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Advanced paternal age is associated with earlier schizophrenia onset in offspring. Results from the national multicentric FACE-SZ cohort

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ABSTRACT

The association between advanced paternal age (APA) and increased risk of schizophrenia (SZ) is well established. The objectives of the present study were to further determine if SZ participants with APA (APA+), *versus* those without (APA-), had: (i) different illness characteristics; (ii) different responses to antipsychotic medication; and (iii) different cognitive characteristics. Participants were a non-selected representative multicentric sample of stabilized community-dwelling people diagnosed with SZ included in the FACE-SZ cohort. 389 participants (73% males, mean aged 32.7 years, mean illness duration 10.8 years) formed the study sample, with each comprehensively evaluated, clinically and neuropsychologically, over 2 days. 118 participants (30.3%) were defined as APA+ according to their father's age at birth (≥35 years). APA+ was associated with a wide range of cognitive dysfunctions in univariate analyses. In multivariate analyses, the only significant difference was the age at onset, with a mean 1.6 year earlier in APA+, compared to APA- (20.7 *vs.* 22.3 years; p=0.02). This difference is independent of sociodemographic characteristics and I.Q. No association with clinical symptomatology and treatment response was found. The present study supports the neomutation hypothesis and confirms APA as a relevant clinical variable to discriminate potential schizophrenia subtypes. Potential underlying pathophysiological mechanisms are discussed.

Introduction

Schizophrenia (SZ) is an etiologically heterogeneous syndrome, with a strong genetic component. The association between advanced paternal age (APA) and increased risk of SZ is well established, having been studied since the late 1950s, reviewed in (Hamlyn et al., 2013; Hubert et al., 2011; Sharma et al., 2015). APA is considered a SZ risk factor, with the highest quality evidence reporting medium effect sizes, often coupled to obstetric complications and cannabis use (Matheson et al., 2011). APA-related de novo mutations are widely assumed to be the underlying causal mechanism. Although such mutations are highly likely, there are alternative explanations, such as an elevated liability to psychiatric illness delaying fatherhood. A recent study has suggested that genetic risk factors shared by older fathers and their offspring are a credible alternative explanation to de novo mutations (Gratten et al., 2016). However, the stronger association between APA and offspring SZ in people without a family history of SZ, strongly indicates that the accumulation of de novo mutations in paternal sperm contributes to offspring SZ risk (Malaspina et al., 2001; Sipos et al., 2004). These studies have also demonstrated that the APA effect on offspring SZ risk is not explained by confounding factors, such as maternal age, family social integration, social class, birth order, birth weight, birth complications, parental education and social ability. APA≥35 years has been demonstrated to be an appropriate threshold for offspring SZ risk (Wohl and Gorwood, 2007).

While the vast majority of these studies have focused on APA as an etiological SZ risk factor, very few studies have explored whether APA has any effect on the clinical course of the illness. A study of 153 American SZ inpatients found no gender difference in age of onset in APA+ SZ patients, *versus* APA- SZ patients, and no difference in treatment response (Rosenfield et al., 2010). APA has been suggested to be associated with a discrepancy between verbal and performance intelligence, and, in female SZ patients, with an earlier age of illness onset (Lee et al., 2011). The authors therefore suggested APA+ patients could be viewed as a distinct clinical subgroup, with a distinct pathophysiology. Opler et al. (2013) observed that APA+ adolescent SZ patients showed a poorer clinical response to paliperidone in a randomized controlled trial of 201 SZ adolescents, whilst there was no association with age of SZ onset (Opler et al., 2013). This was a post-hoc analysis, designed after study completion. The authors underlined that there may be limitations pertaining to generalizability as patient selection was based on a specific criteria, rather than on randomization from a representative sample of patients with early SZ onset. Results from this study may therefore be specific to early onset patients and may not apply to those with onset in adulthood.

The objectives of the present study were therefore to determine if, compared to APA- SZ patients, APA+ SZ patients had different clinical and neuropsychological characteristics in a non-selected representative multicentric sample of community-dwelling SZ patients. It was hypothesized that APA+ SZ patients would have earlier illness onset, lower response to conventional treatments and lower cognitive functioning (Fig. 1).

Experimental procedures

Study population

The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) cohort is based on a French national network of 10 Schizophrenia Expert Centers (Bordeaux, Clermont-Ferrand, Colombes, Créteil, Grenoble, Lyon, Marseille, Montpellier, Strasbourg, Versailles), set up by a scientific cooperation foundation in France, the "Fondation FondaMental" (www.fondation-fondamental.org) and created by the French Ministry of Research in order to create shared and thorough