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Familial Psychiatric Illness and Obstetric Complications in Early-Onset Affective Disorder

A Case-Control Study

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Early-onset affective disorder is associated with obstetric complications and a high familial risk of psychiatric illness, in particular psychosis. In a matched case-control study, we investigated 47 adult in-patients with major depressive disorder or bipolar 1 disorder, who had earlier in life presented to a child psychiatry department. Cases were matched on sex, social class and ethnic group with 47 controls, who were admitted to hospital for affective disorders in adult life but had no psychiatric contact before the age of 21. We found that both psychiatric disorder in first-degree relatives and a history of obstetric complications were associated with early onset. Childhood symptoms did not predict the type of adult affective disorder.

Several studies have reported an association between increased genetic loading and early onset in both bipolar (BP) and unipolar (UP) affective disorder (James, 1977; Weissman *et al*, 1984; Rice *et al*, 1987). James (1977) found the morbid risks (MR) for affective disorders in relatives of BP probands with age at onset less than, or greater than, 30 years to be 26% and 12% respectively. Weissman *et al* (1984) reported a threefold increase in risk of depression in relatives of UP probands with an onset of depression before 20 years of age compared with relatives of probands with an onset after age 40. Weissman *et al* (1988) also demonstrated that early age at onset in parents predicted early onset and greater severity in affected children. Similar findings have been reported for BP disorder by Rice *et al* (1987).

Concordance rates less than 100% in monozygotic twins (e.g. Bertelsen *et al*, 1977) indicate that in addition to genetic factors, environment must contribute to the aetiology of affective disorder. Most interest has centred on the role of adverse social events both in the predisposition to (Brown & Harris, 1978), and the precipitation of (Bebbington *et al*, 1989), affective disorder. Little attention has been paid to physical environmental events, such as obstetric complications (OCs) which, in schizophrenia, are associated with both structural brain abnormalities and early onset (Owen *et al*, 1988; DeLisi *et al*, 1991). This ommission is surprising since increased rates of OCs have also been reported in affective disorder (Lewis & Murray, 1987; Done *et al*, 1991).

In this study, sampling over a 22-year period, we matched early-onset cases of affective disorder to later-onset patients, and compared risks of OCs in these two groups, as well as morbid risk of psychiatric disorders in their first-degree relatives. We wished to replicate the association between early onset and genetic risk of affective disorder, and to test the hypothesis that a history of OCs would also be associated with early onset in affective disorders.

Method

We reviewed the discharge summaries of all adult admissions to the Bethlem Royal and Maudsley Hospitals 1967–88 (some 49 000). All subjects who before 17 years of age had previously been seen in the child psychiatry department of the same hospitals, were identified through psychiatric history and hospital identification number.

We identified 94 subjects with adult diagnoses of depression, manic–depressive psychosis and unspecified psychosis, and assessed them for inclusion in the study. Of these, 37 were excluded because their symptoms did not satisfy the Research Diagnostic Criteria (RDC; Spitzer *et al*, 1978) for bipolar depression with mania (BP1 disorder) or major depressive disorder (MDD), and a further 10 due to inadequate or missing case notes. The remaining 47 cases comprised 24 diagnosed as BP1 disorder and 23 as MDD.

Controls were selected from patients who had been admitted to the same hospitals with adult-onset affective disorder but had had no contact with any psychiatric services before the age of 21. By searching the discharge summaries and case notes from the same period as the cases, 47 subjects were identified and matched to the index cases by diagnosis, sex, socio-economic status and race.

Adult case-note data (family history, obstetric history) were extracted verbatim. These data were used in both cases and controls to minimise observation bias and maximise comparability and were rated by PJ, blind to case/control status, age, sex, race, socio-economic status, presenting complaint and corresponding family or obstetric history.

Family history diagnoses were made according to the Family History Research Diagnostic Criteria (FH-RDC; Endicott *et al*, 1975). We defined a category, 'psychosis', which included all relatives who were admitted to hospital for schizophrenia, BP1 disorder, MDD or unspecified psychosis. OCs were rated as absent, equivocal or definite according to the criteria of Lewis *et al* (1989).

Age at onset in the index cases was defined as the age when the individual first saw a psychiatrist for any problem. In most of our index cases, this was at the children's outpatient clinic at the Maudsley Hospital.

Childhood presentation was rated by PJ according to the criteria developed by Rutter *et al* (1983). There were five diagnostic categories: psychotic symptoms, emotional disorder, conduct disorder, mixed conduct and emotional disorder, developmental delay.

Data analysis

The data were analysed using SPSS-PC (Norusis, 1988) and BMDP (Dixon, 1983). Two-tailed *t*-tests were used for continuous variables and non-parametric statistics (χ^2 and McNemar's test for a matched design) for categorical variables. Conditional logistic regression was used to model interactions between OCs and family history.

Morbid risk (MR) in first-degree relatives was calculated using a modification of Strömgren's (1935) method (Slater & Cowie, 1971; McGuffin *et al*, 1988). The principle involved is that the number of unaffected relatives is weighted according to their age, such that an individual's contribution to the denominator increases as a function of progress through the period of incidence risk for the disorder in question. Thus, the risks (number of affected relatives divided by the number at risk) in two comparison groups are corrected for any differences in age structure of the samples of relatives. We based this age-corrected number of relatives (Bezugsziffer, BZ) on first-discharge data for schizophrenia, and manic-depressive psychosis in England and Wales over the years 1976 to 1986, as described by Takei *et al* (1992; data available from authors) and were thus able to calculate separate BZ estimates for schizophrenia and affective disorders. The statistical significance of differences in morbid risks was ascertained using a modified *t*-test where

$$t = \frac{MR_1 - MR_2}{\sqrt{\frac{MR_1(1-MR_1)}{BZ_1} + \frac{MR_2(1-MR_2)}{BZ_2}}}$$

and also by calculating age-adjusted odds ratios for affected first-degree relatives in cases and controls. Odds ratios of infinity (∞) refer to the situation where there were no affected individuals in one comparison group.

Results

Sociodemographic characteristics of the 47 early-onset cases are displayed in Table 1. There were few differences between bipolar and depressive cases. The male: female ratio was 0.74 in the cases as a whole, 1.18 in the bipolars and 0.44 in the depressives. Males were younger at first psychiatric contact than females (12.7 years, s.d. 3.5, versus 14.1 years, s.d. 1.8; $t = 1.74$, d.f. $= 45$, $P = 0.09$). This difference was accounted for by depressive males (11.5 years, s.d. 4.7, versus 14.3 years, s.d. 2.0; $t = -2.03$, d.f. $= 21$, $P = 0.056$).

Among the index cases, first presentation to hospital occurred on average 2.5 years after parents had first noticed any symptoms; the latter occurred on average at an age of 11.2 years (s.d. 3.2, range 3–16 years). Total number of childhood and adult admissions since first presentation was significantly higher in bipolar than in depressive cases ($\chi^2 = 4.8$, d.f. $= 1$, $P < 0.05$).

The distribution of presenting disorders in childhood and their relation to adult diagnostic categories is shown in Table 2. There were no significant differences in childhood presentation between the two adult diagnostic groups, although bipolars tended to have had more psychotic symptoms in childhood ($\chi^2 = 2.7$, d.f. $= 1$, $P = 0.1$).

Analysis of family history

Family history was analysed in two stages. Firstly, cases and controls were compared in terms of presence or absence

Table 1
Demographic characteristics of cases

		Bipolar 1	MDD	All cases
Male: Female		13:11	7:16	20:27
Mean (s.d.) age at matching: years	Male	34.6 (8.9)	33.9 (7.1)	34.4 (8.2)
	Female	33.2 (6.4)	40.0 (9.0)	37.2 (8.6)
Mean (s.d.) age at childhood presentation: years	Male	13.3 (2.6)	11.5 (4.7)	12.7 (3.5)
	Female	13.7 (1.4)	14.3 (2.0)	14.1 (1.8)
Socio-economic class: %	1+2	6 (25.0)	7 (30.4)	13 (27.7)
	3	12 (50.0)	12 (52.2)	24 (51.1)
	4+5	6 (25.0)	4 (17.4)	10 (21.2)

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Table 2
Adult diagnosis associated with the 5 classifications of childhood presentations

Childhood presentation	Mean age at onset (range)	Adult diagnosis	
		BP 1 disorder male : female (n=13) (n=11)	MDD male : female (n=7) (n=16)
Psychosis (n=11)	13.3 (8.5-15.1)	5:3	1:2
Emotional disorder (n=22)	14.2 (7.0-16.9)	5:4	3:10
Conduct disorder (n=6)	12.2 (7.0-14.8)	0:4	1:1
Mixed emotional/conduct disorder (n=7)	14.3 (12.7-15.9)	3:0	1:3
Developmental delay (n=1)	3.0 (0)	0:0	1:0

Table 3
Distribution of family history of FH-RDC diagnosis in the 47 case-control pairs

	Cases	
	Case positive	Case negative
Any diagnosis [1]		
Control positive	4 pairs	4 pairs
Control negative	19 pairs	20 pairs
Psychotic disorders only [2]		
Control positive	1 pair	4 pairs
Control negative	11 pairs	31 pairs

1. Odds ratio = 4.75 (1.6-14.0), χ^2 = 9.8, P<0.01.
2. Odds ratio = 2.75 (0.9-8.6), χ^2 = 3.3, P = 0.065.

in first-degree relatives of any psychiatric disorder and of psychoses. In keeping with the matched design, analyses were restricted to the discordant pairs (Armitage & Berry, 1987). Next, comparisons were made using morbid risks of MDD, BP1 and schizophrenia. Table 3 shows the distribution in the case-control pairs of psychiatric illness: defined as presence of any psychiatric disorder and of psychosis, respectively. The presence of any psychiatric disorder in relatives was a significant predictor of the early-onset cases (OR = 4.75, 95% CI = 1.6-14, P = 0.005); family history of psychosis fell short of conventional statistical significance (OR = 2.75, 95% CI = 0.9-8.6, P = 0.08).

In order to take into account age differences between relatives of cases and controls, we calculated morbid risks of individual psychotic diagnoses in the relatives and probands. There were 111 first-degree relatives for the BP1 cases, 167 for their controls, 113 for the MDD cases and 130 for their controls. Table 4 shows the number of affected relatives, the age-corrected number of first-degree relatives,

Table 4
Morbid risk of schizophrenia and affective psychoses in first-degree relatives (modified Strömgren method)

	Diagnosis in first-degree relatives								
	Bipolar 1 disorder			MDD			Schizophrenia		
	n	BZ	MR%	n	BZ	MR%	n	BZ	MR%
Bipolar 1 cases	1	37.7	2.7	3	27.2	11.0	4	50.8	7.8*
Bipolar 1 controls	2	81.4	2.5	1	59.3	1.7	0	99.5	0
MDD cases	0	39.4	0	7	29.6	23.6**	0	53.6	0
MDD controls	0	91.7	0	2	74.9	2.7	0	106.2	0

BZ = age-corrected number of relatives; MDD = major depressive disorder; MR% = morbid risk; n = total number of affected relatives. *P<0.05; **P<0.02.

and MRs of BP1 disorder, MDD and schizophrenia for cases and controls.

(a) *Early-onset cases compared with later-onset controls.* Relatives of index cases had a significantly increased MR of both MDD (17.6% v. 2.2%; t = 2.94, P<0.01; odds ratio = 9.3, 95% CI = 3.0-28.9) and schizophrenia (3.8% v. zero; t = 2.04, P<0.05; odds ratio ∞), but not of BP1 disorder (1.3% v. 1.2%; odds ratio = 1.1, 95% CI 0.1-11.6). No relative fulfilled criteria for unspecified psychosis. Analyses were then performed separately for case-control pairs from the two diagnostic groups.

(b) *Early-onset bipolar cases compared with later-onset bipolar controls.* First-degree relatives of early-onset bipolar cases had an increased MR of schizophrenia (t = 2.08, P<0.05, odds ratio ∞), but not of BP1 (odds ratio = 1.1, 95% CI = 0.8-1.4). Morbid risk of MDD appeared higher in these cases (11% v. 1.7%) but this difference was not significant (odds ratio = 7.2, 95% CI = 0.43-121.3).

(c) *Depressed early-onset cases compared with later-onset depressed controls.* First-degree relatives of early-onset depressed cases had a much higher MR of MDD than control relatives (t = 2.61, P<0.02; odds ratio = 11.2, 95% CI = 2.36-53.2). There were no relatives with either BP1 or schizophrenia.

Analysis of obstetric history

The median year of birth for the cases was 1958 (range 1936-70; interquartile range 1948-60) and for the controls 1938 (range 1915-57; interquartile range 1925-50). The distribution of obstetric complications with each case-control pair is displayed in Table 5. None of the controls had a history of definite OCs so formal comparison was limited to the discordant pairs, with a positive history of OCs defined as having a history of either a definite or an equivocal complication. OCs were significantly more frequent in the early-onset cases than in the controls (odds ratio 12.0, 95% CI = 2.1-69.5, P = 0.02; McNemar χ^2 = 7.7, P = 0.006).

Table 5
Distribution of history of obstetric complications among the 47 case-controls pairs

Controls	Cases		
	Absent OC	Equivocal OC	Definite OC
Absent OC	33 pairs	7 pairs	5 pairs
Equivocal OC	1 pair	No pairs	1 pair
Definite OC	No pairs	No pairs	No pairs

Interaction between family history and obstetric complications

Conditional logistic regression was used to investigate interaction between obstetric complications and family history in predicting early-onset affective disorder. Addition of information on family history of any FH-RDC disorder to a model containing OCs resulted in a significant improvement in the fit of the model (likelihood ratio statistic (LRS) = 11.95, $P<0.001$). Addition of information on family history of psychosis to the OC model resulted in an improvement in model fit just short of statistical significance (LRS = 3.5, $P=0.06$). Whichever definition of family history was used, the adjusted odds ratios in the models containing both OC and family history terms were greater than the unadjusted odds ratios (Table 6), although that for family history of psychosis remained non-significant. This increase in adjusted odds ratios indicated some independence between family history and obstetric complications but, unfortunately, a model containing a formal interaction term would not converge due to insufficient data points: this analysis was therefore abandoned.

Discussion

This study demonstrates that obstetric complications, and psychiatric illness in first-degree relatives, are more common in the histories of early-onset cases of affective disorder compared with later-onset controls. Could these results be due to biases in our study design?

Our early-onset cases are an unusual group, representing adult patients who were sufficiently disturbed in childhood to be seen in a child psychiatry department accepting both local and tertiary referrals. The controls, too, contain tertiary referrals. Thus, our results need to be judged against the results from other studies using alternative designs before generalising to other groups of patients.

The validity of our findings can be considered more directly. For selection bias to have accounted for our findings, cases with either a history of OCs or a family history of psychosis would have to have been preferentially included in the study, or controls without these factors preferentially excluded. Over the period of the study, we made considerable effort to ascertain that all suitable cases and controls were selected without knowledge of these variables. Perusal of the referral letters available in the case notes revealed no subjects who came to psychiatric attention because their relatives were being treated for mental illness. The matched design of the study removes possible confounding effects of socio-demographic variables on patterns of referral to child psychiatrists (Zeitlin, 1986), and on the risk of familial psychiatric illness and obstetric mishap.

The young age of cases when first seen introduces a possible observation bias, particularly with respect to obstetric history, as details of development are more likely to be available during childhood. We sought to reduce this problem by rating only the adult case notes. It is the policy of our adult department that developmental details should be sought from an informant, preferably the mother, but there remains the possibility that the recording in adulthood of information regarding OCs was influenced by details in the childhood hospital notes of our cases. Controls tended to be somewhat older than cases in each case-control pair; they were matched for period of discharge from hospital, not birth. If obstetric practices are assumed to have improved with time this would have biased the outcome towards the null-hypothesis of no difference between cases and controls and adds weight to our finding.

Regarding family history, we see no reason why a similar potential bias should have occurred; indeed recording family history obtained in childhood could have resulted in lower numbers of affected relatives, as some relatives could have become ill in the interval between childhood and adult presentations. Use of

Table 6
Unadjusted and adjusted odds ratios associated with obstetric complications and familial psychiatric illness

	Unadjusted OR	OR adjusted for OCs	Adjusted for family history of any disorder	Adjusted for family history of psychosis
Obstetric complications	12.0 (1.6-92.3) $P=0.02$		22.6 (2-251) $P=0.01$)	13.66 (1.6-113) $P=0.02$
Family history of any disorder	4.75 (1.6-14) $P=0.005$	7.7 (1.75-33.5) $P=0.007$		
Family history of psychosis	2.75 (0.88-8.6) $P=0.08$	3.3 (0.85-12.8) $P=0.08$		

age-adjusted numbers of relatives would lead to a further underestimate of the morbid risk in adulthood.

The use of case note information to define family history is known to yield lower risks of illness than when the family interview method is employed (Andreasen *et al*, 1986). However, the estimated risk of depression in the relatives of our controls is not very different from that found by McGuffin *et al* (1988) who interviewed relatives of depressed probands from our hospitals. Most importantly, there is no reason to suppose differential ascertainment from adult case notes for our cases and controls, and the study was designed as a comparison of two groups, not to assess prevalence. Furthermore, the data were sufficiently detailed for us to classify all relatives with evidence of psychosis as having either affective psychoses or schizophrenia according to the FH–RDC; none was classified as having unspecified psychosis. Recording of non-psychotic illness was generally not detailed enough to allow classification except as 'other psychiatric disorder'. We chose not to analyse these non-psychotic illnesses separately because (a) we did not know their true nature; (b) it was impossible to calculate age-adjusted numbers of relatives; and (c) our main hypothesis concerned the occurrence of major depression and psychosis in the relatives. We consider that more weight should be attached to our analyses of morbid risks than to the exploratory analyses where family history was classified simply as positive or negative.

How should our results be interpreted? Our finding of similar childhood presentation of both adult major affective disorder and bipolar disorder is in keeping with Zeitlin (1986) who found that the nature of childhood presentation was of little value in predicting the type of adult affective psychosis.

The association we demonstrated between early onset in affective disorder and high genetic loading is in keeping with other studies (James, 1977; Weissman *et al*, 1984; Rice *et al*, 1987) but, to our knowledge, this is the first time that it has been demonstrated using a matched case-control study. Strictly, the effect of familial loading in our study, measured in terms of odds ratios, refers only to the possible influence of familial factors on the age at onset of affective disorder, rather than its aetiology. However, there is considerable evidence that familial, and indeed genetic factors, are of direct aetiological importance in affective disorder (reviewed by McGuffin & Sargeant, 1991) and, despite the unusual nature of our sample, it seems reasonable to conclude that our findings support the evidence from other types of study indicating that such genetic factors are of greater importance in the aetiology of younger, rather than later onset of disorder.

When case-control pairs were divided by diagnosis and morbid risk analysis performed, the occurrence of affective disorder in relatives supported the notion first proposed by Angst (1966) that depression tends to breed true, whereas both depression and bipolar disorder are found in the relatives of bipolar probands. The pattern of increased risks of depression in the relatives of both bipolar and depressed patients, but bipolar disorder confined to the relatives of bipolar probands, is similar to that found by McGuffin & Katz (1986) in their meta-analysis of recent family studies.

The high risk (23.6%) of depression in relatives of cases and the rather low risk in control relatives (2.7%) may be related to the fact that only severely affected subjects, usually in-patients, were diagnosed as having depression under our criteria. It may be that as well as being associated with early onset, high genetic loading leads to relatively more severe depression (Bebbington *et al*, 1989).

We were surprised to find that in the bipolar group, four first-degree relatives of four different cases (two male) were diagnosed as having schizophrenia; none of the 99.5 age-corrected control relatives had such a diagnosis; indeed, the morbid risk of schizophrenia in the relatives of bipolar cases (7.8%) was considerably above accepted population risks. In order to investigate the possibility of misdiagnosis in the relatives we endeavoured to obtain clinical information on these four individuals, three of whom were female. We were successful in two relatives, both females; the clinical details in both their hospital case notes fulfilled the RDC for schizophrenia. Increased risk of schizophrenia in the relatives of bipolar patients has been previously reported (reviewed by Taylor, 1992) and it remains a possibility that this mixed genetic liability may be particularly characteristic of early-onset illness. Conversely, we found no evidence from the case notes that the probands with schizophrenic relatives were otherwise different from those without. In particular, there was nothing to suggest that the proband diagnoses were incorrect.

The increased risk of OCs in our early-onset cases is particularly interesting; the relationship between OCs, age at onset and affective disorder has not been explored previously, although an association between OCs and affective disorder in a relatively young cohort was recently reported as a serendipitous finding (Done *et al*, 1991). In schizophrenia, an association between OCs and early onset of psychosis has been demonstrated frequently (e.g. Owen *et al*, 1988). Little research has been carried out into the

possible developmental origins of affective disorders (Rodgers, 1990), although a history of abnormal childhood development is not found as commonly as in schizophrenia (Foerster *et al*, 1991*a*,*b*); developmental delay had been noted in only one of our early-onset cases.

We found no evidence to support an interaction between OCs and genetic risk, or the notion that OCs may be due to genetic abnormalities underlying the affective disorder. However, it is unsafe to draw firm conclusions from this negative finding; the analyses had low statistical power, models with a formal interaction term could not be computed, and our analyses concerning interaction used family history terms unadjusted for ages of the relatives.

In conclusion, our results suggest that early-onset affective psychosis is associated with higher levels of genetic and environmental risk factors, here indicated by family history and OCs, respectively. This is consistent with a multifactorial model of transmission (Reich *et al*, 1979) which postulates that both our cases and controls have a certain amount of 'liability' for affective disorder. Depending on the overall sum of genetic and environmental risk factors to which each individual has been exposed, a certain threshold is passed determining the type of disorder and the age at onset. The higher the loading, the earlier the onset and the more severe the symptoms. Following this hypothesis, bipolar cases with early onset who displayed psychotic symptoms in their childhood will be found at the higher extremity of the continuum of liability, whereas late-onset depressives will be sited much nearer to the normal, non-patient population.

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