Incidence and clinical spectrum of rhabdomyolysis in general neurology: a retrospective cohort study

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Abstract

The objective of this retrospective cohort study was to evaluate demographic, clinical and laboratory characteristics of patients with rhabdomyolysis as defined by a serum creatine kinase (sCK) activity $> 950\, \text{U/L}$. A total of 248 patients were recruited from the Department of Neurology, Medical University of Vienna, between 01/2000 and 12/2017, with a median sCK activity of 2,160 U/l (IQR 1,342–4,786). Seizures (31.9\%), illicit drugs/alcohol (9.7\%) and exercise (8.5\%) were the most common trigger factors. Rhabdomyolysis incidence rates in specific neurological diseases as estimated by the ratio between rhabdomyolysis cases and the total number of cases with the corresponding disease were highest in myopathies (49.8/1,000 person-years, 95\% CI 32.3–67.4), followed by epilepsy (16.4/1,000 person-years, 95\% CI 12.8–20.0) and stroke (11.9/1,000 person-years, 95\% CI 8.4–15.4). The half-life of sCK activity was 1.5 days in the total cohort. In myopathies, sCK activity was significantly higher as compared to other disease entities 7 days after the peak measurement ($p=0.0023$). Acute kidney injury (AKI) developed in 18 patients (7.3\%) with no AKI-related deaths during the study period. In conclusion, rhabdomyolysis occurred in a broad range of neurological entities but was associated with a favorable prognosis in most cases rarely resulting in AKI and death.

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Keywords: Rhabdomyolysis; HyperCKemia; Creatine kinase; Myopathy; Acute kidney injury.

1. Introduction

Rhabdomyolysis is a serious and potentially life-threatening condition frequently associated with neuromuscular diseases \cite{1,2} but also reported to occur in a broad range of other neurological diseases including seizures \cite{3}, cerebral ischemia \cite{4}, multiple sclerosis \cite{5} and neuromyelitis optica \cite{6}. Triggering factors further include hypoxia, exercise and infections, including recent reports of rhabdomyolysis as a complication of COVID-19 \cite{7}. The causes of rhabdomyolysis are heterogeneous and linked to the exposure of muscle tissue to mechanical, metabolic or toxic stress inducing increased permeability or disruption of the muscle plasma membrane. This allows creatine kinase and other intracellular components to leak from muscle fibers into the extracellular space, from where they are taken up by the lymphatic system and enter the circulation. Upon muscle tissue damage, serum creatine kinase (sCK) activity begins to rise within 2–12 h, peaks at 3–5 days after the injury, and declines over the subsequent 6–10 days \cite{8}. Serum CK activity is thus commonly used as a biomarker for muscle fiber damage in routine diagnostic assays \cite{9}, with rhabdomyolysis defined as an increase of sCK activity above 5 times the upper limit of normal (ULN) in most studies \cite{10,11}.

Systematic data on demographic characteristics and the incidence of rhabdomyolysis in various neurological
conditions is lacking in literature but yet crucial to avoid reporting bias and to reveal the true burden associated with rhabdomyolysis in clinical routine. We therefore aimed to systematically characterize patients with rhabdomyolysis treated at a tertiary neurological center, and to evaluate various demographic and clinical parameters and model the time course of sCK activity for common neurological diseases.

2. Patients and methods

2.1. Ethical approval and consent to participate

This study was approved by the Ethical Committee of the Medical University of Vienna (EK 1830/2018), with a waiver of the requirement for informed consent because of the retrospective design of the study.

2.2. Study design and patient ascertainment

This retrospective single-center cohort study included all patients with rhabdomyolysis treated at the Department of Neurology, Medical University of Vienna, Austria, during the period from January 1, 2000 to December 31, 2017. Rhabdomyolysis was defined as a sCK activity > 950 U/L corresponding to 5 times the ULN (i.e. 190 U/L) [10,12] irrespective of the temporal dynamics of the elevation, thereby including transient as well as stable sCK activity elevations. Respective out- and inpatients were captured by screening all laboratory tests performed at the Department of Neurology during the study period. Patients admitted to other departments of the Medical University of Vienna but undergoing clinical examinations or laboratory tests at the Department of Neurology (most likely due to neurological comorbidities) were also included to ensure the ascertainment of all patients with neurological diseases. As serum CK activity was routinely screened in all out- and inpatients undergoing acute or routine blood testing at the Department of Neurology, our approach also included patients with sCK activity elevations but without muscular complaints (i.e. incidental sCK activity elevation). Demographic, clinical and laboratory parameters were extracted from medical records. Identified trigger factors included infections, illicit drugs/alcohol, medical drugs, exercise, seizures, immobility/trauma and hypothyroidism.

The rate of acute kidney injury (AKI) defined as an increase of serum creatinine according to stage 1 or higher of the AKI Work Group [13] was assessed in the cohort. The Medical Research Council sum-score (MRC-SS) ranging from 0 (i.e. quadriplegia) to 60 (normal) is a validated tool to assess global muscle strength [14] and was calculated for each individual case at the initial visit in the hospital. The time course of sCK activity was plotted for individual patients with serial measurements, and the half-life of decaying sCK activity together with the sCK activity 7 days after the peak measurement (i.e. steady-state sCK activity) was calculated, with persistently elevated sCK steady-state activities indicative of myopathies [15,16].

2.3. Estimation of rhabdomyolysis incidence

The cohort was grouped according to the most common neurological disease entities accounting for ≥ 5% of the total cohort, and the incidence rate of rhabdomyolysis was then estimated for each disease entity as the ratio between rhabdomyolysis cases and the total number of cases (with and without rhabdomyolysis) for a 5-year period between 2013 and 2017. The total number of cases with confirmed neurological diagnoses treated at the Department of Neurology was retrieved by screening the administrative hospital database (Allgemeines Krankenhaus Informations Management, AKIM) [17] for the corresponding diagnostic codes according to the International Classification of Disease, 10th revision (ICD-10). The estimation of rhabdomyolysis incidence was limited to the period between 2013 and 2017 because of the implementation of the administrative hospital database in 2011 with systematic coding of diagnoses according to the ICD-10 including outpatients in recent years only [17]. The consideration of the total study period for the analysis of rhabdomyolysis incidence with inconsistent coding in previous years could have resulted in an overestimation of the incidence rates.

2.4. Statistical analysis

Descriptive statistics were performed using medians and interquartile ranges (IQR). Statistical analyses were performed using the Mann-Whitney U test for the comparison of two groups and using a one-way analysis of variance (ANOVA) for the comparison of more than two groups. Significant main effects were followed by Tukey’s multiple comparison test. All sCK activities of individual patients were normalized to the corresponding peak sCK activity and plotted over 7 days following the peak measurement. The sCK time course and 95% confidence intervals (CI) were then analyzed by fitting exponential components to sCK activities. A two-sided p value < 0.05 was considered significant. Data processing was performed using the statistical package SPSS v26 (released 2019, IBM Corp., Armonk, NY, USA) and Prism, version 8.4.2 (GraphPad Software Inc., San Diego, CA, USA).

3. Results

3.1. Demographic characteristics

A total of 248 patients with rhabdomyolysis were identified during the study period with a median age of 49.6 years (IQR 30.5–66.8) and males accounting for 60.5% of the cohort (Table 1). Peak sCK activities ranged between 951 U/L and 128,100 U/L with a median of 2,160 U/L (IQR 1,342–4,786). The majority of the cohort (89.1%) had peak sCK activities below 10,000 U/L (Fig. 1A). Previous
episodes of rhabdomyolysis were reported by 31 patients (12.5%). Trigger factors could be identified in 137 patients (55.2%), with seizures causing rhabdomyolysis in 79 patients (31.9%), illicit drugs and alcohol in 24 patients (9.7%) and exercise in 21 patients (8.5%). In 111 patients (44.8%), by contrast, obvious trigger factors could not be determined. Statins were used by 30 patients (12.1%) but not found to be associated with rhabdomyolysis in any of the patients.

### 3.2. Acute kidney injury associated with rhabdomyolysis

Eighteen patients (7.3%) of the cohort developed AKI as a complication, requiring fluid replacement and/or alkaline diuresis. Patients with AKI had significantly higher median creatinine levels (1.55 mg/dL, IQR 1.44–2.78 versus 0.85 mg/dL, IQR 0.65–1.02; \( p = 0.0168 \)) as well as peak sCK activities (4,437 U/L, IQR 1,688–10,510 versus 2,024 U/L, IQR 1,330–4,339; \( p = 0.0333 \)) as compared to patients without AKI. Fifteen patients (6%) of the cohort died due to the underlying neurological disease including 1 patient with status epilepticus and 14 patients with acute stroke, three of which were additionally affected by AKI.

### 3.3. Rhabdomyolysis incidence rates in common neurological diseases

The spectrum of neurological diseases associated with rhabdomyolysis was heterogeneous with epilepsy accounting for the largest group within the cohort (86 patients, 34.7%) followed by stroke (49 patients, 19.8%), myopathies (29 patients, 11.7%), multiple sclerosis (26 patients, 10.5%) and polyneuropathies (16 patients, 6.5%) (Tables 2 and 3, Fig. 1B). In relation to the total number of patients with specific diagnoses treated in the hospital, however, the rhabdomyolysis incidence rate was highest in myopathies (49.8/1,000 person-years, 95% CI 32.3–67.4) followed by epilepsy (16.4/1,000 person-years, 95% CI 12.8–20.0), stroke (11.9/1,000 person-years, 95% CI 8.4–15.4), multiple sclerosis (6.7/1,000 person-years, 95% CI 3.3–10.1) and polyneuropathies (4.1/1,000 person-years, 95% CI 2.3–6.0) (Table 4). Myopathies were also associated with the highest rate of recurrent rhabdomyolysis episodes (20.7% of the patients with rhabdomyolysis, Table 3), indicating a higher susceptibility of myopathies to rhabdomyolysis as compared with the other disease entities. Trigger factors could be identified in all patients with epilepsy and only in 15.4% of multiple sclerosis patients. In stroke, myopathies and polyneuropathies, the rate of identified trigger factors was similar (32.7%, 37.9% and 37.5%, respectively). The rate of AKI varied between disease entities ranging from 0% in patients with multiple sclerosis and polyneuropathies to 7.0% in the epilepsy subgroup and 20.8% in stroke patients. Anticonvulsive drugs were used by 51/86 (59.3%) patients in the epilepsy subgroup (31 patients with levetiracetam, 8 with lamotrigine, 3 with valproate, 3 with oxcarbazepine and 6 with a combination of at least two anticonvulsive drugs). Median MRC-SS were lowest in patients with stroke and polyneuropathies, indicating higher grades of physical disability in these disease entities (Table 5).

### 3.4. Serum CK time course

In the total cohort, sCK activities decayed exponentially with a half-life of 1.5 days (95% CI 1.4–1.6) and a sCK activity of 303 U/L (95% CI 217–369) after 7 days from the peak measurement (Fig. 1C). As myopathies are associated with structural or functional muscle fiber deficits and an increased susceptibility of the muscle cell membrane to disruption commonly resulting in elevated sCK activities, this could have influenced the sCK time course upon rhabdomyolysis in this group. We therefore assessed whether the sCK half-life or the steady-state sCK activity in myopathies was different when compared to conditions not associated with primary muscle fiber deficits (i.e. epilepsy, stroke, multiple sclerosis and polyneuropathies). We did not observe a different half-life of sCK activity in these groups (\( p = 0.6176 \)) but the steady-state sCK activity was higher.
in myopathies as compared to non-susceptible conditions ($p=0.0023$) (Fig. 1D).

### 4. Discussion

Rhabdomyolysis has been associated with high mortality rates of up to 14% in large cohorts [18,19] and up to 42% in patients developing AKI as a complication [19], but disease severity is variable and comprises mildly affected cases and asymptomatic elevations of sCK activity [15]. Prediction scores for renal failure and mortality have therefore been developed to identify patients at risk [18], and clinical features in addition to elevated sCK activity have been proposed for a standardized definition of rhabdomyolysis in literature, including muscle weakness, myalgia, muscle swelling and the acute onset of the condition [11]. Systematic data on large cohorts of different entities can further help here to identify or better define patients at risk for AKI and other complications.

The present study analyzed the incidence, demographic characteristics and outcome of rhabdomyolysis in a large cohort of patients treated at a neurological tertiary center, reporting a favorable disease course with regard to rhabdomyolysis in the majority of patients with sCK activities higher than 950 U/L. AKI was found in 7.3% of the cohort, which was lower than in previous studies with comparable methodologies reporting renal failure rates up to 46% [19,20]. Potential explanations for this discrepancy include lower sCK activities in our study, as sCK activity was directly linked to an impairment of renal function in rhabdomyolysis [20]. Especially sCK activities above 15,000 U/L [21] and 40,000 U/L [18], respectively, were associated with higher AKI rates.
Table 2
Neurological diseases associated with rhabdomyolysis.

| Neurological diseases accounting for ≥ 5% of the cohort | N |
|--------------------------------------------------------|---|
| Epilepsy                                               | 86|
| Generalized tonic-clonic seizures                      | 72|
| Focal seizures                                         | 3 |
| Convulsive status epilepticus                          | 6 |
| Unknown                                                | 5 |
| Stroke                                                 | 49|
| Cerebral ischemia                                      | 41|
| Intracranial hemorrhage                                | 8 |
| Myopathies                                             | 29|
| Hereditary myopathy                                    | 5 |
| Idiopathic inflammatory myopathy                       | 5 |
| Endocrine myopathies                                   | 4 |
| Unspecified myopathies                                 | 15|
| Multiple sclerosis                                     | 26|
| Polyneuropathies                                       | 16|
| Guillain–Barré syndrome                                | 3 |
| CIDP                                                   | 2 |
| MMN                                                    | 1 |
| PNP associated with MGUS                               | 1 |
| Diabetic PNP                                           | 1 |
| Alcoholic PNP                                          | 1 |
| Unspecific (axonal) PNP                                 | 7 |
| Neurological diseases accounting for < 5% of the cohort | N |
| Radiculopathy/spinal disc herniation                   | 8 |
| Parkinson’s disease                                    | 4 |
| Amyotrophic lateral sclerosis                          | 3 |
| Encephalitis                                           | 3 |
| Neuromyelitis optica                                   | 3 |
| Vascular myelopathy                                    | 2 |
| Myasthenia gravis                                      | 1 |
| Brachial neuritis                                      | 1 |
| Traumatic brachial plexus injury                        | 1 |
| Post-polio syndrome                                    | 1 |
| Stiff-person syndrome                                  | 1 |
| Idiopathic intracranial hypertension                   | 1 |
| Cavernoma                                              | 1 |
| Fibromyalgia                                           | 1 |
| Dystonia                                               | 1 |
| Narcolepsy                                             | 1 |
| Unknown                                                | 9 |

CIDP, Chronic inflammatory demyelinating polyneuropathy; MGUS, Monoclonal gammopathy of undetermined significance; MMN, Multifocal motor neuropathy; PNP, Polyneuropathy.

1 Mutations in FKRP (n = 1), DMD (n = 2), DYSF (n = 1), FHL1 (n = 1), PYGM (n = 1).
2 Polymyositis (n = 2), inclusion body myositis (n = 1), necrotizing autoimmune myopathy (n = 1), unspecified autoimmune myositis (n = 1).
3 Hypothyroid myopathy (n = 4).
4 Specific diagnoses could not be determined in these patients.

The high prevalence of seizures or myopathies in our cohort might also have contributed to the lower AKI rates, since both conditions have previously been identified as low risk predictors of AKI [18]. The exact mechanism underlying AKI in rhabdomyolysis is not completely understood, but mechanical injury to the tubules by myoglobin precipitation was suggested to be significantly involved in the pathogenesis [22]. Together with sCK, myoglobin is released from muscle fibers upon disruption of the plasma membrane and is freely filtered by the glomerulus. As compared to sCK, however, myoglobin is characterized by a less predictable metabolism [22,23] and was shown to have a wider interindividual range and lower sensitivity for the diagnosis of rhabdomyolysis [24]. Myoglobin testing is therefore not consistently performed in clinical routine and was lacking in most cases in our study.

We demonstrate a broad spectrum of different neurological disorders to be associated with rhabdomyolysis and provide rhabdomyolysis incident rates for the most common disease entities. It should be noted that diagnoses were deduced from corresponding ICD-10 codes and might thus contain misclassified cases potentially biasing the incidence rates. However, assuming a misclassification ratio around 5–10% at tertiary clinical centers in Austria as previously reported [25,26], we consider misclassification unlikely to have substantially affected the rhabdomyolysis incidence rates reported in this study. A deviation of the incidence rates of 5–10% would still be within the 95% confidence intervals.

Myopathies and epilepsies were among the most frequent entities, with rhabdomyolysis resulting from an increased susceptibility of the muscle cell membrane to disruption due to structural or metabolic deficits in myopathies [2,8] and from prolonged involuntary muscle contraction ultimately leading to muscle fiber damage in epilepsy [3,22,27]. Other less common entities associated with rhabdomyolysis included stroke, polyneuropathies and multiple sclerosis. Prolonged immobilization has been discussed as a risk factor for muscle compression and hypoxia [22,28] and could have contributed to the development of rhabdomyolysis in patients with stroke and polyneuropathies in our cohort. This is supported by the lower MRC-SS in these entities suggesting that patients with stroke and polyneuropathies were more severely affected and immobilized, and thus also more likely to suffer from muscle compression that could have triggered rhabdomyolysis. Multiple sclerosis patients, by contrast, were only mildly affected, and immobilization was thus unlikely to play a crucial role in the pathogenesis of rhabdomyolysis in this entity. Interferon-beta treatment was previously reported to trigger rhabdomyolysis as a rare complication in multiple sclerosis [5,29], but was used by only one patient in our study. As treatment was also initiated long before the event of rhabdomyolysis, and sCK activities normalized again without discontinuation of any specific therapy, drug-induced toxicity was unlikely to have caused rhabdomyolysis in multiple sclerosis patients. Since we rarely found other trigger factors in these patients, rhabdomyolysis appears to be a generally rare phenomenon in multiple sclerosis with unknown etiological factors in most cases.

Future prospective studies utilizing large cohorts could help to elucidate the association between multiple sclerosis and rhabdomyolysis.

Myopathies are associated with an increased susceptibility of muscle cells to metabolic or physical stress that could have influenced the time course of sCK activity in rhabdomyolysis. To analyze this further, we modeled the time course of sCK activity in cases with serial measurements. Serum CK
Table 3
Clinical and laboratory characterization of neurological diseases frequently associated with rhabdomyolysis.

| Neurological diseases accounting for at least 5% of the rhabdomyolysis cohort | Epilepsy | Stroke | Myopathies | Multiple sclerosis | Polyneuropathies |
|---|---|---|---|---|---|
| N (%) | 86 (34.7) | 49 (19.8) | 29 (11.7) | 26 (10.5) | 16 (6.5) |
| Sex, male (%) | 49 (57.0) | 26 (53.1) | 11 (37.9) | 20 (76.9) | 13 (81.3) |
| Age, years (IQR) | 42.8 (27.2–58.3) | 76.1 (64.6–86.8) | 45.5 (35.5–55.1) | 30.1 (26.8–38.9) | 51.8 (37.0–60.2) |
| MRC-SS (IQR) | 60 (60–60) | 60 (56–60) | 60 (59–60) | 46 (39–47) | 2 (12.5) |
| Inability to walk (%) | 0 (0) | 16 (32.7) | 1 (3.4) | 2 (7.7) | 0 (0) |
| Recurrent rhabdomyolysis (%) | 10 (11.6) | 7 (14.3) | 6 (20.7) | 3 (11.5) | 0 (0) |
| Lean body mass, kg (IQR) | 57.0 (52.0–61.0) | 59.5 (52.8–64.3) | 56.0 (53.3–66.8) | 58 (51.0–63.5) | 58.0 (57.0–66.0) |
| Body mass index (IQR) | 24.7 (22.4–27.8) | 25.4 (22.5–30.1) | 28.2 (24.7–33.9) | 24.8 (20.4–28.4) | 24.5 (23.2–26.9) |
| Peak sCK, U/L (IQR) | 2.657 (1.588–6.160) | 1.915 (1.280–4.774) | 2.199 (1.446–4.101) | 1.571 (1.299–2.654) | 1.309 (1.035–2.888) |
| Peak sCK range, U/L | 967–128,100 | 976–42,940 | 999–15,102 | 951–12,918 | 954–23,624 |
| sCK half-life, d (95% CI) | 1.6 (1.5–1.8) | 1.5 (1.3–1.6) | 1.8 (1.1–2.6) | 1.3 (1.0–1.7) | 1.4 (0.9–1.9) |
| sCK after 7d, U/L (95% CI) | 266 (106–399) | 134 (38–230) | 725 (462–968) | 215 (63–368) | 314 (149–471) |
| Trigger factors (%) | 86 (100) | 16 (32.7) | 11 (37.9) | 4 (15.4) | 6 (37.5) |
| Infection (%) | 0 (0) | 1 (2.0) | 0 (0) | 0 (0) | 0 (0) |
| Illicit drugs/alcohol (%) | 15 (17.4) | 1 (2.0) | 3 (10.3) | 0 (0) | 4 (25.0) |
| Medical drugs (%) | 3 (3.5) | 1 (2.0) | 2 (6.9) | 0 (0) | 0 (0) |
| Exercise (%) | 3 (3.5) | 7 (14.3) | 2 (6.9) | 3 (11.5) | 2 (12.5) |
| Seizure (%) | 79 (91.9) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Immobility/trauama (%) | 0 (0) | 2 (4.1) | 0 (0) | 0 (0) | 0 (0) |
| Hypothyroidism (%) | 5 (5.8) | 4 (8.2) | 4 (13.8) | 1 (3.8) | 1 (6.3) |
| Multiple trigger factors (%) | 17 (19.8) | 0 (0) | 0 (0) | 0 (0) | 1 (6.3) |
| Statin use | 7 (8.1) | 15 (30.6) | 1 (3.4) | 0 (0) | 0 (0) |
| Acute kidney injury (%) | 6 (7.0) | 10 (20.8) | 1 (3.4) | 0 (0) | 0 (0) |
| Creatinine, mg/dL (IQR) | 0.84 (0.67–0.98) | 1.08 (0.8–1.57) | 0.78 (0.60–0.99) | 0.76 (0.65–0.68) | 0.88 (0.72–1.12) |
| TSH, μIU/mL (IQR) | 1.20 (0.80–2.09) | 1.56 (0.83–2.32) | 1.95 (1.34–2.89) | 1.37 (1.01–2.34) | 1.93 (1.23–3.30) |
| Sodium, mmol/L (IQR) | 140 (138–142) | 141 (138–143) | 140 (139–141) | 140 (138–142) | 140 (136–141) |
| Potassium, mmol/L (IQR) | 3.9 (3.6–4.3) | 4.0 (3.5–4.4) | 4.3 (4.2–4.5) | 4.2 (4.0–4.5) | 4.3 (3.6–4.8) |
| Phosphate, mmol/L (IQR) | 0.96 (0.77–1.15) | 0.91 (0.76–1.16) | 1.07 (0.10–1.18) | 1.07 (0.98–1.22) | 1.01 (0.89–1.18) |
| Calcium, mmol/L (IQR) | 2.25 (2.16–2.32) | 2.24 (2.14–2.32) | 2.37 (2.28–2.45) | 2.35 (2.27–2.40) | 2.28 (2.15–2.38) |

MRC-SS, Medical Research Council sum-score; TSH, Thyroid-stimulating hormone.

1 Normal: 0.5–0.9 mg/dL (women), 0.7–1.2 mg/dL (men)
2 Normal: 3–4.2 μIU/mL
3 Normal: 136–145 mmol/L
4 Normal: 3.5–5.1 mmol/L
5 Normal: 0.81–1.45 mmol/L
6 Normal: 2.15–2.50 mmol/L

half-life was 1.8 days and longest in myopathies, but the difference was not statistically significant when compared to the other disease entities. In myopathies, however, sCK activity remained significantly higher than in other disease entities after 7 days. As a biomarker for myopathies, persistently elevated sCK activities (termed hyperCKemia) should therefore path the way for further diagnostic testing as also suggested by the European Federation of Neurological Sciences (EFNS) guidelines for cases with sCK activities beyond 1.5 times the ULN [30]. Hereditary diseases were shown to underlie a significant proportion of these cases [15], and genetic testing was proposed in the presence of additional supportive criteria associated with increased genetic susceptibility [31,32].

The retrospective methodology of this study implies some limitations that need to be recognized. Diagnoses and information on muscular complaints and trigger factors were ascertained by the review of medical records and might not have been accurate in all cases. Serum CK activity was routinely screened in all patients undergoing acute or routine blood testing at the Department of Neurology, but as blood testing was not performed in all patients seeking neurological treatment, some patients with (incidental) elevations of sCK activity might have been missed, potentially resulting in an underestimation of rhabdomyolysis cases.

Serial sCK measurements as a requirement for a differentiation between transient and stable elevations of sCK activity were missing in a significant proportion of the cohort. They were predominantly performed in inpatients, who were likely to be more severely affected than outpatients, which could have biased the sCK time course. Moreover, the sCK time course could have been affected by the therapies and co-medications used by some of the patients in the cohort and, finally, as this study included patients from a tertiary clinical center, the findings might be limited with respect to their application to non-tertiary centers. As a result of these limitations, we were unable to unravel the cause or identify other potential trigger factors of rhabdomyolysis in patients, in whom a direct link between rhabdomyolysis and the primary neurological disorder was missing. Unreported drugs or exercise could have contributed to rhabdomyolysis in some of these patients. A prospective
study design would be required to adequately address these issues.

In conclusion, rhabdomyolysis is shown to occur in a broad spectrum of different neurological diseases with the highest incidence in myopathies. AKI was found to constitute a rare complication of rhabdomyolysis in patients with underlying neurological diseases, which might be linked to the lower peak sCK activities in our cohort as compared to other studies. As suggested before [11,18], the implementation of clinical features into a consistent definition of rhabdomyolysis could help to identify patients at risk for AKI and direct clinical management more efficiently.

Declaration of Competing Interest

The authors report no conflicts of interest.

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