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The Impact of Gender and Age at Onset on the Familial Aggregation of Schizophrenia

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Summary. Some recent family studies have shown that the familial risk for schizophrenia is higher in female than in male schizophrenics. It is debated whether the risks for the other disorders, such as schizotypal personality disorder or affective disorders in families of schizophrenics are similarly influenced by the proband's gender. Also, the reason for the effect of proband's gender on the recurrence risk for schizophrenia has not been clarified. This family study (159 probands, 589 first degree relatives) confirms that schizophrenia, but also schizophrenia spectrum disorders were more frequent in families of female compared with male schizophrenics. Neither age at onset in probands nor the interaction between gender and age at onset in probands had a relevant impact on the risk figures in relatives. Affective disorders occurred in families independently of the probands' gender. Aetiological heterogeneity or ascertainment bias may account for the modifying effect of proband's gender in schizophrenia.

Introduction

Increasing evidence emerging from studies on the onset, the follow-up, and treatment response has revealed that schizophrenia is expressed differently in male and in female subjects. Moreover, various putative aetiological and risk factors of schizophrenia have been claimed to exert a sex-specific effect on schizophrenia. A major contribution to this assumption are family studies reporting a lower familial recurrence rate of schizophrenia in male compared with female schizophrenics. Whereas most of the family studies do not report recurrence rates as a function of probands' gender, three of them support this variation of the familial risk by the schizophrenic proband's gender (Bellodi et al. 1986, Goldstein et al. 1990, Wolyniec et al. 1992). Only one of these three studies directly interviewed most of the living relatives (Goldstein et al. 1990, referring to the Iowa 500 study), but owing to the particular recruiting procedure nearly half of the first-degree relatives were dead. The remaining two family studies used the family history technique which is associated with a higher diagnostic error rate. One study (Goldstein et al. 1990) reported a significant excess of schizophrenia in family members of female schizophrenics compared with male schizophrenics. This study also considered the familial risk for other psychotic and spectrum disorders; these disorders, though being closely related to schizophrenia, were not more frequent among relatives of female probands than in relatives of male probands; the figures for schizotypal personality disorder rather point in the opposite direction. The two other family studies mentioned that used the family history approach were not able to clarify the impact of probands' gender on less severe disorders like schizotypal personality disorder.

More specifically, an effect of the interaction between proband's gender and age at onset on the familial risk has recently been proposed. Although a strong relationship between the variation of age at onset and familial risk could not be observed in the previous literature (Kendler et al. 1987) Pulver et al. (1990) found excess familial risk for schizophrenia in male schizophrenic probands with early age at onset as compared with those with late onset, whereas age at onset and familial recurrence risk did not systematically correlate in female index cases.

Another suggestion concerning the impact of the interaction between gender and age at onset emerged from the discussion of the neurodevelopmental basis of schizophrenia (Castle and Murray 1991): it has been proposed that late onset schizophrenia in women might have more in common with affective disorders than it would have with early onset schizophrenia. Assuming this suggestion to be true, gender differences in familial recurrence rates should in particular be due to early onset cases. Furthermore, an excess morbidity of affective disorders might distinguish relatives of female late onset schizophrenics from relatives of early onset cases.

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Empirical support of these suggestions and of a gender-age interaction effect in probands on familial risks is scanty, as very few family studies in schizophrenia are informative on the significance of this interaction effect, in particular with regard to the risk for affective disorders in families. Family studies based on comprehensive direct interviews in most of the relatives including a sufficient number of schizophrenic probands of both gender with a broad variation of age at onset are required to test these hypotheses.

Method

Procedure

This report refers to inpatients with schizophrenia (RDC, Spitzer et al. 1978) and their families who were part of a more comprehensive family study in a cohort of 725 inpatients (between 20 and 65 years of age) consecutively admitted to the Department of Psychiatry, University of Mainz. This hospital serves a mainly urban area. A State Hospital is also located in the same district. There is no preferential reference of first-episode schizophrenics to either of the two hospitals; however, with an increasing number of rehospitalizations patients are preferentially referred to the State Hospital.

Recruited patients were screened with the Schedule for Affective Disorders and Schizophrenia (SADS-LA) for lifetime diagnoses (RDC) of schizophrenia, schizoaffective disorder, major affective disorders, alcoholism, or panic disorder. Patients with these diagnoses were included in the family study if at least one living first-degree relative older than 17 years agreed to be directly interviewed with regard to his and his families' psychiatric morbidity. Furthermore, it was required that the proband would not suffer from recognized organic diseases presenting as major psychiatric syndromes ($n = 629$). One hundred and fifty-nine patients who met the criteria received a lifetime diagnosis of schizophrenia. N = 14 patients with schizophrenia were excluded as there was not a single relative available for direct interview (7 of them had no living first-degree relative at all). Interviews by telephone were not counted as direct interviews. Fifty-two percent of the 159 schizophrenic patients included were male; mean current age was 37.1, SD 11.4 years with 34.9 years in males and 40.2 years in females. Mean age at onset was 26.4, SD 9.2 years with 24.9 years in males and 27.8 years in females.

Psychopathological Assessment

Personal interviews in probands and their relatives were conducted using an extended version of the SADS-LA (Mannuzza et al. 1986), an interview which was used in the majority of recently published family studies. It collects information on signs and symptoms necessary to make RDC diagnoses. The schizophrenia section of the SADS-LA was supplemented by corresponding sections of the Composite International Diagnostic Interview (CIDI) (Robins et al. 1989). The probands' relatives were also asked for the history of psychiatric syndromes in the other members of the same family to be assessed (with the exception of the proband) by using the family history approach (Mannuzza et al. 1985). The family history method provides a semi-structured interview for RDC and DSM-III diagnoses of major affective, schizoaffective, and psychotic disorders, and of alcoholism, drug abuse, and eating disorders; minor and personality disorders are not included. Personality disorders in probands and relatives were assessed with the Structured Clinical Interview for DSM-III Personality Disorders (SCID-II) (Spitzer et al. 1990).

The personal interviews and the family history assessments were conducted by 11 research assistants (advanced medical students with clinical experience in psychiatry, or young physicians) after a common training of at least 20 sessions with all instruments to be used. Test-retest reliabilities for all diagnostic categories to be discussed in this paper were tested separately and were acceptable (kappa-values higher than 0.75) (Leboyer et al. 1991).

Investigation of Family Members

More than 81% of the living first-degree relatives older than 17 years were personally interviewed with the SADS-LA (Mannuzza et al. 1986) and the SCID-II (Spitzer et al. 1990) (Table 1). Diagnostic information on those of the probands' first-degree relatives who refused to be interviewed or who were dead was obtained by family history method from at least one informant per family. The interviewers were blind to the probands' diagnostic status. Medical records were also collected if we had consent to do so.

In order to control for an underreporting of morbidity in family members who were not directly interviewed, only those with valid diagnostic information were identified as relatives in this report; it was required that the relative was directly interviewed or that one of the directly interviewed relatives was sufficiently familiar with the relative on whom he reported (i.e. had lived together in close relationship with him for at least a minimum period of time). In particular, a parent was excluded who had already died when the index subject and his surviving siblings were young (< 10 years) if

Table 1. Description of the sample of first degree relatives under study by probands' gender and age at onset

	Characteristics of relatives by probands' type					
	Relatives of *male* schizophrenics with age at onset of			Relatives of *female* schizophrenics with age at onset of		
	<20 years	20–30 years	>30 years	<20 years	20–30 years	>30 years
Number of probands	30	30	23	21	28	27
Total number of relatives (≥17 years)	114	110	99	76	117	126
Total number of relatives with valid diagnostic information (included)	109	104	82	72	113	109
Mean age (years)	41.8	51.7	54.6	41.9	50.1	54.8
% Male	51.0	50.0	48.0	49.1	48.9	46.3
Number of living first degree relatives	98	86	72	68	104	93
Number of directly interviewed relatives	80	72	64	55	85	81
Mean age (years)	39.9	45.0	51.2	38.6	43.5	48.0
% Male	53.0	50.0	49.5	52.0	50.0	49.2

the second parent was not available for interview. This constellation was preferably seen in index cases born before or shortly after the Second World War. Also, most of the children of index cases who were adopted away and who had lost contact with their biological parents and sibilings were excluded. Table 1 indicates that the proportion of relatives excluded for these reasons was dependent on the proband's age yet did not systematically vary with the gender of the index case (8.0% for male probands and 8.3% for female probands). Altogether, we collected diagnostic information on 589 first-degree relatives of 159 schizophrenic probands.

Final Diagnostic Assessment

This report is based on diagnoses as defined by the Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) for axis-I disorders and selected personality disorders as defined by DSM-III (American Psychiatric Association 1980). Diagnostic assessments were based on the best estimate procedure (Leckman et al. 1982): two experienced psychiatrics combined the information obtained by personal interview (if available), family history information obtained by all sources available, and the case notes (as fas as available) and made a final diagnosis using the RDC manual. The same procedure was applied to probands and relatives; the best estimate procedure was performed independently for probands and relatives. Diagnostic assessments to be reported are lifetime diagnoses following a hierarchical procedure: schizophrenia takes priority over schizoaffective disorders which is followed by bipolar and then by unipolar major affective disorders.

Statistical Methods

Survival analysis (Cox regression model) was used in order to test the impact of gender and age at onset in probands (independent variables) on the risk to develop schizophrenia or other disorders in relatives. The dependent variable (risk to develop a psychiatric disorder in relatives) was defined as either time to onset of the disorder if the relative was affected, or it was censored at current age if the relative was not affected. The Cox regression model simultaneously controls for variable age and age at onset in relatives and allows to control for further variables that might confound the prevalence rate of the disorder in relatives by introducing these variables as co-variates. Besides gender and age at onset in probands, the subsequent analyses regularly included as additional co-variates the relatives' interview status, type of relationship (parent, sibling, child), and gender in relatives as co-variates. Age at onset as an independent variable was transformed into a categorical variable (<20 years, 20–30 years, >30 years). The significance of the effect of a co-variate on the risk in relatives was tested by standard methods (Lee 1980).

Results

Twenty-three (10 males and 13 females) of the 589 first-degree relatives of schizophrenic probands presented with a lifetime diagnosis of schizophrenia. The recurrence risk for schizophrenia (unadjusted for age) was 3.9% (3.8% in male and 4.0% in female relatives). The age adjusted familial lifetime risk (Stroemgren-Weinberg method) was 5.1% (4.9% for males and 5.3% for females). Previous family studies in schizophrenia have reported similar or lower recurrence rates (Kendler 1988).

The recurrence risk was 2.4% (7/295) in families of male schizophrenic probands and 5.4% (16/294) in families of female schizophrenic probands. Table 2 presents the unadjusted rates of schizophrenia in parents, siblings, and children by the schizophrenic probands' gender. Irrespective of the type of relationship between proband and relative male probands carried a lower familial risk than female probands. It is noteworthy at this point that the siblings' mean age was 48.5 years, whereas the children's mean age was 23.9 years. Therefore, the majority of children have not yet passed the age at risk. The lower age of children compared with siblings explains the lower prevalence of schizophrenia among children of schizophrenics compared to their siblings. As expected, the recurrence rates in parents of schizophrenics were lower

Table 2. Rate of schizophrenia (%, unadjusted) in parents, siblings, and children of male and of female schizophrenic probands

Probands' gender	Recurrence rate in relatives					
	Fathers	Mothers	Brothers	Sisters	Sons	Daughters
Male	0% (0/69)	0% (0/72)	7.1% (4/56)	3.6% (2/55)	0% (0/20)	4.3% (1/23)
Female	2.9% (2/68)	2.8% (2/71)	7.3% (3/41)	12.5% (5/40)	5.9% (2/34)	5.0% (2/40)

Table 3. Lifetime prevalence of disorders (%, unadjusted, and frequencies) in first degree relatives of probands with schizophrenia by probands' gender and age at onset

Disorders (RDC) in relatives	Disorders in relatives (%) by probands' type					
	Male probands with age (years) at onset of			*Female* probands with age (years) at onset of		
	<20 (n = 109)	20–30 (n = 104)	>30 (n = 82)	<20 (n = 72)	20–30 (n = 113)	>30 (n = 109)
Schizophrenia	2.8% (3)	1.9% (2)	2.4% (2)	6.9% (5)	5.3% (6)	4.6% (5)
Schizotypal personality disorder	0.9% (1)	1.0% (1)	0% (0)	2.8% (2)	0.9% (1)	0.9% (1)
Other non-affective psychotic disorders	0% (0)	1.0% (1)	1.2% (1)	1.4% (1)	1.8% (2)	0% (0)
Schizoaffective disorder	2.8% (3)	3.8% (4)	1.2% (1)	2.8% (2)	0.9% (1)	2.8% (3)
Bipolar disorder	1.8% (2)	1.0% (1)	2.4% (2)	1.4% (1)	1.8% (2)	0.9% (1)
Unipolar major depression	11.0% (12)	11.5% (12)	12.2% (10)	12.5% (9)	13.3% (15)	14.7% (16)

than in siblings and children (Kendler 1988). Given the relatively low number of parents and the low expected risk of schizophrenia in relatives the absence of schizophrenia among parents of male schizophrenics may be due to random variation.

Apparently, the relative's gender had no impact on the difference between the recurrence risks of female versus male probands (Table 3). As indicated by Table 4, Cox regression analysis corroborated this view: the proband's gender ($P = 0.04$), but not the relative's gender ($P > 0.10$) was of significant impact on the risk for schizophrenia in relatives (controlling for interview status in relatives, age at onset, and duration of illness in probands).

Age at onset was defined to the year of the first psychotic symptoms, and probands were subdivided according to intervals of age at onset as proposed by Kendler et al. (1987). Cases with an age of onset < 20 years were compared with those with an age at onset > 30 years. The impact of age at onset in probands on the risk of schizophrenia in relatives is demonstrated in Table 3 (first line). It is evident from this table that probands with early onset schizophrenia convey a modestly higher familial risk for schizophrenia than probands with later onset schizophrenia, irrespective of the proband's gender. Cox regression analysis (Table 4) indicated that after controlling for the proband's gender, interview status in relatives, and relatives' gender, the effect of age at onset in probands (defined as a continuous variable) shortly failed to be significant ($P = 0.09$). The introduction of an additional interaction term "probands gender by probands' age at onset" indicated no significant additional burden on the recurrence risk in relatives ($P > 0.10$), either.

Table 3 also shows the impact of gender and age at onset in probands on the risk for non-affective psychoses, schizotypal personality disorder, and affective disorders in relatives. The prevalence of schizotypal personality disorder was low in families of schizophrenics, and therefore the distribution by gender and age at onset in probands was prone to random fluctuation. Nevertheless, the figures for schizotypal personality disorder revealed a higher incidence in relatives of female schizophrenics with early age at onset. This effect was not significant ($P > 0.10$) in the Cox regression analysis (using time to onset of schizotypal personality disorder or, alternatively, age as the dependent variable); the lack of significance is partly due to the low base rate of schizotypal personality disorder.

The unadjusted rates of affective disorders in various subgroups of relatives by probands' subtype, displayed in Table 3, were not systematically influenced by probands' gender. It also appeared that age at onset in probands did not systematically co-vary with the familial risk for affective disorder irrespective of whether the proband was male or female. After controlling for interview status and gender in relatives in the Cox regression analysis, the proband's gender failed to be of significant impact on the risk for affective disorder (unipolar or bipolar) in relatives ($P > 0.10$). Analogous results were obtained for the risk of schizoaffective disorders in relatives ($P > 0.10$). The same analysis also revealed that age at onset in probands and the interaction "probands' age at onset by probands' gender" had no effect on the familial risk for affective disorder or for schizoaffective disorder ($P > 0.10$).

Table 4. Effect of gender and age at onset in schizophrenic probands on the risk of schizophrenia in relatives: Cox regression analysis

Independent variables (stepwise):	*Dependent variable:* Time to onset of schizophrenia in relatives	
	Hazard ratios[a] (Odds ratios)	Significance by chi-square test
Relatives' interview status	1.11	$P > 0.10$
Generation	1.69	$P = 0.08$
Gender in relatives	0.82	$P > 0.10$
Gender in probands	1.92	$P = 0.04$
Age at onset in probands (<20 years, 20–30 years, >30 years)	0.72	$P = 0.08$
Age at onset in probands by gender in probands (interaction)	1.21	$P > 0.10$

[a] For dichotomous variables, this corresponds to relative risks; for continuous variables, this is the multiplicative change in relative risk associated with a unit change in the covariate

Discussion

This study contributes to the growing evidence that the risk for schizophrenia is elevated in relatives of female compared with male schizophrenic probands. So far, the reports by Goldstein et al. (1990), Wolyniec et al. (1992), and Bellodi et al. (1986) are supported, but not so Loyd et al. (1985). Furthermore, the consistency of this finding was strengthened as a similar trend was demonstrated for nonaffective psychotic disorders including schizotypal personality disorder. However, in this respect we could not replicate the observation by Goldstein et al. (1990) that schizotypal personality in relatives counteracted the trend of a higher familial load in female compared to male schizophrenics. This discrepancy is surprising given the high degree of similarity with regard to the recurrence risk of schizophrenia for relatives of male (2.4% compared to 2.2%) versus relatives of female schizophrenics (5.4% compared to 5.2%). Nevertheless, it is worthwile to note that in both studies the baserates for schizotypal personality disorder are rather low and, therefore, random fluctuations have a considerable chance to blur the true figures.

With regard to the familial risk for major affective disorders, the present study is in line with the Iowa study: as has already been reported by Goldstein (1988), no significant impact of probands' gender on the rate of major affective disorders in families was observed. In contrast to these studies, the paper by Pulver et al. (1990) reported a trend to a higher risk for unipolar depression in families of early onset male probands; however, this

trend failed to be significant. Given the lack of significance, this divergency might be due to random fluctuation. An alternative explanation might be that Pulver et al. (1990) completely relied on the family history method which might underestimate the risk of psychiatric illness in relatives, especially so in less severe disorders as, for example, in affective disorders. Therefore it cannot be excluded that an underreporting of impairment could operate differently in different proband groups which might explain Pulver's et al. (1990) finding.

Similar to a summary from the previous literature (Kendler et al. 1987), we could not find strong evidence for age at onset in probands co-varying with the degree of familial loading. However, consistently with a part of previous family studies, a trend in favour of a negative correlation between age at onset and degree of familial loading was observed. This trend operated independently of the proband's gender.

In particular, the interaction between gender and age at onset in probands had no impact on the degree of familial loading with schizophrenia. This conclusion clearly contradicts an observation derived from the Baltimore study that early-onset male schizophrenics carried a higher familial risk than late-onset male schizophrenics, whereas the familial risk conveyed by female schizophrenics was independent of the age at onset (Pulver et al. 1990). Again, different methodologies applied in the two studies may explain these differences. A crucial problem in both studies might be the retrospective dating of age at onset in probands. Although case records and direct interviews were used for assessing the age at onset, a considerable error rate might have been unavoidable if the interval between current age and age at onset was long. As no further previous family studies have examined the effect of the interaction between gender and age at onset on the familial loading, further investigations are required for clarification of this issue.

The lack of a significant effect of the interaction between probands' gender and age at onset in probands on the familial risk for schizophrenia as well as on the familial risk for affective disorders argues against the hypothesis that late-onset female schizophrenics are etiologically more related to affective disorders than to "true" schizophrenia (i.e. early-onset schizophrenia in males) (Castle and Murray 1991). However, given the limited sample size and the relatively low prevalence rates it has to be conceded that the power inherent in this sample might not be sufficient to detect the impact of an interaction on the familial risk.

Conclusion

The excess morbidity of schizophrenia in families of female versus male schizophrenic probands as it has now been reported in four family studies requires an explanation.

Four alternatives might be relevant:

1. Different family structures in female and male probands. Female schizophrenics are more likely to be married (Häfner et al. 1989) and tend to have more children (see also Table 3). Consequently, the morbidity in parents contributes less to the familial risk when the proband is female. Given the lower risk for schizophrenia in parents compared to siblings and children as it has consistently been found by the vast majority of family studies (Kendler 1988), the higher number of children of female probands might explain gender differences in recurrence rates. However, Table 3 of this report as well as the Iowa study (Goldstein et al. 1990) and the Baltimore study (Wolyniec et al. 1992) indicate that different numbers of children cannot fully explain the excess familial loading in female probands. Other family studies did not report rates of schizophrenia in children separately.

2. Genomic imprinting. This concept describes the modification in the expression of genes or alleles determined by the transmitting parent's gender (Hall 1990). This phenomenon frequently occurs in human genetics. Assuming a genetic basis of at least a subgroup of schizophrenia, genomic imprinting could account for the excess familial morbidity in female versus male schizophrenics by a suppressed expression of the disorder when it is transmitted from male probands (fathers) to their offspring. Table 2 of this report does not support this view as the risk in children of affected fathers is very similar to the risk in children of affected mothers.

3. Gender specific thresholds on a dimension of liability (Carter effect). Most of the segregation analyses in schizophrenia are compatible with a multifactorial mode of familial transmission (Kendler 1988). This model assumes an underlying dimension of liability reflecting the combined strength of genetic and environment aetiological factors. This dimension is transmitted in families in a way that subjects affected with higher liability are more likely to be related to relatives with a higher mean liability. A particular threshold on this dimension indicates that subjects with liability scores beyond this threshold will receive a lifetime diagnosis of the disorder under study. This model has been found to explain a higher prevalence of pylorus stenosis in males (Carter effect). The assumption of sex specific thresholds predicts (a) that the lifetime prevalence of the disorder differs among genders, and (b) that the recurrence rate is higher among the relatives of probands belonging to the most stringently defined type of the disease. An application of our data to this prediction resulted in a more restrictive threshold of schizophrenia for females compared to males. Another prediction of this model applied to the present study is that (c) male relatives of a particular proband are more likely to present with schizophrenia than female relatives. Whereas it is controversial whether schizophrenia is more common in males than in females (Häfner et al. 1989, Castle and Murray 1991), this report and others (e.g. Goldstein et al. 1990) argue for the independence of the recurrence risk of the relative's gender. Consequently, this proposed explanation is unlikely to be true.

4. Aetiological heterogeneity. It is generally assumed that the aetiology of schizophrenia is heterogeneous. Various

aetiological factors might contribute differently in the two genders: whereas familial factors might operate independently of gender, factors unique to particular subjects that are not shared by the family members (e.g. non-familial obstetric complications) might more frequently operate in male cases (Castle and Murray 1991). As a consequence, male cases are less frequently familial than female cases. Given that the recurrence risk in families will affect male relatives to the same extent than female relatives, this assumption predicts a gender specific difference in the lifetime prevalence with males showing higher rates. The literature on the epidemiology of schizophrenia is ambiguous in this respect: whereas the majority of surveys reported equal prevalences for the two genders, the remaining surveys found a male preponderance (Häfner et al. 1989). Consequently, the thesis of aetiological heterogeneity might explain the observed figures; however, strong evidence for this option is lacking.

5. Sporadic cases in females might be less likely to be hospitalized. The available literature shows that female schizophrenics present with a less severe course than male schizophrenics (Goldstein 1988, Angermeyer et al. 1990). Female cases might be provided with more protective factors or with more efficient coping strategies. Alternatively, protective factors might be more active in females (Häfner et al. 1991, Childers and Harding 1990).

These modifying factors might especially prevent those females with a less impaired familial background (i.e. with less familial loading) from being hospitalized. All family studies available have been conducted in samples of hospitalized index cases; therefore, the validity of this putative explanation cannot be explored by these family studies.

6. Vulnerability of schizophrenia might be expressed as schizoaffective disorder more frequently in females than in males. An elevated lifetime risk for major depressive disorder in females compared to males has been found in nearly all epidemiological samples. This often replicated finding might indicate a stronger female tendency to react with major depression to distress and adverse events. The occurrence of delusions and hallucinations or their psychosocial consequences in females might trigger the syndrome of depression more often than in males. As a consequence, females will more often receive the diagnosis of schizoaffective disorder according to the operationalized diagnostic schedules; the higher prevalence of schizoaffective disorders in females points in this direction. This alternative expression of the liability to schizophrenia might predominantly occur among females with less familial loading which might explain the higher familial loading among females diagnosed as schizophrenia cases compared to males with this diagnosis.

Whereas the first three of the proposed explanations for a higher recurrence risk in female as compared with male schizophrenics are unlikely to be true, the data available cannot discriminate between the last three proposed explanations. Systematic assessment of non-familial risk factors in family studies as well as the assessment of familiality in cases identified by epidemiological studies may clarify this issue.

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