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Research report

Psychiatric disorders in the relatives of depressed probands II. Familial loading for comorbid non-depressive disorders based upon proband age of onset

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Abstract

This study examined familial loading for non-depressive disorders in first-degree relatives (FDRs) of early- (< 20 years of age) and adult-onset (≥ 20 years of age) depressed probands. Our previous work, which demonstrated that FDRs of early-onset probands have higher rates of major depression as compared to FDRs of adult-onset probands, has not yet examined risk for non-depressive disorders in FDRs. In this paper, we focus on best-estimate diagnoses of anxiety disorders, alcoholism, and antisocial personality conducted on 639 first-degree relatives. The FDRs of early-onset probands had significantly higher rates of comorbid transmission of alcoholism and depression, and antisocial personality and depression, respectively. Significant co-transmission of anxiety disorders and depression was found in the FDRs of both early- and adult-onset probands. Future genetic studies of depression, especially early-onset depression, should hence broaden their definitions of phenotypes to include comorbid disorders when searching for the etiology of this complex disorder.

1. Introduction

Although family studies have established that depressive disorders run in families (see Moldin et al., 1991), there is still much uncertainty about the etiological basis of depression because of the broad range of phenotype covered by the rubric 'depressive disorders.' Family studies have been useful in defining potential homogenous subtypes of depression, with much attention given to the finding that there is an increased risk for affective disorders in relatives of adult probands with an early age of onset, especially an onset before 20 years of age (Kupfer et al., 1989; Weissman et al., 1984b, 1988). For example, we have previously reported that 24.2% of first-degree relatives (FDRs) of early-onset probands (onset < 20 years) received a lifetime diagnosis of major depression, as compared to 17.5% of FDRs of probands with an onset between 20 and 29 years,

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11.9% of FDRs of probands with an onset between 30 and 39 years, and 7.6% of FDRs with an onset ≥ 40 years (Weissman et al., 1984b). This finding is consistent with suggestions that early-onset depression may represent a distinct subtype of depressive disorder which has a stronger familial, and perhaps, genetic basis than depression with a later age of onset (see Strober, 1992; Todd et al., 1993).

Most studies have focused on the specificity of the familial loading for depression, especially early-onset depression, in relatives of early-onset probands (e.g., Weissman et al., 1984b, 1988). However, early-onset depression has been found to be associated with a greater degree of comorbidity than late-onset forms (Rhode et al., 1993). If this is the case, then early-onset depression may represent a subtype of affective disorders which reflect a familial diathesis for a broad range of psychiatric illness, and not just depressive disorders. Such a possibility is bolstered by family studies which show that depression, anxiety disorders, and alcoholism are co-transmitted in families at risk for depression (Merikangas et al., 1994), as well as twin studies which suggest that some of the genetic influence on depression may also contribute to other disorders, such as anxiety disorders and alcoholism (Kendler et al., 1992, 1993). Hence, it is important to examine if family members of individuals with *early-onset* depression are at increased risk for non-depressive disorders, in order to clarify the specificity of familial transmission.

This paper extends the findings concerning age of onset and familial loading for depression in a sample of depressed probands and their first-degree relatives in which the noted association between age of onset and familial loading has been demonstrated previously (Weissman et al., 1984b). The analyses were done in conjunction with a complementary family study conducted in Britain, which compared rates of psychiatric disorders among the relatives of depressed probands known to have had prepubertal, adolescent or early adult onsets of depressive disorders (Harrington et al., 1997).

There were two aims in the present investigation. The first aim was to determine if early age of onset of depression in probands was associated with increased comorbidity, as has been suggested by current research (Rhode et al., 1993). The second aim was to determine if early-onset depression in probands was associated with increased rates of disorders other than uncomplicated major depression in relatives, as well as disorders comorbid with major depression, in order to examine the specificity of familial aggregation.

2. Method

2.1. Probands and relatives

The full details of the design, assessment criteria, and procedures have been described elsewhere (Weissman et al., 1984a). Briefly, a case-control family study design was used to examine rates of psychiatric disorders in first-degree relatives (FDRs) of depressed adults and normal control probands. In this paper, we focus only on the sample of 133 depressed adults and their 639 adult FDRs (parents and siblings of probands), because our comparison of interest is between early- and adult-onset depression. All of the probands were white, and were drawn from a Yale University outpatient treatment facility.

Table 1 shows basic descriptive information on the depressed probands, stratified by age of onset. We defined early-onset depression as depression with an age of first onset of < 20 years (see Kupfer et al., 1989; Weissman et al., 1984b). Early-onset probands were, on average, younger than adult-onset probands at assessment. However, there were no gender differences between the early- and adult-onset cases, and a previous paper has shown that there were few sociodemographic differences based on age of onset (Weissman et al., 1984a).

Table 2 shows descriptive information on the 639 adult FDRs. There were no age or gender differences between relatives based on proband age of onset. However, a higher proportion of the FDRs of early-

Table 1
Characteristics of probands

		Proband group		Significance
		Early-onset	Adult-onset	
No. of probands		18	115	
Age first depression	mean	16.3	34.4	< 0.001
	SD	3.85	10.79	
Age at assessment	mean	38.1	46.7	< 0.01
	SD	11.83	11.67	
Female, *n* (%)		11 (61.1)	71 (61.7)	NS

Table 2
Characteristics of first degree relatives (FDRs)

	Proband group		Significance
	Early-onset	Adult-onset	
Number	91	548	
Age mean	52.4	55.3	NS
SD	17.8	16.6	
Female, *n* (%)	49 (53.8)	278 (50.7)	NS
Information, *n* (%)			
Interview	38 (41.8)	145 (26.5)	< 0.05
Informant	31 (34.1)	268 (48.9)	
FH-RDC	22 (24.2)	135 (24.6)	

onset probands received direct interviews, and as discussed later, we control for interview status in our analyses. As discussed in Weissman et al. (1984b), the reasons for not obtaining a direct interview included death, proband refusal, and relative refusal.

2.2. Psychiatric diagnoses

Diagnostic estimates were made by multiple raters, using the best-estimate method (Leckman et al., 1982) with RDC criteria (see Weissman et al., 1984a,b). In this paper we focus on three disorders in probands and relatives-anxiety disorder, alcoholism, and antisocial personality-because of their noted association with depression (e.g., Harrington et al., 1997; Kendler et al., 1992, 1993; Rhode et al., 1993). Only definite and probable diagnoses were included in analyses (see Weissman et al., 1984b).

2.3. Statistical analyses

Proportional hazards models were used to estimate the relative risk of each disorder, adjusted for the observation time (i.e., age) that subjects had to develop the disorder (Cox, 1972). Proportional hazards models were also used to control for potential confounding variables.

3. Results

3.1. Comorbid disorders in early- and adult-onset probands

Table 3 shows the lifetime rates of anxiety disorder, alcoholism, and antisocial personality in probands stratified by early- vs. adult- onset. Anxiety disorder was a common comorbid condition, affecting 2/3 of the early-onset probands and nearly 1/2 of the adult-onset probands. Lower rates were observed for comorbid alcoholism, and only 1 proband was diagnosed with antisocial personality. Although the rates of anxiety disorder and alcoholism were slightly higher in the early-onset probands, the differences in rates based on age of onset did not reach significance.

3.2. Psychiatric disorders in FDRs

Table 4 shows the lifetime rates of anxiety disorder, alcoholism, and antisocial personality in adult FDRs, based on proband age of onset, and on the presence or absence of major depressive disorders in the FDRs. The FDRs of early-onset probands had increased rates of alcoholism, as compared to the FDRs of adult-onset probands, only if they also had major depressive disorder (45.5% vs. 10.8%, $P < 0.01$); this finding is evident by comparing the relative risks shown in Table 4 (3.9 vs. 1.0). Similarly, the FDRs of early-onset probands had increased rates of antisocial personality, as compared to the FDRs of adult-onset probands, only if they also had major depressive disorder (13.6% vs. 0.0%, $P < 0.01$); again, this is clearly shown in the comparison of the relative risks shown in Table 4 (4.7 vs. 0.0). No significant differences emerged in the rates of anxiety disorders based upon proband age of onset; however, in both the FDRs of early- and adult-onset probands, the presence of major depressive disorder increased the risk for anxiety disorders, again as shown in the relative risks presented in Table 4.

In examining the data on comorbid conditions in FDRs of early-onset probands, it is important to determine how many FDRs had psychiatric disorders in addition to major depressive disorder. This issue is

Table 3
Lifetime rates (%) of non-depressive disorders in probands

	Proband group		Significance [a]
	Early-onset	Adult-onset	
Anxiety disorders (%)	66.7	49.6	NS
Alcoholism (%)	16.7	13.9	NS
Antisocial personality (%)	0	0.9	NS

[a] Proportional hazards model.

Table 4
Lifetime rates (%) of non-depressive disorders in first degree relatives (FDRs) based upon proband age of onset and presence/absence of major depressive disorder in FDRs

	Proband group					
	Early-onset			Adult-onset		
	MDD + ($n = 22$)	MDD − ($n = 69$)	RR [a]	MDD + ($n = 74$)	MDD − ($n = 474$)	RR [a]
Anxiety disorders (%)	31.8	10.1	3.1 [b]	17.6	6.3	2.8 [b]
Alcoholism (%)	45.5	11.6	3.9 [b]	10.8	10.8	1.0
Antisocial personality (%)	13.6	2.9	4.7 [b]	0.0	1.3	0.0

[a] Relative risk.
[b] $P < 0.05$.

important because it is possible that only a few individuals had many disorders, and such a pattern of familial transmission would not be visible in the data presented as rates of diagnoses. Table 5 presents a breakdown of the number of FDRs with comorbid diagnoses, as well as the number of diagnoses for each FDR. More than half (12/22) of the FDRs of early-onset met criteria for a psychiatric disorder in addition to major depressive disorder. Of the 12 FDRs with comorbid disorders, half had at least 3 disorders. Also of interest descriptively is that antisocial personality did not occur without the presence of alcoholism, whereas depression did occur jointly with anxiety, and with alcoholism, respectively, in some individuals.

Previous analyses of these data have suggested that diagnoses of relatives were associated with sex, year of birth, and interview status (Weissman et al., 1984b). In order to control for these possible confounding factors, as well as comorbidity in probands, analyses using proportional hazards models were conducted. The analyses controlling for these factors did not give results materially different from those reported above.

Table 5
Percentage of FDRs of early-onset probands with comorbid disorders

Disorders comorbid with major depressive disorder [a]	% of FDRs ($n = 22$)
Anx	9.9
Alc	18.1
Anti	0.0
Anx and Alc	13.6
Anx and Anti	0.0
Alc and Anti	4.5
Anx and Alc and Anti	9.9

[a] Anx, anxiety disorders; Alc, alcoholism; Anti, antisocial personality.

4. Discussion

This study examined the extent to which early-onset depression was associated with familial aggregation for non-depressive disorders. A first finding in the present study was that early- and adult-onset probands did not differ dramatically in terms of comorbid disorders, although descriptively the rates for anxiety disorders and alcoholism were slightly elevated in early-onset probands. The lack of significance may be due in part to the relatively high rates of comorbid disorders in the adult-onset cases, which is consistent with data from recent epidemiological studies (e.g., Regier et al., 1990).

Although there were few notable differences in comorbid conditions in the early- vs. adult-onset depressed probands, there were significant differences in the rates of non-depressive comorbid disorders in their first-degree relatives (FDRs). We found evidence of increased co-transmission of alcoholism with major depressive disorder in the FDRs of early-onset probands, as compared to the FDRs of adult-onset probands. Similarly, evidence of increased co-transmission of antisocial personality and major depressive disorder was also found for the FDRs of early-onset probands, although, as discussed below, such co-transmission may be mediated

by the presence of alcoholism. With regard to anxiety disorders, a different pattern emerged: we found evidence of increased co-transmission of anxiety disorders and major depressive disorder in both the FDRs of early- and adult-onset probands. It is notable that more than half of the FDRs of early-onset probands with major depressive disorder also met diagnostic criteria for at least one other disorder, suggesting that the evidence for co-transmission is not due to just a few relatives with many disorders.

Merikangas et al. (1994) recently reported a strong degree of familial co-transmission of depression, anxiety disorders, and alcoholism, raising the possibility of common etiological factors for these disorders. Recent twin studies have suggested that the genetic influences on depression may overlap to some degree with those which influence anxiety disorders (Kendler et al., 1992) and alcoholism (Kendler et al., 1993). The results of this study suggest that such co-transmission of alcoholism may be especially salient in families of early-onset probands, whereas the co-transmission of depression and anxiety may not be limited only to early-onset depression. In addition, we also found evidence for co-transmission of antisocial personality and depression in the FDRs of early-onset probands, which has received less attention in the literature on depression. It does appear, however, that such co-transmission may reflect the influence of alcoholism, as the FDRs comorbid for depression and antisocial personality also met diagnostic criteria for alcoholism. It should also be noted that in our complementary British study, relatives of child-onset probands had increased rates of a criminal record, as compared to adolescent- and adult-onset probands (Harrington et al., 1997).

The broad conclusions from our study are echoed in our complementary British study (Harrington et al., 1997). However, Harrington et al. (1997) were able to make a finer distinction in 'early-onset' probands by distinguishing between childhood and adolescent-onset. In this study, we did not have a sufficient number of childhood-onset probands to test differences between childhood- and adolescent-onset depression, and thus we were not able to attempt to replicate in the American sample the specific findings reported from the British study.

An important implication from both this study and the British study is that age-of-onset of depression may be a marker for subtypes of depression with differing etiological mechanisms. Specifically, the familial vulnerability indexed by early-onset depression may not be limited to affective disorders, but rather contribute to a broad phenotypic spectrum of comorbid conditions, which is not atypical in genetic studies of psychopathology (e.g., Rende and Plomin, 1994). A focus on this type of familial loading may be useful in planning future studies, which will need to determine the extent to which genetic mechanisms are involved (see Rende and Plomin, 1995; Rutter et al., 1990; Todd et al., 1993). In addition, informative genetic designs could also carry implications for designing preventive and interventive strategies. For example, quantitative genetic methods could help resolve if the association between depression and alcoholism in 'early-onset families' is due to genetic covariation or environmental risk, which would have clear implications for the utility of preventive methods.

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