ELSEVIER

Journal of Affective Disorders 74 (2003) 197–201

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Brief report

Age onset of psychotic versus non-psychotic bipolar illness in men and in women

This work was presented as a poster at the APA Meeting, May 15, 2000, Chicago, IL

Aysegul Yildiz[a,b,*], Gary S. Sachs[b]

[a]*Dokuz Eylul Medical School, Department of Psychiatry, Izmir, Turkey*
[b]*Harvard Medical School, Massachusetts General Hospital, Bipolar Clinic, Boston, MA, USA*

Received 18 December 2000; received in revised form 6 November 2001; accepted 4 December 2001

Abstract

Objective: To investigate the relationship between psychotic symptoms and age at onset of bipolar illness. *Method:* The charts of bipolar patients treated at the Massachusetts General Hospital Bipolar Clinic were reviewed for age of first affective episode, demographics and history of psychotic symptoms. *Results:* Data was obtained for 328 bipolar patients (56.7% females) of whom 42% had psychotic symptoms sometime through the course of their illness. Overall, there was no significant difference in age of onset between the psychotic and non-psychotic groups. Additional analysis carried out separately by gender found significant difference for males but not for females. Age at onset for psychotic males was significantly lower than non-psychotic males. Psychosis was less common in males than females. The mean age of onset for psychotic males was significantly lower than psychotic females. *Conclusion:* This result implies that developmental physiology underlying psychosis in bipolar illness may differ for men and women. The different proportions of males and females in the study samples may account for conflicting results reported in the literature for age of onset of psychotic bipolar illness.

Keywords: Bipolar illness; Psychosis; Age of onset; Gender

1. Introduction

It is unclear whether psychotic forms of bipolar disorder are merely more severe or represent a type of bipolar illness distinct from non-psychotic forms. Studies investigating the relationship of age at onset and psychotic symptomatology of bipolar illness have produced inconsistent results. Four studies investigating the relationship between the incidence of psychotic symptoms and age of onset suggest that

*Corresponding author. Tel.: +90-232-244-4724; fax: +90-232-259-9723.
E-mail address: agul_yildiz@hotmail.com (A. Yildiz).

0165-0327/02/$ – see front matter
doi:10.1016/S0165-0327(02)00003-4

early age at onset of bipolar disorder is associated with a greater frequency of psychosis. Rosen et al. (1983) report a statistically significant negative correlation between the number of psychotic symptoms and age at onset of illness in 71 bipolar patients. The other three studies suggest patients who become ill at a younger age are more likely to be psychotic than those with an older age of onset (Carlson and Strober, 1978; Rennie and Fowler, 1942; Rosenthal et al., 1980).

Another four studies compared adolescent mania with adulthood mania for presence of psychotic symptoms. Two studies found that adolescent mania was associated with higher rates of psychotic symptoms than manic episodes in adults (McGlashan, 1988; Ballenger et al., 1982). Coryell and Norten (1980) however, found no difference in distribution of delusions and hallucinations between 20 bipolar patients first admitted during adolescence and those of 20 bipolar patients first admitted between the ages of 30 and 40. The only prospective comparison of adolescent versus adult manic episodes reported by McElroy et al. (1997) actually found lower rates of psychotic features in the adolescent group.

The inconsistency of the available data may result from differences in sample on methodology. First, the criterion used to define early onset varies across the studies. In addition to variation in age used to define the boundary between early and late onset, some studies defined age of onset on the basis of the first affective episode, while others investigated that issue focusing on mania by comparing adolescent vs. adult presentation. Second, none of these studies examined the possibility of gender influence on the relationship between age of onset and psychotic features in bipolar illness.

The availability of a relatively large sample of systematically assessed bipolar patients at the Massachusetts General Hospital (MGH) Bipolar Clinic offers the opportunity to investigate the relationship between age of onset and psychosis by addressing some of the limitations of the prior studies.

2. Method

The charts of all outpatients evaluated at the MGH Bipolar Clinic between the years 1990–1999 were reviewed. Subjects were included in the analysis if the chart documented any episode sufficient for diagnosis of bipolar illness, the age of first affective episode and the presence or absence of psychotic symptoms. For identifying age of first affective episode and lifetime histories of psychotic symptoms, we reviewed the Affective Disorders Evaluation Form (ADE) and Clinical Monitoring Form (CMF) (Guille et al., 1999). ADE being used for the initial evaluation, consisting of 11 modules provides information on current mood state; lifetime mood disorder diagnosis as well as the first depressive/manic episode in a SCID-DSM-IV oriented manner. CMF providing a systematic follow up consists of 8 parts and include a structurally modified version of SCID mood modules. They both are routinely completed for each bipolar patient evaluated at the MGH Bipolar Clinic by trained research psychiatrists and collect information on the presence of psychotic symptoms (delusions and/or hallucinations). MGH Institutional Review Board approved the study.

Statistical analysis of data was performed by independent samples 2-tailed Student's *t*-test and Chi-square test as appropriate.

3. Results

Sufficient data for analysis was obtained for 328 bipolar patients among a total of about 450 charts reviewed. The sample was 56.7 female and mainly (81.1%) comprised of bipolar-I patients and a small number of bipolar-II (10.7%) and bipolar-NOS (8.2%) patients. Overall 42% ($N = 138$) of the sample had a positive lifetime history of psychosis. Of those with a positive history of psychosis, 95% of the patients were bipolar-I, 3% bipolar-II, and 2% bipolar-NOS.

Overall, there was no significant difference in age of onset between psychotic and non-psychotic groups. The mean age of first affective episode was 20.9 in the psychotic group (those with a positive lifetime history of psychosis), and 21.5 in the non-psychotic group (those with a negative lifetime history of psychosis), ($t_{df=326} = 0.58$, $P > 0.5$). However, additional analysis carried out separately by gender found significant difference for the males, but not for the females. Mean age of onset in psychotic vs. non-psychotic males was 18.4 ± 7.2 and

21.8±10.9 respectively ($t_{df=133} = 2.240$, $P < 0.03$). Mean age of onset in psychotic vs. non-psychotic females was 22.3±9.7 and 21.3±9.9, respectively ($t_{df=184} = 0.702$, $P > 0.4$), (Fig. 1, Table 1).

Lifetime history of psychosis was less common in bipolar males than bipolar females (34.5%, 47.8% respectively, $\chi^2_{df=1} = 5.882$, $P < 0.02$), (Table 1).

The mean age of onset for males with a positive lifetime history of psychotic symptoms was significantly lower than females with a positive lifetime history of psychotic symptoms (18.4±7.2 versus 22.3±9.7, respectively, $t_{df=124} = 2.663$, $P < 0.01$), (Table 1). There was no significant difference in mean age of onset between males and females in the non-psychotic group; $t_{df=188} = 0.37$, $P > 0.7$, or in the bipolar population as general; $t_{df=326} = 1.009$, $P > 0.3$.

When the analyses are limited to only bipolar-I patients ($N = 266$), the mean age of onset for males with a history of psychosis was 18.5±7.25, and the mean age of onset for females with a history of psychosis was 22.27±9.79 ($t_{df=121} = 2.510$, $P < 0.02$). In the non-psychotic group, however, mean age of onset for males was 21.49±10.76, and mean age of onset for females was 21.0±9.59 ($t_{df=133} = 0.277$, $P > 0.7$). Overall, age of onset for bipolar-I males was 20.25±9.55, and age onset for bipolar-I females was 21.70±9.69 ($t_{df=264} = 1.218$, $P > 0.2$).

Table 1
Gender specific relationship between age of onset and incidence psychotic features in bipolar illness

	Psychotic $N = 138$	Non-psychotic $N = 190$	P-value
Mean age of onset	20.9	21.5	$P > 0.5$
Males $N = 142$	18.4	21.8	$P < 0.03$
Females $N = 186$	22.3	21.3	$P > 0.4$
P-value	$P < 0.01$	$P > 0.7$	
Incidence	42.1%	57.9%	
Males	34.5%	65.5%	
Females	47.8%	52.2%	
P-value	$P < 0.02$		

4. Discussion

To the best of our knowledge, this is the first report in the literature to detect a gender specific relationship of age onset and psychotic features in bipolar illness; psychotic bipolar males having an age of onset about 4 years earlier than psychotic bipolar females. The magnitude and direction of this

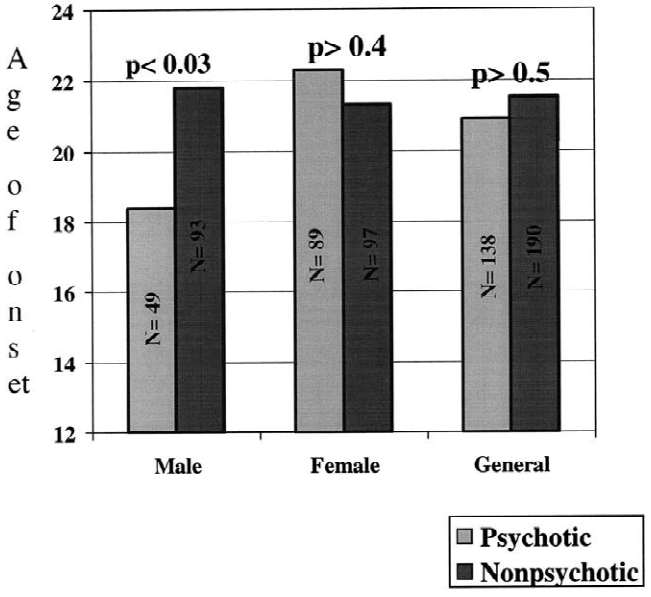

Fig. 1. Gender specific relationship of age at onset of bipolar illness and psychotic features (current or through the course of illness).

observation are remarkably similar to the gender specific difference in age of onset in schizophrenia (mean onset in males about 3–5 years earlier than females) (Castle et al., 1995; DeLisi, 1992; Salem and Kring, 1998; Szymanski et al., 1995). Similarly, an older age of onset in women has been reported in schizoaffective disorder (Angst et al., 1980).

Consistent with the above findings from phenomenological studies, gender specific findings have been reported in neuroimaging studies. Overall, both quantitative and qualitative abnormalities have been observed to be more prominent in male schizophrenic patients than female schizophrenic patients (Okazaki, 1998; Swayze et al., 1992). In bipolar patients, the quantitative abnormalities have been observed to be less striking compared to the schizophrenic patients but again reported to be more prominent in bipolar males than bipolar females (Okazaki, 1998; Swayze et al., 1990; Aylward et al., 1994). The observation of gender specific abnormalities in affective and schizophrenic psychosis may reflect differential influence of sex hormones on brain development in predisposed individuals. Consistent with such hormonal regulation, Kaye et al. (1986) showed that gene expression enzymes are controlled by steroid hormones (estrogen) such as creatine kinase BB isozyme. Several reports suggest that estrogen, like neuroleptic drugs seems to achieve its antipsychotic effect by blocking or decreasing the sensitivity of dopamine receptors and the effect is stronger before the completion of brain maturation (Salem and Kring, 1998; Hafner et al., 1993 and 1991). While, the connection between the present findings and the above biological data remains speculative, our finding of a higher incidence of psychosis among female bipolar patients, however, suggests any damping of dopaminergic activity in women delays the onset of the illness without conferring protection against psychosis. The risk for women to suffer psychosis being greater was more evenly distributed across the life cycle than the risk for men. The risk in men while less than that of women overall, was significantly greater for those with early onset.

While there are limitations to a retrospective study, naturalistic observations from specialized clinics where all the diagnoses made by structural interviews and reliable follow up records maintained are important in phenomenological studies of bipolar illness. Being a referral center and an outpatient clinic, we don't know in what extent our patients represent the bipolar population in general; but it is likely that the above two factors may have at least a partially neutralizing effect on each other in severity.

In conclusion, a gender specific relationship between age at onset and psychotic features in bipolar illness is found. Gender may be a medicating factor which influences the developmental pathopysiologic process relevant for expression of psychosis in both bipolar illness and schizophrenia. Our results support the notion that expression of psychosis in schizophrenia, schizoaffective disorder, and bipolar disorder may arise from common genetic and neurodevelopmental factors.

References

Angst, J., Felder, W., Lohmeyer, B., 1980. Course of schizoaffective psychoses: Results of a follow-up study. Schizophr. Bull. 6, 579–585.

Aylward, E.H., Roberts-Twillie, J.V., Barta, P.E., Kumar, A.J., Harris, G.J., Geer, M., Peyser, C.E., Pealson, G.D., 1994. Basal ganglia volumes and white matter hyperintensities in patients with bipolar disorder. Am. J. Psychiatry 151, 687–693.

Ballenger, J.C., Reus, V.I., Post, R.M., 1982. The atypical clinical picture of adolescent mania. Am. J. Psychiatry 139, 602–606.

Carlson, G.A., Strober, M., 1978. Affective disorders in adolescence: issues in misdiagnosis. J. Clin. Psychiatry 39, 63–66.

Castle, D.J., Abel, K., Takei, N., Murray, R.M., 1995. Gender differences in schizophrenia: Hormonal effect or subtypes? Schizophr. Bull. 21, 1–12.

Coryell, W., Norten, S.G., 1980. Mania during adolescence: The pathoplastic significance of age. J. Nerv. Ment. Dis. 168, 611–613.

DeLisi, L.E., 1992. The significance of age of onset for schizophrenia. Schizophr. Bull. 18, 209–215.

Guille, C., Shriver, A., Demopulos, C., Sachs, G., 1999. A clinical monitoring format for mood disorders. 39th NCDEU Annual Meeting, Abstract book, 109.

Hafner, H., Behrens, S., de Vry, J., Gattaz, W.F., 1991. An animal model for the effects of oestradiol on dopamine mediated behavior: implications for sex differences in schizophrenia. Psychiatry Res. 38, 125–134.

Hafner, H., Riecher-Rossler, A., An Der Heiden, W., Maurer, K., Fatkenheuer, B., Loffler, W., 1993. Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. Psychol. Med. 23, 925–940.

Kaye, A.M., Reiss, N.A., Weisman, Y., Binderman, I., Somjen, D., 1986. Hormonal regulation of creatine kinase BB. Exp. Med. Biol. 194, 83–101.

McElroy, S.L., Strakowski, S.M., West, S.A., Keck, Jr. P.E., McConville, B.J., 1997. Phenomenology of adolescent and adult mania in hospitalized patients with bipolar disorder. Am. J. Psychiatry 154, 44–49.

McGlashan, T.H., 1988. Adolescent versus adult onset of mania. Am. J. Psychiatry 145, 221–223.

Okazaki, Y., 1998. Morphological brain imaging studies on major psychoses. Psychiatry Clin. Neurosci. 52 (Suppl.), S215–S218.

Rennie, T.A.C., Fowler, J.B., 1942. Prognosis in manic-depressive psychosis. Am. J. Psychiatry 98, 801–814.

Rosen, L.N., Rosenthal, N.E., Van Dusen, P.H., Dunner, D.L., Fieve, R.R., 1983. Age at onset and number of psychotic symptoms in bipolar-I and schizoaffective disorder. Am. J. Psychiatry 140, 1523–1524.

Rosenthal, N.E., Rosenthal, L.N., Stallone, F., Dunner, D.L., Fieve, R.R., 1980. Toward the validation of RDC schizoaffective disorders. Arch. Gen. Psychiatry 37, 804–810.

Salem, J.E., Kring, A.M., 1998. The role of gender differences in the reduction of etiologic heterogeneity in schizophrenia. Clin. Psychol. Rev. 18, 795–819.

Swayze, II V.W., Andreasen, N.C., Alliger, R.J., Ehrhardt, J.C., Yuh, W.T.C., 1990. Structural brain abnormalities in bipolar affective disorder. Ventricular enlargement and focal signal hyperintensities. Arch. Gen. Psychiatry 47, 1054–1059.

Swayze, II V.W., Andreasen, N.C., Alliger, R.J., Yuh, W.T.C., Ehrhardt, J.C., 1992. Subcortical and temporal structures in affective disorder and schizophrenia: A magnetic resonance imaging study. Biol. Psychiatry 31, 221–240.

Szymanski, S., Lieberman, J.A., Alvir, J.M., Mayerhoff, D., Loebel, A., Geisler, S., Chakos, M., Koreen, A., Jody, D., Kane, J., Woerner, M., Cooper, T., 1995. Gender differences in onset of illness, treatment response, course, biologic indexes in first-episode schizophrenic patients. Am. J. Psychiatry 152, 698–703.