

1 Central nervous system involvement in patients with acute myeloid leukemia

2 Abstract

3 **Background/aim:** To evaluate the incidence, clinical features, risk factors, and
4 prognosis of central nervous system (CNS) involvement in patients with acute myeloid
5 leukemia (AML).

6 **Materials and methods:** All AML patients who were admitted to Hacettepe University
7 hospital between 2000 and 2021 were evaluated. The medical records of 548 AML
8 cases were retrospectively analyzed.

9 **Results:** The frequency of CNS involvement was 2.4% (n=13) at diagnosis and 4.6%
10 (n= 25) at diagnosis or during follow-up. Parenchymal involvement was seen in 5
11 patients, leptomeningeal involvement was seen in 11 patients. Three patients had both
12 leptomeningeal and parenchymal involvements and 6 patients had optic nerve or ocular
13 involvement. In univariate analysis; younger age and extramedullary involvement at
14 diagnosis were associated with CNS disease at diagnosis and extramedullary
15 involvement at diagnosis was associated with CNS disease during follow-up. In
16 multivariate analysis; younger age and extramedullary involvement at diagnosis were
17 associated with CNS disease at diagnosis and during follow-up respectively. Median
18 overall survival was 5.4 months in patients with CNS disease at diagnosis and 16.9
19 months in patients with CNS disease during follow-up and 16.2 months in patients with
20 no CNS disease.

21 **Conclusion:** CNS disease is a rare complication of AML. Younger age and
22 extramedullary involvement at diagnosis are risk factors for CNS involvement.

23 **Keywords:** Acute myeloid leukemia, central nervous system involvement, risk factors

24 1. Introduction:

1 Acute myeloid leukemia (AML) was the most frequent acute leukemia in adult patients.
2 The incidence is around 3-5 per 100,000 [1]. The central nervous system (CNS)
3 involvement in patients with AML is rare and not identified certainly. Therefore
4 baseline screening is not recommended for the patients without symptoms [2, 3].
5 Clinically symptomatic CNS involvement is not common after treatment. The factors
6 related to CNS involvement are reported as monocytic component predominant AML,
7 systemic relapse of acute promyelocytic leukemia (APL), presence of inversion 16,
8 chromosome 11 anomalies, hyperleukocytosis, lactate dehydrogenase (LDH) elevation,
9 and *FLT3*–internal tandem duplication (ITD) mutations [4-9]. Leukemic cells
10 expressing CD56 adhesion molecule on cell surface were also investigated as a risk
11 factor for CNS involvement [10, 11]. It was found that CNS involvement in patients
12 with AML usually presents as leptomeningeal involvement, but it may also rarely
13 present as a mass in the brain parenchyma in acute myelomonocytic leukemia (French-
14 American-British, FAB, AML-M4 subtype) patients with *inv(16)(p13q22)* or
15 *del(16)(q22)* inversion 16 (+) AML [5].
16 In this study, we aimed to determine the incidence, type, risk factors, and prognosis of
17 CNS involvement in patients with AML.

18 **2. Materials and Methods:**

19 All AML patients who were admitted to Hacettepe University Faculty of Medicine
20 Department of Hematology between 2000 and 2021 were evaluated. Clinical and
21 laboratory data were obtained from patient files and the hospital electronic database.
22 The diagnosis of AML and morphological classification were done using valid
23 international criteria at the time of presentation using bone marrow and peripheral blood
24 microscopic evaluations and flow cytometric analysis. Organomegaly,

1 lymphadenopathy, gum hypertrophy, and histologically documented any tissue
2 involvement were evaluated as extramedullary involvement. The diagnosis of CNS
3 involvement was done by radiological evaluations in patients with suspicious
4 neurological symptoms. Cerebrospinal fluid analysis, biopsies, and ophthalmological
5 examinations were also performed when clinically indicated.

6 Treatment of non- APL AML in patients who were considered suitable for intensive
7 therapy was done by a 3+7 regimen containing an anthracycline (idarubicin,
8 mitoxantrone, or daunorubicin) for 3 days and standard-dose cytarabine for 7 days. Two
9 to 4 cycles of high-dose cytarabine regimens were applied for consolidation[12]. APL
10 patients were treated with all-trans-retinoic acid and anthracycline-based induction and
11 consolidation (generally 3 cycles) regimens[13]. Routine CNS disease evaluations and
12 prophylaxis were not done in any type of disease. Allogeneic stem cell transplantation
13 was aimed in patients without favorable AML subtypes (i.e. APL, CBF-type, and
14 during last few years mutated NPM1/without FLT3-ITD, and biallelic CEBPA
15 mutation).

16 The Ethics Committee of Hacettepe University Faculty of Medicine approved the study
17 protocol (date: 30.04.14, registration number: GO 14/234).

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19 **2.1. Statistical analyzes**

20 SPSS version 17.0 (SPSS Inc, Chicago, IL) was used for statistical analyzes.
21 Categorical data were expressed as number (and/or ratio). Continuous data were shown
22 as median (range). Chi-square test was used to determine whether there was any
23 difference between the CNS involvement subgroups (i.e., no involvement, involvement

1 at diagnosis, involvement at relapse) in terms of categorical variables. In the statistical
2 comparison of continuous variables between the CNS involvement groups, Kruskal-
3 Wallis H test was used. Univariate and multivariate logistic regression analyzes were
4 performed to determine possible parameters at diagnosis that may be related to CNS
5 involvement at the time of diagnosis, at relapse, or anytime. ECOG performance score
6 was excluded from these analyzes because the presence of CNS involvement at the time
7 of diagnosis is expected to impair performance status.

8 Overall survival was used for prognostic evaluation. The time from diagnosis to death
9 for any reason was calculated. The patients who were still alive when they were last
10 seen, were censored on this date. Overall survival was calculated according to the
11 Kaplan-Meier method. The comparison between survival curves was done by log-rank
12 test.

13 P values < 0.05 were considered statistically significant. The parameters with at least
14 borderline significance ($p < 0.1$) in univariate logistic regression analysis were included
15 in the multivariate logistic regression analysis.

16 **3. Results:**

17 **3.1. Patients**

18 Five hundred forty-eight patients were included in the study. 58% of them were male (n
19 =318) and 42% were female (n=230). The median age was 50.9 (18.3-88,1.0). The
20 median follow-up duration of the surviving patients was 32.3 (0.03-358.7) months.
21 Patient characteristics are presented in Table 1.

22 **3.2. Incidence and type of CNS involvement**

1 The incidence of CNS involvement in patients with AML was 2.4% (n= 13) at the time
2 of diagnosis. Twelve cases developed CNS disease during follow-up in spite of no
3 involvement at the time of diagnosis. So the frequency of CNS involvement at the time
4 of diagnosis or follow-up was 4,6% (n= 25).

5 Parenchymal involvement was seen in 5 patients, leptomenigeal involvement was seen
6 in 11 patients. Three patients had both leptomenigeal and parenchymal involvement
7 and 6 patients had optic nerve or ocular involvement. Cranial palsy, mental alteration,
8 head and neck pain, seizure, paralysis, blurred vision, and loss of balance were seen as
9 symptoms in patients with CNS involvement.

10 **3.3. Risk factors for CNS involvement**

11 Univariate and multivariate analyzes for CNS involvement at diagnosis, at relapse and
12 anytime are summarized in Table 2. In the univariate analysis, age, white blood cell,
13 LDH, $\beta 2$ microglobulin, extramedullary involvement, number and location of
14 involvement, AML subtypes, and flow cytometry results were evaluated. Age was
15 associated with CNS involvement at the time of diagnosis in univariate (p: 0,001) and
16 multivariate analyzes (p:0.006). Extramedullary involvement at diagnosis was related to
17 CNS involvement during follow-up in univariate (p:<0.001) and multivariate analyzes
18 (p:0.001). Both age and extramedullary involvement were related to CNS involvement
19 at any time in univariate(p:0.002 and p:0.001, respectively) and multivariate (p:0.002
20 and p:0.001, respectively) analyzes.

21 **3.4. The prognosis**

22 The median overall survival duration of patients with CNS involvement at diagnosis
23 (5.4 months [0-13.6; 95% confidence interval, CI]) was shorter than those without CNS

1 involvement (16.2 months [10.4-22; 95% CI]) or CNS involvement during follow-up
2 (16.9 months [0-62.4; 95% CI]). No statistical significance was observed (p: 0.5)
3 probably due to the low patient number (Figure).

4 **4. Discussion**

5 In the literature, data about CNS involvement in adult patients with AML is rare. The
6 CNS involvement data generally comes from studies involving pediatric AML patients
7 [14, 15]. In our study, CNS involvement in AML was 2.4% at the time of diagnosis, and
8 4,6% throughout the disease course. Abbot et al. and Felix et al. showed CNS
9 involvement in 29% and 16% of patients at the time of diagnosis in pediatric population
10 respectively. [16, 14]. These CNS involvement rates were quite higher than adult
11 population. Del Principe et al. showed CNS involvement with routine CNS evaluation
12 regardless of clinical symptoms in 11% of adult patients at the time of diagnosis [17]. In
13 other studies, CNS involvement rates were between 0.6% and 1.8% in patients with
14 AML at the time of diagnosis. CNS involvement rates were between 2,9% and 5.1%
15 throughout the disease [8, 7, 18, 19, 9]. Del Principe et al. reported that FAB M4-M5
16 type and high LDH levels were associated with CNS involvement at the time of
17 diagnosis [17] Cheng et al. showed that high white blood cell counts and inversion 16
18 were associated with CNS involvement at the time of diagnosis. Alakel et al. showed
19 that complex karyotypes, high LDH levels, FAB M5, and FLT3 mutation were related
20 to CNS involvement at the time of diagnosis [8]. Rozovski et al reported that young age,
21 African-American ethnicity and high LDH levels were risk factors for CNS
22 involvement. Holmes et al. [5] and Shihadeh et al. [6] reported a higher incidence of
23 CNS involvement in APL and FAB M4-M5 AML respectively compared to other AML
24 types. Some studies have shown that high white blood cell count, peripheral

1 eosinophilia, high LDH level, male gender, age <50 were risk factors for CNS
2 involvement at the time of diagnosis [20, 18, 21]. Jabbour et al showed that age, high
3 LDH level, and FLT 3 mutation were independent risk factors for CNS involvement in
4 multivariate regression model. In our study, younger age was associated with CNS
5 involvement at the time of diagnosis. We found that extramedullary involvement at
6 diagnosis was related to CNS involvement during follow-up. Age and extramedullary
7 involvement were related to CNS involvement at any time.

8 Although CNS involvement at diagnosis was not a prognostic factor in pediatric
9 patients with AML [16, 15], it was associated with poor prognosis in adult AML
10 patients [20, 22]. Castagnola et al. reported that median overall survival after CNS
11 involvement was 2 months (1-5 months) [2]. Del Principe et al. and Alakel et al.
12 showed that patients with CNS involvement at the time of diagnosis had shorter overall
13 survival [17, 8]. In our study, the median overall survival in patients with CNS
14 involvement at the time of diagnosis was shorter than patients who did not experience
15 this complication as similar to the other studies. There was no statistically significant
16 difference between the two groups probably due to low number of patients with CNS
17 disease.

18 Our study has the advantage of a high total patient number, diagnosed during two
19 decades. We are aware that it has some limitations inherent to retrospective studies,
20 such as some missing data.

21 **5. Conclusion:**

22 CNS involvement occurs rarely (4.6%) in AML. Younger age and extramedullary
23 involvement at diagnosis are risk factors for CNS involvement.

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12 Table 1. Characteristics of the patient groups.

	CNS involvement				P
	At diagnosis (N: 13)	Only during relapse (N: 12)	Anytime (N:25)	Absent (N: 523)	
Gender (F/M)	4/9	6/6	10/15	220/303	0.61
Age (median, range)	31.4 (18.9-49.5)	48.5 (25.6-72.7)	40.2 (18.9-72.7)	51.9 (18.3-88.1)	<0.001
Age (<65 vs older)	13/0	11/1	24/1	391/132	0.016

ECOG (0-1 vs 2-4)	7/6	8/4	15/10	419/93	0.018
De novo/secondary AML	13/0	9/3	22/3	445/78	0.19
AML M4-5 vs other	2/5	4/5	6/10	76/221	0.44
White blood cell (median, range)	10600 (2300- 231600)	39850 (700- 98700)	18900 (700- 231600)	7850 (200- 321300)	0.19
White blood cell ($>30 \times 10^9/L$) (yes/no)	3/10	6/4	9/14	129/335	0.075
Lactate dehydrogenase (median, range)	632 (236- 7222)	552 (277- 2755)	619 (236- 7222)	490 (65- 8490)	0.43
Lactate dehydrogenase (>1000 IU/L) (yes/no)	3/6	3/5	6/11	71/243	0.47
B2-microglobulin (median, range)	1950 (1402- 2705)	1584 (430- 1733)	1584 (430- 2705)	2243 (818- 8372)	0.12
Other extramedullary involvement (yes/no)	7/5	9/2	16/7	104/360	<0.001
ELN* genetic risk group (Favorable/Intermediate/High)	2/3/3	3/3/4	5/6/7	81/148/55	0.35
CBF**-type vs other	1/6	1/7	2/13	27/195	0.98
APL [@] vs others	1/5	1/5	2/10	33/153	0.99
Duration between diagnosis-CNS involvement (months)	0 (0- 0.47)	8.6 (0.8- 49.2)	0.46 (0- 49.2)	NA	
Patern of involvement	5, 2, 1, 4	6, 1, 4, 1	11, 3, 5,	NA	0.25

(LM ^{@@} , LM&P [#] , P, Optic nerve/Eye)			5		
Method of diagnosis (Clinical&radiological/histopathologic al)	8/4	9/3	17/7	NA	0.65
Systemic high-dose ^{##} chemotherapy/intratecal chemotherapy/ CNS radiotherapy	7/8/2	1/5/1	8/13/3	NA	
Allogeneic stem cell transplant (yes/no) [*]	1/12	5/7 ^{**}	6/19	131/390	0.14

- 1 The sum of the values in the cells may be less than the total number due to missing
- 2 values *European LeukemiaNet, **core-binding factor, @acute promyelocytic leukemia,
- 3 @@leptomeningeal, # parenchymal, ##Higher than 1g/m² cytarabine and/or 500 mg/m²
- 4 methotrexate, *before CNS involvement in 4 cases, NA: not applicable
- 5
- 6 Table 2. Univariate and multivariate analyzes for CNS involvement at diagnosis, at
- 7 relapse and anytime.

	Univariate logistic regression [*]		Multivariate logistic regression ^{**}	
	Exp(B) (95% CI [#])	P	Exp(B)	P
Risk factors for CNS involvement at diagnosis				
Age	1.089 (1.037-1.143)	0.001	1.091 (1.025-1.162)	0.006
Lactate	1 (1-1.001)	0.075		

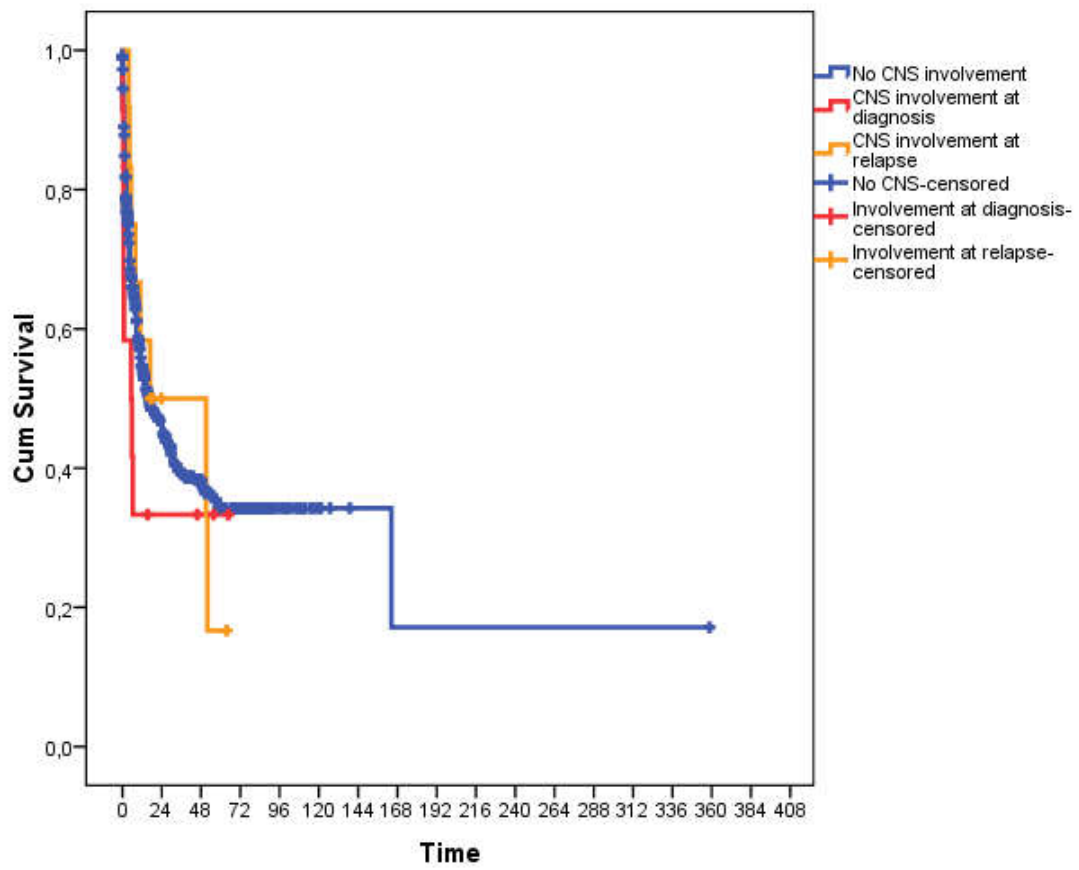
dehydrogenase				
Other extramedullary involvement	4.48 (1.39-14.4)	0.012		
Risk factors for CNS involvement at relapse				
>30x10 ⁹ /L white blood cell	3.127 (0.938-10.421)	0.063		
Other extramedullary involvement	16.591 (3.581-76.856)	<0.001	12.934 (2.712-61.681)	0.001
Risk factors for CNS involvement anytime				
Age	1.044 (1.016-1.073)	0.002	1.049 (1.017-1.082)	0.002
Other extramedullary involvement	7.912 (3.170-19.747)	<0.001	6.263 (2.428-16.156)	<0.001

1 *Parameters selected for multivariate analysis (P<0.1) are presented. ** Significant

2 parameters (P<0.05) are presented. # confidence interval

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2 Figure. Overall survival according to CNS involvement status

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