Periodic catatonia: a schizophrenic subtype with major gene effect and anticipation

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Abstract In a family study involving 139 probands with DSM-III-R catatonic schizophrenia and 543 first-degree relatives, we investigated age-specific morbidity risk according to Leonhard's clinical distinction between systematic and periodic catatonia. This dichotomy is based on different types of symptomatology, course, and outcome. In systematic catatonia the age-corrected morbidity risk was 4.6%. In periodic catatonia, however, there was an age-corrected morbidity risk with homogenous psychoses of 26.9%, and more parents than siblings were affected. This points strongly to a major gene effect in periodic catatonia. Furthermore, a pairwise comparison of patients and their parents revealed patterns of anticipation, i.e., the probands' age at the onset of disease was significantly earlier than that of their parents (P < 0.001). Similarly, anticipation was apparent in pedigrees with three successive generations affected. This inheritance pattern with homogenous psychoses and anticipation indicates that genes with trinucleotid repeat expansion or other repetitive elements affecting gene expression may be involved in the etiology of periodic catatonia. Thus, periodic catatonia as a specific clinical subtype of schizophrenia is a promising candidate for molecular genetic evaluation.

Key words Schizophrenia · Periodic catatonia · Inheritance · Anticipation · Leonhard classification

Introduction

Anticipation refers to the unusual pattern of genetic disorders whose age of onset is progressively earlier in successive generations. This phenomenon, however, tended to be discounted as a biased assessment (Harper et al. 1992). Recently, the discovery of a new form of human mutation provided a specific biological explanation for several inherited diseases with anticipation. In Huntington’s disease, myotonic dystrophy, fragile X-syndrome, spinocerebellar ataxia (SCA 1), and dentatorubral-pallidoluysian atrophy (DRPLA) unstable expansions of trinucleotide repeats were identified in coding/noncoding regions of distinct genes. Repeat length and instability were directly associated with earlier age of onset in successive generations (Ross et al. 1993).

Besides the current psychiatric classification systems (in DSM-III-R), Leonhard (1979) classified schizophrenia between systematic and unsystematic forms based on different types of symptomatology, long-term course, and outcome. This highly operationalized classification system is of outstanding validity and reliability (Astrup 1979; Lindvall et al. 1986; Trostorff and Leonhard 1990; Franzek and Beckmann 1992; Warkentin et al. 1992; Ungvari 1993). Periodic catatonia is one clinical subtype of unsystematic schizophrenia. Its course is typically bipolar in both hyperkinetic as well as akinetic states. Characteristically, symptoms of one pole are mingled with those of the other. The distortion of psychomotor activity leads to grimaces, parakinetik movements, stereotypes, impulsive actions with aggressiveness, and negativistic behavior. This polymorphic catatonic symptomatology is manifest in remittent course. After one or more attacks residual states develop with increasing poverty of movements, blunted affect, and lack of motivation. In contrast, systematic catatonia usually begin insidiously and run a chronic, progressive course without remissions. The irreversible, treatment-resistant residual states of systematic catatonia are clinically well-defined and can be reliably distinguished from periodic catatonia (Franzek and Beckmann 1992). Leonhard reported that the heredity pattern of systematic catatonia is significantly different from that of periodic catatonia. For systematic catatonia he found a positive family history with regard to schizophrenia in 3-4% of patients, whereas approximately 20% with periodic catatonia had a familial loading with homogenous psychoses.
As one part of an extensive family study on systematic and periodic catatonia, we investigated familial aggregation of psychoses among all first-degree relatives for both diseases. We explored the occurrence of anticipation in periodic catatonia and discussed the results with regard to the recent findings on trinucleotid repeat expansions affecting gene expression.

Subjects and methods

Recruitment of patients and diagnostic assessment

Probands were drawn from all consecutively admitted inpatients and from outpatient care at the Department of Psychiatry Wuerzburg University and from wards with chronically ill patients at the Lohr/Main State Hospital. Patients were recruited from April 1991 to October 1992. As a first step, one of us (G.S.) screened the hospital records of 749 patients as to whether they had displayed cata-

onic symptoms cross-sectionally and/or in the long term. A total of 183 patients exhibited catatonic features at least once during their illness. These patients were personally examined by two experienced psychiatrists (E.F. and H.B.) independently working and diagnosed along the lines of Leonhard’s nosology. The case notes that were at their disposal did not contain any information about familial affiliation. In a subsample of 32 patients both investigators had a coefficient of agreement of 0.93 (Cohen’s Kappa) within Lohr. This corresponds to the high interrater reliability of a previous study (Franzek and Beckmann 1992). Of the 183 patients, 44 did not fulfill diagnostic criteria of either systematic or periodic catatonia. Thus, the final diagnostic group consisted of 139 probands. All of them met the diagnostic criteria of schizophrenia of the catatonic type according to DSM-III-R. There were 83 patients (42 males and 41 females) with periodic catatonia and 56 patients (42 males and 14 females) with systematic catatonia. In periodic catatonia the mean age at the time of assessment was 46.5 years (SD ± 16.8 years). The mean duration of the disease was 22.7 years (SD ± 15.0 years). The mean age at first hospitalization was 24.8 years (SD ± 9.6 years). Men were insignifi-

antly younger at the time of first hospitalization (23.2 years; SD ±

8.0 years) than women (26.5 years; SD ± 10.8 years).

In 56 patients with systematic catatonia the mean age at the time of study was 40.7 years (SD ± 14.1 years). The mean duration of the disease was 21.0 years (SD ± 13.7 years), and the mean age up on initial hospitalization was 20.8 years (SD ± 7.0 years) with no difference in age up on initial hospitalization between women (20.7 years; SD ± 7.8 years) and men (20.8 years; SD ± 6.9 years).

This study was approved by the appropriate ethics committee and was performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

Evaluation of morbidity risk in first-degree relatives and anticipation

In order to get reliable data concerning morbidity risk, age at first hospitalization, and familial psychopathology, we only allocated relatives with documented psychiatric hospitalization to the group of affected family members. Hospital records were available for all these relatives. Extensive pedigree data were conducted on each patient’s family. In order to exclude multiple ascertainment, consecutively admitted members of a proband’s family were not considered as probands. The multiinformant family psychiatry history was not applied in this report (Weissmann et al. 1986).

Definition of the age of onset in mental illnesses is a matter of debate (DeLisi 1992). Because of the fact that all hospital records could be traced, we decided to use age up on initial hospitalization to define age of onset. This is a rather conservative approach defining the age of onset. However, periodic catatonia usually begins with acute and severe hyperkinetic or akinetic attacks that nearly always lead to hospitalization (Astrup 1979; Franzek and Beckmann 1992). Therefore, in most cases of periodic catatonia the age of first hospitalization coincides with the time of the onset of disease. Systematic catatonia, however, begins insidiously in most cases. Therefore, age of onset of the systematic catatonic probands may be lower than estimated with this method.

In order to analyze anticipation (progressively earlier age of onset in successive generations), we included only probands with definite unilinear parental transmission. Patients whose parents were both affected were excluded. The appearance of anticipation in these patients might be the result of an additive effect of disease genes from both parental lines.

Results

Life-table analysis of morbidity risk in first-degree relatives

Figure 1 shows that the age-specific morbidity risk for schizophrenia was substantially greater for first-degree relatives of patients with periodic catatonia than for patients with systematic catatonia. Probands with systematic catatonia had 220 first-degree relatives (parents and siblings). Four of 109 parents and 3 of 111 siblings were affected. The age-corrected morbidity risk for relatives of systematic catatonic patients was at a level of 4.6%. Probands with periodic catatonia had 323 first-degree rel-

Statistical methods

A difficult statistical problem in family studies is the fact that relatives do not constitute strictly independent data points. This has remained unresolved in recent family studies on schizophrenia (Kendler et al. 1993; Maier et al. 1993). In this report we also decided to consider the generations as one group of relatives for each schizophrenic subgroup. The life-table analysis was used to examine age-specific morbidity risk (Kaplan-Meier estimates). The difference in life-table curves was determined by the log-rank χ² statistic with 1 df. Pairwise intergenerational differences (age at first hospitalization among parents and probands) were compared using nonparametric Wilcoxon matched-pairs statistics and Spearman rank correlation.

Figure 1 Morbidity risk in systematic catatonia and periodic catatonia. Systematic catatonia revealed no evidence of increased familial aggregation in schizophrenia in 220 first-degree relatives. The age-corrected morbidity risk was 4.6%. In contrast, periodic catatonia followed a pattern of dominant inheritance. The age-specific morbidity risk among 323 first-degree relatives was 26.9%, and there were more affected parents than siblings. The morbidity risk in the two schizophrenic subgroups was different at a level of P<0.0001 (life-table analysis)