients with the sporadic type, though clinically indistinguishable from the familial type patients, may share other pathophysiological pathways in which advanced parental age may be a candidate mediator. Few studies have been conducted concerning the role of parental age in sporadic SCZ in Greece. This study implies that high maternal age maybe an important risk factor for sporadic SCZ, maybe higher than advanced paternal age. However, future studies could help clarify both the role of PA and MA in the pathophysiology of the disorder. Since parental age is linked not only to the novel cases of psychosis, but to autism and various neurodevelopmental disorders[36,37] optimal age of parenthood may have significant implications in public health.

Συσχέτιση της αυξημένης γονεϊκής ηλικίας με τη σποραδικού τύπου σχιζοφρένεια

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Η εμφάνιση νέων, σποραδικού τύπου, περιστατικών σχιζοφρένειας (ΣΧ) έχει συσχετισθεί, μεταξύ πολλών υποψηφίων επιγενετικών παραγόντων, με την προχωρημένη πατρική και την προχωρημένη μητρική ηλικία. Η πιο κοινή υπόθεση ως προς την επίδραση της πατρικής ηλικίας αφορά την αύξηση των *de novo* μεταλλάξεων κατά τη διαδικασία σπερματογένεσης, ενώ η υπόθεση για τον ρόλο της μητρικής ηλικίας, αν και αμφιλεγόμενη, στηρίζεται κυρίως σε μελέτες οι οποίες τη συσχετίζουν με αυξημένη συχνότητα περιγεννητικών επιπλοκών. Το δείγμα μας αποτελείται από 462 άτομα με δια-

ταραχές σχιζοφρενικού φάσματος (ΔΣΧΦ) στον άξονα Ι κατά DSM-IV-TR, από τα εξωτερικά ιατρεία του Αιγινητείου Νοσοκομείου. Τα άτομα αυτά ελέγχθηκαν για κληρονομικότητα και χωρίστηκαν περαιτέρω σε μία ομάδα με τον σποραδικό τύπο της διαταραχής (χωρίς αναφερόμενο οικογενειακό ιστορικό σε συγγενείς έως 2ου βαθμού) και μία ομάδα με τον οικογενή τύπο ΔΣΧΦ (θετικό κληρονομικό ιστορικό). Οι δύο ομάδες ασθενών συγκρίθηκαν είτε ως προς την ηλικία του πατέρα είτε ως προς την ηλικία της μητέρας κατά τη γέννησή τους. Η ομάδα με τον οικογενή τύπο χρησιμοποιήθηκε ως ομάδα ελέγχου. Σκοπός αυτής της αναδρομικής μελέτης αρχείου ήταν να εξεταστεί κατά πόσο η προχωρημένη γονεϊκή ηλικία κατά τη γέννηση μπορεί να παίζει ρόλο στη νέα εμφάνιση μη συναισθηματικής ψύχωσης στους απογόνους. Χρησιμοποιώντας ανάλυση λογιστικής παλινδρόμησης, διαπιστώθηκε ότι ο κίνδυνος εμφάνισης σποραδικού τύπου ΔΣΧΦ, σε σύγκριση με τον οικογενή τύπο, ήταν στατιστικά μεγαλύτερος σε σχέση τόσο με την προχωρημένη μητρική ηλικία (OR=4,39, p=0,001) όσο και με την αυξημένη ηλικία του πατέρα (OR=1,92, p=0,012). Μετά την προσαρμογή για τον αποκλεισμό πιθανών συγχυτικών παραγόντων και συγκεκριμένα της ηλικίας του άλλου γονέα και του φύλου του ασθενούς, ο κίνδυνος για τον σποραδικό τύπο ΔΣΧΦ παρέμεινε στατιστικά σημαντικός τόσο για τη μητρική ηλικία (OR=4,04, p=0,002) όσο και για την πατρική ηλικία, αν και για την τελευταία υπήρξε μείωση της στατιστικής ισχύος (OR=1,72, p=0,049). Ελάχιστες μελέτες έχουν διενεργηθεί στον ελληνικό πληθυσμό για τον ρόλο της γονεϊκής ηλικίας στην εμφάνιση ΣΧ. Η παρούσα μελέτη συμφωνεί με τη διεθνή βιβλιογραφία από την οποία επισημαίνεται ότι η προχωρημένη πατρική και μητρική ηλικία πιθανώς αυξάνει τον κίνδυνο για εμφάνιση σποραδικού τύπου ΣΧ. Επιπλέον, η αυξημένη μητρική ηλικία ενδεχομένως αυξάνει τον κίνδυνο για τον σποραδικό τύπο, σε σχέση με τον οικογενή τύπο ΣΧ, περισσότερο από ό,τι η προχωρημένη πατρική ηλικία. Οι ασθενείς με τη σποραδική μορφή ΔΣΧΦ, μολονότι κλινικά αδιαφοροποίητοι σε σχέση με αυτούς με την οικογενή της μορφή, μπορεί να μοιράζονται διαφορετικούς υποκείμενους παθοφυσιολογικούς μηχανισμούς στους οποίους η γονεϊκή ηλικία, ιδιαίτερα η προχωρημένη μητρική ηλικία, μπορεί να αποτελεί πιθανό μεσολαβητή. Ωστόσο, μελλοντικές έρευνες θα μπορούσαν να συνεισφέρουν στο να ξεκαθαρίσει ο ρόλος της γονεϊκής ηλικίας στην παθοφυσιολογία της διαταραχής.

Λέξεις ευρετηρίου: Φάσμα σχιζοφρένειας, σποραδικός/οικογενής τύπος, γονεϊκή ηλικία, πατρική ηλικία, μητρική ηλικία.

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