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Gestational length affects neurocognition in early-onset schizophrenia

Charlotte M. Teigset [a], Christine Mohn [a], Bjørn Rishovd Rund [a,b,*]

[a] Vestre Viken Hospital Trust, Research Department, Wergelandsgate 10, 3004 Drammen, Norway
[b] Department of Psychology, University of Oslo, Postboks 1094 Blindern, 0317 Oslo, Norway

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ABSTRACT

Obstetric complications (OC) have been linked to an increased risk for schizophrenia in offspring, especially in early-onset schizophrenia (EOS). Extensive cognitive deficits occur in EOS, although no study has yet to investigate the relationship between OC and cognition in EOS. This study aims to examine the frequency of OC in EOS compared to controls, and also investigates the relationship between OC and neurocognitive dysfunction in the two groups. Nineteen EOS patients and 53 healthy controls were tested with the MATRICS Consensus Cognitive Battery (MCCB), and the cognitive measures were combined with OC data from the Norwegian Birth Registry. The results indicated no group differences in OC in EOS and healthy controls, but a shorter gestational length in the EOS group led to significant decreases in the overall neurocognitive composite score, and in processing speed. This suggests that the poorer neuropsychological performances commonly found in EOS may be partly attributable to the length of gestation. The worsened neurocognitive functioning did not appear among controls, so gestational length had a different impact on the two groups. Our findings indicated that a shorter gestational length did not increase the risk for developing EOS, but did significantly affect the cognitive difficulties in this group.

1. Introduction

According to neurodevelopmental models, schizophrenia is the behavioral outcome of deviations in early neurodevelopment, including prenatal insults such as obstetric complications (OC) (Brown, 2006; Brown et al., 2005; Cannon et al., 2002). Several studies and meta-analyses indicate an association between OC and the later development of schizophrenia, and suggest three groups of complications; complications of pregnancy, abnormal fetal growth and development, and complications of delivery (Brown et al., 2011; Byrne et al., 2007; Cannon et al., 2002; Clarke et al., 2012).

While fetal hypoxia has strong support as a risk factor for schizophrenia (Clarke et al., 2012; Rosso et al., 2000), it has also been proposed to mediate the effects of other OC (Cannon et al., 2000; Clarke et al., 2012). Research also indicate an association between schizophrenia and prenatal exposure to infection (Brown, 2006; Brown et al., 2000, 2009; Mittal et al., 2008b), to inflammation (Cannon et al., 2014; Chaves et al., 2015), to stress (Holloway et al., 2013; Khashan et al., 2008; Malaspina et al., 2008; van Os and Selten, 1998) and to diabetes (Cannon et al., 2002; Van Lieshout and Voruganti, 2008). Though the results diverge, a few studies find a relationship between risk of schizophrenia and a low birth weight, especially below 2500 g (Abel et al., 2010; Gunnell et al., 2003; Hultman et al., 1999; Lahti et al., 2015), a low and high birth weight (Gunnell et al., 2003; Moilanen et al., 2010) and a low gestational age (Byrne et al., 2007; Geddes et al., 1999; Nosarti et al., 2012). However, the direct association between OC and schizophrenia has been debated, and cohort studies have mostly failed to confirm this effect (Rosso et al., 2000). In a Scottish population study by Kendell et al. (2000), there were no significant associations between OC and schizophrenia in one birth-cohort, while a caesarean section and long-lasting labor were more common in a later birth-cohort. Similar results were found in a Finnish study with no significant primary effect of OC on the risk of schizophrenia (Clarke et al., 2011).

A meta-analysis suggests that risk of schizophrenia associated with OC might be particularly important for those with a young age at symptom onset, indicating that it involves neurodevelopmental impairment (Verdoux et al., 1997). Recent studies support these findings; Preti et al. (2012) detect an associations between OC and earlier age of onset, while Rubio-Abadal et al. (2015) claim that lower birth weight and more OC determine an earlier onset-age. Because research indicates different results due to age of onset, several studies have examined young people with psychosis. A common cut-off point in early-onset schizophrenia (EOS) has been on symptom onset before 18 years of age, which includes

* Corresponding author at: Department of Psychology, University of Oslo, Postboks 1094 Blindern, 0317 Oslo, Norway.
E-mail addresses: charlotte.teigset@psykologi.uio.no (C.M. Teigset), h.c.mohn@psykologi.uio.no (C. Mohn), b.r.rund@psykologi.uio.no (B.R. Rund).

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about 5% of the schizophrenia population (Cannon et al., 1999; Frangou, 2013; Holmen et al., 2012; Juuhl-Langseth et al., 2014). EOS patients are especially interesting for research because they are in their adolescence, a period with extensive brain maturation and alterations in cognitive structures and functions (Juuhl-Langseth et al., 2014). Consequently, they provide unique neurodevelopmental data that may contribute to a better understanding of schizophrenia at all ages (Rapoport et al., 2012; Remschmidt, 2002). Nonetheless, most studies of OC and schizophrenia include all patients, thus; a majority with onset after 18 years of age (adult-onset schizophrenia (AOS) (Juuhl-Langseth et al., 2014; Oie et al., 2011)), implying that the findings from AOS studies could potentially be influenced by the small number of participants in the sample with EOS.

So far, little is known about the role of prenatal insults on EOS (Margari et al., 2011). One study reports no relationship between OC and EOS (Margari et al., 2011). In a populations with onset before 13 years of age, Matsumoto et al. (1999) detect an association between OC and psychosis, while Ordonez et al. (2005) find no such relationship. A number of studies use obstetric material collected from maternal recall, which may be unreliable (Kotlicka-Antczak et al., 2014; McIntosh et al., 2002). We have found only two studies on OC and early psychosis that have used information from birth registries in comparison to healthy controls (Cannon et al., 2000; Rosso et al., 2000). Both centered on hypoxia-associated OC, and found that these complications increased the odds of earlier onset of psychosis but not of later onset. The studies used median splits for age of onset, hence implying that the mean age in the early psychosis group was above 18 (27.1/21.5, respectively). Even so, the findings indicate that complications during pregnancy and birth may have a specific impact on early psychosis. Consequently, studies of the relationship between OC and EOS are of particular interest.

It has been suggested that cognitive dysfunction is a central feature of schizophrenia that often exists prior to symptoms, which reflects underlying abnormalities in brain neurodevelopment (Frangou, 2013; Rund, 2009; Rund et al., 2015; Seidman et al., 2006). Patients with EOS and AOS seem to have a similar cognitive profile (Holmen et al., 2010; Oie et al., 2011), but EOS is reckoned to be more severe with worse premorbid abnormalities, as well as worse long term symptomatic and functional outcomes (Frangou, 2013; Kumra and Charles Schulz, 2008). In understanding the course of the abnormal brain development in schizophrenia, some suggest an association between OC and cognitive impairment (Ellman et al., 2012; Freedman et al., 2013; Ochoa et al., 2013; Torniainen et al., 2013). Comprehending the manner in which OC and cognition coalesce may help clarify the pathway that underlies psychotic illness, which is essential for developing primary prevention strategies (Mittal et al., 2008a).

Earlier findings indicate that OC may have a specific impact on EOS (Cannon et al., 2000; Rosso et al., 2000), as well as on neurocognition (Ellman et al., 2012; Freedman et al., 2013; Ochoa et al., 2013; Torniainen et al., 2013). Still, we find no previous study that has examined the relationship between OC and cognition in EOS. So far, most research on OC and neurodevelopment have investigated AOS and single OC measures, such as hemoglobin levels during pregnancy (Ellman et al., 2012), maternal infections (Brown et al., 2009), maternal influenza (Ellman et al., 2009) or birth weight (Freedman et al., 2013; Torniainen et al., 2013).

There are reasons to believe that different OC would likely affect different areas of cognition. In one study, Brown et al. (2009) found that prenatal infections were associated with impaired executive function in schizophrenia. While previous research has identified strong associations between executive dysfunction and structural and functional deficits in the prefrontal cortex (Goldberg et al., 1990; Rusch et al., 2007), both deficits might be affected by gestational exposure to infections. Other research suggests that schizophrenia cases that have been exposed to influenza during gestation have a higher risk of impairments in verbal tasks (Ellman et al., 2009), whereas hypoxia-associated OC were found to be unrelated to language acquisition deficits in the premorbid period (Bearden et al., 2000). Interestingly, reductions in neurocognitive performance among those exposed to OC was less extensive in the healthy control group with the same labor-conditions (Ellman et al., 2012; Ellman et al., 2009; Freedman et al., 2013), which may indicate a greater effect of OC on neuropsychological development in schizophrenia. This underscores the importance of studies in which an assessment of healthy controls is included, as well as studies that aim to identify the magnitude of specific OC on specific domains of cognition in schizophrenia.

Ochoa et al. (2013) examined a wider range of OC in relation to cognitive functioning, and found that first episode schizophrenia (FES) patients with a higher level of "neurodevelopmental contribution" (including OC) had a significantly slower processing speed than that of other FES patients. Healthy controls were not evaluated. Even though Ochoa et al. (2013) did not consider OC separately, the findings supported an association between fetal development and cognition in schizophrenia.

The present study is the first to investigate a relationship between OC and cognitive deficits in EOS. Earlier results from our research group have found significant neurocognitive deterioration in EOS patients (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012), and an interesting question is whether there may be associations between OC and cognition in the same sample.

Due to previous research that indicates an association between OC and earlier age of symptom onset in schizophrenia; our first research hypothesis is that we expect to find a higher frequency of OC among EOS patients than among healthy controls. Furthermore, findings suggest an association between OC and cognitive dysfunction in schizophrenia. There are reasons to assume that different OC may affect different areas of cognition, such as executive functions and processing speed. Our second hypothesis is therefore that OC affect the overall cognition in EOS, but have a more profound impact on executive functions and processing speed.

2. Materials and methods

2.1. Subjects

The patients were participants in the Early-onset Study (starting in 2005), a broader research project at the University of Oslo on early-onset psychotic disorders (Holmen et al., 2010; Juuhl-Langseth et al., 2014; Thormodsen et al., 2012). The patients were recruited from different inpatient and outpatient units in Oslo and the region of Eastern Norway, and were included if they were between 12 and 18 years of age and met the diagnosis criteria for a broad schizophrenia-spectrum disorder according to DSM-IV (Paranoid schizophrenia: n=2 (11%), Undifferentiated schizophrenia: n=6 (32%), Schizoaffective disorders: n=3 (16%), Residual schizophrenia: n=1 (5%) and Psychosis not otherwise specified (NOS): n=7 (7%)). The exclusion criteria were a history of central nervous system pathology or trauma (loss of consciousness for greater than 30 min and/or any neurological sequelae), or with an estimated IQ less than 70. Out of a total of 29 patients, 21 gave their written informed consent to the collection of data about obstetric complications from The Norwegian Medical Birth Registry (NMBR). Two of the participants were not born in Norway and had to be excluded, resulting in a total of 19 patients used for further analysis.