

GUEST EDITORIAL

Elderly persons with elderly fathers – do they face additional risks?

Psychogeriatric research has explored many factors likely to influence our mental health in later life, but one which has received surprisingly little attention given the current interest in genetic determinants has been paternal age. We now know that both delayed motherhood and delayed fatherhood may have a significant detrimental effect on the mental health of the offspring, but by different mechanisms. While delayed motherhood has been associated with higher rates of obstetric and perinatal problems, delayed fatherhood has been associated with higher risk of new inheritable-mutation disorders. Tarin *et al.* (1998) have postulated that this is because aging leads to a reduction in the activities of antioxidant enzymes within the seminal plasma and spermatozoa making them more vulnerable to mutational changes. In most syndromes the mutation rate increases with paternal age at an exponential rate. This rate is much higher than in elderly women, perhaps due to the greater number of cell divisions in the male germ line (Crow, 1997).

High paternal age has been found to have a robust association with numerous neuropsychiatric disorders including psychoses (El-Saadi *et al.*, 2004), in particular schizophrenia (Malaspina *et al.*, 2001; Tsuchiya *et al.*, 2005), and to a lesser extent with epilepsy (Vestergaard *et al.*, 2005) and autism (Reichenberg *et al.*, 2006). Together these findings suggest the role of an increase in paternal germ cell mutation with age which may at least partly explain the persistence of these disorders within the human population given that persons with neuropsychiatric disorders have lowered fertility and reduced chances of marriage.

The impact of paternal age on cognitive functioning is of particular interest in relation to aging populations given that genetic determinants of IQ are now thought to exercise a greater influence than environmental factors with aging. Given the substantial and complex impact of genetic factors on intelligence, it might be expected that *de novo* genetic events in male germ cells may be likely to have a detrimental effect on information processing abilities in offspring, and the effects of this become more visible with aging. Evidence from a birth cohort suggests that there is a U-shaped relationship between paternal age and IQ at adolescence controlling for maternal age, education, social class, sex, birth order, birth weight and obstetric complications (Malaspina *et al.*, 2005). The adverse effect of paternal age was found in this study to be greater in relation to performance than to verbal IQ.

Most studies of paternal age and intellectual functioning have been carried out on children and young adults, so that very little is known about how this

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factor may impact on mental health and cognitive functioning at higher ages. The relationship between paternal age and Alzheimer's disease (AD) is an old book which has been opening and shutting for over a quarter of a century with conflicting results ranging from increased risk (Urakami *et al.*, 1989), no relationship (Corkin *et al.*, 1983; Hofman *et al.*, 1990; Fratiglioni *et al.*, 1993), or even increased risk with younger paternal age (Farrer *et al.*, 1991). The principal limitations of most of these studies, however, has been their small sample sizes (mostly case-control studies), naïve statistical analyses (often univariate), failure to take adequate account of confounding factors, and mistakenly confounding sex adjustment with sex stratification. More recent studies based on larger population cohorts, and able to control for multiple interacting and confounding factors, suggest a more complex link. Re-analyzing previous case-control studies by meta-analysis, van Dijn *et al.* (1994) found an increased risk with higher paternal age. Whalley (2001) conducted an integrative analysis of Scottish data and found increased paternal age to be a significant risk factor for both AD and vascular dementia in men only. An earlier study had also found increased paternal age to be related to pre-senile dementia in men only (Whalley *et al.*, 1995). A further refinement of the question is proposed by Bertram *et al.* (1998) who assessed the probability of carrying a major gene for AD in a series of 206 AD cases and found that fathers of patients with a low major gene probability were significantly older than high probability groups and controls. These observations are consistent with the *de novo* mutation hypothesis. On the other hand, there has been little interest in looking at paternal age and late-life cognitive functioning in the absence of dementia.

And what of fragility for other disorders? There are in fact very few studies of mental health and paternal age other than AD. Ptok *et al.* (2000) reported no relationship with either dementia or depression in a short article in *International Psychogeriatrics* in 2000, but this study was based on a simple ANOVA comparison of clinical groups adjusting only for sex. Moreover the groups did not contain many subjects whose fathers were over 40 (the high-risk group identified in studies of other neurological disorders in younger subjects). There are a number of difficulties inherent in evaluating the question of mental health and parental age, not the least of which is the fact that more recent population genetic studies have incidentally found that second and third children in a family are commonly by another father without the child's knowledge (personal communication).

Birth cohort data is of course the best source for tracking the relationship between paternal age and late-life mental health, limiting errors due to mortality bias, inaccurate recall of father's age and correct identification of the father. Rodgers (1990) has already reported that older age of fathers in a U.K. birth cohort was associated with higher offspring 'present state examination' scores at 36 years in men. Evaluations of more recent examinations of the cohort will reveal whether this vulnerability continues into old age, and how it may interact with other aging-related factors. From a longitudinal population study of psychiatric disorders in the elderly conducted in Montpellier, in the south of France, we have found a relationship between older fathers and a probability of depressive disorders in late life (unpublished observations). Given current interest in genetic

determinants of mental health in late life, it is perhaps timely to look again at the role of paternal age, especially given the availability of large population data sets with DNA banks and increasingly better phenotype data. While women have long been concerned about the effect of increasing maternal age on the well-being of their offspring, the question has received little publicity in regard to men. The question needs to be asked whether older fathers are putting their children at greater risk not only of childhood neurological disorders but also of a sadder old age.

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