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Review

HyperCKemia and rhabdomyolysis in the neuroleptic malignant and serotonin syndromes: A literature review

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Abstract

Neuroleptic malignant syndrome and serotonin syndrome are two syndromes whose molecular bases remain poorly understood. The phenotypes of both syndromes overlap with other syndromes that have a clear genetic background, in particular *RYR1*-related malignant hyperthermia. Through a literature review, performed according to the PRISMA guidelines, we aimed to report the clinical features of both syndromes, and the results of genetic testing performed. 10 case series and 99 case reports were included, comprising 134 patients. A male predominance of 58% was found. The median age was 35 (range 4–84) years. Eight patients experienced recurrent episodes of rhabdomyolysis. Genetic analysis was performed in eleven patients (8%), revealing four *RYR1* variants, three likely benign (p.Asp849Asn, p.Arg4645Gln, p.Arg4645Gln) and one variant of uncertain significance (p.Ala612Thr). This review underlines that a subset of patients with neuroleptic malignant syndrome and serotonin syndrome develop recurrent episodes of rhabdomyolysis. This recurrent pattern suggests a possible underlying (genetic) susceptibility. However, the genetic background of neuroleptic malignant syndrome and serotonin syndrome has only been investigated to a very limited degree so far. The increasing availability of next generation sequencing offers an opportunity to identify potentially associated genetic backgrounds, especially in patients with recurrent episodes or a positive family history.

Keywords: Serotonin syndrome; Neuroleptic malignant syndrome; Rhabdomyolysis; *RYR1*.

1. Introduction

Rhabdomyolysis is a severe and potentially life-threatening medical emergency involving the dissolution of skeletal muscle cells, due to a wide range of etiologies that ultimately all converge in a common pathway leading to irreversible muscle breakdown [1]. Whilst in some instances rhabdomyolysis may be exclusively due to external triggers (e.g., trauma, local ischaemia, exertional exercise), recent observations suggest that such events more commonly reflect a synergistic effect of predisposing genetic and environmental factors [2]. Specific phenotypes elicited by pharmacological agents (malignant hyperthermia (MH), neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS)) feature

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muscle breakdown as an essential part of a more widely defined syndrome, and are all considered part of the rhabdomyolysis spectrum.

MH is a well described pharmacogenetic disorder which clinically manifests as a hypermetabolic crisis when an MH-susceptible (MHS) individual is exposed to volatile anesthetics (*e.g.,* halothane, isoflurane, sevoflurane, desflurane) or the depolarizing muscle relaxant succinylcholine. An MH reaction typically features a critically increased body temperature (often in excess of 42 °C), muscle rigidity or spasms, rhabdomyolysis, tachycardia, and other life-threatening symptoms. MH has been associated with specific mutations in the *RYR1, CACNA1S* or *STAC3* genes, all of which ultimately result in excessive cytoplasmic calcium accumulation in response to both pharmacological and non-pharmacological triggers. To date, 48 *RYR1* and two *CACNA1S* variants have been unequivocally classified as MH diagnostic variants (https://www.emhg.org/genetics).

In contrast to MH, the genetic background and pathophysiology of NMS or SS are relatively poorly understood. SS is a potentially fatal condition, most likely caused by high levels of serotonin (5-hydroxytryptamine, 5-HT) in the synaptic cleft, leading to an overactivation of the central and peripheral serotonin receptors. The reaction is thought to be concentration dependent, and is often the result of concomitant exposure to two or more serotonergic agents. Monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors are the medications most commonly associated with SS [3]. Simultaneous prescription of medication inhibiting the cytochromes P450 (CYPs) is associated with increased serum concentration of serotonergic drugs, leading to potentially toxic levels. Similarly, genetic polymorphisms in these CYP enzymes, in particular CYP2D6, CYP3A4, and CYP2C19, increase the serum concentration of serotonergic medication and thus the risk of reaching a potentially toxic serum concentration [4]. In addition, it appears that polymorphisms in the 5-HT-2A receptor may predispose to the development of SS [5].

NMS is most likely caused by impaired function of central dopamine pathways [6]. This hypodopaminergic theory is based on the observation that NMS typically develops after exposure to dopamine antagonists, or acute withdrawal of dopamine agonists, referred to as the neuroleptic malignant-like syndrome (NMLS) [7]. NMS is a rare but potentially life-threatening reaction to almost any of a group of antipsychotic drugs or major tranquilizers (neuroleptics). A genetic basis for the disorder had been suspected but has not been proven yet; a case series of identical twins, and a mother and two daughters all experiencing NMS, support this suspicion of an underlying genetic risk factor [8].

Some authors have suggested that NMS may be genetically related to MH [9-11], taking into account that the clinical triad of autonomic dysfunction, altered mental status and rhabdomyolysis is seen in both MH and NMS, but also SS. The hypothesis of *RYR1* involvement in NMS and SS is also supported by the observation that other similar (non-anesthesia) related clinical syndromes with rhabdomyolysis such as exertional heat stroke (EHS) and exertional rhabdomyolysis (ERM) have also been associated with (MH-related) *RYR1* variants [12]. The overlap in clinical presentation and pathophysiological pathways suggests that there might be similarities between the genetic background underlying MH/ERM/EHS and NMS/SS.

In the present study we aim to review the clinical features of patients with hyperCKemia or rhabdomyolysis events in the context of NMS and SS. In addition, we aim to describe genetic testing (where performed) in particular in patients with clinical features suggestive for a monogenic background (i.e., recurrent episodes or a positive family history).

2. Methods

A systematic review was performed according to the guidelines of "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) [13]. Methods of the analysis and inclusion criteria were specified in advance and documented in a permanent record in Prospero (Registration number CRD42018115828).

Cohort studies, case control studies, case reports and case series were included. No publication date or publication status restrictions were imposed. Patients of any age were included if a diagnosis of rhabdomyolysis was made and in addition the diagnosis of NMS or SS was considered definite or probable. A separate search was performed on all cases of rhabdomyolysis induced by the use of the recreational drug 3,4-methylenedioxymethamphetamine (MDMA/ecstasy), since not all literature considers this as a specific form of SS [14]. In cases where CK levels were unknown, or serum CK levels did not exceed 1.5 times the upper limit of normal (ULN), the study was excluded as not fulfilling the diagnostic criteria for hyperCKemia (>1.5x ULN) or rhabdomyolysis (>10x ULN) [15]. Meta-analyses, review articles, conference abstracts, articles not in English, animal studies, and studies of which no full-text was available, were also excluded.

A literature search was performed in MEDLINE, EMBASE, Psycinfo and the Cochrane Library from inception to January 31, 2019. The following keywords and all known synonyms for these keywords were used: 'Neuroleptic malignant syndrome', 'Serotonin syndrome', 'MDMA', 'Rhabdomyolysis'. In addition, based on clinical similarities and in particular considering rhabdomyolysis as a shared clinical endpoint, we conducted an additional search for *RYR1*, given that the part of the NMS- and SS-related rhabdomyolysis spectrum is possibly associated with *RYR1* variants. The search strategy is detailed in Appendix 1. Eligibility assessment was performed by two independent reviewers (N.K, J.W) in an unblinded standardized manner. Each study was reviewed for eligibility based on title and abstract. The full text of presumably eligible studies was evaluated to decide whether the study fulfilled the inclusion criteria. In case of discrepancies between the two reviewers, consensus was reached after discussion; if no agreement could be reached, a third reviewer was consulted.

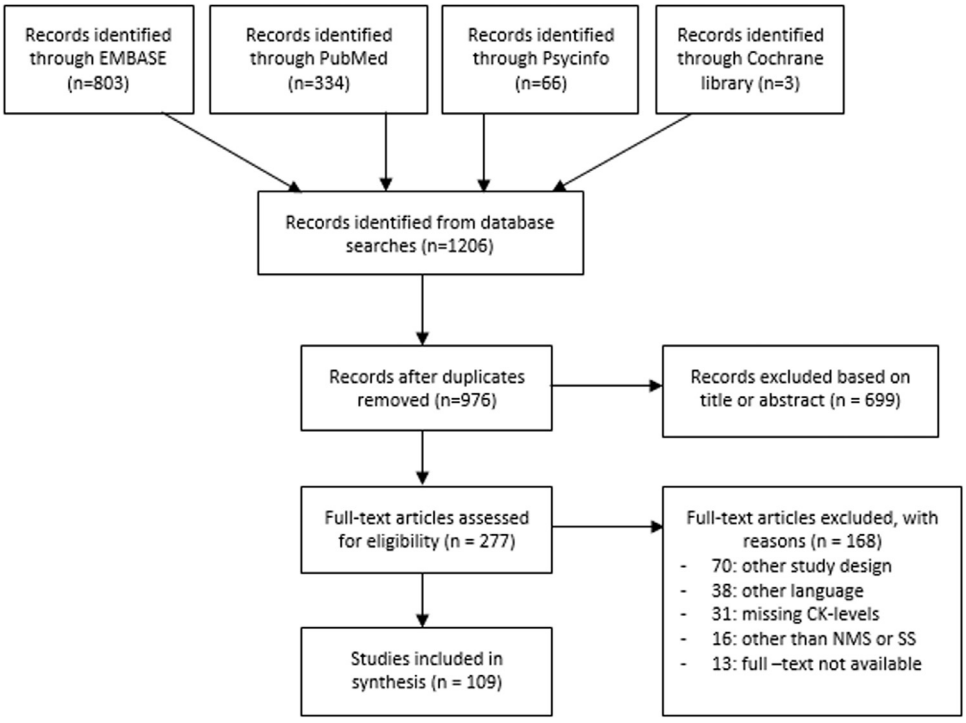

Fig. 1. Flow diagram of the study selection process.

We developed a data extraction sheet, which was then pilot-tested on ten randomly-selected included studies, and subsequently refined accordingly. One review author (N.K.) extracted the data items from included studies. Information was extracted from each included study on (1) clinical characteristics (including age, sex, medical history, family history, temperature and mental status during the episode); (2) laboratory results (including peak CK levels, myoglobinuria, genetic testing); (3) neurological symptoms and examination (including myalgia, muscle cramps/weakness/swelling, extrapyramidal symptoms, hyperreflexia, clonus); (4) outcome (including recurrence, death). The number of episodes was divided into three groups: recurrent, non-recurrent and unknown. If multiple episodes of rhabdomyolysis were reported in one patient, the first episode was used for describing the data.

Based on our experience with exertional rhabdomyolysis, the following clinical features were considered suggestive for a monogenic background: 1) recurrent rhabdomyolysis and/or 2) a positive family history of neuromuscular disorders, in particular MH and rhabdomyolysis [16].

Categorical data were compared using the χ^2 test, or Fisher exact test in case of less than 5 patients. Continuous variables were compared using the Mann-Whitney U test.

3. Results

The search yielded a total of 1206 studies. After removal of duplicates, 976 studies remained. After reviewing the titles and abstracts, 699 studies were excluded because they did not meet the eligibility criteria. The full text of the remaining 277 studies was examined in more detail. It appeared that 168 citations did not meet the inclusion criteria (Fig. 1).

3.1. Study characteristics

A total of 109 studies (10 case series and 99 case reports) were included, comprising 143 cases of which 134 cases met our inclusion criteria. These included 60 cases of SS- and 74 cases of NMS-related rhabdomyolysis.

3.2. Clinical features

Characteristics of the patients are described in Table 1. The median age was 35.0 years (range, 4–84). 77 (58%) were male, 57 (43%) were female. Death was reported in 23 patients (17%). In eight patients, rhabdomyolysis was recurrent (6%). Myoglobinuria was reported in 38 patients (27%). Results of the neurological examination during the episode of rhabdomyolysis are listed in Table 2.

3.2.1. Serotonin syndrome

A total of sixty patients with SS, 33 male and 27 female, were included. Those patients had a median age of 23 years (range 4–75). The median maximum temperature during the episode was 39.5 °C (range 35.4–43.3). The median peak CK level was 10,888 (range 354–196,000 IU/l). Thirty three cases could be attributed to the prescription of a specific medication, twenty seven cases (45%) involved SS due to intoxication with MDMA. Patients with MDMA intoxication were younger than patients in whom medication was

Table 1
Patient characteristics and etiology.

	Neuroleptic malignant syndrome ($n=74$) *n* (%)	Serotonin Syndrome ($n=60$) *n* (%)	Total ($n=134$) *n* (%)	*p*-value
Etiology				
Medication	74 (100.0)	33 (55.0)	107 (78.7)	–
MDMA	–	27 (450)	27 (21.3)	
Sex				
Male	44 (59.5)	33 (55.0)	77 (57.5)	0.604
Female	30 (40.5)	27 (45.0)	57 (42.5)	
Age				
Median*	45.0 (9–84)	23.0 (4–75)	35.0 (4–84)	<0.001
Average**	45.5 (17.93)	28.3 (15.34)	37.7 (18.81)	
Peak CK (IU/L)				
Median*	15,059 (572–220,000)	10,888 (354–196,000)	12,663 (354–220,000)	0.409
Average**	30,181 (41,823)	24,401 (37,553)	27,593 (39,925)	
ULN 1.5 – 10x	12 (16.2)	8 (13.3)	20 (15.0)	
ULN >10x	62 (83.8)	52 (86.7)	114 (85.0)	
Max temp (°C)	*(n=72)*	*(n=56)*	*(n=128)*	
Median*	39.5 (35.4–42.8)	39.5 (35.4–43.3)	39.5 (35.4–43.3)	0.535
Average**	39.6 (1.66)	39.7 (2.00)	39.7 (1.81)	
Max temp >38.5 °C				
Yes	52 (70.3)	44 (73.3)	96 (71.6)	0.286
No	22 (29.7)	12 (20.0)	34 (25.4)	
Not reported	–	4 (6.7)	4 (3.0)	
Recurrent				
Recurrent	6 (8.1)	2 (3.3)	8 (6.0)	0.296
First episode	44 (59.5)	12 (20.0)	56 (41.8)	
Not reported	24 (32.4)	46 (76.7)	70 (52.2)	
Mental status				
Normal	2 (2.7)	1 (1.7)	3 (2.2)	–
Comatose	26 (35.1)	18 (30.0)	44 (32.8)	
Agitated	16 (21.6)	20 (33.3)	36 (26.9)	
Confused	15 (20.3)	9 (15.0)	24 (17.9)	
Elevated mood	1 (1.4)	–	1 (0.7)	
Altered	8 (10.8)	1 (1.7)	9 (6.7)	
Not reported	6 (8.1)	11 (18.3)	17 (13.7)	
Outcome				
Dead	15 (20.3)	8 (13.3)	23 (17.2)	0.148
Alive	46 (62.2)	49 (81.7)	95 (70.9)	
Not reported	13 (17.6)	3 (5.0)	16 (11.9)	
Drug overdose				
Yes †	3 (4.1)	39 (65.0)	19 (14.2)	<0.001
No	71 (95.9)	21 (35.0)	115 (86.8)	
Relevant family history				
Positive	–	–	–	–
Negative	3 (4.1)	2 (3.3)	5 (3.7)	
Not reported	71 (95.9)	58 (96.7)	129 (96.3)	

Values are depicted as * median (range) and ** average (standard deviation), † auto-intoxication including all patients with MDMA intoxication. Abbrevations: CK = creatine kinase, MDMA = methylenedioxymethamfetamine, ULN = upper limit of normal.

prescribed (23.4 compared to 34.7 years, $p < 0.001$). Twelve patients (20%) had attempted suicide through overdosing with antidepressant medication. Hyperreflexia was more often reported as a key feature in SS compared to NMS (37% vs. 4.1%, $p=0.020$). In addition, convulsions were reported more often in patients with SS (47%, $p=0.026$).

3.2.2. Neuroleptic malignant syndrome

In the group of 74 patients with NMS, 44 were male and 30 were female; they had a median age of 45 years (range 9–84). Patients had a median maximum temperature of 39.5 °C (range 35.4–42.8). The median peak CK level was 15,059 IU/L (range 572–220,000). Rigidity was reported more

Table 2
Results of the reported neurologic symptoms and examination.

	Neuroleptic malignant syndrome *(n = 74)*		Serotonin syndrome *(n = 60)*		*p*-value
Neurological examination	Yes (%)	No (%)	Yes (%)	No (%)	
Myalgia	4 (5.4)	–	8 (13.3)	2 (3.3)	0.495
Muscle weakness	5 (6.8)	–	6 (10.0)	–	–
Muscle swelling	1 (1.4)	1 (1.4)	4 (6.7)	–	–
Tremor	12 (16.2)	1 (1.4)	15 (25.0)	–	0.464
Diaphoresis	23 (31.1)	2 (2.7)	17 (28.3)	–	0.348
Increased tone	10 (13.5)	3 (4.1)	6 (10.0)	2 (3.3)	0.656
Rigidity	54 (73.0)	4 (5.4)	17 (28.3)	5 (8.3)	0.059
Myoclonus	3 (4.1)	1 (1.4)	19 (31.7)	–	0.174
Hyperreflexia	3 (4.1)	2 (2.7)	22 (36.7)	1 (1.7)	0.020
Clonus	–	–	14 (23.3)	1 (1.7)	–
Convulsions	5 (6.8)	3 (4.0)	28 (46.7)	1 (1.7)	0.026

Table 3
Characteristics of the group of patients experiencing recurrent episodes of NMS and/or SS compared to patients with a single episode. Temperature involved the maximum temperature measured during the rhabdomyolysis episode.

	Recurrent episode *(n = 8) n (%)*	Single episode *(n = 126) n (%)*	*p*-value
Syndrome			
NMS	6 (75.0)	68 (54.0)	0.296
SS	2 (25.0)	58 (46.0)	
Sex			
Male	4 (50.0)	73 (57.,9)	0.723
Female	4 (50.0)	53 (42.1)	
Age*	43.5 (20–70)	33.5 (4–84)	0.280
Peak-CK*	16,807 (754–170,800)	12,980 (259–220,000)	0.914
Temperature*	38.2 (35.4–41.2)	39.5 (35.4–43.3)	0.059
Fever			
Yes	3 (37.5)	93 (73.8)	0.029
No	5 (62.5)	29 (26.2)	
Mental status			
Normal	1 (12.5)	2 (1.6)	
Comatose	3 (37.5)	41 (32.5)	
Agitated	2 (25.0)	34 (27.0)	
Confused	1 (12.5)	23 (18.3)	
Elevated mood	–	1 (0.8)	
Altered	–	9 (7.1)	
Not reported	1 (12.5)	16 (12.7)	
Outcome death			
Yes	2 (25.0)	21 (16.7)	0.332
No	4 (50.0)	91 (72.2)	
Not reported	2 (25.0)	14 (11.1)	

* indicated as median (range).
Abbrevations: CK = creatine kinase, NMS = neuroleptic malignant syndrome, SS = serotonin syndrome.

commonly in patients with NMS compared to SS (73% vs. 28%, $p = 0.053$)

3.3. Presumed genetic susceptibility and genetic screening

Table 3 shows the characteristics of the subset of eight patients experiencing recurrent episodes of NMS and/or SS. Table 4 shows the characteristics of the individual cases. Genetic testing was performed in one case report and one case series, comprising eleven patients (8%).

3.3.1. Serotonin syndrome

Out of 60 patients with SS, two patients developed recurrent episodes of rhabdomyolysis. Both patients developed SS and also had experienced an episode of NMS in their history or at follow up (patients 1 and 2, Table 4). Of these, genetic screening was performed in one patient. This patient, a 20-year-old woman, developed rhabdomyolysis after exposure to MDMA [17]. Two weeks later, she developed NMS after being exposed to haloperidol. Performing both RT-PCR, covering the complete *RYR1* transcript, and sequence analysis of genomic DNA, a presumed pathogenic variant in the *RYR1* gene was revealed (c.2545G>A in exon 20 resulting in an amino acid change p.Asp849Asn). Her asymptomatic mother carried the same variant and was considered MH negative after caffeine-halothane contracture testing.

3.3.2. Neuroleptic malignant syndrome

Recurrent episodes of rhabdomyolysis due to NMS were reported in six patients (patients 3–8, Table 4). Seven patients had experienced an adverse drug reaction (other than rhabdomyolysis) to antipsychotics in their history. One case series included limited *RYR1* genetic testing in ten patients with NMS. Six *RYR1* variants known to be associated with malignant hyperthermia were analyzed, with negative test results. However, comprehensive *RYR1* screening was not performed [10].

In 129 cases (96%) no information regarding family history was provided, and five patients mentioned a negative family history. In one patient, a debatable positive family history involved an asymptomatic mother carrying a *RYR1* variant (patient 1, Table 4).

4. Discussion

This systematic review identified 109 studies fulfilling the selection criteria, comprising 74 cases of NMS and 60

Table 4
Characteristics of individual patients with recurrent episodes of rhabdomyolysis.

#	Syn-drome	Author (year)	Sex, age	Episode	Peak CK (IU/L)	max T (°C)	Medication (time after first administration)	Regime, outcome	Additional information
1	SS	Russell (2012) [17]	F, 20	1	>20,000	41.0	Unknown quantity MDMA (24 h)	Supportive care, resolution rhabdomyolysis	*RYR1* analysis: c.2545G>A p.Asp849Asn in exon 20
				2	>30,000	39.5	NR	Treatment with dantrolene, resolution of CK-levels	
				3	>11,124	40.9	Haloperidol (NR)	Discontinuation of haloperidol and active cooling, improvement and discharge on day 42	
2	SS	Rajapakse (2010) [35]	M, 43	1	170,800	41.2	Venlafaxine (2 weeks)	Bicarbonate hemodialysis and discontinuation venlafaxine, normalization of CPK within 2 weeks	Possible episode of NMS after administration of a phenothiazine six months earlier
3	NMS	Aggarwal (2014) [36]	M, 23	1	23,614	38.0	Paliperidone 9 mg d.d.(2 weeks)	Intravenous hyperhydration and discontinuation paliperidone	
				2	10,487	37.2	Ziprasidone 60 mg 2d.d. (2 weeks) Lithium 900 mg d.d. (2 weeks)	i.v. hyperhydration and discontinuation ziprasidone, lithium for 3 weeks	
				3	994	37.4	Haloperidol 5 mg d.d Benztropine 1 mg 2d.d. (3 weeks)	i.v. hyperhydration and discontinuation haloperidol	
				4	1493	NR	Quetiapine 100 mg 2d.d. (7 days)	Ceasing quetiapine, start olanzapine. No adverse effects reported after 2 months	
4	NMS	Mohan (2014) [37]	M, 48	1	1344	35.4	Quetiapine (unknown)	Discontinuation quetiapine, normalization CK	
				2	1263	NR	Aripiprazole (10 days)	Discontinuation aripiprazole, normalization CK	
				3	25,810	NR	Amisulpride (5 years)	Discontinuation amisulpride, normalization CK	
				4	9728	NR	Olanzapine (5 years)	Discontinuation amisulpride, normalization CK, No adverse effects reported after start clozapine,	
5	NMS	San Gabriel (2015) [38]	M, 42	1	27,847	38.3	Olanzapine 20 mg d.d.(10 years) Clozapine 1 mg 3d.d. (unknown) Haloperidol cumulative: 5 mg p.o. + 15 mg i.m. and 100 mg chlorpromazine i.m.	i.v. hyperhydration and discontinuation neuroleptics, resolution of CK-levels	
				2	200,000	NR	Quetiapine 100 mg d.d. (16 days)	i.v. hyperhydration and discontinuation quetiapine, resolution of CK-levels	
				3	27,966	NR	Clozapine (20 days)	Discontinuation of clozapine, 10 ECT sessions, discharge	
6	NMS	Cooper (2009) [39]	F, 60	1	754	37.9	Periciazine 10 mg a.n. (3 weeks)	Treatment with bromocriptine, resolution of symptoms. ECT for persistent catatonia	Co-ingestion of simvastatin
				2	884	37.5	Quetiapine 125 mg d.d. (4 weeks)	Discontinuation simvastatin, resolution of symptoms	
7	NMS	Allsop (1987) [40]	F, 44	1	>10,000	NR	Fluphenthixol depot (4 weeks)	Treatment with dantrolene 20 mg 3 times daily, death due to gastrointestinal bleeding complicated by intravascular coagulation	A similar episode had occurred 5 years earlier
8	NMS	Jones (1989) [41]	F, 70	1	3300	39.4	Chlorpromazine 25 mg 3d.d. (NR) Isocarboxazid 10 mg (NR)	Discontinuation neuroleptics, improvement within 24 h	Six occasions of unexplained confusional state with rigidity and autonomic dysfunction in the last two years

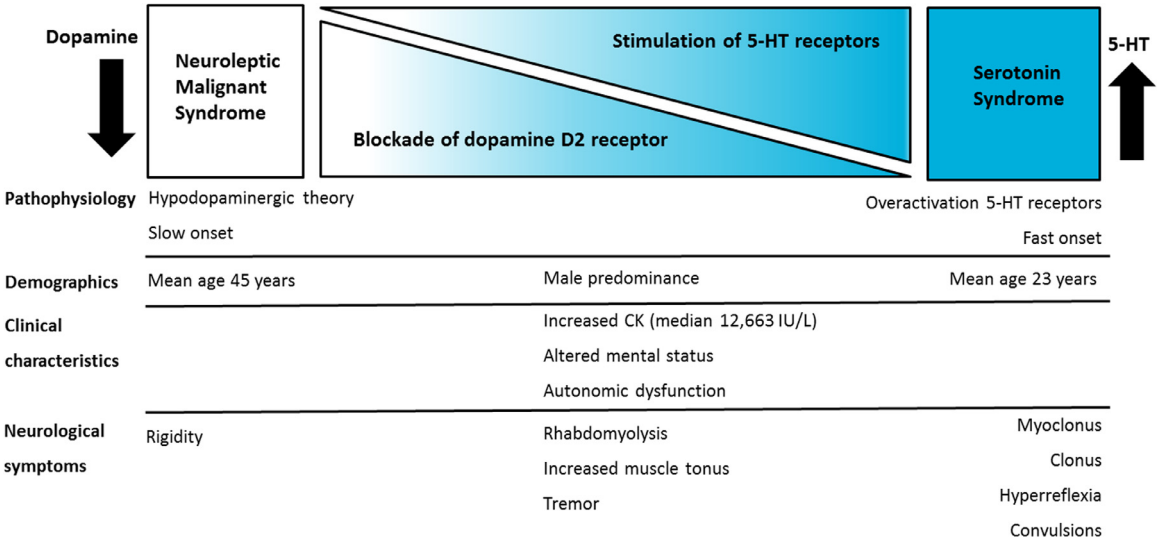

Fig 2. Summary of the clinical phenomenology of the Serotonin syndrome and Neuroleptic malignant syndrome.

cases SS associated with hyperCKemia or rhabdomyolysis. In both subsets, a male predominance of 60% (NMS) and 55% (SS) was found. Cases with SS more often involved an auto-intoxication with medication (20%) or recreational drugs (45%) than cases with NMS (4%) ($p < 0.001$), reflecting that SS is a concentration-dependent syndrome and NMS is considered an idiosyncratic reaction [18]. Eight patients experienced recurrent episodes of rhabdomyolysis. Those involved six patients with recurrent NMS, and two patients with SS that had experienced NMS at different timepoints.

Many of the clinical characteristics of both syndromes overlap. It has been discovered that the pathways of serotonin and dopamine are very much intertwined, and it may be therefore that symptoms associated with both SS and NMS are reflected by a final shared pathway [19]. However, hyperreflexia and convulsions were reported more often in patients with SS, both features supportive of central origin. A summary of the clinical phenomenology of both syndromes is depicted in Fig. 2.

The mean age in our subset of patients with NMS is similar to the average median age of 39 years found in a recent systematic review involving also NMS patients without rhabdomyolysis [20]. The age of patients with SS in our review is below the mean age of 58 found in a large French retrospective study, also after separating MDMA-induced SS from medication induced SS (mean ages of 23 and 35, respectively) [21]. For both NMS and SS, the mean age was higher compared to the age of onset in patients with MH, experiencing a first adverse reaction at a mean age of 18 years [22]. Presumably, this is due to the prescription of antipsychotics and antidepressants at an older age, or the prescription of multiple neuroleptics at a higher age, compared to potentially MH-triggering anaesthetics and muscle relaxants that are administered throughout lifetime, or even preferentially in the pediatric age group.

The male preponderance seen in our review is also observed in malignant hyperthermia, not in keeping with what is expected in a strictly monogenic autosomal-dominant disorder [23, 24]. It has been previously hypothesized that the male predominance in MH was caused by men being more frequently exposed to types of surgery commonly associated with MH. However, a study on in vitro contracture test (IVCT) outcome reported a significant difference in sex distribution, with males revealing a positive IVCT more frequently [24], probably reflecting additional hormonal or other sex-dependent variables. In addition, there is a higher use of antipsychotics in men compared to women, and men are known also to adhere to medication more consistently [25]. Also, in a study on acute intoxications in six Dutch hospitals, intoxications due to substance abuse was more frequently seen in men (66.0%) [26].

The mortality rate in both subsets of patients was 20% (NMS) and 13% (SS), respectively. Mortality rates in MH have decreased from 80% thirty years ago, to <5% in 2006 [23], because of the introduction of Dantrolene into pharmacological MH management. In more recent studies in our cohort, less deaths were reported in both groups (mortality of 13% from 2000 to 2018, 27% from 1984 to 1999).

The cumulative recurrence rate of 6% in our present study (8% in NMS and 3% in SS) is lower than in studies on rhabdomyolysis in general. In a retrospective study performed in 2005, 475 hospitalized patients with rhabdomyolysis were described, reporting a recurrence rate of 11% in a group with various etiologies [27]. A subgroup analysis of 38 NMS patients in this study revealed a recurrence rate of 25%. No investigations into possible underlying genetic susceptibilities were performed in these subjects. In 56% of all cases in our study, information on possible previous episodes in the patient's medical history was lacking, likely pointing to an underestimation of recurrence rates. In patients with recurrent

Table 5
Overview of genetic testing in patients with episodes of rhabdomyolysis due to psychiatric agents in our present study, and previous studies.

Study	Nucleotide	Protein	Pathogenicity
Russell, 2012	c.2545G>A	p.Asp849Asn	Likely benign, not evolutionary conserved (Ser-or Ala-in other vertebrates)
Miyatake, 1996	c.7281C>T	p.Ala2427=	Likely benign, silent variant present in 10% of the Asian population
Sato, 2010	c.13934G>A	p.Arg4645Gln	Likely benign, not evolutionary conserved (Tyr, Ala, Ser-or Thr-in other vertebrates) detected in one person with MHS
	NR	p.Ala612Thr	Variant of uncertain significance
Dlamini, 2013	NR	p.Tyr2426Cys	Variant of uncertain significance,
	NR	p.Thr4288_Ala4290dup	Variant of uncertain significance

Abbrevations: NR = Not reported.

episodes, no discernable factors (for example, presence of intercurrent illness, fever, exercise) were reported that may have modified the presentation.

The mother of patient 1 carried the same *RYR1* variant (c.2545G>A in exon 20 resulting in an amino acid change p.Asp849Asn) but was tested negative for caffeine-halothane contracture testing (CHCT), leading the authors to conclude that the RYR1 variant was non-contributory to the phenotype. However, a recent study shows that the majority of patients with ERM related to pathogenic *RYR*1 variants had a negative CHCT (or in vitro contracture test (IVCT)), indicating that these tests do not have the same discriminatory value for *RYR1*-related rhabdomyolysis as for *RYR1*-related MH [28]. Interestingly, a case report published in 2003 reported a patient with NMS in whom contracture testing with caffeine and halothane was negative, but in an analogous setting, the patients isolated muscle was found to react pathologically towards contracture testing with neuroleptics [29].

We also identified additional cases in the literature in whom rhabdomyolysis was triggered by exposure to antipsychotics, but who were not diagnosed as NMS or SS and were therefore not included in the current review. These patients are summarized in Table 5. Dlamini et al. sequenced *RYR1* in 39 unrelated families with rhabdomyolysis and identified 9 heterozygous variants in 14 families [2]. Two patients were on olanzapine treatment at the time of presentation with rhabdomyolysis. In both patients, a *RYR1* variant was found, one of which the authors mentioned to be associated with MH (p.Tyr2426Cys). However, to date, the relation of this variant with MH remains unclear, although it localizes to the MH mutational hotspot affecting the central domain of the RyR1 protein. The second patient on olanzapine treatment involved the p.Thr4288_Ala4290dup variant, that has been reported in three MHS individuals of which two also had a history of exercise induced rhabdomyolysis. Since all these individuals also had a second *RYR1* variant, the specific role of the p.Thr4288_Ala4290dup in MH and rhabdomyolysis remains uncertain [30].

In 2010, Sato et al. performed post mortem genetic analysis on eleven psychiatric patients who died of hyperthermia, most likely caused by NMS [31]. This paper was not included in our quantitative data-analysis because it did not report CK levels. Two patients carried a *RYR1* variant resulting in an amino acid change: 1) p.Arg4645Gln, a variant probably not pathogenic, based on evolutionary conservation, and 2) p.Ala612Thr, a substitution affecting a conserved amino acid residue that might have plausibly contributed to the event of rhabdomyolysis, regarding its location near the common p.Arg614Cys diagnostic MH variant.

To our knowledge, this is the first literature review describing all reported patients with hyperCKemia or rhabdomyolysis in the context of NMS and SS. However, the quality of data obtained from most reports was considered low; neurological examination was often not or only incompletely described, resulting in a substantial amount of missing data. In addition, information regarding recurrent episodes family history, or genetic testing was often absent. Therefore, it is impossible to ascertain if or if not some clinical characteristics were not present, or if the author decided not to describe a negative test result. Furthermore, only few studies included information concerning the patient's medical and family history.

Genetic testing was performed in only a small amount of studies of patients (8%). Therefore, based on the currently available data, there is little evidence to suggest that all patients should undergo genetic testing, however, these recommendations may change if additional information based on more comprehensive genetic testing in such cohorts becomes available. Although highly desirable, considering the comparative rarity of these presentations, performing a prospective study is not feasible. Based on the results in our present study we would advise to perform additional genetic testing, for example through an NGS-based rhabdomyolysis panel, in patients with drug-induced rhabdomyolysis and features suggestive of genetic susceptibility, such as a positive family history or recurrent episodes. To inform such an approach, it is, firstly, important to recognize specific genotype-phenotype correlations of genetic disorders associated with rhabdomyolysis to further determine the diagnostic approach, and to decide which candidate genes are opportune for testing [32]. Secondly, although the *RYR1* gene is a likely candidate for these presentations, *RYR1* is also

an extraordinarily complex gene with over 5000 amino acid residues that harbors many, often common missense variants (over 2000 already known) [33]. Performing next generation sequencing on a large gene such as *RYR1* will therefore in all likelihood reveal a large number of variants of unknown significance. Although *RYR1* analysis therefore requires a very careful and informed approach, in our view *RYR1* sequencing should be considered in particular in patients with recurrent episodes, considering the presence of *RYR1* variants in a proportion of the patients with NMS- or SS-related rhabdomyolysis we found in our literature review.

Identification of the genetic background implicated in these pharmacogenetic syndromes is important for several reasons. Firstly, in line with a personalized medicine approach, an informed decision can be made to avoid certain pharmacological agents in individuals where those may be harmful due to a specific genetic predisposition. Secondly, specific measures may be taken (for example, prescription of the specific ryanodine receptor antagonist Dantrolene in cases where *RYR1* has been implicated) to prevent recurrent episodes [34]. Thirdly, in cases where diagnostic MH variants in *RYR1* have been identified, genetic counseling of the patient and their families may prevent life-threatening MH events. The potential to identify the genetic background of NMS and SS has massively increased in recent years, due to the increasing availability of next generation sequencing, but appears not to have been fully utilized yet in these conditions.

5. Conclusion

Many of the clinical characteristics of SS and NMS overlap, except for hyperreflexia and convulsions (SS) and rigidity (NMS). This review underlines that a subset of patients develop recurrent episodes of rhabdomyolysis during NMS or SS, or both syndromes during different timepoints, suggesting a possible underlying (genetic) susceptibility. The genetic background of NMS and SS has been investigated only to a very limited degree so far, but the increasing availability of next generation sequencing offers an opportunity to identify potentially associated genetic backgrounds, especially in patients with a positive family history or recurrent episodes.

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Appendix

A: search strategy
Search PubMed

1 Neuroleptic Malignant Syndrome[Mesh]
2 Neuroleptic malignant syndrome*[tiab]
3 malignant neuroleptic syndrome*[tiab]
4 Antipsychotic malignant syndrome*[tiab]
5 malignant antipsychotic syndrome*[tiab]
6 NMS [tiab] OR NMSs [tiab]
7 1 or 2 or 3 or 4 or 5 or 6
8 Serotonin Syndrome[Mesh]
9 Serotonin syndrome*[tiab]
10 Serotonin Uptake Inhibitors/adverse effects[MeSH]
11 8 or 9 or 10
12 N-Methyl-3,4-methylenedioxyamphetamine[Mesh]
13 MDMA[tiab]
14 Methylenedioxymethamphetamine[tiab]
15 Ecstasy [tiab] OR XTC [tiab]
16 3,4-Methylenedioxyamphetamine/analogs and derivatives[Mesh]
17 12 or 13 or 14 or 15 or 16
18 Rhabdomyolysis[Mesh]
19 Rhabdomyolysis[tiab]
20 Rhabdomyolyses[tiab]
21 Myoglobinuria[tiab]
22 hyperCK*[tiab]
23 18 or 19 or 20 or 21 or 22
24 Ryanodine Receptor Calcium Release Channel[Mesh]
25 Ryanodine Receptor*[tiab]
26 RyR1[tiab]
27 24 or 25 or 26
28 7 or 11 or 17
29 23 or 27
30 28 and 29

References

[1] Torres PA, Helmstetter JA, Kaye AM, Kaye AD. Rhabdomyolysis: pathogenesis, diagnosis, and treatment. Ochsner J 2015;15:58–69.
[2] Dlamini N, Voermans NC, Lillis S, Stewart K, Kamsteeg EJ, Drost G, et al. Mutations in RYR1 are a common cause of exertional myalgia and rhabdomyolysis. Neuromuscul Disord 2013;23:540–8.
[3] Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med 2005;352:1112–20.
[4] Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J 2013;13:533–40.
[5] Francescangeli J, Karamchandani K, Powell M, Bonavia A. The serotonin syndrome: from molecular mechanisms to clinical practice. Int J Mol Sci 2019;20.
[6] Nisijima K, Shioda K, Iwamura T. Neuroleptic malignant syndrome and serotonin syndrome. Prog Brain Res 2007;162:81–104.
[7] Toru M, Matsuda O, Makiguchi K, Sugano K. Neuroleptic malignant syndrome-like state following a withdrawal of antiparkinsonian drugs. J Nerv Ment Dis 1981;169:324–7.
[8] Otani K, Horiuchi M, Kondo T, Kaneko S, Fukushima Y. Is the predisposition to neuroleptic malignant syndrome genetically transmitted? Br J Psychiatry 1991;158:850–3.
[9] Adnet PJ, Krivosic-Horber RM, Adamantidis MM, Haudecoeur G, Adnet-Bonte CA, Saulnier F, et al. The association between the neuroleptic malignant syndrome and malignant hyperthermia. Acta Anaesthesiol Scand 1989;33:676–80.
[10] Miyatake R, Iwahashi K, Matsushita M, Nakamura K, Suwaki H. No association between the neuroleptic malignant syndrome and mutations in the RYR1 gene associated malignant hyperthermia. J Neurol Sci 1996;143:161–5.
[11] Pothen N, Kansal S, Rais T, Doumas S, Solhkhah R. A look at genetic linkage between clozapine-induced agranulocytosis, malignant

hyperthermia, neuroleptic malignant syndrome, and statin-induced myopathy. Innov Clin Neurosci 2019;16:28–31.
[12] Sagui E, Montigon C, Abriat A, Jouvion A, Duron-Martinaud S, Canini F, et al. Is there a link between exertional heat stroke and susceptibility to malignant hyperthermia? PLoS ONE 2015;10:e0135496.
[13] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj 2009;339:b2700.
[14] Hall AP, Henry JA. Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. Br J Anaesth 2006;96:678–85.
[15] Kyriakides T, Angelini C, Schaefer J, Sacconi S, Siciliano G, Vilchez JJ, et al. EFNS guidelines on the diagnostic approach to pauci- or asymptomatic hyperCKemia. Eur J Neurol 2010;17:767–73.
[16] Voermans NC, Snoeck M, Jungbluth H. RYR1-related rhabdomyolysis: a common but probably underdiagnosed manifestation of skeletal muscle ryanodine receptor dysfunction. Rev Neurol Paris 2016;172:546–58.
[17] Russell T, Riazi S, Kraeva N, Steel AC, Hawryluck LA. Ecstacy-induced delayed rhabdomyolysis and neuroleptic malignant syndrome in a patient with a novel variant in the ryanodine receptor type 1 gene. Anaesthesia 2012;67:1021–4.
[18] Berman BD. Neuroleptic malignant syndrome: a review for neurohospitalists. Neurohospitalist 2011;1:41–7.
[19] Steele D, Keltner NL, McGuiness TM. Are neuroleptic malignant syndrome and serotonin syndrome the same syndrome? Perspect Psychiatr Care 2011;47:58–62.
[20] Gurrera RJ. A systematic review of sex and age factors in neuroleptic malignant syndrome diagnosis frequency. Acta Psychiatr Scand 2017;135:398–408.
[21] Abadie D, Rousseau V, Logerot S, Cottin J, Montastruc JL, Montastruc F. Serotonin syndrome: analysis of cases registered in the French pharmacovigilance database. J Clin Psychopharmacol 2015;35:382–8.
[22] Strazis KP, Fox AW. Malignant hyperthermia: a review of published cases. Anesth Analg 1993;77:297–304.
[23] Rosenberg H, Pollock N, Schiemann A, Bulger T, Stowell K. Malignant hyperthermia: a review. Orphanet J Rare Dis 2015;10:93.
[24] Islander G, Rydenfelt K, Ranklev E, Bodelsson M. Male preponderance of patients testing positive for malignant hyperthermia susceptibility. Acta Anaesthesiol Scand 2007;51:614–20.
[25] Oruch R, Pryme IF, Engelsen BA, Lund A. Neuroleptic malignant syndrome: an easily overlooked neurologic emergency. Neuropsychiatr Dis Treat 2017;13:161–75.
[26] Duineveld C, Vroegop M, Schouren L, Hoedemaekers A, Schouten J, Moret-Hartman M, et al. Acute intoxications: differences in management between six Dutch hospitals. Clin Toxicol Phila 2012;50:120–8.
[27] Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Med Baltim 2005;84:377–85.
[28] Knuiman GJ, Küsters B, Eshuis L, Snoeck M, Lammens M, Heytens L, et al. The histopathological spectrum of malignant hyperthermia and rhabdomyolysis due to RYR1 mutations. J Neurol 2019.
[29] Reif A, Schneider MF, Hoyer A, Schneider-Gold C, Fallgatter AJ, Roggendorf W, et al. Neuroleptic malignant syndrome in Kufs' disease. J Neurol Neurosurg Psychiatry 2003;74:385–7.
[30] Kraeva N, Sapa A, Dowling JJ, Riazi S. Malignant hyperthermia susceptibility in patients with exertional rhabdomyolysis: a retrospective cohort study and updated systematic review. Can J Anaesth 2017;64:736–43.
[31] Sato T, Nishio H, Iwata M, Kentotsuboi Tamura A, Miyazaki T, et al. Postmortem molecular screening for mutations in ryanodine receptor type 1 (RYR1) gene in psychiatric patients suspected of having died of neuroleptic malignant syndrome. Forensic Sci Int 2010;194:77–9.
[32] Scalco RS, Gardiner AR, Pitceathly RD, Zanoteli E, Becker J, Holton JL, et al. Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis 2015;10:51.
[33] Brandom BW, Bina S, Wong CA, Wallace T, Visoiu M, Isackson PJ, et al. Ryanodine receptor type 1 gene variants in the malignant hyperthermia-susceptible population of the United States. Anesth Analg 2013;116:1078–86.
[34] Scalco RS, Voermans NC, Piercy RJ, Jungbluth H, Quinlivan R. Dantrolene as a possible prophylactic treatment for RYR1-related rhabdomyolysis. Eur J Neurol 2016;23:e56–7.
[35] Rajapakse S, Abeynaike L, Wickramarathne T. Venlafaxine-associated serotonin syndrome causing severe rhabdomyolysis and acute renal failure in a patient with idiopathic Parkinson disease. J Clin Psychopharmacol 2010;30:620–2.
[36] Aggarwal R, Guanci N, Marambage K, Caplan JP. A patient with multiple episodes of rhabdomyolysis induced by different neuroleptics. Psychosomatics 2014;55:404–8.
[37] Mohan T, Kennedy A, Bastiampillai T, Hayward S. Interpretation of recurrent isolated creatine kinase elevation. Aust N Z J Psychiatry 2014;48:962–3.
[38] San Gabriel MC, Eddula-Changala B, Tan Y, Longshore CT. Electroconvulsive in a Schizophrenic Patient With Neuroleptic Malignant Syndrome and Rhabdomyolysis. J ect 2015;31:197–200.
[39] Cooper JM, Jones AL. Neuroleptic malignant syndrome or a statin drug reaction? A case report. Clin Neuropharmacol 2009;32:348–9.
[40] Allsop P, Twigley AJ. The neuroleptic malignant syndrome. Case report with a review of the literature. Anaesthesia 1987;42:49–53.
[41] Jones EM, Dawson A. Neuroleptic malignant syndrome: a case report with post-mortem brain and muscle pathology. J Neurol Neurosurg Psychiatry 1989;52:1006–9.