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Advancing paternal age at birth is associated with poorer social functioning earlier and later in life of schizophrenia patients in a founder population

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ABSTRACT

Consistent associations have been found between advanced paternal age and an increased risk of psychiatric disorders, such as schizophrenia, in their offspring. This increase appears to be linear as paternal age increases. The present study investigates the relationship between early deviant behaviour in the first 10 years of life of patients as well as longer term functional outcome and paternal age in sporadic Afrikaner founder population cases of schizophrenia. This might improve our understanding of Paternal Age-Related Schizophrenia (PARS). Follow-up psychiatric diagnoses were confirmed by the Diagnostic Interview for Genetic Studies (DIGS). An early deviant childhood behaviour semi-structured questionnaire and the Specific Level of Functioning Assessment (SLOF) were completed. From the logistic regression models fitted, a significant negative relationship was found between paternal age at birth and social dysfunction as early deviant behaviour. Additionally, regression analysis revealed a significant negative relationship between paternal age at birth and the SLOF for interpersonal relationships later in life. Early social dysfunction may represent a phenotypic trait for PARS. Further research is required to understand the relationship between early social dysfunction and deficits in interpersonal relationships later in life.

1. Introduction

Children of older fathers have an increased risk of genetic disorders. Growing evidence suggests that, independent of maternal age, the offspring of older fathers are more susceptible to a wide range of conditions. (Goriely and Wilkie, 2012) Studies have shown consistent associations of advanced paternal age (APA) with an increased risk of schizophrenia in offspring (Malaspina et al., 2001), as well as a range of other psychiatric morbidities, such as autism spectrum disorder (Grether et al., 2009; Hultman et al., 2011), bipolar disorder (Frans et al., 2008), epilepsy (Vestergaard et al., 2005), obsessive-compulsive disorder (Wu et al., 2012), and reduced cognitive abilities in infancy and childhood (Saha et al., 2009).

There appears to remain a notable lack of consensus on how to define what constitutes advanced paternal age itself. Some authors are more specific in this regard while others reason that there is no definite cut-off point beyond which paternal age should be considered "advanced". Paternal age-related schizophrenia (PARS) was operationally defined by Rosenfield et al. (2010) as those with no family history of schizophrenia or psychosis and whose father's age at birth was 35 years or older.

The literature suggests that for many disorders there is no obvious cut-off point beyond which paternal age should be considered "advanced". Rather, there appears to be a linear increase in risk of the disorder with increasing paternal age. Miller et al. found a J-shaped curve for the relationship between paternal age and risk of schizophrenia. In a meta-analysis of paternal age and schizophrenia risk in male versus female offspring, it was found that there is a significant increase in risk of schizophrenia in the offspring with increasing paternal age (≥ 30 years of age). It was also found that there is a significant increase in risk of schizophrenia in the offspring of younger fathers (< 25 years of age), which may also be associated with an increased risk in males, but not in females. The population attributable risk percentage (PAR %) was 10% for paternal age ≥ 30% and 5% for paternal age < 25 in all studies (Miller et al., 2010).

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Malaspina et al. estimated that for each decade of paternal age, the relative risk of schizophrenia increased by 1.40 in male offspring and 1.26 in female offspring (Malaspina et al., 2001). Of interest is that more than a quarter of schizophrenia cases in Malaspina et al.'s cohort were attributable to the paternal age effect. (Malaspina et al., 2002).

Recent genomic studies have reported that the age of the fathers at conception is an important factor in determining the number of de novo mutations in their offspring (Kong et al., 2012). Accumulated mutations and chromosomal abnormalities in reproductive germ cells might account for the largest part of the risk of mental disorders associated with advanced paternal age (Goriely et al., 2013). New mutations may explain why schizophrenia is maintained in the population, despite the significant reproductive disadvantages of affected individuals (Malaspina et al., 2001).

On the other hand, there are researchers who believe that the causal link between paternal age and de novo mutations is still premature (Jaffe et al., 2014). The paternal age effects may increase the risk of schizophrenia through epigenetic mechanisms associated with the developmental environment, both intra-uterine and postnatal.

Patients with schizophrenia and their first-degree relatives have impaired social functioning, hence, it follows that impaired social functioning may represent an intermediate phenotype of the illness. Research results of social functioning studies in the general population and advanced paternal age suggest that the risk pathways between advanced paternal age and schizophrenia, at least partially, include mildly deleterious effects of social functioning (Weiser et al., 2008).

Schizophrenia is regarded as a disease affected by multiple genes and environmental factors, but these factors can also contribute to the manifestations of other mental disorders or intermediate phenotypes such as poor cognitive or social functioning. Deleterious effects of the risk factors are manifested as mental illness only when individuals cross a certain severity threshold (Weiser et al., 2008). Thus, advanced paternal age might not be a risk factor for a specific mental disorder such as schizophrenia, but rather increases the risk for brain malfunction that rarely crosses the threshold for a clinical diagnosis.

The research question that culminated from the literature regarding advanced paternal age, schizophrenia and social functioning pre- and post-onset of the illness was as follows: how does increasing paternal age at birth correlate with early deviant behaviour in the first ten years of life (which would include social functioning), and with the specific level of functioning in adulthood in sporadic cases with schizophrenia and schizoaffective disorder in a founder population?

2. Methods and materials

2.1. Subject recruitment

Over the years, a number of families with schizophrenia have been recruited from the Afrikaner population for a collaborative study. (Karayiorgou et al., 2004) These subjects form part of a cohort of cases enrolled in ongoing genetic research, being conducted collaboratively by the Department of Psychiatry, University of Pretoria and the Laboratory for Human Genetics, Columbia University, New York.

The families in this cohort are of varying structure, including both sporadic cases and multiple affected family members. Demographic data, including paternal ages of patients, was available. Each subject who met the criteria for schizophrenia or schizoaffective disorder (APA, 1994) underwent a careful, in-person diagnostic evaluation using the Diagnostic Interview for Genetic Studies (DIGS) at recruitment (Nurnberger et al., 1994).

The Afrikaner population in South Africa is a genetically and environmentally homogeneous population who have descended from mostly Dutch immigrants who settled in South Africa from 1652 onwards (Karayiorgou et al., 2004). In addition to the genetic homogeneity, the Afrikaners are valuable for genetic studies because they present a close-knit family structure and offer the potential to perform detailed genealogical analysis, which affords reliable discrimination of familial and non-familial (sporadic) forms of the disease (Xu et al., 2012). We identified and extracted the sporadic cohort (i.e. no history of schizophrenia in first- or second-degree relatives) from within the original cohort. A subset of probands from this sample was re-contacted for participation in the current study by the principal clinical investigator of the collaborative study. These probands were selected dependent on the presence of a sporadic form of the disease.

2.2. Study design and participants

This observational retrospective cohort study included 41 Afrikaner South African patients; 35 males and 6 females. Their ages at evaluation for the present study ranged from 16 to 62 years with a mean age of 37 years. Their paternal ages at birth ranged from 17 to 46 years with a mean of 30.8 years.

Preceding our interviews, subjects had each been formally diagnosed with schizophrenia or schizoaffective disorder by an experienced consultant psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) at Weskoppies Psychiatric Hospital, Pretoria.

The criteria used for being classified as an Afrikaner included: Afrikaans language, typical Afrikaans surname of both parents and grandparents on the paternal and maternal side, and genealogical tracings by a genealogist (Karayiorgou et al., 2004).

2.2.1. Stability of diagnosis

The lifetime diagnoses originally assigned to the 41 subjects were remarkably stable across the three groups. The initial study diagnosis was made by a best-estimate process using medical records and collateral information. The diagnoses remained the same in all but four cases. The stability of diagnoses was confirmed by the re-administration of the DIGS and collecting other relevant data. The absence of a positive family history was also confirmed at re-evaluation, therefore verifying the sporadic nature of the illness.

One patient had a dual diagnosis of Asperger Syndrome and schizophrenia at initial assessment. After follow up assessment the diagnosis of Asperger Syndrome was discarded. The modification of diagnosis from schizophrenia to schizoaffective disorder in three patients was done because the longitudinal course of the illness was taken into account and a more accurate picture of the mood symptoms was available at the follow up evaluation. The reliability coefficients for schizoaffective disorder are lower than for other diagnoses made in the DIGS (Nurnberger et al., 1994). It remains difficult to assess reliably the mood syndrome criteria in the DSM IV of schizoaffective disorder.

No major categorical diagnostic changes were made and in all 41 patients psychosis remained central to their clinical presentation, supporting the reliability of the final best-estimate process initially employed in making a lifetime diagnosis.

2.3. Variables examined

Our study consisted of confirmation of the patient's psychiatric diagnosis, based on a follow-up psychiatric interview using the DIGS (Nurnberger et al., 1994). The interviews were administered by two investigators training in psychiatry and were overseen by