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REVIEW

Neuroleptic malignant syndrome or catatonia? Trying to solve the catatonic dilemma

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Abstract
Rationale A substantial overlap exists between catatonic phenomena and features of neuroleptic malignant syndrome.
Objectives The objective of this study is to examine whether catatonia can be distinguished from neuroleptic malignant syndrome and to identify symptoms that may have discriminatory power.
Methods We conducted a literature search to identify relevant studies up to and including the year 2012. A total of 386 studies containing 490 case reports were included. To evaluate the discriminant value of each feature, we performed binominal regression analyses with the diagnosis as the dependent variable. First, all features were entered into the model as independent variables. In a second step, a stepwise backwards analysis was conducted to eliminate criteria with low discriminant value.
Results The most common symptoms in patients with neuroleptic malignant syndrome were fever (87.7 %), rigor (85.9 %), laboratory evidence of muscle injury (70.5 %), and tachycardia (62.1 %) and in patients with catatonia were mutism (78.0 %), rigor (73.0 %), stupor (54.0 %), and agitation (49.0 %). Eleven variables with statistically significant discriminatory power remained after statistical analysis: diaphoresis (odds ratio (OR) 10.011), rigor (OR 9.550), fever (OR 7.317), tremor (OR 4.064), laboratory evidence of muscle injury (OR 3.542), leukocytosis (OR 3.081), negativism (OR 0.262), posturing (OR 0.241), waxy flexibility (OR 0.223), stupor (OR 0.158), and stereotypy (OR 0.122).
Conclusions Catatonia and neuroleptic malignant syndrome can be distinguished, at least on a descriptive level. There is a strong syndromal overlap. Our findings might be influenced by the fact that they are based on case reports, which reflect the respective authors' clinical opinion of the patient's condition.

Keywords Neuroleptic malignant syndrome · Catatonia · Diagnosis

Introduction

Motor symptoms are common in psychiatric disorders. In 1874, Kahlbaum described 21 patients with a pattern of severe motor disturbances and coined the term "catatonia" (Kahlbaum 1874). Later on, Kraepelin (1899) incorporated this syndrome into the concept of dementia praecox. Subsequently, throughout the twentieth century catatonia was mainly considered to be a subtype of schizophrenia. Nowadays, catatonia is regarded rather as an independent psychopathological syndrome than as a distinct form of schizophrenia (Taylor and Fink 2003). Consequently, DSM-5 recognizes catatonia as a specifier and not as an independent diagnostic class (APA 2013); the specifier is defined by the presence of three or more of twelve psychomotor features (listed in Table 1). The introduction of an independent specifier in the DSM-5 should improve the recognition of catatonia across the range of different mental disorders and facilitate its treatment (Tandon et al. 2013). Catatonia can cause serious medical complications that can have a fatal outcome. In 1934, Stauder (1934) coined the term "lethal catatonia", but other authors have referred to "pernicious" or "malignant" catatonia (Gabris and Müller 1983; Philbrick and Rummans 1994).

Since the introduction of neuroleptic medication in the 1950s, motor symptoms in patients with a psychiatric disorder such as schizophrenia have mainly been considered to be side

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Table 1 Frequency of diagnostic key features

Diagnostic criteria	Symptoms	Diagnoses provided by the authors		Statistics	
		Neuroleptic malignant syndrome (n=390) Absolute/relative (%)	Catatonia (n=100) Absolute/relative (%)	OR	CI 95 %
Neuroleptic malignant syndrome	Altered blood pressure	162/41.5	10/10	1.366	0.473–3.948
	Altered consciousness	139/35.6	10/10	1.366	0.473–3.948
	Diaphoresis	170/ 43.6	6/6	9.688*	2.315–40.539
	Dysphagia	58/14.8	13/13	0.973	0.269–3.514
	Fever	342/87.7	30/30	7.170*	2.580–19.927
	Incontinence	57/14.6	1010	0.485	0.128–1.832
	Laboratory evidence of muscle injury	275/ 70.5	20/20	3.763*	1.448–9.776
	Leukocytosis	149/38.2	12/12	3.238	0.989–10.596
	Mutism	125/32.1	78/78	0.914	0.302–2.771
	Rigor	335/85.9	73/73	12.294*	3.231–46.776
	Tachycardia	242/62.1	21/21	1.980	0.702–5.578
	Tremor	105/26.9	8/8	4.337*	1.025–18.347
Catatonia	Agitation	142/36.4	49/49	0.535	0.220–1.298
	Catalepsy	15/3.8	13/13	1.132	0.233–5.492
	Echolalia	7/1.8	8/8	0.307	0.041–2.290
	Echopraxia	2/0.5	4/4	4.351	0.312–60.703
	Grimacing	6/1.5	12/12	0.665	0.072–6.163
	Mannerism	7/1.7	12/12	0.256	0.037–1.790
	Mutism	125/32.1	78/78	0.914	0.302–2.771
	Negativism	33/8.5	35/35	0.256*	0.090–0.730
	Posturing	30/7.7	44/44	0.268*	0.097–0.743
	Stereotypy	18/4.6	33/33	0.189*	0.061–0.588
	Stupor	99/25.1	54/54	0.137*	0.047–0.397
	Waxy flexibility	40/10.3	32/32	0.192*	0.059–0.632

OR odds ratio, *CI* confidence interval

*p<0.05

effects of the neuroleptic treatment (Delay and Deniker 1968). In this context, primarily French psychiatrists described a condition with rigidity, hyperthermia, and autonomic dysfunction after exposure to neuroleptic medication, which they called "neuroleptic malignant syndrome" (NMS) (Delay and Deniker 1968). DSM-IV tried to provide diagnostic criteria for neuroleptic malignant syndrome (APA 1994). However, DSM-5 abstains from such an exact list of criteria (APA 2013). According to the criteria of DSM-IV, neuroleptic malignant syndrome is characterized by severe muscle rigidity and elevated temperature associated with the use of neuroleptic medication and the additional presence of two or more of the characteristic features listed in Table 1 (APA 1994).

A substantial overlap exists between symptoms that are considered to be catatonic phenomena and those that are considered to be features of neuroleptic malignant syndrome. However, in clinical practice, it may be important to distinguish between the two conditions with respect to the treatment strategy. Brenner and Rheuban (1978) referred to this situation as a "catatonic dilemma". While catatonia and neuroleptic malignant syndrome were traditionally considered to be two independent entities, several authors now assume that they are variants of the same disorder with a common pathophysiological process (Fricchione et al. 2000, Fink at al. Fink and Taylor 2001; White and Robins 2000).

Against this background, the present review aimed to examine whether it is possible to distinguish between catatonia and neuroleptic malignant syndrome and, if a difference was found between these two conditions, to identify signs and symptoms with discriminatory power.

Material and methods

Relevant publications were identified by searching for a combination of the terms "neuroleptic malignant syndrome" and "catatonia" in MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, PsycINFO, and PSYNDEX.

Because of the lack of systematic clinical trials on the differentiation between neuroleptic malignant syndrome and catatonia, we decided to focus on the numerous case reports that were published up to and including the year 2012. In addition, we conducted a manual search for relevant publications by examining the reference lists in retrieved articles. Case reports fulfilling the following criteria were included: (i) diagnosis of neuroleptic malignant syndrome or catatonia, (ii) underlying psychiatric disorder, (iii) age range of patients from 18 to 65 years, and (iv) article written in English or German. To ensure the validity of our study identification strategy, two authors of this review (FUL, MJ) conducted an independent search. Any potential disagreement between authors was discussed and a consensus reached.

Data on signs and symptoms were extracted if the signs and symptoms are listed in the catatonia specifier of the DSM-5 (APA 2013) or mentioned in the diagnostic criteria for neuroleptic malignant syndrome in DSM-IV (APA 1994). To evaluate the discriminant value of each feature, we conducted binominal regression analyses with the diagnosis (catatonia or neuroleptic malignant syndrome), as provided by the authors of the respective articles, as the dependent variable. The diagnoses were checked for plausibility and then adopted in the analysis. Although logistic regression analysis is an unusual procedure applied to a review article, this procedure provides a robust method in order to analyze dichotomous data. In a first step, all features were entered into the model as independent variables. In a second step, a stepwise backwards analysis was conducted to eliminate criteria with a low discriminant value. Odds ratios were calculated for each criterion and Nagelkerke's R^2 was calculated as an indicator of model fit. Differences in age and sex were examined with the t test and chi-square test, respectively. All statistical analyses were performed with SPSS.

Results

A flow diagram of the process used to identify studies is shown in Fig. 1. All of the studies included were published after 1973; the highest number of studies was published in 1991. A total of 386 articles containing 490 case reports (390 with a diagnosis of neuroleptic malignant syndrome and 100 with a diagnosis of catatonia) were included in the final analysis. No statistically significant differences in age or sex were found between the two diagnostic groups (neuroleptic malignant syndrome and catatonia).

The frequency of diagnostic key features (criteria for neuroleptic malignant syndrome and catatonia specifier) in both diagnostic groups is shown in Table 1. The most common symptoms in patients with neuroleptic malignant syndrome were fever (87.7 %), rigor (85.9 %), laboratory evidence of muscle injury (70.5 %), and tachycardia (62.1 %). In contrast, the most common symptoms in patients with catatonia were mutism (78.0 %), rigor (73.0 %), stupor (54.0 %), and agitation (49.0 %). However, the data showed a considerable overlap between the two diagnostic groups, e.g., with respect to features like rigor, fever, or agitation. Furthermore, one should note that mutism is a diagnostic feature of both neuroleptic malignant syndrome and catatonia.

In the first step, we conducted a binominal regression analysis. Nagelkerke's R^2 (0.775) suggested that 78 % of the variance could be explained with the model. Second, we conducted a stepwise backwards logistic regression analysis. In the final model Nagelkerke's R^2 was still 0.759. The twelve variables remaining are shown in Table 2.

To summarize, fever, laboratory evidence of muscle injury, leukocytosis, rigor, diaphoresis, and tremor were predictive for a diagnosis of neuroleptic malignant syndrome. On the other hand, negativism, posturing, stereotypy, stupor, and waxy flexibility were predictive for a diagnosis of catatonia. An overview of the impact of symptoms for diagnostic decision making on the basis of odds ratios is provided in Fig. 2.

Discussion

Our results indicate that it is possible to distinguish between neuroleptic malignant syndrome and catatonia on a descriptive level. The logistic regression analyses revealed twelve signs and symptoms with a significant discriminatory power (fever, laboratory evidence of muscle injury, leukocytosis, rigor, diaphoresis, tremor, negativism, posturing, stereotypy, stupor, tachycardia, and waxy flexibility). Several clinical signs and symptoms indicate the presence of neuroleptic malignant syndrome (in descending order of strength of association: diaphoresis, rigor, fever, tremor, laboratory evidence of muscle injury, leukocytosis) whereas others rather indicate catatonia (in descending order of strength of association: negativism, posturing, waxy flexibility, stupor, and stereotypy). In this context, one should consider that Gurrera et al. (2011) identified rigidity, mental status alteration, creatine kinase elevation, sympathetic nervous system lability, tachycardia plus tachypnea, and a negative work-up for other causes as clinical expert consensus criteria for malignant neuroleptic syndrome using the Delphi method. The crucial question is whether our model will be useful in clinical practice. For example, rigor and fever were identified as predictors for a diagnosis of NMS (frequency of 85.9 and 87.7 %, respectively), but both features were also frequent in catatonia (73.0 and 30.0 %, respectively). Previous studies also reported such an overlap (Koch et al. 2000; Goforth and Caroll 1995). For example Koch et al. (2000), reported that 94 % of patients fulfilling the DSM-IV criteria for neuroleptic malignant syndrome also fulfilled clinical criteria for catatonia according to Bush-Francis Catatonia Rating Scale. This overlap, however,

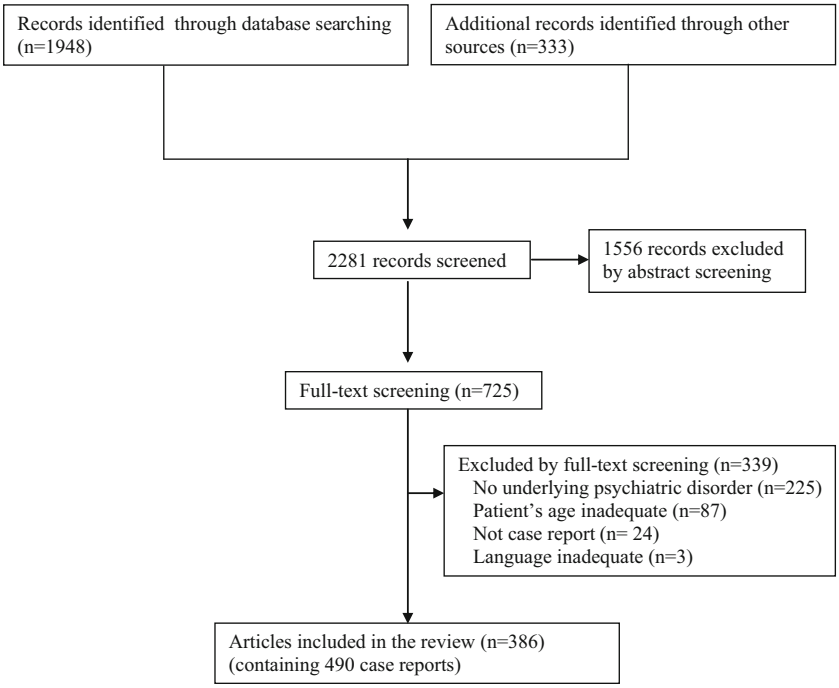

Fig. 1 Identification of studies

seriously limits the usefulness of such features for the diagnostic distinction between neuroleptic malignant syndrome and catatonia.

At first view, our findings seem to lend support to the hypothesis that neuroleptic malignant syndrome and catatonia are two different conditions which can be distinguished by several signs and symptoms. Previous studies, e.g., Castillo et al. (1989), also identified a couple of discriminating factors for both conditions. On the basis of their results, the authors emphasized the contrast between neuroleptic malignant syndrome and catatonia, also with respect to the assumed underlying pathophysiological processes (Castillo et al. 1989). On this note, Northoff (2002) hypothesized that neuroleptic malignant syndrome may be regarded as a "subcortical motor syndrome" with a dysregulation of the dopaminergic system, while catatonia may display a "cortical motor syndrome" with a primarily GABAergic alteration.

Conflicting conclusions, however, were drawn by authors such as Fink and Taylor (2001)—who proposed the term "malignant catatonia" to connect the concepts of neuroleptic malignant syndrome and catatonia—because both conditions not only display a similar clinical picture but also usually

Table 2 Symptoms remaining after stepwise backwards logistic regression analysis

Symptoms	OR	CI 95 %
Stereotypy	0.122*	0.042–0.352
Stupor	0.158*	0.065–0.384
Tachycardia	2.211	0.897–5.454
Waxy flexibility	0.223*	0.077–0.651
Posturing	0.241*	0.094–0.615
Negativism	0.262*	0.096–0.710
Leukocytosis	3.081*	1.050–9.043
Laboratory evidence of muscle injury	3.542*	1.467–8.553
Tremor	4.064*	1.090–15.149
Fever	7.317*	2.940–18.210
Rigor	9.550*	3.088–29.536
Diaphoresis	10.011*	2.689–37.271

OR odds ratio, *CI* confidence interval

*$p<0.05$

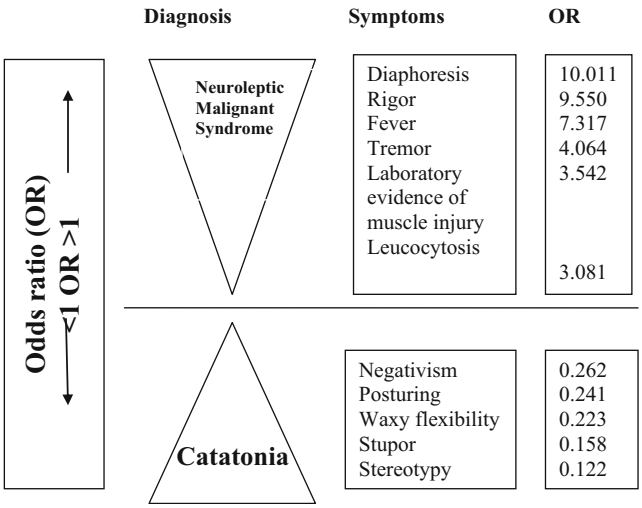

Fig. 2 Impact of statistically significant symptoms on diagnostic decision making

show good response to treatment with intravenous benzodiazepines or electroconvulsive therapy (ECT). Furthermore, White and Robins (2000) described 17 patients who developed symptoms compatible with a diagnosis of neuroleptic malignant syndrome after administration of neuroleptics. However, the fact that all 17 patients had already shown catatonic symptoms before administration of the drugs was regarded as a serious challenge to the authors' assumption of two different nosological or pathophysiological conditions. Lastly, authors like Gillman (2010) even proposed that NMS may be solely a "chimera".

Our findings mainly reflect the way that clinical decisions are made to distinguish between neuroleptic malignant syndrome and catatonia. The criteria of both diagnoses are based on partially overlapping signs and symptoms and on the assumption of a possible pathological agent in terms of neuroleptic medication (APA 2013). Therefore, the diagnostic distinction between neuroleptic malignant syndrome and catatonia mainly depends on the physician's clinical opinion without the possibility of an external validation (Feinstein 1977) of both diagnoses. Such an external validation could refer to pathophysiological processes on the one hand and factors such as treatment response or outcomes on the other (Feinstein 1977). It seems unlikely that the "catatonic dilemma" (Brenner and Rheuban 1978) will be solved on the level of cross-sectional signs and symptoms. Therefore, we need to search for neurobiological markers or try to characterize patients with respect to their psychopathological long-term course (White and Robins 2000).

The strength of the present review is the large number of included case reports. However, one has to consider a serious limitation. The analyses are limited by the absence of an external validation of the diagnoses, which is lacking for both neuroleptic malignant syndrome and catatonia. There is a strong syndromal overlap between catatonia and neuroleptic malignant syndrome, and our findings regarding the diagnostic distinction might be influenced by the fact that they are based on case reports and reflect the respective authors' clinical view of the patient's condition. Furthermore, signs and symptoms described in the case reports may have been diagnosed using different criteria. This may reduce the comparability of the results included in the present review. Finally, case studies of either catatonia or neuroleptic malignant syndrome may selectively report symptoms in order to support the respective diagnosis. Nevertheless, our results indicate that neuroleptic malignant syndrome and catatonia can be distinguished at least on a descriptive level as we were able to identify several symptoms with discriminatory power.

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Conflict of interest F. U. Lang has received financial support for congresses from AstraZeneca and Janssen-Cilag and remunerations from Lundbeck. M. Jäger has received remunerations and financial support for congresses from AstraZeneca, Eli Lilly und Janssen-Cilag. T. Becker reports research funding to the department (Psychiatry II, Ulm University) from Astra Zeneca, GlaxoSmithKline and AFFECTIS Pharmaceuticals AG. The department has received funds and honoraria to a minor extent for seminars, invited speakers and hospitality from Astra Zeneca, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Janssen Cilag, Eli Lilly, Lundbeck, Novartis, Pfizer, and Wyeth. S. Lang declares no conflict of interest.

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