

항정신병약물성 악성증후군에 관한 3증례 및 개관

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Three Cases of Typical Clinical Characteristics and Overview of Neuroleptic Malignant Syndrome

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ABSTRACT

We report on three cases of typical clinical characteristics and treatment response in neuroleptic malignant syndrome(NMS), and reviewed the literatures of NMS. NMS was first recognized as a life-threatening complication of dopamine receptor antagonists, and defined as a catatonic-like states associated with fever, obtundation, muscle rigidity, and unstable vital sign in patients taking neuroleptic agents. Concepts of NMS have changed because medications other than classic neuroleptic drugs have been implicated as triggering agents and syndromes identical to NMS have been observed in other conditions. The important neurochemical features are probably functional dopamine deficiency and ensuing hyperactivity of excitatory amino acid neurotransmission in the basal ganglia and hypothalamus. Recognition of NMS and early discontinuation of neuroleptics are the most important step in its management. Supportive care includes management of hyperthermia and fluid replacement. Controversial therapeutic measures include the application of dopamine receptor agonists, excitatory amino acid antagonists, or dantrolene. Psychiatric patients with a history on NMS and psychotic relapse necessitating antipsychotics do not commonly redevelop NMS.

KEY WORDS : Neuroleptic malignant syndrome · 3 cases · Overview.

서 론

1950 (antipsychotics : AP)

chlorpromazine

가 . 가

가 .

(Tardive Dyskinesia) (Neuroleptic Malignant Syndrome : NMS)

AP

, NMS

, NMS

(catatonic - like state)

‘ Syndrome malin ’ neurovegetative

Delay (1963) AP

, , ‘ syndrom

malin des neurolepticus ’

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AP
. 1960 NMS
, 1968 NMS

가 . 1970 AP obilin 3 + ,

가 , ,

가 , NMS 9 NMS AP

. Caroff(1980) diazepam 60mg , 11

60 NMS가

, NMS AP 19

0.5 1% 20% chlorprothixene 100mg 30

CPK 48 I.U. . 3

(hyperthermic synd - 2

rome) NMS , Caroff

. 1986 300

, NMS 가 Index Medicus

NMS Extrapyramidal Symp -

tom with fever, Drug induced Malignant Syndrome(DMS)

Hypodopaminergic hyperpyrexia Syndrome

(Lazarus 1989 ; Levin -

son Simpson 1986).

clozapine AP, , MAO , lor -

azepam, atenolol NMS가

. NMS가

가 ,

가 (1990 ; 1983 ;

1983 ; 1983 ; 1990). 가

3 가 NMS

, AP

가 , NMS

증 례

증 례 1 :

37 2

3 calcaneal fracture

separin 50mg , chlorpromazine . 37

. 2

39.2 chlorpromazine 1000mg

CPK 427 I.U. ur - , haldol 20mg 가

, 5 haldol 8

증 례 2 :

19 ch -

lorpromazine 600mg benztropine 2mg

19 38 . 23

haldol 10mg ha -

ldol 20mg

, , , , ,

, 39

NMS haldol

WBC 18400, CPK 659, sGOT 90, sGPT

37 . 32 Bromocriptine 15mg,

diazepam 15mg, benztropine 2mg . 35

가 , , , , ,

lithi -

um, thioridazine 73 2

, 6

증 례 3 :

24 2

33 chlorpromazine 600mg

haldol 10mg

haldol 20mg . 34

, , , , ,

NMS

benztropine 6mg diazepam 15mg

sGOT 88, sGPT 49, CPK 3339 I.U.

. 37

chlorpromazine 1000mg

, haldol 20mg 가

, 5 haldol 8

mg

AP

NMS가

역학, 임상특징 및 유발요인

가 AP NMS가

NMS가 가 Keck (1991) 20% AP

가 NMS가 AP NMS Imipra-NMS

3.23% 0.02 0.5 mine

1% (Addonizio 1986 ; Keck 1987 ; 가

Pope 1986b). 15 30%(20%) , depot NMS가

38% ,

4% . 가 NMS NMS

(Levi - 가 NMS

nson Simpson 1986 ; Shalev Munitz 1986).

NMS AP NMS

AP (Pope 1991). NMS

NMS가 가 (Caroff 1980 ; Pope 1991 ; Rosebush Stewart 1989 ; Shalev Munitz 1986).

AP NMS가 AP가 AP가

4 50%, 1 80%, 10 90%가, 1 3 AP가 AP가

96%가 NMS AP가 de-

가, AP mpson 1986). AP가 (Levinson Si-

NMS , AP 가 AP

3 30 haloperidol

. NMS lithium (Hermesch 1992). 가 AP가

, 가 AP 가 AP

lithium 가 NMS

가 (Janicak 1988). 2/3 가 가

3 5 가 AP NMS

12 14 (30 ,

15 ± 10) , depot 2 3 NMS chlorpromazine, halo-

(Caroff 1980 ; Hermesch 1992 ; Lazarus peridol, loxapine(Chong Abbott 1991) AP

1989 ; Rosebush Stewart 1989). , clozapine(Anderson Powers 1991 ; DasGupta Young 1991 ; Miller 1991), risperidone(Raitasuo 1994), remoxipride(Koponen 1993)

80%가 40 (26) 10 AP, metoclopramide(Friedman 1987) domperidone

90 가 (Levenson 1985). (Spirt 1992) AP가 , rese-

, NMS 가 rpine

Chlorpromazine 500 700mg (Caroff 1980 ; Lazarus 1989 ; Levinson Simpson 1986).

가 depot

가 ,

가 ,

가 AP가 NMS

가 depot

가 NMS

AP가 (lithium carbonate, benzodiazepine)

(Cohen Cohen 1974 ; Janicak 1988 ; Levinson Simpson 1986).

NMS

, AP

NMS

NMS

가 (Shalev 1988).

원 인

1. 원 인

AP

. AP

NMS 가

(Levinson Simpson 1986).

NMS

AP가 metoclopramide , a - methyltyr - osine, tetrabenazine, reserpine

(Friedman 1985 ; Keyser Rodnitzky 1991),

dextroamphetamine AP

NMS

가 NMS 가

가 . Nigrostriatal pathway

, brainstem re - ticular activating system

2. 도파민이 아닌 다른 Catecholamine의 가능성

NMS CSF HVA urinary 3 - M - hydroxyphen - ylglycol 가, apomorphine clonidine challenge test NMS가

epine - ph - rine, norepinephrine NMS

sympa - thoarenomedullary component

. AP가

가 NMS norepinephrine (Gurrera Ro - meo 1992).

3. Catecholaminergic system과 다른 신경전달물질간의 복합 상호작용

NMS GABA 가

. NMS GABA

. Diazepam lorazepam GABA - mimetic DA/GABA NMS가

GABA

가

4. Opioid system

NMS endogenous opioid system 가

5. 다른 가설들

NMS AP 가

. Ca, c - AMP, intracellular messenger pos - tsynaptic molecular level

가 가

증상 및 검사조건

NMS

가 hypothalamic adrenergic cri - sis가

가 가 , , , (Cohen Cohen 1974 ; Lazarus 1989). 가 lithium 가

NMS가 NMS 30000/mm³ 가가 가 40% 40 42 98% 가 CPK AP 가 15000I.U. AP 가 myoglobulinuria 가 Aldolase, 가 LDH, sGOT, sGPT 95% 가 SIADH, DIC, Na 가 100% locked-in syndrome 95%, 가 adrenergic crisis NMS halo-thane (Caroff 1980 ; Levenson 1985 ; Rosebush Stewart 1989 ; Shal-ev Munitz 1985). 1/3 (Caroff 1980 ; Lazarus 1989 ; Rosebush Stewart 1989). (Caroff 1980 ; Gurrera Romeo 1992 ; Harsch 1987 ; Hermesch 1992 ; Rosebush Stewart 1989 ; Shal-ev Munitz 1985 ; Tormey 1987 ; Wedzicha Hoffbr and 1984).

진단 및 감별진단

NMS 16 25% NMS Levenson(1985) myoglobin (CPK 가), 가 myoglobin (1990 ; 가) NMS 가 Levenson 1985). NMS myoglobinuria . Pope (1986b) , 가, CPK NMS가 myoglobinuria가 nizio (1986) , Addo- AP rapid intra-muscular neuroleptization, NMS Laza- AP lithium rus (1989) AP

가 가 .
 atypical, paradoxical, probable possible 9.6 ± 9.1 (23% : 48 , 63% : 1
 NMS (Gurrera 1992). , 82% : 2 , 97% : 1). lithium, ,
 NMS가 . Amantadine
 , NMS AP levedopa NMS가
 MAOI , NMS
 , phenezine, lorazepam, atenolol (Harsch 1987 ; Laz -
 NMS nonneu - arus 1989).
 roleptic malignant syndrome Cohen (1987)
 NMS
 (ma -
 lignant hyperthermia), lethal catatonia,
 (Caroff 1980 ; Lazarus 1989 ; Rosebush
 Stewart 1989). 가 ,

sarcoplasmic Caion metabolism 가
 (MacLennan 1990). Lethal 가
 catatonia anti -
 NMS AP organic lethal catatonia embolic stocking
 NMS AP benzodiazepine
 catatonia NMS lethal (Harsch 1987 ; Lazarus 1989).
 , NMS가
 AP (Cohen
 1987 ; Lazarus 1989). 가
 AP가 ,
 NMS dantrolene, ,
 benzodiazepine (Pearlman
 Addonizio 1986 ; Sakkas 1991 ; Shalev Munitz 1986).

3. 약물치료

NMS 가
 dantrolene, ,
 benzodiazepine (Pearlman
 Addonizio 1986 ; Sakkas 1991 ; Shalev Munitz 1986).
 1) Dantrolene
 hydantoin

치 료

1. 조기진단과 AP의 투여중단

AP
 NMS 가 AP
 , GABA 가 CPK
 가 48

1 2
가 가

dantrolene

10mg/kg

1 10mg/kg single I.V. bolus dose 50 600
mg/day 400

mg 4 1 5
dantrolene

2) 도파민 촉진제

direct DA agonist bromocriptine indir -
ect DA agonist amantadine Car -
bidopa/Levodopa(Sinemet) DA agonist

10

1

ting depot

NMS

가

Amantadine 100mg 2 3

Amantadine mesolimbic mesoc -
ortical DA pathway 가

Bromocriptine carbidopa/levodopa nigrpstriatal DA
pathway amantadine

가 Bromocriptine 7.5 45 mg 3

NMS

3) Dantrolene과 DA agonist의 병합투여

Dantrolene , bromoc -
riptine 가 가

ler(1985) 가 Mul -
dantrolene

ocriptine dantrolene , Laz -
arus(1989) dantrolene ,

가 가 가

Fogel Goldberg(1985) CPK

amantadine benzodiazepine , dantrolene bro -
mocriptine , CPK , my -
oglobinuria,
Levinson simpson(1986)

1 2mg/kg

rolene 가

4) 항콜린성 약물

benztropine
가

1 2 bromocriptine dantrolene

5) 전기충격요법

가

droperidol
succinylcholine

가 GABA
가
NMS

DA/GABA

가 NMS

lithium , NMS
(Addoni -
zio Susman 1987 ; Hermesh 1988).

6) 기 타

Benzodiazepine 1.5 2mg
lorazepam

NMS

sodium nitroprusside minoxidil 10mg
3 Dantrolene 가

Ca channel bloc -
pridino -

ker verapamil
lum mesylate가 가

7) 재치료전략

NMS 2

가 AP, lithium, carbamazepine, benzodiazepine, ECT, NMS가, Pope (1991) (1986) 가 NMS가, Levinson Simpson, AP, Lazarus (1989) 3, risk ratio, NMS, benefit/ 가, 19, 24, 37, Leve- nson(1985), NMS, AP가, 38, CPK, sGOT, sGPT 가, (Shalev Munitz 1986). Caroff Mann(1988) AP NMS (Caroff 1980 ;Gurrera Romeo 1992 ;Harsch 1987 ;Hermesch 1992 ;Rosebush Stewart 1989 ;Shalev Munitz 1985 ;Tormey 1987 ;Wedzicha Hoffbrand 1984). NMS AP, Clozapine (Wellner Kornhuber 1992). NMS 3, NMS, 고 찰, 3, 1, 결 론, chlorpromazine 50mg 가 2, NMS AP, CPK 가 urobilin 3+, 2 19, chlorpromazine 600 mg, benztropine 2mg 20, 가 haldol, NMS, ceptor, 가 CPK, sGOT, sGPT, 3 24, chlorpromazine 600mg 30, 가 ha- ldol 10mg, NMS가, CPK, sGOT, sGPT, 가, ch- lorpromazine haldol, NMS (Caroff 1980 ; Hermesch 1992 ; Lazarus 1989 ; Rosebush Stewart 1989). AP 가 1, 2, 가, 가, 가, NMS, AP, DA re-

1980

clozapine

AP

NMS

중심 단어 :

참고문헌

강병조 · 김승업(1990) : Neuroleptic Malignant Syndrome. 대한정신약물학회지 1 : 43-46

김영진(1983) : Neuroleptic Malignant Syndrome. 신경정신의학 22 : 498-503

송정중 · 채영래 · 백인호(1990) : Neuroleptic Malignant Syndrome에 합병되어 나타난 급성신부전증 1예. 신경정신의학 29 : 957-960

오동렬 · Davis JM(1993) : 항정신약물성 악성증후군. 신경정신의학 32 : 472-483

이범상(1983) : 정신약물에 의한 치명적 이상고열증. 신경정신의학 22 : 301-306

정영조 · 오세중 · 오석환(1990) : Neuroleptic Malignant Syndrome 4예. 신경정신의학 29 : 1165-1173

Addonizio G, Susman VL(1987) : ECT as a treatment alternatives for patients with symptoms of neuroleptic malignant syndrome. J Clin Psychiatry 48 : 102-105

Addonizio G, Susman VL, Roth SD(1986) : Symptoms of neuroleptic malignant syndrome in 82 consecutive inpatients. Am J Psychiatry 143 : 1587-1590

Anderson ES, Powers PS(1991) : Neuroleptic malignant syndrome associated with clozapine use. J Clin Psychiatry 52 : 102-104

Caroff SN(1980) : The neuroleptic malignant syndrome. J Clin Psychiatry 41 : 79-83

Caroff SN, Mann SC(1988) : Neuroleptic malignant syndrome. Psychopharmacol Bull 24 : 25-29

Chong LS, Abbott PM(1991) : Neuroleptic malignant syndrome secondary to loxapine. Br J Psychiatry 159 : 572-573

Cohen S, Fligner CL, Raisys VA, Luthi R, Dunner DL(1987) : A case of nonneuroleptic malignant syndrome. J Clin Psychiatry 48 : 287-288

Cohen WJ, Cohen NH(1974) : Lithium carbonate, haloperidol and irreversible brain damage. JAMA 230 : 1283-1287

DasGupta K, Young A(1991) : Clozapine-induced neuroleptic malignant syndrome. J Clin Psychiatry 52 : 105-107

Delay J, Pichot P, Lempriere T(1963) : L'emploi des butyrophenones en psychiatrie. Etude statistique et psychometrique. Sumpos internazionale sull l'Haloperidole Triperidol, Milano : 305-319 : Taken from : J Clin Psychiatry 413 : 79-83

Fogel BS, Goldberg RJ(1985) : Neuroleptic Malignant Syndrome. N Engl J Med 313 : 1292

Friedman JH, Feinberg SS, Feldman RG(1985) : A neuroleptic malignantlike syndrome due to levodopa therapy withdrawal. JAMA 254 : 2792-2794

Friedman LS, Weinrauch LA, D'Elia JA(1987) : Metoclopramide-

induced neuroleptic malignant syndrome. Arch Int Med 147 : 1495-1497

Gurrera RJ, Chang SS, Romero JA(1992) : A comparison of diagnostic criteria for neuroleptic malignant syndrome. J Clin Psychiatry 53 : 56-62

Gurrera RJ, Romero JA(1992) : Sympathoadrenomedullary activity in the neuroleptic malignant syndrome. Biol Psychiatry 32 : 334-343

Hermesh H, Aizenberg D, Lapidot M, Munitz H(1988a) : Risk of malignant hyperthermia among patients with neuroleptic malignant syndrome and their families. Am J Psychiatry 145 : 1431-1434

Hermesh H, Aizenberg D, Weizman A, Lapidot M, Mayor C, Munitz H(1992) : Risk for difinite neuroleptic malignant syndrome. A prospective study in 223 consecutive inpatients. Br J Psychiatry 161 : 254-257

Harsh HH(1987) : Neuroleptic malignant syndrome : Physiological and laboratory findings in a series of nine cases. J Clin Psychiatry 48 : 328-333

Janicak PG, Bresnahan DB, Sharma R, Davis JM, Comaty JE, Malinick C(1988) : A comparison of thiothixene with chlorpromazine in the treatment of mania. J Clin Psychopharm 8 : 33-37

Keck PE Jr, Pope HG Jr, McElory SL(1987) : Frequency and presentation of neuroleptic malignant syndrome : A prospective study. Am J Psychiatry 144 : 1344-1346

Keck PE Jr, Pope HG Jr, McElory SL(1991) : Declining frequency of neuroleptic malignant syndrome in a hospital population. Am J Psychiatry 148 : 880-882

Keyser DL, Rodnitzky RL(1991) : Neuroleptic malignant syndrome in Parkinson's disease after withdrawal or alteration of dopaminergic therapy. Arch Int Med 151 : 794-796

Koponen HJ, Lepola UM, Leinonen EV(1993) : Neuroleptic malignant syndrome during remoxipride treatment. European Neuro-psychopharmacology 3 : 517-519

Lazarus A, Mann SC, Caroff SM(1989) : The Neuroleptic Malignant Syndrome and Related Conditions. Washington DC, American Psychiatric Press, pp.3-56

Levenson JL(1985) : Neuroleptic malignant syndrome. Am J Psychiatry 142 : 1137-1145

Levinson DF, Simpson GM(1986) : Neuroleptic-induced extrapyramidal symptoms with fever : Heterogeneity of the 'neuroleptic malignant syndrome.' Arch Gen Psychiatry 43 : 839-848

MacLennan DH, Duff C, Zorzato F, Fujii J, Phillips M, Korneluk PG, Frodis W, Britt BA, Worton RG(1990) : Ryanodine receptor gene is a candidate for predisposition to malignant hyperthermia. Nature 343 : 559-561

Miller DD, Sharafuddin MJA, Kathol RG(1991) : A case of clozapine-induced neuroleptic malignant syndrome. J Clin Psychiatry 52 : 99-101

Pearlman CA(1986) : Neuroleptic malignant syndrome : A review of the literature. J Clin Psychopharmacology 6 : 257-273

Pope HG Jr, Aizley HG, Keck PE Jr, McElory SL(1991) : Neuroleptic malignant syndrome : Long-term follow-up of 20 cases. J Clin Psychiatry 52 : 208-212

Pope HG Jr, Keck PE Jr, McElroy SL(1986b) : Frequency and presentation of neuroleptic malignant syndrome in a large psychiatric hospital. Am J Psychiatry 143 : 1227-1233

Raitasuo V, Vataja R, Elomaa E(1994) : Risperidone-induced neur-

- oleptic malignant syndrome in young patient. Lancet 344 : 1705*
- Rosebush P, Stewart T(1989)** : *A prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry 146 : 712-725*
- Sakkas P, Davis JM, Janick PG, Wang ZY(1991)** : *Drug treatment of the neuroleptic malignant syndrome. Psychopharmacology Bulletin 27 : 381-384*
- Shalev A, Hermesh H, Munitz H(1988)** : *The role of external heat load in triggering the neuroleptic malignant syndrome. Am J Psychiatry 145 : 110-111*
- Shalev A, Munitz H(1986)** : *The neuroleptic malignant syndrome : Agent and host interaction. Acta Psychiatry Scand 73 : 337-347*
- Spirit MJ, Chan W, Thieberg M, Sachar DB(1992)** : *Neuroleptic malignant syndrome induced by domperidone. Digestive Diseases & Sciences 37 : 946-948*
- Tormey WP, Cronin T, Devlin JD(1987)** : *Hyponatremia masquerading as malignant neuroleptic syndrome. Br J Psychiatry 150 : 412*
- Wedzicha JA, Hoffbrand BI(1984)** : *Neuroleptic malignant syndrome and Hyponatremia. Lancet 963*
- Weller M, Kornhuber J(1992)** : *Clozapine rechallenge after an episode of 'neuroleptic malignant syndrome.' Br J Psychiatry 161 : 855-85*