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A rating scale for neuroleptic malignant syndrome

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Abstract

The development of a rating scale for neuroleptic malignant syndrome (NMS) is described. The clinical and laboratory features of NMS were categorised into six domains after a thorough literature review and examination of patients. The reliability of this scale was established on 25 NMS patients and 50 control subjects based on chart reviews. A factor analysis supported a six-factor solution. The validity of the scale was indicated by the relationship of the severity rating to duration of illness and outcome. The inter-rater reliability of the scale was established prospectively in 10 subjects. The scale offers a measure of severity of NMS in the clinical setting so as to support the clinical diagnosis, monitor patients and determine their progress. The scale may be applicable not only to NMS or suspected NMS but also to NMS-like syndromes such as lethal catatonia.

Keywords: Psychiatric rating scale; Psychometrics; Extrapyramidal symptoms; Movement disorder; Catatonia; Diagnosis; Factor analysis

1. Introduction

Neuroleptic malignant syndrome (NMS) is an uncommon but serious side effect of neuroleptic drugs that was first described by Delay et al. (1960). Reports of its incidence in psychiatric inpatients receiving neuroleptic drugs vary widely, from 0.02% to as high as 3.23%, based on retrospective reviews (Pelonero et al., 1998). Much of this discrepancy stems from the lack of a consensus on the definition of NMS, and the fact that many criteria sets for its diagnosis have been published (Levenson, 1985; Addonizio et al., 1986; Roth et al., 1986; Pope et al., 1986; American Psychiatric Association, 1994; Sachdev et al., 1997). Most criteria sets recognise fever and muscle rigidity as the core features of the syndrome, with many associated features that support the diagnosis (American Psychiatric Association, 1994). However, even these 'core' features remain somewhat contentious (Pelonero et al., 1998).

There are a number of reasons for the controversies in the diagnosis of NMS. First, the diagnosis remains one of exclusion with no diagnostic test or features that are pathognomonic of this syndrome. The diagnosis cannot be made until medical conditions such as encephalitis, toxic encephalopathy, status epilepticus,

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heat stroke, and malignant hyperthermia can be ruled out (American Psychiatric Association, 1994). Second, it is probably a spectrum rather than a categorical disorder, with *forme fruste* being common and partial in their symptomatology (Addonizio et al., 1986). All the features of NMS, such as muscle rigidity, fever, and autonomic instability can be caused by neuroleptics in the absence of NMS. Neuroleptics have also been reported to produce the catatonic syndrome without the other features of NMS (Fricchione, 1985). Third, atypical neuroleptics are not free of the risk of NMS and may indeed not have a lower risk than the classical drugs (Sachdev et al., 1995). However, the presentation with atypical drugs, in particular, clozapine, may be different, especially with a lack of rigidity (Sachdev et al., 1995; Pelonero et al., 1998). Fourth, a syndrome like NMS may be provoked in the absence of neuroleptic drugs by the abrupt cessation of dopaminergic drugs in Parkinson's disease or treatment with dopamine-depleting drugs (e.g., reserpine, tetrabenazine) (Friedman et al., 1985). Fifth, lethal catatonia is recognised as an idiopathic syndrome that resembles NMS, suggesting an interaction between the psychiatric disorder and medication in the development of NMS (Mann et al., 1986). Some authors have regarded NMS as a variant of lethal catatonia, with the features of the two syndromes being indistinguishable and the major difference being the presence or absence of a neuroleptic agent as its provocation (Fink and Taylor, 2003).

A review of the literature suggests a range of symptoms for NMS, which can be broadly categorised into the following: fever, extrapyramidal rigidity, autonomic instability, altered consciousness and catatonia/movement disorder. It is uncertain how many of these features must be present for a definitive diagnosis, although it is clear that one feature is never enough and two may only sometimes be sufficient. Further, the presence of laboratory abnormalities (elevated creatine kinase level and leucocyte count) is suggestive but not essential for diagnosis (Levenson, 1985; Addonizio et al., 1986; Pelonero et al., 1998). The diagnosis of NMS therefore depends upon expert judgment, after weighing the alternatives and considering the range of manifest symptoms. The rating scale presented in this study was not developed for a primary diagnosis of NMS, but to rate its severity in someone with a probable or definitive diagnosis. The published literature suggests, consistent with the spectrum concept, that more severe NMS is characterised by the presence of more severe as well as a wider range of symptoms. For this reason, a scale for NMS would have much clinical utility in delineating the position of a particular patient on the spectrum of severity, in identifying individuals who may be at risk, and in following up the progress of a patient with suspected or established NMS. No such scale has so far been published, although scales for catatonia have been described (Bush et al., 1996; Northoff et al., 1999; Bräunig et al., 2000).

2. Methods

2.1. The development of a rating scale

After a thorough review of the literature, the varied clinical features of NMS were categorised into five domains and these, along with the laboratory indices, comprised the six items of the scale. The categories are heterogeneous, with fever and altered consciousness representing single symptoms, while extrapyramidal rigidity, autonomic instability and movement disorder are composite items. These were scaled to give an overall equal weight to all six items. The items of the scale were developed over 12 months in which five patients with NMS were prospectively examined to consider the appropriateness of the items. The scale was then administered to 25 NMS patients and 50 control subjects to investigate its statistical properties and to establish reliability and validity.

2.2. Subjects

The charts of 25 patients with NMS, who had all been admitted to hospital, were identified from psychiatric units in New South Wales. They met the following criteria for diagnosis: (1) fever (oral temperature higher than 37.5 °C on at least two occasions); (2) extrapyramidal features (at least one): (a) moderately severe rigidity or (b) at least two of the following: mild rigidity, dysphagia, short shuffling gait, resting tremor, dystonia, dyskinesia, and creatine kinase level above 400 U/l; or (c) creatine kinase level above 1000 U/l; (3) either (a) altered consciousness or catatonia or (b) autonomic instability characterized by two or more of the following: systolic (30 mm above baseline) or

diastolic (20 mm above baseline) hypertension, labile blood pressure (variability more than 30 mm systolic or more than 20 mm diastolic at different readings), tachycardia (30 bpm above baseline), intense diaphoresis, incontinence, and tachypnea (more than 25 beats/minute); and (4) absence of identifiable physical illness. These subjects also met the operational criteria of Friedman et al. (1985) for a definite ($n=23$) or probable ($n=2$) diagnosis of NMS (with oral temperature of 37.5 °C). Only inpatients were included because of the detailed documentation needed to complete the scale.

Each patient with NMS was matched with two comparison subjects, also treated with neuroleptic medication in the same psychiatric unit and who had no evidence of NMS on the following variables: age (within 2 years), sex, primary psychiatric diagnosis, and time of admission (within 1 month of index patients) in that order.

2.3. Data collection

Two research assistants, who completed the rating scales on each subject, independently reviewed the case records. The inter-rater reliability was determined and the intra-class correlation coefficients were >0.8 on all items rated.

2.4. Statistical analysis

A factor analysis with Varimax rotation was performed using all items of the scale. The solution was later forced to yield a smaller number of factors. The analysis was repeated after collapsing five items into categorical (0, 1) variables: rigidity (0, ≥1), temperature (0, ≥37 °C), consciousness (0, ≥1), creatine kinase (≤2, >2), and leucocytosis (0, ≥1). A reliability analysis was performed to determine Cronbach's alpha coefficient (Cronbach, 1951) for the complete sale and the change in alpha if particular items were deleted. A receiver operating characteristic (ROC) curve was plotted to determine the cut-off for the scale. Validity was examined by examining the relationship of severity of rating with the duration of illness and sequelae. All analyses were performed using the SPSS-PC version 10.0 (SPSS Inc., 1999).

3. Results

Table 1 presents the result of the first factor analysis. Three items were excluded because of missing data (poverty of speech, choreiform movements and dysphagia). A six-factor solution, which accounted for 81.8% of

Table 1
Results of first factor analysis ($n=25$)

Cluster	Item	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	Factor 6
I	Creatine kinase level	0.75017	0.03289	−0.03612	0.04543	−0.06055	−0.19042
	Posturing	0.74658	−0.13361	−0.07083	0.02987	0.06158	0.45087
	Leucocytosis	0.71620	0.20864	−0.02908	0.20330	0.30077	−0.28343
II	Systolic BP	−0.04911	0.93723	0.19999	0.06587	−0.08945	−0.07154
	Diastolic BP	0.19375	0.91069	0.14876	−0.14529	0.09969	−0.13519
	Tachypnea	0.42556	0.58432	0.55270	−0.11679	−0.16779	0.09934
	Incontinence	0.69000	0.46280	−0.09463	0.22615	−0.14135	−0.05936
III	Tachycardia	−0.12175	0.17973	0.84230	−0.15461	−0.05171	−0.10881
	Waxy flexibility	0.28298	−0.09363	−0.73575	−0.23652	−0.26951	0.07406
	Mutism	0.66691	0.30318	−0.63507	0.05687	0.29561	0.37184
IV	Temperature	0.38683	−0.25482	0.08491	0.77277	−0.07675	0.00507
	Diaphoresis	0.17587	0.08781	0.63891	0.64965	0.18391	0.03069
	Resting tremor	−0.08412	0.44224	0.04378	0.60617	0.00994	−0.39157
V	Extrapyramidal rigidity	0.23123	0.37439	0.01296	−0.19277	0.80430	−0.04939
	Dystonia	−0.08221	−0.40788	0.19113	0.20360	0.76289	0.10758
VI	Level of consciousness	−0.09839	−0.17530	−0.08633	−0.08524	−0.08524	.01099

The following items were excluded because of missing data: poverty of speech, choreiform movements, and dysphagia. Factor clusters were interpreted as follows: I, laboratory investigations; II, autonomic instability; III, catatonia; IV, fever; V, extrapyramidal symptoms; and VI, altered consciousness. Note that there is some overlap of items in terms of factor loadings.
BP: blood pressure.

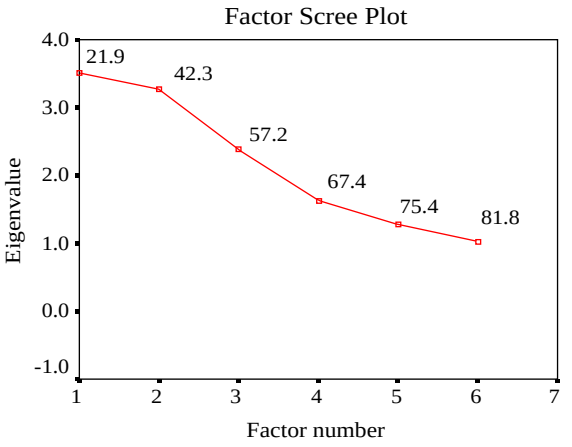

Fig. 1. Factor scree plot showing the variance explained by each factor. Factors with eigenvaule >1 are included. The cumulative percentage of variance is indicated above the mark for each factor.

the variance, was obtained. An examination of the loadings of the various items on the factors suggested that five of the six categories included in the scale loaded on separate factors. The only exception was catatonia/movement disorder, the items of which had high loadings on a number of factors. Because of the clinical salience of this feature and the inappropriateness of categorizing it with any other feature, catatonia/movement disorder was retained as a separate item in the scale. Fig. 1 presents the factor scree plot (Catell, 1966). It suggests that forcing a three- or four-factor solution discarded a large proportion of the variance and a six-factor solution presented an acceptable compromise between the number of factors and the eigenvalue.

The ratings for the 25 patients with NMS were analysed for internal consistency of the scale using the Reliability Analysis subcommand of the SPSS-PC package. When all items were entered into the analysis, Cronbach's alpha was 0.6875. If the five items mentioned above were used as categorical variables, alpha was 0.649. Table 2 presents the statistics for the scale. Two items (tachycardia and waxy flexibility) had a negative but small correlation with the total score. The term 'tachycadia' was redefined as pulse rate >100. The sub-items for catatonia/movement disorder were re-examined. Mutism had a high correlation ($r=0.67$) with the total score; its weight in the scale was increased.

On the final scale, the mean (SD) score for cases was 13.3 (4.0) (range 8–25) and for controls 0.64 (0.6) (range 0–3). The sensitivity and 1-specificity were plotted for different scores on the scale to obtain an ROC graph (Fig. 2). This suggested a cut-off of '4' for a diagnosis of NMS. We suggest from this scale that: score 0–4: no NMS; 5–8: possible NMS; and >8: definite NMS. However, as is argued later, the scale is not designed to diagnose NMS but to rate its severity once a clinical diagnosis has been made. If the clinician suspects the diagnosis and alternative explanations for the syndrome, such as encephalitis and hyperthermia,

Table 2
Statistics used for the scale

Item	Scale mean if item deleted	Scale variance if item deleted	Corrected item—total correlation	Alpha if item deleted
Creatine kinase level	11.8000	13.6000	0.6322	0.6092
Posturing	13.8667	17.4095	0.4619	0.6576
Leucocytosis	13.7333	17.3524	0.4869	0.6557
Incontinence	13.7333	17.6381	0.4159	
Mutism	13.9333	16.6381	0.6699	0.6378
Systolic blood pressure	13.8000	18.7429	0.1470	0.6871
Diastolic blood pressure	13.8667	17.9810	0.3240	0.6708
Tachypnea	14.2000	19.4571	0.0276	0.6933
Tachycardia	13.6000	20.4000	−0.2280	0.7153
Waxy flexibility	14.1333	19.9810	−0.1312	0.7058
Temperature	11.8667	16.1238	0.4253	0.6531
Diaphoresis	13.5333	18.1238	0.3890	0.6683
Resting tremor	14.0667	18.7810	0.1704	0.6846
Extrapyramidal rigidity	12.8000	16.0286	0.3820	0.6602
Dystonia	14.0667	18.3524	0.2817	0.6756
Level of consciousness	12.0000	15.7143	0.2233	0.7084

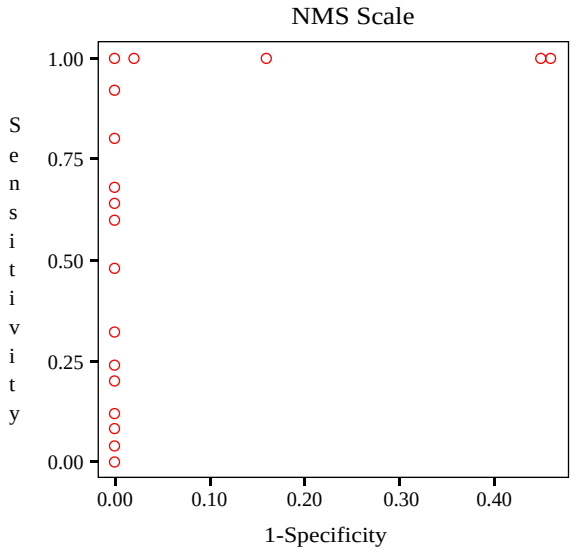

Fig. 2. Receiver operating characteristic curve for sensitivity and 1-specificity for the NMS scale, rated on 25 NMS patients and 25 control subjects.

from other causes are lacking, a rating scale score >8, with a score of 2 or more in at least three domains, is strongly supportive of the clinical diagnosis. The final form of the scale, along with instructions for its administration, is presented in the Appendix.

3.1. Validity

Since the items were drawn from those recognised to be characteristic of NMS, the scale has face validity. The scale was clearly able to distinguish between cases and controls, with no overlap between the two groups on the scores, thus supporting its discriminant validity. The score on day 2 of the NMS correlated well (Spearman's $\rho = 0.67$, $P < 0.05$) with the duration of illness, the latter being determined as the time taken for all symptoms of NMS to resolve. Three cases of NMS had permanent sequelae; all three had scores >20 on the scale. The scale therefore has predictive validity.

3.2. Inter-rater reliability

The scale was independently administered to 10 subjects (5 with NMS and 5 with neuroleptic treatment but no NMS) by two raters. The intra-class correlation coefficient for the total score was 0.84. The coefficients for all items were >0.7 (range 0.72–0.93).

4. Discussion

A rating scale for NMS is presented with demonstrated reliability and validity. The scale incorporates the major clinical features of NMS and rates them on their severity. Equal weight is given to the six major domains of NMS symptomatology. The statistical properties of the scale support this decision. It is acknowledged that a patient with NMS will not always score positively on all items of the scale. In severe cases, however, symptoms are likely to be present in most or all domains (Addonizio et al., 1986), and this will be reflected in the total score. As the syndrome evolves in a patient, the score will increase until it reaches a plateau before resolution occurs and the score decreases back to normal. The scale will therefore prove useful in the follow-up of patients suspected of or diagnosed with NMS.

The scale was not primarily designed to diagnose NMS, although it may assist in the clinical evaluation toward reaching a diagnosis. For a diagnosis, prior knowledge that the patient has been recently exposed to neuroleptics or other drugs known to cause NMS is essential. Other physical disorders that may account for some or all the symptoms must be excluded. The patient must have symptoms in three or more categories for a definitive diagnosis (Sachdev et al., 1995). It is possible, for example, for a patient being treated with neuroleptics, who has severe extrapyramidal symptoms and anticholinergic side effects, to have a high score on the scale but no suggestion of NMS. If this patient also develops fever or suffers from altered consciousness, i.e., has three or four domains affected, NMS should be suspected even if the score may rise by only two–three points. The scale is therefore not for routine use in all patients being administered neuroleptic drugs, but only in cases in which NMS is suspected, suspicion of which is a clinical imperative. In such a patient, a total NMS rating of >8 and a rating of ≥2 in three or more domains of the scale should lead to a diagnosis.

The scale does not include some features of NMS such as myoglobinuria, renal failure, and pulmonary infection, which are to be recognised as complications of the syndrome rather than its defining features. It recognises that the laboratory investigations are but supportive of the diagnosis. Since the symptoms of NMS fluctuate, not all features are necessarily present simultaneously. However, the scale is intended to be

used cross-sectionally to rate the severity at a particular time point. The scale does not take etiology into consideration, so it can arguably be used for the NMS-like syndrome induced by the withdrawal of dopaminergic drugs (Friedman et al., 1985) or for the rating of lethal catatonia (Mann et al., 1986). There are a number of rating scales available for catatonia (Bush et al., 1996; Northoff et al., 1999; Bräunig et al., 2000). These differ from the current scale as they focus on primarily 'catatonic' symptoms such as motor (rigidity, catalepsy, mannerisms, stereotypy, etc.) or behavioral (mutism, staring, grimacing, negativism, etc.) manifestations but do not cover the full range of features seen in NMS.

The NMS rating scale requires further refinement and independent validation on patients from other centers. In the meantime, it offers a measure of severity of NMS in the clinical setting so as to support the clinical diagnosis, monitor patients and determine their progress. At present, there is no empirically proven treatment of NMS. One reason for the lack of controlled investigations of NMS is the lack of a reliable and valid measure to determine outcome. It is hoped that this scale will facilitate controlled investigations of the treatment of NMS, which continues to remain an important problem in the management of psychotic patients.

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Appendix A

NMS RATING SCALE

Patient's Name: _____Date: _____

Rater: _____Time of rating: _____ am/pm

Rating performed: For whole day/one time point

Item								Sub-total	Score
Oral temperature	0	1	2	3	4	5	6	____	____
Extrapyramidal symptoms:									
•Rigidity	0	1	2	3				____	
•Dysphagia	0	1						____	
•Resting tremor	0	1	2					____	____
•Autonomic instability:									
•Systolic BP	0	1						____	
•Diastolic BP	0	1						____	
•Tachycardia	0	1						____	
•Diaphoresis	0	1						____	
•Incontinence	0	1						____	
•Tachypnea	0	1						____	____
Altered consciousness	0	1	2	3	4	5	6	____	____
Catatonia/movement disorders:									
•Posturing	0	1						____	
•Poverty of speech	0	1						____	
•Mutism	0	1	2					____	
•Choreiform movements	0	1						____	____
•Dystonia	0	1						____	
Laboratory investigations:									
•CK level (U/L)	0	1	2	3	4			____	
•Leucocytosis	0	1	2					____	____

Sum total _____/36

NMS Rating Scale

Instructions for use

The scale is designed to be used in patients with suspected or diagnosed NMS. It may be used for NMS-like syndromes including malignant (lethal) catatonia. The items are rated over 1 day. It may be used at one time point, but this should be clearly stated.

1. Oral temperature: Fever is rated positive on this scale if it is idiopathic and considered to be part of NMS. If there is another obvious cause of fever, such as infection, rate 0. The highest temperature in a 24-h period is rated. The reference ratings refer to oral temperature. Add 0.2 °C to axillary temperature and subtract 0.5 °C from rectal readings. The reference ratings are: 0 (<37 °C); 1 (37.037.4 °C); 2 (37.537.9 °C); 3 (3838.9 °C); 4 (3939.9 °C); 5 (4041.9 °C); and 6 (=42 °C).

2. Extrapyramidal symptoms: These are best assessed at the time of rating, but dysphagia may have been present at any time within the 24-h period of rating.

Rigidity is best assessed in the flexor muscles of the wrist and elbow and for neck rotation by passive movement with and without recruitment. Ratings are as follows: 0 nil (no rigidity); 1 mild (slight rigidity present, particularly obvious on recruitment of muscles with jaw clenching); 2 moderate (definitely present to a significant degree but produces no limitation of passive movement); and 3 severe (rigidity that produces some limitation of passive movement).

Dysphagia is present when the patient complains of difficulty in swallowing or nursing observation suggests this problem. Drooling of saliva may be one indication. Rate as: 0 absent; 1 present.

Resting tremor: Subject should be seated with arms supported on the chair's arms or in the lap. Observe for medium-frequency tremor, which may have a pill-rolling quality. Rate as positive if patient has cog-wheeling. Rate as: 0 no tremor, 1 present intermittently and/or unilaterally, and 2 prominent bilateral resting tremor.

3. Autonomic instability: Feature must be documented to have been present at any time within 24 h. Rate as: 0 absent; 1 present.

Systolic blood pressure rise=30 mm above baseline for the subject (or =150 mm if no baseline reading available).

Diastolic blood pressure=20 mm above baseline (or =100 mm if no baseline reading available).

Tachycardia: heart rate=30/min above baseline (or =100 if no baseline reading available).

Diaphoresis: Profuse sweating not accounted for by ambient temperature or analgesic use to lower temperature.

Incontinence: Fecal or urinary incontinence not accounted for by altered consciousness or catatonic state.

Tachypnea: Respiratory rate=15/min above baseline (or =40/min if baseline not available.

4. Altered consciousness: 0: If no alteration of consciousness or altered consciousness can be explained by other causes; 1: Perplexity obvious on examination but patient is fully oriented; 2: Mild disorientation in time or place; 3: Fluctuating level of consciousness with periods of normality, nursing observation useful for this item; 4: Sustained delirium that is clinically obvious or with support of abnormal EEG; 5: Stuporose patient who responds to painful stimuli; and 6: Comatose patient, totally unresponsive.

5. Catatonia/movement disorder: The rating of this item is complicated by the fact that some symptoms may have been present before the onset of NMS as part of the primary psychiatric syndrome. If any feature was present before neuroleptic use, rate 0 for that feature. All items are rated on a 0 or 1 scale except mutism, which is rated on a 0, 1 and 2 scale. Posturing is the unexplained maintenance of an abnormal posture for a prolonged period. Poverty of speech is a reduction of both spontaneous speech and that in response to questions that developed following the NMS. Mutism is the unexplained lack of speech, which may be intermittent (rate 1) or continuous (rate 2). Patients may develop choreiform movements or a dystonia (such as retrocollis, opisthotonus, trismus, or oculogyric crises).

6. Laboratory investigations:

CK level (U/L):	<200	rate "0"
200–400	rate "1"	(0 if i.m. injection in previous 24 h)
400–1000	rate "2"	(1 if i.m. injection in previous 24 h)
	1000–10,000	rate "3"
	>10,000	rate "4"
Leucocytosis	<15,000	rate "0"
	15,000–30,000	rate "1"
	>30,000	rate "2"

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