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Bruno Pfuhlmann · Ernst Franzek · Helmut Beckmann

Absence of a subgroup of chronic schizophrenia in monozygotic twins. Consequences for considerations on the pathogenesis of schizophrenic psychoses

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Abstract In the region of Lower Franconia, Germany, all twins born after 1930 and hospitalized for a schizophrenia spectrum psychosis were ascertained in a systematic twin study comprising 22 monozygotic (MZ) and 25 dizygotic (DZ) pairs. One aim of the study was to compare concordance rates between MZ and DZ pairs with regard to various diagnostic classifications. Two experienced psychiatrists independently classified the probands according to DSM-III-R, ICD-10, and Leonhard's classification. Schizophrenic psychoses were found among MZ and DZ pairs in equal proportions according to DSM-III-R and ICD-10 criteria. In contrast, when Leonhard's classification was applied it became apparent that systematic schizophrenias, which represent the core group of schizophrenias in Leonhard's nosology, were completely lacking among the 34 ill MZ twins. Among the 30 ill DZ twins, 6 suffered from a systematic schizophrenia ($p < 0.01$). Unsystematic schizophrenias and cycloid psychoses occurred among MZ twins at a frequency of 58.8% and 41.2%, respectively. In the course of his own twin-investigations, Leonhard also observed an absence of systematic schizophrenias in MZ twins, although his twins were not systematically ascertained. This striking finding requires an explanation regarding its significance for the etiology of chronic schizophrenic psychoses. In view of the absence of other conclusive theories, one speculative explanatory model is that specific psychosocial factors, i.e., a lack of communication during childhood, may result in distinct biological damage to functional brain systems and, thus, may play a role in the pathogenesis of these psychoses.

Key words Schizophrenia · Monozygotic twins · Leonhard classification · Etiology

B. Pfuhlmann (✉) · E. Franzek · H. Beckmann
Psychiatrische Universitätsklinik, Füchsleinstraße 15,
D-97080 Würzburg

Introduction

The question of the significance of genetic versus environmental factors has always been one of the main problems of research into the causes of psychotic illnesses. Twin studies with monozygotic (MZ) pairs promise to be particularly informative since they allow studies to be conducted on genetically identical individuals. Twin studies have been firmly established in clinical-genetic research ever since Galton [28]. Meanwhile, an abundance of twin findings has been obtained in psychiatry, with research focusing on subjects with schizophrenic illnesses [6, 10, 11, 13, 14, 22]. Unfortunately, the diagnostic criteria used are inconsistent, and this, irrespective of the methodological problems of recruiting suitable groups of subjects, makes it difficult to compare the results. In clinical-genetic research, however, a reliable and valid description of phenotypes which defines clearly distinguishable and homogenous groups is very important. It is precisely this, which most psychiatric classifications fail to do. In other words, they are not able to demarcate clear-cut clinical states with distinct constellations of symptoms, stability of diagnosis and defined prognosis at the phenotypical level.

Applying Karl Leonhard's differentiated nosology of endogenous psychoses [17] could be an important step forward in this regard. Compared with the ICD-10 [29] and DSM-III-R [2] or DSM-IV [3] classification systems, Leonhard's classification seems to permit a better distinction of homogenous phenotypes on the basis of which significant biological results could be ascertained [4, 15]. Leonhard was also continuously engaged in twin research and recorded a series of interesting findings [17]. He was surprised, most of all, by the fact that among 69 MZ twins suffering from a psychosis he could not find a single case of systematic schizophrenia, whereas there were 12 cases of systematic schizophrenia among his 42 DZ twins.

In Leonhard's nosology, systematic schizophrenia represents schizophrenia in a strict sense. It concerns illnesses which begin insidiously and run a chronic course,

developing distinctly defined, irreversible residual syndromes. Systematic schizophrenia was subdivided by Leonhard into systematic catatonia, systematic paraphrenia, and hebephrenia. These subgroups also show clear-cut, highly characteristic individual forms whose diagnosis requires the presence of all the defining criteria and is, thus, highly operationalized. Systematic schizophrenia represents one of the five independent main groups of endogenous psychoses in Leonhard's classification. The complete absence of one of these groups in MZ twins is a highly remarkable observation. Since Leonhard did not carry out any systematic twin survey, it cannot be ruled out that he may have overlooked a significant group of psychotic twins.

To clarify this issue, a systematic polydiagnostic twin study was conducted which applied not only the DSM-III-R [2] and ICD-10 [29] standard classification systems, but also Leonhard's nosology. The aim of the study was to investigate whether the application of Leonhard's classification provides more extensive evidence of the role of genetic versus environmental factors in the etiology of schizophrenia spectrum psychoses than do the other classifications. The study also investigated whether there were any differences in the frequency of each of the diagnostic categories among MZ and DZ twins when different diagnostic classifications were used.

Patients and methods

The exact details of the methodological procedures have already been discussed elsewhere [9]. Twins born after 1930 and hospitalized for a psychiatric disorder in the region of Lower Franconia were ascertained by means of a systematic survey of approximately 30.000 case histories recorded in the psychiatric hospitals of this region. Subjects with psychoses which did not correspond to the schizophrenia spectrum were not considered. The diagnoses in the medical records were coded according to ICD-9. Case history diagnoses of the ICD-9 categories 295.0–295.9 and 297.0–297.9 were selected. In order to be included in the study, the index twins also had to fulfill the more narrowly defined criteria of DSM-III-R for psychoses of the schizophrenia spectrum, i.e., the categories 295.1–295.4, 295.6, 295.7, 295.9, 297.10, and 298. Only same-sex pairs were included. Zygosity was established by the Institute for Human Genetics of Bonn University and the Institute for Forensic Medicine of Würzburg University by the molecular genetic method using high polymorphous microsatellites. The zygosity questionnaire of Torgersen [27] was applied simultaneously.

Twenty-two MZ twin pairs (12 male, 10 female) and 25 DZ twin pairs (13 male, 12 female) with at least one partner suffering from schizophrenia spectrum psychosis were included. The mean age of the total collective was 40 years at the time of the investigation (SD 13 yrs., range 22–65 yrs.). Two experienced diagnosticians (H.B., E.F.), working independently, formulated diagnoses of all recruited twins according to DSM-III-R, ICD-10, and Leonhard's classification. The index twins were diagnosed by H. B., who had no information on the diagnosis of the twin's partner or on the zygosity of the twin pair. The psychopathology was documented by an extensive case history based on medical records as well as on the results of a detailed personal examination. The examination included a semi-structured interview using the „Schedule for Affective Disorders and Schizophrenia, Lifetime Version, modified for the study of Anxiety Disorders" (SADS-LA). The co-twins were classified by E.F. in the same manner as the index twins, using the same instruments and documentation. Zygosity was not determined until the diagnoses and concordance or discordance had been established. Both investigators recorded high kappa values when testing the interrater reliability of their diagnoses in another collective of schizophrenic patients [7].

Results

After screening the case records, a total of 452 twins were found, which corresponds to a ratio of one twin in every 66 patients. As this rate corresponds to the proportion of twins in the total population, it can be assumed that no significant number of hospitalized twins was overlooked. Seventy-seven index twins from 66 same-sex twin pairs had received inpatient treatment for a psychosis of the schizophrenia spectrum in accordance with the ICD-9 diagnosis of the case records. In the case of six pairs, one twin had already died and in a further eight pairs, either one or both partners refused to participate in the study. A diagnosis of a schizophrenia spectrum psychosis according to DSM-III-R criteria could not be maintained in five cases. The study group was therefore made up of 47 same-sex twin pairs (22 MZ and 25 DZ) with at least one index twin suffering from schizophrenia spectrum psychosis. In one MZ and three DZ pairs, the zygosity diagnoses were based solely on the zygosity questionnaire and a similarity test since not enough blood had been obtained for a molecular genetic analysis. In the remaining 43 pairs, the molecular genetic diagnosis of zygosity corresponded in 97.6% of the cases with the diagnosis obtained from the questionnaire and similarity test.

At the time of the investigation, the mean age of the MZ twins was 41 years (SD 12 yrs., range 22–63 yrs) and that of the DZ twins 39 years (SD 13 yrs, range 22–65 yrs). The female MZ pairs were significantly older than the male MZ pairs (47 ± 11 years vs. 37 ± 12 years; U-test, $p < 0.05$). Among the DZ pairs females showed a higher mean age as well (43 ± 15 years vs. 34 ± 10 years in males), but the difference was not significant. A total of 64 subjects (33 male, 31 female) from the 47 pairs suffered from psychoses of the schizophrenia spectrum. According to DSM-III-R criteria there were 30 schizophrenias, 17 schizoaffective disorders, five delusional disorders, eight schizophreniform disorders as well as four atypical psychoses. Applying ICD-10 criteria, 30 schizophrenias, 15 schizoaffective disorders, five delusional disorders, 11 acute polymorphous psychotic disorders and three other non-organic psychotic disorders were diagnosed. The classification according to Leonhard resulted in 27 cycloid psychoses, 31 unsystematic schizophrenias and six systematic schizophrenias. The Leonhard diagnoses were distributed among DSM-III-R and ICD-10 diagnoses as shown in Table 1. Without exception, the systematic schizophrenias also fulfilled the DSM-III-R and ICD-10 criteria for schizophrenia, whereas the unsystematic schizophrenias and the cycloid psychoses were distributed among a wide spectrum of DSM-III-R and ICD-10 diagnoses.

The distribution of diagnoses of the schizophrenia spectrum psychoses according to the zygosity of the twins is shown in Table 2. In the classification along the lines of

Table 1 Distribution of Leonhard-diagnoses within DSM-III-R and ICD-10

Cycloid psychoses (n = 27)			
DSM-III-R:		*ICD-10:*	
Schizophrenia	4 (14.8%)	Schizophrenia	4 (14.8%)
Schizoaffective disorder	13 (48.1%)	Schizoaffective disorder	11 (40.7%)
Schizophreniform disorder	7 (25.9%)	Acute polymorphous psychot. dis.	10 (37.0%)
Delusional disorder	1 (3.7%)	Delusional disorder	1 (3.7%)
Atypical psychosis	2 (7.4%)	Other non organic psychotic dis.	1 (3.7%)
Unsystematic schizophrenias (n = 31)			
DSM-III-R:		*ICD-10:*	
Schizophrenia	20 (64.5%)	Schizophrenia	20 (64.5%)
Schizoaffective disorder	4 (12.9%)	Schizoaffective disorder	4 (12.9%)
Schizophreniform disorder	1 (3.2%)	Acute polymorphous psychot. dis.	1 (3.2%)
Delusional disorder	4 (12.9%)	Delusional disorder	4 (12.9%)
Atypical psychosis	2 (6.4%)	Other non organic psychotic dis.	2 (6.4%)
Systematic schizophrenias (n = 6)			
DSM-III-R:		*ICD-10:*	
Schizophrenia	6	Schizophrenia	6

Table 2 Schizophrenia spectrum psychoses and zygosity

	Monozygotic twins (ill: n = 34)	Dizygotic twins (ill: n = 30)
DSM-III-R		
Schizophrenia	16 (47.0%)	14 (46.7%)
Schizoaffective disorder	9 (26.5%)	8 (26.7%)
Schizophreniform disorder	5 (14.7%)	3 (10.0%)
Delusional disorder	2 (5.9%)	3 (10.0%)
Atypical psychosis	2 (5.9%)	2 (6.7%)
ICD-10		
Schizophrenia	16 (47.0%)	14 (46.7%)
Schizoaffective disorder	7 (20.6%)	8 (26.7%)
Acute polymorphous psychotic disorder	7 (20.6%)	4 (13.3%)
Delusional disorder	2 (5.9%)	3 (10.0%)
Other non-organic psychotic disorder	2 (5.9%)	1 (3.3%)
Leonhard		
Cycloid psychoses	14 (41.2%)	13 (43.3%)
– anxiety-happiness psychosis	6 (17.6%)	9 (30.0%)
– confusion psychosis	2 (5.9%)	3 (10.0%)
– motility psychosis	6 (17.6%)	1 (3.3%)
Unsystematic schizophrenias	20 (58.8%)	11 (36.7%)
– affect-laden paraphrenia	7 (20.6%)	6 (20.0%)
– cataphasia	2 (5.9%)	–
– periodic catatonia	11 (32.3%)	5 (16.7%)
Systematic schizophrenias	–	6 (20.0%)
– systematic paraphrenias	–	1 (3.3%)
– systematic catatonias	–	2 (6.7%)
– hebephrenias	–	3 (10.0%)

DSM-III-R and ICD-10, there are no significant differences with regard to the frequency of the respective diagnoses among MZ and DZ twins. In the diagnoses according to Leonhard's criteria, on the other hand, there is a more frequent occurrence of unsystematic schizophrenias among MZ than among DZ twins (58.8% and 36.7% respectively). This difference is, above all, due to the different frequency of periodic catatonia (32.3% among MZ twins vs. 16.7% among DZ twins). The complete absence of an overall diagnostic category, i.e., of systematic schizophrenias in MZ twins, is even more striking. In the case of DZ twins, systematic schizophrenia occurred in 20.0% of all ill twins, which is a significant difference compared with the group of MZ twins (test for proportions, $z = 2.67$, $p < 0.01$). All the DZ pairs with an index twin suffering from a systematic schizophrenia were discordant. These results made it impossible to calculate and compare concordance rates for this diagnostic category.

Discussion

This systematic, polydiagnostic twin study on schizophrenia spectrum psychoses did not yield any significant differences between MZ and DZ twins when comparing the frequency of the individual diagnoses according to the criteria of DSM-III-R and ICD-10. Using Leonhard's classification, MZ twins were found to be completely free of systematic schizophrenias, which represent schizophrenias in a strict sense. Leonhard also made this observation in the course of his twin investigations [17], but as he did not carry out any systematic twin ascertainment, he may have overlooked some relevant patients. This, however, seems highly improbable in the present study since a systematic survey was made of all twins hospitalized for schizophrenic psychoses and systematic schizophrenia is a serious illness which almost always requires hospitalization.

In interpreting this remarkable finding, genetic explanations do not seem particularly plausible, especially since systematic schizophrenias exhibit only very slight familial loading [8]. It is also difficult to attribute the absence of an illness in MZ twins to twin-specific intrauterine or birth complications given the fact that this same illness occurs in DZ twins.

In view of these difficulties, Leonhard's hypothesis that there may be psychosocial influences in the development of systematic schizophrenia which are not effective in MZ twins seems worth considering. Psychosocial factors in the etiology of schizophrenia, especially in twins, often refer to the psychodynamic assumption that a diffuse ego boundary [1] contributes to the occurrence of such psychoses. This hypothesis, however, can hardly help explain the etiology of schizophrenic psychoses since twin studies have shown a similar frequency of twins among schizophrenic patients and in the general population. Furthermore, MZ twins do not suffer from schizophrenias any more frequently than DZ twins [1, 10].

In contrast, Leonhard's understanding of psychosocial influences [16] was quite different from that normally applied [19]. He attached great importance to an analysis of sibling interaction. He assumed that an appropriate interaction with the social environment is highly significant for the adequate biological development of higher functional brain systems. The neurobiological considerations of Seitelberger [25] as well as recent findings of O'Kusky [21] and Meisami and Firoozi [18] point in a similar direction. According to these studies, a lack of stimulation from external sources in a critical postnatal phase of development may result in a malfunction or even a complete loss of function in a not properly developed neuronal system. Such a lack of stimulation of higher brain systems above all might occur in the case of a serious communication deficit during critical stages of childhood. It is during childhood, for example, that the ability to monitor the adequacy of one's own spoken message, and thus also to modify these utterances and adapt them to the given situation, is acquired [5]. A deficiency of communication may have a negative effect on the development of such abilities. This is also conceivable of a whole series of other higher mental functions.

One further problem is, how a non-specific factor, such as a lack of communication, can result in many distinct clinical pictures like the various subgroups of systematic schizophrenia. Leonhard assumed there must already be a disposition or „system weakness" in a specific higher functional brain system that is dependent on interaction with environmental stimuli. Such a „system weakness" would not in itself cause the illness, but could determine the target for the biological impairment resulting from a lack of stimulation. It could therefore also determine the distinct clinical picture. The „system weakness" may, for instance, reflect a hereditary disposition [8], but could also occur as a result of pre- or perinatal complications which seem to play an important role in the pathogenesis of systematic schizophrenia [26].

Leonhard thus hypothesized that the absence of MZ twins with systematic schizophrenia might be due to the fact that the close contact and strong pair attachment between MZ twins might guarantee communication of a kind that provides a sufficient external stimulation to prevent a failure of higher functional brain systems. In Leonhard's view, such a failure represents the biological correlate of systematic schizophrenia. The psychosocial situation of MZ twins indeed seems to be different from that of DZ twins and other persons with regard to both the attachment of the partners to each other and their treatment by the environment [12, 20, 24]. The special features of this psychosocial constellation should not remain without an effect on communication and interpersonal interaction, since it could be demonstrated that MZ twins spent significantly more time together and played significantly more often together during childhood and adolescence than DZ twins [20]. Thus, in view of the absence of other conclusive theories, Leonhard's ideas regarding a possible role of a communication deficit between siblings in the etiology of systematic schizophrenias should at least be viewed as a possible explanatory model.

Of course, it is a highly speculative model intended to permit an interpretation of an unexplained empirical observation. It could nevertheless be tested, namely by looking for MZ twin pairs in which the partners were separated or one partner had died in early childhood. The fact remains, however, that the absence of a significant group of schizophrenic illnesses in MZ twins represents a highly remarkable finding that requires explanation and consequently should be investigated further.

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