Advanced Paternal Age and the Risk of Schizophrenia: A Literature Review

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Average parental age is increasing in most Western countries, reflecting the changes in professional and social life. Literature shows that in England and Wales from 1993 to 2003, the rate of older paternal age (35 to 54 years) increased from 25% to 40% and the mean paternal age increased from 29.2 years to 32.1 years. Advanced paternal age is associated with accumulated environmental insults over time and is strongly associated with reductions in fertility due to impaired spermatogenesis. It is well known that in males, germ-line mutations are high due to the increased frequency of cell division over the life course.
The correlation between advanced paternal age (APA) and schizophrenia is the focus of numerous studies, and an increased risk for schizophrenia in children of older fathers is a well-replicated finding regardless of culture and nationality, with approximately 26.6% of cases of schizophrenia attributed to APA. The focus of studies on this topic has now shifted toward searching for the etiology of this relationship. Etiological heterogeneity, complex patterns of gene-gene and gene-environment interaction and inadequately elucidated schizophrenia pathophysiology are among the explanations invoked to explain our inadequate understanding of the etiopathogenesis of schizophrenia. Environmental influences are also explored in various studies and will be covered in this article.

**POPULATION-BASED STUDIES**

Many studies show a significant link between APA and the incidence of schizophrenia in offspring. Several of these studies have corrected for the effects of confounding factors, yet the link between APA and schizophrenia remains significant. Malaspina et al conducted a population-based cohort study of 658 patients that showed that paternal age is a strong and significant predictor of a diagnosis of schizophrenia, but not of other psychiatric disorders. The authors suggested that de novo sperm mutations that accompany advancing paternal age might be responsible for the association with schizophrenia.

In 2002, Brown et al conducted a study using the data from the birth cohort of the Prenatal Determinants of Schizophrenia Study, and concluded that there was a significant association between APA and schizophrenia, as well as schizophrenia-spectrum disorders. This association persisted after the analysis was controlled for maternal age and other possible confounders.

To investigate the association, Dalman and Allebeck conducted a population-based case-control study comprising 524 patients with schizophrenia and 1,043 matched comparison participants selected from registers. The results showed that the probability of schizophrenia in offspring of older fathers (>45 years) was 2.8 times that of offspring of younger fathers (age 20 to 24 years).

**EFFECT OF GENDER DIFFERENCES, PERSONALITY TRAITS**

A case-control study was conducted on a Danish longitudinal register, which included 7,704 schizophrenia patients and 192,590 individually time-, age-, and sex-matched population controls consisting of parents and siblings while controlling for family socioeconomic and demographic factors and family history. A gender effect was identified in which the increased risk associated with APA was particularly prominent for female offspring.

However, another population-based cohort study conducted in Sweden on 754,330 people found no strong evidence of any marked difference by gender and the association between paternal age and schizophrenia. Hazard ratios increased by 1.65 (1.32-2.06) for men and by 1.40 (1.03-1.89) for women for every 10 years of paternal age.

Many studies have indicated that “schizotypy” or schizotypal personality traits reflect a genetic background of schizophrenia and run in the pedigree of patients with the disorder. To support this hypothesis, Zammit et al studied confounding variables such as older fathers having personality disorders that are passed down to their offspring in relation to an increased risk for developing schizophrenia. These variables were found to be likely contributors to the relationship in question.

Another study looked at the behavior of fathers with such traits, some of which are characterized by impaired sociality, which may lead to relatively later marriages and fatherhood. However, the odds ratio in those studies representing the strength of the association between paternal age and schizophrenia risk remained unchanged after adjustment for a family history of psychosis or by paternal schizotypy, indicating that the association in this case is unlikely.

APA at birth as a risk for schizophrenia in offspring has also been reported in previous studies exclusively conducted in Western countries and Israel. To see if similar findings can be replicated in countries with socially and culturally varied attitudes toward marriage, including factors such as age at marriage, Tsuchiya et al conducted a case-control study in a Japanese population. The researchers found that an association between APA and the risk for schizophrenia in offspring was consistent with previous studies.

**SOCIAL, ENVIRONMENTAL FACTORS**

The roles of child development and environmental factors were also explored in many studies with varied results. Using case-control studies conducted in the Northern Hemisphere for a meta-regression, both high latitude and low ambient temperature were found to increase paternal age-related schizophrenia risk significantly. Victoria et al performed a cross-sectional study on 240 patients and 400 controls without any psychiatric disorders and found that the average paternal age of the schizophrenic group was 1.2 years older than the control group.

Zammit et al examined children from the Avon Longitudinal Study of Parents and Children (ALSPAC) to determine whether psychosis-like symptoms (PLIKS) during adolescence are associated with a family history of schizophrenia or APA. The researchers found only weak evidence that PLIKS was associated with APA.
Another issue to consider is that having older parents may have psychological consequences on children, and that increased parental age could result in earlier loss of parents, which is identified as a risk factor for schizophrenia. Byrne et al, however, suggest that the psychological distress caused by the death of an aging parent does not account for the relationship between risk for schizophrenia and APA.

Saha et al conducted a birth cohort study on children drawn from the US Collaborative Perinatal Project to examine the relationship between paternal and maternal ages and selected behavioral measures in children. APA was associated with a significantly increased risk of adverse externalizing behaviors at age 7 years. For every 5-year increase in paternal age, the odds of higher externalizing behaviors were increased by 12%. The relationship persisted after adjusting for potential confounding factors. Lastly, a case-control study by Rosenfield et al assessed whether the symptoms and gender differences in paternal age-related schizophrenia (PARS) are consistent with those of schizophrenia in general. The results showed that PARS is associated with similar symptoms and age at onset in males and females, more severe symptoms during medication-free periods, and more responsiveness to antipsychotics, bolstering the possibility that PARS has a diverse etiopathogenesis.

**THE INFLUENCE OF GENETICS**

It is thought that the spermatogonial stem cell divisions occurring during the life-course of males result in higher mutational rates and cytogenetic abnormalities in the sperm of older men. The mutation rate of the male germ line has recently been estimated to be twice that of the female germ line. Literature shows that there is also more probability of germ line cell mutations found in sperm (by age 50 years, there are 840 cell divisions) compared with the ovocyte in utero (22 cell divisions).

Heat exposure may also increase the exposure of spermatozoa to mutagenic metabolites, leading to more and earlier mutations. Byrne et al, however, suggest that the increased risk for schizophrenia associated with increased rates of chromosomal aberrations, including micro deletions in chromosomal regions 1q21.1, 2p16.3, 15q11.2, 15q13.3, as well as micro duplications in chromosomal regions 15q13.1 and 16p11.2.

Gauthier et al studied the gene encoding the synaptic scaffolding protein SHANK3 in 285 controls and 185 schizophrenia patients with unaffected parents. The study identified two de novo mutations (R1117X and R536W) in two families. One of the mutations (R1117X) was found in three affected brothers, suggesting germ line mosaicism. Zebra fish and rat hippocampal neuron assays were used to assess phenotypic differences between zebra fish with the mutated SHANK3 gene and those with the wild type gene. The R1117X mutant revealed behavior and differentiation defects with a reduction in the size of the head, eyes, and trunk, and embryos that were unable to swim in response to touch. This suggests that the R1117X mutation, and possibly many other mutations, result in dramatic loss of SHANK3 gene product, a scaffolding protein that promotes formation and maturation of dendritic spines. Thus, the increased risk for schizophrenia with APA may be explained by an age-related increase in paternal de novo mutations, such as the R1117X mutation.

Perrin et al also hypothesized that the relationship between schizophrenia and APA is related to point mutations during spermatogenesis that occur in increasing frequency as the male ages. The researchers proposed the dysregulation of epigenetics as a possible etiology. Epigenetic processes utilize DNA methylation and demethylation, as well as changes in chromatin structure, to control gene expression. Dysregulation of this process can lead to disorders such as Beckwith-Wiedemann syndrome, Prader-Willi syndrome (PWS), and Angelman syndrome.

Interestingly, 5% to 10% of patients with PWS experience schizophrenia-like symptoms, which are associated with errors of imprinting the correct paternal chromosome. Also of significance is the fact that the gene affected in PWS is 15q11-13, which lies adjacent to a region linked to schizophrenia (15q13-14) in some studies, implying that imprinting errors may influence the expression of certain genes implicated in schizophrenia.

The persistence of schizophrenia in the population despite reduced fertility could also be explained by the transgenerational accumulation of paternally derived mutations. Folate deficiency in males could amplify copy-error mutations in the male germ cell lines. Epigenetic processes could be compromised in the sperm of older fathers and these mechanisms can contribute to the increased risk for schizophrenia in the offspring of older fathers. The explanation behind the intra- and interindividual epigenetic variability in the male germ line is that epigenetic signals are generally reprogrammed in the germ line, although it appears that such reprogramming may not be fully complete across all regions of the genome.

Hypermethylated repetitive and transposable elements in the genome are often not efficiently reprogrammed. It is thus possible that de novo struc-
tural mutations, which are often associated with repetitive DNA sequence motifs, may be subjected to differential epigenetic reprogramming, associating both mutagenic and epigenetic processes in the phenotypic manifestation of increased paternal age. 17

CONCLUSION

Several distinct mechanisms are proposed to explain the significant association between APA and schizophrenia: 1) de novo point mutations; 2) CNVs; 3) aberrant epigenetic regulation; and 4) chromosomal abnormalities. All of these processes occur at higher rates as paternal age increases. There is also evidence to suggest that the first three mechanisms may specifically be related to the biogenesis of schizophrenia. 20

Although the association between APA and schizophrenia is well established, the significance of this association has yet to be determined in practice. In a society where the average paternal age continues to increase, APA will undoubtedly lead to additional cases of schizophrenia beyond the background incidence rate. Using both genetic and epidemiological research will help elucidate the biogenesis of schizophrenia and the significance of its association with advanced paternal age. Currently, the mechanism behind the association between APA and schizophrenia is unclear, providing the need for translational research across multiple disciplines.

REFERENCES

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