Predictors of schizophrenia—a review

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Schizophrenia is an aetiologically heterogeneous syndrome that usually becomes overtly manifest in adolescence and early adulthood, but in many cases subtle impairments in neurointegrative function are present from birth; hence it is considered to be a disorder with a neurodevelopmental component. The strongest risk factor that has been identified is familial risk with genetic loading. Other risk factors include pregnancy and delivery complications, infections during pregnancy, disturbances of early neuromotor and cognitive development and heavy cannabis use in adolescence. Unfortunately, to date it has not been possible to utilize the predictors of the disorder that have been identified in primary preventative interventions in a general population. However, some authors have claimed that in future it might be possible to reduce the risk for developing schizophrenia through general health policy. In clinical settings, it is helpful to map out possible early risk factors, at least familial risk for psychosis, especially in child, adolescent and young adult mental patients. Furthermore, in the future we may have predictive models combining data from genetic factors for schizophrenia, antenatal risk factors, childhood and adolescent development and clinical symptomatology, as well as brain structural and functional abnormalities.

Introduction

Schizophrenia may be the most severe of the mental illnesses.[1] Symptoms of schizophrenia are traditionally divided into positive symptoms such as auditory hallucinations and delusions, and negative symptoms such as social withdrawal, flattened affect, poor motivation and depressed mood.[2] The estimated lifetime prevalence is about 1%, varying from 0.5% to 1.5% in different parts of the world,[3] with exceptional higher rates in some population isolates.[4] Less than half (20–40%) of patients diagnosed with schizophrenia or schizophrenia spectrum disorders have been found to show substantial clinical improvement after follow-up

averaging 5–6 years.[5,6] The outcome of schizophrenia in developing countries has been claimed to be generally more favourable.[7]

The risk for schizophrenia has been found to be somewhat higher in men than in women, with the incidence risk ratio being 1.3–1.4.[8] Schizophrenia tends to develop later in women, but there do not appear to be any differences between men and women in the earliest symptoms and signs during the prodromal phase.[9] In developing countries, no significant sex differences have been found in incidence.[10]

Schizophrenia is an aetiologically heterogeneous syndrome that usually becomes manifest in adolescence and early adulthood with the onset of psychotic symptoms.[9] Nowadays schizophrenia is considered to be a neurodevelopmental disorder[11] with its pathogenesis stretching back to gestation and early childhood;[12] there may also be a neurodegenerative element[13]. There is a familial component which is likely to be mainly genetic[3,14,15]. Various candidate genes which may contribute to the development of schizophrenia have recently been identified.[16,17] However, environmental factors have also been found to play a role in the aetiology of the disease.[18] It has been proposed that a small proportion of the variance in liability to schizophrenia might be explained by unique environmental factors, both biological and psychosocial.[15] So far, causes of the disease remain incompletely understood. Nevertheless, some risk factors, mainly biological components, have been identified.

In this review we aim to describe possible risk factors involved in the development of schizophrenia. We have done this by means of a selective review of literature, focusing on events during pregnancy, childhood and adolescence.[19,20] The premorbid predictors are divided into genetic, biological and psychosocial risk factors at different stages of early life.

Genetic factors

Twin, adoption and family studies provide consistent evidence that genetic factors are important in the familial aggregation of schizophrenia.[21] Schizophrenia has a high heritability, with a 10-fold increase in risk to siblings of probands. Nevertheless, 85% of individuals with schizophrenia have no first-degree relative with the illness.[22] Recent evidence has suggested a role for several candidate genes in the aetiology of schizophrenia; these include the genes for proteins such as Neuregulin 1 (at the chromosomal location 8p), Dysbindin (at 6p), catechol-O-methyltransferase (at 22q), the 5-HT2A receptor (at 13q) and G72 protein (D-amino-acid oxidase) (at 13q).[16,23] These candidate genes appear to be involved in neurodevelopment, i.e. brain structure and in neurotransmitter systems, such as the serotonergic, glutamatergic and dopaminergic systems.[4,23] A genome-scan meta-analysis

of linkage studies has identified regions that may increase susceptibility to schizophrenia in diverse populations in many chromosomes, especially 2q, but also 5q, 3p, 11q, 6p, 1q, 22q, 8p, 20q, 14p, 16q, 18q, 10p, 15q, 6q and 17q.[17] At present there are no tests which can detect susceptibility genes for schizophrenia in clinical use. Indeed, it has even been questioned whether the genetic contribution is detectable by linkage strategies as it may be epigenetic, i.e. related to gene expression rather than to sequence variation.[24] Familial predisposition to schizophrenia is not only to the schizophrenia syndrome itself but also to 'schizophrenia-like' personality disorders and probably some non-schizophrenic non-affective psychoses.[25]

The pattern of inheritance is complex. It is plausible that many genes and many environmental factors interact. However, heredity is probability, not fate.[4] Concordance rates between monozygotic twins are reported to be approximately 30–65% compared with 5–15% in dizygotic twins.[4,26,27] Therefore if one twin has schizophrenia, the relative risk for the other twin may increase to 50 in monozygotic twins and to ~5–15 in dizygotic twins.[4,26,27] The clinical pictures encountered in non-schizophrenic monozygotic co-twins are variable, ranging from a duplication of the schizophrenic psychosis to schizotypal and paranoid personality disorder to neurotic symptoms and even clinical normality.[27]

The genotype–environment interaction can be defined as a genetic control of sensitivity to environmental factors, or environmental control of gene expression.[28] The results from a Finnish adoption study support a role for genotype–environment interaction in the development of schizophrenia.[18,29] Thus some genotypes are more likely to develop disease in the event of exposure to certain environmental factors. In the case of genotype-environment interaction, diseases will tend to cluster in families not because of direct genetic effects, but because relatives are more vulnerable to the risk-increasing effect of prevalent environmental risk factors.[30] Wahlberg *et al*.[31] found that adoptees at risk for schizophrenia had more mental health disorders than adoptees without such a risk if their adoptive parents had elevated communication deviance, i.e. language production that is ambiguous and hard to understand.

Risk factors for schizophrenia during pregnancy and delivery

Many pre- and perinatal risk factors for schizophrenia have been identified, although these tend to have a modest effect, with typical odds ratios or relative risks of ~2. These factors include antenatal exposure to influenza, especially during second trimester, and other respiratory infections, rubella during pregnancy, hypoxia-related obstetric complications, low

birth weight and prenatal growth retardation (in males only). So far, the evidence is less secure for antenatal stress and malnutrition in pregnancy.[32]

Prenatal infections

Various studies have shown a 5–8% winter–spring excess of births for schizophrenia. Among other explanations, infections have been seen as a viable possibility.[33] For example, maternal influenza A in pregnancy has been suspected to have a connection with schizophrenia in the offspring.[32] The evidence has been mainly ecological in nature with imprecise measurement of exposure, which has typically been defined through influenza epidemics in the population or on maternal recall of influenza infection after pregnancy.[34] Such data have suggested that the offspring of mothers who were in the second trimester of pregnancy when exposed to influenza A are twice as likely to have schizophrenia as those not exposed at all antenatally or exposed earlier or later in pregnancy.[35,36] However, not all studies using this methodology have replicated these findings.[37] Importantly, in the first study using serologically documented prenatal exposure to influenza, Brown *et al*.[34] found that influenza exposure, especially during the first trimester, might increase the risk of schizophrenia (odds ratio 7.0; 95% confidence interval 0.7–75.3). However, the confidence interval is broad and includes unity, and so the results may be somewhat unreliable. Prenatal exposure to rubella has also been connected to non-affective psychosis.[38]

Famine in pregnancy

Nutritional deficiency in pregnancy may play a role in the origin of some cases of schizophrenia.[39] The risk for schizophrenia increased 2-fold in offspring exposed to famine during early gestation and conceived at the height of the famine during the Dutch Hunger Winter of 1944–1945;[39] the causality is still a matter of debate. Congenital central nervous system defects have been associated with antenatal famine in the same population.[32]

Obstetric complications

Obstetric complications have been linked to schizophrenia in the offspring in numerous studies.[40,41] The majority of the evidence has come from case–control studies, but at least one population-based prospective cohort study has shown a link between severe obstetric complications (operationally defined as perinatal brain damage) and future

schizophrenia.[42] Geddes *et al.*[40] concluded from a meta-analysis that some abnormalities of pregnancy and delivery are associated with development of schizophrenia, perhaps via hypoxia. There were significant associations between schizophrenia and premature rupture of membranes, gestational age <37 weeks and use of resuscitation or an incubator, whereas the associations between schizophrenia and birth weight <2500 g or forceps delivery were of borderline significance.[40] A review by Cannon *et al.*[41] concluded that three groups of complications were significantly associated with schizophrenia: complications of pregnancy (bleeding, diabetes, rhesus incompatibility, pre-eclampsia), abnormal fetal growth and development (low birth weight, congenital malformations, reduced head circumference) and complications of delivery (uterine atony, asphyxia, emergency Caesarean section). In Nigeria, obstetric complications and childhood brain injury were found to be increased among adult patients with schizophrenia when compared with patients with mania.[43] These risk factors may not be specific to schizophrenia; it is possible that they also predispose to other mental disorders, such as affective disorders.[32,44]

Psychosocial factors during pregnancy and delivery

Some studies suggest an association between antenatal stress and schizophrenia. The children of mothers whose husband died while they were pregnant have been found to have a significantly increased rate of schizophrenia compared with children who lost their father in infancy in the first year of life.[45] In The Netherlands, rates of schizophrenia have been found to be very slightly higher in individuals exposed *in utero* to war and flood disaster than in reference subjects.[46,47]

In the Northern Finland 1966 Birth Cohort the risk of later schizophrenia among unwanted children was elevated 2.4-fold compared with wanted or mistimed children, even after adjustment for confounding by sociodemographic, pregnancy and perinatal variables.[48] Unwantedness might be a marker for features associated with risk in either the mother or the child. In the same cohort, the level of schizophrenia in the offspring of antenatally depressed mothers was elevated by a factor of 1.5-foldly, but the association was not statistically significant.[49,50] Those mothers of schizophrenia patients with a psychotic first-degree relative had suffered from depressed mood during pregnancy twice as often as other mothers. The familial risk for psychosis, including genetic risk for psychosis, might explain the elevated prevalence of depressed mood during pregnancy among the mothers of the offspring who went on to develop schizophrenia.

Possible risk factors for schizophrenia in childhood and adolescence

Disturbances of early development

Prospectively collected measures of premorbid function have consistently revealed neuromotor abnormalities and developmental delays. In the British 1946 Birth Cohort pre-schizophrenic children were found to have delayed motor and speech development by the age of 2 years.[51] In the Northern Finland 1966 Birth Cohort the ages that children learned to stand, walk and become potty-trained were related to subsequent risk for schizophrenia and other psychoses; earlier milestones reduced the risk, whereas later milestones increased it.[52] Cannon *et al.*[53] showed, in a birth cohort from New Zealand, that children who went on to develop schizophreniform disorder had persistently poor motor function over repeated measurements in childhood. In an innovative study using home movies filmed during childhood, pre-schizophrenic individuals could be differentiated from their healthy siblings by viewers who were blind to the psychiatric outcomes.[54]

Urbanization

According to Boydell and Murray,[55] there is substantial evidence, at least in Western countries, that urban birth and/or living in a town as a child are associated with increased risk of schizophrenia. In a Swedish study the incidence of schizophrenia was elevated among men brought up in cities compared with those who had had a rural upbringing.[56] In Denmark, the risk for schizophrenia in the capital has been found to be double than in rural areas.[57] The reason for this finding is unknown. Some hypothetical explanations which might explain the urban–rural differences include pre- and postnatal infections, selective migration, genetic factors and differences in the availability of psychiatric services[57].

Migration

Migration has been associated with increased risk of schizophrenia, especially among the second generation born in the new homeland.[55] People of African and Caribbean origin living in the UK have been found to have 2.4- to 18-fold increased rates of schizophrenia.[58] Among other possible explanations, there have been reports linking social isolation to schizophrenia.[55] Incidence rates in migrants have been reported to be significantly higher compared with native-born individuals, with the rate ratio median being 4.6.[10]

Other family environmental factors

In the British 1946 Birth Cohort, schizophrenia in offspring has been linked with problems in mothers' general understanding and management of their children (odds ratio 5.8).[51] Goldstein[59] concluded that communication deviance in the family increased the risk for schizophrenia. Having a positive relationship with both the mother and father might be protective against schizophrenia among high-risk children.[60] These findings may be explained by gene–environment interaction.

In Finnish studies some possible stress factors have not generally been linked to schizophrenia. Very early temporal separation from parents and transfer to adequate nursing homes immediately after birth because of tuberculosis in the family did not predict schizophrenia,[61] and neither did living in a single-parent family in childhood,[62] low socio-economic status,[63] or the size of the family of origin and multiparity.[64] The connection between childhood socio-economic status and schizophrenia is not yet entirely resolved.[65] Low or high socio-economic status in the family of origin has been found to be at least a modest risk factor for schizophrenia in some studies, while other studies report no increased risk.[65]

Only few infections in childhood have been linked to schizophrenia, and with discrepant results. In the Northern Finland 1966 Birth Cohort an association was found between childhood central nervous system viral infections and schizophrenia.[66] The infections might have disrupted nerve cell functioning or immune response. However, in the British 1958 Birth Cohort schizophrenia was not connected to common childhood illness, but was associated with neurological soft signs and previous meningitis and tuberculosis.[67] In another Finnish study virologically confirmed childhood central nervous system infections were not found to increase the risk of schizophrenia.[68]

Premorbid cannabis abuse

Schizophrenia has been associated with dysfunctions of dopaminergic, serotonergic and glutamatergic neurotransmission, which may also be affected by substance abuse.[69] Cannabis use was associated with a slightly increased risk of schizophrenia in a dose-dependent fashion in 50 000 Swedish conscripts (the adjusted odds ratio for linear trend was 1.2).[70] In a review by Arseneault et al.[71] of five prospective population-based studies, cannabis use was estimated to confer an overall 2-fold increase in the relative risk for later schizophrenia on an individual level. In particular, those cannabis smokers who have genetic vulnerability or some baseline psychiatric symptoms have increased risk of schizophrenia.[72] At the population level, elimination of cannabis use might reduce

the incidence of schizophrenia by ~8% if there is a causal relationship.[71] In a study of 2400 young Germans, cannabis use was concluded to produce a moderate increase in the risk for psychotic symptoms (at follow-up 4 years later the adjusted odds ratio was 1.7), but to have a much stronger effect in those with evidence of predisposition for psychosis.[73]

Premorbid cognitive and scholastic performance

Schizophrenia patients, when considered as a group, have intellectual impairments, some of which predate the onset of psychotic symptoms. Individuals who later develop schizophrenia have been found to perform below average on standardized measures of intelligence in childhood, adolescence and young adulthood, and to show lower premorbid IQ than the general population (reviewed by Aylward *et al.*[74]) The lower the IQ, the higher is the risk for later development of schizophrenia.[51,75,76]

Poor school performance can be seen as a premorbid sign. Repeating a grade, difficulties in completing the final level of schooling, and social and behavioural difficulties have also been found to be risk factors for developing schizophrenia.[75] In the Northern Finland 1966 Birth Cohort, 14-year-olds who were below their expected normal grade were three times more likely to develop schizophrenia than those in their normal grade, but low school marks (as measured by teacher ratings of performance) did not predict schizophrenia.[75] Developmental continuity, indicated by early developmental deviation in the first year of life associated with lower school performance at age 16 years, has been found to be stronger among children who develop psychoses later in life than among normal controls and those admitted to hospital for non-psychotic psychiatric disorder.[76,77]

Neuroanatomical abnormalities

Schizophrenia has been connected to neuroanatomical abnormalities. Whether these predate the onset of symptoms or develop progressively during the illness has so far been unclear.[78] There has been one study in which magnetic resonance brain images were obtained from 75 subjects who were at ultra-high risk for the development of psychosis.[78] Some of the grey-matter abnormalities linked to psychosis were found to predate the onset of frank symptoms. The subjects who developed psychosis were found to have less grey matter in the right medial temporal, lateral temporal and inferior frontal cortex and in the cingulate cortex bilaterally than the individuals who did not develop the illness.[78] The neurobiological deterioration processes driving schizophrenia might be active 1–2 years before the actual onset of the illness, and 2–3 years after its onset.[22]

Neurodevelopmental model

Brain development starts antenatally and continues in childhood and adolescence, and brain structures can depend on a combination of biological events and psychosocial factors.[79] Early abnormalities may have adverse effects on neurodevelopment and aberrant neural circuitry which eventually lead to psychopathology.[80] Disorders characterized by this process, which typically become manifest during the first few years of life, have traditionally been referred to as neurodevelopmental disorders; examples are autism and phenylketonuria. When evidence emerged that schizophrenia was characterized not only by psychotic symptoms which had their onset in adolescence and early adulthood, but that in many cases there were abnormalities (cognitive, behavioural and morphological) dating back to early childhood and the peri- and even prenatal period, a neurodevelopmental model of pathogenesis was proposed.[81,82] The neurodevelopmental model has proved extremely influential in schizophrenia research, and numerous studies have provided evidence to support its tenets. However, despite this, the key pathophysiological disruptions in the disorder and their precise relationships to the proposed aetiological factors are still not clearly understood. Figure 1 shows a life course developmental model with possible aetiological and disease course components.[83] The figure 1 has been modified from the article by Isohanni *et al*.[83]

Discussion

Schizophrenia is an aetiologically heterogeneous syndrome that usually becomes overtly manifest in adolescence and early adulthood, but in many cases subtle impairments in neurointegrative function are present from birth.

A distinction can be made, at least in theory, between risk indicators, which are manifestations of risk but not causal themselves, and risk modifiers, which are on the direct causal pathway. In practice, it may be very difficult to differentiate between the two. Even though studies of early risk factors of schizophrenia have generally made adjustments with confounding factors, there may still be many risk modifiers that have not yet been studied. Prediction in the sense of finding early causes, or fragments of causes, is completely different from trying to predict who will get schizophrenia, and the latter art depends crucially upon which population one is looking at. Risk for schizophrenia seems to be considerably greater in the case of close relatedness to an affected person than
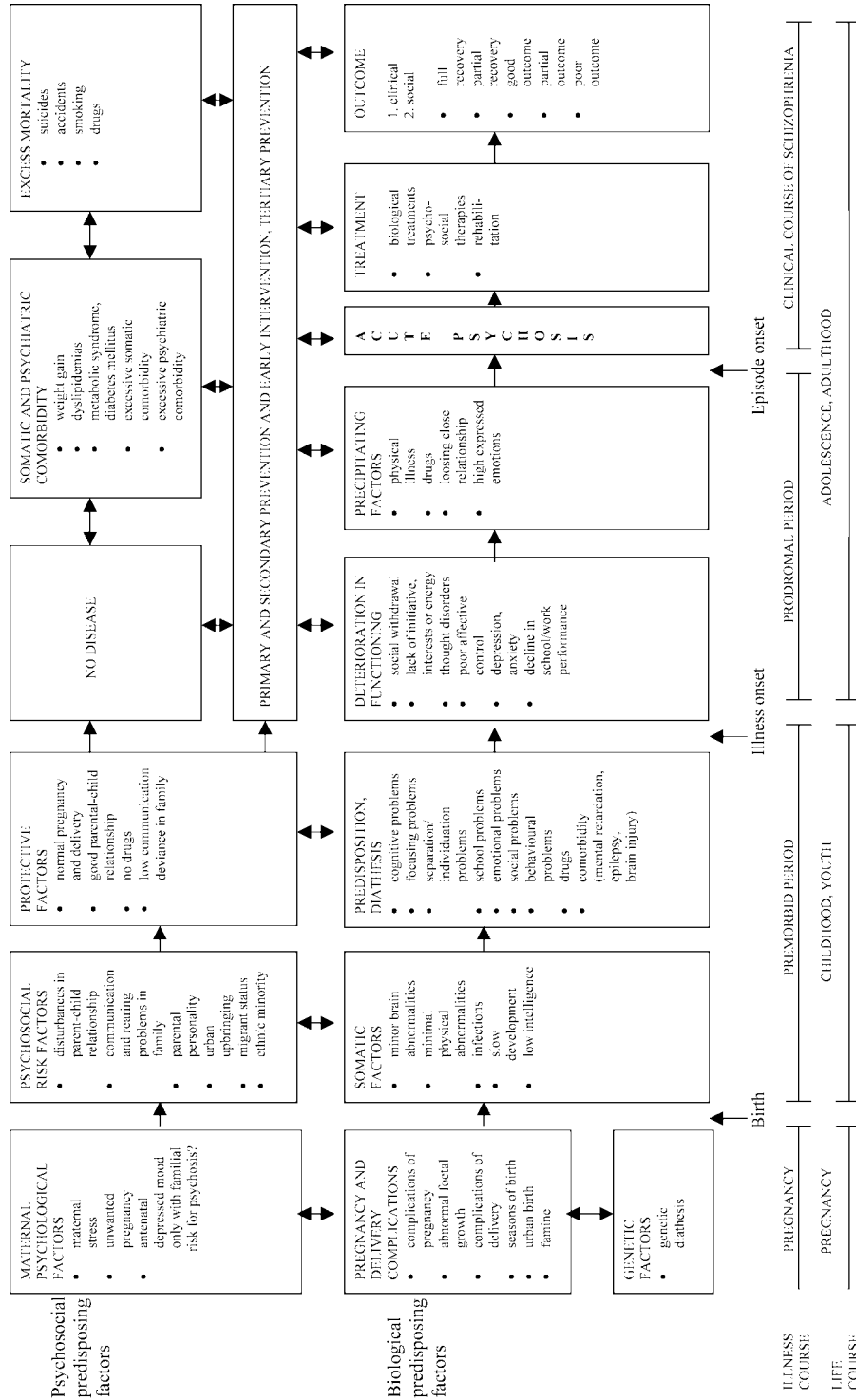
Fig. 1 A life course developmental model of schizophrenic psychoses with possible aetiological and disease course components. Modified from Isohanni M, Isohanni I, Koponen M, et al., (2004) *Current Psychiatry Reports* **6**, 168–75. Permission has been obtained from the copyright holder.

in those exposed by the putative environmental factors discussed above.[4] Nevertheless, even familial risk with a history of a psychotic close relative may not be useful for practical purposes of prediction and primary prevention in the general population.

It might be thought that the difficulty in predicting who might go on to develop schizophrenia would preclude primary preventative interventions. Even so, it has been argued that it is at least theoretically possible to reduce the risk for developing schizophrenia through general health policy promoting positive trends in pregnancy, delivery, childhood and adolescence which may benefit health and mental health during the life course.[84–86]. However, the frequency of schizophrenia might be influenced by industrialization and general development of a country from poverty to affluence through a complex combination of effects, such as cephalopelvic disproportion secondary to changes in nutrition and increased infant survival after improved obstetric and neonatal care.[87]

It seems reasonable that information about the risk of illicit drug use (especially cannabis) should be given to adolescents and (young) adults, especially to those at familial risk for psychosis or showing prodromal unspecific signs. One specific suggestion might be to introduce enhanced attention and care during the pregnancy and delivery of mothers with psychosis and also for mothers who have had a psychotic close relative, although whether specific interventions such as this are effective has not yet been tested. In clinical settings, it is helpful to map out possible early risk factors, at least familial risk for psychosis, especially in child, adolescent and young adult mental patients. Efforts should also be made to identify and attempt to find good models for treating prodromally symptomatic high-risk patients in the pre-onset phase of schizophrenia,[88] even though this practice and secondary prevention may be accompanied with risk for side effects of the treatments introduced, stress and stigmatization[89]. Furthermore, in the future we may have predictive models combining data from genetic factors for schizophrenia, antenatal risk factors, childhood and adolescent development and clinical symptomatology, as well as brain structural and functional abnormalities.

Acknowledgements

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