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A history of obstetric complications is associated with the risk of progression from an at risk mental state to psychosis

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ABSTRACT

Objective: Clinical criteria for diagnosing Clinical High Risk for psychosis are now available. However, an understanding of the factors modulating the risk of subsequent development of frank psychosis in "at risk" individuals remains elusive. The aim of the study was to identify associations between obstetric history and the development of psychotic disorders in individuals with an At Risk Mental State (ARMS).
Methods: Obstetric data was obtained from the medical records of 82 individuals meeting ARMS criteria. The participants were followed up for a mean period of 42.3 (±28.3) months for transition to psychosis.
Results: A history of at least one obstetric complication (OC) endorsed as definite on the Lewis and Murray Obstetric Complications Scale was found to be associated with increased risk of transition to schizophrenia (OR: 6.57, 95% CI:1.89–22.85). The number of definite OCs was found to be positively correlated with the proportion of converters ($p < 0.0001$). The probability of conversion to schizophrenia was found to increase with a decrease of Apgar-1 and Apgar-5 scores (ORs: 0.40, 95% CI:0.22–0.74 and 0.25, 95% CI:0.10–0.63, respectively).
Conclusions: The findings emphasise the potential value of including obstetric data in algorithms estimating the likelihood of transition of an ARMS to full-blown psychosis.

1. Introduction

Schizophrenia is today considered a neurodevelopmental disorder. Its development is characterized by abnormal cognitive and psychosocial functioning, which can be present for years before frank psychotic symptoms appear (Murray, 1994). The pathological process may progress through a prodromal or prepsychotic phase, nowadays known as a Clinical High Risk - CHR or At Risk Mental State - ARMS (Yung et al., 1996). This state is regarded as an important part of early psychosis management (Fusar-Poli, 2017; National Institute for Clinical Excellence, 2013; NHS England, 2014). The implementation of specific interventions targeting the prevention or postponement of psychosis development has been proposed for this stage of illness (Fusar-Poli, 2017; Joa et al., 2015; Seidman and Nordentoft, 2015; Sommer et al., 2016). However, the concept of ARMS seems to be far from perfect, especially in terms of its prediction of transition to psychosis (Fusar-Poli et al., 2012). ARMS is also non-specific in terms of its outcome (Fusar-Poli et al., 2017a; Nieman and McGorry, 2015). Hence, it seems important to define features characterizing those "at risk" individuals who progress into full blown psychotic illness. This, in turn, is essential for the individualization of therapeutic strategies (McGorry, 2016).

The limited possibility to estimate the risk of progression from an ARMS to full-blown psychosis may be a consequence of the fact that little is known of the factors outside the CHR criteria that can increase the risk of transition. Current research typically leans towards the genetic and environmental factors already suggested to be involved in the development of schizophrenia-spectrum illness. Obstetric complications (OCs) are commonly listed among the environmental biological factors which may contribute to neurodevelopmental pathology resulting in psychotic symptoms. A wide variety of pre-and perinatal trauma, including hypoxia-related complications (Cannon et al., 2002; Zornberg et al., 2000), premature birth (Mathiasen et al., 2011; Nielsen et al., 2013; Nosarti et al., 2012; Takayanagi et al., 2014), low birth weight (Abel et al., 2010; Indredavik et al., 2010; Kunugi et al., 2001; Moilanen et al., 2010; Rifkin et al., 1994), prenatal infections (Brown and Susser, 2002; Nielsen et al., 2016) and maternal malnutrition (Roseboom et al., 2011; Susser et al., 1996) are considered as potentially increasing the risk of developing schizophrenia;

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however, "causality remains elusive from these correlations" (Clarke et al., 2006).

It seems important to be aware that the vague term "OCs" is neither qualitatively accurate nor time specific, encompassing as it does, the wide range of adverse events which occur in various phases of brain development. This may be a key reason why no unequivocal explanation has been found for the mechanism of action by which OCs act as a risk factor for future psychosis. However, the role of hypoxic events resulting in the reduction of overall gray matter and hippocampal volume is emphasized (Cannon et al., 2002; Haukvik et al., 2010; Nicodemus et al., 2008). The early brain insult may contribute to increased vulnerability to other factors which interfere the processes of brain development (Lewis et al., 1989). Hence, it is essential to regard OCs as only one of a range of interacting factors known to be associated with the future development of a psychotic disorder, (like genetic loading, childhood trauma or cannabis abuse), and to see an ARMS as only one of the stages of this complex process (Shah et al., 2013).

OCs appear also to be non-specific in terms of their potential consequences. They operate as a risk factor for many neurodevelopmental disorders, including psychiatric ones (de Haan et al., 2006; Gardener et al., 2011; Mwaniki et al., 2012; Wang et al., 2017).

An early measure of the potential consequences of pre- and perinatal insult is the Apgar score. Apgar score is an index used worldwide to evaluate the overall status of the neonate in the first, fifth and tenth minutes of life (Apgar-1, −5, and −10, respectively) (Apgar, 1953). It has been demonstrated to still have value in contemporary practice more than 60 years since its introduction (Iliodromiti et al., 2014). The Apgar score can be depressed by a variety of unfavourable pre- and perinatal events, including hypoxia, prematurity, head injury, infection and many other factors (Committee on Obstetric Practice American Academy of Pediatrics, 2015). Although nonspecific in terms of causes and possible outcomes (Ehrenstein et al., 2009; Gardener et al., 2011; Odd et al., 2008), Apgar score reflects the severity and/or accumulation of OCs.

Despite the limitations given above, obstetric adversity has been established to play a role in the diathesis-stress model of schizophrenia (Pruessner et al., 2017; Walker and Diforio, 1997). In contrast to studies in full-blown psychosis, the number of studies on prenatal insults in CHR individuals remains limited. Those of a case-control nature report higher rates of OCs in ARMS individuals compared to healthy controls (Ballon et al., 2008; Kotlicka-Antczak et al., 2014). In their meta-analysis, Fusar-Poli et al. (2017b) indicate OCs as a factor accounting for an enhanced vulnerability to psychosis in an "at risk" state. A literature review, however, highlights only two studies of a follow-up character which examine the role of OCs in the conversion of an "at risk" state to psychosis (Mittal et al., 2009; Yun et al., 2005): both had methodological limitations and their results were conflicting. No follow-up studies regarding the history of OCs in ARMS cohorts, based on medical records, have been performed.

The aim of the study was to identify associations between the history of OCs and the probability of developing full-blown psychosis in individuals with an ARMS.

2. Methods

2.1. Subjects and settings

Eighty-two individuals diagnosed as presenting ARMS were included in the study. They were participants of the Programme of Recognition and Treatment (PORT) affiliated with the Medical University of Łódź. The programme is aimed at young individuals at risk of developing psychosis. Participants in the programme are referred both from primary and secondary mental health services (in- and out-patient psychiatric clinics); self-referral by telephone or through the PORT website is also possible. The inclusion criteria for the programme were as follows: 1) age 14–29 years and 2) meeting ARMS criteria (Yung et al., 2004). The exclusion criteria included 1) the presence of a known organic disease of the central nervous system and other severe general medical conditions, 2) evidence of mental retardation and 3) a diagnosis of psychotic disorder according to ICD-10 criteria. More detailed information regarding the programme has been given previously (Kotlicka-Antczak et al., 2015).

Additional inclusion criteria for the present study included the availability of medical documents reporting the course of pregnancy and delivery, and a minimum 24-month follow-up period, unless the transition to psychosis occurred. The latter criterion was formulated on the basis of a literature search which shows that most transitions occur within 24 months from the diagnosis of an "at risk" state (Fusar-Poli et al., 2012, 2013). All the subjects included in the study were PORT participants meeting the above mentioned criteria, who were consecutively referred to the PORT centre between October 2010 and February 2015.

The study was carried out in accordance with the latest version of the Declaration of Helsinki. The study protocol was accepted by the Medical University of Łódź Ethics Committee. Written informed consent was obtained from all participants. If the subject was a minor, further consent was also obtained from a parent.

2.2. Procedures

2.2.1. Demographic and clinical data assessment

Demographic data was obtained with the use of a semi-structured interview.

ARMS was diagnosed with the use of a Comprehensive Assessment of At-Risk Mental States-CAARMS (Yung et al., 2005), Polish version (Jaracz et al., 2012). The condition is found if an individual 1) presents positive symptoms which do not reach the level of psychosis either in their frequency or intensity, this is known as an attenuated psychotic symptoms (APS) subgroup, or 2) during the past year had a psychotic episode which resolved spontaneously within one week, the brief limited intermittent psychotic symptoms (BLIPS) subgroup, or 3) meets the criteria of schizotypal personality disorder or has a family history of psychosis in first degree relative, the vulnerability (VUL) subgroup. A substantial deterioration in psychosocial functioning is additionally required in all cases (Yung et al., 2005). The CAARMS composite score as a sum of the scores achieved in four positive domains in each case weighted by their frequency score was also calculated (Lim et al., 2015).

Each participant entering the PORT programme was subjected to a complex diagnosis incorporating an examination of physical state, including neurological assessment. This served to establish potential exclusion criteria.

2.2.2. Obstetric history assessment

Data regarding the history of OCs were obtained at the entry to the study. They were derived from medical records included in Child Health Books (CHBs). These are official documents which the hospital is obliged to present to the parents on discharge after delivery. CHBs include essential information regarding the course of pregnancy and delivery as well as data on the status of the child during the stay in hospital.

OCs found in the CHBs were classified as "definite" or "equivocal" according to the Lewis and Murray Obstetric Complications Scale (Lewis et al., 1989). The scale was derived as a consensus of six previous scales used in psychiatric or obstetric research designed for rating OCs. The OCs included in at least four of the source scales were classified as "definite", while the OCs included in three or fewer of the scales, as well as those about which the information was incomplete or not otherwise specified, were described as "equivocal".

Birth weight and maternal age at delivery, as well as Apgar-1 and Apgar-5 scores obtained from CHBs were also assessed. The Apgar score analysis was enriched as complementary objective obstetric data and a first measure of the impact of potential OCs on newborn status.

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