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Birth weight and obstetric complications determine age at onset in first episode of psychosis

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ABSTRACT

Background: Earlier age at onset of psychosis (AOP) has been associated with poor social adjustment and clinical outcome. Genetic and environmental factors such as obstetric complications, parental history of psychosis, advanced paternal age at time of birth, low birth weight and gestational age, and use of drugs have been described as bringing AOP forward. This study aims to evaluate the relationship between AOP and these factors in a sample of first episode of psychosis (FEP) patients.
Methods: Clinical and sociodemographic data, age at FEP, age of parents at birth, parental history of psychosis, drug-use habits of the mother during pregnancy and of the patient before psychotic onset, and Lewis and Murray obstetric complication scale were obtained from 90 patients with FEP. Statistical analysis was performed by means of Pearson correlations, Chi-square tests, Student T-test analyses and a linear regression model using SPSS version 22.
Results: Pre-eclampsia, need for incubator at birth, use of forceps, parental history of psychosis, and low birth weight were associated with an earlier AOP. Use of forceps and birth weight are the variables which best predict AOP in FEP. Stimulant drugs, which were mostly used together with cannabis and cocaine, were the only substances associated with an earlier AOP.
Conclusions: Our findings are consistent with previous study results and underline the role of the prenatal period in the development of psychosis and the importance of careful monitoring of pregnancy and delivery, especially in cases with familial history.

1. Introduction

A better understanding of age at onset in mental disorders is highly relevant for targeting research on prevention and early intervention, but also because early age at onset is often found to be associated with greater severity, persistence and lack of treatment response (Kessler et al., 2007). This issue bears special importance in schizophrenia, an etiologically heterogenous disorder that usually becomes overtly manifest in adolescence and early adulthood, although in many cases subtle impairments in neurointegrative function are present from time of birth (Mäki et al., 2005).

According to the ABC study of schizophrenia (Häfner et al., 2013), men with lower age at onset of schizophrenia show a less favorable social course and socially adverse behavior. Early onset of illness has also been associated with poor psychosocial functioning (Ochoa et al., 2006), high financial dependence and poorer educational and vocational adjustment (Lay et al., 2000), and with a greater likelihood of subsequent hospital readmission (Eaton et al., 1992; Rabinowitz et al., 2006). Also, earlier age at onset of psychiatric symptoms has been observed to be associated with conversion to non-affective psychosis in ultra-high risk individuals (Amminger et al., 2006).

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Most studies have shown that age at onset of schizophrenia differs according to gender (Abel et al., 2010a). Moreover, men show increased incidence rates of psychosis between the ages of 15 and 24 years old, while women show a more moderate increase between the ages of 15 and 29, exhibiting a second (but lower) peak between the ages of 45 and 49 (Hafner et al., 1998).

Genetic and environmental factors have been described as causing enduring liability to psychotic disorder, and, in addition, genes and environment have been shown to interact synergistically (Tournier, 2013). Some of these factors have been described as determinants of age at onset of schizophrenia.

Obstetric complications (OCs) have been related to the age at first presentation with schizophrenia by a number of studies and reviews (Ardizzone et al., 2009; Cannon et al., 2000; Dalman, 2001; Mittal et al., 2008). It has been suggested that fetal hypoxia is likely involved in the varieties of OCs associated with risk for schizophrenia, such as emergency cesarean section, bleeding during pregnancy, and preeclampsia (Mittal et al., 2008). An increased susceptibility to schizophrenia has been associated with low birth weight, especially below 2500 g (Hultman et al., 1999; Gunnell, 2003; Abel et al., 2010b; Lahti et al., 2014), with both low and high birth weight (Gunnell, 2003; Moilanen et al., 2010), and with low gestational age (Geddes et al., 1999). A recent study performed in patients at risk of psychosis and FEP showed a higher rate of occurrence of OCs compared to healthy controls (Kotlicka-Antczak et al., 2014). Epidemiologic studies have also yielded evidence suggesting that infections contracted during pregnancy play a role in schizophrenia etiopathogenesis (Brown and Derkits, 2010). In addition to influenza infection, toxoplasmosis and herpes simplex virus type 2 have also recently been linked to psychosis (Buka et al., 2001).

Family history of psychosis has been observed to have a small but significant impact on age at onset of psychosis (AOP), as well as on negative symptoms and duration of untreated illness (Esterberg and Compton, 2012). Moreover, no sex differences in AOP are observed in samples with a family history. Other authors have also detected that the protective effect of estrogen is antagonized by an elevated genetic risk (Häfner et al., 2013).

Increased paternal age is associated with several diseases, possibly due to the age-associated increase in sporadic *de novo* mutations in male germ cells (Malaspina et al., 2002; Crow, 2003; Torrey et al., 2009). In a recent review (Hubert et al., 2011), an increased risk of schizophrenia was found in offspring of fathers older than 35 years. Fewer studies have been performed regarding maternal age at birth and risk of schizophrenia, though Lopez-Castroman et al. (2010) found that risk for psychotic disorders showed a significant linear increase only with advancing maternal age, and not paternal age as is more often reported.

Childhood adversity and trauma have also been associated with psychosis and are considered important determinants of psychotic disorders (Varese et al., 2012). Previous studies have found evidence that odds of reporting a psychotic experience are greater in those who have been exposed to early trauma (Morgan et al., 2014).

Substance use before onset of psychosis can act as an immediate precipitant of psychosis. Cannabis has been the drug most closely related to earlier AOP (Large et al., 2011). Previous studies (Estrada et al., 2011; Stefanis et al., 2014) have observed in patients with schizophrenia-spectrum disorder that age at first cannabis use correlates positively with AOP and also that levels of cannabis use are associated with a younger age at presentation of psychosis (Stone et al., 2014). In studies performed with first episode of psychosis (FEP) patients, cannabis use was associated with an earlier age at onset of schizophrenia, especially among women (Allegri et al., 2013), with the gender difference in age at onset lower among cannabis smokers (Donoghue et al., 2014). In contrast, substance-use did not differ in AOP in a systematic meta-analysis performed by Large et al.(2014).

Our study aimed to focus on perinatal and familial antecedents and use of substances before psychotic onset. We sought to offer new perspective by examining how these factors can affect psychosis onset in patients with an FEP, since these patients can provide a more accurate and precise AOP and a reduced recall bias for the risk factors we aim to study.

1.1. Objectives

Our study aimed to evaluate the relationship between AOP and parental age and psychosis antecedents, OCs, birth weight, and gestational age in patients with an FEP. Use of drugs during pregnancy and previous to psychotic onset were also examined.

Our hypothesis was that presence of OCs, parental history of psychosis, older parents, and lower birth weight and gestational age were related to an earlier AOP.

2. Materials and methods

2.1. Sample

A total of 90 patients with FEP were included. The patients were recruited from adult and child and adolescent mental health services at *Parc Sanitari Sant Joan de Déu* and *Hospital Sant Joan de Déu* respectively, both hospital and community psychiatric services. These centers cover Barcelona and its metropolitan area.

The inclusion criteria were two or more psychotic symptoms (criteria A DSM-IV: delusions, hallucinations, disorganized speech, catatonic or disorganized behavior, and negative symptoms), age between 7 and 65 years, fewer than 6 months since the first contact with medical services, and duration of untreated psychosis of less than 1 year.

The exclusion criteria were intellectual disability (IQ < 70), previous brain injury, or dementia.

All selected individuals were informed of the study objectives and methodology by their psychiatrist and signed the required informed consent form. In the case of children and adolescents, informed consent was obtained from parents and from the service users themselves. The present study was approved by the Ethics Committee of *Sant Joan de Déu* (Barcelona) and it complies with the provisions of the Declaration of Helsinki.

2.2. Instruments

AOP was defined as decimal age at the time when the first psychotic symptoms appeared. Socio-demographic characteristics, clinical variables (diagnosis), age of parents at time of birth, and substance use (alcohol, cannabis, cocaine, opioids and stimulating drugs) before first psychotic symptoms were assessed through a questionnaire using the Structured Clinical Interview for DSM (SCID) (First et al., 2002). Clinical diagnoses made one year after the first psychiatric contact according to DSM-IV criteria were collected prospectively (Table 1) for a more accurate description of the sample.

Parent (mother and father) history of psychosis was assessed through the Andreasen interview with the patient and his/her relative (Andreasen et al., 1977). OCs were measured using the Lewis and Murray Obstetric Complication Scale (Lewis and Murray, 1987), yielding scores on an ordinal scale (as the number of complications). The scale was administered to the mother of the patient to assess the presence of several OCs. The OCs included were infections during pregnancy, preeclampsia, hemorrhage, gestational age under 37 or over 42 weeks, more than 36 h of labor, cesarean