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Case Report

Use of Measuring Creatinine Kinase in Detection of Emerging Catatonia: Literature Review and Case Series Report

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Abstract

Catatonia, particularly malignant catatonia (MC), continues to manifest in severe sequalae such as hyperthermia, rhabdomyolysis, cardiovascular collapse and failure, and even death as, although identification of the syndrome has significantly improved once its developed, several precarious factors continue to inhibit prompt and efficacious treatment. In this context, we evaluated the cases of six patients who were treated at our center for eventual MC manifestation with the aim of elucidating a pre-MC sensitive presentation pattern, common finding, or other granular data point that may have predictive value for MC. Patient chart review and granular data comparison revealed an association between creatine kinase (CK) level trends and catatonia diagnosis. Data were uniformly transformed for percent change to establish overall trends and subsequently analyzed for correlative strength via nonlinear regression. When comparing the inter-sample percent change of CK level to time, a moderate correlation was found (R2 = 0.3784). Analysis of nonlinear regression modeling using least squares for appropriateness of fit using runs test suggested minimal deviation

from the model (p = 0.1566). In conclusion, in patients presenting with features that cause a suspicion of catatonia, CK level measurements may be implemented and utilized to more promptly make the diagnosis and begin potentially life-saving treatment or avoid life-threatening treatment.

Keywords
Catatonia; malignant catatonia; Bush-Francis Catatonia Rating Scale (BFCRS); creatine kinase; diagnosis; neuropsychiatric syndrome; case report

1. Introduction

Despite the potential for severe complications and adverse events in untreated catatonia, its status as a neglected and understudied condition has persevered since its first description in 1874 by Karl Ludwig Kahlbaum [1]. Furthermore, this phenomena continues in spite of several retrospective studies suggesting a much higher true prevalence of catatonia than initially diagnosed [1-3]. Indeed, in their landmark study, Bush et al. not only generated a standardized examination, the Bush-Francis Catatonia Rating Scale (BFCRS), for establishing a diagnosis of catatonia with markedly significant measurements of both inter-rater reliability and validity, but also found catatonia may have been underdiagnosed by a factor of 14 within psychiatric patients and brought increased attention to the syndrome [4, 5]. Subsequently, groups such as Taylor et al. made further headway in the development of diagnostic criteria for catatonia by bringing attention to the lack of inherent specificity within symptoms such as immobility and excitement in comparison to more specific symptoms such as catalepsy and echophenomena in addition to establishing a temporal criterion [6, 7]. More recently, a meta-analysis reported a pooled catatonia prevalence of 7.8% across 19 studies composed of 7612 total patients with low heterogeneity (I^2 = 39%) and an absence of any publication bias [8].

Nonetheless, catatonia, particularly malignant catatonia (MC), continues to manifest in severe sequalae such as hyperthermia, rhabdomyolysis, cardiovascular collapse, and even death as, although identification of the syndrome has significantly improved once its developed, several precarious factors continue to inhibit prompt and efficacious treatment [9]. Most notable are its abrupt nature of development and progression, lack of established predisposing factors, resemblance to conditions such as neuroleptic malignant syndrome (NMS) and serotonin syndrome, and deceptive presentation which frequently mimics psychosis and leads to MC-exacerbating treatment with antipsychotics [7, 10, 11].

In addition, while the BFCRS's contribution to the progression of our understanding and ability to more accurately diagnose catatonia should not be mitigated, its application has limitations which leave room for improvement. In a similar manner, the proposed alterations of Taylor et al., which allowed for more precise definitions and criteria to be implemented for a more stringent and specific diagnostic approach, may also benefit from further development and revision. For example, in a review of the most widely used catatonia rating scales, Kirkhart et al. analyzed the extent to which each scale accounted for the 28 unique terms that had been used in the diagnosis of catatonia, of which the BFCRS only contained 21 (75%)[12]. Furthermore, the authors not only

found a lack of congruence between some of the individual criteria and their provided definitions, but also low specificity in certain criteria such immobility/stupor and an absence of severity-adjusted feature score contributions [12]. As a result, the BCFRS has potential to confuse clinicians who are not well-versed in catatonia and potentially lead to ineffective, imprecise, and erroneous diagnoses, effectively negating the entire purpose of its development. To address these shortcomings, Taylor et al. proposed a weight-based scale that not only categorized features based on impact towards a catatonia diagnosis, but also streamlined and refined the terminology of the criteria for catatonia to 11 features in order to simplify administration and interpretation of catatonia rating scale [7]. However, as a result of these proposed alterations of reduced criteria quantity and increased specificity, the sensitivity of the scale was brought into question as only 11/28 terms (39.3%) used to describe catatonia found by Kirkhart et al. can be accounted for [12].

Over the last few decades, various groups have also linked the diagnosis of catatonia to elevated levels in CK [13-15]. However, these studies largely focused on previously-established diagnoses of catatonia rather than the potential to use CK level trends in helping establish a *new* diagnosis; that is, while CK level *elevations* have been found in already-diagnosed catatonic patients, the potential utility of CK level trends in helping identify catatonia prior to its peak precipitation has yet to be investigated [13-15].

Thus, further studies are needed to both mitigate the downsides of identified gaps in current catatonia rating scales and, more importantly, attempt to transition from the current reactive MC damage-control treatment model into a more proactive and damage-avoiding one.

In this context, we evaluated the cases of six patients who were treated at the Loyola University Medical Center (LUMC) for eventual MC manifestation with the aim of elucidating a pre-MC sensitive presentation pattern, common finding, or other granular data point that may have predictive value for MC and allow clinicians to anticipate, rather than mitigate, catatonic manifestations. The project was assigned a status of Exempt by the Institutional Review Board.

2. Materials and Methods

Patients recently diagnosed with catatonia were selected for this study after meeting the following criteria: i) patients demonstrated catatonic symptoms in accordance with BFCRS; ii) patients did not meet criteria for catatonia-like syndromes including, but not limited to: nonpsychiatric stupor, encephalopathy, stroke, stiff-person syndrome, locked-in syndrome, malignant hyperthermia, status epilepticus, or autism; iii) patients did not fully meet criteria for catatonia upon presentation but eventually developed catatonia; iv) patients were formally diagnosed with, and treated for, catatonia. Collected patient data were evaluated for trend commonalities within objective metrics generated prior to MC manifestation and sustained through MC presentation. Data were uniformly transformed for percent change to establish overall trends and subsequently analyzed for correlative strength via nonlinear regression using Prism 8.4.3 (GraphPad Software, USA).

3. Results

Patient chart review and granular data comparison revealed an association between creatine kinase (CK) level trends and emerging catatonia diagnosis. Individual patient CK levels compared to time can be seen in Figure 1. Data transformation evaluating rates of CK level changes versus

time was used to pool data values between patients so that trends can be compared rather than numerical values, the result of which can be seen in Figure 2. When comparing the intersample percent change of CK level to time, a moderate correlation was found (R^2 = 0.3784). Analysis of nonlinear regression modeling using least squares for appropriateness of fit using runs test suggested minimal deviation from the model and can be visualized in the plot of residuals within Figure 3 (p = 0.1566).

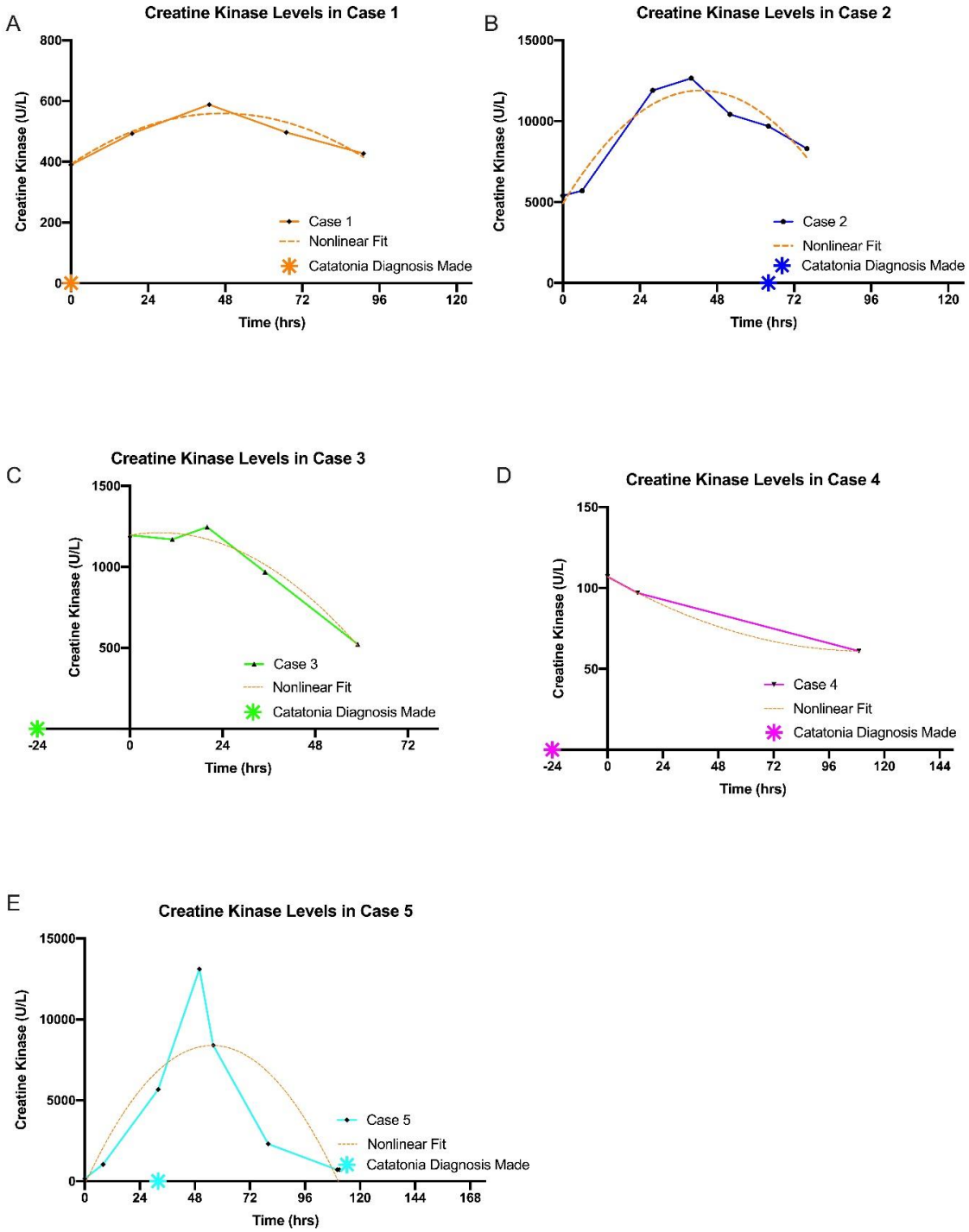

Figure 1 CK levels over time superimposed by time at which catatonia diagnosis was made.

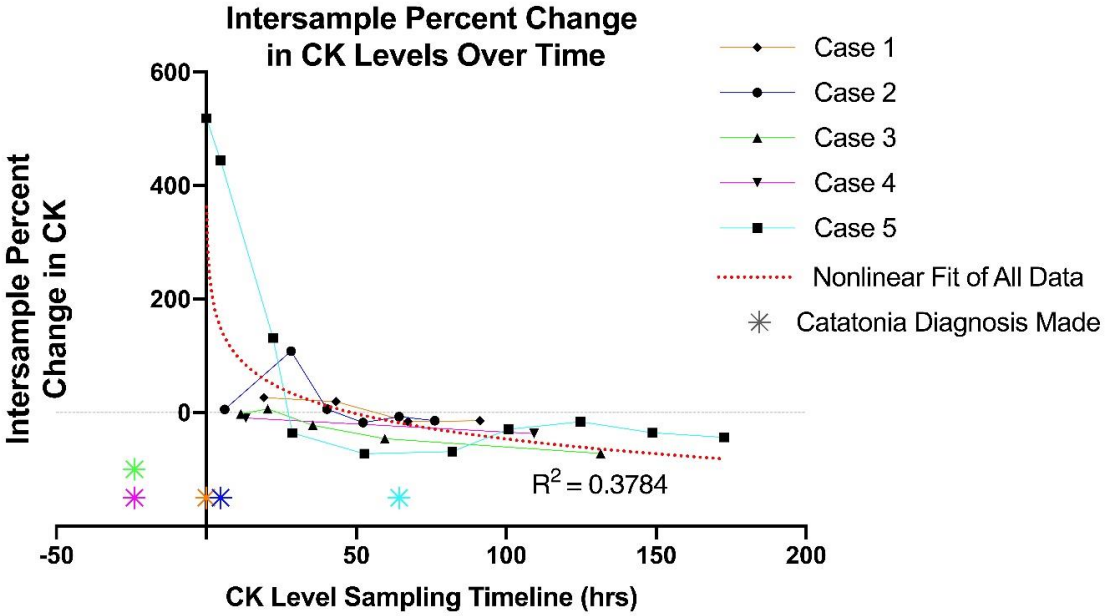

Figure 2 Percent change between CK levels over time superimposed by nonlinear fit of all data points.

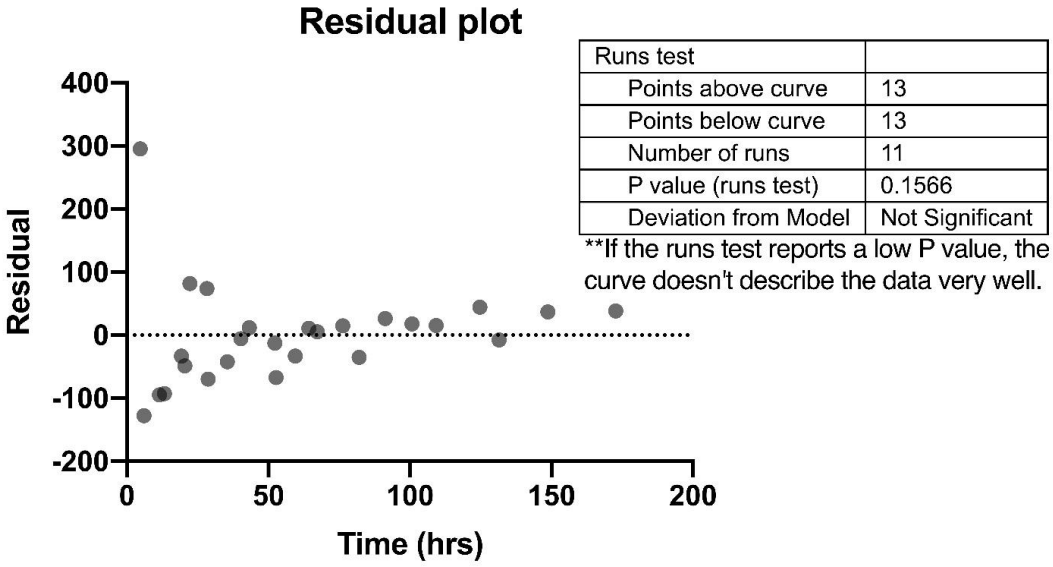

Figure 3 Residual plot of all data points across all patients for which CK levels were obtained reflecting a 50:50 split in data points that fall above or below the curve, indicating minimal deviation of data points from the nonlinear model.

4. Case Presentations

4.1 Case 1

13-year-old male presented to the emergency department (ED) for mutism, bradykinesia, and fixed gaze. Previous psychiatric history included disruptive mood dysregulation disorder and

oppositional defiant disorder. BFCRS was 9. He responded well to a lorazepam challenge. The next day, he required a rapid response due to fever (>102 F), tachycardia (>140 bpm), and decreased responsiveness. Agitation, rigidity with some negativism, and mild waxy flexibility soon followed. Following administration of lorazepam and bromocriptine, he stabilized. However, he continued to have instances of agitation, periodically requiring restraints and doses of lorazepam, clonidine, and hydroxyzine. Lorazepam and bromocriptine were tapered down once his temperature decreased. Supraventricular tachycardia was noted on day 14 with a heartrate >170 bpm, possibly due to a rapid lorazepam taper. Lorazepam was increased and heart rate stabilized. The episodes of agitation and violence continued until his home oxcarbazepine was exchanged for carbamazepine on day 31. Lorazepam was exchanged for diazepam on day 35. However, agitation and violence reemerged, leading to diazepam's discontinuation the following day. The patient then stabilized and was discharged to an intensive outpatient program.

4.2 Case 2

29-year-old male with past medical history of asthma and bipolar I disorder admitted following a violent altercation. WBC was 23.7 k and CK was 5405. CK increased, with a peak of 12,650 on day 3. Patient exhibited signs of catatonia including echolalia and bradykinesia. Lorazepam was started, and CK decreased, but patient required increased lorazepam and valproic acid (VA) due to agitation, psychosis, and verbigeration. On day 15, patient was transferred to inpatient treatment but soon re-presented with abdominal pain. CK and BFCRS were 75 and 0, respectively.

On day 39, patient re-presented with dysarthria, unsteady gait, and a fall with no loss of consciousness. Patient was tachycardic, VA and CK levels were 14.2 and 131, respectively. Patient received paliperidone palmitate long-acting injectable twice at inpatient facility, along with VA 1500 mg. The Consult Liaison team restarted VA 250 mg BID and lorazepam. Due to persistent tachycardia, no improvement in catatonia, and elevated metric on liver function tests, bromocriptine replaced VA. Patient developed echolalia and spontaneous laughter, and Amantadine replaced the bromocriptine which led to improvements. During a lorazepam taper on day 90, he had a temperature of 99.1°F with tachycardia, and lorazepam was increased.

On day 94, vitals were stable, and patient was able to walk. He was medically cleared for discharge home.

4.3 Case 3

21-year-old male with history of schizoaffective disorder (on olanzapine, aripiprazole, and lorazepam) presented to the ED after command auditory hallucinations led him to jump out of a third-story window. Labs revealed a normal CBC (complete blood count) and complete metabolic panel (CMP) with cannabinoids detected on urinalysis.

He was admitted for surgical fixation and received his normal antipsychotic regimen on days 1-2. On day 2, his temperature was 102.4°F, with normal CBC, which resolved with Acetaminophen. On day 3, he developed restlessness, sudden head movements, and left hand shaking with hypertension, tachycardia, and temperature of 98.8°F. Lorazepam challenge was initiated with moderate response. CK was 1,196 and downtrended throughout the remainder of admission. He was maintained on Lorazepam 2 mg q6h and Amantadine 50 mg BID before taper regimen.

4.4 Case 4

57-year-old female with history of developmental delay, hydrocephalus status post ventriculoperitoneal shunt, subdural hematoma, seizure-like episodes, and unclear psychiatric history who presented to the ED with vomiting and altered mental status. Eventually found to be severely hyponatremic (118 mEq/L). Patient had been on haloperidol 5 mg q6h for several years and benztropine 0.5 mg BID, which was recently changed to risperidone 6 days prior at an outside hospital.

She was found to have tongue protruding and lip smacking beginning 17 days prior, raising suspicion for tardive dyskinesia. Trials of benztropine and risperidone, aripiprazole, and valproate were conducted. BCFRS revealed a severity score of 10 and screening score of 7. CK of 107. Positive response to 1 mg IV lorazepam challenge.

She was maintained on lorazepam and amantadine. Taper was attempted twice during admission with regression to unresponsiveness. She was eventually discharged on lorazepam and amantadine with further tapering recommended in the outpatient setting.

4.5 Case 5

52-year-old male with history of diabetes mellitus, Bipolar I Disorder (on VA and lithium) presented for confusion after minor motor vehicle collision. Computed tomography and magnetic resonance imaging of the head were normal. He was somnolent but became agitated and restless.

He continued to be restless and received quetiapine 25 mg. His agitation worsened, he developed a fever of 101.3°F, despite being given lorazepam repeatedly, and was started on vancomycin and piperacillin/tazobactam empirically. He was started on bromocriptine for possible malignant catatonia. At admission, CK was 168, increased to 5664 after fever. He became less responsive, with constant thrashing on the bed while closing his eyes and grunting and was intubated.

He remained intubated for eight weeks. The patient had recurrent cyclic fevers up to 102.7°F. Various doses and frequencies of lorazepam and bromocriptine were administered; fever began to respond after adding amantadine to lorazepam and bromocriptine.

Patient was successfully extubated and was transferred to an outside hospital for ECT, ECT was not needed and he was transferred to rehab after being afebrile.

4.6 Case 6

47-year-old male with past medical history of hypertension, diabetes mellitus (DM), cerebrovascular accident with residual right-sided weakness, and blindness presented with worsening mental status and aggressive behavior for one week. At the ED, he was combative and given lorazepam 2 mg. His agitation appeared to resolve.

On later evaluation, the patient was somnolent, did not follow commands, and was unable to open his eyes to voice. He demonstrated rhythmic movements of the mouth and was unable to speak complete statements. He was started on lorazepam 1 mg q6h for possible catatonia due to prior positive response to lorazepam. VA 250 mg was also started for mood lability and agitation. All antipsychotics were held.

Over the next week, the patient demonstrated significant improvement on lorazepam. Upon discharge, the patient was placed on a lorazepam taper over one month, along with continued VA and the recommendation to follow-up with outpatient psychiatry and home health.

5. Discussion

In this study, we attempted to identify a potential method to help overcome the temporal barrier of diagnosing catatonia and mitigate the consequences of solely approaching catatonia in a reactive manner. We found that CK level trends may have a role in providing physicians with a supplementary method that can be used adjunctively with previously established catatonia scales and help identify the syndrome earlier and avoid potentially exacerbating treatment options. In addition, our findings suggest analysis of CK trends may have implications in the development of the first sensitive and objective measure used in identifying emerging catatonia. Lastly, the results of our investigation also function to incorporate dimensions of feasibility and practicality into the catatonia diagnosis arsenal. These findings are of significant importance as not only do they provide a simple and widely accessible method for catatonia diagnosis that is unambiguous, but also they allow for earlier detection that can significantly simplify treatment, reduce patient suffering, and even lower the lethality of catatonia through the early avoidance of antipsychotics.

The primary finding of this case series study is that quantitatively measurable parameters exist that may provide evidence which allows the physician to be able to anticipate a catatonia presentation and take proactive actions to mitigate presentation risk or more promptly and efficiently provide appropriate treatment. Nevertheless, despite the quantitative CK pattern observed in the five cases in which CK was measured, there still remained a need to rule out syndromes with presentations that strongly resemble catatonia, most notably neuroleptic malignant syndrome (NMS). Indeed, due to its presentation and similarity in responding to benzodiazepines and bromocriptine, NMS has not only been extensively compared to catatonia, but also it has even been categorized as a form of catatonia, eventual manifestation of catatonia, and as a completely distinct syndrome, thus necessitating an NMS evaluation for each of our cases [2, 16-19].

For example, in case 1, while the patient's fever certainly caused concern for NMS, his fever failing to exceed 104°F along with the remainder of his clinical presentation, such as the mutism, waxy flexibility, and agitation made NMS less likely and favored catatonia [20-22]. In case 2, the patient initially presented with features of echolalia, psychosis, and agitation and subsequently given Haldol. CBC demonstrated a leukocytosis of 23.7 K cells/mm^3 which, in combination with his agitation and psychosis, prompted a CK level to be ordered. In conjunction with his presentation and lab values, NMS was considered, however, due to his lack of lead-pipe rigidity, CK levels' lack of elevation into the tens of thousands, and afebrile status, it was ruled out [20-23]. The patient from case 3 was also evaluated for NMS, however, it was ultimately ruled out in favor of catatonia due to his fever peaking at 102.4°F, development of restlessness, sudden head movements, and normal CBC and CMP, after which CK levels were trended [20]. In comparison, case 4 was more briefly considered as a potential NMS manifestation given the only conventional NMS criterion met was altered mental status [20-22]. Case 5 required more meticulous evaluation for NMS due to becoming febrile, demonstrating elevated CK levels, and developing a hyporesponsive state, however, NMS was eventually ruled out due to a combination of fever peaking at 102.7°F,

inadequate CK level elevations, and becoming less responsive rather than developing lead-pipe rigidity [20]. In a similar sense, NMS was also considered for case 6, however, due to the patient's afebrile status, somnolence rather than lead-pipe rigidity, and development of mutism and repetitive movements, NMS was ruled out [20]. Additionally, the patient in case 6, due to his initial presenting symptoms and history, was administered a lorazepam challenge rather early during his stay and exhibited a marked improvement in symptoms in addition to a blunting of any potential exacerbations. This likely underscores the crucial temporal factor within catatonia treatment and the criticality of antipsychotic avoidance when catatonia is suspected, both of which are likely to result in significantly reduced adverse events.

The potential overarching implication of these cases seems to be interloped between two major diagnostic tools, the patient's presentation and CK level trends, and indicate delaying antipsychotic initiation for patients in whom both catatonia is suspected and CK levels are elevated may prove to reduce the burden of catatonia exacerbation and severe presentation. Nevertheless, the elusive and ambiguous presentation of catatonia poses significant risks as treatments for the conditions it mimics, such as antipsychotics for certain variants of schizophrenia or bipolar disorder, have been repeatedly documented as inducing and exacerbating catatonia [24-26]. As demonstrated in all three out of five patients who had CK levels measured prior to a diagnosis of catatonia being made, not only do the temporal and visual trend progressions of CK levels corroborate, but also the proportional changes in CK levels between samples. In addition, these same three patients were not diagnosed with catatonia until either the peak of our model's prediction where values are most abnormal and interpretable or multiple days after with values that corroborate with the trend's suggestion that the proposed CK changes had already occurred. Furthermore, the remaining two patients for whom we had CK levels but made the diagnosis of catatonia multiple days prior to any CK levels were also in line with our model's prediction. Indeed, the two patients' individual trends demonstrated minimal and slow proportional changes in their CK levels, suggesting both that our proposed abnormalities in CK levels phenomenon had already occurred and, based on the temporal delay of these minimal and slow changes, that the diagnosis of catatonia would have been approximately in line with our model's prediction. These findings provide evidence that may help clue a physician to the diagnosis of catatonia and have significant implications. Additionally, the CK level trend similarities and the generated model reported in this study are the first to evaluate the utility of CK levels beyond simply identifying whether they are elevated or not by evaluating their proportional progression as well as temporal presentation both in general and relative to catatonia diagnosis. Indeed, while several groups have found elevated CK levels to be associated with catatonia, none were found in which analysis evaluated CK level trends or CK level with regard to time [9, 11, 16, 25-27].

Our findings also function to not only address some of the limitations of previously established catatonia rating scales such as the ambiguity inherently within catatonia interpretation and administration of both the BFCRS and Taylor et al. criteria, but also they propose the first feature based on a purely objective physiologic metric [4, 7, 12]. This has major ramifications as, currently, catatonia rating scales are entirely subjective and open to interpretation as they are composed of a set of vaguely described behaviors, categorized into limited qualitative descriptors that have divergent definitions, and defined in an overtly general and inclusive manner. The culmination of these characteristics results in catatonia scales within which the developers and other catatonia

experts demonstrate significant validity and inter-reliability, however, the opposite has been found for physicians who have not had extensive experiences treating catatonic patients [12]. As such, we believe our findings' unique contribution of providing a catatonia feature that both relies on objective metrics and provides non-catatonia experts with straightforward and easily interpretable data allows for more universal identification of catatonia and the potential to improve treatment efficiency and efficacy as a result.

Furthermore, the findings presented herein are also highly practical in terms of very low costs, lack of any extra time or effort required from the physician, universal availability, and ubiquity in the workup of a wide variety of disease processes. Indeed, with an approximate $4 hospital cost per measurement, assessing CK levels is a trivial decision when considered from a financial point of view as the average cost per hospital stay in the US has been estimated at approximately $52,697 [28, 29]. In addition, unlike previous scales such as BFCRS and Taylor et al. criteria which must be administered by an experienced physician in person and may necessitate lengthy travel time at large institutions. On the other hand, ordering a CK level requires essentially no extra time as it is done through the click of a button and is a universal and ubiquitously used assay in the modern era, thus requiring no additional expertise from the providing physician. Additionally, CK levels have extensively been established as being involved in a multitude of disease processes, thus, measuring CK could prove useful in the diagnosis of other conditions and disorders [30-32]. In fact, this concept is the foundation of this study as our cohort simply happened to have their CK levels measured for the workup of other potential conditions rather than catatonia, thus suggesting increased model resolution should a greater number of CK levels per patient be available. However, further studies are needed to further develop this notion and whether there are any practical clinical applications.

This study has several limitations. First, it is important to note that only five out of the six presented patients had any CK levels measured throughout their hospitalization, thus limiting the generalizability of our model and its accountability for our cohort's catatonic progressions. It is also important to bring attention to the nonspecific nature of CK levels and the vast number of conditions in which they may be elevated when muscular damage has occurred, thus leading to their ubiquitous nature in modern medicine, however, this pervasive quality simultaneously implies convenience in diagnostic workup implementation and execution. Indeed, CK levels simply happened to be measured in our patient population, thus, while there were drastically different quantities of levels measured for each patient, timepoints throughout hospital stay at which levels were measured, and differing intervals which limited our analysis to a coarse set of results, it was the ubiquity and nonspecificity of CK levels within patient evaluations that allowed for them to demonstrate a potential utility in establishing a catatonia diagnosis. Additionally, this is a retrospective case series in which we did not control for a variety of potentially confounding factors such CK level alterations due to medications and health conditions, age, gender, et cetera, all of which could have significantly altered the results of this study. Notwithstanding these limitations, we believe our results are unique and relevant to the field as they provide a greatly needed framework for the improvement and progression of current catatonia diagnostic methods and treatment strategies.

In conclusion, in patients presenting with features that cause a suspicion of catatonia, CK level measurements may be implemented and utilized to more promptly make the diagnosis and begin potentially life-saving treatment or avoid life-threatening treatment. In patients who would

otherwise be monitored and treated in a reactive manner once catatonia has developed, evaluating CK level trends may allow for improved patient outcomes without jeopardizing long-term patient health.

Author Contributions

All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Conception & design: All authors. Data Acquisition: All authors. Analysis and interpretation: All authors. Drafting the manuscript: All authors. Critical revision: All authors. Final Approval: All authors.

Competing Interests

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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