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*Analysis of selected laboratory parameters based on blood tests
in patients with bipolar affective disorders*

Bipolar affective disorder, whose prevalence depending on criteria ranges from 0.4–1.5% (12) to as much as 5% (1) (including its atypical forms, so-called subliminal spectrum of bipolar disorders according to Akiskal) is a disease whose etiology remains unknown. It includes bipolar I (alternating periods of mania and depression), bipolar II (alternating periods of hypomania and depression), and bipolar III (a brief period of hypomania occurring during depression treatment with antidepressant drugs). The classification of this disorder also covers mixed states with rapid alternation of the manic and depressive periods, as well as the so-called unipolar mania, and seasonal affective disorders (1, 12).

The most recent research on the pathogenesis of these disorders focuses on psychoneuroendocrinological and psychoimmunological aspects. It attempts to link emotional processes to changes in neurotransmission within the CNS, hormonal changes (the hypothalamus-pituitary-adrenal axis), immunological changes (the significance of various cytokines), as well as structural changes in the CNS and genetic predisposition (13, 7, 8).

The analyses of changes in the immune system during the periods of mania and depression have produced some interesting results. The research mainly concentrates on the levels of leukocytes, lymphocytes, monocytes, and cytokines in various stages of the disease (2, 7, 8).

The role of exogenous factors, such as somatic conditions, or influence of various substances (including medicines) or vitamin deficiencies on the initiation of pathogenic processes in depression and mania are another issue (12).

The effect that folic acid and vitamin B12 deficiencies have on the nervous system, and especially on the mental state of the patient (which is reflected in some of the laboratory parameters in the blood count, e.g. MCV) is an interesting problem (4, 5, 10). Low concentration of these vitamins in the blood may result in mania as well as depression unconnected with bipolar affective disorder, or trigger the manic or depressive period in the course of bipolar disorders (4, 6, 11). A lot of research is devoted to unipolar depression, while there is still little scientific report on vitamin deficiencies in particular stages of bipolar affective disorders (4, 6, 11, 14).

Some authors focus on vitamin supplementation, i.e. vitamin B12 and folic acid, during the treatment of bipolar disorder in people with their deficiency, as well as people whose reaction to medication commonly administered in bipolar disorder is unsatisfactory, as treatment potentialization (6, 14). Further research is necessary to confirm the effect of those vitamins and their deficiencies on specific stages of bipolar affective disorder, which is reflected by raised laboratory parameter MCV (14).

The objective of this study was to detect possible relations between selected laboratory parameters of the blood picture (MCV, levels of leukocytes, monocytes, and lymphocytes) and variables connected to sociodemographic data of the examined

patients with bipolar affective disorder, its course, duration, clinical features, stages and the type of the disorder (type I or II).

MATERIAL AND METHODS

The examined group consisted of 43 patients (21 females, 22 males) of the Neuropsychiatric Hospital in Lublin, hospitalized with diagnosed bipolar affective disorder as described in the ICD-10. The average age in the group was 48.58 years (SD = 11.26), the average age for women was 49.95 (SD = 12.35), for men 47.27 (SD = 10.23). The inclusion criteria were the following: 1) the presence of bipolar affective disorder in recent clinical picture, as described in the International Classification of Disease and Health Problems – X, 2) age 20-66 years. The exclusion criteria were as follows: 1) symptoms of organic CNS impairment, 2) dependence on alcohol or other addictive substances, tobacco use (over 4 cigarettes per day), 3) serious somatic disease or features of inflammatory infection in the somatic picture (found during physical examination and OB>10 mm/h), 4) taking medicines that significantly influence the values of the laboratory parameters which this study is based on (lithium, clozapine, hydroxyurea, chemotherapies such as trimethoprim).

The following methods were applied: 1. A sociodemographic questionnaire, designed by the authors, that included basic sociodemographic data as well as information concerning the disease (received from the patients themselves and their medical records). 2. Results of blood tests of the patients of the psychiatric ward routinely performed by the admission to hospital were used for the analysis (the tests were done by the Laboratory of the Neuropsychiatric Hospital in Lublin, which has the International Quality Certificate STRECK / STATS' USA Omaha). 3. Statistical methods used in the analysis: the Kendall Tau b correlation coefficient, the Mann-Whitney U test, the ANOVA test (one-way analysis of variance), independent samples Student's t-test, the independence chi-square test, the Kolmogorov Smirnov normality test and Levene's test. 4. In the analysis of data the following ranges of normal laboratory parameters were used (consistent with the norms of the laboratory) (Table 1).

Table 1. Normal ranges

Results	M – monocytes %	L – lymphocytes %	MCV fl.	WBC thousand
Low	less than 4	less than 20	up to 76	less than 4.0
Norm	4–8	20–45	77–92	4.0–10.0
High (raised)	more than 8	more than 45	93 or more	more than 10.0

RESULTS

SOCIODEMOGRAPHIC DATA

1. Dwelling place – the numbers of rural dwellers (48.8 %) and urban dwellers (51.2 %) in the examined group were similar.

2. Months of birth of patients in the examined group (Fig. 1).

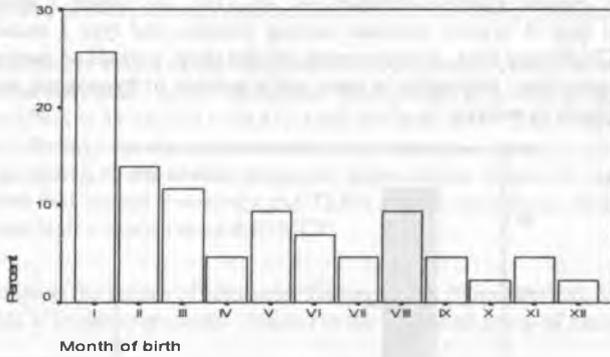


Fig. 1. Percentage of births in particular months in the group of patients

As Figure 1 indicates, most of the patients were born in winter months, i.e. January (22.9%) or February (12.5%). These results are consistent with the observations published in numerous articles worldwide concerning the seasonal nature of births of patients with mood disorders (15). The data on more frequent births of patients with bipolar affective disorders in winter months are interesting.

3. Marital status. The majority of patients were married – 47.6%; with 33.3% the number of divorced persons was also high, as well as that of persons who had never been married – 19.1%. These results confirm other reports about high percentages of unmarried and divorced people among patients with bipolar affective disorder (12).

INFORMATION CONCERNING THE DISEASE

1. Number of hospitalizations. The average number of hospitalizations was 7.79 (SD = 6.4) and ranged from 1 to 21 stays in hospital.

2. Interrelations between the type of bipolar affective disorder and sociodemographic data.

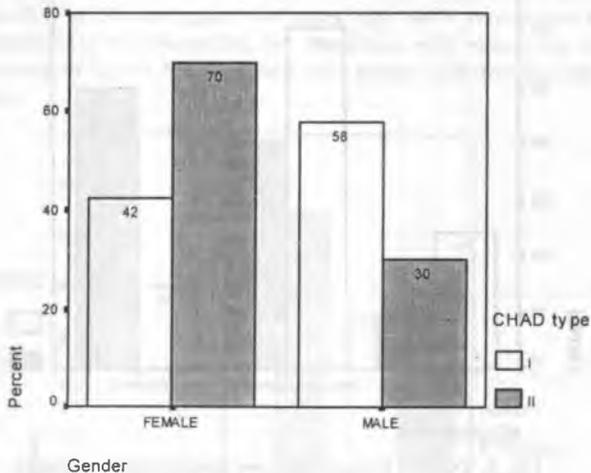


Fig. 2. Type of bipolar affective disorder and sex

A. Type of bipolar affective disorder and sex (Fig. 2). Figure 2 indicates that bipolar affective disorder type II is more common among females, and type I among males ($p < 0.05$, according to the Chi-Square test). As many other articles show, periods of mania typical of bipolar disorder type I occur more frequently in men, while periods of hypomania are characteristic of bipolar disorder type II in women.

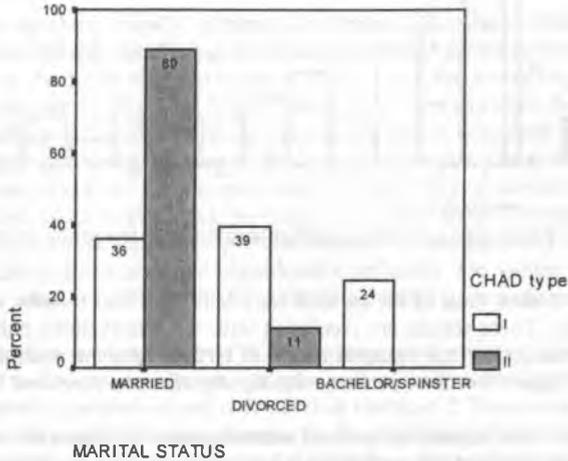


Fig. 3. Type of bipolar affective disorder and marital status

B. Type of bipolar disorder and marital status (Fig. 3). As Figure 3 indicates, married people suffer from bipolar affective disorder type II most often (according to the Chi-Square test $p < 0.05$), while type I is more common among divorced and unmarried people.

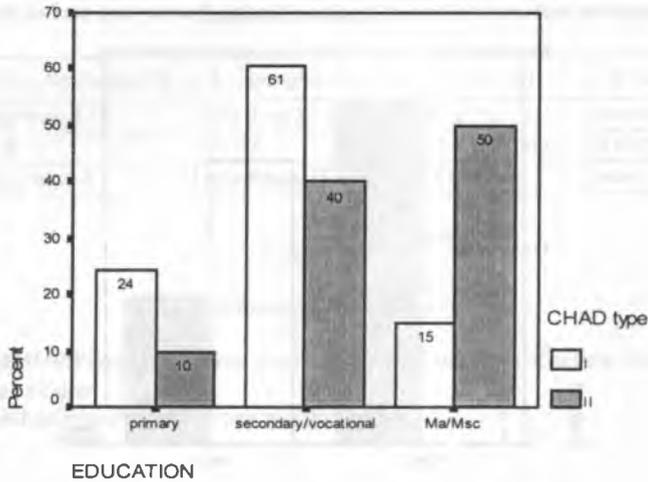


Fig. 4. Type of bipolar affective disorder and education

C. Type of bipolar affective disorder and education (Fig. 4). As Figure 4 indicates, bipolar disorder type II is indeed more prevalent among people with higher education (significance level of the chi-square test $p < 0.05$).

BLOOD LEVELS OF MCV, MONOCYTES AND LYMPHOCYTES IN THE EXAMINED PEOPLE

The average laboratory values of the variables MCV, L (lymphocytes), M (monocytes) based on the patients' blood counts fell within the normal value ranges and were as follows: MCV $X = 91.16$ (SD = 5.89); L% $X = 31.58$ (SD = 10,47); M % $x = 6.29$ (SD = 2.4). The percentage of the ranges of laboratory findings for chosen parameters in the examined group of patients is presented below (Table 2), according to the normal ranges as shown above (Table 1). As Table 2 shows, 72.1% of the patients had normal leukocytes and 73.8% normal monocytes, while as many as 17 patients – 39.5%, had high – raised (abnormal) MCV.

Table 2. Percentage of the ranges of laboratory findings for L (lymphocytes), M (monocytes) and MCV (mean corpuscular volume) in the examined group of patients

Results	Lymphocytes		Monocytes		MCV	
	N	%	N	%	N	%
Low	6	14.0	5	11.9	1	2.3
Normal	31	72.1	32	73.8	25	58.1
High	6	14.0	6	14.3	17	39.5
Total	43	100.0	43	100.0	43	100.0

ANALYSIS OF INTERRELATIONS BETWEEN LABORATORY PARAMETERS AND SOCIODEMOGRAPHIC VARIABLES

1. MCV and demographic data. An analysis of interrelations between marital status, education, dwelling place and MCV showed no statistically significant correlations. However, on making a comparative analysis for age, a significant influence of age on MCV level was observed (the analysis was made on the basis of the Kendall Tau b correlation coefficient, significance level $p < 0.01$). It has been observed that the older the patients the higher their MCV levels.

The average MCV level among female patients fell within the norm – it equaled 89.52 by SD = 6.39, while among male patients the average MCV level equaled 93.0 by SD = 5.03, which ranked as high (raised) (Fig. 5). As Figure 5 indicates, high MCV was detected in 45% of males and in 33% of females. These observations are consistent with reports by other authors (14) regarding the prevalence of higher MCV in men with bipolar affective disorder than in women with the same disease.

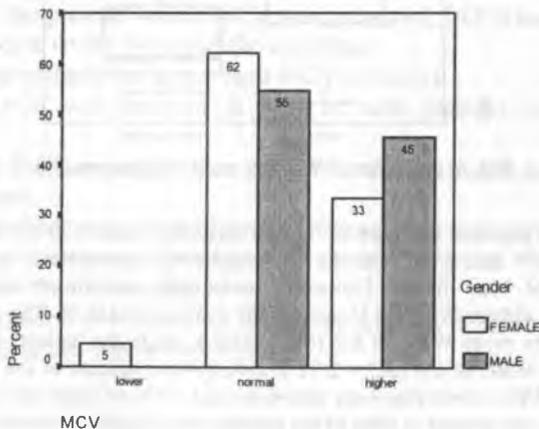


Fig. 5. MCV and the sex of the patients in the examined group

2. Interrelations between monocytes and demographic data. The results of the analysis of the Kendall Tau b correlation coefficient confirmed that age (correlation coefficient = 0.191; $p < 0.04$), sex (correlation coefficient = 0.254; $p < 0.025$) as well as education (correlation coefficient = 0.306; $p < 0.007$) significantly influence the level of monocytes. It can be concluded that the older the patients the higher their monocytes levels. In the analysis of the influence of sex on monocytes the averages of 5.7 (SD = 1.97) for women and 6.8 (SD = 2.67) for men were observed. These results are normal monocytes values for both sexes, but it can be concluded that mean monocytes are higher in men than in women.

ANALYSIS OF INTERRELATION BETWEEN LABORATORY PARAMETERS
AND SELECTED CLINICAL FEATURES OF BIPOLAR AFFECTIVE DISORDER

1. Current phase of disease and leukocytes level (WBC). The patients were divided into two groups depending on which phase of the disorder they were in, i.e. mania or hypomania and depression or hypodepression, for an analysis of their WBC values as compared to mean WBC values (Fig. 6). Student's t-test for equality of means was computed. The assumption of t-test were met. The WBC variable is normally distributed in both groups – according to the Kolmogorov Smirnov test, $p \text{ value} > 0.1$. Variances are homogeneous – Levene's test, $p \text{ value} > 0.1$. On the basis of the t-test it was proved that WBC means are not equal in the two groups ($t = 2.73$, $p \text{ value} < 0.01$). The mean WBC in mania or hypomania equalled 8.4 (SD = 2.15), while in depression or hypodepression the mean WBC values were considerably lower, equaling 6.6 (SD = 1.88). In 71% of the patients in the manic phase and in 93% of the patients in the depressive phase WBC values were normal, while as much as 29% of the patients in the manic phase had raised WBC but only 7% of the patients in the depressive phase. The patients in the manic phase had considerably higher WBC values. Figure 6, based on quartiles, illustrates the significant difference in WBC between mania and depression.

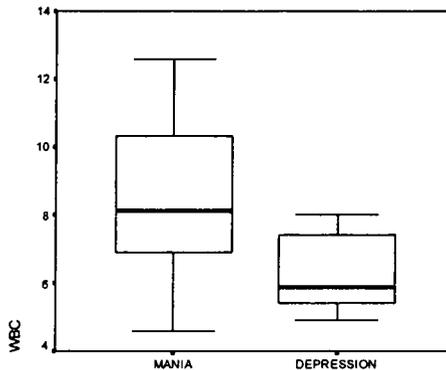


Fig. 6. Quartiles of WBC in mania and depression

2. Interrelations between the type of bipolar disorder (type I or II) and monocytes (M), lymphocytes (L), MCV and WBC. For the M, L and MCV parameters, statistically significant correlations have not been found. However, statistically significant interrelation has been discovered for WBC (Mann-Whitney U coefficient = 69.5, $p < 0.005$). The patients with bipolar disorder type I had the mean WBC of 8.2 (SD = 2.05), while the patients with bipolar disorder type II had the mean WBC of 6.4 (SD = 2.31). Twenty-four percent of the patients with bipolar disorder type I had WBC levels that were above normal, 76% of them had normal WBC levels. The WBC parameter was normal in 90% of the patients with bipolar disorder type II; it was raised (high) in 10% of patients.

DISCUSSION

Abnormal increase in MCV in 39.5% of the patients may suggest its connection to folic acid and/or vitamin B12 deficiencies in patients with bipolar affective disorder. The concentration of these vitamins is apparent in the blood count, i.e. in MCV (5, 4, 9, 11, 14). Since the 1960s, acid folic and vitamin B12 deficiencies in such medical conditions as depression in the course of uni-or bipolar affective disease (3, 9, 14, 11), dementia (4), and psychotic disorders (14, 6), have been the focus of wide research. There are nations whose eating habits promote a diet rich in acid folic, which is known to contribute to low morbidity rate for depression (e.g. Taiwan or Hong Kong).

A low intake of folic acid may be a risk factor for depression (3, 9, 11). Consequently, using folic acid and vitamin B12 in the treatment of depression in uni-and bipolar disorders in people with diagnosed deficiencies of these vitamins significantly improves the prospects, quickens clinical improvement and enhances a faster reaction to antidepressant, normothymic and neuroleptic drugs (14). Both vitamin B12 deficiency as well as folic acid deficiency play an important role in patients with depressive disorders, including the depressive period in the bipolar affective disorder. Many articles show that the prevalence of these deficiencies in depressive patients is meaningfully higher than in control groups of healthy people (14, 3, 9). There are few articles on the deficiencies of these vitamins in bipolar affective disorder alone. The vitamins, however, are important to the human body as they take part in the metabolism of S-adenosylmethionine (SAM), which, as a source of methyl groups, plays a deciding role in the functioning of the CNS (10). The influence of folic acid on the phospholipids of the cellular membranes of neurons is also significant.

The results showing a higher percent of raised MCV in men (45%) as opposed to women (33%) seem interesting. These differences have also been observed by other authors (14), especially men suffering from depression – in recurrent depressive disorders as well as in periods of depression in bipolar affective disorders. This is possibly related to the disease rather than, e.g., abuse of alcohol, which is more common among men. Only people who do not drink alcohol were admitted to this study, in cases of any uncertainty patients were disqualified.

The increase in MCV with age was also observed. This reflects other research articles published worldwide (3, 9, 11). There is, however, little data on the increase in WBC during the periods of mania compared with depression. This connection seems interesting, yet it must be confirmed by further research.

CONCLUSIONS

1. In 39.5% of the patients whose MCV was measured, 14.0% had monocytes levels and 14.0% lymphocyte levels increased above normal.
2. The older the patients the higher their MCV ($p < 0.01$).
3. Increased MCV was detected in 45% of male patients and 33% of female patients.
4. The average MCV among women patients was classified as normal, while it was above normal for men.
5. Age, sex, and education significantly influence the monocytes level. It can be concluded that the older the age the higher the monocytes level. The mean monocytes level is higher in men than in women.
6. WBC was raised above normal in 29% of the patients in the manic phase but only in 7% of the patients in the depressive phase.

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SUMMARY

The effect that folic acid and vitamin B12 deficiencies have on the nervous system, and especially on the mental state of the patient (which is reflected in some of the laboratory parameters in the blood count, e.g. MCV) is an interesting problem. Low concentration of these vitamins in the blood may result in weaker response to medication in both mania and depression in bipolar affective disorder. A lot of research has been devoted to unipolar depression, while there is still little scientific report on vitamin deficiencies in particular stages of bipolar affective disorders. Abnormal increase in MCV in 39.5% of our patients may suggest its connection with folic acid and/or vitamin B12 deficiencies in patients with bipolar affective disorder. The objective of this study was to detect possible relations between selected laboratory parameters of the blood picture (MCV, levels of leukocytes, monocytes, and lymphocytes) and variables connected with sociodemographic data of the examined patients with bipolar affective disorder, its course, clinical features, stages and the type of the disorder (type I or II). The examined group consisted of 43 patients (21 females, 22 males) of the Neuropsychiatric Hospital in Lublin, hospitalized with diagnosed bipolar affective disorder as described in the ICD-10. The average age in the group was 48.58 years (SD = 11.26), the average age for women was 49.95 (SD = 12.35), for men 47.27

(SD = 10.23). A sociodemographic questionnaire was applied with further information received from the patients themselves and their medical records. Results of blood tests of the patients of the psychiatric ward routinely performed by the admission to hospital were used in the analysis (the tests were done by the Laboratory of the Neuropsychiatric Hospital in Lublin). 1. In 39.5% of the patients whose MCV was measured, 14.0% had monocytes levels and 14.0% lymphocyte levels increased above normal. 2. The older the patients the higher their MCV ($p < 0.01$). 3. Increased MCV was detected in 45% of male patients and 33% of female patients. 4. The average MCV among women patients was classified as normal, while it was above normal for men. 5. Age, sex, and education significantly influence the monocytes level. It can be concluded that the older the age the higher the monocytes level. The mean monocytes level is higher in men than in women. 6. WBC was raised above normal in 29% of the patients in the manic phase but only in 7% of the patients in the depressive phase.

Analiza wybranych parametrów laboratoryjnych na podstawie morfologii krwi u pacjentów z zaburzeniami afektywnymi dwubiegunowymi

Interesującym problemem jest wpływ niedoboru kwasu foliowego i witaminy B12 na układ nerwowy i zwłaszcza stan psychiczny chorego (co znajduje swoje odbicie w niektórych parametrach laboratoryjnych morfologii krwi, np. MCV). Niskie stężenia tych witamin we krwi mogą przyczyniać się do słabszej odpowiedzi na leczenie zarówno stanów maniакаalnych jak i depresyjnych w przebiegu zaburzeń afektywnych dwubiegunowych. Więcej badań na świecie poświęcono na ten temat depresji jednobiegunowej, natomiast nadal jest mało doniesień naukowych dotyczących niedoborów witaminowych w poszczególnych fazach zaburzeń afektywnych dwubiegunowych. Podwyższone powyżej normy wyniki parametru laboratoryjnego MCV u 39,5 % pacjentów w naszej pracy mogą świadczyć o związku tych danych z niedoborami kwasu foliowego i/lub witaminy B12 w badanej grupie chorych z zaburzeniami afektywnymi dwubiegunowymi. Celem pracy było poszukiwanie związków pomiędzy wybranymi parametrami laboratoryjnymi morfologii krwi (MCV, poziomem leukocytów, monocytów, limfocytów) a zmiennymi socjodemograficznymi badanych pacjentów z CHAD – zaburzeniami afektywnymi dwubiegunowymi, przebiegiem, cechami klinicznymi oraz fazami choroby i typem CHAD (typ I i II choroby). Grupę badaną stanowiło 43 pacjentów (21 kobiet, 22 mężczyzn) hospitalizowanych w Szpitalu Neuropsychiatrycznym w Lublinie z rozpoznaniem zaburzeń afektywnych dwubiegunowych wg ICD-10. Średnia wieku w badanej grupie wynosiła 48,58 lat (SD = 11,26), odpowiednio dla kobiet 49,95 lat (SD = 12,35), dla mężczyzn 47,27 lat (SD = 10,23). Zastosowano kwestionariusz socjodemograficzny, a inne dane uzyskiwano od samych pacjentów oraz z dokumentacji medycznej. Wykorzystano do analizy wyniki morfologii krwi rutynowo pobieranej u pacjentów na oddziale psychiatrycznym przy przyjęciu do szpitala (wyniki pochodziły z Laboratorium Szpitala Neuropsychiatrycznego w Lublinie). 1. U 39,5 % badanych w zakresie MCV, 14,0 % w odniesieniu do monocytów oraz 14,0 % limfocytów stwierdzono poziomy tych parametrów przekraczające górną granicę normy. 2. Im wyższy wiek badanych, tym wyższy poziom MCV ($p < 0,01$). 3. U 45 % ogółu badanych mężczyzn oraz 33 % kobiet stwierdzono podwyższony poziom MCV. 4. Średni poziom MCV w grupie kobiet mieści się w granicach normy, natomiast w grupie mężczyzn plasuje się w przedziale wyników wysokich. 5. Wiek, płeć oraz wykształcenie istotnie wpływają na poziom monocytów. Można wnioskować, że im wyższy wiek, tym wyższy poziom monocytów. Mężczyźni mają wyższy przeciętny poziom monocytów niż kobiety. 6. Podwyższony powyżej górnej granicy normy parametr WBC zaobserwowano u 29 % pacjentów z manią, a tylko u 7 % z depresją.