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EDITORIAL

What is schizophrenia? 25 years of research into schizophrenia - the Age Beginning Course Study

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Abstract

We studied a population-based sample of 232 first-onset cases of schizophrenia aged 12 to 59 years at first admission retrospectively back to illness onset and prospectively up to 11.2 years later. We compared them with psychiatrically healthy age- and sex-matched population controls and equally matched first-admission patients diagnosed with major depression. At schizophrenia onset women are several years older than men. The social factors tested did not explain the finding. Women's higher level of social development at onset is associated with a better medium-term functional and social outcome. Prodromal schizophrenia and depression are equal in length and diagnostically distinguishable only after the onset of positive symptoms. The sex difference in age at onset, invariable across cultures and ethnicities, is explained by a protective effect of oestrogen, which down-regulates D2 receptors. A higher genetic load antagonizes this effect. Long-term symptom-related illness course exhibits a plateau after three years, the positive symptom dimension after two years, the depressive and the negative dimensions do so after three to five years. The most prevalent symptom is depressive mood. Male first episodes are more frequent and more severe in the first half of life, female ones in the second half. Aetiological conclusions will be drawn.

Key words: Schizophrenia and depression; Symptom dimensions; Types of illness course; Sex; Age

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Core tip: We studied schizophrenia from onset to 134 mo following first admission: age at onset is higher for women because of oestrogen. Prodromal schizophrenia and depression split diagnostically only after the onset of positive symptoms. Illness course exhibits a plateau after three years, positive symptoms do so after two,

depressive and negative symptoms after three to five years. Depressive mood is the most prevalent symptom. Male first episodes are more frequent and more severe in the first half of life, female ones in the second half. Late-onset schizophrenias feature paranoid delusions, early-onset illnesses various severe pathology. Aetiological conclusions will be drawn.

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INTRODUCTION

For more than one hundred years researchers have tried to answer the questions of what schizophrenia actually is and how it is related with affective disorder. Fascinating novel research methods have been developed and a considerable amount of knowledge has been amassed on different aspects, but we still lack conclusive answers to these questions. A quarter of a century ago (in 1987), as we launched our A (ge) B (eginning) C (ourse) Schizophrenia Study[1,2], the situation was very much the same. But we were daring enough to embark on a journey to gain insight into some aspects of the nature of the disorder.

STRATEGY AND AIMS

We proceeded from a finding already reported by Emil Kraepelin[3] and confirmed by numerous studies[4]: women's several years' higher age at first admission for schizophrenia compared with men's. After testing and confirming its transnational and transcultural validity on data from the Danish and the German case-register and the WHO ten-country study, with four sites in low-income developing countries and seven sites in industrialized countries, we set the first goals for our study: (1) finding an explanation for the sex difference in age of onset; and (2) collecting detailed information on the prodromal symptoms and demonstrating how the disorder unfolds prior to first admission.

This exceptional study was conducted by the same team of researchers in several consecutive steps from its planning and launch on January, 1st, 1987 to its completion on May 31st, 2012 and financed by the German Research Foundation (DFG) over those 25 years. Data analysis is still going on. Our aim was to produce generally valid results by applying a systematic, methodical approach and both traditional and advanced statistical techniques. For the sake of the generalizability of the results, the study was designed as a population-based, multiply controlled follow-up study. On the basis of the results achieved new research objectives were defined and novel hypotheses were tested. We studied symptoms, symptom dimensions and social parameters at the prodromal stage, in the first episode, over the medium- (5-year-) and the long-term (11.2-year) course of schizophrenia in the entire study sample and a subsample of 130 first admissions. We conducted eight cross-sectional assessments and mapped the illness course retrospectively on a monthly basis. We compared our population-based sample of 276 first admissions with a diagnosis of schizophrenia (= 232 first psychotic episodes) in age range 12-59 years with healthy controls drawn from the population of the catchment area and with age- and sex-matched first admissions for unipolar depression. We analyzed how age, sex, primary and secondary risk factors, hormonal factors, level of social development at illness onset and illness behaviour influence the disorder. We studied how symptomatology changes over the life-cycle in a sample of 1109 consecutively first-admitted patients with schizophrenia spectrum disorder.

Limited space permits us to present only excerpts from this large-scale study and to draw a few conclusions.

MAJOR FINDINGS

The prodromal stages of schizophrenia and moderately severe and major depression last for several years (in schizophrenia: mean 4.8 years, median 2.3 years) and cannot be discriminated from each other until positive symptoms appear. As long as this is the case, it is also impossible to make any predictions about the diagnosis-related illness course. The most frequent symptom over the entire course of schizophrenia, depressive mood, is also the most frequent initial symptom in both disorders. Prodromal depression in schizophrenia is associated with a greater amount of depressive and positive symptoms in the first illness episode, but not in the further course of the disorder.

Male incidence of schizophrenia shows a pronounced peak in age group 15 to 24 years, female incidence a lower peak in age group 15 to 29 years and a second - narrower and still lower - peak at menopausal age in age group 45 to 49 years. This finding is accounted for by the age-dependent protective effect of oestrogen, confirmed in animal experiments. Underlying it is probably a sensitivity-reducing effect on D_2 receptors. The protective effect is antagonized by genetic load - for example in co-twins and siblings of individuals diagnosed with schizophrenia. Beyond the menopausal age the sex ratio in the incidence of schizophrenia is reversed: in old age men develop psychosis more rarely and, when they do, present milder symptoms than their female peers.

Functional and social impairment appears at the prodromal stage. The severity of that impairment depends on the individual's sex and level of social development at illness onset. The social course of schizophrenia is less favourable for young males than females because of men's younger age at illness

onset and their greater prevalence of socially adverse behaviour. At higher age, when males have lost the socially adverse behavioural parameters frequent at younger age, men tend to develop milder, primarily paranoid symptoms and suffer less severe social losses. Schizophrenia is a disorder of all ages. Considering the entire lifespan, there is not any major sex difference in schizophrenia incidence, although there are numerous epidemiological studies, mostly based on lower age limits (45-55 years) and treated or hospitalized patients, and meta analyses reporting a higher lifetime risk for males[5].

The course of schizophrenia as such and the trajectories of the symptom dimensions as based on mean values show plateaus starting some two to five years after the first episode, and positive symptoms do so earlier than negative symptoms. Underlying these different patterns are irregularly occurring episodes of symptom exacerbation, which differ in duration depending on the symptom dimension.

CONCLUSION

Considering the remarkable finding that both the symptom-related and the social course of schizophrenia depend on age and sex, considering further the temporal variability of psychopathology and the fact that, according to mean values, the disorder does not progress, it seems reasonable to conclude that schizophrenia is not a unitary disorder. At its early prodromal stage, it is indistinguishable from mood disorder. Throughout the illness course, depressed mood is the most prevalent symptom in schizophrenia. Although the long-term trajectories of the individual symptom dimensions resemble each other, there is a certain degree of autonomy that cannot be overlooked in their remission following the first psychotic episode or in the frequencies and durations of their exacerbations. Schizophrenia does not convey the picture of a stable residual state caused by an early developmental disorder, nor does it look like a progressive neurodegenerative process. It rather gives the impression of a condition resulting from a susceptibility to recurrent crises in the neural functions that underlie the symptoms. Hence, rather than knowing what schizophrenia really is we have merely achieved a little better understanding of what it is not.

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