SCHIZOPHRENIA, RISK AND PREDICTION IN THE CONTEXT OF GENETIC/ENVIRONMENTAL INTERACTIONS

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Rezumat:

În cazul unei afecţiuni severe precum schizofrenia, identificarea factorilor de risc asociaţi cu această maladie reprezintă un element fundamental atât pentru prevenţia cât şi pentru identificarea patofiziologiei ei. Însă stabilirea unei relaţii între anumiţi factori de risc şi afecţiunea respectivă este dificilă deoarece factorii de risc consideraţi ca fiind asociaţi cu schizofrenia sunt influenţaţi de o multitudine de variabile, atât genetice cât şi de mediu, fiecare având o contribuţie relativ limitată la apariţia bolii. În plus predicţia unui eveniment atât de rar precum schizophrenia este cu atât mai grea. Dificultăţi suplimentare în acest demers sunt create de faptul că definiţia fenotipică a schizofreniei este relativ vagă, precum şi graniţa dintre schizofrenie, alte afecţiuni psihice şi normalitate. Anumite soluţii au fost propuse, dar deocamdată nici un nu este complet satisfăcătoare. Identificarea unor factori de risc pentru apariţia anumitor manifestări ale bolii, probabil biologic mai simple decât ansamblul sindromologic al schizofreniei, ar reprezenta una dintre soluţii. Asemenea manifestări (clinice sau subclinice) includ ideile delirante, halucinaţiile, tulburările gândirii, care pot fi prezente chiar dinaintea manifestării complete a bolii. O altă modalitate complementară, de tip endofenotipic, o reprezintă studierea anumitor manifestări non-specifice schizofreniei, cum ar fi unele aspecte ale funcţionării cognitive sau trăsături de personalitate, care, într-o formă atenuată, probabil că există şi în alte afecţiuni psihice şi posibil şi la unele persone fără afecţiuni psihice. Avantajul acestei ultime abordări ar fi creşterea numărului manifestărilor evaluate, în acelaşi timp cu menţinerea relativei simplităţi a fenotipului (endofenotipului) investigat. În ciuda avantajelor şi plauzibilităţii ştiinţifice a acestei metode endofenotipice, există unele dificultăţi asociate şi acestei metode. Este posibil ca interacţiunile genetice, epigenetice şi de mediu care au determinat apariţia ideilor delirante ori a afectării cognitive să fie atât de complexe încât să mascheze legătura dintre factorul de risc prezumat şi endofenotipul studiat. Utilizarea practică a cunoştiinţelor referitoare la factorii de risc în ceea ce priveşte predicţia apariţiei şi prevenţia acestei afecţiuni va trebui probabil să mai aştepte până când legătura patofiziologică dintre factorii de risc specifici şi manifestările caracteristice bolii vor fi elucidate.

Cuvinte cheie: schizofrenie, factori de risc, predicţii.

Abstract:

For a debilitating illness like schizophrenia, identifying the risk factors leading to its manifestation is crucial towards prevention of the disease as well as for understanding its pathophysiology. However, identification of the relationship between risk factors and the disease whose likelihood they are presumed to herald, is encumbered by the fact that the risks for schizophrenia are affected by a multitude of interacting genetic and environmental variables, each with its own limited contribution. Furthermore, prediction of any rare event such as the incidence of schizophrenia is particularly burdensome. Moreover, the vague definition of the schizophrenia phenotype and the blurry boundaries between it, other mental illnesses and normality further hamper efforts to use risk factors to predict the manifestation of the illness.

A number of remedies have been suggested, none of which are fully satisfactory. Identifying risks for disease manifestations, which are biologically simpler that the full-blown syndrome of schizophrenia is one solution. Such manifestations (either clinical or subclinical) can include delusions, hallucinations, thought disorders which may be present before the full manifestation of the disease. Another complementary endophenotypic approach would be to study the non-specific manifestations of schizophrenia such as aspects of the cognitive impairment or of personality traits, which in a more attenuated form are shared with most other mental disorders, as well as with a proportion of the non-mentally ill population. The advantage of the later approach would be to increase the incidence of the manifestation investigated, yet maintain the relative simplicity of the phenotype (endophenotype). However, despite its advantages and plausibility, associating risk to endophenotypes is not flawless. It is conceivable that the genetic, epigenetic and environmental interactions leading to delusions or to cognitive impairments are sufficiently complex and heterogeneous to obscure the link between a risk and the endophenotype. The use of risks towards predicting and preventing schizophrenia will probably have wait until the pathophysiological link between the specific risk factors and specific illness manifestations are elucidated.

Key words: schizophrenia, risk factors, prediction.

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Despite the spectacular achievements in cardiovascular medicine exemplified by heart transplants, intravascular stents or fibrinolitic drugs, their impact on cardiovascular mortality and morbidity at the population and individual levels pales in comparison with the impact of identifying and reducing risks through diet and physical activity, as well as pharmacotherapy aimed at lowering blood pressure and plasma cholesterol levels. The predictability of the morbidity associated with the presence of cardiovascular risk factors and the impact of preventive measures has been repeatedly demonstrated over the last 40 years [1, 2, 3, 4, 5, 6, 7, 8, 9]. Theoretically the same should be true for schizophrenia, in that the impact of primary or secondary prevention at the population and at the individual level should exceed the impact of treating patients with already established illness [10]. Indisputably, intervention at the individual level with antipsychotics has had a major impact on the morbidity and mortality associated with schizophrenia. Yet, the treatment is far from satisfactory for the majority of chronically ill patients treated with antipsychotics, their families as well as their respective psychiatrists [11, 12]. Conceivably in the foreseeable future novel and more effective pharmacological interventions will be available that will induce remission and prevent exacerbation in larger proportions of patients than currently available drugs do [13]. Potential new treatment target might include dopamine D_1 agonists, dopamine D_3 receptor antagonists, nicotinic 7 or alpha4beta 2 receptor agonists, 5-HT modulators, GABA-A receptor modulators, muscarinic M_1/M_4 agonists, positive mGLUR2/3 and mGLUR2/3 modulators, Catechol-O-methyltransferase inhibitors, alpha-2 adrenergic receptor agonist or antagonist, glutathione prodrugs, and studies testing the efficacy of some of these compounds are ongoing [14, 15, 16]. However it is improbable that such treatment interventions will completely erase the impact of the schizophrenic illness on cognitive, social and vocational development as well as the emotional sequela. On the contrary social and cognitive decline occur during premorbid and prodromal periods [17, 18] and affect future development even if the first episode of psychosis is rapidly abated. Hence, attempts to intervene as early as possible during the premorbid or prodromal phases are justified. Whether these interventions should affect the environment (for example changing the social milieu, increasing educational opportunities) or the maturation and functioning of the CNS by pharmacological intervention or a combination of the two is far from clear. However, testing, devising and implementing preventive interventions could be costly and not devoid of adverse effects. To reduce the potential for adverse effects and the cost it is essential to define *risk factors* and at-risk populations and test and implement the preventive intervention only in these populations.

The term risk factor was coined by Thomas Dawber in a seminal paper reporting the first results of the Framingham study [9, 19]. Being at risk for a disease, means that an individual is more likely to develop that disease, than someone selected randomly from the general population. Risk factors can arise from every domain of life: biological, social, cultural, and environmental. To qualify as a risk factor a variable must be present prior to the onset of the disorder and have a higher frequency in individuals who will be affected compared to controls. A similar but not identical notion is a *marker* for a disease [20] A marker is a sign whose detection indicates a particular disease state (for example, the presence of an antibody may indicate an infection). A putatively examples of such a markers in schizophrenia might be the presence of minor physical anomalies, which are more frequently in schizophrenic people than in controls [21] or abnormal electrophysiological reactivity [22].

Risk factors and markers as defined above are not necessarily on the pathophysiologic pathway to the disease but can be epiphenomena. Classical example of epiphenomena is the association between being in a hospital and death. As opposed to risks and markers, the prodrome which precedes the disease, is part and parcel of it although its manifestation differs from the full blown manifestation of the condition. The disease can manifest in the absence of prodrome, risk factors or markers, or never manifest in spite of the presence of risk factors and markers. Nevertheless, presence of risk factors is used in attempts to predict disease manifestation. The relationship between a risk factor and the disease or the "event" whose likelihood it is presumed to herald is affected by many variables, including duration of exposure to the risk factor, intensity and timing, as well as interactions with other risk factors and with the individual's genetic make-up [23, 24, 25].

Making predictions is one of the most important characteristics of human race. Scientists of all kinds, physicians, meteorologists, military leaders and stock analysts are continuously trying to make predications based upon the presence of many interacting risks. An example for the complex interactions between risk factors and an event could be illustrated by the relations between war (as risk factor) and the precipitous decline of a particular stock (as the event). Military conflicts lead to political and economic instability and are usually associated with a decline in the average indexes of the stock market (www.djindexes.com). Nevertheless, some stocks may prosper (e.g. those producing military equipment) despite the decline of the average indexes or drop with the rest of the index if the conflict is of such nature that not use of the specific piece of equipment is expected. This rather complex relationship appears because both the presumed risk factor (the war) and the event (precipitous stock decline) are affected by a multitude of factors. The military conflicts can vary as extent, type, and global context; compare, for example, the First World War with the war in Yugoslavia. The distance of the particular stock exchange from the military conflict can also affect the impact of the war on a particular stock. Similarly the markets are affected by

other economic and social factors (www.londonstock-exchange.com). Even predictions of the outcome of the conflict, made by political commentators or predictions of how the war is going to affect the markets made by stock analysts, can by themselves affect the stock markets, as a self-fulfilling form of prophecy. The general economic mood during the war (which in itself is affected by the stock market indexes) also influences the fluctuations of the market. Furthermore, the war-related decline of the stock market can lead to decline in the global economy and become a "risk factor" for political instability and military conflicts such as the effect of the stock market crash and Great Depression on Germany. In addition, increase in the interest rate can lead to decline of the stock market [26] and to a slow down of the global economy, which in turn is associated with political instability and increased risk for war. Although the mechanisms through which war, economic decline, and stock markets interact might be better understood than the mechanisms by which genes and environment interact to affect behaviour, the example above illustrates how making prediction based on risks might be problematic.

Modifiability is a characteristic of risk factors for diseases that makes their identification worthwhile. Risk factors that can be modifiable are these which can be attenuated or eliminated by manipulations of the social or biological environment, whereas non-modifiable risk factors are those which are not amenable to change. The amount of dietary lipids consumed is a modifiable risk for coronary occlusion [27] obesity is partially modifiable [28] while mutations in the gene(s) coding for hyper-lipidemia [29] is an example of non-modifiable risk. In the case of schizophrenia amount or quality of premorbid education is a modifiable risk for cognitive impairment [30], risk for head trauma is partially modifiable [31], and mutations in the gene(s) coding for COMT [32] are non-modifiable risks.

An example of an apparently straightforward relationship between risk factors for a CNS disease and prevention is phenylketonuria (PKU). Hyper-phenylalaninemia (HPA) results from genetically mediated defective hydroxylation of phenylalanine in the liver by phenylalanine hydroxylase (PAH), and the high blood levels of phenylalanine cause damage to the brain. The brain damage caused by HPA is highly variable, ranging from moderate elevation of plasma phenylalanine with no clinical consequences to the severe form of phenylketonuria and irreversible mental retardation. Removing phenylalanine from the diet significantly reduces the damage to the brain, with no cases of severe mental retardation if treatment is initiated during the first weeks of life [33]. Conversely, almost all untreated or late-treated cases of classic PKU have IQ scores < 70 [34]. PKU can be seen as a genetic risk factor which acts in concert with other factors (parental education and IQ, SES -socio-economic status, level of medical care) to determine the IQ score. Hyperphenylalaninemia can also result from defects in genes quite distinct and different from the gene which is usually associated with PKU. On the other hand, the clinical syndrome may be absent in individuals carrying defective genes for PKU [35]. The trait for PKU can result from more than 490 different mutations of the phenylalanine hydroxylase *PAH* gene (the enzyme implicated in phenylalanine metabolism) (PAH Mutation Analysis Consortium Database, www.mcgill.ca/pahdb). Some of these mutations will produce synonymous phenylalanine hydroxylase structures with exactly the same level of catalytic activity or vary to certain degree the efficacy of the enzyme's activity [35]. The mutations lead to a variety of clinical and biochemical phenotypes with different degrees of severity, from mild hyperphenylalaninemia to classical PKU. In producing the net result IQ level, the level of hyperphenylalaninemia will interact with the myriad of factors (both genetic and environmental) in which effect IQ.

An example of the complex interactions between risks and event is the relationship between traumatic brain injury (TBI) and schizophrenia. Patients with schizophrenia are exposed to TBI more than the general population [36]. Some [37] but not all [38] studies, recently reviewed [39] indicate that the incidence of schizophrenia-like psychosis is 2 to 3 times greater in people with TBI then in the general population. However, individuals who will develop schizophrenia in the future are more prone to TBI because of clumsiness, distractibility or poor coordination [40, 41]). On the other hand TBI is also a risk factor for cognitive impairment [42] and cognitive impairment might be a risk factor for schizophrenia [43]. To make matters more complicated, the consequences of TBI on cognitive impairment are genetically mediated [31] regardless of the presence or absence of schizophrenia.

To conceptualise and hopefully clarify the genetic/environmental interactions leading to schizophrenia one has to account for some of the main characteristics of the disease: the overwhelming majority of the affected individuals do not have an ill first degree relative, more than half of the monozygotic twin pairs are discordant for the disease, and manifestation of the disease is heterogeneous despite repeated attempts to define more homogenous phenotypes. This pattern coincides with the common, polygenetic disease model with epigenetic and environmental interactions such as diabetes or ASCVD [44]. Confirming this hypothesis is the plethora of reports since the 2000 identifying susceptibility genes for schizophrenia (*DTNBP1*, *NRG1*, COMT, *G72/G30*, *TRAR4 RGS4*, *PPP3CC, ZDHHC8*, *AKT1)* some with good biological plausibility [45, 46]. The fact that the reports on susceptibility genes are not always replicated [47], does not necessarily detract from their validity. On the contrary, it might validate the polygenetic characteristics of schizophrenia, the heterogeneity of the phenotype, and the epigenetic and environmental influences. Thus, because of the intervening epigenetic and environmental effects the same mutation can result in several phenotypes. Similarly the

same phenotype could result from different gene-gene interactions or gene-environment interactions. This was demonstrated in a twins study which demonstrated an overlap in the genetic susceptibility for mania, schizoaffective disorder and schizophrenia [48]. A different study [49] showed that the gene encoding D-amino acid oxidase activator - *G72/G30* locus on chromosome 13q, one of the regions implicated in genome scans of schizophrenia and bipolar disorder, confer risk for both disorders. Also, genetic analysis has implicated DISC1 in schizophrenia, schizoaffective disorder, bipolar affective disorder, and major depression [50]. Both brain-derived neurotrophic factor (BDNF) and catechol-*O*-methyltransferase (COMT) have been proposed as candidate genes associated with schizophrenia [51] and affective disorders [52]. Moreover it seems that the BDNF Val66Met gene polymorphism diminishes some cognitive function (as verbal memory performance) in both schizophrenic patients and healthy volunteers [53]. COMT gene is also proposed to be a candidate gene associated with anxiety disorders [54] and slight alterations in cognitive functioning [51] which in turn is present in schizophrenia. Furthermore the COMT Val158Met genotype is also associated with cognitive impairment in individuals with bipolar disorder [55]. This concept was also demonstrated by a similar analysis [56] of patients with bipolar disorder, which found an association between the D-amino acid oxidase activator (DAOA)/G30 locus (which has been reported in schizophrenia) and those patients with bipolar disorder and a history of persecutory delusions. This might indicate that the (DAOA)/G30 locus mediates persecutory delusions regardless of diagnosis. Interestingly, there also seems to be an association between hypnotizability and the COMT gene [57].

Similar to the genetic conundrum, environmental factors associated with schizophrenia are also associated with other psychiatric disorders and manifestations. For example, childhood adversity [58], prenatal famine [59], migrant status [60] and urban dwelling [61] are associated not only with schizophrenia, but also with depression. Childhood abuse is associated with schizophrenia [62] personality disorders, major affective disorders [63] dissociative disorders [64] and panic disorder [65]. Also, perinatal complications are associated not only with schizophrenia, but with autism, anorexia nervosa, and affective disorders [66].

Adding to the lack of specificity of the genetic and environmental risk factors is the poor definition of the schizophrenia phenotype itself. Door to door epidemiological surveys indicate that 10-20% of the general population, who do not seek psychiatric help and lead apparently normal lives, experience psychotic-like symptoms such as conceptual disorganization, suspiciousness, unusual beliefs and even hallucinations [67, 68]. Furthermore, individuals whose main symptoms are mood abnormalities (unipolar depression and bipolar disorder) also experience suspiciousness, unusual beliefs, delusions and hallucinations. Major depression with psychotic features occurs in over 20% of patients hospitalized for major depressive disorder [69] and 58% of patients with bipolar disorder had a lifetime history of at least one psychotic symptom [70]. Moreover, some individuals manifest in late adolescence or early adulthood declining social and vocational functioning, neglect of personal hygiene and mild cognitive impairment which is characteristic to schizophrenia without ever experiencing psychosis. These people are considered to be afflicted by schizotaxia [71] and depending on circumstances develop schizophrenia, schizotypal personality disorder or remain stable [72].

Evidence presented here indicates that the phenotype of schizophrenia is affected by a multitude of genetic [25] and environmental factors [73, 74, 75, 76, 77] each increasing the odd ratios to manifest the disease by a magnitude of 1.5-4 folds. For the prediction of a rare disease such as schizophrenia with an incidence rate of 3-5 new cases per 10.000 population per year [78], a 4 fold increased risk only raises the probability of later manifesting the illness to 2–4%. Hence, belonging to a high risk group as currently defined is not sufficient to accurately predict the syndrome of schizophrenia and does not justify implementation of preventive measures. A number of solutions have been suggested to identify risk factors that can improve prediction and understanding of the pathophysiologic relationship between the risk and the clinical manifestation.

Studies of genetic and environmental risk factors in complex polygenic disorders such as schizophrenia might benefit from identification of endophenotypes, which hopefully represent more fundamental yet simpler aspects of brain function along the pathway between disease and distal genotype [79]**.** It is presumed that endophenotypes are one step closer then full disease to the genetically determined aspects of illness in the chain of genes-proteins-cells-systems-endophenotypes-behaviours-psychiatric disorder [80]. An endophenotype could be neurophysiologic, biochemical, endocrine, neuroanatomic, neuropsychological or a personality trait. Some endophenotypes such as the score obtained by a schizophrenic patient on a neuropsychological test have the potential advantage of being more amenable to objective quantification than clinical symptoms. However it is conceivable that studying endophenotypes associated with schizophrenia would not represent the universal panacea of studying schizophrenia. It is possible that some of the difficulties in studying the phenotypes of schizophrenia, such as lack of specificity, plurigenicity, epistaticism and stochastic events can also be found in the case of endophenotypes. Also because of the overlap in genetic susceptibility between schizophrenia and other mental disorders, it is quite possible that some endophenotypes may also be shared by several disorders.

Delusions or hallucinations are considered classical manifestations of schizophrenia. Again, the correlation between gene/genes and clinical manifestations is not straightforward. For example a polymorphism in

the dopamine D3 receptor (DRD3) gene, which results in a serine to glycine substitution (Ser9Gly), has shown association with delusional disorder in one study [81], but not in another [82] study.

Other examples or risks specifically associated with particular aspects of schizophrenia are the association between positive symptoms and history of childhood trauma and abuse [83, 84], or deficit schizophrenia with cytomegalovirus antibody seropositivity [85].

Over the last 50 years a large amount of epidemiologic and molecular biology knowledge has accumulated, linking environmental and genetic risks to the schizophrenic illness or to aspects of the illness. Current research efforts are focused towards tracing the pathophysiologic pathway from risk to symptoms to illness, one interesting such approach being the concomitant use of genetic and neuroimaging tools [86, 87].

Understanding the pathophysiologic pathway is useful in assigning relative weight to individual risks, and to understand the interactions between risks. Furthermore, understanding the physiologic pathway from risk to manifestation is relevant towards devising preventive interventions. One such an example represents the understanding of the pathway between the high level of cholesterol, plaque formation, coronary narrowing and death from coronary heart disease. The discovery and consequently introduction of the cholesterol lowering drugs resulted in a reduction of the progression of coronary atherosclerosis, fewer subsequent coronary events and reduced mortality [88]. Conceivably understanding how risks such as famine, eclampsia or other perinatal maternal unfavourable events might affect in-utero neuronal migration and how faulty neuronal migration might affect behaviour, could be helpful to predict schizophrenia and device preventive measures.

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