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Prenatal tobacco smoke exposure, risk of schizophrenia, and severity of positive/negative symptoms

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ABSTRACT

Prenatal exposure to cigarette smoke causes chronic fetal hypoxia, dysregulation of endocrine equilibrium, and disruption of fetal neurodevelopment associated with brain malfunction, all of which potentially could induce vulnerability to schizophrenia. A total of 212 schizophrenia patients aged 14–30 years, and 212 matched controls were studied. Prenatal tobacco smoke exposure of the schizophrenia patients was compared to that of the normal controls by applying logistic regression analysis and controlling for several confounding factors. The outcomes of interest were comparison of the frequency of maternal and paternal smoking between patients and controls, as well as the severity of positive and negative symptoms between the offspring of smoking and nonsmoking parents. Among the mothers of schizophrenia patients and controls, 92 (43.4%) and 46 (21.7%) smoked, respectively. Maternal smoking during pregnancy had a significant unique contribution on increasing the risk for development of schizophrenia ($p = 0.001$), and a greater severity of negative symptoms ($p = 0.023$). Paternal smoking did not have a significant effect on the risk of schizophrenia, or severity of negative symptoms. The findings suggest that maternal smoking during pregnancy puts offspring at an increased risk for later schizophrenia, with increased severity of negative symptoms. Given the wide practice of smoking during pregnancy, fetal exposure to tobacco smoke could be a major preventable neurodevelopmental factor that increases vulnerability to schizophrenia.

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1. Introduction

Neurodevelopmental factors operating during intrauterine and early postnatal life have been associated with schizophrenia, but this association is not invariably observed (Weinberger, 1995; Cannon et al., 2002). Maternal smoking during pregnancy is associated with an increasing number of detrimental effects on the fetus and child. Of interest is the tobacco smoke induced dysregulation of the fetal endocrine equilibrium, as indicated by the reduced concentrations in cord-blood of several hormones, including the dominant estrogen in pregnancy estriol, whereas the concentration of cortisol is increased (Varvarigou et al., 2009) indicating that tobacco smoke activates the hypothalamic–pituitary–adrenal axis. Also, the levels of erythropoietin and hemoglobin in cord-blood of newborns whose mothers smoked are increased indicating chronic fetal-tissue hypoxia (Varvarigou et al., 1994). This effect may result from the tobacco-induced compromise of the uteroplacental blood-flow (Lehtovirta and Forss, 1978), which restricts oxygen and nutrient delivery to the fetus. The tissue oxygenation index within the first day of life is decreased and the antioxidant status is disturbed in neonates whose mothers smoked during pregnancy (Pichler et al., 2008).

A large body of research has shown that the deleterious effect of prenatal exposure to tobacco smoke is also directed to neurodevelopment and later psychopathology (Abbott and Winzer-Serhan, 2012). Naeye and Peters (1984) first reported that maternal smoking is associated with a mild delay in intellectual development and behavioral abnormalities in the offspring. Subsequent reports associated prenatal tobacco smoke exposure with an increased risk for neurodevelopmental impairment (Olds et al., 1994; Jacobsen et al., 2007), and attention deficit, hyperactivity and conduct disorder symptoms (Thapar et al., 2003; Button et al., 2007; Gatzke-Kopp and Beauchaine, 2007). Also, an association between maternal smoking during pregnancy and psychotic symptoms is reported (Spauwen et al., 2004; Zammit et al., 2009). A Finnish study of children up to 18–20 years old showed that offspring of mothers who smoked carried an increased risk for all psychiatric diagnoses, except for schizophrenia and anorexia (Ekblad et al., 2010). Also, no association between prenatal exposure to tobacco smoke and development of schizophrenia was observed by Baguelin-Pinaud et al. (2010).

Cigarette smoke contains a great number of chemicals, some of which are psychoactive (Rose, 2006). Nicotine is the principal psychoactive agent in tobacco and nicotine addiction depends on the interaction of this tobacco alkaloid with nicotinic acetylcholine receptors (nAChRs). Nicotine by binding to nAChRs mimics the effect of

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acetylcholine (Ginzel et al., 2007) and, thus, it acts as a cholinergic stimulant. Nicotine in the tobacco smoke readily crosses the placenta and reaches the fetal tissues, including the brain. Animal studies showed that prenatal exposure to nicotine induces upregulation of nAChRs followed by cholinergic hypoactivity during withdrawal (Abreu-Villaça et al., 2004), apoptotic cell death in undifferentiated hippocampal cells (Berger et al., 1998), persistent structural abnormalities into adolescence in the hippocampus and somatosensory cortex (Roy et al., 2002), permanent change in synaptogenesis and synaptic function (Slotkin et al., 2007), and alteration in the trajectory of neurodevelopment (Slotkin, 2008).

Also, prenatal exposure of experimental animals to nicotine causes postnatal malfunction of the dopaminergic system (Fung and Lau, 1989; Muneoka et al., 1999). Dopamine impairment is critically implicated in the neurobiology of schizophrenia. Positron emission tomography (PET) imaging studies supply converging evidence of presynaptic increased dopamine synthesis in schizophrenia patients (McGowan et al., 2004; Kumakura et al., 2007; Nozaki et al., 2009). Conversely, PET studies investigating postsynaptic D_2 receptors have found reduced densities of these receptors, not only in the thalamus but also in other brain regions, such as the amygdala, cingulate gyrus, and temporal cortices (Talvik et al., 2003; Buchsbaum et al., 2006).

At the molecular level, in adolescent rats prenatally exposed to nicotine, the expression of the nAChR submits α3, α4, α5, and β4 was reduced in the ventral tegmental area, and the α3 mRNA increased in the nucleus accumbens (Chen et al., 2005). Long-term changes in various cell adhesion molecules that affect different neurotransmitter systems are reported in rats exposed during fetal life to nicotine indicating its long-lasting effects on the reorganization of cytoskeleton pathways (Cao et al., 2011). Direct measures in first trimester abortuses showed that the gene expression pattern of nAChR α4 and α7 subunits was altered in the pons, medulla, and cerebellum when mothers were smokers. Also, maternal smoking altered differentially in the same brain regions the muscarinic receptor m_{1-3} mRNA. These findings indicate that fetal exposure to tobacco smoke impairs the development of the cholinergic system in human brain (Falk et al., 2005). Morris et al. (2011) reviewed the literature on the effect of fetal exposure to tobacco smoke on human neurodevelopment and observed that the long-term neurobehavioral impairments caused by prenatal exposure of laboratory animals to nicotine correlate well with the data from human epidemiological studies investigating the long-term effect in offspring exposed to maternal smoking during fetal life.

Because fetal exposure to tobacco smoke has a deleterious effect on neurodevelopment and it is a risk factor for a variety of psychiatric disorders, this study aims to investigate whether prenatal exposure to cigarette smoke carries an increased risk for later schizophrenia, as well as whether it may affect the phenotypic expression of the disorder. Comparison of the positive/negative symptoms between prenatally exposed and unexposed to cigarette smoke patients was prompted by the existing phenotypic heterogeneity within the disorder and its potential association with environmental factors.

2. Methods

2.1. Study population

A total of 212 schizophrenia patients (hospitalized 155, outpatients 57; male 128, female 84) at the Psychiatry Department of the General University Hospital of Patras, from 2002 to 2008, were studied. Patients were successively enrolled provided that they were ≤30-year-old, accepted to participate, and their parents were available for interviewing. In addition, 212 normal individuals, matched for sex, age, educational level and place of residence were used as controls. Exclusion criteria for patients and controls were the presence of mental retardation and maternal illicit drug use during pregnancy, as well as schizophrenia for controls. Sociodemographic variables are listed in Table 1. The study was approved by the Ethics Committee of the University Hospital, and written informed consent was obtained.

2.2. Procedures

Patients' diagnostic assessment was made prospectively and parental smoking status during pregnancy retrospectively. Diagnoses were according to DSM-IV, Text Revision (American Psychiatric Association, 2000), by applying the structured clinical interview of DSM-IV-Patient Edition for Axis I disorders (First et al., 1995). For validation of the diagnoses, 72 randomly selected patients with schizophrenia and 39 with various psychiatric disorders were reexamined by a staff psychiatrist who was unaware of the diagnoses of the first evaluator. Also, within 5 days from the onset of the psychotic episode, the psychopathology and symptom severity were assessed with the structured clinical interview for Positive and Negative Syndrome Scale (PANSS) (Key et al., 1987), as adapted for Greek population by Lykouras et al. (1994). The age-at-onset of psychosis was determined by the first appearance of active phase symptoms.

Parents' smoking status was investigated by interviewing both of them separately. All characterized as smokers smoked throughout pregnancy. Alcohol consumption by mothers, and alcohol and illicit drug use by patients were recorded. None of the participating mothers admitted use of drugs during pregnancy. A positive family history (FH) of schizophrenia was considered when a first or second degree relative had a hospital diagnosis of schizophrenia. Also, the list of 15 symptoms assessing complications during pregnancy and labor (Lewis et al., 1989), collectively named obstetric complications (OCs), was used.

2.3. Statistical analysis

Reliability of diagnosis of schizophrenia was tested with the unweighted κ for two raters. For detection of variables that have a significant unique contribution on predicting the development of schizophrenia, logistic regression analysis (LRA) was performed. As potential predictors (yes/no) were tested: maternal and paternal smoking during pregnancy, maternal alcohol consumption during pregnancy, FH of schizophrenia, patients' alcohol and illicit drug use, and OCs. Gender, age, educational level, and place of residence were not tested because patients and controls were matched for these parameters.

Table 1
Sociodemographic characteristics of 212 schizophrenia patients and 212 population control subjects.

Characteristic	Patients	Controls
Male[a]	128	128
Age, yrs.[b]	24.0 ± 4.9	24.0 ± 4.1
Smoking mothers	25.9 ± 4.0	26.7 ± 3.9
Nonsmoking mothers	26.1 ± 4.3	26.2 ± 4.2
Maternal smoking[a]	92	46
Paternal smoking[a]	157	124
Education, yrs.[b]	11.4 ± 2.9	11.4 ± 2.8
Maternal age[c], yrs.[b]	26.0 ± 4.2	26.3 ± 4.2
Paternal age[c], yrs.[b]	31.4 ± 4.6	31.8 ± 4.5
Residence[a]		
Urban/semiurban	162	162
Rural	50	50
Family history[a,d]	116	17
Obstetric complications[a]	55	32

[a] Number of subjects.
[b] Mean ± SD.
[c] At time of patients'/controls' birth.
[d] First and second degree relative with schizophrenia.

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