Family Illness History, Obstetric Complications and Age of Onset in Bipolar Patients

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Abstract: The study examined the relationship between obstetric complications, genetic risk and age of illness onset in bipolar disorder.

Thirty DSM-IV bipolar I patients in remission (ages 21-39yr, mean 30.7 $\pm$ 6.1yr.) and twenty seven healthy controls (ages 19-39yr, mean 27.7 $\pm$ 7.0yr.) were investigated using structured interview, life chart and pregnancy and birth complications questionnaire. Family history, pregnancy and birth complications and age of illness onset were collected. Comparisons were made between patients and controls and *also* between patient groups with age of illness onset before and after the age of 21 years.

Obstetric complications were more common in patients (effect size= 0.48) than controls but this was not significant statistically (Fisher's exact test, p=0.13). There was a non-significant excess in early onset patients. Family histories of mood disorder were found in 22 out of 30 bipolar subjects, but rates in early and late onset groups did not differ (p=0.35).

The study failed to find evidence of either increased rates of obstetric complications in bipolar disorder patients or of a link between age of illness onset and a family history of mood disorders. The power of the study was limited by a sample size and difficulties in obtaining unequivocal obstetric data. The finding is in agreement with a recent metanalysis. The large effect size indicates that larger study of obstetric complications in bipolar disorder subjects is justified, looking particularly for subgroups for which there may be an association between complications and clinical variables.

INTRODUCTION

Whilst bipolar disorder appearing in childhood has been recognised since the time of Kraepelin [1], changes in the incidence of bipolar disorder with age remains controversial and of uncertain ***a***etiological significance. Recently, attention has been drawn by the Bipolar Collaborative Network, spanning the U.S. and Europe, to major differences in the incidence of paediatric/adolescent onset bipolar disorder. Results suggesting that in the U.S. 61% of patients have an onset before the age of 19, compared to 30% in Europe. A range of putative genetic, social, environmental and iatrogenic factors have been suggested which may modify the age of the first presentation of bipolar disorder [2].

Previously, a number of investigators have suggested that the age of onset of bipolar disorder may delineate subgroups of the disorder. Subjects with an onset in early adulthood are more likely to have a family history of affective disorder, alcoholism and a history of obstetric complications [3-5]. Carlson *et al*. [6] compared such patients with similar patients whose illness onset was after the age of 45 and found that the earlier onset was not in relation to variability in the course or prognosis of the disorder. However, late onset bipolar disorders are more frequently associated with medical or neurological complications [7]. According to Krauthammer and Klermann [8] symptomatic mania arising in association with certain diseases (infections, neoplasms, epilepsy and metabolic disturbances) or drugs is termed secondary and is characterised by a late onset (over 40 years) and lower rates of family history. Attention has recently focussed on the particular features of juvenile bipolar disorder (for review Goodwin and Jamison [9] and these may represent a further subgroup of bipolar disorder.

An association between obstetric complications, structural brain abnormality and early onset schizophrenia has been reported in a number of investigations [10,11] and reviewed recently [12]. Although broadly defined or apparently unrelated, obstetric complications may share a common pathophysiology, namely foetal hypoxia [13]. O'Callaghan *et al*. [14] have demonstrated that patients with schizophrenia have increased rates of obstetric complications and this was associated with an early illness onset. By contrast, little research has been carried out into the relationship between obstetric complications and age of onset of bipolar affective disorder. However, increased risks of perinatal birth complications have also been reported in bipolar disorder [5,15-18]. The significance of such findings in the causation of bipolar disorder is still unclear; Scott's review and metanalysis of literature [12] failed to find a significant association between obstetric complications and bipolar disorder.

Several reports suggest that structural brain changes and cognitive impairment occur in bipolar disorder [19-24]. As in schizophrenia, these findings have been taken by some to support the notion of a probable neurodevelopmental contribution to the aetiology of bipolar disorder. Therefore, structural abnormalities seen in bipolar may be due to abnormali-

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ties in the brain development during early pregnancy or related to perinatal damage [25].

The relation between obstetric complications, family history of affective disorder, and the age of illness onset has not been systematically investigated in patients with bipolar disorder. The aim of the study is therefore to test the hypotheses:-

(1) that bipolar patients would have increased frequency of pregnancy and birth complications than normal controls and

(2) that family history of affective disorder and obstetric complications are more frequent in patients with an early age of illness onset (< 21 years), compared to patients with a later onset of illness (> 21 years).

MATERIALS AND METHODOLOGY

Subjects

DSM-IV bipolar I affective disorder patients (n=30) were selected from the North East of England bipolar affective disorder population using inclusion/exclusion criteria. The selection criteria were used to sample younger and homogenous group of bipolar patients in remission. Therefore euthymic bipolar I patients under the age of 40 years who were also required to have at least two illness episodes, none of which is drug or ECT induced to ensure bipolarity, were recruited. Consultants from the relevant hospitals in the region were asked to provide list of names of patients with bipolar disorder who might participate in this study. One hundred and three patients were suggested. The case records of each patient were then examined and 50 patients were excluded according to the inclusion/exclusion criteria, for example, because of inadequate information or uncertainty concerning diagnoses, possible schizoaffective disorder and those presenting with only hypomanic episodes. Some of these patients were excluded because they had only one manic episode, and two patients were excluded due to history of epilepsy and another one due to soft neurological signs. Out of the selected 53 patients, 16 patients failed to respond and only three patients refused to participate. 33 patients agreed to participate, 2 patients could not complete the investigation and one patient failed to attend. Thirty patients (11 male, 19 female) therefore took part in the study. Twenty seven healthy volunteers (14 male, 13 female) with no history or family history of psychiatric or physical illness were recruited (from amongst patients' spouses, friends, staff and community). The recruited control subjects were matched for age and gender with bipolar patient group to provide two comparison groups. Bipolar patient group was then divided into two groups matched for age and gender but differ in age of onset of illness. The mean age of onset of 21 years was taken as the cut-off point to divide the patients into early-onset and late-onset groups. In this study onset refers to the first manifestation and/or first presentation of bipolar affective disorder leading to psychiatric care. Comparisons were made between the whole patient group and controls and between two patient groups age and gender matched but differ in age of illness onset. The relationship between obstetric complications and family history of affective disorder was also examined.

After complete description of the study to the subjects, both patients and controls gave written informed consent to participation and the investigation was approved by the Joint Ethics Committee, Newcastle and North Tyneside Health Authority.

Investigations

Demographic data and information concerning family history, obstetric complications, course of illness and mental and physical status were collected using structured interview, life chart, pregnancy and birth complications questionnaire and Beck's Depression Inventory (BDI) [26]. The BDI was used to screen for presence of depression and a clinical examination was performed to exclude mania.

At interview, family history of affective disorders, other psychiatric disorders, suicide or admissions to psychiatric hospital were verified. Attempts were made to corroborate and establish the nature and diagnosis of any reported family history and whether or not treatment and admission were required.

In order to ascertain the presence and frequency of obstetric complications in patients and controls, information about pregnancy and birth was collected using a multiple response, with spaces to give details, questionnaire. Subjects were asked to consult parents when completing the questionnaire. Independent informants were interviewed whenever possible to verify the relevant information. The information was then rated using obstetric complications scale modified from the scale described by Owen *et al*. [10]. Each subject was assessed and rated as having a history of definite, equivocal or absent (no obstetric complications).

Age at illness onset or first contact with psychiatric services was extracted from each case records during which a course of illness and treatment chart was completed. This chart shows the patient's age at illness onset or first contact with psychiatric services, number and type of episodes and treatment received. The chart was then corroborated and confirmed with the patient and family at interview.

Statistical Analysis

Statistical calculations were carried out using the programme Minitab (PC version 10.2) for basic data analysis and testing. The programme G Power [27] was used for power calculations. Student " t" tests were used to compare the demographic (parametric) data between the groups. 2x2 chi^2 or Fisher's exact test was used for categorical data relating to family illness history and birth complications. Equivocal or uncertain data relating to these areas were not included in the statistical analysis.

Study Power

G-Power [27] was used to calculate the power of the study. To achieve a power of 90% to detect effect sizes of 0.5 (0.3,0.8) at p=0.05 using chi-squared tests, sample sizes of 43 (117,17) would be needed. The corresponding figures for 80% power are 32 (88,13). Our sample size of 30 patients and 29 controls is calculated to have power to reveal medium effect sizes between patients and controls (but lesser power for comparisons between early- and late onset subjects) if unequivocal data was available for all subjects. In practice this was not achieved, and actual power available is set out later.

RESULTS

Demographic Data

Subjects characteristics, family history of affective disorders and obstetric complications are summarised in Table **1**; Figs. (**1**, **2**) display family illness history and obstetric complications. Subjects were aged between 19 and 39 years, with illness onsets ranging from 13 to 35 years. Nine (30%) of subjects had an illness onset before the age of 19, as expected of European studies [2]. Of these 9 subjects, the age of onset and (n) were 13 years (1), 16 years (2), 17 years (1), and 18 years (5).

Family Histories of Affective Disorder

There was a high incidence of family illness history in our group, with 22 out of 30 (79%) affected. This high rate of incidence was most marked in the early onset group, with 14 out of 16 subjects (88%) affected. However, differences in the incidence of family illness history between the groups did not reach significance (Fisher's exact test, p=0.35). In both groups 57% of the affected individuals were first degree relatives.

Obstetric Histories

Obstetric complications rated as definite are more likely to be accurate. Therefore, in this study comparisons were made using complications rated as definite only. Examples of the complications rated definite include subjects whose birth complications included ante-partum haemorrhage, maternal hypertension, difficult labour, twin birth, 5 weeks premature, low birth weight, breech delivery and problems with the cord.

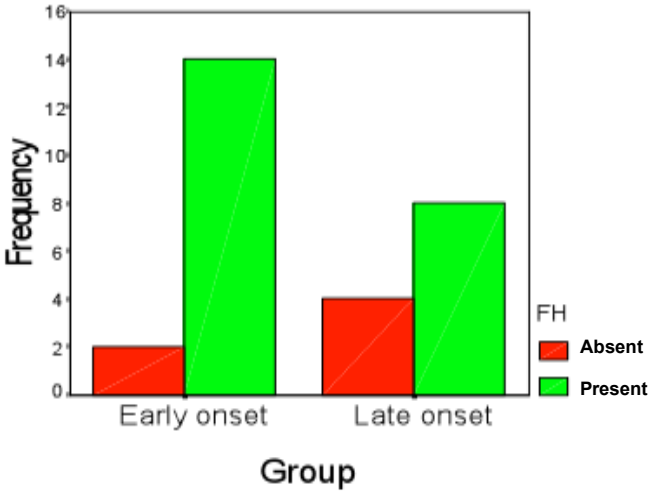

Fig. (1). Family history (FH) of affective disorder in patients.

Obstetric complications were reported in 10 controls, of which 6 were definite, and in 18 patients of which 13 were

Table 1. Subjects Characteristics

Characteristic	Controls (n = 27)	All Patients (n = 30)	Early Onset Group (n = 16)	Late Onset Group (n = 14)
Age Mean ± SD	27.70 ± 6.97	30.67 ± 6.10	27.56 ± 5.92	34.21 ± 4.14***
Gender M:F	14:13	11:19	3:13	8:6
Age at Onset (Years) Mean ± SD	-	21.37 ± 4.84	17.94 ± 1.88	25.29 ± 4.14***
Illness Duration (Years) Mean ± SD	-	-	9.62 ± 7.19	8.93 ± 3.81
Number of Episodes* Mean (SD) Range		4.35 (1.84) 2-10		
Time Since Last Episode* Mean (SD) Range		1.8 years (1.5) 0.5-6.0 years		
Type of Last Episode* Manic (n) Depression (n)		20 9		
Family History of AD n & %	-	22 (79%)	14 (88%)	8 (67%)
History of Definite PBC n & %	6 (30%)	13 (50%)	8 (57%)	5 (42%)
Left Handed	4 (15%)	3 (10%)	-	-
White	26 (96%)	27 (90%)	-	-

AD = affective disorder; PBC = pregnancy and birth complications.
*** p<0.001 difference early onset vs. late onset patients (two sample t-test). *Figures for both groups.

definite (Fig. **2**). The difference in obstetric complication rates between patients and controls gives rise to a medium effect size (0.48, G power) but did not achieve significance (Fisher's exact test, p=0.13 single tailed). The study, with unequivocal obstetric data on 37 subjects (patients and controls) had a 75% power to find an effect size of 0.48, falling just short of the 42 subjects with unequivocal data needed to achieve 80% power.

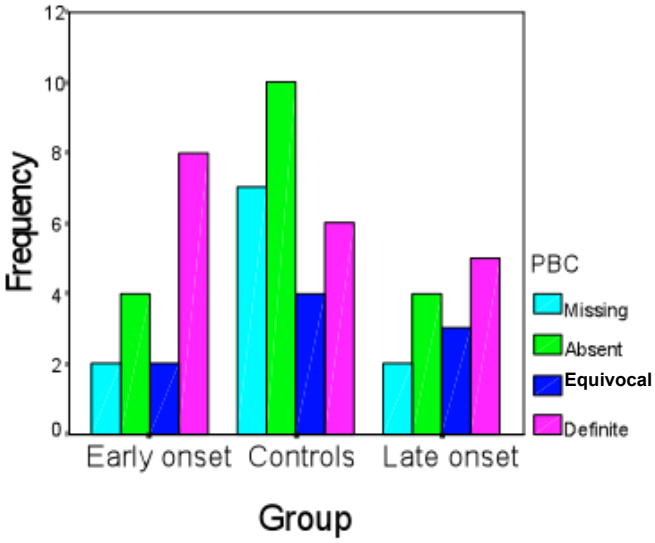

Fig. (2). Pregnancy and birth complications (PBC).

DISCUSSION

A principal aim of this paper was to test the hypothesis that subjects with bipolar disorder would have experienced an increased rate of obstetric complications at birth. Although we found a medium effect size (0.48) linking bipolar disorder and birth complications, this did not achieve statistical significance, possibly due to insufficient statistical power. Insufficient power, 75%, to find this effect size resulted from a modest sample size, compounded by difficulties in obtaining unequivocal birth histories from sufficient patients. No significant differences were seen between early and late onset cases for which statistical power was even less. The effect size found between subjects and controls, although non-significant would justify a further study, especially in view of the relative paucity of robust published data [12].

A future study should consider an increased sample size and more reliable ways of ascertaining subjects' birth histories, for example maternal interviews, examining obstetric records-see below.

Nevertheless, the finding that bipolar disorder, irrespective of family history or age of onset, is not associated significantly with increased risk of obstetric complications is consistent with a metanalysis of other studies [12]. In particular, Browne *et al.* [28] found no difference in rates of obstetric complications between bipolar and controls which were unrelated to family history of psychiatric disorder or age at first diagnosis. A link, if established, between bipolar disorder and birth complications would justify further investigations to elucidate the mechanisms by which pregnancy, labour or perinatal complications influence the risk of developing bipolar disorder [29] and to pinpoint their relevance to the possible neurodevelopmental origins of bipolar disorder.

Although many subjects in the study had a family history of mood disorders, especially in the early onset group (14/16 *vs* 8/12), these results did not achieve significance. Previous studies have shown that early onset patients had more relatives with bipolar illness compared with patients who had their illness onset after 20 years of age [30], and that the morbid risks for affective disorders in relatives of bipolar patients with age at onset less than or greater than 30 years to be 26% and 12% respectively [4]. Furthermore, early age at onset in parents with bipolar disorder predicted early onset and greater severity in affected offspring [31]. Whilst the findings in the present study do not support the notion that early and late onset patients differ significantly in the rates of familial affective disorder and therefore in their genetic propensity to the development of the disorder, power limitations do not allow us to exclude it. However, there was a trend for patients with positive family history of affective disorder to have obstetric complications (Chi-squared; p=0.063). Guth *et al.* [5] noted an association between early onset bipolar disorder and increased rates of family history and obstetric complications. The authors argue that their findings are consistent with a mutifactorial model of transmission. The interaction between obstetric complications and genetic risk requires further investigation, albeit in larger patient cohorts with more robust birth histories.

Limitations

Late onset patients were significantly older and also had a smaller age range. Consequently the two patient groups could not be matched for age. The early onset group had longer duration of illness than late onset group but the difference was not statistically significant. These differences were inherent to the study objectives and design which was to investigate younger adult bipolar patients by restricting the age to less than 40 years of age. In an attempt to delineate subgroups of bipolar patients that might be characteristically different, the patients were divided into two groups on the basis of age of onset. However, there are problems with definitions of "early" and "late", emphasised by differences emerging between Europe and the US. The mean age of onset of bipolar disorder (21 years) in our patient group was used to divide the patient group into early and late onset groups. Ideally a gap of several years would be used to separate the two groups by age of onset to avoid patients clustering around the mean. However, this was prevented by the availability of subjects. An alternative approach would be to treat age as a continuous variable. However, earlier studies found this approach less informative [32].

The use of a questionnaire to obtain obstetric data has its limitations. Information about family history of affective disorder was obtained by scrutinising the case notes and by interviewing patients and their informants. This technique is practical and somewhat comprehensive but may be inaccurate since it relies on subjects' recollection of such problems. A family study technique where all proband relatives are interviewed to verify the diagnoses is an alternative method that could be employed in future research.

Selection of subjects from tertiary referral centres was limited to minimise disproportionate selection of difficult to

treat subjects. The requirement to be euthymic at the time of testing will have limited the number of treatment resistant subjects. However, obstetric complications may be much more frequent in bipolar patients with poor outcome, an issue which may warrant further investigations.

CONCLUSION

The results from the present study suggest that bipolar disorder, contrary to the study hypothesis, is not associated with significantly higher levels of pregnancy and birth complications, although effect sizes and power limitations may justify a further study.

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