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Paternal age and mental health of offspring

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Abstract

The influence of paternal age on the risk for sporadic forms of Mendelian disorders is well known, but a burgeoning recent literature also demonstrates a paternal age effect for complex neuropsychiatric conditions, including schizophrenia, autism, bipolar disorder and even for learning potential, expressed as intelligence. Mental illness is costly to the patients, the family and the public health system, accounting for the largest portion of disability costs in our economy. The delayed onset of neuropsychiatric conditions and lack of physical manifestations at birth are common frequencies in the population that have obscured the recognition that a portion of the risks for mental conditions is associated with paternal age. Identification of these risk pathways may be leveraged for knowledge about mental function and for future screening tests. However, only a small minority of at-risk offspring are likely to have such a psychiatric or learning disorder attributable to paternal age, including the children of older fathers.

Introduction

Childbearing is increasingly postponed in developed countries, with any concern by clinicians and prospective parents largely focused on the age of the mother. Indeed, advanced maternal age is associated with infertility and some birth defects, and menopause imposes a clear upper limit to unaided female reproduction. One view is that fathers continue to produce “fresh” sperm, whereas oocytes age and become damaged. To the contrary, paternal age has a large influence on offspring health. As ages of mothers and fathers are highly correlated, studies that only examine maternal age can show strong effects, even if the risks are attributable to paternal age. Some conditions thought to be

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attributable to maternal age are also attributable to paternal age, including infertility and Down's Syndrome[1, 2]. The evidence is clear that studies examining the influence of maternal age on reproduction and offspring health must account for paternal age effects.

The association of advancing paternal age with increasing risks for rare genetic disorders has been known for many decades, but the awareness that fathers' age can influence mental health in offspring is relatively recent. A coherent epidemiological literature with confirmatory animal studies demonstrates that the offspring of older fathers are at increased risk of mental conditions, including schizophrenia, bipolar disorder, autism spectrum disorder, poor social functioning and lesser intelligence[3-7]. Practitioners may be blindsided about the influence of paternal age on offspring mental health and learning for a number of reasons. First of all, these are common conditions so an effect of paternal age explains only a small portion of the population-attributable risks for these disorders. Next, these conditions manifest years after birth and they are generally unassociated with any congenital physical abnormalities. Finally, the later mean age of fathers in the population may have shifted notions about the definition of an older father, commonly defined as >40 years. However, the risk for most conditions is linearly associated with paternal aging, so the risks to offspring of fathers in who are in their 30's may be doubled in comparison to offspring with a father in his 20's. An autism study furthermore demonstrated that a paternal age related vulnerability may persist across generations, with age of grandfathers independently associated with the autism risk in their grandchildren[4].

Mechanisms

The association between increasing risks for psychiatric and cognitive conditions and advancing paternal age is ascribed to the introduction of *de novo* mutations into the population. Spermatogonia acquire genomic alterations over the repeated cell replication cycles, as occurs in somatic cells. Following puberty, spermatogonia undergo 23 meiotic events per year, so at ages 20 and 40 years, a man's germ cell precursors have undergone approximately 200 and 660 such meisoses, respectively. Thus, during a man's life the proportion of spermatogonia carrying *de novo* mutations steadily increases[8].

Moreover, some mutations may confer a selective advantage to spermatogonia, allowing these clones to expand at the expense of other clones as men age. In the “selfish spermatogonia” model[9], which has also been applied to psychiatric conditions[10], mutations that favor within-testis expansion of specific mutant clonal lines will skew the mutational profile of sperm as men age. Some of the genetic architecture supporting this expansion could also affect neurodevelopment, increasing the risk for brain disorders, or for dopamine metabolism, increasing risks for psychosis. This is feasible because mutations in the paternal germline show a propensity to occur in the tyrosine kinase receptor – RAS – MAPK signaling pathway and provide a selective advantage of specific sperm clones harboring these mutations to outcompete the others and appear to be significantly overrepresented. A recent study evaluating the germline mutation rate in teenage and elderly fathers on short tandem repeats showed that the paternal germline mutation rate is strictly monotonous increasing and that the lowest mutation rates occur at the age group of 15 to 25 (23-25 certain paternal mutations observed)[11].

In addition to paternal aging, other potential damaging exposures to the male germ line could increase mutation rates, including toxic exposures, infections, nutritional deficiencies and even psychological stress of the father, particularly in puberty. Epigenetic processes are compelling mechanisms to explain some of the epidemiological associations between environmental exposure and disease. It is appreciated that life course exposures can alter our gene expression through epigenetic changes, but epigenetic modulation of gene expression may also arise through exposures of parents or be related to their ages[12].

Longer telomere length is frequently mentioned as a potential benefit of later paternal age, as it is a predictor of longevity. However, any value of longer telomere length does not blunt the risk for schizophrenia, as longer telomere lengths are reported in the disease for later paternal age in males and for a family history of psychiatric illness in males and females[13].

Advancements in fields other than psychiatry leveraged paternal age effects in rare diseases to make genetic discoveries. Some resistance to the hypothesis that paternal age is related to offspring mental health outcomes, which has been long accepted for effects of maternal age and birth order, is yielding to the number of consistent and rigorous studies. Below we consider schizophrenia and intelligence in greater depth, as these are, respectively, the most and least disabling of the psychological and learning conditions associated with paternal age.

Schizophrenia

Schizophrenia is a severe neuropsychiatric syndrome with a prevalence of 0.30%-0.66% and an incidence of 10.2-22.0/100,000 persons per year. The symptoms typically begin in late adolescence or early adulthood, whereupon lifelong disability typically ensues. Its onset is defined by the emergence of psychosis in the setting of deteriorating function and other symptoms[14]. Before the onset of psychosis, during a prodromal period of several weeks to many years, nonspecific and variable subtle abnormalities worsen and coalesce into the classic disease features. These include alterations in the perception of reality, changes in the form and content of thoughts and speech, and social and emotional deficits including a disturbed sense of self, social dysfunction, apathy, and peculiar behavior[15].

A single study in 1979 from a United Kingdom registry demonstrated that cases with schizophrenia had older fathers than other subjects[16], although further research was curtailed by the enduring interpretation that these findings just reflected delayed childbearing by genetically vulnerable men; i.e. these fathers were socially awkward or had some other schizophrenia-related constitutional impairment. Reproductive clinicians thus had not harbored concern about later paternal age and offspring mental health for seemingly healthy fathers. By contrast, the emerging data show that paternal age is older in sporadic cases, which is consistent with de novo events.

The first study to test the hypothesis that advancing paternal age was related to an increasing risk for schizophrenia in light of *de novo* mutations or epigenetic effects was the Jerusalem Perinatal Cohort Schizophrenia Study[17]. It demonstrated a linear increase in the risk of schizophrenia with increasing paternal age after adjusting for mother's age. Each decade of the father's age multiplied the risk of schizophrenia by 1.4 (1.2-1.7, p<.0001), so that the RR

for offspring of fathers aged 45+ was tripled compared with those of fathers aged 20-24. In contrast, effects of maternal age were minimal. One quarter of all cases were attributable to effects of fathers' ages in this population. Paternal age explained a quarter of the risk for all schizophrenia in the Jerusalem cohort if categories of paternal age beginning at age 30 were included in the calculation. The absolute number of affected cases was 1/198 offspring for fathers at age 20, 1/131 for those age 30 and 1/61 offspring for father of age 50 years.

Paternal aging was also associated with increasing risks for schizophrenia across ethnically diverse and geographically distinct cohorts and registries, including ones from the United States[18-22], and Denmark[23, 24]. Two studies that were not based on prospective cohorts or registry data did not demonstrate an effect of advanced paternal age on the risk for schizophrenia, including one that used siblings as controls[25] and another small sample[26]. These studies found around 15% of the total population burden for schizophrenia was attributable to paternal age, but they only calculated the effects of categories of paternal age beginning at 35 or 45 years of age. While the absolute risk to children from fathers in their early thirties are only slightly increased, a very large number of fathers bear children at these ages, so their affected offspring may comprise a large portion of the affected offspring in a population.

Several conservative meta-analyses confirmed the effect of APA on schizophrenia risk[19, 27-30]. Collectively, the studies also showed a tripled risk for schizophrenia in the offspring of the oldest group of fathers in comparison with the risk from younger fathers. Furthermore, the research demonstrated that the paternal age effect is not explained by other factors, including family history of psychosis, maternal age, parental education and social ability, family social integration, social class, birth order, birth weight, or birth complications.

The notion that psychotic diseases were influenced by molecular changes in the male germ line met with resistance, even though only a small minority of cases have any family history of psychosis. For example, Petersen and colleagues[24] reported that paternal age at birth of first child, but not later born children, was associated with schizophrenia. They proposed that some fathers had “selection into late fatherhood” rather than genomic changes in sperm. Likewise Miller[31] proposed that paternal age effects were explained by older men being more likely to father children with mothers who had histories of psychosis. However another study found that paternal age is younger in familial cases, counter to this claim[32]. D'Onofrio et al[20], using a unique case-sibling design, also found strong evidence supporting the *de novo* mutation hypothesis.

Epigenetic changes associated with male germ line aging are also likely to be relevant. DNA methylation and demethylation are active processes in spermatogenesis as a number of genes are differentially methylated in the germ lines of male versus female parents. Methylation processes may also be vulnerable to aging and can produce aberrations in gene expression that may be transmitted across the generations. Milekic et al[33] examined epigenetic effects in sperm through genome-wide DNA methylation screening to compare young and old mice. This study showed a substantial decrement in sperm methylation for

older mice in transcriptional regions, with concomitant alterations in brain gene expression and behavior for these neurodevelopmental genes.

The impact of paternal age on the risk for disease is large, averaging 15-25 % of cases, based on the epidemiological studies. In light of the de novo mutation perspective, it is possible that multiple genes can undergo various mutations that produce psychosis on a common genetic vulnerability profile. If the determinant genes for psychosis are largely sporadic, then identification of disease-specific genes for psychosis through multiplex pedigrees may be limited. Different affected family members may have different deterministic mutations, perhaps acting on a nonspecific genetic vulnerability for multiple psychiatric conditions.

Bipolar Disorder

Bipolar disorder, also known as manic-depressive illness is typified by cycles of mania and depression, including shifts in mood, energy, activity levels, and the ability to carry out daily tasks. Some persons are also psychotic and symptoms can be chronic and severe, with half of cases beginning before age 25 years. Bipolar disease in offspring is also related to APA. One study found the risk was 37% higher for children whose fathers were older than 54 years at their birth compared to children of younger fathers in adjusted analyses[34]. This study showed the effect of paternal age effect was strongest in individuals with an early disorder onset. Another Swedish cohort study compared with offspring born to fathers 20 to 24 years old to those who were 45 years or older using sibling comparisons, finding a 24-fold increase of bipolar disorder for bipolar disorder for the older fathers[20].

Autistic Spectrum Disorders

Austim is defined by persistent deficits in social communication and social interaction; restricted, repetitive patterns of behavior, interests, or activities and significant impairments in social, academic and occupational functioning. The condition, which can present on a spectrum from mild to severe, is usually recognized in the first two years of life and is consistently associated with APA. A study that used sibling comparisons in the Swedish Registry[20] showed a tripled risk for autism for the offspring whose fathers in the older paternal age group. An Israeli study showed a more than 5 fold increase in autism risk for the offspring of men 40 years or older compared with offspring of men younger than 30 years[35]. It is notable that increases in autism diagnoses have paralleled the secular changes in paternal age have occurred in parallel.

Learning and intelligence

The first report to find associations between learning ability and paternal age was published over 30 years ago by Auroux[36]. This report was based on a series of rat studies. Rat pups of older sires showed diminished learning capacity on an avoidance-conditioning test and had decreased spontaneous activity at 10 and 13 weeks of age with no evident physical findings. He next translated this discovery to humans[37], showing a “U shaped” relationship between paternal age and cognition in male French military recruits. Another study showed paternal age > 35 years was related to decreased reading ability in girls[38].

Following the discovery of the paternal age effect for schizophrenia, several studies replicated Auroux's[36] findings associating paternal age with relationship of Intelligence. In the same cohort as the schizophrenia study, Malaspina et al[7] showed paternal age was related to offspring intelligence, particularly nonverbal intelligence. Offspring with paternal ages 25-44 years had the highest IQ scores. Fathers younger than 25 and older than 44 years sired offspring with lesser mean intelligence scores. These are notably mean effects and some offspring at both extremes of paternal age had high intelligence. These results withstood adjustments for parental education, social class, sex, birth order, birth weight, and birth complications. While the paternal age effects were related to nonverbal IQ in this study, the offspring of the oldest mothers independently had lower verbal and nonverbal intelligence. Another study by Saha et al[39] that used data from the U.S. Collaborative Perinatal Project (CPP) examined paternal age effects in 33,437 children at 8 months, 4 years, and 7 years. In this study paternal age was associated with poorer scores in five out of six neurocognitive tests and maternal age conversely predicted increasing scores on the same tests.

Rodent studies supported the biological underpinnings of these effects, confirming paternal age effects on learning and behavior, including decreased social and exploratory behaviors for offspring of ten month old sires compared to those of two-month-old sires[40]. Another study comparably showed reduced capacity for passive-avoidance learning for offspring of older sires[41] and another found alterations in cortical growth, which are perhaps relevant to the behavioral findings[42]. Both schizophrenia and autism entail reduced learning ability, so these findings may be relevant to the mechanism linking later paternal age to these conditions[35, 43-45].

Conclusions

The weight of epidemiological and animal model data linking advancing paternal age with offspring mental health is impressive and cannot be ignored. While the largest portion of offspring of older fathers may not have any mental health conditions, the tripled risk with paternal aging for these relatively common conditions is of interest and concern. Much research on health outcomes has focused on pregnancy and early life exposures, but now the exposures of the father, including aging of the germ cells, should also be considered. Future methodology may entail mutational analysis and exome sequencing for clinically relevant mutations or *de novo* events that are shown to affect gene function.

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