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Early-onset major depression in parents and their children

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Summary

In a study of 6–23-year-old offspring of depressed and of normal parents, an inverse relationship between the rates of major depression among the children and the age of onset of major depression in their proband parents was found. The children of parents who had an onset of major depression that was younger than age 20 years overall had the highest risk of major depression. There was specificity in the findings in that these higher rates were nearly all accounted for by prepubertal onsets of major depression in their children. There was a 14-fold increased risk of onset of depression before age 13 in the children of probands who had onset less than age 20. These results were not confounded by the current age of the proband or the children, by interview status (children were interviewed), by comorbidity in the parents or by assortative mating. Future family genetic studies should examine the rates and patterns of illness of the biological relatives of probands with prepubertal-onset major depression.

Key words: Major depression; Parents and children; Early onset

Introduction

In a previous report of a study of the relatives of probands with major depression and of normal controls, we found an inverse relationship between the age of onset of major depression in the probands and the risk of major depression in their relatives (Weissman et al., 1984b). The earlier the age of onset of major depression in proband, the higher was the risk in relatives. The relatives of probands whose onset of major depression occurred when they were younger than 20 years of age had the highest risk of major depression when compared with the relatives of probands with a later age of onset of major depression or with relatives of normals. In fact, probands with a first onset of depression after age 40 had familial loadings of major depression that were only slightly higher than families of normal controls. This study

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suggests that early age of onset increased the risk of major depression as well as the specificity of transmission of early-onset major depression. There was an eightfold increase of early-onset major depression in the relatives of the probands who themselves had early-onset major depression as compared to the relatives of controls. These effects held even after controlling for possible confounding effects such as the distribution of the relatives' current age, family size, assortative mating, and demographic and clinical characteristics.

In our previous studies of families, the offspring under 18 years of age were not directly interviewed, and information was based on a family history obtained primarily from the mother. In this current study, the data are based on direct interviews with the children and with the parents about the children, as well as on school and medical records from which child psychiatrists' best estimates of the child's diagnoses were derived. More specifically, we examine the relationship between the age of onset of major depression in the proband parent and the rates and age of onset of major depression in their offspring who were 6 23 years of age at the time of the interview.

Method

Probands

The proband parents derive from the family study of major depression which includes 215 probands, 133 with a history of treated major depression, and 82 normal (never psychiatrically ill) controls drawn from a community survey. For complete methodology of the proband selection, see Weissman et al. (1982, 1984b) and for complete methodology and findings with regard to the offspring, see Weissman et al. (1986, 1987).

The probands were white and were group-matched by age and sex. Diagnostic data on the probands were obtained through direct SADS-L interviews, multiple relatives and clinical records. The criteria for major depression were modified to be more stringent than the RDC so that 4 weeks of symptoms and evidence of impairment in major social role were required. The test–retest reliability of age of onset of major depression over 4 years was examined in a separate analysis of 143 adult probands and relatives, and was found to be excellent (intraclass correlation 0.71). There was a tendency for older respondents (ages 45+ years) to systematically increase the age of onset of their depression across the two interviews, but the increase was only a few years (Prusoff et al., 1988).

At the time of the original study, 104 of the 215 probands had children between the ages of 6 and 17 years. Because 6 years had elapsed, offspring who were under the age of 18 at the time of the initial study were as old as age 23 at the time of the reinterview. Thus, those probands with offspring ages 6–23 at the time of the current study were included in these analyses. Of 104 eligible probands, 91 (87%) with 220 offspring agreed to participate. Three probands in the normal groups found to have developed a major depression since their participation in the earlier study were excluded from the normal groups and were included in the depressed groups. The final sample of 91 probands and 220 offspring included: 32 normal probands who had 83 children; 10 probands with onset of major depression before age 20 who had 19 children; 20 probands with onset of major depression between ages 20 and 29 who had 44 children, and 20 probands with onset age 30 and later who had 74 children. A separate paper on this issue will deal with the findings in children by parental concordance in diagnosis (Merikangas et al., 1988).

Assessment of children

The diagnostic assessment of the children was made with the Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Epidemiologic Version (K-SADS-E) (Puig-Antich et al., 1985; Orvaschel et al., 1982); test–retest reliability among prepubertal children (Chambers et al., 1985) and inter-informant reliability among adolescent inpatients (Gammon et al., 1983) have been demonstrated for it. The K-SADS-E is the core of a comprehensive interview that we assembled to be administered to a parent about the child and the child about him/herself.

Child psychiatrist best-estimate diagnosis

As in the adult sample, a best-estimate diagnostic procedure was employed for making the final diagnosis of the child (Leckman et al., 1982). A

child psychiatrist and a psychologist, who had not been involved in the interviewing process and were blind to the clinical status of the parent, reviewed all sources of information (i.e., parent's, child's, teacher's and pediatrician's reports, and clinical records when available) and independently assigned a diagnosis. The initial level of agreement between the two best estimators on child diagnoses was 83%. Discrepancies in diagnoses by the independent final evaluators were resolved by arriving at a consensus. The consensus was used for the best-estimate diagnosis.

The reliability of the best-estimate procedure was tested in a separate study. A second child psychiatrist reviewed all available information on 38 randomly selected children and made best-estimate diagnoses. Agreement between the two psychiatrists on child's diagnosis was excellent, with Kappas as follows: major depression 0.89; any attention deficit disorder 0.87; any conduct disorder 0.93; any anxiety 0.69; any substance abuse 0.92; and any diagnosis 1.0.

The best-estimate methods described above differed from those used in the original development of the K-SADS which was a consensus method based on reconciling differences between parents and children at interview.

Data analysis

In order to investigate the association between early-onset depression in probands and early-onset (< 13 years) depression in children, controlling for age and sex of child, proportional hazards models were applied to the data on children of depressed probands as follows.

(1) A proportional hazards model was run with the outcome variable being depression with a first onset at < 13 years. Age of onset of disorder was treated as a survival time, with censoring occurring when no disorder appears by the end of the follow-up period. The follow-up period was considered to be from birth to age at interview for those less than 13 years of age, and birth to 13 years for those greater than 12 years of age. Results obtained from this analysis give the relative risks of having early-onset depression in children of early-onset probands vs. children of late-onset probands.

(2) A proportional hazards model was also run with the outcome variable being major depression with a first onset $\geqslant 13$ years. The follow-up period here was considered to be the time between age 13 and age at interview; as a result, children whose age at interview was less than 13 years or children who had a first onset at < 13 years were not included in this analysis. Results obtained from this analysis give the relative risk of having late adolescent-onset (> 13 years) depression, in children of early-onset probands vs. children of late-onset probands.

Comparison of these two relative risks will indicate whether or not there is an association between early-onset depression in probands and early-onset depression in their children, or whether early-onset depression in probands increases the risk of depression in their children, regardless of the child's age at onset.

Results

Characteristics of the sample

There were 220 eligible children from 91 families. The majority of children were over the age of 11 (Table 1). The mean age was 17 years and there

TABLE 1

AGE AND SEX OF CHILDREN STRATIFIED BY PROBAND'S CLINICAL STATUS AND AGE OF ONSET OF MAJOR DEPRESSION

Figures in parentheses are percentages.

Sex and age (years) of children	Age of onset (years) of major depression in probands			Normals	Total
	< 20	20–29	30+		
Boys					
6–11	2 (0.5)	5 (11.4)	10 (13.5)	3 (3.6)	
12–18	3 (15.8)	7 (15.9)	12 (16.2)	17 (20.5)	
19–23	1 (5.3)	10 (22.7)	19 (25.7)	16 (19.3)	
Girls					
6–11	2 (10.3)	5 (11.4)	1 (1.4)	7 (8.4)	
12–18	6 (31.6)	9 (20.5)	13 (17.6)	25 (30.1)	
19–23	5 (26.3)	8 (18.2)	19 (25.7)	15 (18.1)	
Number of children	19	44	74	83	220
Number of probands	10	20	29	32	91

N.S. Differences in age and sex of child by proband groups.

TABLE 2

PROBAND CHARACTERISTICS BY PROBANDS' AGE AT ONSET OF MAJOR DEPRESSION

N = 91; figures in parentheses are percentages.

Characteristics of probands [a]	Age of onset (years) of major depression in probands			Normals
	< 20	20–29	30+	
Numbers	10	20	29	32
Mean age (years)	43.9	41.9	48.8	46.0
Sex of proband				
Female	4 (40.0)	14 (70.0)	16 (55.2)	18 (56.3)
Education of proband				
More than high school	1 (10.0)	5 (25.0)	5 (18.5)	3 (10.0)
Marital status				
Married/remarried	6 (60.0)	6 (31.6)	23 (82.1)	26 (83.9)
Separated/divorced/widowed	4 (40.0)	14 (68.4)	6 (17.9)	6 (16.1)
Number of marriages				
One	9 (90.0)	13 (65.0)	23 (79.3)	29 (90.6)
Two or more	1 (10.0)	7 (35.0)	6 (20.7)	3 (9.4)
Social class [b]				
I, II, III	7 (70.0)	8 (40.0)	1 (37.9)	6 (50.1)
IV	3 (30.0)	11 (55.0)	14 (48.3)	14 (43.8)
V	0 (0.0)	1 (5.0)	4 (13.8)	2 (6.3)
Religion				
Catholic	6 (60.0)	14 (70.0)	21 (72.4)	24 (75.0)
Protestant	1 (10.0)	3 (15.0)	4 (13.8)	4 (12.5)
Jewish	1 (10.0)	2 (5.0)	0 (0.0)	2 (6.3)
Other	2 (20.0)	2 (10.0)	4 (13.8)	2 (6.3)
Psychiatric treatment				
Hospitalization	3 (30.0)	6 (30.0)	7 (24.1)	0 (0.0)
Outpatient treatment	10 (100.0)	17 (85.0)	20 (69.0)	0 (0.0)
Suicide gestures or attempts	4 (40.0)	4 (20.0)	5 (17.2)	0 (0.0)

[a] Data missing on two subjects.

[b] Based on Hollingshead–Redlich two-factor index of social position.

were no significant differences in the age and sex distribution of children stratified by the probands' age of onset. Not shown here, there was no significant difference in mean age of onset of major depression in children by sex of child.

The children of depressed probands by age-of-onset groups and the normal proband parents were comparable on demographic factors (Table 2). All families were white and the groups did not differ significantly by the proband parents' current age, sex, education, marital status, number of marriages, social class, and religion. While depressed probands did vary from normals on clinical variables, there were no significant demographic differences by age of onset of depressed probands.

In terms of overall demographic characteristics, approximately 30% of these parents came from the upper middle class and over 10% had some college education; about 80% had at least a high school education and were currently married.

Diagnoses in children by proband's age of onset

Table 3 presents the children's psychiatric diagnoses by the proband's clinical status and age of onset of major depression. It should be noted that

TABLE 3

RATES/100 OF PSYCHIATRIC DISORDER IN CHILDREN STRATIFIED BY PROBANDS' CLINICAL STATUS AND BY AGE OF ONSET OF MAJOR DEPRESSION

DSM-III diagnosis in children	Age of onset (years) of major depression in probands			Normals	Significance of the difference		
	< 20	20–29	30+		Overall	< 20/ 20+	
Major depression	57.8	36.4	32.4	21.2	***	**	
Major depression, stricter criteria	52.6	31.8	24.3	12.1	***	**	
Dysthymia	26.3	20.5	21.5	14.5	NS	NS	
Any anxiety disorder	57.9	40.9	36.5	20.5	***	NS	
Any substance abuse	21.1	15.9	13.5	8.4	NS	NS	
Any diagnosis	78.9	81.8	73.0	59.0	**	NS	
					Overall	< 20/ 20–29	< 20/ 30+
Number of diagnoses, mean (S.D.)	3.7 (0.52)	2.3 (0.34)	2.1 (0.27)	1.6 (0.25)	***	**	***
Age of onset of MDD, mean (S.D.)	11.0 (1.2)	13.6 (0.96)	13.6 (0.78)	16.7 (0.90)	***	*	*
Current age, mean (S.D.)	15.4 (1.1)	16.5 (0.71)	17.4 (0.55)	16.5 (0.52)	NS	NS	NS

*$P < 0.10$, ** $P < 0.05$, *** $P < 0.01$.

the any anxiety disorder, any substance abuse or any diagnoses noted on this Table includes the categories in the DSM-III as assessed by the K-SADS-E. Compared to the children of normals, the children of depressed probands, regardless of age of onset of depression, had higher rates of major depression by DSM-III as well as by stricter criteria of major depression requiring 4 weeks of symptoms and impairment in major social role, anxiety disorder, number of diagnoses and any diagnoses. The rate of dysthymia or substance abuse in children did not vary by proband's group. There was an inverse relationship between the proband's age of onset and rates of illness in children. The children of the probands with an age of onset under 20 years had the highest rates of all of these disorders, with the exception of 'any diagnosis', where there was little variability by age of onset. However, when the rates of illness in children of probands with onset of major depression before age 20 years were compared to children of probands with onset age 20 years or older, only major depression by DSM-III and by stricter criteria was significantly increased.

The mean age of onset of depression in children by the proband's age of onset of major depression was also examined (Table 3). The children of probands with major depression with an onset less than 20 years had an age of onset of depression that was significantly younger than the children of

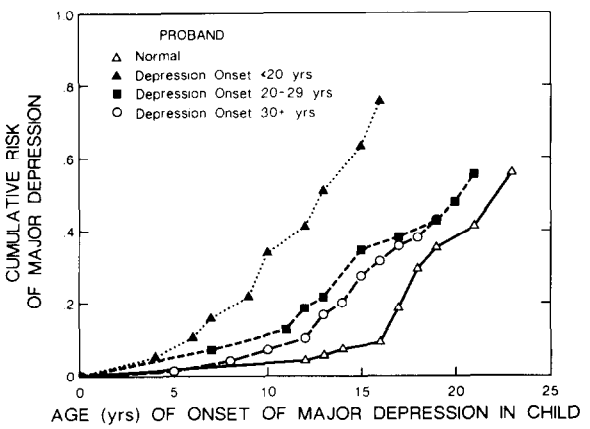

Fig. 1. Cumulative risk of major depression in child by age of onset of major depression in proband.

normals and the children of probands from the other onset groups. The average age of onset of major depression in these children was 11 years, as compared to an average age of onset of 13.6 years in the children whose parents had an onset between the ages of 20 and 29 or at age 30 or older, and as compared to an average age of onset of 16.7 years in the children of normals.

In order to determine if the actual age of the child by onset group might be confounding these results, we examined the mean age of the children from parents in the three onset groups as well as the children of normals. There were no significant differences in the mean ages of the children. Thus a differential birth cohort effect could not account for the findings.

Fig. 1 presents the findings on the effect of age of onset of depression in probands on children's rates. This graph shows the cumulative rates of experiencing a first onset of depression at some time between birth and a specified age in the child, and the age of onset of major depression in the probands' children as well as in the children of normals. Onsets over age 20 years in the children have been excluded for the two younger-onset groups because the numbers were too small to be reliable. Fig. 1 presents the data using major depression according to DSM-III in the child as the outcome.

It is clear from this figure that the cumulative risk of major depression in the children of normals is the lowest. By far the highest rates and the earliest age of onset are in the children of probands with an onset of major depression under the age of 20 years. Similar analyses were done using the stricter criteria of depression requiring 4 weeks' duration and impairment in major social role. The patterns for both sets of criteria are similar. In fact, when the stricter criteria of major depression in children are used, there is a greater relative difference in rates between the children of probands with onset under 20 years of age compared to children of probands with later onsets, suggesting that the children of probands with the earliest age of onset are also experiencing more severe depression. The survival curves, using DSM-III criteria as the outcome, were found to be significantly different from one another when the normal proband group was included (generalized Wilcoxon = 34.765, $P = 0.0000$) or when only the three depressed proband groups were included (generalized Wilcoxon = 14.576, $P = 0.0007$). Similarly, when using stricter criteria as the outcome, the curves were significantly different whether the normal proband group was included (generalized Wilcoxon = 32.00, $P = 0.0000$) or excluded (generalized Wilcoxon = 13.627, $P = 0.0011$).

It is interesting to note on Fig. 1 that the rate of depression increased by age for children in all proband groups. Even the children of normals around age 15 showed a markedly increased risk, suggesting that the late adolescent period is an age when many children become depressed even where there is no familial aggregation.

Specificity of age of onset of major depression

We next examined the effect of age of onset of probands and early and late adolescent-onset depression in children. Our rationale for dividing the children into early (< age 13) and late adolescent-onset (age 13 years and over) was based on our earlier findings (Weissman et al., 1987) that major depression in probands, *regardless of age of onset in probands*, was only associated with early, mostly prepubertal onset of depression in children. Children of normal probands were as likely to have a first onset of depression after around age 14 as were children of depressed probands. By dividing the age of onset at age 13, we would be certain to get all prepubertal onsets.

Consequently, our analytic strategy was (a) to investigate the association between age of onset of depression in probands and early-onset depression in children, and (b) to confirm our earlier finding that major depression in probands was not associated with late adolescent onset of depression in children (regardless of age of onset of depression in the probands). To consider age of onset in the parent as well as in the child as a continuous variable in the analysis (one as outcome and the other as correlated in the Proportional Hazards model) would not be making full use of this a priori finding.

Table 4 shows how the relative risk for early-onset depression (defined as age of onset less than 13 years) in children varies with age of onset in proband, controlling for age and sex of child. The relative risk of onset of major depression under

TABLE 4

RELATIVE RISK OF MAJOR DEPRESSION (MDD) AMONG CHILDREN BY AGE OF ONSET IN PROBAND AND AGE OF ONSET IN CHILD [a]

Age of onset (years) of MDD in proband	Relative risk by age of onset for MDD in child	
	< 13 years	⩾ 13 years
< 20	14.2 ***	4.3 *
20–29	5.6 *	1.3
30+	3.0	1.3

[a] Controlling for age and sex of child, the relative risks are based on comparison between the children of the depressed and the normal probands.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

age 13 years was 14.2 in the children of probands with onset under age 20 years, only 5.6 in the children of probands with onsets between ages 20 and 29, and 4.3 for onsets after age 12 in the children with onsets in probands under 20 years. The relative risks for onsets over age 12 were not significantly increased in children of probands with onsets between 20 and 29 or over 30. Nor were the relative risks of onset under age 13 significantly increased in the children of probands with onsets over 30.

The key fact to note in this Table is that age of onset of proband is clearly associated with early-onset (i.e., under age 13 years) major depression in children, the relative risk being much higher (14.2) in the children of probands with onset under 20 years compared to children of normals.

Comorbid disorders in parents

Other factors which could be contributing to the findings include differential rate of comorbid disorders in the probands or in the co-parents. The rate of comorbid disorders in the probands by onset group was examined and did not vary significantly by proband's age of onset for the major diagnostic categories. Moreover, the rate of disorders in the co-parent did not vary significantly by proband age of onset. There was no assortative mating for early-onset major depression. No families were found in which both the spouse and the proband had an onset of major depression less than age 20 years.

Discussion

In this study of offspring aged 6–23 years of depressed and of normal parents, we found an inverse relationship between the rates of major depression among the children and the age of onset of major depression in their proband parents. The children of parents who had an onset of major depression before age 20 years had the highest risk for major depression as well as the highest risk for a prepubertal-onset depression. The findings were not confounded by the current age of the proband or the children, nor by interview status (children were interviewed), by comorbidity in the proband or spouse or by assortative mating.

The age of onset of major depression as an important source of heterogeneity has been reported in many family studies (see Weissman et al., 1984b for a review). It is a consistent finding in cross-cultural family studies (Smeraldi et al., 1987). Previous studies defined early onset as under 30 or 40 years. Our previous family study of adult relatives suggested that the highest familial loading was in probands with onset under age 20 and that a closer examination of depression first having an onset in childhood or in adolescence was warranted. The previous convention of dividing early and late onset at age 30–40 follows the commonly held view that major depression is a disorder of middle-aged and elderly persons and that it does not occur in children. This view has been changing rapidly with the closer study of children and adolescents that has resulted from the availability of diagnostic assessments for these younger age groups.

Our findings suggest that prepubertal depression occurs in the children of probands who themselves have had a very early onset of depression and that depression which occurs in the children of normals is at a later age during adolescence. Of particular interest was the fact that our findings on the age of onset persisted even when the stricter criteria of major depression were applied to the children. In our previous study, where we showed that the onset of major depression at less than 20 years in adults was related to both an increased risk of depression and an early age of onset of depression among the adult first-degree relatives,

we were studying adults and information on childhood symptoms was defined retrospectively. We may not have been able to precisely define the onset of illness in childhood. This study had the advantage of having direct interviews of children.

It should be emphasized that association between age of onset of depression in children and parents was not continuous but only held for onset in children under 13 years. Our findings also suggest that somewhere between ages 15 and 19, the period of late adolescence, a large number of children report depression, regardless of their parent's clinical status. These high rates may not have the same meaning from the point of view of familial aggregation. These episodes may not reoccur or even be recalled on follow-up. The clinical significance, persistence and recurrence and recall into adulthood of these disorders reported in childhood and adolescence are still unclear. While there have been some longitudinal studies (see Weissman, 1988 for a review), these have been limited. Our 2-year follow-up of these children will provide some information on the continuity of these disorders. However, longer follow-up periods may also be important to resolve the issue of the continuity of childhood and adult depression. We cannot determine from a family study design if genetic factors are involved. Moreover, other control groups of parents, including parents with other psychiatric disorders as well as parents with medical but not psychiatric disorders, would be useful to determine the specificity of findings in children to parental depression.

The findings on the relationship between age of onset of parents and that of offspring, we think, should be pursued. It may be that prepubertal-onset depressions have the highest genetic loading. Future family studies which sample the probands from prepubertal-onset major depression and examine rates and patterns of illness in families would be of interest.

Whatever the mechanisms for our findings, it seems relatively well established that the offspring of depressed parents are at an increased risk for major depression as well as a variety of other health problems (Weissman et al., 1986) and that the earlier the onset of the parent's depression, the greater the risk to the child. These findings clearly have implications for secondary prevention in children and suggest that direct inquiry into the past and current psychiatric status of parents as well as their children may be useful for detecting new cases of depression in the children.

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