Iran J Psychiatry 2021; 16: 3: 370-373

Case Report

Can Neutrophil-Lymphocyte Ratio Be a Useful Criterion for Neuroleptic Malignant Syndrome in the Absence of Leukocytosis?

Tevfik Kalelioglu[1*], Guler Celikel[2], Ozlem Devrim Balaban[2], Nesrin Karamustafalioglu[2], Jennifer Kim Penberthy[1]

Abstract

Objective: Neuroleptic malignant syndrome (NMS) is a rare but severe side effect of antipsychotic medication. Neutrophil-lymphocyte ratio (NLR) is a simple marker used to measure systemic inflammation.
Method: In this case report we explore the relationship of inflammation in the etiology of NMS. In our case involving NMS, although there was no leukocytosis, the NLR was increased up to systemic infection levels.
Conclusion: We hypothesized that systemic inflammation may take a role in developing NMS. If so, NLR could be a new marker of NMS that may be able to provide more sensitive results than leukocyte levels.

Key words: *Antipsychotic Agents; Inflammation; Lymphocyte; Neuroleptic Malignant Syndrome; Neutrophil*

1. Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, Virginia, United States of America.
2. Department of Psychiatry, Bakırköy Mental Health Research and Teaching Hospital, Istanbul, Turkey.

***Corresponding Author:**
Address: Department of Psychiatry and Neurobehavioral Sciences, University of Virginia, Charlottesville, Virginia, United States of America, Postal Code: 22903.
Tel: 90-544834 6643, Email: tevfikkaleli@hotmail.com

Article Information:
Received Date: 2019/04/23, Revised Date: 2021/02/14, Accepted Date: 2021/03/09

Neuroleptic malignant syndrome (NMS) is a severe side effect of antipsychotic medication. Although mechanisms underlying NMS are not fully understood, hypodopaminergic state has been proposed as a potential triggering factor. The main symptoms of NMS are hyperthermia, muscle rigidity, autonomic imbalance, and changes in consciousness after initiation of antipsychotic treatment (1).

Laboratory findings of NMS may include increased levels of creatinine phosphokinase (CPK), leukocyte, and liver enzymes. About 40% of cases demonstrate increase in leukocyte levels (2). In our case report we aimed to discuss the role of inflammation in NMS and the usefulness of neutrophil to lymphocyte ratio (NLR) as a potential criteria to utilize, even in the absence of leukocytosis .

Case Report

A 30-year-old woman with a 17-year history of bipolar affective disorder was transferred to acute care psychiatry service with acute exacerbation of symptoms of manic episode. She had no previous medical or substance abuse history. Before hospitalization, zuclopenthixol acuphase 50 mg IM, haloperidole 10 mg IM, biperiden five mg IM., chlorpromazine 100 mg IM. were applied as needed because of affective elevation at another hospital. At admission, the patient received treatment with clozapine 800 mg/day, amisulpirid 800 mg/day, and chlorpromazine 200 mg/day. She was treated with haloperidol 20 mg/day IM, and biperiden 10 mg/day IM. The dose of clozapine, chlorpromazine, and valproat were diminished gradually and amisulpride was stopped .

On the seventh day of hospitalization, the patient developed rigidity, tremor and incontinence without fever. Haloperidol was stopped for probability of NMS, and ECT was initiated on the eighth day of hospitalization. On day 11 and 12 of hospitalization, haloperidol IM was used for acute agitation. Rigidity, confusion, diaphoresis, tremor, tachycardia, and incontinence occurred at the following day. The patient's temperature was 36.3 C°, heart rate was 110 per minute, respiratory rate was 15 to-20 per minute, blood pressure fluctuated between 90/70 and 110/70 mm/hg, and oxygen saturation was 97%. Laboratory findings revealed increased levels of CPK (> 2000 IU/L; normal range= 20-200), aspartate aminotransferase (AST) (188 U/L; normal range= 5-45), alanine transaminase (ALT) (66 U/L, normal range= 5-40), lactate dehydrogenase (LDH) (581 IU/L; normal range = 60-200), C-reactive protein (CRP) (1.84 mg/dL; normal range= 0-0.5), and erythrocyte sedimentation rate (ESR) (44 mm/hour; normal range= 0-20). Leukocyte count (6.35 103/µL; normal range= 4.1-11.2) was in normal range. Neuroimaging, EEG (electroencephalogram), and chest x-ray imaging showed no abnormalities. Urinalysis and thyroid hormones were in normal range. There was no focus for infection (pulmonary, urinary etc).

On day 19, a confusional state developed and by day 20 of the hospitalization, bromocriptin 5mg/day was initiated with the diagnosis of NMS according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders). On the 29th day of admission, all symptoms of NMS disappeared. Antipsychotic treatment was initiated with clozapine 12.5 mg/day because of agitation. The patient developed rigidity as cogwheel sign, dystonia, altered mental status, and autonomic dysregulation after 6 days of clozapine initiation and was admitted to the intensive care unit on the 37th day of admission. After 6 days of hospitalization in intensive care unit, she was transferred back to psychiatry service. On the 43th day of hospitalization, the patient's bromocriptine was elevated to 10 mg/day to address rigidity and dystonia. At the 57th day, no symptom of NMS were observed (nearest NLR value mesasured on the 62nd day). The patient's informed consent was provided for the publication of this case presentation.

Discussion

Previous case reports suggest an association between systemic inflammatory response and developing NMS (3, 4). Increased levels of acute phase reactants such as α-1 antichymotrypsin and fibrinogen, elevated ESR, C-reactive protein, and IL-6 cytokine levels, decreased negative acute phase reactants as albumin, serum Fe indicate that an inflammatory reaction occurs in NMS (3, 4). Based on these findings, Anglin et al. (2010) speculate that there may be a neuroimmunological involvement in these cases. The authors argue that NMS and acute phase response have common findings of fever, tachycardia, diaphoresis, unstable blood pressure, tissue injury, altered consciousness, and leukocytosis (5).

The NLR is a relatively new and simple marker used to measure systemic inflammation (6). In previous studies, mean NLR levels of neuropsychiatric illness were reported in bipolar disorder manic episode as 3.09 ±1.9 (7), 2.8±1.67 (8), in euthymic episode as 2.8 ± 0.81 (7), and in schizophrenia as 2.6 ± 1.1 (9). NLR is a relatively new marker for psychiatric disorders; thus, no cut-off level or disease-specific values have been identified.

A recent study, investigating the NLR values in healthy adults has shown that NLR has ranged from 0.78 to 3.53 (10). In another study conducted by Gurol et al. (11), NLR levels in a healthy group were 4.19 ± 4.36, a group with local infection had findings of 5.68 ± 8.99, and findings for systemic infection were 11.78 ± 14.04, with additional findings for sepsis as13.16 ± 6.38, and septic shock as 16.87 ± 9.55. The authors recommend a cut-off NLR value <5 for healthy group. Increasing levels of NLR indicates different levels of infections such as local infection (5 to 10), systemic infection (10 to 13), sepsis (13 to 15), and septic shock (≥15). (11) This study aimed to make a comparison and better understanding of NLR

findings. In a recent study, it has been suggested that NLR levels above 4 may be useful for diagnosing NMS (12). In our case, the patient's NLR level was above 9 at the time of NMS diagnosis before initiation of NMS treatment. We did not observe fever and leukocytosis during hospitalization. Although leukocyte levels were in a normal range, NLR levels were nearly as high as those found at a systemic infection level. In addition, the NMS development after starting clozapine showed a NLR level of >5, which is between the cut-off level of local infection levels. Strikingly, in our case we observed a connection between NMS treatment and NLR levels. Leukocyte, neutrophil, lymphocyte counts and NLR levels during hospitalization are presented in Table 1 .

Table 1. Laboratory Follow Up during Hospitalization

Day of hospitalization	Clinical Status and Treatment	WBC (10^3/μL)	NEU (10^3/μL)	LYM (10^3/μL)	NLR
Day 1	-Clozapine 600 mg/day↓, valproat↓, clorpromazine 100mg/day↓, amisulpirid stopped, -Haloperidol 20 mg/day IM. And biperiden 10 mg/day IM. initiated				
Day 2	-Clorpromazine 300 mg/day ↑				
Day 7	-Rigidity, tremor, neck dystonia, incontinence (+) -Fever (-) -Haloperidol IM. stopped	6.35	5.13	0.52	9.73
Day 8	-Valproat stopped -ECT initiated				
Day 11-12	-Haloperidol IM (p.r.n)				
Day 13	-Rigidity, CPK↑, confusion, diaphoresis, tremor, tachycardia, incontinence (+) -Fever (-) -All medication stopped -i.v. hydration	5.86	4.62	0.50	9.13
Day 15-19	-i.v. hydration + biperiden -Bromocriptine was initially held because of differential diagnosis	4.93 4.45	3.88 3.10	0.49 0.69	7.88 4.44
Day 19	-Confusion(+++)	5.64	4.60	0.46	9.82
Day 20	-Bromocriptin 5 mg/day initiated -Broncospasm(+)	4.85	3.82	0.49	7.66
Day 24		3.44	2.60	0.37	7.01
Day 26		4.54	3.36	0.70	4.74
Day 29	-No symptom of NMS -Excitation -Clozapine 12.5 mg/day initiated	5.59	3.93	1.08	3.63
Day 33	-Clozapine 50 mg/day -Dystonia at neck-biperiden i.m.				
Day 34	-Rigidity, dystonia, cogwheel sign, altered mental status (+), autonomic dysregulation -Fever (-) -Clozapine stopped, i.v hydration	5.1	3.89	0.71	5.47
Day 37	-Confusion to stupor progression, vomiting, autonomic dysregulation -Transferred to intensive care unit.				
Day 37-42	-Bromocriptine 5 mg/day, i.v. hydration	3.86 3.35 4.38	2.45 2.27 3.13	0.95 0.64 0.66	2.57 3.50 4.72

Day 42	-Interned to psychiatry service				
Day 43	-Rigidity, dystonia, cogwheel sign (+) -Fever (-) -Bromocriptine 10 mg/day↑				
Day 51		4.27	2.98	0.72	4.1
Day53	-Added lorazepam for excitation				
Day 55	-ECT was stopped at 15th session				
Day 57	-No symptoms of NMS -Bromocriptine 2.5 mg/day ↓				
Day 62		3.85	2.81	0.70	3.96
Day 75		3.92	2.65	0.67	3.95
Day 82		3.99	2.74	0.83	3.30

WBC; white blood cell, **NEU**; Neutrophil, **LYM**; Lymphocyte, **NLR**; Neutrophil-lymphocyte ratio.

Limitation

Methodologically, it is difficult to perform a clinical study regarding the relationship between inflammatory markers and NMS because of the rarity of cases and difficulties in storing blood specimens. It may be insufficient to support our hypothesis over one case.

Conclusion

In our case NLR level was as high as systemic infection levels, even though with the absence of leukocytosis. In our opinion, NLR could be a new criterion of NMS which would allow for more sensitive findings than leukocyte levels alone. Further studies are needed to support our hypothesis. Specifically, we propose that NLR may be a useful choice for a prospective study to test the neuro-inflammation hypothesis of NMS.

Acknowledgment

None.

Conflict of Interest

None.

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