Neurodevelopmental antecedents of early-onset bipolar affective disorder

ENGILBERT SIGURDSSON, ERIC FOMBONNE, KAPIL SAYAL and STUART CHECKLEY

Background Developmental impairments have been identified as a risk factor for early-onset schizophrenia. Affective symptoms are more common in children and adolescents with disordered neurodevelopment than in healthy controls.

Aims To test the hypothesis that severe early-onset mood disorders are associated with developmental antecedents.

Method We retrospectively identified 38 adolescent cases (15 female, 23 male; mean age 14.4 years, range 11–18) who met ICD–10 Research Diagnostic Criteria for a manic episode, bipolar affective disorder or psychotic depression, and 41 controls (25 female, 16 male, mean age 14.2 years, range 11–18) with depression but without psychotic features.

Results Cases were significantly more likely to have experienced delayed language, social or motor development (OR 5.5, 95% CI=1.4–21.6, P=0.01), in particular those who develop psychotic symptoms (OR 7.2, 95% CI=1.8–28.6, P=0.003).

Conclusions Compared to early-onset unipolar depression, neurodevelopmental antecedents are over-represented in early-onset bipolar disorder. The validity of this finding was supported by contemporaneous IQ scores that are not subject to the same potential biases as case-note ratings.

Declaration of interest None.

Although premorbid developmental impairments are well documented in early-onset schizophrenia (Jones *et al*, 1994; McKenna *et al*, 1994; Hollis, 1995), it remains unknown whether early-onset bipolar affective disorder is associated with developmental antecedents. Evidence from a large historic cohort study suggests that juvenile affective disturbances are associated with neurodevelopmental delays (van Os *et al*, 1997) and two recent studies have identified a significant excess of affective symptoms among children with neurodevelopmental abnormalities (Hellgren *et al*, 1994; Goodman & Graham, 1996). In addition, Crow and co-workers have reported that premorbid motor abnormalities, restlessness and hostility in childhood are more common in subjects who experience affective psychosis as adults than in healthy controls drawn from the same birth cohort (Crow *et al*, 1995; Done *et al*, 1994*b*). Because early-onset bipolar affective disorder is a very rare disorder with up to 10–18 years' latency between clinical onset and developmental impairments, we devised a case–control study to examine further its potential association with developmental abnormalities.

METHOD

We hypothesised that adolescents who develop severe affective illness in the form of a manic episode, bipolar affective disorder or depressive psychosis are significantly more likely than adolescent controls with non-psychotic unipolar depression to have a history of neurodevelopmental antecedents in the form of delayed language, social or motor development. In contrast to the studies cited above, we used a comparative case–control design with psychiatric rather than healthy controls to test the specificity of the association between developmental antecedents and early-onset bipolar affective disorder among psychiatric patients. Moreover, we set out to explore: the possible role of birth insults, in particular whether these accounted for developmental antecedents in the sample; and whether or not the direction of any observed association was supported by available IQ scores for cases and controls, assuming that IQ acts as a proxy measure for neurodevelopmental impairments.

Subjects

The subjects comprised patients seen at the Maudsley and Bethlem Royal Hospital Child and Adolescent Department between 1974 and 1996; this includes in-patient and out-patient units and a variety of district and tertiary referral national teams. Children and adolescents coming for an assessment in the Department have a mental state examination and a parental interview undertaken according to a semi-structured format. These data are used to compile case-note summaries, to make a multi-axial diagnosis and to rate clinical item sheet summaries for 'definite' occurrence, 'dubious or minimal' occurrence or 'absence' of specified symptoms and other relevant information, which are stored in a computerised database (Hollis, 1995). The item sheets include items such as IQ estimates, proband and parental country of birth, referral pathways and psychosocial risk factors. Information on developmental impairments or perinatal insults is not included in the item sheet database.

Selection of cases

We identified case notes of all patients aged 18 years or less whose diagnosis during their first episode of psychiatric disorder between 1974 and 1991 had been manic–depressive illness (ICD–8 and ICD–9 code 296) or hypomania, mania or bipolar affective disorder between 1992 and 1996 (ICD–10, F31, F32.3, F33.3). The ICD–10 Research Diagnostic Criteria (ICD–10 RDC; World Health Organization, 1993) were applied to those case notes that could be located and rated. A potential number of 68 case notes were identified using the item sheet database, but nine case notes could not be located during three separate attempts, and three were excluded because the subjects later developed schizophrenia. Of the 56 case notes examined, 18 (18/56=32% attrition) did not allow an unequivocal rating of diagnosis and either developmental delay (achieved for 38/38) or perinatal insults (achieved for 37/38).

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In this way 38 case notes were rated (the bipolar affective disorder group), of which 32 met the ICD–10 RDC for hypomania, mania or bipolar affective disorder and six met the criteria for a severe depressive episode with psychotic features. The subgroup with severe depression and psychotic symptoms was kept with the bipolar group because they appear to be at a very high risk of developing bipolar disorder in adolescence (Strober & Carlson, 1982; Akiskal *et al*, 1983). The cases are referred to as the early-onset bipolar group below.

Selection of controls

Forty-one adolescents aged 18 years or younger who met the ICD–10 RDC for mild, moderate or severe depression without psychotic features served as controls in the study (the unipolar depression group). None had shown symptoms suggestive of mania or psychosis during the index episode, or later on during follow-up, as far as could be ascertained from their case notes. They were drawn from a list of cases diagnosed with neurotic depression (ICD–8 and ICD–9 300.4) or manic–depressive illness, the depressive type with no history of manic or psychotic symptoms (ICD–8 and ICD–9 296.1) between 1974 and 1991, and from a list of patients who had experienced a depressive episode or recurrent depressive disorder without psychotic features (ICD–10 F32.0–2 and F33.0–2) between 1992 and 1996.

Some 92 potential controls with non-psychotic unipolar depression were initially identified. They were 11–18 years of age during their first encounter with services at the Maudsley and Bethlem Royal Hospitals between 1974 and 1996. It was not possible to locate 17 case notes during three separate attempts and, of the remaining 75 case notes, 34 (34/75=45% attrition) did not contain sufficient detail to allow the ICD–10 RDC to be applied unequivocally to the index episode and to rate either developmental antecedents (39 out of 41) or perinatal insults (41 out of 41).

Measures

Demographic data, diagnoses and clinical course

Demographic data, the onset and length of the index episode and the temporal sequence of the development of psychiatric symptoms and of the pathways into care were rated by the first author (E.S.). Diagnosis was reached by first rating the detailed item check-list from the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; World Health Organization, 1992) during the reading of the case notes before applying the ICD–10 RDC (World Health Organization, 1993) to the symptoms extracted from the case notes and their time course.

Index episode

A few subjects had had previous episodes of affective illness before their first presentation to the Maudsley or Bethlem Royal Hospitals. If adequate information was available on these previous episodes and their antecedents, they were rated as the index episode. If not, the first episode of assessment at the Maudsley Hospital served as the index episode. Age at onset was defined as age of occurrence of definite psychiatric symptoms at the onset of the index episode.

Ethnicity

Ethnicity was not rated directly because such ratings from case notes proved difficult. Country of birth of proband, mother and father had, however, been rated contemporaneously over the years and parental country of birth could therefore be used as a proxy measure of ethnicity in the study. Three summary categories were used during the analysis and presentation of results: parents born in the UK or Ireland; parents born in the West Indies or Africa; and parents born elsewhere.

Perinatal insults

Case notes were used to rate the history of perinatal insults on a Likert scale: 0=absent; 1=minimal; and 2=definitely present. They were rated as 'absent' if there was no mention of such insults in the personal history of the subject, and as 'minimal' if the delivery was referred to as being protracted or requiring active obstetric intervention and this was reported to have led to some foetal distress noted on delivery but with no other sequelae. The rating 'definite' applied to cases where perinatal complications such as protracted delivery or use of forceps was identified and treatment in intensive care or in an incubator had subsequently been required during the perinatal period. The latter two categories were combined during the analysis owing to low cell counts for each, and a binary variable was created for perinatal insults being either absent or present.

Developmental delay

Delayed development of language, social skills and motor milestones was similarly rated on a Likert scale, using the Denver Developmental Screening Test (DDST) as a quantitative reference for developmental delay during the first six years of childhood (Frankenburg & Dodds, 1967, 1969). Trainees receive this quantitative reference during their induction period in the Department of Child and Adolescent Psychiatry at the Maudsley Hospital. If, according to the case notes, developmental milestones fell above the 10th percentile reference value in the DDST or an explicit statement was made in the case notes about normal development, we rated developmental delay as absent.

If a subject fell below the 10th percentile reference value on at least one of the DDST motor or language items or on at least two personal or social developmental items, the rating 'minimal developmental delay' was applied. A higher threshold was applied for personal or social developmental items because rating them objectively from case notes proved to be more difficult than rating language or motor development. The rating 'minimal developmental delay' was also used if the assessing clinician had stated that there was a history of delay in motor, language or social development without giving the quantitative criteria on which that judgement was based. Examples of delayed motor and language milestones would include, for example, not walking by age 18 months or not communicating verbally by age 3 years.

If there was a delay in achieving more than one motor or language milestone or more than two social milestones (<10th percentile on DDST), the rating 'definite developmental delay' was applied. This rating also applied if there were gross abnormalities of social development in childhood that were not included in the DDST where social developmental delay is very narrowly defined and restricted to the age group 0–6 years. These included major problems in relating to peers, siblings and adults, including severe adjustment problems at school. No subjects had typical autistic-type impairments, and minor adjustment problems at school or school refusal were not included because these commonly influence whether a young person with depression is referred to psychiatric services for an assessment.

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A binary variable was created for developmental delay owing to low cell counts in some cells by categorising them as being either absent or present. The latter category incorporated 'minimal' and 'definite' developmental delay.

Intelligence measures

Intelligence quotient test scores (Wechsler Intelligence Scale for Children (Wechsler, 1949) or Wechsler Intelligence Scale for Children – Revised (Wechsler, 1974)) were found in the notes for 33 subjects: 16 cases (42.1%) and 17 controls (41.5%). For the remaining 46 subjects, IQ estimates as recorded in the item sheets were used, reflecting the assessing clinician's best estimate on the basis of all the available information. All subjects could therefore be ranked within IQ bands (50–69, 70–84, 85–99, 100–114, 115–129, 130+). A binary variable was created by using 85 as a cut-off to differentiate between subjects of low, borderline or subnormal intelligence and those of average or high intelligence. This variable was used in some Mantel–Haenszel and logistic regression analyses only. All subjects who had an IQ estimate below 85 had this confirmed by IQ testing.

Family history

Family history was rated on a Likert scale (not present, second-degree relative only, first-degree relative) for mood disorders, bipolar affective disorder and psychosis. Owing to low cell counts, a binary variable was created for each of these three categories of illness (i.e. family history either being present or absent in first- or second-degree relatives). Because manic episodes are very hard to diagnose reliably through the family history method, we only rated family history of bipolar affective disorder as positive when the relative had been diagnosed by a psychiatrist and had received treatment with a mood stabiliser. We have therefore probably underestimated the prevalence of bipolar affective disorder among relatives.

Reliability

The first author (E.S.) rated all case notes for ICD–10 RDC. Interrater reliability of the clinical diagnoses was studied by having 27 case notes rated by another author (K.S.) who was blind to the ratings of the first author. Mild and moderate depression were collapsed into one diagnostic category, as were hypomania and mania without psychotic symptoms. The kappa value was 0.88 ($P<0.001$), 25 out of 27 diagnoses being concordant.

Interrater reliability was also assessed for developmental delays. Excerpts of relevant information on personal history were extracted from another set of 27 case notes and rated by K.S. using the DDST as a quantitative reference. He was kept blind to the diagnoses of these cases. For the binary variable 'developmental delay' of language, social or motor development the kappa value was 0.81 ($P<0.001$).

Analysis

Software SPSS 6.1.3 for Windows and Stata version 5.0 were used to analyse the data. Fisher's exact test was used to compare categorical variables. For continuous variables, Student's *t*-test was employed when the assumptions of normality and homogeneity were met. When appropriate, the variables were transformed so that these assumptions were better met, or non-parametric tests such as the Mann–Whitney *U*-test were used. All reported tests of significance are two-sided. A conventional level of statistical significance was used ($\alpha=0.05$).

A priori power calculations showed that using a significance level of 0.05, and if 7–10% of controls but 35% of cases had experienced developmental impairments, then 39 to 50 subjects, respectively, would be needed in each group to achieve 80% power of detecting the difference in rates as statistically significant.

RESULTS

Sample characteristics

The sample comprised 79 subjects whose mean age was 14.3 years (range 11–18 years, s.d. 2.0). The bipolar group included 23 males and 15 females. The unipolar depression group consisted of 16 males and 25 females. Other basic demographic and clinical characteristics of each group are presented in Table 1. Although the country of birth for the probands did not differ significantly between cases and controls, highly significant differences were found for parental country of birth. Cases were much more likely to have mothers as well as fathers who were born in the West Indies or in Africa (Table 1).

Sixty-one per cent of the cases were referred by psychiatrists and the remainder largely by general practitioners, but 60% of controls were referred by general practitioners and the remainder mainly by psychiatrists, social workers and educational psychologists ($P<0.001$, χ^2 test). A lower proportion of cases (61%) than controls (73%) resided in greater south London, but this was not significant (Table 1).

Perinatal insults and developmental antecedents

Perinatal insults were equally common in both groups, being present in around 15% of cases and controls (OR 0.89, 95%

Table 1 Demographic and clinical characteristics of the sample

	Bipolar group (n=38)	Unipolar depression group (n=41)	P value[1]
Mean age (range; s.d.) at onset of index episode	14.4 (11–18; 1.9)	14.2 (11–18; 2.2)	0.66
Female, *n* (%)	15 (39%)	25 (61%)	0.052
Either parent of Afro-Caribbean origin, *n* (%)[2]	14 (37%)	1 (2.4%)	0.001
Living in greater south London, *n* (%)	23 (61%)	30 (73%)	0.34
Anomalous parenting situation, *n* (%)[3]	15 (39%)	17 (41%)	1.0
Prepubertal or pubertal, *n* (%)	6 (16%)	10 (24%)	0.41
IQ test scores[4]			
Full-scale IQ (s.d.)	88.8 (16.1)	105.8 (12.9)	0.002
Verbal IQ (s.d.)	92.6 (15.9)	105.1 (13.1)	0.01
Performance IQ (s.d.)	84.9 (15.9)	103.9 (14.9)	0.002

1. Student's *t*-test for continuous variables; Fisher's exact test for categorical variables.
2. Either or both parents born in the West Indies or Africa.
3. Not living with two natural or adoptive parents.
4. Forty-two per cent of the sample tested (16 bipolar, 17 unipolar) with the WISC or the WISC–R.

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CI=0.25–3.2) (Table 2). Age at onset was 1.2 years lower for subjects who had experienced perinatal insults, but this difference fell marginally short of statistical significance (means 13.3 *v.* 14.5 years, P=0.065, t-test). Delay of language, social or motor development was significantly more common for cases than controls (OR 5.5, 95% CI=1.4–21.6). Only minimal confounding was identified and the effect size remained robust and significant (P=0.036, likelihood ratio test) in a multivariate logistic regression model after adjusting for potential confounders such as age, gender, social class, parental country of birth, referral source and area of residence (OR 5.9, 95% CI=1.0–34.8). The slightly higher P value and wider confidence interval in the multivariate model is partly explained by loss of precision owing to 11 missing values, including social class ratings for 10 subjects. Similar effect sizes were obtained for 'minimal', 'definite' and the composite measure, 'any developmental delay'.

The analysis of developmental impairments was repeated following stratification by gender, age, social class, parental country of birth, catchment area and main source of referral, but no significant effect modification was found.

Nine males and six females in the whole sample were rated as being delayed in their neurodevelopment. Age at onset of the index episode did not differ according to presence of developmental delay (14.1 years where delay present *v.* 14.4 where no delay; P=0.69, t-test). The χ^2 test for trend was non-significant for age of onset and developmental delay (P=0.48, age in years: 11–13, 14–15, 16–18).

Significant differences were found for ratings of individual developmental categories such as delayed language (OR 8.6, 95% CI=1.0–73.5) and social development (OR 8.6, 95% CI=1.0–73.5), while differences for motor development were of lower magnitude and fell marginally short of statistical significance (OR 3.7, 95% CI=0.92–15.0) as reported in Table 2.

Intelligence level

The IQ test scores were significantly lower for cases than controls (Table 1). Cases were also significantly more likely to have an IQ estimate below 85 than controls (OR 92.0, 95% CI=1.22–396.6). Within the bipolar group a small but statistically significant mean performance–verbal difference was observed (d=7.7, P=0.002, paired t-test, 15 d.f.) whereas the difference fell short of statistical significance for controls (d=1.2, P=0.059, paired t-test, 16 d.f.).

Family history

Family history of mood disorders was not significantly more common among cases than controls (OR 0.82, 95% CI=0.33–2.1), as shown in Table 2. Family history of bipolar affective disorder was only found among relatives of patients with bipolar affective disorder (OR 10.6, 95% CI=0.55–204.3). Family history of psychosis was more common in the bipolar group, but the difference was non-significant (OR 2.8, 95% CI=0.67–11.8).

Subgroup analyses

Cases who had developed psychotic symptoms during the index episode or during subsequent episodes in adolescence or early adulthood (32 out of 38 cases) were significantly more likely to have experienced developmental impairments than the unipolar depression controls (OR 7.2, 95% CI=1.8–28.6). In fact, all the developmental delays identified in the bipolar group were restricted to this subgroup (Table 2).

Because cases were significantly more likely than controls to have one or two parents of West Indian or African extraction (Table 1), the over-representation of Afro-Caribbeans among the cases could have spuriously inflated the association between developmental impairment and early-onset bipolar affective disorder. However, cases of Afro-Caribbean extraction consistently had a lower rate for all developmental delays than non-Afro-Caribbean cases, although, owing to small subgroup numbers, the difference failed to reach statistical significance (Table 2). The opposite trend was observed for family history of bipolar affective disorder and psychosis (Table 2). Only the Afro-Caribbean subgroup was significantly more likely than the unipolar

Table 2 Rate comparisons between cases, controls and subgroups

	Bipolar group (cases, n=38)		Unipolar depression group (controls, n=41)		P-value[1]	Psychosis cases[2] (n=32) %	Non-Afro-Caribbean cases[3] (n=24) %	Afro-Caribbean cases[4] (n=14) %
	n/available ratings	%	n/available ratings	%				
Perinatal insults	5/37	14	6/41	15	0.85	16	22	0
Developmental delay	12/38	32	3/39	8	0.01	38	38	21
Developmental delay, language	7/38	18	1/39	3	0.029	22	21	14
Developmental delay, social	7/38	18	1/39	3	0.029	22	21	14
Developmental delay, motor	9/38	24	3/39	8	0.065	28	29	14
IQ estimate/test score below 85[5]	8/38	21	0/41	0	0.0023	25	25	14
Family history of mood disorder	22/37	59	25/39	64	0.81	61	57	64
Family history of bipolar disorder	4/37	11	0/39	0	0.052	10	4	21
Family history of psychosis	7/37	19	3/39	8	0.19	19	9	36

1. Fisher's exact test, two-sided. This applies to the comparison between columns 1 and 3.
2. Cases who developed psychotic symptoms in adolescence.
3. Neither parent born in the West Indies or Africa.
4. Either parent born in the West Indies or Africa.
5. All subjects with an estimated IQ < 85 had psychometric testing (WISC or WISC–R).

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controls to have a first- or a second-degree relative with bipolar affective disorder (P=0.016, Fisher's exact test; OR 24.0, 95% CI=1.2–500.2) and psychosis (P=0.023, Fisher's exact test; OR 6.7, 95% CI=1.3–33.3).

DISCUSSION

Our main hypothesis was supported by the data. Neurodevelopmental antecedents were observed in 15 subjects (19% of sample) but were largely restricted to the cases (32%: 12/38 cases *v.* 8%: 3/39 controls) (Table 2). The marked rate discrepancies in developmental antecedents were statistically significant at the 0.01 level and hence unlikely to have arisen by chance. Because the sample size is modest, the power is limited for rare exposures and effect modifiers but is near 80% for detecting the observed differences in developmental delays. There is, however, a substantial risk of type II error when other less common exposures are compared, and negative findings must therefore be interpreted with caution. No confounders were identified that could account for the observed rate differences.

Some inherent limitations of the retrospective case–control design must be considered before accepting the observed association as true. The significantly higher proportion of cases of Afro-Caribbean extraction raises the issue of the representativeness of our case series. A similar excess was observed in a recent study carried out at the Maudsley Hospital, where Afro-Caribbeans were significantly overrepresented among cases of juvenile schizophrenia compared to non-psychotic age- and gender-matched controls from the Maudsley Hospital register (Hollis, 1995). Although having a parent who was born in Africa or the West Indies was strongly associated with being a case in our study, this was inversely associated with developmental delays. These ethnic differences would hence have served to lower the observed odds ratio for neurodevelopmental antecedents.

Bias

If selection bias were to explain the observed rate differences, one would have to postulate a tendency among referrers to refer cases with the more severe forms of affective illness to secondary and tertiary psychiatric services if their cases had low IQ or learning difficulties. Because low intelligence and learning difficulties were infrequently mentioned in referral letters and admission summaries, this option seems unlikely to account for the very marked rate differences observed in the sample.

Case-note ratings have obvious limitations but, as explained in the Method section, only case notes of satisfactory quality were included in the study. Moreover, several studies have shown the content validity and reliability of the item sheet database to be very high (Thorley, 1982, 1987; Goodman & Simonoff, 1991; Fombonne, 1998). Differential recall bias or observer bias could, none the less, have caused under- or overestimation of the exposure under study. However, high interrater reliability was achieved in this study for developmental antecedents blind to diagnostic status. In addition, contemporaneous IQ scores and estimates showed significant differences in the same direction and they could not have been susceptible to the same biases.

Misclassification

Diagnostic misclassification may have arisen in assigning subjects to either of the groups compared. Interrater reliability was high for diagnostic status, and misclassification in either direction would have biased the results towards unity, assuming that errors of classification were independent of exposure status. Such misclassification is improbable because developmental impairments were restricted to those cases of bipolar affective disorder with the most severe psychopathology (i.e. psychotic symptoms) who would be least likely to be misclassified.

The unipolar depression controls are at risk of developing early-onset bipolar affective disorder, which could have been missed in some instances because we could not follow them up and had to rely on information in available case notes. Such misclassification would attenuate the observed odds ratio.

In order to minimise the risk of misclassification of exposure, case notes were excluded where there was insufficient information available to rate both diagnosis and development or where no explicit statement was made about development being normal. This led to a greater attrition of potential controls (45%) than cases (32%), as described above.

Although cases have, on average, been more unwell than controls, the notion of retrospective information bias being introduced as a result of this is improbable because numerous registrars assessed these subjects over the period 1974–1996. These raters were obviously blind, at the time, to the hypotheses of this study. Although their approach and quality of clinical practice may have varied and introduced imprecision into developmental histories, this would serve to push the observed association towards unity but should not bias the results.

Design issues

The origins of juvenile bipolar affective disorder remain a neglected area of research for several reasons. First, because it is a rare disorder with a prevalence around 1% among adolescents in the community (Lewinsohn *et al*, 1995), which often does not lead to psychiatric referral until early adulthood (Lish *et al*, 1994), few adolescents with bipolar affective disorder are assessed at most psychiatric hospitals each year. Second, the latency period between potential vulnerability factors, such as early neurodevelopmental delays, and the onset of bipolar affective disorder in adolescence may be as long as 15–18 years. Ideally, such developmental data would be collected from prospective cohort studies to minimise recall bias. However, very large cohorts, probably including tens of thousands of subjects, would be required for cohort studies to have acceptable power. The true incidence rate of bipolar affective disorder among adolescents is unknown, but is probably of a similar order of magnitude as the estimated incidence rates in adults: 10–30 per 100 000 per year (Boyd & Weissman, 1981). Moreover, the cohort design is inefficient for the examination of rare diseases unless the attributable percentage risk is high. To examine the feasibility of expensive and time-consuming cohort studies addressing the association under study, it is therefore appropriate first to employ the case–control design.

The design issues are complicated further by the fact that early-onset bipolar affective disorder is not easily recognised as a mental disorder by parents, teachers and primary-care physicians (Geller & Luby, 1997). Losses to follow-up are also likely to be a problem for potential cases in a cohort study because many of these lead very chaotic lives during their adolescence following the onset of their illness.

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Cohort studies of sufficient size would have to rely on parents or teachers, rather than researchers, identifying potential cases of bipolar affective disorder. Potential gains in reliability and validity of measurement of developmental antecedents would therefore have to be weighed against the risk of sub-optimal validity in the measurement of the outcome: early-onset bipolar affective disorder. One alternative is to study small familial samples. These may, however, not be representative of the majority of cases of bipolar affective disorder owing to inflated genetic loading, for example. Another option would be to use nested case–control designs within large national cohorts of adolescents or adults who have been followed up at regular intervals. Although the long latency can, theoretically, be overcome in this way, the latency between early developmental milestones and the time when these are measured could be several years and recall bias could still remain a problem.

Comparison with other studies

Two historic cohort studies have addressed the relationship between childhood affective disturbances and neurodevelopmental impairments. Van Os *et al* (1997) studied the association between neurodevelopmental, cognitive and socio-behavioural factors in childhood and affective disorder of early and late onset in a national birth cohort of 5362 individuals born in the UK during the same week in 1946. Subjects with childhood affective disturbance, measured on a teacher questionnaire at ages 13 and 15 years, attained motor milestones significantly later in early childhood than controls, and had double the risk of speech abnormalities observed on medical examination at the ages of 6 and 15 years. The authors concluded that affective disturbances, especially the early-onset forms, are preceded by impaired neurodevelopment. The fact that we selected our controls from a population of adolescent patients with affective disturbances thus adds weight to our findings.

In a similarly designed survey of subjects born during the same week in 1958, Crow and colleagues (Done *et al*, 1994*a*; Crow *et al*, 1995) identified all subjects in this birth cohort who had been treated as adults in hospitals for a psychiatric disorder between 1974 and 1986. The 35 subjects thus identified with affective psychosis (PSE–CATEGO diagnoses) were found to be less clearly abnormal in their social behaviour than those with schizophrenia at ages 7 and 11 years, but 'neurotic' girls were significantly more socially maladjusted than controls at age 11 years. Two brief reports from the same team describe over-representation of premorbid motor abnormalities and poorer intellectual performance in childhood for adult subjects with affective psychosis or schizophrenia than controls from this birth cohort (Crow *et al*, 1994; Done *et al*, 1994*b*).

Hellgren *et al* (1994) carried out a prospective population-based cohort study on a sample of 56 Swedish adolescents who had met criteria for neurodevelopmental deficits during the screening of 3500 children at the age of 6 years. On follow-up ten years later they were compared with 45 controls for axis I and axis II DSM–III–R diagnoses. A significant excess risk of adolescent psychiatric disorder was found among the cases, major depression being particularly common. Interestingly, in light of our findings, four cases (7%) but no controls developed manic or hypomanic episodes during follow-up.

Several studies have found obstetric complications to be associated with early onset of affective disorder (Lewis & Murray, 1987; Done *et al*, 1991; Guth *et al*, 1993). We also observed a lower age of onset for subjects who had experienced perinatal insults, but this fell marginally short of statistical significance. Our data do not, however, suggest that the rate differences in developmental impairments between cases and controls were caused by perinatal insults. Only 5 out of 11 subjects who had experienced perinatal insults were among those 15 who had a history of developmental delays. Moreover, rates for perinatal insults did not differ significantly between cases and controls.

Because the subgroup with psychotic features was more likely to have experienced developmental antecedents than the bipolar group as a whole, it would appear from our data and the study of van Os *et al* (1997) that severity and early onset of affective illness are associated with aberrant neurodevelopment, as has been postulated in early-onset schizophrenia (Jones *et al*, 1994; McKenna *et al*, 1994; Hollis, 1995). Whereas studies using largely categorical measures such as our own may imply the presence of a separate neurodevelopmental subgroup in psychotic disorders, studies employing continuous measures such as IQ or birthweight are consistent with a continuous distribution of risk. For instance, Cannon *et al* (1997) found a significant linear association between low birthweight and poor premorbid social adjustment in childhood on the basis of maternal recall in adults with schizophrenia.

We conclude that our findings add to the increasing evidence that neurodevelopmental impairments act as vulnerability factors for early-onset affective disturbances, particularly the more severe ones. These findings now require replication in retrospective and prospective studies on early-onset affective illness. Further comparative studies on subjects who have a history of neurodevelopmental impairments are also called for.

Interestingly, Biederman *et al* (1996) have reported that over 20% of children and adolescents with attention-deficit hyperactivity disorder (ADHD) develop bipolar affective disorder. These cases tend to have a more severe ADHD symptom profile and lower IQ than those who do not. Delineating the boundaries and understanding the similarities between severe juvenile mood disturbances and other disorders that are associated with neurodevelopmental antecedents, such as early-onset schizophrenia, childhood hemiplegia and ADHD, clearly remains an intriguing area for further research.

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CLINICAL IMPLICATIONS

- Early-onset bipolar affective disorder is associated with neurodevelopmental antecedents in the form of delayed language, social and motor development.
- Adolescents with early-onset bipolar affective disorder who have experienced developmental antecedents are at high risk of developing psychotic symptoms.
- Subjects with severe early-onset mood disorders have, on average, a lower IQ than those with mild or moderate forms of juvenile affective illness.

LIMITATIONS

- Our sample was selected at one site and replication at other centres is indicated.
- Case-note ratings may have introduced information bias.
- Because the sample size is modest, the power to detect weak associations or effect modifiers was limited.

ENGILBERT SIGURDSSON, MRCPsych, The Maudsley Hospital, Denmark Hill, London SE5 8AZ; ERIC FOMBONNE, MRCPsych, Institute of Psychiatry, Denmark Hill, London SE5 8AF; KAPIL SAYAL, MRCPsych, The Maudsley Hospital, Denmark Hill, London SE5 8AZ; STUART CHECKLEY, FRCPsych, Institute of Psychiatry, Denmark Hill, London SE5 8AF

Correspondence: Engilbert Sigurdsson, The Maudsley Hospital, Denmark Hill, London SE5 8AZ, UK. Tel: 0171 703 6333; e-mail: E.Sigurdsson@iop.kcl.ac.uk and E.Sigurdsson@lishtm.ac.uk

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