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Epidemiology and risk factors of schizophrenia

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Abstract

Schizophrenia is a severe mental disorder that affects approximately one percent of the general population. The pathogenesis of schizophrenia is influenced by many risk factors, both environmental and genetic. The environmental factors include the date of birth, place of birth and seasonal effects, infectious diseases, complications during pregnancy and delivery, substance abuse and stress. At the present time, in addition to environmental factors, genetic factors are assumed to play a role in the development of the schizophrenia. The heritability of schizophrenia is up to 80%. If one parent suffers from the condition, the probability that it will be passed down to the offspring is 13%. If it is present in both parents, the risk is more than 20%. The opinions are varied as to the risk factors affecting the development of schizophrenia. Knowing these factors may greatly contribute to prevention of the condition.

Abbreviations:

ADHD	- attention-deficit/hyperactivity disorder
ADRA2A	- adrenergic receptor-2a
BDNF	- brain-derived neurotrophic factor
CMV	- cytomegalovirus
COMT	- catechol-O-methyltransferase
CTNNA3	- catenin, alpha 3
CTNX3	- cortexin 3
DISC1	- disrupted in schizophrenia 1
DISC2	- disrupted in schizophrenia 2
DRD3	- dopamine receptor 3
DSM-IV	- Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DTNBP1	- dystrobrevin-binding protein 1
ELSPAC	- The European Longitudinal Study of Pregnancy and Childhood
GABA	- γ-aminobutyric acid
GWAS	- genome-wide association studies
LSD	- lysergic acid diethylamide
MTHFR	- methylenetetrahydrofolate reductase
NRG1	- neuregulin 1
OPRM1	- opioid receptor, mu-1
SMR	- standardized mortality ratios
SNAP-25	- synaptosomal associated protein of 25 kDa
SNP	- single nucleotide polymorphism

REVIEW ARTICLE

INTRODUCTION

Descriptions of schizophrenia were found in ancient texts. Therefore, scientists assume that the condition dates back to several thousand years before Christ. However, schizophrenia was more carefully described in the last two centuries. That is why some experts suggest that schizophrenia is a disease that has affected the population in only the last two centuries and that some factors of that era such as industrialization, population density increase and urbanization may have contributed to its development (Tandom *et al.* 2008).

The term *schizophrenia* was coined in the early 1900s by Paul Eugen Bleuler, a Swiss psychiatrist, who used the Greek words *skhizein* (to split) and *phrēn* (mind). The disease itself is very old as seen from the fact that its characteristic features were mentioned as early as in the Hebrew Bible and referred to as měshuggā.

Schizophrenia is a severe mental disorder characterized by profound disruption in cognition and perception, inadequate emotionality and impaired ability to behave properly. In the worldwide population, approximately 1% of patients suffer from this severe condition. Schizophrenia is still among as yet incurable diseases and its causes remain unknown. At the beginning of the 20st century, genetic factors have been thought to play a role. Recently, schizophrenia is understood as a neurodevelopmental disorder with a difficult and lengthy diagnosis. An individual may suffer from the condition for as long as several years before it is apparent and the characteristic symptoms are clearly manifested.

People between 15 and 30 years of age are at highest risk for developing the disease. The course of schizophrenia varies among patients. It manifests itself as acute episodes. After several episodes, the condition may resolve and approximately one-third of patients return to normal life. The remaining two-thirds either continue to have recurrent episodes that alternate with periods of minimal symptoms or have frequent symptoms that worsen and, as a result, the sufferers are unable to take care of themselves. Patients with schizophrenia often cannot work and live independent and full lives. It has been reported that patients with schizophrenia may have lives shorter by as much as 20% when compared with the mean life expectancy in the healthy population. Patients are at a higher risk for suicides, study of Palmer *et al.* (2005) estimates that 4.9% of schizophrenic patients will commit suicide during their lifetimes, usually near illness onset. The causes are loss of social life and inability to cope with normal life events. In patients with schizophrenia, the family plays an important role in their return to normal life. Such patients need much support and constant encouragement during everyday activities. In recent decades, despite major changes in the treatment options, the proportion of recovered cases has not increased. Based on the available data, 1 in 7 individuals with schizophrenia may recover (Jääskeläinen *et al.* 2013). Given the severity, consequences and unknown etiology, much attention must be paid to the study of all potential risk factors, contributing to prevention of the condition.

EPIDEMIOLOGY OF SCHIZOPHRENIA

Some studies on schizophrenia state that the disease is generally unequally distributed in the society. It tends to be more prevalent in lower socio-economic groups. Recent meta-analyses have confirmed the assumption that males have a higher lifetime risk of developing schizophrenia than women. This relative risk is 1.4 times higher in males (Aleman *et al.* 2003).

McGrath *et al.* (2008) evaluated three systematic reviews on the incidence, prevalence and mortality of the schizophrenia. They stated that contrary to previous interpretations, the incidence of the schizophrenia showed prominent variation between sites. The median incidence of schizophrenia was 15.2/100,000 persons, and the central 80% of estimates varied over a fivefold range (7.7–43.0/100,000). The rate ratio for males : females was 1.4 : 1. Prevalence estimates also showed prominent variation. The median lifetime morbid risk for schizophrenia was 7.2/1,000 persons. On the basis of the standardized mortality ratio, people with schizophrenia had a two- to threefold increased risk of dying (median standardized mortality ratio = 2.6 for all-cause mortality), and this differential gap in mortality had increased over previous decades. Compared with native-born individuals, migrants had an increased incidence and prevalence of the schizophrenia. Exposures related to urbanicity, economic status, and latitude were also associated with various frequency measures. McGrath *et al.* (2008) concluded that the epidemiology of schizophrenia is characterized by prominent variability and gradients that could help guide future research.

Prevalence

Lifetime prevalence

Generally, the prevalence of schizophrenia ranges from 0.14 to 0.46%. Recently, Szkultecka-Dębek *et al.* (2015) conducted a literature search from Central and Eastern Europe and she found the lifetime prevalence of schizophrenia variation from 0.4% to 1.4%. In Finland, lifetime prevalence was estimated according to the DSM-IV criteria at 0.87% for schizophrenia and 0.32% for schizoaffective disorder (Perälä *et al.* 2007). These data should be considered approximate as due to age-specific mortality or migration, they cannot fully reflect demographic variations between different populations.

Prevalence in the Czech Republic

The prevalence of schizophrenia calculated from the number of treated patients in 2013 was highest in the capital city of Prague (0.608%) and lowest in the Central Bohemian Region (0.307%). The mean prevalence in the Czech Republic was 0.462% in the year 2013. Thus, the Czech Republic ranks among the countries with high

prevalence rates. On the other hand, given the fact that on average, one percent of the population worldwide suffer from schizophrenia, equal to 100,000 individuals in the Czech population, the actual number is approximately half that (about 50,000 patients) (ÚZIS ČR 2014).

Incidence

A systematic review showed that the incidence of schizophrenia ranged from 7.7 to 43.0 per 100,000, or from 0.077 to 0.43 per 1,000 population (Saha *et al.* 2007). The exact onset of the disorder is rather difficult to determine. In studies, the onset is usually defined as the first visit to a psychiatrist for symptoms of schizophrenia. In the Czech Republic, a total of 48,603 persons received medical care for schizophrenia in 2013 (ÚZIS ČR 2014). Those included 22,382 males and 26,221 females; there were 5,184 newly diagnosed cases. The highest and lowest incidence rates were in the capital city of Prague (0.79/1,000) and South Bohemian Region (0.24/1,000), respectively.

Mortality

Saha *et al.* (2007) examined the distribution of standardized mortality ratios (SMRs) and pooled selected estimates using a random-effects meta-analysis and identified 37 articles drawn from 25 different nations. The median SMR for all persons for all-cause mortality was 2.58 (10%–90% quantile, 1.18–5.76), with a corresponding random-effects pooled SMR of 2.50 (95% confidence interval, 2.18–2.43). No sex difference was detected. Suicide was associated with the highest SMR (12.86); however, most of the major causes-of-death categories were found to be elevated in people with schizophrenia. The SMRs for all-cause mortality had increased during the previous decades (p=0.03). The authors stated that with respect to mortality, a substantial gap existed between the health of people with schizophrenia and the general community. This differential mortality gap had worsened in the previous decades. They (Saha *et al.* 2007) concluded that in light of the potential for second-generation antipsychotic medications to further adversely influence mortality rates in the decades to come, optimizing the general health of people with schizophrenia warranted urgent attention.

ETIOPATHOGENESIS

In patients with the schizophrenia, magnetic resonance imaging has shown a reduction in volume of some brain structures (amygdala and/or hippocampus), enlargement of brain ventricles as well as a loss of white matter (Butterworth 1998). Individuals who develop schizophrenia have a specific biological susceptibility to the condition which is either congenital or acquired in the early phases of life (Šerý *et al.* 2010). Schizophrenia is assumed to be associated with abnormalities of information processing (White & Siegel 2015). Neurotransmitter systems and intracellular signal transduction are impaired. Given the brain's complexity and function, several neurotransmitter systems are likely to be affected. The most studied neurotransmitter in the relationship with the schizophrenia is dopamine (Andreou *et al.* 2014), with regard to both etiopathogenesis and therapeutic options. Another important neurotransmitter is glutamate (Nanitsos *et al.* 2005; Šerý *et al.* 2015a). The risk gene variants are involved in glutamatergic system and in the development of neuronal network connectivity.

RISK FACTORS

Although the causes of schizophrenia remain unclear, genetic and epidemiological studies have revealed numerous genetic and environmental risk factors (Modinos *et al.* 2013).

Environmental risk factors

Many epidemiological studies have been concerned with the impact of the environment on the development of schizophrenia.

Several risk factors for schizophrenia have already been identified. Certain childhood and adolescent risk factors predict the age of onset of psychosis in patients with and without a familial component (i.e. a relative with schizophrenia or schizoaffective disorder).

Scherr *et al.* (2012) examined the risk factors for schizophrenia including obstetric complications, birth during winter or spring, behavioral deviances or delayed motor and speech development, exposure to adverse life events and exposure to substance use within a group of 100 patients (45 females, 55 males). They found that birth complications and cannabis abuse were predictors for an earlier onset of schizophrenia in patients with non-familial schizophrenia. No environmental risk factors for an earlier age of onset in familial schizophrenia were identified.

Evidence of variations in schizophrenia incidence rates has been found in genetically homogenous populations, depending on changes within time or space of certain environmental characteristics. The consideration of the impact of environmental risk factors in etiopathogenetic studies has put the environment in the forefront of research regarding psychotic illnesses. Various environmental factors such as urbanicity, migration, cannabis use, childhood traumas, infectious agents, obstetrical complications and psychosocial factors have been associated with the risk of developing schizophrenia. These risk factors can be biological, physical, psychological as well as social and may operate at different times in an individual's life (fetal period, childhood, adolescence and early adulthood). Whilst some of these factors act on an individual level, others act on a populational level, modulating the individual risk (Matheson *et al.* 2012). These factors can have a direct action on the development of the schizophrenia, or on the

other hand act as markers for directly implicated factors that have not yet been identified (Vilain *et al.* 2013).

Date of birth, place of birth and seasonal effects

Schizophrenia often affects persons born at the end of winter and beginning of spring (Martínez-Ortega *et al.* 2011; Schwartz 2011). Winter is the high season for influenza and other acute respiratory tract infections (a flu epidemic). Viral infections in pregnancy may cause changes in the brain potentially leading to schizophrenia. Data on more patients with schizophrenia being born during winter months are relatively convincing but the reasons for that have not been elucidated. The most likely explanation is combination of the following factors – light intensity, toxins, nutrition, temperature, weather and infectious agents.

Of particular importance is sunshine providing the human body with nearly 90% of the needed vitamin D. In pregnant women, a lack of the vitamin may result in fetal growth factor insufficiency, having a negative impact on the brain development. Both low and high concentrations of neonatal vitamin D are associated with increased risk of schizophrenia (McGrath *et al.* 2010).

People born in urban areas are at approximately double the risk of developing schizophrenia. The higher the density of population, the higher the risk for schizophrenia (Szöke *et al.* 2014). It is assumed that the urban lifestyle such as stress, excess noise, pollution, crime, illegal drug availability, family breakdown and other negative factors may contribute to the development of schizophrenia.

Pregnancy and birth complications

The search for an association between schizophrenia and birth complications has yielded results supporting developmental and non-genetic models of the disease (Dorrington *et al.* 2014). The most frequently reported complication that may be a risk factor is fetal hypoxia (Boydell 2001). Birth complications potentially contributing to an increased risk for developing schizophrenia are preeclampsia, malformations and vacuum extraction. Some form of perinatal damage is most prominent in children of mothers with schizophrenia (Vigod *et al.* 2014). These children constitute a more vulnerable group at a high risk. They have a slightly lower birth weight that is associated with developmental abnormalities during the first year of life. These findings confirm the effect of stress in pregnancy as a triggering factor in genetically predisposed individuals.

Brain development may be impaired by intra-uterine bleeding. However, more frequent are birth complications leading to brain ischemia or damage to the skull. Nerve tissue compression in newborns may result from a narrow birth canal or intense contractions during labor.

Pregnancy and birth complications appear to be a significant risk factor for the development of schizophrenia (Cannon *et al.* 2002). Awareness of the risks may be used in prevention in the form of careful monitoring and early therapeutic interventions in these individuals (Clarke *et al.* 2006a).

Infection

The evidence for an infectious etiology of the condition is indirect and often little specific. However, it cannot be overlooked. Acute and subacute changes are due to bacterial, protozoan and viral infections (Flegr *et al.* 2014; Konat 2015; Müller *et al.* 2015).

Influenza virus infection during pregnancy is a known risk factor for neurodevelopmental abnormalities in the offspring, including the risk of schizophrenia (Landreau *et al.* 2012). The peak of this effect occurs during the 6th month of intrauterine development in humans (Takei *et al.* 1995). It has been shown to correlate with serologically proven infection in the mother (Mednick *et al.* 1990). Exposure to influenza A virus during development results in a transient increase in kynurenic acid concentration that could disrupt normal brain development and lead to cognitive deficits later in life. It may support the understanding of how viral-induced changes in tryptophan metabolism during development may contribute to schizophrenia-related symptoms later in life (Laccarino *et al.* 2013).

An infection known to be associated with congenital malformations of the central nervous system is measles. Early prenatal exposure to measles may pose a risk for the development of psychosis and schizophrenia in adulthood (Yolken 2004). Avramopoulos *et al.* (2015) found that inflammatory processes and infection may modify the risk for psychosis and he suggests that the genotype at schizophrenia-associated human leukocyte antigen loci modifies the effect of these variables on the risk to develop schizophrenia.

Substance and drug abuse

Drug abuse is one of the most frequent complications of psychotic conditions. These drugs include lysergic acid diethylamide (LSD), phencyclidine, methamphetamine, cocaine, opiates, alcohol, tobacco and cannabis. Drug abuse may cause psychosis in individuals with a history of psychosis or those susceptible to it. Sometimes, it is difficult to distinguish the onset of drug abuse from the onset of prodromal symptoms. However, the characteristic symptoms of schizophrenia may be often preceded by substance dependence.

The most frequently abused substances are cannabis, alcohol and tobacco (McLoughlin *et al.* 2014). Although some studies suggest that the use of cannabis in adolescence is associated with an increased risk for the development of schizophrenia, others refute the association. Some authors claim that the use of cannabis may only trigger schizophrenia in vulnerable individuals (Boydell 2001; Semple *et al.* 2005; Hickman *et al.* 2007; Tandom *et al.* 2008).

Many schizophrenia patients become dependent on tobacco (Le Foll *et al.* 2015). Chemicals in tobacco smoke are capable of suppressing numerous symp-

toms accompanying schizophrenia. Nicotine, for instance, improves attention, information processing and memory typically impaired by the condition. As it has been shown to lower the blood levels of certain antipsychotics, the doses in these patients have to be monitored and increased if needed.

Alcohol, another addictive substance, has been reported to be abused by 50% of patients with schizophrenia (Thoma & Daum 2013). If these patients do not abstain from both drugs and alcohol, they are at risk of relapse.

Stress

Stress is an individual response of the organism to excessive physical, emotional or intellectual demands. The body is set to deal with short-term stress but prolonged stress may considerably harm mental health.

These risk factors include childhood trauma, head injury, family breakdown or death in a family, negative family atmosphere, bad parenting as well as infections (Morgan & Fisher 2007). According to Clarke *et al.* (2006b), as many as 59% of males and 69% of females hospitalized for schizophrenia have been physically or emotionally maltreated. The rates are even higher in some other studies.

The mental development of the fetus is mainly at risk during the first weeks of gestation (influence of prenatal stress). It has been reported that individuals born to mothers who experienced a considerably stressful event in the first trimester of their pregnancy may be more likely to develop schizophrenia than their counterparts born to mothers who had uneventful pregnancies.

Studies of children whose biological mothers were ill showed a higher prevalence of mental disorders in these children as compared with those born to mothers without a history of psychiatric illness. Children raised in well-functioning families had no problems, unlike those living in families classified as poorly functioning.

Individuals whose childhood was accompanied by numerous negative experiences and frequent stress could be much more prone to injuries and chronic health problems in the future (Dvir *et al.* 2013). These are also findings from the large international European Longitudinal Study of Pregnancy and Childhood (ELSPAC) with participation from the Research Center of Preventive and Social Pediatrics, Faculty of Medicine, Masaryk University in Brno in the last two decades (for more information see web page http://www.elspac.cz/). In the Czech Republic, more than 5,000 couples and their children have been followed in the towns of Brno and Znojmo. It has been reported that as many as 46% of patients experienced a stressful event in the three months preceding their first attack of schizophrenia. For patients with schizophrenia, even a minor stressful event may be the cause leasing to their hospitalization.

Stress is thought to aggravate the course of schizophrenia by increasing production of cortisol which subsequently damages the hippocampus. Research has shown that patients affected by schizophrenia have reduced hippocampal volume as compared with individuals without the condition. Those with hippocampal damage suffer from memory impairment and inability to store new information. Schizophrenia is not the only disorder aggravated by stress but the so-called stress cascade plays an important role in its course.

Other potential risk factors are the effects of an inadequate diet in pregnancy. Most studies claim that schizophrenia is associated with lower levels of unsaturated fatty acids in brain tissue found post-mortem (Arroll *et al.* 2014). The effect of breastfeeding has also been studied. Breast milk is important for the developing brain (Sørensen *et al.* 2005). Unlike formula or cow's milk, breast milk contains large amounts of long-chain unsaturated fatty acids such as docosahexaenoic acid, an important component of the neuronal membrane.

Advancing paternal age is an independent risk factor for schizophrenia (Zammit *et al.* 2003). Increased numbers of patients with schizophrenia have been observed in the lower social groups.

Genetic influences

Ever since schizophrenia was first identified, it has been apparent that there is an increased prevalence in some families. While some claimed that only genetic factors play a role, others acknowledged the negative impact of the environment only. At present, genetic as well as environmental factors are thought to predispose to the development of the schizophrenia. It has been reported that heritability of schizophrenia could be up to 80% (Hosak 2013). If one parent suffers from the condition, the likelihood that it will be passed down to the offspring is 13%. If it is present in both parents, the chance is more than 20%. If schizophrenia develops in one monozygotic twin, there is more than a 50% chance that the other will also be affected.

Prior to the genome-wide association era, candidate gene studies were a major approach in schizophrenia genetics (Hosak 2013). A study of more than 70 candidate genes for schizophrenia (e.g. DISC1, DISC2, COMT, DTNBP1 and NRG1) showed that candidate gene literature had not yielded clear insights into the genetic basis of schizophrenia. A likely reason why candidate gene studies had not achieved their primary aims was inadequate statistical power (Farrell *et al.* 2015).

GWAS studies compare genotype and allele frequencies of thousands to millions polymorphisms (SNPs) in groups of thousands of human subjects and, in principle, they should be able to identify relevant genes by comparing patients and controls (Šerý *et al.* 2014). The initial promise of GWAS has not been, however, always fulfilled and the problem grew in complexity. It seems that GWAS based on mere correlation of thousands DNA polymorphisms with corresponding pathology data sets obtained from patients and control subjects but lacking a specific prior concept may not bring rapid progress as originally expected. Furthermore, as new results from

whole genome genotyping of thousands of schizophrenia patients have been pouring in, the roles of non-coding RNA and the contribution of epigenetic factors in pathogenesis of schizophrenia have been neglected.

Schizophrenia has a complex etiology that is far from understood. Data are being collected enabling the study of interactions between genes and the environment. A confluence of data from genetic and environmental exposure studies points to the role of infections and immunity in the pathophysiology of the schizophrenia. Single nucleotide polymorphism (SNP) in the gene CTNNA3 was identified that may provide clues to gene-environment interactions. Grove *et al.* (2014) reported that carriers of the minor allele for the SNP had a 5-fold risk of later developing schizophrenia if their mothers were CMV positive, while the children not carrying the allele had no excess risk from maternal CMV.

Schizophrenia is believed to arise from complex gene-environment interactions. Brain-derived neurotrophic factor (BDNF) is involved in neuronal development, differentiation and plasticity (Drtílková *et al.* 2008; Šerý *et al.* 2011). A functional single nucleotide polymorphism that results in a valine (Val) to methionine (Met) substitution at codon 66 (Val66Met) results in the aberrant sorting and release of mature BDNF through the activity-dependent secretion pathway. The Val66Met polymorphism has been linked to impaired neurocognitive function in healthy adults, and identified as a locus of risk for a range of neuropsychiatric disorders including schizophrenia, ADHD and alcoholism (Drtílková *et al.* 2008; Šerý *et al.* 2011; Kheirollahi *et al.* 2015). A comprehensive review by Notaras *et al.* (2015) showed that the Val66Met polymorphism modulates a range of clinical features of schizophrenia, including age of onset, symptoms, therapeutic responsiveness, neurocognitive function and brain morphology.

Several case-control association studies between schizophrenia and SNP's have been performed in the Czech Republic. The relationships between schizophrenia and CTNX3, OPRM1, DRD3, SNAP-25, MTHFR and ADRA2A genes in samples of typical European population were described (Šerý *et al.* 2010; Lochman *et al.* 2013a; 2013b; Šerý *et al.* 2015b). In one from last schizophrenia association studies a strong association between schizophrenia and a single nucleotide polymorphism in the *CTXN3* gene (cortexin 3) was reported (Šerý *et al.* 2015a). Available evidence suggests that cortexin 3 is involved in brain ontogeny, particularly in the development of GABAergic neurotransmission and metabolism of amyloid precursor protein which could, in turn, impact on neuronal maturation, migration and synaptogenesis.

CONCLUSION

Schizophrenia is a disorder of many mental functions. While some patients may be relatively cured and may never develop schizophrenia symptoms, others may require lifelong hospitalization in a psychiatric care facility (Hosakova & Jarosova 2015). The schizophrenia is a serious mental condition associated with impaired reasoning and a distorted perception of reality; sometimes, the coordination of movement may be impaired as well, mainly in its catatonic form. Schizophrenia most frequently affects individuals in late adolescence and early adulthood. Subsequently, the disease influences the major part of their lives as well as the lives of those around them.

Although the exact cause is mostly unknown, genetic and environmental factors are thought to play a considerable role. At the present time, no tests or methods are available that could detect schizophrenia in the examined person. The entire diagnostic process depends upon analyzing information provided by the patient and observation of the patient. The differential diagnosis may be based on imaging methods.

Given the current knowledge and potential risks, adequate care for both physical and mental health is necessary; special attention should be paid to pregnant women to help them provide their children with optimal development. Although the schizophrenia may develop in any individual, future research is likely to show that the development of this condition may be slightly modified by an adequate approach to one's health, particularly in those with a family history of schizophrenia. Considerable attention should be paid to the study of potential risk factors. Confirming the risks may help direct the efforts to prevent the disease.

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