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Case Report

Psychiatry Section

A Rare Case of Myxedema Coma with Neuroleptic Malignant Syndrome (NMS)

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ABSTRACT

Myxedema coma or hypothyroid crisis is an endocrine emergency and needs ICU management. Neuroleptic malignant syndrome (NMS) is another medical emergency which needs high degree of clinical suspicion else mortality can be high. There is a paradox in co existence of myxedema coma and NMS. While one is hypometabolic state another is hypermetabolic state and both can be precipitated by antipsychotics use. Hypothermia and flaccidity commonly expected in myxedema coma may mask fever and rigidity of classical NMS contributing to diagnostic problem and treatment delay. Scientific literature on coexistance of myxedema coma and NMS is sparse. We hereby report first case with coexisting myxedema coma and NMS in a patient of schizophrenia treated with antipsychotic, where classical symptoms of NMS were masked by myxedema coma. Prompt diagnosis and effective management by a team resulted in favourable outcome in our patient. This case is reported to alert intensive care physicians to atypical manifestations of NMS in presence of hypothyroidism.

Keywords: Atypical antipsychotics, Atypical neuroleptic malignant syndrome, Hypothyroid crisis, Primary hypothyroidism

CASE REPORT

A 40-year-old female relapsed with five month history of persecutory delusions, reduced self care, social withdrawal, mutism and disturbed biodrives. She was a known case of schizophrenia since 2002. There was no history of hypertension, diabetes or ischemic heart disease. She was evaluated by a psychiatrist in another hospital and was gradually managed with tab olanzapine 20 mg, tab haloperidol 15 mg, tab clonazepam 6 mg and tab trihexyphenidyl 4 mg in divided doses. Injection fluphenazine deconate depot 50 mg IM/ monthly was also given for few months as she continued to exhibit agitation, social withdrawal and mutism. Finding little response after four month of outpatient treatment ECT was planned and scheduled dose of injection fluphenazine deconate was omitted. During pre ECT evaluation she was found to have swelling over all four limbs and pericardial effusion on sonography. She was detected to have primary hypothyroidism and anaemia (normochromic normocytic) thus ECT was postponed. She was managed for hypothyroidism and initially given 400 micrograms of levothyroxin infusion. She was discharged in walking state after a week on tab levothyroxin 100 mcg OD, tab olanzapine 20 mg, tab amisulpride 100 mg Bd,tab trihexyphenidyl 4 mg and tab clonazepam 2mg per day. Patient improved after that and remained well for about five days, on fifth day evening she developed high grade fever, reduced talking and subsequently became mute and was brought to service hospital in emergency. On Examination patient was drowsy, opening eyes to painful stimulus, Temp 102^{0}F, BP 88/54 mm Hg (with 2 ionotropes), Pulse 98/min regular, all peripheral pulses palpable, the respiratory rate was 18/min. There was pallor ++ and, and physical stigmata of hypothyroidism in form of thick edematous lips, facial puffiness, thick dry tongue, coarse dry skin and swelling over hands and feet. The Glasgow coma scale was E2 VT M4 (6/11T). Pupils were bilateral equal & reactive. Deep tendon jerks were absent and plantars were flexor. There was generalized hypotonia in all four limbs. Rest of the systemic examination did not show any abnormality. Investigation at the time of admission revealed hemoglobin of 4.8 gm/dl, TLC 12700 per cu mm, urea 30 mg/dl, creatinine 1.2 mg/dl, sugar 100 mg/dl, serum electrolyte Na 135 mEq /l, K 4 mEq /l, Ca 9mg/dL. Thyroid function test T3 - 0.13 ng/ml (0.6 - 1.81), T4 - 1.40 mcg/ dl (5.01 - 12.45), TSH 165.85 mIU/L (0.55-4.78), cortisol (at 8AM) 12 µg/dl (5 - 25), LFT- aspartate transaminase (AST) 480 IU/L(< 40), alanine transaminase (ALT) 410 IU/L(< 40), amylase 118 U/L(< 90). Urine, blood, CSF cultures were sterile and CSF gram staining was negative for any infection. X-ray chest and USG Abdomen were normal, echocardiography revealed pericardial effusion, EEG revealed slow wave more prominent on left suggestive of either anxious state or deep sleep. Cardiac monitoring revealed low voltage. Patient was given ventilatory support for hypoxemia, ionotropes Infusion (dopamine 5 mcg/kg/min, noradrenaline 5 mcg/ min), IV Fluids and injection ceftriaxone 2 gm iv BD (empirically). A provisional diagnosis of severe decompensated hypothyroidism with myxedema coma was made as free thyroxine level was very low and TSH level was more than 100 mIU/L. Her myxedema coma was managed with oral loading dose of levothyroxine 500 µg and tab levothyroxine 100µgm given eight hourly through nasogastric tube. Injection hydrocortisone 100 mg IV eighth hourly was also started. As the presentation was due to fever and altered sensorium in background of antipsychotic use psychiatric referral was sought. CPK levels were raised 2546 IU/L (<175 IU/L) and showed rising trend (Max - 3745 IU/l) next day, urine for myoglobinuria was negative. The diagnosis was revised to NMS with myxedema coma on second day. Antipsychotics were stopped along with dopamine agonist tab bromocriptine 2.5 mg three times a day was added to the treatment and increased to 10 mg daily. She responded to the treatment and was weaned off ventilatory support on 3rd day, became fully conscious on 4th day and was afebrile 5th day onwards. Serial CPK showed declining trend after first two reports (2105 IU/L, 903 IU/L, 305.3 IU/L, and 125 IU/L) and normalized after 12 days. She was rechallenged with tab aripiprazole 2.5 mg BD on 17th day after due consent. Her delusions and agitation slowly remitted and was stabilized on tab aripiprazole 10 mg. She was discharged after 27 days of hospitalization in walking state on tab levothyroxine 100 µgm/day and tab aripiprazole 10 mg/day.

Author	Age	Diagnosis	Offending Agent	Thyroid Levels	NMS Finding	Risk Factors	Treatment
Moore 1990	55 F	Personality Change Encephalopathy	Thioridazine 50 mg Several doses	T4- 40 nmol/l (50-150) TSH- 50mU/L normal < (7.4)	CPK 12,360 U/l (normal < 175) Fever 41ºC Rigidity drowsy	Organic brain syndrome	Oral L-thyroxine Iv fluid cooling
Moore 1990	32 F	Obsessive Compulsive Disorder	Thioridazine 50mg, Haloperidol 10 mg (one day)	T4-14.4 pmol/l (11-22) TSH(70IU/L)	Fever 38.5ºC Rigidity CPK>2000 Altered Sensorium	agitation	Cooling Dantrolene Thyroxine .1mg oral
Hatch 2001	54 M	Alzheimer's disease Hypothyroidism	Quitiapine 50mg (2days)	NA	CPK not done Fever Altered sensorium Rigidity tremors	encephalopathy	L-thyroxine 88 µg/day Lorazepam
Kawajiri 2002	59 M	Parkinson's Disease Depression	L-DOPA Amitriptyline Etizolam (several days)	T4 - 0.6 ng/dl (0.9-2.3) TSH -108.7 mU/ml (0.2-4.2)	Fever/altered sensorium/high CPK rigidity	Withdrawal of Benzodiazapine Organic brain syndrome	Bromocriptine Dantrolene
Dixit 2015	40 F	Schizophrenia	Olanzapine 20 mg (several months), Amisulpride 200mg (5days)	T4-1.40 mcg/dl (5.-12.45) TSH 165.85 mIU/L (.55–4.78)	Fever, altered sensorium CPK-3745 IU/l,	Polydrug therapy Metabolic encephalopathy	Iv L-thyroxine Ionotropes Iv Hydrocortisone Oral thyroxine Bromocriptine

[Table/Fig-1]: Characteristics of case reports of nms coexisting with primary hypothyroidism

DISCUSSION

Myxedema coma (MC) is an endocrine emergency due to often neglected or untreated hypothyroidism having high mortality rates of about 15-20% [1]. NMS on the other hand is another emergency due to rare but lethal adverse effect of antipsychotic use. The incidence of NMS was 1.41 per 1,000 cases treated with neuroleptics and the mortality was 38% [2]. The incidence of MC in western world is 0.22 per million per year [3]. While there is no such study from India, one study reported high prevalence of abnormal thyroid hormone levels (hypothyroidism was 8.2% & subclinical hypothyroidism was 8.4%) with female preponderance [4].

MC usually presents in chronic undiagnosed or untreated patients of hypothyroidism who face secondary insult or it may be iatrogenic [5]. In background of thyroid hormone deficiency antipsychotics like thioridazine alone or combination of sertraline and aripiprazole can precipitate MC [1,6,7]. Fever is unlikely to occur in MC where hypothermia is expected along with hypotonia. In our patient temp of 102^{0}F was unexplained. She remained febrile for five days. Her investigations were all sterile for any infection. Fever rose in temporal relationship with altered sensorium, recent antipsychotic exposure, autonomic imbalance, rising CPK titer, leukocytosis, deranged LFT and absence of myoglobinuria or rigidity. Our patient satisfied the Levenson's criteria [8] for NMS by fulfilling two major criteria (fever and raised CPK excluding rigidity) and four minor criteria (tachycardia, altered sensorium, autonomic instability and leukocytosis excluding diaphoresis). Our patient shared several known risk factors for NMS like dehydration, exhaustion, polypharmacy, depot neuroleptic and metabolic encephalopathy.

NMS diagnosis is based on normal tetrad of fever, rigidity, autonomic instability and altered mental state. Many diagnostic criteria have been proposed for NMS, but because of its variable presentation, no single set of criteria is used universally. Fever or rigidity may not be present in atypical NMS as it commonly occurs with use of atypical antipsychotics [9,10]. Our patient exhibited unexplained fever but not rigidity as it is possible that MC masked the rigidity as systemic illness can mask typical sign of NMS [11]. Secondly our patient might have partial or milder form of NMS due to concurrent use of atypical antipsychotics like olanzapine and amisulpride.

Scientific literature with regards to MC coexisting with NMS is sparse. While MC is hypometabolic state NMS is hypermetabolic state. We are first to report MC with NMS from India. Only few cases of primary hypothyroidism with NMS have been reported between 1990 and now [12-14] to the best of author's knowledge and MC was not reported in them [Table/Fig-1]. None of the cases were managed with ionotropes and bolus levothyroxin. NMS likely results from a complex interaction between the agent and a susceptible host. It is metabolic changes secondary to primary hypothyroidism in central dopaminergic tracts increases dopaminergic activity making person vulnerable to idiosyncratic reaction of neuroleptic blockade [12,13] precipitating NMS. High potency conventional neuroleptic like haloperidol and fluphenazine are more likely to cause NMS due to predominant D2 receptor blockade in central dopaminergic tracts and atypical antipsychotics like olanzapine and aripipazole can also cause NMS but have weaker affinity for D2 receptor blockade and have lesser mortality than conventional neuroleptics [15]. Key to prevent reoccurrence of NMS are small doses, gradual titration, adequate hydration and avoiding high potency drugs. For rechallenging antipsychotic of different class with low dopamine affinity like quetiapine, clozapine or aripiprazole can be considered [16]. In comparison with other antipsychotics, quetiapine has been shown to possess a favorable safety profile, with no requirement for thyroid monitoring during treatment [17].

Prompt diagnosis and effective management using appropriate drugs including dopamine agonist resulted in favourable outcome in our case. This case has been reported as MC needs ICU management and NMS coexisting with MC has not been reported so far. Secondly ICU physicians should be aware of atypical features of NMS as systemic illness like hypothyroidism can mask symptoms of classical NMS creating diagnostic difficulties. Lastly in cases of failure to recognize thyroid dysfunctions psychotropic medications can trigger both endocrine and psychiatric emergencies

CONCLUSION

Intensive care physicians should be aware of atypical or partial manifestations of NMS as systemic illness like MC can mask the typical features of NMS. Prompt diagnosis and management is the key to favourable outcome.

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