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WHAT'S ON MY MIND

Letter from the Founding Facilitator

Welcome to Volume 1/Issue 2 of the RRNMF Neuromuscular Journal. I think you will enjoy the content of this issue and I am pleased that we are getting a number of submissions to the new journal. As in the first issue, this issue has a collection of original articles (New Stuff), single case reports (Clinic Stuff), a review article (Looking Back Stuff), and an imaging article (Visual Stuff). In addition, we have the "answer" with references from the Visual Stuff piece in Issue 1.

There are two articles in the New Stuff category. Dr Govindarajan and his colleagues at University of Missouri-Columbia report their experience with using edavarone in ALS. This is a retrospective report but provides good data. Eventually we need prospective data in the form of a comparative effectiveness study in a real world situation (not a pharmaceutical company driven trial) in which patients are put on edavarone with or without riluzole or riluluzole alone. Until then these retrospective clinic experiences are important. Our KUMC group led by Dr. Mamatha Pasnoor looked at a group of patients with CIDP by various criteria and then determined response rates to IVIG based on if they met one of the published criteria. The bulk of the work on this project was done by Charles (Drew) Roach when he was a medical student at KUMC. Drew is now a neurology resident at Washington University in St Louis. Well done , Drew!

The two cases in Clinic Stuff are very interesting. One is again by the Columbia, Missouri group and the first author is Sara Hooshmand They report a case of scapuloperoneal myopathy and cardiomyopathy that has a novel myosin heavy chain mutation. Family history suggested an autosomal dominant disorder. The simultaneous co-occurrence of the heart and skeletal muscle involvement is unusual. The second Clinic Stuff is an unusual GBS variant case seen by Felix Chang and Jon Katz and they consulted with Gil Wolfe and myself on it a number of years ago. For some reason, the case was not published and so I encouraged the group to submit it to our new journal. The patient had bilateral ptosis, so from this standpoint it was one of the GBS variants originally described by Dr Ropper. There was no extremity weakness but the patient did complain of tingling in the extremities and some mild difficulty swallowing. But additionally the patient had limb myokymia clinically and by EMG in the first dorsal interosseous muscle and he complained of involuntary movements of the fingers that came on suddenly with the bilateral ptosis. The authors believe this extends the phenotypic spectrum of this GBS variant.

The group from then Department of Neurology at the University of Columbia was a big contributor to this issue as Drs Digala, Haider and Govindrajan also supplied a nice review article (Looking Back Stuff) on various neuromuscular causes of weakness in the ICU setting. Drs Merchant and Twydell in Grand Rapids Michigan submitted a dramatic image in Visual Stuff showing an infiltration access in the pectoral is minor and gluteus minimus muscles due to tuberculosis. And Dr Shabani gives us the answer on the Videos he published last month!

Finally, we have an amazing cover in which we show a painting in the Metropolitan Museum of Art that is a Rembrandt self portrait as a young man. We obtained the image from Creativecommons.org. We plan on having an art image on every issue cover.

Please give us feedback on this new journal. And please submit articles. I promise we will provide a hassle free and friendly peer review process by our Facilitators (e.g., editor/reviewers).

I would like to thank our KU Digital Publishing Services staff who are helping me enormously as we launch this new publication: Marianne Reed who leads the group and Pam LeRow. We could not get these first two issues out without their help.

Rick

The following are my farewell comments to the KUMC research Community on my retirement from KUMC in May 2020.

HALE AND FAREWELL COMMENTS

By Dr. Barohn

Dear Colleagues,

In February, I announced that I accepted a position as Executive Vice Chancellor for Health Affairs for the University of Missouri Health System at the University of Missouri-Columbia and will be leaving the University of Kansas Medical Center after nearly 20 years of service.

I want to extend a sincere thank you to the University of Kansas Medical Center community for the opportunity to serve and lead in several capacities, including as Chairman of the Department of Neurology, Vice Chancellor for Re-

search, President of the Research Institute, and Director of Frontiers: University of Kansas Clinical and Translational Science Institute. It has been an honor to work alongside some of the brightest and most dedicated faculty and staff at KU Medical Center.

As a result of the commitment to excellence by so many of you, KU Medical Center is now a major clinical and translational research leader in the United States. I am very proud of what we have achieved together. I have spent most of my academic career at KU Medical Center and will always have a special place in my heart for this institution and the many outstanding colleagues with whom I have worked.

I am confident that Matthias A. Salathe, MD, will provide a steady hand at the helm of the KU Medical Center research enterprise as the Interim Vice Chancellor of Research. As a nationally recognized leader in pulmonary disease, Dr. Salathe has done an amazing job in rejuvenating the research program in the Department of Internal Medicine. His strong leadership and dedication to research will be tremendous for this institution.

I am also assured that the future of clinical and translational research at KU Medical Center and in the Kansas City region is in good hands as Mario Castro, MD, MPH, is set to take over leadership as Director of Frontiers. Dr. Castro, also a highly regarded pulmonary research physician in the Department of Internal Medicine, is the Director of the Rainbow Clinical and Translational Science Unit. I look forward to hearing of the wonderful things to come from Frontiers under his leadership.

I am very excited to begin my journey at the University of Missouri. It is truly amazing that I've been given an opportunity to make a significant impact at another academic medical institution at this stage in my career. I feel extremely fortunate for the honor to be part of KU Medical Center and the University of Missouri.

I am grateful to so many of you at KU Medical Center—fellow faculty, researchers, clinicians, administrators, staff, residents, fellows, and students—and hope to personally express my gratitude to many of you before I leave on Friday, May 8, 2020. Unfortunately, I may have to reach out via telephone or Zoom due to the current COVID-19 situation. However, I will only be two short hours away in Columbia, Missouri, and will undoubtedly be back in Kansas City often. Please keep in touch.

With appreciation,

Rick

The following is my message to the graduating medical students at the University of Missouri-Columbia School of Medicine in May 2020. This was both a hale and farewell as I was really introducing myself to these graduating doctors.

GRADUATES OF 2020

What a pleasure it is for me to address your class on this big day. I am the incoming Executive Vice Chancellor for Health Affairs and in this role I will be working closely with Dean Zweig and Jonathan Curtright, the CEO of MU Health Care, to move our enterprise into the next decade. While I am arriving at the same time that you are graduating from the medical school, what we both have in common is that we are entering a new phase of our medical careers. Of course you are just entering the most dynamic and gratifying part of your careers as you become a physician and can make an enormous impact on individual patients and society. I, on the other hand, am beginning a new path late in my career, and I hope I can still have an impact on health care delivery and research and education. But I envy you as your are taking the first steps as physicians. There are so many many challenges and opportunities that are literally just around the corner for all of you. And in the next few years you will have an exponential growth curve as a physician in both your knowledge base and in your skills as you embark on the journey to become a mature physician. I know the training which you have received at this great medical school will serve you well in this journey. Dean Zweig and I look forward to hearing from you in the years to come. Please check in and let us know where your journey has taken you. The main advice I would like to give you as you begin the path as a physician is to always regard every patient you encounter with empathy and make an attempt to connect with them as a fellow human being and not just as a patient. In this very odd covid era many of us have been seeing our patients on zoom. I have been doing a zoom telemed clinic for three years for ALS patients that live in rural Kansas. It is amazing to me how much we can do as physicians remotely through this technology. And I am repeatedly struck by how grateful the patients are for the connection that can still be obtained via telemed. And it occurred to me during my last telemed clinic in Kansas City last week that it works because the patients can feel that I am truly concerned about them no matter if I am holding their hand in person or looking at them directly through a monitor. After all of the knowledge and skills you learn in medical school and residency and fellowship, I really believe that what is the most important is the empathy you show your patients in every encounter. Having empathy will not only make you a better physician but will make your journey a labor of love. Thank you for allowing me to be a part of this most important day.

Clinical Experience of Edaravone in Amyotropic Lateral Sclerosis

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ABSTRACT

Objective. To describe clinical experience with edaravone in ALS over a period of 12 months

Methods. The current study retrospectively investigated characteristics in a group of patients (n=31) with ALS who underwent edaravone treatment. Information including age, gender, race, and site of onset of symptoms were collected for all patients. Adverse events with edaravone therapy was documented where available.

Results. The average age of the patients observed was 62.09 years, with 18 males and 13 females. 18 patients had limb onset, 12 bulbar onset, and 1 diaphragmatic onset. 7 of the 31 patients discontinued treatment at the end of one year. The average age of patients who discontinued edaravone was 65.71 years, of whom which 3 had limb onset, 3 bulbar onset, and 1 diaphragmatic onset. No perceived benefit, port complications, systemic bacteremia, and development of atrial fibrillation were documented as reasons for discontinuation of therapy.

Conclusion. Edaravone is well tolerated in ALS patients at the end of one year. Lack of perceived benefit and port related complications are common reasons for discontinuation of treatment

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder affecting upper and lower motor neurons throughout the nervous system, resulting in gradual paralysis and death in 3-5 years from onset.[1] ALS presents in the 50s to 60s and is the most common neurodegenerative disorder of midlife, with one to two new cases per 100,000 people per year.[1-3] The exact etiology of ALS is unknown, but it is thought to be attributed to the diverse, complex, and combined mechanisms involved in protein, RNA, and cytoskeletal homeostasis which are influenced by both genetic and environmental factors.[1] The presence of oxidative stress has been credited to initiating many of these cellular changes and agreed to be, at least in part, responsible for the onset and progression of ALS.[4-7]

Despite avid research in the field and over 50 randomized controlled trials testing therapies for ALS, treatment is currently limited to only two FDA-approved drugs that may improve survival by merely a few months.[5, 9] Riluzole, approved in 1995, was the first medication to be used for ALS treatment. It is thought elicit its therapeutic effects by suppressing excitatory neurotransmitter release. A second drug, edaravone was approved for ALS treatment in May 2017 and slows ALS progression by acting as an antioxidant to reduce free radical damage.[1] Edaravone was originally marketed in Japan in 2001 as a drug to eliminate lipid peroxides and hydroxyl radicals in order to protect neurons from free radical damage during and acutely after cerebral infarction.[10-13] Mitsubishi Tanabe Pharma Corporation (Tokyo, Japan) then began investigating edaravone as an ALS treatment. The initial randomized controlled trial conducted failed to find statistically significant benefit, but post-hoc analysis and secondary clinical trials demonstrated that edarvone slowed progression of ALS in a subset of patients, evaluated using ALS Functional Rating Scale (ALSFRS-R) scores.[14-16] These Japanese studies led to Edaravone's eventual approval in the United States in May 2017. Criticisms of the trials include the narrow parameters of the study population and the short duration of the trials.[9] Because edaravone is a relatively new drug there is minimal data from U.S. studies on patient outcomes and perspectives, and because the original randomized controlled trials were only conducted over six-month time periods, long-term effects of the drug are essentially unknown.

Edaravone treatment is a time-intensive process for the patient and his or her caregiver(s). The drug is administered via intravenous infusion daily for 14 days, followed by a 14-day break period, and then repeated infinitely until the patient decides to discontinue the medication or dies from his or her neurodegenerative disease. IV infusion requires travel to an infusion center or presence of a home health nurse to administer the medication. Many obstacles face patients receiving edaravone treatment, including insurance approval of the medication, extended distances to infusion centers costing patients valuable time and money, insurance approval of home healthcare services, and guilt surrounding the caregiver's use of time and resources.

Materials and Methods

This study is a retrospective chart review of patients attending a University-based hospital approved by the Institutional Review Board (IRB). The study population includ-

ed patients with ALS who were undergoing care through University of Missouri Health Care.

These patients started on edaravone for management of symptoms due to ALS by the same physician were included in the study. Information including age, gender, race, site of onset of symptoms, ALSFRS-R score, FVC and FEV1/FVC were collected for all of these patients. Adverse events with treatment where available were documented.

The analysis of the data included summarizing patient demographics and changes in FVC in form of descriptive statistical variables including mean, standard deviation, ranges and percentages. Comparison of FVC and ALSFRS-R at different intervals was done by using Wilcoxon signed rank test. All statistical analyses were done using SPSS v22 software (IBM, Armonk, NY).

Results

The entire cohort participating in the study consisted of 31 patients with a mean age of 62.09±8.97 years and 58.04% of the patients had the onset of the disease as the lower limb making it the most common site of origin in our cohort. 54.8% of these patients were found to suffice the El Escorial criteria of definite disease. The demographics and clinical profile of these patients is summarized in Table 1.

Table 1: A summary of the characteristics of patients included in the study.

Average age	62.09±8.97 years
Sex	
Male	18
Female	13
Race	
White	30
African American	1
Onset location	
Lower Limb	18
Bulbar	12
Diaphragm	1
El Escorial Criteria	
Definite	17
Probable	12
Possible	1

Out of the 31 patients enrolled in the study, 7 of patients discontinued the drug. These patients had the average age of 65.71±9.15 years and the reasons of discontinuation of the drug included no perceived benefit by the intervention (28.5%) and port site complications (28.5%) amongst other reasons. The reasons why the drug was discontinued are summarized in Table 2.

Table 2: Reasons for discontinuation of drug amongst the seven patients.

Reason for Discontinuation	Number of Patients who Discontinued
No perceived benefit	2
Atrial fibrillation	1
Port site complications	
Port migration	1
Port site reaction	1
Systemic bacteremia	2

Discussion

Seven of our thirty-one patients, nearly one-quarter, started on edaravone for ALS discontinued treatment by one year of therapy. Reasons for discontinuation included no perceived benefit of treatment by patient and adverse events. Adverse events included port site complications (dermatitis and redness around the port), systemic bacteremia, and atrial fibrillation. We are unable to determine if the adverse events which influenced discontinuation are related to edaravone administration. Of the adverse events recorded in our patients, dermatitis is the only established adverse reaction, and has been reported in 8% of patients.[16-18] Bacteremia is common among patients with frequently accessed medication ports, like those receiving daily edaravone injections 14 days each month.[19] Atrial fibrillation is secondary to a plethora of cardiac and non-cardiac causes and risk factors, and thus is a nonspecific occurrence. Meta-analysis by Lou et al indicated that prevalence of adverse events was similar in patients receiving edaravone and those receiving a placebo.[20] This may suggest that adverse events prompting discontinuation may be more closely linked to patients' predisposing factors.

Of those who discontinued treatment, 28.57% did not determine the drug was effective. We sought to determine reasoning for this perception. This retrospective cohort study found no association between patient characteristics (i.e. sex, race, onset location, El Escorial Criteria diagnosis) and discontinuation status. We have hypothesized several direct and indirect factors which may have contributed to impression of drug ineffectiveness, including difficulty of in-

fusion process, medication cost, and presence of advanced disease. Development of an orally administered form of edaravone may shift perspectives by eliminating infusion process difficulties.[21-22]

Judging therapeutic interventions as clinically or statistically significant can be difficult for complex, mortiferous diseases such as ALS. With lack of serum biomarkers to track disease progress, it is difficult to determine which measures of a disease (i.e. ALSFRS-R, pulmonary function testing, etc.) are most accurate and representative. To enhance analysis of ALS treatments, we propose employing patient opinion of effectiveness as an additional assessment when determining clinical significance because it is a valuable part of treatment success.

Limitations to our study stem from its retrospective nature. We had no control over cohort assignment or data collection. This may have introduced bias into aspects of our data.

In conclusion, when considering edaravone treatment physicians should balance the therapeutic effect, experience of adverse events, and patient perspective of benefit.

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CIDP Diagnostic Criteria and Response to Treatment

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ABSTRACT

Introduction. Diagnostic criteria for CIDP have been proven useful for clinical trials. However, use of these criteria in clinics has been limited by time constraints and unknown usefulness in predicting outcomes.

Methods. A retrospective chart review of CIDP patients at the University of Kansas seen between 2008 and 2014 was performed. We determined the diagnostic criteria fulfilled by each patient and assessed treatment responses. A positive response was defined by improvement sensory or motor examination as determined by a neuromuscular physician.

Results. There were 38 total patients included in the study. The response rate to IVIG in patients who fulfilled EFNS/PNS criteria was 20/22 (90.1%). Among patients who fulfilled AAN criteria, 8/9 (88.9%) responded positively to IVIG. Slightly lower response rates were seen in patients fulfilling INCAT criteria and Saperstein criteria at 10/15 (66.7%) and 12/17 (70.6%), respectively.

Discussion. EFNS/PNS and AAN criteria can similarly predict IVIG treatment response.

Keywords: *Chronic Inflammatory Demyelinating Polyneuropathy, Retrospective Chart Review, Diagnostic Criteria, Treatment Response, IVIG, EFNS/PNS.*

Introduction

Chronic Inflammatory Demyelinating Polyneuropathy is known to be an immune-mediated peripheral neuropathy, but the precise pathogenesis has yet to be fully elucidated.[1] It is a relatively rare disease with an estimated prevalence of 4.7 per 100,000 adults.[2] Although the "typical" form of CIDP presents clinically with symmetric, proximal and distal weakness, hypo- or areflexia, and mainly large fiber sensory loss, there is a large range of clinical heterogeneity in the disease.[3] Various diagnostic criteria have been developed to help diagnose this condition in clinical and research settings including AAN, Saperstein, INCAT, and EFNS/PNS. Currently, the most commonly used, especially in research settings, is the EFNS/PNS criteria that was developed in 2010.

The major highlights of the diagnostic criteria that were used in this study are reviewed in Table 1. Generally speaking, all of the criteria rely on clinical, electrophysiological, and supportive studies to make the diagnosis of CIDP. Additionally, disorders that may appear similarly to CIDP

Table 1: Major clinical and diagnostic features of various criteria.

	Clinical	Nerve Conduction Studies	Other
EFNS/PNS	>2 mo, hypo/areflexia, proximal and distal weakness, sensory deficits	Must fulfill at least **1 out of 7** parameters to be considered "definite" CIDP	LP results, MRI, Abnormal sensory electrophysiology, objective improvement following immunomodulatory therapy, sural nerve biopsy
AAN	>2 mo, hypo/areflexia, motor dysfunction, sensory dysfunction of >1 limb or both	Must fulfill at least **3 out of 4** parameters, more stringent than other criteria.	LP results, Nerve Biopsy (supportive)
Saperstein	>2 mo, hypo/areflexia, **symmetric** proximal and distal weakness, or exclusively distal weakness, sensory loss	Must fulfill at least **2 out of 4** of the AAN parameters	LP results, Nerve Biopsy (supportive)
INCAT	> 2 mo, hypo/areflexia, progressive or relapsing motor or sensory dysfunction in more than 1 limb	Must fulfill at least **2 out of 4** parameters or **1 out of 3** of slightly different parameters	LP results, Nerve Biopsy (can be used if electrodiagnostic testing is not conclusive)

must be excluded. The major differences between the criteria are in the electrophysiological parameters. For example, the AAN criteria tends to be more conservative in defining parameters of demyelination such as abnormal conduction velocity and prolonged distal latency compared to the other criteria. Furthermore, some criteria such as EFNS/PNS only require 1 out of 7 electrophysiological parameters be fulfilled to meet diagnostic standards while AAN requires 3 out of 4.

At the present time, it is unclear whether or not these criteria have clinical applications beyond assisting in diagnosis. The goals of this study were to identify patients with a clinical diagnosis of CIDP who fulfilled the diagnostic criteria under investigation and also determine whether fulfilling certain criteria had any implications in treatment response.

Methods

Using the Neuromuscular database at the University of Kansas Hospital, we searched for ICD-9 and PNS codes specific for CIDP. Using this method, we identified 53 potential patients for the study. Following identification, we collected patient data from the clinical record including date of diagnosis, clinical presentation, nerve conduction study data, initial treatment, and clinical response to the initial treatment. Data was collected from the initial patient visit at the time of diagnosis and the initial follow-up after therapy. Using this information, we were able to determine which patients fulfilled EFNS/PNS, INCAT, Saperstein, or AAN diagnostic criteria. We subsequently determined whether or not these patients responded to the initial treatment that was given. Treatment response was defined by improvement in sensory or motor examination as determined during initial follow-up by the examining neuromuscular physician.

Patient Characteristics

There were a total of 53 patients identified for potential inclusion in the study based on our data search. After initial data collection, 15 patients were excluded leaving 38 who were ultimately included in the study. Of those excluded, 10 patients did not have a formal diagnosis of CIDP by a neuromuscular physician and five had insufficient data in the records to assess which diagnostic criteria they fulfilled (Figure 1).

The male to female ratio of those included in the study was 22 to 16. The age range at diagnosis was 17 to 81 years (mean 51.5, SD ± 12.9). Of the 23 patients who had CSF

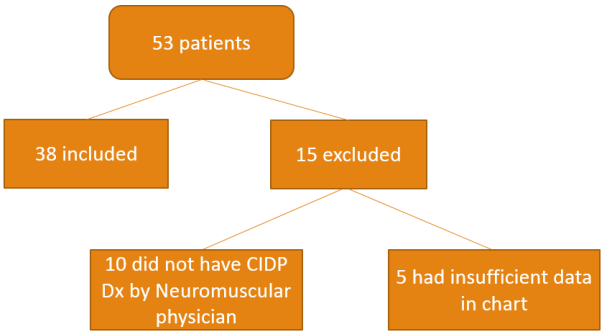

Figure 1: Patient Entry Criteria

data available, 78% had elevated CSF protein without pleocytosis.

Diagnostic Criteria

A basic overview of the requirements for each diagnostic criteria we assessed is provided in Table 1. A total of 28 of our patients fulfilled the "Definite" EFNS/PNS criteria (73.68%) and another five fulfilled the "Probable" EFNS/PNS criteria (13.16%). Saperstein and INCAT criteria were fulfilled by 20 patients each (52.6%), and ten patients fulfilled the criteria proposed by AAN (26.3%). Of the 25 patients who fulfilled multiple criteria, seven fulfilled all of the diagnostic criteria under investigation. All of the patients that fulfilled either the AAN, Saperstein, or INCAT criteria also fulfilled the EFNS/PNS criteria, and eight patients fulfilled the EFNS/PNS criteria alone. All but five patients fulfilled at least one of the diagnostic criteria. (Figure 2)

Treatment Response

A complete representation of response rates to various therapies in our study is provided in Table 2. A positive treatment response was defined by improvement in motor or sensory examination as determined during initial follow-up by a neuromuscular physician. The median time to follow-up at which treatment response was assessed was 6 months. A total of 29 patients in our study received IVIG as an initial therapy. Of those patients, 22 responded positively (75.9%). Of those who met EFNS/PNS criteria, 20 out of 22 patients had a positive response (90.1%), and patients who fulfilled AAN criteria responded at a similar rate of 88.9%. Patients fulfilling Saperstein criteria responded at a rate of 70.6%, and 66.7% of the INCAT patients responded favorably. Response rates for those receiving steroids were slightly lower overall when compared to IVIG. A total of 9 patients received steroids and 6 of those patients had a

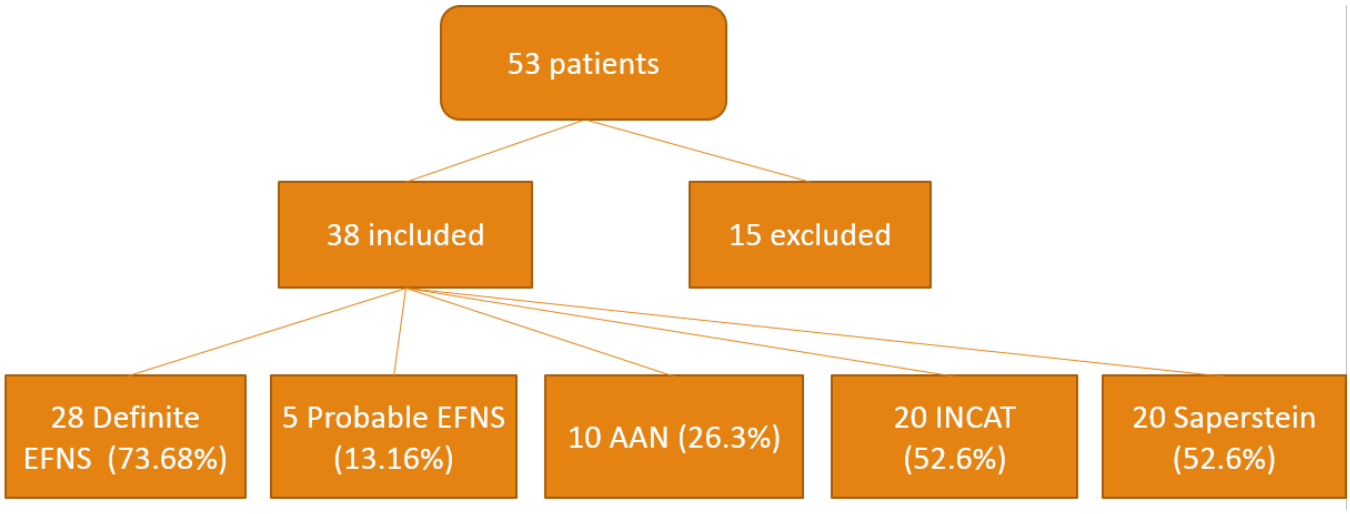

Figure 2: Number of patients fulfilling each criterion.

positive response. Of those meeting EFNS/PNS criteria, five out of 8 responded favorably (62.5%). Similar numbers were seen for those meeting AAN (66.7%), INCAT (71.4%) and Saperstein (50%) criteria. The time to follow-up at which treatment response was measured ranged from one to 29 months (mean 7.5 months, SD ± 6.8).

Discussion

The diagnostic criteria under investigation in this study have varying sensitivities and specificities[4]. A retrospective study by Breiner in 2014 showed that the 2010 EFNS/PNS definite criteria had a sensitivity of 73.2% and a specificity of 88.2% which is favorable compared to other diagnostic criteria for CIDP[4]. The relatively high sensitivity of the EFNS/PNS criteria is consistent with the findings of this study as the majority of our patients fulfilled this criteria. Conversely, the AAN criteria has a specificity of 100%, but the sensitivity for possible CIDP is only 25%.[4] This is also consistent with our findings as a much smaller percentage of our patients fulfilled the AAN criteria.

The ICE trial, a randomized placebo controlled study, demonstrated the efficacy of IVIG in patients with CIDP.[5] This trial used the INCAT diagnostic criteria for inclusion in the study and found that 54% had functional improvement in the INCAT disability score during the first 24 weeks of treatment IVIG.[5] A more recent phase III trial published in 2017 by Kuwabara et al. found that 77.8% of patients had improvement in INCAT disability scores when treated with IVIG after 28 weeks of therapy.[6] In contrast to the ICE trial, patients in the Kuwabara et al. study fulfill the EFNS/

Table 2: Comparison of treatment responses of patients fulfilling various CIDP criteria.

Therapy	Number Responded Overall	Number Responded EFNS/PNS	Number Responded AAN	Number Responded INCAT	Number Responded Saperstein
IVIG	22/29 (75.9%)	20/22 (90.1%)	8/9 (88.9%)	10/15 (66.7%)	12/17 (70.6%)
Steroids	6/9 (66.7%)	5/8 (62.5%)	2/3 (66.7%)	5/7 (71.4%)	2/4 (50%)
PLEX	2/4 (50%)	2/4 (50%)	0 (0%)	2/3 (66.7%)	1/2 (50%)
Mycophenolate Mofetil	2/3 (66.7%)	2/3 (66.7%)	1/1 (100%)	1/2 (50%)	1/2 (50%)
Azathioprine	0/1 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

PNS definite or probable criteria prior to enrollment. Our findings were consistent with the data in these trials in that patients fulfilling the EFNS/PNS criteria in our study responded at a higher rate (90.1%) than those fulfilling the INCAT criteria (66.7%). The slightly higher response rates seen in our study compared to previous trials may be related to differences in outcome measures.

Prior to this study, there was limited data comparing the treatment responses of patients fulfilling different diagnostic criteria for CIDP. This information has clinical significance in that it may help predict outcomes in patients with this condition. Using the results of this study in conjunction with previous studies on the sensitivity and specificity data of these criteria, it could be argued that neurologists should use the EFNS/PNS criteria when predicting treatment response for patients with CIDP. The high sensitivity and specificity of the EFNS/PNS criteria along with the relatively high treatment response rates seen in this study suggest that it may be favorable to other diagnostic criteria in clinical settings. Patients who fulfill the EFNS/PNS criteria appear to have equal or superior treatment response rates compared to patients fulfilling more specific criteria, such as those proposed by the AAN, suggesting little clinical benefit when using the most specific diagnostic criteria.

Limitations of this study include its retrospective nature and the descriptive statistical analysis used to compare treatment responses. In addition to this limitation, it should be noted that data was only obtained from two time points, and although the median time to follow-up was 6 months, there was considerable variation between patients. Future studies should include long-term follow-up data to determine whether or not initial response rates predict clinical stability or future response to therapy. Furthermore, our study used an "all-or-none" approach when determining patient response to therapy, so there may be significant variability in functional outcomes even between patients with a positive response. Using tools utilized in other studies such as the INCAT disability score would be helpful in assessment of the degree of improvement between patient subsets and would allow for easier comparison with previous studies.

In conclusion, this study provides information on some of the diagnostic criteria used for CIDP and a possible relationship with these criteria to treatment responsiveness. Despite differences in sensitivities and specificities, the response rates to IVIG appear to be similar for those meeting AAN and EFNS/PNS criteria. Additional studies that have longer follow-up and that use a functional outcome measures to stratify treatment responsiveness are needed to support these findings.

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ICU Related Neuromuscular Complications

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ABSTRACT

The spectrum of neuromuscular diseases encountered in the ICUs today has rapidly evolved over the last decades. Multiple predisposing factors are involved in the development of neuromuscular complications in intensive care patients. Those complications broadly classified into weakness from the preexisting neuromuscular disease exacerbated by critical illness or the complication of the critical illness itself. Patients, when unresponsive, confused, or sedated precludes careful clinical examination. A careful schematic approach that involves acquiring extensive history, any underlying infections, use of any offending medications, and the course of presenting illness will help in delineating the underlying etiology. Here in this review, we describe many causes and the pathophysiology that contribute to the development of neuromuscular weakness in the ICU. A comprehensive investigation protocol must strictly be adhered to all the cases in the ICU settings to reduce the mortality and morbidity.

Keywords: *Critical illness polyneuropathy, critical illness myopathy, ICU related neuromuscular weakness, myopathy, complications of sepsis.*

Introduction

Critically ill patients in the ICU get exposed to multiple risk factors that increase the likelihood of damage to the peripheral nervous system. Fluid and electrolyte disturbances, catabolic stressors, nutritional deficiency, and medications collectively increase the risk for neuromuscular damage, thus prolonging hospital stay, delaying recovery and increasing morbidity and mortality.[1, 2] The most common causes of neuromuscular weakness in ICU patients are critical illness neuropathy and critical illness myopathy, which usually presents as failure to wean off from ventilator and decreased limb movements.[1,2,4,5] The incidence rate for acquiring weakness from critical illness neuropathy (CIN) and critical illness myopathy (CIM) has drastically increased and is twice as common as primary neuromuscular causes such as GBS and motor neuron diseases.[3,4] Recently, CIM is more commonly encountered than CIP. Early diagnosis and prompt treatment are necessary as complications such as ventilatory failure and aspiration pneumonia significantly increase morbidity and mortality.

Classification

Although there are multiple causes for generalized weakness in a patient in ICU motor weakness can be broadly classified due to:

1. NEUROMUSCULAR COMPLICATIONS OF CRITICAL ILLNESS
2. PRE-EXISTING NEUROMUSCULAR DISORDERS

Motor weakness can further lateralized to the anatomical site of involvement of a disease process. Table 1 provides common causes of ICU associated weakness in neuromuscular patients.

1. Neuromuscular Complications of Critical Illness

ICU acquired neuromuscular weakness is a major cause of morbidity in critically ill patients.[3-4] It significantly affects the overall prognosis and increases the length of hospitalization.[3-4] The three most common causes of acquired neuromuscular weakness in ICU patients are critical illness polyneuropathy, critical illness myopathy, and prolonged neuromuscular blockade.

CIP affects between one third and half of the most severely critically ill patient in the intensive care units (ICU).[2,5] A systematic review reported a median prevalence of CIP as 43% (interquartile range 25–75%) in over 31 studies.[3] Critical illness polyneuropathy and myopathy is seen in approximately 25–45% of critically ill patients who are admitted to intensive care units.[5]

Both CIP and CIM present as symmetrical, diffuse flaccid muscle weakness affecting extremities and respiratory muscles with relative sparing of cranial nerves.[2-3,5] Multiple possible factors play a role in the development of neuromuscular weakness in critically ill patients; the major ones are systemic inflammatory response syndrome (SIRS), corticosteroid use, and neuromuscular blocking agents.[2,5] See Figure 1.

Critical Illness Polyneropathy

CIP usually presents as sensorimotor axon loss polyneuropathy, affecting distal muscles more than proximal muscles in the early course, later progressing to generalized muscle weakness with absent reflexes.[2-3,5] It was initially described as a rare complication secondary to sepsis and multi-organ failure.[2,4,6] The majority of the patients have

Table 1: Causes of generalized weakness in ICU and their anatomical localization

Localization	Preexisting Neuromuscular Disorder	Complication of Critical illness
Spinal cord	Trauma Infarction Transverse myelitis	Unknown
Anterior horn cell	ALS Poliomyelitis	Hopkins syndrome
Peripheral nerve	GBS Chronic inflammatory demyelinating polyneuropathy	Critical illness polyneuropathy
Neuromuscular junction	Myasthenia gravis Lambert-Eaton syndrome Botulism	Prolonged neuromuscular blockade
Muscle	Muscular dystrophy Polymyositis Metabolic/congenital Mitochondrial	Critical illness myopathy

concomitant encephalopathy due to underlying sepsis or organ failure.[2,7] Hyperglycemia, hypoalbuminemia, and parenteral nutrition are also known to exacerbate the development of CIP.[5,7] Impaired microcirculation due to inflammatory responses leads to decreased nerve perfusion resulting in nerve hypoxia.[6-7]

The earliest clinical suspicion arises when it is difficult to wean the patient from a ventilator, and other common presentations include tetraplegia and absent deep tendon reflexes.[4,7] Severity is proportional to the length of ICU stay.[5,7]

The most important diagnostic test is the Electro diagnostic study (nerve conduction+ electromyography). Nerve conduction velocities may be normal or reduced, but the amplitude of sensory responses and motor responses is significantly decreased or even absent.[3,7] Features of acute denervation such as fibrillation, positive sharp waves, and reduced recruitment are evident in needle electrode studies. Motor unit potential has a long duration, high amplitude and polyphasic morphology.[3] Nerve biopsy shows severe axonal degeneration of motor and sensory fibers affecting distal segments primarily.[3]

Treatment usually comprises aggressive management of SIRS and supportive measures such as fluid resuscitation, antibiotic therapy, and physical therapy.[5] Recovery usually occurs over weeks to months.[2,5] Long term progno-

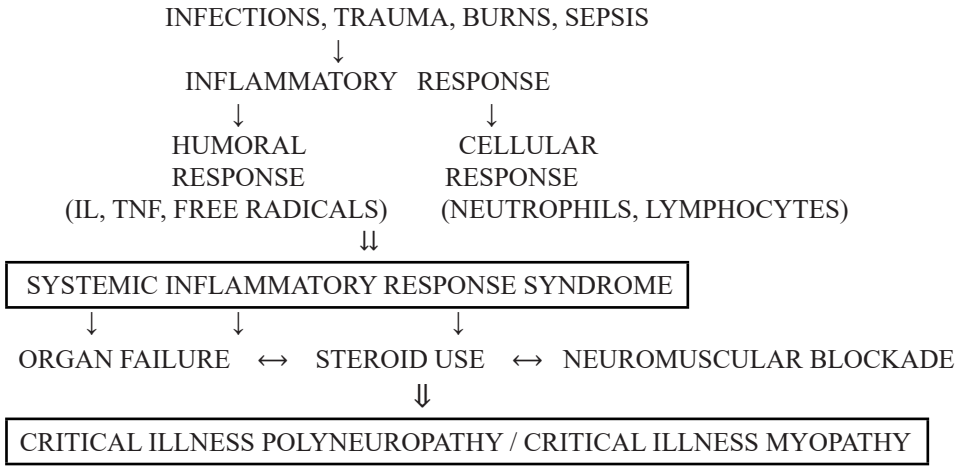


Figure 1: Pathogenesis of development of critical illness polyneuropathy/myopathy in ICU

sis depends upon the severity of the underlying disease process and patients with only CIM having a better prognosis than those with CIN only or even those with CIN+CIM.[5]

Critical Illness Myopathy

CIM is the major contributor of ICU related neuromuscular weakness.[2-3,5] CIM usually develops in patients taking prolonged high dose steroids or on neuromuscular blocking agents.[6,8] It characteristically presents as diffuse weakness affecting both limbs, affecting distal muscles and proximal muscle groups. Facial muscle and sometimes ocular muscle involvement can be seen.[8]

Myosin loss is the hallmark finding of CIM.[8] Corticosteroid use causes myosin loss, which is further triggered by the use of neuromuscular blockade agents used commonly in ICU settings. CIM can be further sub-classified as thick filament myopathy, catabolic myopathy, and acute necrotizing myopathy of intensive care.[9] See table 2 for more details.

Elevated muscle enzyme (CK) is observed in necrotizing sub types and in other two subtypes it is either normal or only occasionally elevated.[9] Electro diagnostic studies play an essential role in the diagnosis of CIM with nerve conduction studies exhibiting low amplitude or even absent motor responses, whereas sensory responses are preserved. Needle EMG studies show short duration, polyphasic, and low amplitude motor unit action potentials. EMG at rest is positive for fibrillation potentials/ Positive sharp waves.[3]

Muscle Biopsy shows muscle fiber necrosis, atrophy, and regeneration, mostly affecting type II fibers, in the absence of any inflammatory marker. Selective loss of thick filament (myosin) in the absence of thin filament (actin) is the hallmark.[2,5,9]

Management is usually conservative. Discontinuation of steroids and neuromuscular blockade agents is recommended. There is growing evidence in support of using intensive insulin therapy for reducing the incidence of both CIM and CIP.[3] Although target blood glucose is to reach normal fasting levels with insulin infusion, an optimal dose remains controversial as intermediate blood glucose levels are safer as shown in a multi-center randomized trial.[3]

Prognosis usually depends upon the severity of illness.[3,5]

Table 2: Subtypes of critical illness myopathy encountered in the intensive care unit

SUBTYPES	THICK FILAMENT MYOPATHY	CATABOLIC MYOPATHY	NECROTIZING MYOPATHY OF INTENSIVE CARE
UNDERLYING CAUSES	Corticosteroid use, NM blockade agents, severe asthma exacerbation	Interleukin-1 and TNF induced damage seen in respiratory failure, shock, sepsis	Overwhelming infections, toxic shock

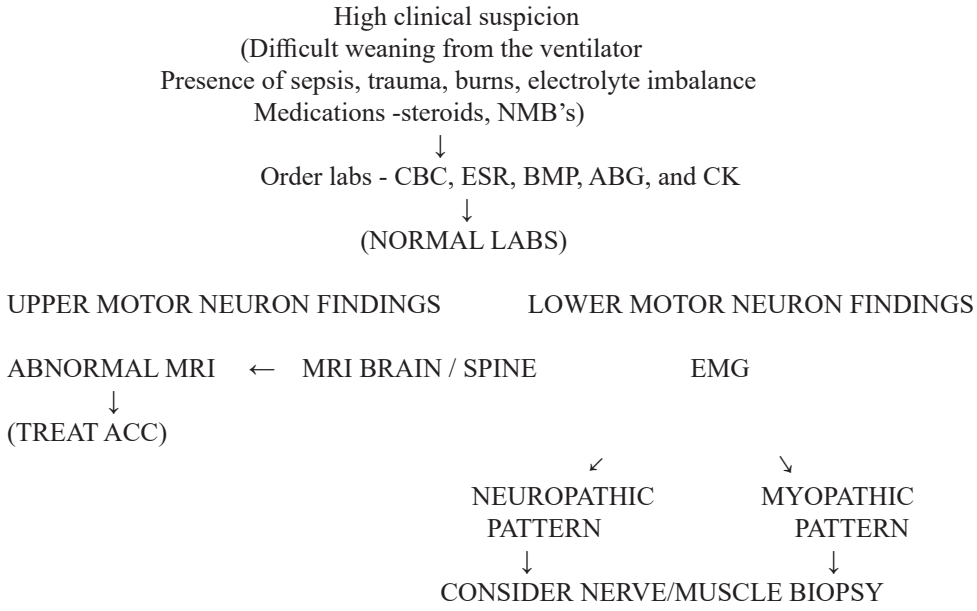
Neuromuscular Blockade

The disturbance in the neuromuscular transmission secondary to the use of neuromuscular blocking agents has been increased in recent years.[1] Competitive non-depolarizing neuromuscular blocking agents (NMB's) such as pancuronium, vecuronium, and newer benzylisoquinoline NMB's such as atracurium, cisatracurium are used extensively in ICU settings to aid in mechanical ventilation.[1,10] Concomitant antibiotic (aminoglycoside) and polypeptide antibiotics increases this block. Prolonged neuromuscular blockade by drugs, electrolyte disturbances, and metabolic acidosis acts synergistically with sepsis and SIRS in the pathogenesis of CIM and CIP.[1,5,10-11] Slow repetitive stimulation demonstrates an abnormal decrease in the compound muscle action potential. Careful evaluation of the concomitant drugs must be checked in case of any unexplained weakness.[1]

Established treatment of ICU related weakness is not available. The one successful intervention studied so far is intense insulin therapy that targets blood glucose of 80-110 mg/dL. This intervention reduced electro physiologically diagnosed polyneuropathy by 49% in patients in the intensive care for 7 days. In some series of patients IVIG is reported to be beneficial although further studies are needed. Also, preventing the factors that could trigger weakness from certain antibiotics like aminoglycosides must be employed.[11,19]

Hopkins syndrome (Post-asthmatic amyotrophy)

Although rare, Hopkins syndrome (post-asthmatic amyotrophy) is poliomyelitis like illness, which presents acutely following an asthmatic attack, mostly in the pediatric age group.[12-14] It is an anterior horn cell disorder that presents as an acute flaccid paralysis of the limbs post



(CBC: complete blood count, ESR: erythrocyte sedimentation rate, BMP: basic metabolic panel, ABG: arterial blood gas analysis, CK: creatine kinase, ACC: accordingly, MRI: magnetic resonance imaging, EMG: electromyography)

Figure 2: Approach to weakness in an ICU setting

asthma attack classically.[12-13] The sensation of touch and pain, bowel, and bladder sphincter functions preserved.[13] It could pose a diagnostic challenge to the neurologists if asthma were not diagnosed previously in the patient.[12] The pathogenesis of the disease, elucidated by the combination of viral infection and immunocompromise in the patient, which aids the viral invasion into the anterior horn cell.[13-14] Immunoglobulin (IVIG) and pulse therapy with corticosteroids are the mainstays of therapy.[13-14] Approach to muscular weakness in the ICU is depicted in figure 2.

2. Weakness Due to Preexisting Euromuscular Disorders

Spinal cord disorders. Motor weakness due to spinal cord disorders can be further classified into compressive and non-compressive myelopathy. Compressive myelopathy causing quadriparesis can be due to degenerative changes, trauma, tumor infiltration, abscess formation secondary to an infection, and syringomyelia.[15]

The most common cause of non-compressive myelopathy is transverse myelitis. Transverse myelitis is mostly idiopathic or post-infectious secondary to infection with viruses (CMV, Herpes, and Coxsackie) or bacteria (Mycoplasma, Legionella). Other causes include multiple sclerosis, Devic's disease, and collagen vascular disease.[16-18]

Transverse myelitis can be diagnosed with high clinical suspicion as it presents characteristically with bilateral signs and symptoms, a demarcated sensory level with progression period ranging from hours to weeks. CSF shows characteristic pleocytosis/ or high immunoglobulin levels, and MRI shows increased segmental contrast enhancement.[18]

The standard care of treatment for transverse myelitis includes IV corticosteroids such as methyl prednisone or dexamethasone, which helps in reducing spinal cord swelling and inflammation. Plasma exchange can be tried in refractory cases.[16]

Anterior Horn Cell Disorders

Amongst anterior horn cell disorders, Amyotrophic lateral sclerosis (ALS) is the well-known culprit causing respiratory weakness, and in 10% as presenting compliant[19-20] due to primary phrenic motor neuron involvement. The most common cause of ICU admission in these patients is acute decompensation secondary to respiratory distress precipitated by an infection.[20]

ALS presents with characteristic simultaneous upper and lower motor neuron involvement. The most common presenting symptoms include weakness, atrophy, fascicula-

tion, difficulty swallowing, slurred speech.[21-22] The disease is usually relentlessly progressive, with death occurring in 50% in 3 years and 80% in 5 years.[22] The most common complication encountered in ALS patients in ICU is aspiration pneumonia, secondary to respiratory failure, which almost always requires tracheostomy and percutaneous endoscopic gastrostomy(PEG) tube placement.[20,23] The electrophysiological study is the choice of investigation, which shows widespread denervation on EMG.

Other disease processes involving the anterior horn cell include poliomyelitis, which has been successfully eradicated.[21] West Nile fever is also known to cause meningoencephalitis with acute flaccid paralysis, which usually presents with GBS like symptoms.[21,24-25] CSF fluid shows a lymphocytic predominant pleocytosis.[21,24-25] ELISA for IgM and IgG is highly sensitive and is the initial choice of investigation in cases with high clinical suspicion.

Peripheral Nerve Disorders

Amongst the peripheral nerve disorders, GBS is well known to cause weakness in the ICU.[20] GBS usually occurs weeks after flu-like or diarrheal illness caused by infectious agents such as CMV, EBV, HSV, Mycoplasma, Chlamydia, and Campylobacter.[26-27] Weakness follows a characteristic fashion as rapidly progressive ascending motor and sensory paralysis, which later progresses to respiratory weakness and bulbar involvement.[26] Autonomic involvement is also commonly seen, presenting as postural hypotension, fluctuation in blood pressure, and cardiac dysrhythmias.[20,26-28] Respiratory paralysis is the most common indication for ICU admission.[20] About 30% of patients require ventilator support at some time during the illness.[20,26,29]

The most characteristic lab finding in GBS is CSF albuminocytological dissociation, which usually occurs 48 hours after the illness.[27] Electro diagnostic studies show the slowing of nerve conduction velocity in addition to conduction block and temporal dispersion.[27]

Table 3: Provides a comparison between West Nile poliomyelitis and GBS.

Features	West Nile poliomyelitis (16)	GBS
Onset	infectious	post-infectious
Weakness	asymmetric	symmetric ascending
Sensory symptoms	uncommon	common
Bladder issues	common	uncommon
Encephalopathy	common	uncommon
CSF	pleocytosis	albuminocytological dissociation
NCS/EMG	Fibrillation/positive waves	Conduction blocks and temporal dispersion

Management of GBS in ICU settings is governed by two parameters, i.e., vital capacity, and ABG. Intubation is recommended if VC <12-15 ml/kg, falling VC, and in patients with retained secretions.[29] The recommended treatment options are IVIG or Plasma Exchange.[26,29]

Plasmapheresis is usually recommended in patients unable to ambulate, worsening forced vital capacity, bulbar muscle involvement, and in those requiring intubation and ventilation. Five sessions of Plasma exchange over 10 -14 days is recommended with the exchange of a total of 200ml of plasma/ kg body weight.[20,29] Albumin is the ideal replacement solution for exchange.[31] Blood pressure should be monitored every 30 minutes during the exchange period.

IVIG in the dose of 2g/kg divided over five consecutive days is the recommended treatment. IgA deficiency must be ruled out before starting the therapy.[32] The patient must be monitored for the development of side effects such as headache, malaise, nausea, and others. Combination therapies of IVIG and Plasma exchange are not recommended and have no added benefits over individual treatment.[20,30,36] Steroids are not helpful in the treatment of GBS in ICU patients.

Neuromuscular Junction Disorders

The most common myasthenic syndrome encountered in ICU includes myasthenia gravis (MG).[33] The underlying defect in Myasthenia gravis is the decreased number of available acetylcholine receptors (AChRs) at neuromuscular junction secondary to antibody-mediated immune destruction, thus compromising the neuromuscular conduction and presenting as the motor weakness.[34] The distribution of muscle weakness has a characteristic fashion involving extraocular muscles, facial, bulbar, and later respiratory

involvement, and it usually presents as diplopia, dysphagia, difficulty in swallowing, and dysarthric speech.[29,33-34] In almost 85% of patients, the weakness becomes generalized, affecting the limb muscles.[35]

Myasthenic crisis is the most common reason for ICU admission in patients with MG. Myasthenia crisis is associated with respiratory compromise, presenting as respiratory muscle insufficiency and inability to handle excessive oral and respiratory secretions that require intubation and mechanical ventilation.[34,36-37]

In the setting of clinical worsening of myasthenia prompts excessive dosage of cholinesterase inhibitors, which increases the risk of cholinergic crisis. It is rare to see cholinergic crisis without concomitant myasthenia crisis. Cholinergic crisis is characterized by excessive secretions, diaphoresis, bradycardia, urinary urgency, bronchospasm, cramps, and weakness secondary to the peak of nicotinic and muscarinic toxicity. It typically occurs 2 hours after the last dose, and treated with atropine, pralidoxime, and/or glycopyrrolate.[29]

The most common precipitants of the myasthenic crisis include intercurrent infections, aspiration, sepsis, surgical procedure, medications, and pregnancy.[38] About 30-70% of seronegative myasthenic patients may have antibody directed against Muscle-specific tyrosine kinase (MUSK), such patients tend to have severe disease and high frequency of respiratory crisis compared to AChR positive patients.[39-40]

A vital capacity less than 1 liter or (<20-25 ml/kg) or a negative inspiratory factor (NIF) <20 cm of H2O indicates significant respiratory weakness; both measurements commonly used to define a myasthenic crisis.[29, 33-34]

Around two-third to 90% of the patients with a crisis require intubation and mechanical ventilation and ICU management of the complications. Sepsis is the most common complication encountered in patients with the crisis in ICU settings.[29]

IVIG and Plasma exchange is the mainstay of treatment in crisis patients.[36] A typical course of IVIG is 2g/kg body weight daily for five days[19]; Five rounds of plasma exchange every other day for ten days is standardized therapy. IVIG is generally administered to total dose off 1g/Kg. most common side effects secondary to infusion are headache, nausea and fever. Renal failure and myocardial infarction form the hypercoagulability and aseptic meningitis is also reported.[29]

The use of 5 days pulse therapy with high dose intravenous methylprednisolone reported to improve symptoms in the severe myasthenia with fewer side effects.[40]

Botulism and tick paralysis are amongst the other neuromuscular junction disorders encountered in ICU. More than 110 cases are reported per year in the United States.[41] Botulism presents with flaccid paralysis, areflexia, and autonomic disturbances. Early diagnosis is imperative as early antitoxin therapy is associated with a decreased hospital stay, morbidity, and mortality.[42] Mechanical ventilation is the mainstay of treatment. Tick paralysis is associated with areflexia, ascending motor paralysis, and preserved sensations.[43-44] A careful search for the ticks and their removal aids in the rapid resolution of symptoms.[43-44]

Muscle Disorders

Inflammatory myopathies commonly encountered in the ICU are dermatomyositis and polymyositis. Both present with proximal muscle weakness and pain.[45] Dermatomyositis has characteristic skin lesions such as purplish periorbital (heliotrope) rash, which spreads to back and neck as shawl sign and Gottron's sign presenting as a rash over knuckles.[45-46] Dermatomyositis is also more commonly associated with malignancies.[46]

The initial investigation for diagnosis involves CK levels, definitive diagnosis made by muscle biopsy, and H&E stain. Steroids are the mainstay of treatment for inflammatory myopathies.[45-46]

Electrolytes Disturbances

Hypokalemia is the main culprit associated with weakness due to electrolyte disturbances in ICU patients.[47] Low magnesium is associated with increased mortality by 2 to 3 fold in the ICU patients. IV Magnesium as slow infusions of magnesium sulfate is the preferred in the ICU in cases of hypomagnesemia.[47]

Hypokalemic periodic paralysis presents with a recurrent weakness that can later progress to respiratory failure.[48] Patients with hypokalemia <3.5 mEq/l respond well to oral or IV potassium replacement. In refractory cases, hypophosphatemia should be suspected.[49]

Conclusion

Multiple predisposing factors are involved in the development of neuromuscular weakness in a critically ill patient in ICU. It could be due to a preexisting neuromuscular disease, which got exacerbated in critical illness or the complication of the critical illness itself. A thorough history and physical examination are of paramount importance, and should not be omitted even though the majority of patients are unresponsive, confused, or sedated. Particular impor-

tance should be given to the clues, such as the use of offending medications, underlying infections, history, and course of presenting illness, which help significantly in delineating the underlying disease process. Nevertheless, extensive imaging studies, biopsies, electrodiagnostic studies are required to reach the diagnosis in the majority of critically ill patients. A comprehensive investigation protocol must strictly adhere to all cases of weakness in ICU settings.

The spectrum of neuromuscular disease encountered in ICUs today has rapidly evolved over the last decades. Nowadays, weakness due to CIM and CIP presents twice to thrice more commonly than due to primary neuromuscular disorders.

Early diagnosis and prompt treatment are necessary not only to reduce morbidity and mortality in critically ill patients but also to reduce skyrocketing health care expenses.

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Scapuloperoneal Myopathy and Cardiomyopathy with a Novel MYH7 Mutation: A Case Report

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Introduction

Myosin heavy chain 7 (MYH7) gene encodes for myosin heavy chain-beta (MHC-β), which is the major protein comprising thick filaments in cardiac muscle and in slow twitch type 1 fibers of skeletal muscles.[1]

MYH7-related myopathies have variable clinical features, onsets, and are emerging as a group of muscle diseases that affect a wide range of age groups.[11] MYH7 gene mutation-related myopathy has been reported in hypertrophic cardiomyopathy (HCM, MIM # 196200), dilated cardiomyopathy (DCM, MIM # 115200), Laing distal myopathy (MPD1; MIM # 160500), myosin storage myopathy (MSM, MIM # 608358), and congenital fiber type disproportion (CFTD, MIM # 255310).[2-4] Additionally, scapuloperoneal, limb girdle muscle form, multi-mini-core disease with variable cardiac involvement has been reported with MYH7 gene mutations. [13-14]

While individuals with MYH7-related myopathies will present with cardiac or skeletal involvement, it is less common to see cardiac and skeletal involvement co-occurring in a single individual.[2,11] In this case report, we describe a patient with ascending muscular weakness and dilated cardiomyopathy with a heterozygous MYH7 gene mutation.

Case Report

A 66-year old right-handed woman presented to the outpatient Neurology Clinic for evaluation of progressive ascending weakness and dyspnea. The patient first noted lower extremity weakness in her 20s that has slowly progressed to her upper extremities in her 50s. The patient reported an extensive family history of progressive muscular weakness and cardiomyopathy. The patient reported her father passed away from a myocardial infarction 43 years old, and son died from heart failure at 33 years old. Per patient, no further details were known about the cause of death. Patient reported no formal genetic testing has been done for any family members and was not interested in genetic testing despite it being offered at our clinic.

Upon presentation to the Neurology clinic, patient stated she is no longer able to raise her arms above her head, bend to put her shoes on, and has difficulty using her hands. Patient also reported new onset of exertional dyspnea.

Neurological examination of mental status and cranial nerves were intact. On a manual muscle test, patient was unable to raise her arms above her head. Her strength on Medical Research Counsil (MRC) 0/5 strength of deltoids bilaterally, 4/5 strength of triceps and biceps bilaterally, and 3/5 strength at wrist extensors bilaterally. The patient had wasting of the thenar eminences and weak hand grip bilaterally. Furthermore, the patient had a 3/5 strength of hip flexion bilaterally, 3/5 strength of knee flexors and extensors bilaterally, and 1/5 strength of ankle dorsiflexion bilaterally. Reflexes were 1+ bilaterally throughout exam, and the patient had a wide-based, waddling gait. Lastly, high arched feet with hammertoes were noted.

There was no elevation of serum creatinine kinase, and EMG showed myopathic process. Muscle biopsy of the deltoid reported from outside facility revealed myopathic changes with mini cores. Unfortunately, no biopsy images were available from outside institution. The cardiac evaluation included EKG and Echocardiogram. EKG reveals first degree AV block with anterior ischemia. Patient's echocardiogram revealed features of dilated cardiomyopathy, including left ventricular dilation with reduced systolic function and normal wall thickness. The genetic panel was conducted through PerkinElmer Genomics and revealed c.4522_c.4524del (p.Glu1508del) resulting in pathogenic mutation of MYH7, with a scapuloperoneal myopathy and cardiomyopathy phenotype.

Discussion

MYH7, which encodes for myosin heavy chain-beta, plays a crucial role in cardiac contractility and skeletal muscle fibers. Previous studies have reported mutations in the NH globular head, and COOH tail of MYH7 gene resulted in cardiomyopathy and skeletal myopathies, respectively.[5,8] However, research has shown that the location of the mutation and phenotypes do not necessarily correspond. [6-10] Our case report reveals the location of the MYH7 gene mutation is in the COOH tail domain (c.4522_c.4524del: p.Glu1508del) , which resulted in co-occurring scapuloperoneal and dilated cardiomyopathy in an adult patient. Similar to our case report, there has been reported cases of skeletal muscle myopathy with associated cardiomyopathy.[5,7-8,10,15-17]

Specifically, a study by Yüceyar et al has many parallels to the case report we present. [7] One member from the study family reported by Yüceyar had a unique presentation of a

slowly progressive scapuloperoneal type weakness with a normal creatine kinase level. In this individual, Yüceyar reported exertional dyspnea with echocardiogram findings of dilated cardiomyopathy.[7] These unique combination findings were almost identical to the patient described in our case report. However, in contrast to our report, Yüceyar identified a homozygous mutation in MYH7 exon. Of the cases reported with co-occurring skeletal myopathy and cardiomyopathy findings, only two to date were noted to be homozygous.[7-8]

Our case, like the majority of MYH7 mutations with co-occurring skeletal and cardiac myopathies, demonstrated a heterozygous mutation.[5,10,15-17] Furthermore, while our patient's family was not interested in receiving genetic testing, the history of multiple family members affected in each generation is highly suggestive of an autosomal dominant pattern of transmission.

In conclusion, this case report highlights the pertinent family history that is commonly associated with MYH7 mutations. It also illustrates the variability in the phenotypic presentation of this novel mutation. [9-11] While it is still not well understood why different MYH7 mutations result in various phenotypes, we hope that this unique combination of clinical findings will help increase awareness to the broad phenotypic spectrum related to MYH7-myopathies.

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Bilateral Ptosis and Limb Myokymia: Regional Variant of Guillain-Barré Syndrome?

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Keywords: *Guillain-Barré syndrome, ptosis, antiganglioside antibodies, myokymia.*

Introduction

Guillain-Barré syndrome (GBS) typically presents with distal paresthesias, ascending paralysis, and areflexia. Several variants have been described, most notably the Miller-Fisher syndrome (MFS) which accounts for about 5% of all GBS cases.[1,2] Less common regional variants include pharyngeal-cervical-brachial (PCB) weakness, paraparesis, facial diplegia with distal paresthesias, and severe ptosis without ophthalmoplegia.[3,4] Ptosis without ophthalmoplegia occurs in approximately 8% of patients with typical GBS but is also seen in regional forms, particularly the PCB variant.[3,5] Isolated bilateral ptosis as an initial sign of GBS with subsequent limb paralysis or paresis has been reported.[3,6-7] However, bilateral ptosis with subsequent limb myokymia but without ophthalmoplegia, facial or extremity weakness has not been reported in the literature to our knowledge.

We describe a patient who developed severe bilateral ptosis over several days. There was no facial or extremity weakness although he did have limb myokymia. Laboratory studies excluded common causes of ptosis and were suggestive of GBS. We believe our patient extends the clinical spectrum of GBS, and that binocular ptosis represents a mild regional variant of this neuropathy.

Case Report

A 44-year-old man developed drooping of both upper eyelids following a full day of fishing. Over one week the ptosis progressed to the point that he had to hold up his eyelids in order to see. He also noticed tingling in his extremities, mild difficulty swallowing, and involuntary movement in his left forearm and hand. He denied limb weakness, blurry or double vision, nausea or vomiting, diarrhea, constipation, and bladder involvement. There was no antecedent illness, and no other family members were ill.

Neurologic examination one week after onset showed bilateral symmetrical ptosis with full extraocular movements that persisted four months after onset (Figure 1a). Otherwise, cranial nerves, strength, sensation, and deep tendon reflexes were normal. In addition, there was a visible undulation in the left first dorsal interosseous muscle causing abduction-adduction movements of the index finger. Involuntary movements of his forearm had resolved three months earlier. Neurologic examination was otherwise normal.

Edrophonium testing was negative. Head magnetic resonance imaging, acetylcholine receptor antibodies, Lyme titers, thyroid function tests, serum lactate, and cre-

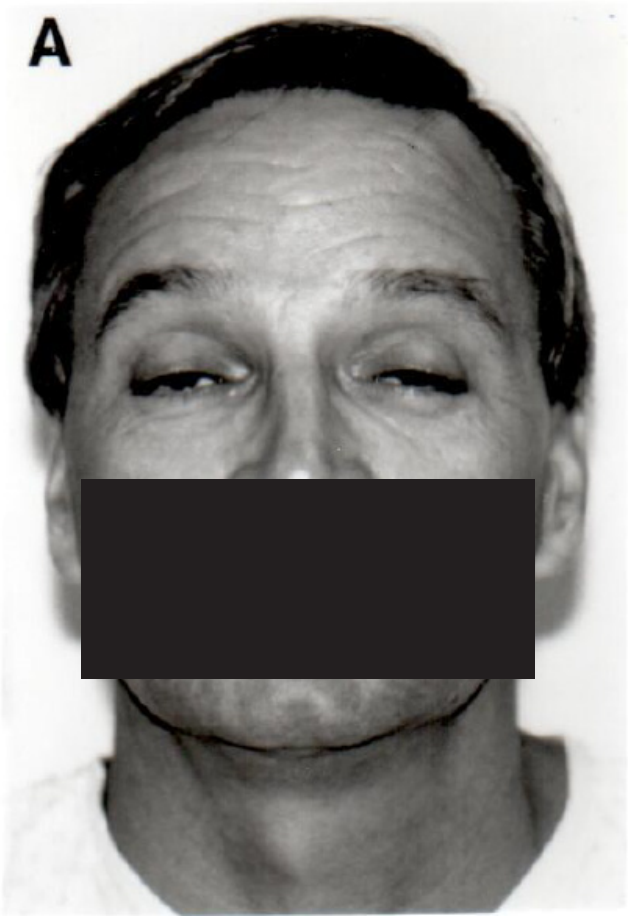

Figure 1a. Photograph of patient demonstrating symmetric ptosis four months after onset.

atine kinase were normal. CSF evaluation seven days after the onset of symptoms showed 1 WBC/mm3 and protein of 71 mg/dl (normal 15-50 mg/dl). Nerve conduction studies including repetitive stimulation were normal. IgM GM1 antibodies (47.0mg/mL, high titer >22.0mg/mL), IgM asialo GM1antibodies (63.7mg/mL, high titer >22.0mg/mL), and IgG asialo-GM1 antibodies (4.6mg/mL, high titer >4.5mg/mL) were elevated (Associated Regional and University Pathologists, Salt Lake City, UT). IgG GM1 antibody was not detected.

Lumbar puncture four months after onset showed a CSF protein of 54 mg/dl. Antiganglioside antibodies were no longer elevated. Antibodies to GQ1b were negative (Athena Diagnositics, Worcester, MA). Nerve conduction studies and F responses of the right median, ulnar and peroneal nerves, as well as 3 and 50 Hz repetitive stimulation of the left ulnar nerve and 3 Hz repetitive stimulation of the facial nerve, were normal. Electromyography (EMG) demonstrated a myokymic discharge in the left first dorsal interosseous muscle with a frequency of 2.7 Hz and 3-5 motor units per discharge (Figure 1b). Large amplitude motor units and mildly reduced recruitment were localized to distal arm muscles.

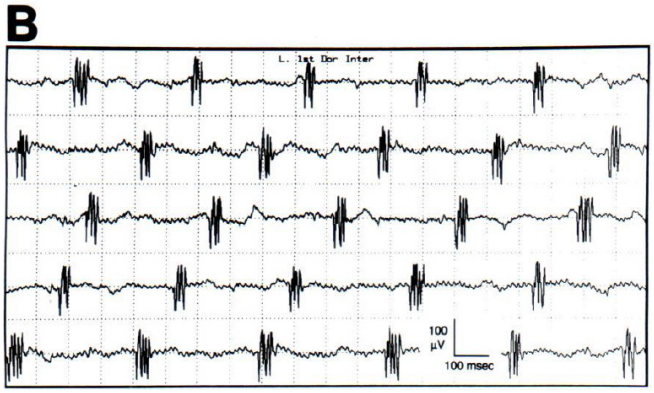

Figure 1b. Myokymic discharge with a frequency of 2.7 Hz recorded from the left first dorsal interosseous muscle.

Pyridostigmine bromide provided no benefit. The paresthesias and swallowing difficulty resolved after two months. The ptosis and myokymia began to improve after five months with further resolution at 8 months after onset.

Discussion

Our patient's subacute progression, slow improvement over months, elevated CSF protein, and myokymia led us to a diagnosis of GBS. Laboratory and radiologic studies excluded other causes of bilateral ptosis including myasthenia gravis and intracranial lesions. Botulism and diphtheria were not serious diagnostic considerations in a setting of elevated CSF protein, normal nerve conduction studies and repetitive stimulation, and absent visual and gastrointestinal symptoms.[3,5] There was no evidence of myopathy.

Ptosis without ophthalmoplegia is a recognized feature of GBS and is seen in the PCB variant. The eyelid drooping and mild swallowing difficulty in our patient are suggestive of the PCB variant which resembles botulism and is characterized by ptosis, severe dysphagia, shoulder girdle weakness, and respiratory failure.[3] Ropper popularized the concept of regional variants in GBS. These variants include "abortive forms" that maintain an atypical pattern throughout the illness and "transitional forms" which begin with a regional pattern and evolve into the more typical syndrome.[3] We believe our patient's illness represents a mild "abortive form" of GBS.

Myokymia and grouped repetitive discharges on EMG are important indicators of demyelinating disorders,[8-9] and in one series were present in 17% of patients with GBS.[10] Myokymia appears early in the course of GBS, usually involving facial muscles and lasting two to three weeks.[10] However, limb myokymia also occurs and may persist for several months.[10,11] Other causes of limb myokymia include radiation injury, direct toxic effects, ischemia, and nerve compression, none of which were serious diagnostic considerations in our patient.

Our patient had normal reflexes and muscle strength. Motor weakness and reduced tendon reflexes are key diagnostic criteria for classic forms of GBS.[12] Clinical criteria for regional variants have also included hyporeflexia or areflexia.[5] However, reflexes are preserved in a small percentage of patients with typical GBS and may be spared in unaffected limbs in regional variants.[3,13] For instance, reflexes are preserved in the legs of patients with the PCB variant[3] and in mild cases of MFS.[14-15] Patients with a GBS variant characterized by facial diplegia and paresthesias may have normal reflexes in early stages and may only lose their ankle jerks.[16] It is possible our patient developed hyporeflexia between office visits, but it was never documented.

The search for an antigen target in GBS has been inconclusive. IgG antibodies to the ganglioside GQ1b are elevated in MFS patients,[17] and a large proportion of GBS patients demonstrate antibodies to one or more gangliosides, including GM1 and asialo- GM1.[18-21] Our patient initially had high titers of IgM and IgG antiganglioside antibodies which were no longer detected at four months. This time course is in accord with anti-acidic glycolipid antibody titers measured longitudinally in GBS patients[19] and serial anti-GM1

titers from patients who developed an axonal form of GBS following parenteral ganglioside injections.[18] Still, many GBS patients do not have elevated antiganglioside antibodies, raising considerable uncertainty about a pathophysiologic role for these circulating factors.

In conclusion, we believe our patient had a mild, abortive form of GBS. Regional presentations of GBS may result from an immunologic response localized in distribution or limited in intensity and from antigenic differences among peripheral nerve populations. Our patient demonstrates that GBS may present in a highly localized manner and underscores the difficulty in setting clinical limits on this syndrome.

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TB Myositis in a Patient with Dermatomyositis Post Immunosuppression

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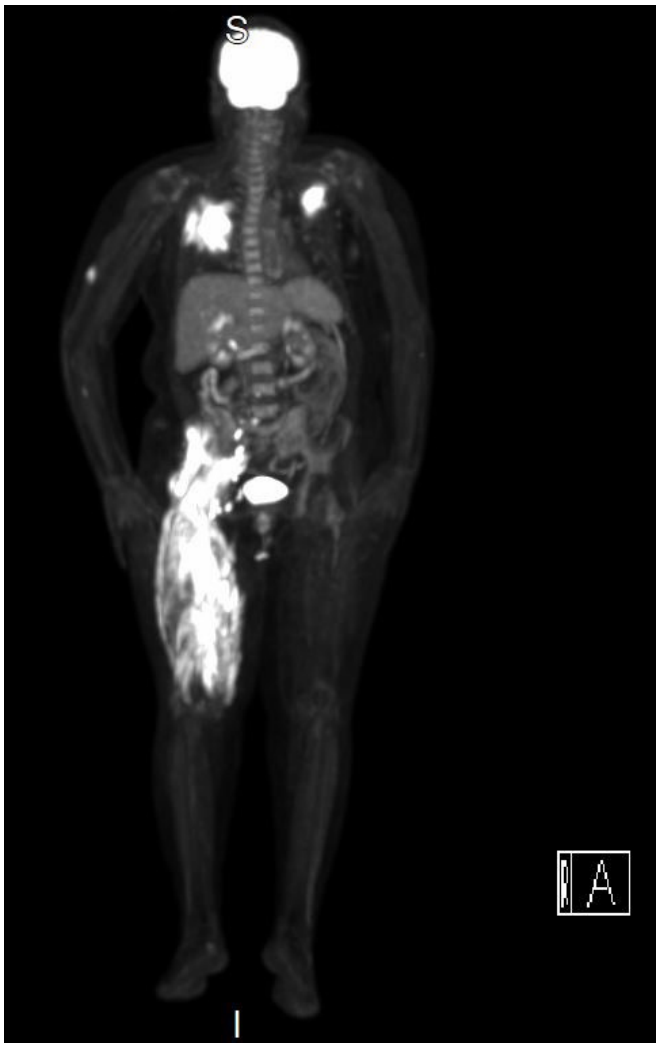
55-year-old African female with a history of initially refractory TIF1-y antibody positive dermatomyositis, with progressive proximal muscle weakness with difficulty swallowing, requiring regular inpatient admissions with the administration of IV steroids and IVIG. The patient was started on immunosuppression with mycophenolate as a steroid sparing agent. The patient slowly improved after initiation of immunosuppression, with a significant reduction in her rash, weakness, and dysphagia. After a few months of therapy, the patient noted pain in the right axilla and proximal right lower extremity with swelling and pain limiting her mobility. There was a concern for underlying malignancy for which PET scan was done, which showed hypermetabolic edema and swelling of musculature involving right thigh, right pectoral minor and left scapularis consistent with infectious or inflammatory myositis. Concern for focal dermatomyositis was raised and the patient received pulse IV steroids over 5 days with initial improvement. The patient later developed fevers, night sweats and chills, for which the patient was seen in ED. Initial vitals were concerning for sepsis, due to which patient was started on broad-spectrum antibiotics. CT scan of the chest and right lower extremity were done which showed, no pulmonary infiltrates, 5 cm right pectoralis minor and 9.4 cm right gluteus minimus fluid collection consistent with abscess.



PET scan showing hypermetabolic edema of right pectoralis minimus, right thigh and left scapularis muscle consistent with myositis.

Interventional radiology was consulted, and abscesses were aspirated, aspirate from chest wall was positive acid-fast bacilli, concerning for mycobacterium. Cultures were sent to the health department and were noted to be positive for TB. At this time, it was noted that the patient had a prior diagnosis of latent TB when she moved to the United States. The patient was started on Myambutol, Nydrazid, Levaquin, Rifampin, and Bactrim.

Tuberculous infections continue to be one of the deadliest infections around the world, with a significantly low incidence rate (2.8/100000) as compared to developing countries. Even with a low incidence rate, there is always a concern for reactivation of latent TB with the initiation of immunosuppression. Tb myositis is one of rare presentation and that can be difficult with diagnosis, especially in a patient who has an underlying autoimmune condition that could have a similar presentation. We recommend getting prior workup to rule out tuberculosis prior to the initiation of immunosuppression.

Answers, Discussion and Teaching Points for *Myopathies with Contracture*

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ABSTRACT

The two videos show physical examination of two patients with contractures. The answers are at the end of this file along with further discussion as to how to approach a case of muscle contracture and myopathy, as well as teaching points.

Keywords: *Contractures, Neuromuscular, Myopathy.*

Questions:

Q1/ A 34-year-old man who walked on his toes as a child and had Achilles tendon surgery. As he grew older, he developed weakness of the triceps and knee flexors and extensors. He had two healthy brothers and no family history of muscle disease. Examination findings are shown in the video number 1. CPK was: 477 IU/L, Electromyography (EMG) showed mixed long and short duration MUAPs in the tested proximal muscles. (see video 1)

Cardiac involvement is typically a feature of the following myopathy:

A. Oculopharyngeal muscular dystrophy (OPMD)
B. Emery-Dreifuss muscular dystrophy (EDMD)
C. Facioscapulohumeral muscular dystrophy (FSHD)
D. Collagen VI myopathies

Q2/ A 32-year-old woman who walked on tiptoes at age 5 years for which she had an elongation of the Achilles tendon bilaterally. She had one healthy sister and no family history of muscle disease. She developed a fixed mild proximal legs weakness since childhood. CPK level was slightly elevated and EMG was myopathic. Physical findings are shown in video 2.

Contractures are common in the following myopathies:

A. Limb Girdle muscular dystrophy type 2 B (LGMD2B)
B. Myotonic dystrophy
C. Bethlem myopathy
D. FSHD

Discussion:

It is important to differentiate between metabolic contractures, a feature of some metabolic myopathies which are painful, occur during exercises and are electrophysiologically silent, and myopathic contractures which limit passive stretch ability of a muscle to its proper length due to fibrosis. While most advanced myopathies are associated with contractures due to fibrosis, the development of contractures while the muscles are still functional, is a feature of only a few myopathies.

Contractures are an important diagnostic clue, especially, most of the contractures-associated myopathies carry no other specific features (normal or mild CK elevation, myopathic EMG and muscle biopsy). Such differentiation is important to select the right genetic testing and to facilitate the identification of some fatal myopathies due to cardiac arrhythmias which can be prevented by a defibrillator and or a pacemaker. Toe walking during childhood is an important sign of contracture of the calf muscles and many patients undergo surgical repair of the Achilles tendon for it. Such a finding should prompt a search for other contractures and a family history of muscle disease or sudden death.

There are two major groups of myopathies with contractures:

1. Bethlem myopathy: this is characterized by:
   - It is caused by Collagen VI mutations in one of the three collagen VI genes COL6A1, COL6A2 and COL6A3
   - Mutations cause two main types of muscle disorders: Ullrich congenital muscular dystrophy, an autosomal recessive disease with a severe phenotype, and a mild to moderate phenotype, Bethlem myopathy which is usually autosomal dominant.
   - Clinically, this group is characterized by muscle and connective tissue involvement, including weakness, joint laxity and contractures, and abnormal skin findings. Bethlem myopathy is proximal and contractures are characteristically distal, affecting finger flexors and to a lesser extent, they affecting ankles and elbows.
   - Although considered benign, 10% of patients need nocturnal respiratory support and 2/3 of patients require a walking aid after age 50 years.
   - Cardiac involvement is rare.

2. Emery-Dreifuss muscular dystrophy (EDMD): this is characterized by:
    - Early contractures, often before any significant weakness, of elbows, Achilles tendons, and post-cervical muscles
    - Slowly progressive muscle wasting and weakness with a distinctive humero-peroneal distribution (i.e. proximal in the upper limbs and distal in the lower limbs) early in the course of the disease.
    - Cardiac conduction defects (ranging from sinus bradycardia, prolongation of the PR interval on electrocardiography to complete heart block). Cardiomyopathy may also supervene. Thus, affected individuals may die suddenly from heart block, or develop progressive cardiac failure.
    - Responsible mutations affect Emerin and Lamin A and C genes. There are two main modes of inheritance; X-linked (Emerin) and autosomal dominant (Lamin). Rare autosomal recessive inheritance has also been described. EDMD can be also caused by mutation of FHL1 and SYNE genes.

Teaching points:

1. Toe walking history should prompt a search for contractures of other joints and family history of muscle disease or sudden death.
2. If contractures are out of proportion to weakness, consider EDMD
3. If finger flexors are contracted, consider Bethlem myopathy
4. Cardiac monitoring is essential for all EDMD patients.

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Answers:

Answer 1:

B-Blood genetic testing revealed a heterozygous pathogenic mutation in Lamin A (LMNA) gene, confirming EDMD

Answer 2:

C- Blood genetic testing revealed a Heterozygous De Novo Pathogenic mutation of Collagen 6A2 (COL6A2) gene confirming Bethlem myopathy.