Case Report

Neuroleptic Malignant Syndrome: A Review and Report of Six Cases

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The typical symptoms and signs of neuroleptic malignant syndrome (NMS) consist of fever, muscle rigidity (stiffness, myoclonus, rod-like), alterations of consciousness (confusion, agitation, aggression, or catatonia), autonomic nervous system disturbances (i.e., hypertension, tachycardia, tachypnea, profuse sweating, and urine incontinence), abnormal blood tests such as low serum electrolytes, elevated serum creatinine phosphokinase (CPK) level, and leukocytosis. Muscle rigidity is often associated with myonecrosis, myoglobinuria, and elevated serum CPK. The mortality among NMS cases is in the 10 to 70% range depending on the severity of the symptoms and time of therapeutic approach. Mandatory therapy should include removal of causative agents, correction of body fluid and electrolytes, administration of benzodiazepine, clonazepam and bromocriptine (dopamine agonist), proved life-saving medications.

The authors reported herein six cases with unusual clinical features of NMS. Four of them had been on antipsychotic for a year before becoming anorexic, dehydrated, agitated, and violent with paranoid delusion. One instance with underlying delirium tremens developed NMS after receiving haloperidol (30mg IV) in addition to diazepam (200mg IV) within 24 hours. Another patient was found to suffer from severe NMS after receiving bupropion (Dopamine inhibitor antidepressant) 300 mg. /day. All patients displayed cardinal signs and symptoms of NMS in addition to dehydration and pallor. They were treated in the psychiatric ward and recovered rapidly from NMS after receiving clonazepam and bromocriptine and removal of the offending agents.

Keywords: *Catatonia, Neuroleptic malignant syndrome, Serotonin syndrome*

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The Neuroleptic Malignant Syndrome (NMS) which is regarded as a medical emergency is uncommon and its mortality is between 10% and 70% although some authors have reported as high as 76% due to cardiovascular collapse, renal failure, and respiratory failure[1-3]. Dementia, Parkinsonism, dyskinesias and ataxia may be the permanent neurological sequel among survivors. NMS has been described among patients of all ages particularly those exposed to antipsychotic drugs (APs) or dopamine (DA) receptor blockers or those who abruptly discontinued antiparkinson drugs[4-6]. The incidence varies from 0.02 to 2.4% of patients who received these drugs. Clinically, it is characterized by muscle rigidity, fever, alteration of consciousness, autonomic nervous system (ANS) disturbance, leukocytosis, anemia, myonecrosis, myoglobinuria, and elevated serum creatinine phosphokinase (CPK). Serial measurement of serum CPK, thus, is necessarily in monitoring the severity and the risk of renal failure although serum CPK may be normal if benzodiazepine or muscle relaxants are given early. Hyperthermia (fever) is believed to be the result of blocking heat loss pathway in the anterior hypothalamus or increasing heat production from muscle rigidity. The latter may be due to catecholamine-induced changes in intracellular calcium ion. Moreover, APs and lithium may cause direct toxicity to muscle tissues. Hyperthermia then leads to irreversible damage to the cerebellum

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or other parts of the brain, which results in permanent neurological sequel. The pallor or anemic state found in NMS patients may be the result of iron role in central DA receptor function. The clinical course of this condition is variable from hours to months. Certain symptoms such as agitation may mistakenly be considered as exacerbation of psychosis, fever for infection and incontinence for normal pressure hydrocephalus. Early diagnosis and proper therapeutic approach are necessary to avoid serious medical complications, expenses, and certain invasive medical procedures (i.e., brain computerized scan, lumbar puncture, unnecessary antibiotics, etc). In the present communication, the authors describe six cases of NMS to call attention to this potentially fatal syndrome.

Material and Method

The authors encountered six patients who had made an excellent recovery from NMS in the inpatient unit of the Department of Psychiatry, King Chulalongkorn Memorial Hospital. All clinical records were studied in detail.

Results

The clinical features and laboratory data of the six patients are given in Table 1. There were five men and a woman. The youngest patient was a 17-year-old male adolescent. Three patients were between the ages of 20 and 40 years. Three cases presented with schizophrenia or schizoaffective and one each with dementia, delirium tremens (DT), and major depressive disorder (MDD) with psychosis. Depression was found in two cases and multiple suicidal attempts were noted in one case (case 1). Involuntarily hospitalization due to agitation, verbal (obscene words) and physical aggression, and paranoia occurred in four cases. Case 6 was catatonic, dazed, mute, and had low food intake for 2 days before she was admitted for regression, crying for hours and delusions that she would be raped. Only case 2 was brought to the hospital because of seizure-like symptoms from DT. Computed tomograph (CT) revealed multiple cerebral infarctions in case 1 and cerebral atrophy in case 2. Extrapyramidal signs were noted in all cases in varying degree i.e., tremors, muscle rigidity, seizure-like, and involuntary movements such as lip-pouting, persistent pacing. Most patients displayed evidence of ANS disturbances including tachycardia, hypertension or labile blood pressure, and profuse sweating. Four had high fever while two patients had a warm body. All patients tended to take off their clothes or soak themselves wet with water. They also looked pale but only the DT case was anemic (Hct 29%, Hb 9g/dl). Routine laboratory data including white cell and red cell count, serum electrolyte were unremarkable except serum CPK that varied from 515 to 3070 iu/l. Only case 4 and 5 showed ele-vated CPK at admission (911, and 515 iu/l respectively) because NMS was suspected before admission. Symptoms of NMS in the present series occurred after receiving antipsychotic, antidepressant, lithium, and bupropion (dopamine receptor blocker). Case 2 developed sudden onset of high fever, profuse sweating, hypertension, urine incontinence, and elevated serum CPK after the use of diazepam and haloperidol at high doses for treating DT in the emergency room. Case 6 began with toxic psychosis hypertension, tachycardia, visual hallucination, and full bladder after receiving haloperidol 5 mg and diazepam (DZP) 10 mg, IV in the emergency room for her delusions and tearful outburst. This was followed by fluoxetine 20 mg. and imipramine 75 mg in the psychiatric ward that induced full bladder (1200ml. of urine) and anticholinergic toxic psychosis in two days. Her psychiatric symptoms recovered rapidly when all medications were discontinued and lorazepam (LZP) was given. However, five days later, she developed a high fever as well as other clinical signs of NMS when she received quetiapine (75 mg/day) and urecholine (15 mg/day). She acted bizarrely (i.e., crawling on the floor and both arms banging to the body like a flying bird) and her serum CPK rose from 118 iu/l to 1618 iu/l. All medications were again discontinued and she was given bromocriptine (BMC) 25 mg/day, carbamazepine (CBZ) 400 mg/day, tianeptine 12.5 mg/day and DZP 30 mg/day. Her vital signs and her bizarre behaviors returned to normal within a few hours. Her mental status gradually improved a week later. However, when BMC and CBZ were taken off, she became agitated and high fever returned after a few day of treatment. She recovered rapidly when these drugs were resumed and continued for a week. She was doing well with tianeptine (serotonin selective reuptake enhancer-SSRE antidepressant) 12.5 mg and LZP 1 mg daily when seen as an outpatient. Three other patients developed NMS symptoms within 24 hours and two within 72 hours after receiving drug combinations (AP, lithium, and antidepressants). Clinically, all patients in the present series improved within a few hours and serum CPK level greatly decreased when bromocriptine was given and the offending drugs removed. Electroconvulsive therapy (ECT) was applied in three cases for their underlying mental illnesses (cases 3, 4, 5). There was no fatality in the present series.

Table 1. Clinical and psychiatric features

Case	Age Sex Onset	Diagnosis	Psychiatric symptoms	Previous medication	Current medication (In hospital)	Extrapyramidal signs	ANS symptoms	Fever	Serum CPK (i.u/l)	Home medication
1	71 Male 24 hr	Multiinfarct dementia, MDD with psychosis and suicidal attempts	Insomnia, body pain, aggression, nihilistic delusion, refused food, hypertalkative with obscene words	Various (typical/atypical) APs for 5 years, CZP, Bupropion, Venlafaxine XR and Mirtazapine	Clozapine25, CNP, Bupropion300, Valproate200, and Trihexylphenidyl	Finger tapping lip pouting	Tachycardia, hypertension, urine incontinence, sweating, pallor	High	3070	Venlafaxine XR 75 Mirtazepine 60, CNP 4, CBZ 400, Lorazepam 3
2	48 Male 24 hrs	Delirium tremens, cerebral atrophy	Seizure -like, agitation, confusion, food refusal	unknown	Diazepam 250 Haloperidol 30	Tremors, myoclonus	Tachycardia, hypertension, urine incontinence, pallor, sweating	High	716	Lorazepam 10
3	17 Male 72 hrs	Mild mental retardation (IQ = 85) Schizoaffective	Agitation, paranoid, aggression (verbal, physical), mania, grandeur delusion, anorexia	Various (typical/atypical) APs for 6 years	Li, CZP 150, CNP 8, Chlopromazine 100, Verapamil, and THP	Restless, persistent pacing, tremors	Labile blood pressure and pulse rate, pallor	Warm body	1875	Risperidone 6, Lorazepam 3, Li 900, and ECT*
4	27 Male 72 hrs	Schizophrenia with depression for 5 years Tardive dystonia	Restless, paranoid, violent, withdrawn, refused food, always soaked himself wet	Various (typical/atypical) APs, Trihexyphenidyl	Ris 4,VPA 1000, Clomipramine 50, Bupropion 300	Neck spasm, tremors	Tachycardia, pallor	Warm body	911 to 1488 (2 days later)	Bupropion 300, DZP30, TRZ, THP, CMP 50, and ECT*
5	40 Male days	Schizoaffective for 20 years	Paranoid, aggression (verbal physical), insomnia, refused food, always soaked himself in bathtub for hours	Thioridazine100, Trihexylphenidyl 2	Haloperidol 5 IV, Diazepam 10 IV, Clozapine 100	Rigid posture	Tachycardia, hypertension, pallor	High	515 115	Li 600, CZP 100, CBZ 400, THP, ECT*
6**	26 Female 12 hrs	Major depressive disorder with psychosis for 2 months	Tearful for hours, fear to be raped, mute, dazed, refuse food for 2 days, tearful for 2 hours in emergency room	Fluoxetine, Trazodone	Haloperidol, DZP, Fluoxetine, IMP, Quetiapine, Urecholine	Rigidity, myoclonus, crawling	Tachycardia, hypertension, pallor, full bladder	High	1618	Tianeptine 37.5, Lorazepam 1

* needed electroconvulsive therapy (ECT) to: control psychotic symptoms ** Anticholinergic toxic psychosis on the 5th day
AP = Antipsychotic drug, CBZ = Carbamazepine, CMP = Clomipramine, CNP = Clonazepam, CZP = Clozapine, DZP = Diazepam, IMP = Imipramine ,Li = Lithium, Ris = Risperidol, THP = Trihexyphenidyl, TRZ = Thioridazine, VPA = Valproate

Discussion

Although NMS is often found in patients with schizophrenia or affective disorder, this syndrome can occur in diverse psychiatric illness as well as alcoholism as noted in the present report. It has also been reported in non-psychiatric patients such as Huntington's chorea, Wilson's disease, mental retardation, alcohol withdrawal and dementia as seen in case 1 and case 3 who had received APs. NMS is more common among the young and middle-aged adults because they are the largest age group of patients with mental disorders[1]. Generally, NMS is most often associated with conventional APs usages[2]. It has also been reported with Iithium and antidepressants especially when combined with APs[3,4]. High dose of benzodiazepine and haloperidol were certainly the cause of NMS in case 2 and case 6. Recently, NMS associated with atypical APs, even at the low dosage, has been found increasing as noted in the presented cases and should alert physicians to an expected increase in frequency of this syndrome as these offending drugs become widely available and are increasing in usage[5-7]. Other medications that may induce NMS include antidepressant drugs due to relative central hypodopaminergic state, or dopamine--serotonin disequilibrium, abrupt withdrawal of anticholinergic or antiparkinson drugs and G-aminobutyric acid (GABA) hypoactivity (i.e., a high dose of benzodiazepine or baclofen withdrawal).

NMS often begins less than 10 days after the initiation of drugs for acute psychotic treatment although the duration of the onset can be as short as 4 hours or as long as 65 days in chronic psychotic patients with ongoing AP therapy. Therefore, it can run a chronic or even recurrent course[8]. Five of the presented patients developed the clinical features of NMS within 72 hours. According to some authors, more than 90% of the studied cases, the full clinical pictures developed within 48 hours after the first symptom appeared[2,3].

The involuntary movement described in case 6 is unusual and has not been described before. Warm body temperature was observed in two cases. This could represent atypical or partial NMS as suggested by several authors[1,2]. In addition, high fever tends to be the last sign while mental state alterations and ANS disturbances usually precede other signs. Therefore, the present findings support the view that NMS may manifest with varying features. The authors suggest that patients who developed mental state alterations in association with variation in pulse and blood pressure as well as involuntary movements after the use of APs with or without antidepressants and lithium should at least have their blood tested for the level of serum CPK other than routine laboratory tests. Serum CPK measurement thus should be done on newly admitted agitated, catatonic psychiatric patients[9]. Moreover, the incidence of NMS is increasing among children and adolescents treated with an atypical AP drug[10]. It should be noted that all six patients were thin, dehydrated, and looked pale. Dehydration has often been found among NMS cases as noted in the presented patients who received only a low dose of combined drug medications. Pallor could be due to peripheral vasoconstriction that may precede hypertension and it could represent an anemic condition that correlated with NMS. Although the relationship between these clinical features and NMS is not clear, the possibility of NMS should be considered when prescribing these offending drugs particularly to patients who were anemic and dehydrated.

The proper diagnosis of NMS may be difficult to make if muscle rigidity or fever is mild. At present, the diagnosis of NMS is based on these cardinal signs as mentioned above, particularly when all symptoms and signs occur simultaneously. The problems of recognition arise especially in cases when the signs are innocuous or patients are uncooperative or the cardinal signs are overlooked or misattributed in addition to its varying severity. For example, it may begin as catatonia as seen in case 6. If fever is detected, it will usually provoke a search for an infection. Thus, NMS should be listed in the differential diagnosis of fever of unknown origin especially in the elderly who were on these offending agents[11]. Patients with normal pressure hydrocephalus may present as confusion, ataxia from muscle rigidity, and urine incontinence mimicking NMS. Serotonin syndrome (SS) may share many clinical similarities to NMS but pallor is seen only in NMS while flushing, nausea, diarrhea are observed in SS[12,13]. Lethal catatonia (LC) cannot be distinguished from NMS in some patients but LC usually begins with extreme psychotic excitement, whereas NMS often begins with muscle rigidity. Therefore, general medical conditions and mental state changes are important signs of NMS in addition to the evidence of leukocytosis, and elevated serum CPK level.

Bromocriptine (BMC) at the dosage of 5 mg, 3-4 times daily appears to be effective for this syndrome as seen in the presented patients whose clinical signs and symptoms improved rapidly within a few hours. BMC should be continued for at least 2 weeks,

depending on the length of AP therapy. Dantroline is also an effective drug but it is not available in Thailand. Benzodiazepine, carbamazepine[14] and anticholinergic agents have also been useful in controlling muscle rigidity at the beginning of NMS symptoms. Some authors have suggested that ECT, calcium, folate, and iron supplement should be given because low Ca2+ level may cause muscle rigidity and low iron level may aggravate movement disorder while ECT may be useful for the treatment of NMS as well as the underlying psychiatric conditions[15].

Although there was no fatality found in the present series, most authors have reported the mortality in NMS cases between 10% and 70% due primarily to cardiovascular complication, renal and respiratory failure. Recognition of the early prodromal signs/symptoms of NMS and proper therapeutic approach, thus, are essential in avoiding serious neurological complication as well as fatal out come.

Conclusion

The present study reported six patients who displayed cardinal signs and symptoms of NMS after receiving either antipsychotics or antidepressants. Physicians should consider the possibility of NMS particularly in patients who have been exposed to these causative agents. The prevalence of NMS may be higher than the authors have thought as various antidepressant and atypical antipsychotic drugs become more widely available and increase in usage. Early diagnosis and prompt therapeutic approach is necessary in avoiding this potentially fatal syndrome.

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กลุ่มอาการ neuroleptic malignant syndrome: การทบทวนวารสารและรายงานผู้ป่วย 6 ราย

ดวงใจ กสานติกุล, บุรณี กาญจนถวัลย์

กลุ่มอาการ neuroleptic malignant syndrome (NMS) ประกอบด้วย ไข้, กล้ามเนื้อเกร็ง, ความรู้สึกตัวเปลี่ยนแปลง เช่น ซึม, สับสน กระวนกระวาย ก้าวร้าว ระบบประสาทอัตโนมัติแปรปรวน เช่น ความดันโลหิตสูง หัวใจเต้นเร็ว หอบ เหงื่อออกมาก กลั้นปัสสาวะไม่ได้ การตรวจทางห้องปฏิบัติการจะพบการเพิ่มขึ้นของเม็ดเลือดขาว และระดับของ serum creatinine phosphokinase (CPK) อาการกล้ามเนื้อเกร็งมักร่วมไปกับการตายของกล้ามเนื้อ การตรวจพบ myoglobinuria และการเพิ่มระดับของ serum CPK โดยปกติกลุ่มอาการ NMS มักจะพบในผู้ป่วยที่ใช้ยาต้านโรคจิต แต่ยาต้านโรคซึมเศร้า อาจทำให้เกิดกลุ่มอาการ NMS ได้จากการเกิดภาวะ central hypodopaminergic หรือ dopamine - serotonin ขาดความสมดุล กลุ่มอาการNMS มีอัตราการเสียชีวิต 10-70% ขึ้นกับความรุนแรงของอาการและระยะเวลาก่อนได้รับการรักษาที่เหมาะสม การรักษาที่เป็นการช่วยชีวิตคือ การระงับการใช้ตัวยาที่เป็นสาเหตุร่วมไปกับการให้ยา bromocriptine 20-30 มิลลิกรัมต่อวัน, lorazepam, clonazepam และแก้ไขภาวะขาดน้ำและเกลือแร่ คณะผู้ศึกษาได้รายงานผู้ป่วย NMS 6 ราย โดยผู้ป่วย 4 ราย เกิดอาการ NMS ภายหลังได้รับยาต้านโรคจิตเป็นเวลานาน ผู้ป่วย 1 ราย ซึ่งมีโรคพิษสุราเรื้อรัง (delirium tremens) เกิดอาการ NMS ภายหลังได้รับยา haloperidol (30mg/iv) ร่วมกับ diazepam (200mg/iv) เพียง 24 ชั่วโมง และผู้ป่วยอีก 1 ราย มีอาการภายหลังได้รับยาต้านโรคซึมเศร้า bupropion 300 mg ต่อวัน ผู้ป่วยทั้ง 6 รายหายจากกลุ่มอาการภายหลัง ได้รับ clonazepam และ bromocriptine รวมทั้งการแก้ไขอาการขาดน้ำ ปรับสมดุลของเกลือแร่ในเลือดและระงับการใช้ยาที่ทำให้เกิดกลุ่มอาการดังกล่าว