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Detection of Demografic and Clinical Risk Factors Associated with Neuroleptic Malignant Syndrome: Evaluation of Cases in The Turkish Literature

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ABSTRACT

Detection of demografic and clinical risk factors associated with neuroleptic malignant syndrome: evaluation of cases in the Turkish literature

Objective: Neuroleptic malignant syndrome (NMS) is a severe adverse effect which can be seen during antipsycotic treatment. The aim of this study was to evaluate the demographics, clinical features, psychiatric diagnoses, laboratory findings, treatment and complications of NMS cases reported in the Turkish literature.

Methods: Twenty-one out of 22 articles which were published in 2010 and before and full texts were accessed by cross referencing after scanning NMS key words at Turkish Psychiatry Index were included in this study. Clinical and laboratory findings, treatments and developing complications of 32 cases were evaluated.

Results: Thirty-two patients with a mean age of 27.3±12 years were identified. 40.7% of the cases were diagnosed with schizophrenia or other psychotic disorders while 34.4% were diagnosed with bipolar disorders. Rigidity, disturbances of consciousness, fever, sweating were present in most of the NMS cases. Sixteen (50%) NMS cases were taking classical antipsychotics while 4 (12.5%) of them were taking atypical antipsychotics during the diagnosis of NMS. The most common treatment choices for NMS were bromocriptine, electroconvulsive therapy and dantrolene. Aspiration pneumonia and acute renal failure were the most common complications due to NMS. It was reported that 6.3% (n= 2) of the cases died.

Conclusion: It was remarkable that the mean antipsychotic dosages in MNS cases were within therapeutic limits. Detecting the risk factors for NMS would help clinicians prevent probable complications of NMS.

Key words: Neuroleptic malignant syndrome, demografic factors, risk factors

ÖZET

Nöroleptik malign sendrom gelişiminde demografik ve klinik risk etkenlerinin araştırılması: Literatürdeki Türkçe olguların değerlendirilmesi

Amaç: Nöroleptik malign sendrom (NMS), antipsikotik kullanımı sırasında görülebilen ciddi bir yan etkidir. Bu çalışmanın amacı, NMS tanısıyla bildirilen Türkçe olguları demografik özellikler, klinik bulgular, laboratuvar değerleri, tedavi ve gelişen komplikasyonlar açısından değerlendirmek ve klinisyenlere gündelik pratikte yardımcı veriler sağlamaktır.

Yöntem: Bu çalışmaya, 2010 yılında ve öncesinde yayımlanmış olan ve Türk Psikiyatri Dizini'nde NMS anahtar kelimeleriyle yapılan tarama sonrasında tam metnine çapraz referanslama yoluyla ulaşılan 22 makaleden 21'i dahil edilmiştir. Bu makalelerden ulaşılan 32 olgu; klinik bulgular, laboratuvar değerleri, tedavi ve gelişen komplikasyonlar açısından değerlendirilmiştir.

Bulgular: Yaş ortalaması 27.3±12 olarak belirlenen olguların %40.7'sinin şizofreni ve diğer psikotik bozukluklar, %34.4'ünün ise bipolar bozukluk tanısı ile takip edildiği saptanmıştır. Rijidite, bilinç değişikliği, ateş, terleme olguların çoğunluğunda tabloya eşlik etmekteydi. NMS bulgularının, 16 (%50.0) olguda sadece tipik antipsikotik tedavi alırken, 4 (%12.5) olguda ise sadece atipik antipsikotik tedavi alırken geliştiği gözlendi. NMS tedavisinde en sık tercih edilen seçenekler bromokriptin, EKT ve dantrolendi. NMS'ye bağlı en sık gelişen komplikasyonlar ise, aspirasyon pnömonisi ve akut böbrek yetmezliğiydi. Olguların % 6.3'ünün (n=2) yaşamını yitirdiği bildirilmişti.

Sonuç: NMS tanısı konduğu sırada kullanılmakta olan antipsikotik ilaç dozlarının terapötik aralıkta saptanması dikkat çekicidir. NMS'nin ortaya çıkışında risk etkenlerinin belirlenmesi, klinisyenlerin olası komplikasyonları engellemede erken önlem almasını sağlayacaktır.

Anahtar kelimeler: Nöroleptik malign sendrom, demografik faktörler, risk faktörleri

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INTRODUCTION

Neuroleptic malign syndrome (NMS) is a rare but potentially fatal adverse effect of antipsychotic medications.

NMS was first described by Delay et al. (1) in 1960 after the introduction of antipsychotic medications in 1952 as "akinetic hypertonic syndrome" and was characterized by hyperpyrexia, extrapyramidal and pulmonary symptoms due to antipsychotic use. Prevalence of NMS among psychiatric patients receiving antipsychotic treatment is between 1 and 1.5% (2). NMS can be seen at all ages but twice in men than women (3). Mortality was close to 40% before 1984 but now currently decreased to 11.6% (4).

The most widely accepted theory explaining pathophysiology of NMS is central dopamine blockade. All antipsychotic treatments exert their effects by D2 dopamine receptor antagonism. Blockade in nigrostriatal and hypothalamic dopaminergic tracts results in cardinal symptoms of NMS (5). NMS-like condition occurring after reducing doses of dopaminergic medications or withdrawal of the medications; usage of dopaminergic medications in the treatment of NMS and NMS-like symptoms observed in patients with central dopaminergic tract lesions support this hypothesis (6). In studies done to determine the role of other monoamines in NMS pathophysiology, it was detected that levels of 5-hydroxy indolacetic acid which is serotonin metabolite in cerebrospinal fluid (CSF) did not differ between NMS case and control group but noradrenalin levels were found to be significantly higher in NMS cases (7).

Gurrera proposed that catecholamine levels increase in NMS and sympatho-adrenal dysfunction and irregularities in vasomotor activity may arise consequently (8).

NMS is generally seen in patients taking atypical antipsychotics (particularly ones having high potency), tricyclic antidepressants and methoclopramide which are low potency D2 receptor antagonists or when doses of anti-parkinsonian medications are being tapered (9). Dehydration, previous history of NMS, high doses, parenteral antipsychotic administration, depot antipsychotics, anti-parkinsonian medication use, organic brain syndrome, bipolar disorder and mental retardation (MR) are described as risk factors for NMS (3).

Cardinal symptoms of the syndrome are alterations of consciousness, autonomic dysfunction, fever and movement disorders. Alterations of consciousness may vary from agitation to coma and body temperature is usually over 38.5°C. Sweating, tachycardia, variable blood pressure, tachypnea, cardiac arrhythmia, sialorrhea and incontinence are among symptoms of autonomic dysfunction. Movement disorder is generally observed as rigidity but other extrapyramidal system findings such as dysarthria, dyskinesias and Parkinsonism may also be observed (10).

Although there are no specific laboratory findings of NMS, high levels of creatine kinase (CK), high WBC count, high levels of plasma myoglobin, myoglobinuria, elevated transaminases (ALT, AST), creatinine and urea levels may also be detected when hepatic and renal functions are impaired (11). CK levels are elevated in most of the cases and severe elevation can also be seen due to rhabdomyolysis.

Recognizing the syndrome, withdrawal of the responsible agent and maintaining fluid and electrolyte balance are important features of NMS treatment. Dehydration is frequently encountered in acute phase so supportive hydration treatment should immediately be started. Although no specific pharmacological treatment is available, lorazepam, dopamine agonists, dantrolene and Electro-Convulsive Therapy (ECT) are leading options to be implemented according to clinical status. Dopaminergic medications such as bromocriptine and amantadine reduce NMS symptoms such as Parkinsonism and mortality risk. Dantrolene can be used for severe hyperthermia, rigidity and hypermetabolic conditions. ECT is also among therapeutic options when pharmacotherapy is unresponsive (6).

Complications due to NMS generally occur due to immobilization developed after rigidity. Rhabdomyolysis may develop due to reduced fluid and may cause acute renal failure. Venous thrombosis and pulmonary emboli may also develop due to dehydration, immobilization and rigidity (12). Myocardial infarction,

sepsis and disseminated intravascular coagulation (DIC) may also be added to the clinical picture according to severity of NMS (13).

Severe complications and even death may occur during NMS course despite treatment and due to its nature; its occurrence cannot be predicted. For this reason, performing prospective clinical studies is difficult.

We aimed to evaluate 32 cases with NMS whom were accessed at Turkish Psychiatry Index and from cross references for clinical findings, laboratory values, treatment and complications and detect demographic and clinical predictors related with NMS.

METHODS

Grouping Collected Data

Twenty-one out of 22 articles which were published in 2010 and before and full texts were accessed by cross referencing after scanning NMS key words at Turkish Psychiatry Index were included in this study (15-36). One article which full text could not be accessed was excluded (37).

Rigidity, mutism, alterations of consciousness, urinary incontinence and sweating which are among clinical signs of 32 NMS cases reported at total 22 articles were classified as present/absent/not determined according to accompaniment to clinical picture as reported in the articles. Highest values reported during disease course were taken into consideration when evaluating fever, blood pressure, pulse, respiration rate and laboratory values. ALT and AST values were classified as normal (under 50), slightly elevated (50-100), severely elevated (100 and over). Data which are not mentioned in articles were not included in the calculation.

Cases were classified according to medications used as typical antipsychotics, atypical antipsychotics, combination of mood stabilizers and typical antipsychotics, combination of typical and atypical antipsychotics, multiple medication use (additional antidepressants and benzodiazepines) and treatments other than antipsychotics. Dosages of antipsychotics were calculated as equivalent dosages of 1000 mg chlorpromazine (38). Duration of use of medications were reported as days and anticholinergic and depot antipsychotic use were evaluated separately. When recovery duration of NMS was being calculated, days which patients were discharged were taken into consideration.

Statistical Methods

Data collected from articles were entered into SPSS 13 software and descriptive statistics were used. While chi-square test was used to compare categorical variables, distribution of numerical variables was analyzed by Kolmogorov-Smirnov test and variables consistent with normal distribution were compared by Student's t-test, variables not consistent with normal distribution were compared by Mann-Whitney U test. Correlations between risk factors were evaluated by Pearson correlation test and variables affecting time till recovery from NMS were evaluated by stepwise linear regression test. Level of significance was accepted as $p<0.05$ for all statistical analyses.

RESULTS

Socio-demographic Characteristics

Number of women (n=16) and men (n=16) were found equal and mean age was found 27.3±12.0. NMS symptoms were observed when 34.4% (n=11) of the reported cases were being treated for bipolar disorder, 25.0% (n=8) for psychotic disorder, 12.5% (n=4) for behavioral disorders due to mental retardation, 9.4% (n=3) for schizophrenia and 6.3% (n=2) for schizoaffective disorder. Mental retardation was reported in 21.9% of patients and it was found that 56.3% of cases diagnosed as NMS were treated on outpatient basis and 43.7% were treated as inpatients.

Symptoms and Signs of Neuroleptic Malign Syndrome

Rigidity which is the cardinal sign of NMS was reported in 96.9% of cases and undefined in 3.1%.

Mean body temperature was 38.8±0.9°C. Disorders of consciousness were found in 84.4% of cases but not present in 15.6%. Mutism was present in 62.5%, urinary incontinence in 43.8%, sweating in 59.4% of cases.

Mean systolic blood pressure was found 139.3±32.6 mmHg, mean diastolic blood pressure was found 86.4±22.4 mmHg and pulse rate was found 121.5±21.3 per minute. Respiration rate was reported at only 18.8% of cases in the literature and mean rate were 29.7±6.3.

Mean CK level of patients was found 5292±9454.8 and mean WBC count was found 14389±5247.6. ALT levels were found severely elevated in 28.1%, mildly elevated in 15.6% and normal in 9.4% of cases and not specified in 46.9%.

Moderately positive linear correlation was found between CK levels, WBC count, body temperature, dose of medication used, duration till recovery and duration of antipsychotic use during NMS (p=0.019, r=0.43). No significant correlation was found between other variables (Table 1).

AST levels were found severely elevated in 28.1%, mildly elevated in 15.6% and normal in 12.5% of cases and not specified in 43.8%. NMS clinical symptoms occur after an average of 14.3±20.1 days after initiation of treatment.

Medications Used

Half of the patients were treated by typical antipsychotics, 12.5% were treated by atypical antipsychotics, combination of mood stabilizers and typical antipsychotics were used in 12.5%, antidepressants and benzodiazepines were added in 12.5% and typical and atypical antipsychotics were used in combination in 12.5% and NMS developed in 6.3% of patients when using methoclopramide. Fifty-percent of patients were receiving anticholinergics and in 34.4% of patients anticholinergic use were not reported. Depot form use was found 25%. When administration types of medications were evaluated, it was found that 40.6% of patients were using oral, 25%

Table 1: Evaluation of correlation between NMS risk factors

		CK	WBC	Dosage equivalent to 1000 mg chlorpromazine	Time passed until laboratory values normalized (day)	Ages (years)	Duration of antipsychotic use (day)	Body temperature
CK	r	1	0.05	0.43	-0.08	0.43*	-0.10	-0.07
	p		0.80	0.06	0.70	0.01*	0.59	0.69
	n	29	27	19	24	29	29	29
WBC	r	0.05	1	0.12	-0.24	0.10	0.27	0.09
	p	0.80		0.64	0.27	0.58	0.17	0.62
	n	27	27	17	23	27	27	27
Dose equivalent to 1000 mg chlorpromazine	r	0.43	0.12	1	0.34	0.04	-0.06	0.18
	p	0.06	0.64		0.16	0.84	0.76	0.43
	n	19	17	22	18	21	22	20
Time passed until laboratory values normalized (day)	r	-0.08	-0.24	0.342	1	-0.12	-0.03	-0.12
	p	0.70	0.27	0.165		0.55	0.84	0.56
	n	24	23	18	27	26	27	25
Age (years)	r	0.43*	0.10	0.046	-0.12	1	0.27	0.03
	p	0.01*	0.58	0.843	0.55		0.13	0.84
	n	29	27	21	26	31	31	29
Duration of antipsychotic use (day)	r	-0.10	0.27	-0.068	-0.03	0.27	1	-0.02
	p	0.59	0.17	0.763	0.84	0.13		0.87
	n	29	27	22	27	31	32	30
Body temperature	r	-0.07	0.09	0.185	-0.12	0.03	-0.02	1
	p	0.69	0.62	0.435	0.56	0.84	0.87	
	n	29	27	20	25	29	30	30

NMS: Noroleptik Malign Syndrome, CK: Creatine kinase

Table 2: Evaluation of factors affecting duration until recovery from NMS

Model	B	S.E.	Beta	t	p
Age (years)	-0.32	0.27	-0.44	-1.18	0.29
CK	0	0	0.28	0.49	0.64
Systolic BP	0.15	0.20	0.59	0.77	0.48
Diastolic BP	-0.06	0.29	-0.13	-0.20	0.85
WBC	-0.001	0	-0.44	-1.92	0.11
Dose equivalent to 1000 mg chlorpromazine	0.01	0.01	0.81	2.86	0.03*
Duration of antipsychotic use (day)	0.26	0.15	0.53	1.77	0.14

Dependent variable: Time passed until laboratory values normalized, S.E: Standard Error, CK: Creatine Kinase, BP: Blood pressure

of patients were using intramuscular, 12.5% of patients were using both oral and intramuscular, 3.1% of patients were using intravenous medications. Mean equivalent dosage for 1000 mg chlorpromazine of medications used was found 895.1±568.1.

NMS Treatment and Complications

Only 34.4% of patients were treated by bromocriptine and benzodiazepines were added in 18.8% of patients, ECT in 12.5% of patients and dantrolene in 6.3% of patients to bromocriptine. Benzodiazepine and biperiden treatment was administered in 6.3% of patients. It was also reported that only ECT was administered in 9.4% of patients and 3.1% were treated by only dantrolene or only intravenous fluids.

Acute renal failure developed in 9.4% of cases and frequency of pneumonia due to aspiration was found 15.4%. Pancreatitis, hypocalcaemia and convulsions as complications of NMS were found in 3.1%, multiple complications (hypocalcaemia, pneumonia, flexion contracture) were found in 6.3% of cases and 6.3% of cases died. Average duration between recovery from NMS clinical course and normalization CK levels to discharge of patients was found 22.7±17.2 days. When variables affecting the duration till recovery were analyzed by stepwise linear regression method, only medication dosage was found predictive (p=0.03) (Table 2).

DISCUSSION

Although NMS can be seen at every age, it was reported more frequent in patients between 20 and 50 years old. Likewise, average age of 27.3 of cases reported from Turkey is consistent with international literature. On the other hand, although NMS was reported to be seen nearly twice-fold in men than women (3), we found equal frequencies of men and women in our study. This difference may be due to relatively low numbers of cases included in our study. It was reported in the literature that NMS symptoms and signs may frequently develop in patients with mood disorders due to increased sympathetic nervous system activity (3,8,33,39). NMS symptoms and signs developed in 34.4% of cases in our study when being followed-up for bipolar disorder which is consistent with the literature.

Other risk factors reported for development of NMS are newly initiated antipsychotic treatment, rapid dose escalation, intramuscular treatment and high dose antipsychotic use (40,41). However, it was reported in some studies that development of NMS is not correlated with duration of antipsychotic use and high doses antipsychotic use (42,43). Not exceeding maximum recommended doses of antipsychotic drugs in our study (average dose of medications in our study was 900 mg/day which is equivalent to 1000 mg/day chlorpromazine) suggests that NMS may occur independent from therapeutic dose. Besides, although NMS can be seen at any stage during antipsychotic treatment, it often occurs at first 2 weeks (33). It was found in our study that NMS symptoms and signs start at an average of 14 days. For this reason, clinicians should be cautious of NMS occurrence particularly in the first weeks of antipsychotic treatment. Presence of MR in particular may be a risk factor for NMS development. It was also reported in the international literature that NMS risk is higher in presence of MR

(3,30). Although small sample size of our study makes it difficult to interprete this, it is noteworthy that statistically significantly higher doses of antipsychotics are used in patients with MR. It is important for clinicians to select antipsychotic treatment in patients with MR and recognize prodromal symptoms and signs of NMS such as early neurological and autonomic signs. When NMS is diagnosed, causal treatment should immediately be stopped. However, it may sometimes be difficult to recognize prodromal signs when symptoms progress rapidly (44). NMS developed in 56% of outpatients in our study throughout follow-up. This may be due to easier recognition of prodromal symptoms and signs in outpatients.

Main symptoms and signs of NMS are fever over 38.5°C, rigidity, autonomic instability and alteration of consciousness. In the studies, fever, tachycardia, alteration of consciousness and rigidity were reported in all patients (39,44,45). Similarly, rigidity, alteration of consciousness and sweating were present in most of the patients in our study and average body temperature was found 38.8°C. For this reason, in the presence of signs such as rigidity, alteration of consciousness, fever and sweating, clinicians should not wait for examination results and taking early precautions keeping NMS in mind will contribute to preventing from complications.

Although there is not any pathological laboratory tests specific to NMS, CK levels are frequently measured over 1000 U/L and leucocytosis is also present (3,46). No significant difference was found between antipsychotic dosages and age, CK level, WBC count and recovery duration and CK levels rise by increasing age. This suggests that NMS may develop in young patients without an evident increase in CK levels.

Most antipsychotic treatments are related with risk of NMS. Although this risk is higher with typical antipsychotics, there are case reports with atypical antipsychotics such as clozapine, olanzapine, quetiapine and risperidone (47,48). Most of the NMS cases reported in the literature developed during haloperidol and depot fluphenazine use. It was reported that wider use of these medications compared to atypical antipsychotics might have caused higher number of cases with NMS (49). It was also reported that motor symptoms and signs are less severe, CK levels are less elevated, NMS criteria are partially met in some patients and primary symptoms such as rigidity and fever may be lacking in NMS due to atypical antipsychotics (50,51). Utilization of typical antipsychotics in half of the cases at time of NMS diagnosis in our study supports these data.

NMS symptoms and signs generally subside after withdrawal of antipsychotic treatment. NMS signs may subside by supportive treatment such as fluid replacement and prevention of electrolyte imbalance in early cases, IV dantrolene and/or bromocriptine can be added to treatment in addition to preventive/supportive treatment of renal failure in more severe cases (44). Dopaminergic agents such as bromocriptine and amantadine were reported to reduce recovery period and prevent mortality (4). There are studies both reported that benzodiazepines may be effective in moderately severe cases of NMS showing catatonic characteristics or do not have any clinical efficacy or contribution (6). ECT can be used in cases which pharmacotherapy is inadequate (6,44). In our study, in addition to supportive therapy, only 34.4% of patients were treated by bromocriptine and combination therapy was used in 43.9% of patients.

The most important complication of NMS is rhabdomyolysis. Renal failure, aspiration pneumonia, pulmonary emboli, pulmonary edema and sepsis are frequently seen. Mortality is between 10 and 70% in NMS (52). Death may be due to respiratory failure and cardiac arrest in early period and to renal or multi-organ failure in late phases (53). The most frequent complication observed in cases at our study was aspiration pneumonia and mortality was found as 6.3%.

Our study has some limitations. Relatively small number of cases and not evaluating cases reported abroad make the generalizability of findings difficult. On the other hand, not extracting data recorded by structured data form detected in longitudinal follow-up makes data quality and standardization more difficult. However, lack of any regulation previously done in Turkey makes our research original. We think that risk factors and consequences found by taking cases reported from Turkey into consideration will contribute to clinicians in their general practice.

CONCLUSION

NMS is an adverse effect which is being seen relatively rare by increasing use of atypical antipsychotics compared to typical ones and may be fatal. Determining risk factors of NMS will provide early precautions for clinicians to prevent possible complications.

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