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CONTENTS

What's In This Issue?

There are two other pieces in the What's On Your Mind section. One are some thoughts I wanted to pass on regarding the racial inequities issues that I had heard on the radio. The radio story talked about two "viral" epidemics.... the COVID- 19 epidemic and the epidemic of slavery. This is such an important problem in our society that I wanted to included it in this issue. Then Dr Bedlack has a nice piece reflecting on Lou Gehrig's battle with ALS and did he in fact have a reversal (? Or plateau) based on an analysis of his baseball metrics. In the New Discoveries/New Stuff section we have two papers by the University of Missouri-Columbia group (my new institution!) led by Dr Govindarajan : one on obstetrics-gynecological complications of neuromuscular disorders and the other on a series of patients presenting with myasthenia gravis that mimicked stroke events. Since COVID - 19 is the medical topic of the day, I asked two of our associate facilitators to write a piece for the "Looking Back and Looking Forward at Stuff " section on the neuromuscular complications of COVID-19. Drs GIl Wolfe and Yuebing Li enlisted Dr. Tiffany Pike-Lee to be the lead author on this important review article. In "Clinic Stuff" we have a case from Dr. Mantilla and KUMC group where he trained on a case of COVID-19 and rhabdomyolysis in the setting of statin use as well as a fascinating case , also from the KUMC group, on a case of hereditary amyloidosis with neuropathy that initially resembled CIDP. The "Visual Stuff" contribution is from Drs Pocock and Vu at the University of South Florida where they show dramatic pictures of the effects of CMT on the hands and feet over three generations. For the "Proposed Stuff" section I offered the never funded grant myself and KUMC colleagues submitted to the Patient Centers for Outcomes Research (PCORI) in which we proposed to compare four different drug therapies for excess sialorrhea in patients with ALS. If nothing else, the readers of the journal can see how we put together that PCORI grant. I still think it is a worthy study but I do not think PCORI finds it an interesting enough problem to fund. Finally, for the "Meeting Stuff" section I asked Dr Govindarajan to publish the abstracts the University of Missouri Neurology Departments research day last year. I want to offer this journal as a place to have any neurology department or neuromuscular fellowship program to publish their annual research day abstracts. It's not too late to submit your research day abstracts from the academic year that just ended.

Rick

COVID-19 and COVID-1619

Letter from the Founding Facilitator

Keywords: *COVID-19, Civil War, Civil Rights, COVID-1619, Jim Crow*

I heard an amazing news story recently this week that many of you may have heard as well. Pastor Raphael G. Warnock, PhD from the Ebenezer Baptist church in Atlanta was interviewed. He also happens to be running for the senate in Georgia. This of course is the church where Martin Luther King, Jr was a preacher too. Reverend Warnock said we are dealing with two viral plagues. COVID-19 and COVID-1619. COVID-19 came on our shores around January or February of this year and appeared in the world shortly before that. As our scientist across the world are working on a vaccine for COVID-19, there is a concern that the virus can mutate so that it will be difficult to come up with an effective vaccine, or that the vaccine will have to be altered frequently, such as is done with the influenza flu vaccine. COVID-1619 appeared on our shores in the year 1619 when the first 50 African slaves were brought to the colony of Jamestown in Virginia to serve as slave labor. We have been plagued with the 1619 virus ever since. The American Revolution in the late 1700s did nothing to stamp out this virus. The Civil War in the mid-1800s was the first attempt to "treat" this horrible infection on our land and had some remarkable success. But that success was soon rolled back as COVID-1619 mutated into the Jim Crow south and throughout the nation as we endured government accepted segregation for nearly 100 years. Then the Civil Rights movement led by Martin Luther King, Jr and others made remarkable progress through peaceful protests to change legislation in the USA to give equal rights to all races. Again, for the last 50 years we have seen a dramatic rollback of that success with the next COVID-1619 mutation and the rise of mass incarceration and judicial system injustice toward African Americans and in particular African American men. Now we have the opportunity to once again have a societal therapeutic approach to racial injustice by saying we will not tolerate this form of injustice any longer. The time has at long last come for meaningful, real change. I need to be part of this new movement for social change. Let's attack both COVID-19 and COVID-1619 so they never come back.

Rick

"A Great Yankee's Indian Summer: Did Lou Gehrig Experience a Temporary ALS Reversal While Playing in August 1938?"

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ABSTRACT

Nineteen thirty-eight was the last full season played by baseball slugger Lou Gehrig before amyotrophic lateral sclerosis (ALS) forced him to retire. He struggled to hit and field well for much of the season, and his final statistics—a .295 batting average, 29 home runs, 114 runs batted in—were unusually low for him. But in mid-season, Gehrig enjoyed a streak in which he seemed to regain his previous power. This three-week stretch, not studied closely by neurologists or baseball historians until now, suggests that the "Iron Horse" may have experienced a temporary ALS reversal, which can be instructive for researchers and those coping with the disease.

Keywords: *Gehrig, ALS.*

Amyotrophic lateral sclerosis (ALS) is often referred to as "relentlessly progressive,"[1] but this is not always true. For at least 40 years, it has been known that some people with ALS can experience periods of clinical stability ("plateaus") or improvement ("reversals").[2,3] ALS reversals are most often small in magnitude and temporary,[4] but can on rare occasions be large and persistent.[5] Here, in the interest of raising awareness about the non-linear progression of ALS, we analyze the last full baseball season of Lou Gehrig in greater detail than ever before. We argue that Gehrig experienced a temporary ALS reversal in August of 1938. We explain why we think awareness of such reversals is important.

In early 1938, Lou Gehrig experienced the first symptoms of the disease that would eventually bear his name and take his life.[6] In spring training, sportswriters noticed he was not hitting the ball as hard as usual, and Gehrig himself said his hits lacked "the proper zoom."[7] He opened the regular season in a deep slump, and by early August, his batting average, home run total and overall run production were well below his career norms.[8] Several sportswriters said the "Iron Horse" should end his renowned consecutive games streak, which by then stretched for more than two thousand games over 13 years. [9]

Then, for three weeks beginning August 7th, Gehrig's power somehow returned. His batting average and slugging percentage rose dramatically (see Table 1) and he resumed smacking the long drives he was renowned for. During one especially good ten-game stretch he piled up six doubles, six home runs and 22 runs batted in.[10] One homer sailed out of Philadelphia's Shibe Park and bounced on the porch of a house across the street. Sportswriter Rud Rennie of the *New York Herald Tribune* declared: "He is the menace of old. The fans sense it. They greeted him yesterday with those bursts of hurrahs which they reserve for strong men whom they expect to do big things."[11]

Gehrig's "Indian summer" did not last; by season's end he was hitting mostly singles. His batting average fell and his slugging percentage plummeted (Table 1). Poor play forced him to retire early in the 1939 season. He was diagnosed with ALS that June and lived only another two years.

There is certainly more than one possible explanation for Gehrig's remarkable but temporary surge in August 1938. He was apparently injury-free during the period in question, after playing with a fractured thumb during the latter part of July.[12] A few sportswriters noted that "Larrupin' Lou," as he was known, had begun using a lighter bat during the surge,[13] which in theory would enable to him to swing faster and generate more power when he hit the ball,

Table 1. Gehrig's batting average and slugging percentages at different times. Batting average = hits divided by at-bats. Slugging percentage = total bases divided by at-bats.

	Batting Average	Slugging Percentage
Career	.340	.632
April 18-August 6, 1938	.274	.486
August 7-August 26, 1938	.352	.743
August 27-October 2, 1938	.308	.436

compensating for the weakening of his muscles. Other writers reported that after experimenting with different batting stances during the 1938 season, he went back to his traditional stance, with both feet pointed toward home plate. "He returned the style of hitting that made him famous," Rennie wrote.[14] He may have simply enjoyed a hot streak, like all good hitters do. And of course, he could have faced a run of below-average pitchers, throwing fastballs that were too slow and curveballs that failed to curve.

However, all of these possible explanations have some caveats. Regarding injuries, it should be noted that for most of the '38 season, and in fact for most of his 2,130-game consecutive game streak, Gehrig was in good orthopedic health, with no ACL tears, major bone breaks or any of the other ailments that normally sideline athletes. The times when he did play through injuries—like the famous occasion in 1934 when he batted once, then left the game so he could rest his aching lower back—were the exception, not the rule. Regarding equipment and technique, it was hardly unusual for Gehrig (or other players) to start using lighter bats or adjust their stances as the six-month season wore on. In 1930, for example, Gehrig tapered the weight of his bats from 38 ounces to 36½.[15]

Regarding hot streaks, they were commonplace for Gehrig, even as he moved into his mid-thirties. In August 1937, for example, he hit .357 with eleven home runs; in June 1936, he batted .453 and his homers numbered an even dozen. What makes his three-week surge in August 1938 stand out is that it was the only time that season he consistently hit the ball with power. In just 24 games, he racked up one nearly one-third of his home run and RBI (runs batted in) totals for the entire season. The rest of the season, his big hits were much more sporadic.

The most telling figure regarding the surge is the sudden spike in Gehrig's slugging percentage. Slugging percentage is a player's total bases divided by his at bats; the more extra-base hits he gets, the higher his slugging percentage. For the first four months of the '38 season, Gehrig was hitting relatively few doubles, triples and home runs, and in 95 games through August 7, his slugging percentage stood at .486, a low mark for him. Then, his August surge, the big hits returned, and his slugging percentage for that period was a strong .743. After the surge, between August 26 and the end of the season, Gehrig's slugging percentage fell back to .436. Even though his batting average stayed around the .300 mark, he was hitting mostly singles, a sign of his diminishing power.

Did Gehrig face weaker than normal pitching during his streak? In a word, no. We were not able to compile a cumulative ERA (earned run average) for all the pitchers Gehrig faced before, during and after his August surge. Even if we could, the numbers might be misleading, because the American League in the 1930s was dominated by hitting, not pitching, and even good AL pitchers had ERAs that were historically high. We can say that during his 20-day surge, Gehrig faced several very good pitchers, in addition to an assortment of average and mediocre ones. His first home run during the surge was off Mel Harder, a career 223-game winner having a good season (17-10 record, 3.83 ERA). His last home run during the surge was off Hall of Famer Bob Feller, who also had a good season (17-11, 4.08 ERA, league-leading 260 strikeouts.) His game-winning double on August 18th came against the Washington Senators' best pitcher, Dutch Leonard (12-15, 3.43 ERA). A game-winning homer he hit on August 23 was off a good young White Sox pitcher, Johnny Rigney (9-9, 3.56 ERA). He also had multiple-hit games during the streak against Johnny Allen (14-8, 4.19) and Thornton Lee (13-12, 3.49). All of these pitchers had relatively long, successful careers, and all had better-than-league average ERAs in 1938.

Not all of the competition Gehrig faced was so good. His six-RBI day on August 20th came against a punching bag of a pitcher named Buck Ross (9-16, 5.32 ERA). The five RBIs he racked up on August 16th came off two mediocre Senators pitchers, Ken Chase (9-10, 5.58) and Chief Hogsett (5-6, 6.03). But overall, it cannot be said that Gehrig faced unusually weak pitching during his turnaround.

A final possible explanation is that Gehrig experienced a temporary ALS reversal. In ALS, progression of weakness occurs when the processes causing death of motor neurons (denervation) overwhelm the body's ability to compensate via collateral sprouting (reinnervation).[16] In ALS models, the progression of weakness can be affected either by slowing denervation[17] or by promoting re-ennervation.[18] Perhaps one or the other or both somehow occurred naturally in Gehrig that summer. Gehrig never explicitly said he felt better or stronger during the three-week period in question. However, there is evidence beyond his batting performance that he was feeling robust and energetic. Between August 12 and August 27, the Yankees played ten doubleheaders in sixteen days, all of them during the day in hot summer conditions. (Only two major league stadiums had lights in 1938.) Gehrig played every inning of every game except for one where, after getting four hits, he sat out the final two

innings.[19] During his lone off-day during a week of doubleheaders, he was reported to be fishing off the coast of Brielle, New Jersey.[20]

This is all perfectly consistent with Gehrig's reputation as the iron man of baseball. It is not consistent with the profile of a man who, at that moment, was feeling the symptoms of ALS.

In contrast, during the last two weeks of the season Gehrig removed himself early from three games and was described in one newspaper story as looking fidgety and "far off stride" at bat.

"These are the same symptoms he showed early in the year," said the report.[21] When Gehrig took part in a September 18th home run contest, to see which player could hit the ball the farthest, he finished last among six participants,[22] one of whom hit just 10 home runs in his entire major league career. Clearly, any ALS reversal experienced by Gehrig had faded away.

There are important takeaways from the Indian Summer of Lou Gehrig's 1938 season. It can be referenced when educating newly diagnosed patients about the non-linear progression of ALS and about the extraordinary things that are possible in spite of the disease. It should be kept in mind when trying to interpret anecdotal reports of improved muscle strength in people with ALS. These improvements are not necessarily the result of some associated treatment. They can be part of the natural history of the disease. And finally, temporary and especially dramatic and sustained ALS reversals may be worth studying; if we can understand why these occur, we may someday be able to make them happen more often.

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Most of the baseball-related quotes and facts in this article stem from *Last Ride of the Iron Horse: How Lou Gehrig Fought ALS to Play One Final Championship Season*, written by Dan Joseph, published in 2019 by Sunbury Press.

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[7] *Last Ride*, p. 42.

[8] Ibid., p. 100, 104

[9] Ibid., p. 61, 98-99

[10] www.baseball-reference.com/players/gl.fcgi?id=gehrilo01&t=b&year=1938. All of Gehrig's statistics cited in this article are drawn from his pages on baseball-reference.com.

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[12] Ibid., p. 96.

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[20] *Last Ride*, p. 111.

[21] *New York Daily News*, Oct. 4, 1938.

[22] *Last Ride*, p. 114.

Obstetric-Gynecological Complications in Neuromuscular Disorders

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ABSTRACT

Background and Objective: The data on the obstetric and gynecological complications in patients diagnosed with neuromuscular diseases is very limited and is primarily obtained from various case reports, series, and small studies. The objective of our study was to analyze prevalence of these complications in a large cohort of patients with various neuromuscular diseases.

Methods: This study is a retrospective chart review of patients diagnosed with various neuromuscular diseases at the University of Missouri, Columbia, from 2012 to 2017. We included patients who have at least one year follow up with us. We collected data on patient demographics, neuromuscular disease diagnosed, obstetric complications, and gynecologic complications. Data are reported as means ± SEM, and the results reported using prevalence rates.

Results: Ninety-five female patients were identified. Among them, 97% were Caucasian, and 3% were African-American with a mean age of 47.96 years. Neuromuscular diseases identified among them are Myasthenia Gravis (44%), Muscular Dystrophy (23%), Amyotrophic Lateral Sclerosis-ALS (16%), Charcot-Marie-Tooth disease-CMT (10%), and Spinal Muscular atrophy- SMA (7%). The majority of the patients reviewed have had no obstetric complications- (89.40%). The most common obstetric complication recorded was C-section (8.40%). 41% of women did not have any gynecological complaints. Urine incontinence (24.20%) is the most common complication.

Conclusion: C-sections and urinary incontinence are common obstetric and gynecological events seen in women with neuromuscular disease.

Keywords: *Obstetric events in NMD, Neuromuscular diseases, Myasthenia Gravis, Spinal muscular atrophy, Charcot-Marie-Tooth disease, Muscular dystrophies.*

Introduction

The data on obstetric and gynecological complications in patients with neuromuscular diseases (NMD) is limited and is primarily obtained from various case reports, case series, and small studies.[1-2] Previous studies have found that neuromuscular disorders, although debilitating, generally have a favorable outcome in pregnancy[1-3] yet data on antenatal, perinatal periods are lacking. Further gynecological complications are not commonly reported in these studies. With newer treatments and improved supportive care, many patients are living longer and deciding to have families and neuromuscular physicians are commonly asked to provide guidance during obstetric and gynecological events.[2] In our study, we report both gynecological and obstetric histories of 95 patients diagnosed with various neuromuscular diseases (NMD), i.e., Myasthenia gravis, Myotonic Dystrophy, ALS, Spinal Muscular atrophy, and Charcot-Marie-Tooth disease.

Methods

This is a retrospective chart review of patients diagnosed with various neuromuscular diseases at the University of Missouri, Columbia, from 2012 to 2017. We reviewed the clinic notes from the neurology, obstetrics and gynecology, family medicine, internal medicine clinic visits for each patient. We included patients who have at least one year follow up with us and seen atleast one of the specialists listed above.

We collected data on patient demographics, neuromuscular disease diagnosed, obstetric complications, and gynecologic complications. Data are reported as means ± SEM, and the results reported using prevalence rates. This study was approved by the Institutional Review Board (IRB) at the University of Missouri, Columbia, MO.

Results

Ninety-five female patients were identified. Among them, 97% were Caucasian, and 3% were African-American with a mean age of 47.96 (+/-10.2 years) years as depicted in table 1.

Table 1: Patient demographics

Number of patients	N=95
Mean age	47.96 (+/-10.2)years
Race	Caucasian- 97% African-American- 3%

Neuromuscular diseases identified among them are Myasthenia Gravis (44%), Muscular Dystrophy (23%), Amyotrophic Lateral Sclerosis-ALS (16%), Charcot-Marie-Tooth disease-CMT (10%), and Spinal Muscular atrophy- SMA (7%) as shown in figure 1.

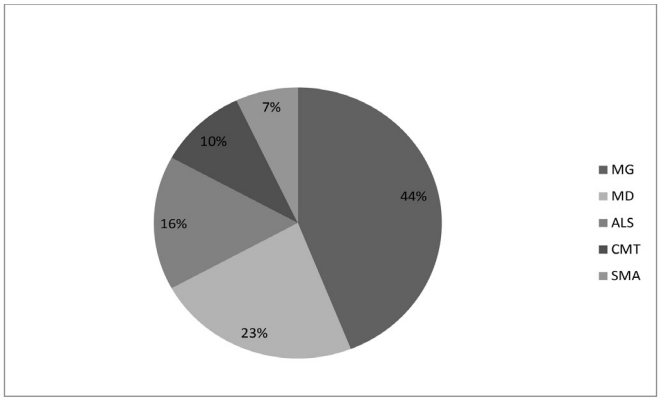

Figure 1. Distribution of the types of neuromuscular diseases evaluated. MG-Myasthenia Gravis, MD-Muscular Dystrophies, ALS-Amyotrophic Lateral Sclerosis, CMT- Charcot-Marie-Tooth disease, and SMA- Spinal Muscular atrophy.

The majority of the patients reviewed had no obstetric complications- (89.40%). In our study group, 40 got pregnant, and the number of pregnancy events recorded was 98. The most common obstetric complication recorded was C-section (8.40%). Other complications recorded were prolonged labor (1.10%) and Placenta Previa (1.10%). Among the study group, patients diagnosed with SMA and CMT, not a single obstetric complication was recorded. Women diagnosed with Myasthenia Gravis reported having the highest obstetric complications among all the neuromuscular diseases reported. 41% of women did not have any gynecological complaints. Urine incontinence (24.20%) is the most common complication, post-menopausal bleeding

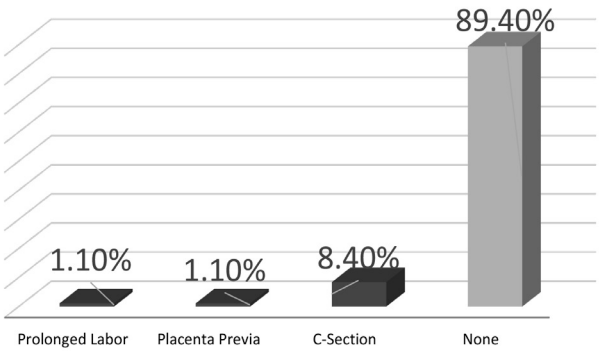

Figure 2. Distribution of the types of OB complications evaluated among women with a neuromuscular disease.

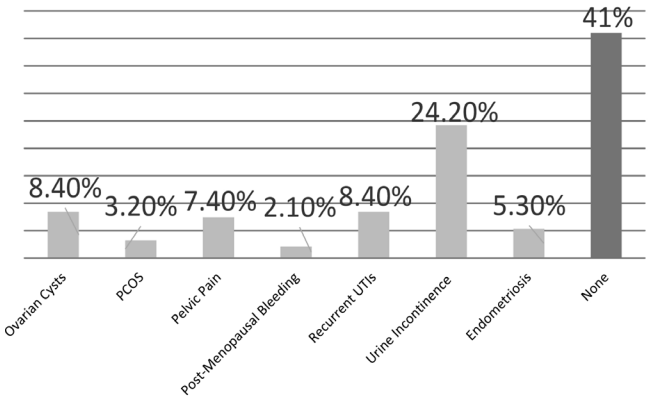

Figure 3. Distribution of the types of GYN complications evaluated among women with a neuromuscular disease.

(2.10%). Other complications were ovarian cysts (8.40%), recurrent UTIs (8.40%), pelvic pain (7.40%), endometriosis (5.30%), Polycystic ovarian syndrome (PCOS-3.20%). Women diagnosed with Myasthenia Gravis reported having the highest obstetric complications among all the neuromuscular diseases reported. The distributions of the obstetric and Gynecological complications, evaluated among the study population are depicted in the figures 2 and 3 respectively.

Discussion

The multi-disciplinary team must take into account managing women considering to become pregnant.[3,6] MG is an auto-immune disorder affecting the women of reproductive age twice more than men.[5] Myasthenia neither has any effect on fertility, and it is not uncommon to witness patients who are pregnant, nor does the pregnancy have any effects on the disease course.[2,5] However, the disease exacerbations are seen mostly in the first trimester and post-partum.[3,5-6] In a retrospective evaluation of pregnant women with myasthenia, the rate of C-section was as high as 78.3%. The rate of C-section in our study is 8.40% for all the NMDs combined. Although C-section is necessitated, vaginal deliveries are considered safe in the absence of any myasthenia crisis.[6]

Muscular dystrophies (MD) are a rare set of genetically inherited diseases, characterized by muscular weakness and wasting.[7] In prior surveys, complications like pre-term labor, placenta previa, and others are reported in myotonic dystrophy type 1. Also, these women have a higher rate of urinary tract infections.[8] In our study, the rate of placenta previa reported was 1.10%.

ALS is uncommon in women of reproductive age, and the association of the disease reported through few case

reports is purely coincidental.[3] We lack data, that would clearly state to limit maternal survival.[3]

CMT is the most common hereditary motor and sensory neuropathies. It is reported through the case reports that pregnancy does not contribute to disease severity[9] and the outcome of pregnancy in these patients is promising with complications not higher than the normal population.[10] In our study, 10% of the patients diagnosed with CMT and as mentioned majority patients reviewed had no obstetric complications (89.40%).

Spinal muscular atrophy is an autosomal recessive neurodegenerative disease characterized by progressive loss of anterior horn neurons.[11] 7% of our study patients diagnosed with SMA and none of them were reported to have any obstetric complication. Although subtype I is fatal, Subtypes II, III & IV may consider pregnancy as they reach the reproductive age.[11] There is no evidence that it affects fertility, and the pregnancy outcomes are at par with the normal population, giving a positive outlook for those who consider becoming pregnant.[11] Although there are risks, the multidisciplinary approach to evaluate each case is strongly recommended.[11]

The data on the association of gynecological complications and neuromuscular disease is not well established. In our study, the most common complication is urinary incontinence in the study patients. In a retrospective study, it was reported that patients with inherited neuromuscular diseases (Muscular dystrophies and Spinal muscular atrophy) develop urinary tract symptoms.[12] The most common presenting complaint was urinary incontinence in this study, as seen in our study group.[12]

Besides these, additional studies are imperative to set the appropriate guidelines for the management of pregnancy and address reproductive health issues in them. The addition of OBGYN physicians to the multidisciplinary neuromuscular disease clinics, where these patients are getting treated can be considered as the survival and quality of life improve in many of our neuromuscular patients.

The limitations of our study are, not all the patients in our study cohort were assessed by the neuromuscular physician during pregnancy. Also, since there is no control group, it is hard to say that the complications recorded in our study group are about the same as the rest of the population. The other limitation is we included only women in our study, as our objective is to describe the obstetric and gynecological complications.

Conclusion

C-sections and urinary incontinence are common obstetric and gynecological events seen in women with neuromuscular disease

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Myasthenia Gravis Mimicking Acute Cerebrovascular Events

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ABSTRACT

Background and Objective: Myasthenia gravis (MG) is an immune-mediated disorder that can sometimes present acutely with a focal neurological deficit and thus mimic a cerebrovascular event. The objective of this study was to describe the clinical characteristics in a large cohort of patients who were initially misdiagnosed with an acute vascular event and later diagnosed with MG.

Methods: This is a retrospective chart review of patients who were initially diagnosed with an acute cerebrovascular event but subsequently found to have MG. The chart review was done for the period from January 2013 to December 2017, and patients with at least one-year follow-up included. Data are reported as means ± SEM, and the results reported using prevalence rates.

Results: Twenty-one patients met our inclusion criteria. Among them, 13 (61.9%) were female with a mean age of 56.7 ± 4.07 years. Ten were MGFA class 3a; seven were MGFA class 2b, 3 were MGFA 3b and one was MGFA class 2a. Eighteen patients were acetylcholine receptor antibody positive; one was MuSK positive, and the rest two seronegative. Slurred speech (8 patients, 38.1%) was the most common symptom that resulted in misdiagnosis, followed by hemibody weakness (7 patients, 33.3%) and dysphagia (3 patients, 14.3%). Smoking (12 patients, 57.1%) and hypertension (11 patients, 52.4%) were common risk factors for cerebrovascular disease. Small vessel disease was suspected the most common etiology (15 patients, 71.4%) of the vascular event. Ten patients had received thrombolytic therapy, and sixteen patients were on antiplatelets. Four patients who presented recurrent symptoms placed on anticoagulants.

Conclusion: Acute presentation of bulbar symptoms and hemibody weakness resulted in the misdiagnosis of MG.

Keywords: *Myasthenia Gravis, Stroke mimics, acute cerebrovascular event.*

Introduction

Myasthenia Gravis (MG) is the most common primary disorder of neuromuscular junction (NMJ) transmission. Myasthenia gravis is an autoimmune disease in which antibodies bind to receptors at the post-synaptic membrane of the neuromuscular junction, inducing various degrees of muscle weakness. The annual incidence of MG is 8 to 10 cases per 1 million persons, and prevalence is 150 to 250 cases per 1 million making it one of the rare diseases.[1] The hallmark of the disease is a fluctuating weakness.[1-2] In some cases, MG can present acutely with focal neurological deficits, thus mimicking an acute cerebrovascular event.[3] Previous studies have included case reports/case series that have described acute bulbar weakness in older patients as being misdiagnosed as stroke.[3,7-8] The objective of this study was to describe the clinical characteristics in a large cohort of patients who were initially misdiagnosed with an acute vascular event and later diagnosed with MG.

Methods

This is a retrospective chart review of patients diagnosed with myasthenia gravis from January 2013 to December 2017. The inclusion criteria were: 1) Patient's age > 18 years. 2) Patients initially diagnosed with an acute cerebrovascular event, but the subsequent diagnosis was Myasthenia Gravis. 3) Patients who have had at least one year follow up.

Patient demographics, clinical presentation, vascular risk factors, type of vascular event, treatment given for the vascular event, patient MGFA class at diagnosis, antibody status were recorded. Data are reported as means ± SEM, and the results reported using prevalence rates. This study was approved by the Institutional Review Board (IRB) at the University of Missouri, Columbia, MO.

Results

During the study period, 33 patients were identified with 21 patients included in the study as they had at least a one year follow up. 13 (61.9%) were female, and 8 (38.1%) were male. 19 (90.5%) patients were Caucasians with a mean age of 56.7 ± 4.07 years. Slurred speech (8 patients, 38.1%) was the most common symptom that resulted in misdiagnosis, followed by hemi body weakness (7 patients, 33.3%) and dysphagia (3 patients, 14.28%). 18 (85.71%) patients were acetylcholine receptor antibody positive, and 1 (4.76%) was MuSK positive, and two were seronegative diagnosed based on a repetitive nerve stimulation confirmed by single-fiber EMG. These patient demographics and characteristics are described below in table 1.

Table 1. Demographics and Clinical Characteristics of the Patients (n=21)

Age (years)	56.7 +/- 4.07 yrs
Sex (male : female ratio)	8 (38.1%): 13 (61.9%)
Race (Caucasian: African-American)	19 (90.5%): 2 (9.5%)
Initial clinical symptoms- n (%)	Slurred speech - 8 (38.1%) Hemibody weakness - 7 (33.3%) Dysphagia - 3 (14.3%) Ptosis - 2 (9.5%) Double vision - 2 (9.5%) Blurred vision - 2 (9.5%) Dizziness - 1 (4.8%) Headache - 2 (9.5%) Wrist drop - 1 (4.8%)
Antibody Status - n (%)	Acetylcholine - 18 (85.7%) Musk -1 (4.8%) Seronegative - 2 (9.5%)

18 (85.7%) presented to the Emergency room, while 1 (4.8%) presented to the Primary care practitioner (PCP) clinic and 2 (9.5%) to the Neurology clinic. Smoking (12 patients, 57.1%) and hypertension (11 patients, 52.4%) were common vascular risk factors.

All patients underwent emergent CT-head to rule out bleeding. 10 (47.61%) patients acutely treated with intravenous tPA. Follow up MRI brain showed no evidence of infarct in any of these ten patients. In 10 patients who received tPA the duration of symptoms was within 3.5 hours. In 11 other patients the duration ranged from 2 to 6 hours (median=4 hours).

At the time of follow up in our clinic, 10 (47.61%) patients were on dual antiplatelets, and 4 (19.04%) patients who presented recurrent symptoms were placed on anticoagulation due to suspicion of cardioembolic etiology while seven were on single antiplatelet therapy. CT Angiogram (CTA) was subsequently done in all the patients. CTA was normal in 15 (71.42%) patients, while 2 (9.1%) each had unilateral chronic carotid artery dissection and extracranial vertebral artery stenosis (40% occlusion) and 1 (4.8%) had incidental basilar artery aneurysm (20mm in diameter).

Caucasian. Follow-up visits of these patients led to the diagnosis of Myasthenia Gravis, in which 10 (47.61%) patients were MGFA class 3a, 7 (33.33%) were MGFA class 2b, 3 (14.28%) were MGFA class 3b and 1 (4.8%) was MGFA class 2a. The characteristics like risk factors, image findings, and other variables of the misdiagnosed patients shown in table 2.

The titers of AchR binding antibody ranged from 8nmol/L to 50nmol/L (mean 20.8nmol/L, normal values< or= 0.02nmol/L).[4] RNS decrement ranged from 15% to 55% (mean=25%) with spinal accessory nerve stimulation and trapezius recording.

Mean concentric density with concentric needle electrode and voluntary contraction of extensor digitorum communis ranged from 38 micros in patient 1 and 50 micros in patient 2.

Discussion

Myasthenia Gravis (MG) is most commonly underdiagnosed in the elderly (5). The presenting features, especially bulbar symptoms in the elderly, pose a significant diagnostic challenge to the neurologists, as they have a broad differential diagnosis. It is also intriguing to note that bulbar symptoms can be predominantly seen as an initial presentation in the elderly, thus posing a diagnostic challenge.[5-6]

Acute and focal presentations are uncommon in myasthenia and have been reported in a few cases in the literature.[7-8] Ocular presentations (diplopia, ptosis) are the most common focal presentations seen in almost 53% of myasthenia gravis patients. The next common is the focal bulbar symptoms presenting as either dysphagia or dysarthria is seen around 28% of myasthenia patients, but isolated dysphagia as presenting complaint is seen only in 6%.[9]

Our study reported two patients with ptosis misdiagnosed as stroke. Ptosis, although commonly seen in myasthenia, when presented atypically, could give rise to a diagnostic dilemma. In a 58-year-old acute presentation of ptosis with facial droop gave rise to the suspicion of stroke.[2]

In our study, the most common symptom in misdiagnosed patients is slurred speech. Fatigability, the characteristic finding of myasthenia, is not always seen in such bulbar symptoms, increasing the chance of misdiagnosis.[7-8,12]

The focal weakness of extremities as an initial complaint, although rare, occurs in 14% to 27% of myasthenia cases[8] and can lead to misdiagnosis. In our study 7 patients presented with hemibody weakness and one presented with wrist drop. Cerebrovascular events are on the rise in young-

Table 2. Characteristics of the Misdiagnosed Population

Variables	Patients n=21	
CT Angiography findings	Normal	15 (71.4%)
	Vertebral dissection	1 (4.8%)
	Basilar aneurysm	1 (4.8%)
	Carotid dissection	2 (9.5%)
	Vertebral occlusion	2 (9.5%)
Treatment for Stroke n (%)		
	Anti-platelets	16 (76.2%)
	Anticoagulant	4 (19%)
	Endovascular Treatment	1 (4.8%)
	None	3 (14.3%)
Place of presentation n (%)		
	Emergency Room	18 (85.7%)
	Primary care physician	1 (4.8%)
	Neurology Clinic	2 (9.5%)
Stroke risk factors n (%)		
	Hyperlipidemia	2 (9.5%)
	Smoking	12 (57.1%)
	Hypertension	11 (52.4%)
	Diabetes Mellitus	4 (19%)
How MG was subsequently diagnosed n (%)		
	Positive antibody titers: 8nmol/L to 50nmol/L (mean 20.8nmol/L)	19 (90.5%)
	Repetitive nerve stimulus	18 (85.7%)
	Single fiber electromyography	2 (99.5%)
MGFA Class n(%)		
	2a	1 (4.8%)
	2b	7 (33.3%)
	3a	10 (47.6%)
	3b	3 (14.3%)

er patients,[10] thus posing diagnostic challenge when patients present with acute symptoms to the emergency room.

An isolated symptom of diplopia is seen in 50% and dysphagia in 15% of myasthenia patients. In our study cohort, two patients presented with diplopia and two with dysphagia. In one previous case report, myasthenia presented with diplopia secondary to unilateral abducens nerve palsy.[11] Dysphagia with dysarthria reported in an elderly patient with myasthenia got misdiagnosed as a stroke due to the high index of suspicion.[12]

Symptoms like dizziness though uncommon, was reported in addition to other constellation of symptoms like facial palsy and leg weakness in a patient misdiagnosed as Stroke.[13]

Headache, though occasionally reported as an initial complaint in myasthenia patients, could be secondary form the concomitant ocular complaints like diplopia. In a retrospective study of 184 Myasthenia patients, tension-type headache is reported in 38.6% and migraine headache in 4.9%.[14]

The limitations of our study are, the cohort is only from our emergency department, and we are unaware of the true extent of the misdiagnosis. Also, we cannot entirely rule out the overlapping vascular events at the time of presentation, which makes the diagnosis complicated.

Conclusion

Acute presentation of bulbar symptoms and focal weakness in patients with vascular risk factors resulted in the misdiagnosis of myasthenia gravis as a cerebrovascular event.

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Neuromuscular Complications in COVID-19: A Review of the Literature

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Keywords: *COVID-19, Viral infections, Pneumonia, Neuromuscular complications, Immunosuppression, Guillain-Barré syndrome, Miller Fisher syndrome, Myelitis, Myasthenia gravis.*

Introduction

Coronavirus disease of 2019 (COVID-19) is caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 belongs to the betacoronavirus family which includes severe acute respiratory syndrome coronavirus (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV).[1] All viruses from the betacaronavirus family pose a public health threat as they are known to cross species barriers and lead to high pathogenicity and mortality in humans.[1] The COVID-19 global health pandemic has resulted in 8,242,999 cases and 445,535 deaths worldwide as of June 18, 2020.[2] There are currently no vaccines available to prevent infection with COVID-19 and no proven drug therapies. While the central nervous system complications of COVID-19 are becoming increasingly recognized including headache, seizure, encephalopathy, and cerebrovascular event, neuromuscular complications of COVID-19 are just beginning to be documented.[3-4] Patients with several neuromuscular disorders may also be at increased risk for exacerbation or progression of underlying disease due to COVID-19 associated respiratory muscle injury and long-term usage of immunosuppressive or immunomodulatory therapies.[5]

In this review we focus our discussion on two ways that COVID-19 critically impacts neuromuscular medicine: (1) serious complications and outcomes associated with the viral infection and; (2) management considerations for neuromuscular patients on immunotherapies during the COVID-19 pandemic. A comprehensive PUBMED literature search was completed on June 13, 2020 using keywords "coronavirus" and "neurology," yielding a total of 547 publications. All articles in the English language were reviewed, and those with detailed information on neuromuscular manifestations were included.

Neuromuscular Complications of COVID-19

Guillain-Barré syndrome (GBS)

At the time of this literature search, the most commonly reported neuromuscular complication of COVID-19 was GBS. While GBS has been infrequently described in SARS-CoV-1 and MERS-CoV, it seems to be relatively common in COVID-19.[5] Up to the search date, 27 cases of COVID-19 associated GBS were reported, 3 of whom were described as the Miller Fisher variant.[7-25] Report origins were worldwide including Austria (1),[11] China (1),[23] France (1),[9] Germany (1),[17] Italy (10),[7-8, 14,16,21] Iran (1),[18] Morocco (1),[20] Spain (3), [24-25] Switzerland (3),[12] Turkey (1),[1] and United States (4).[10,15,19,22] Table 1 shows the essential characteristics and clinical courses of the 27 GBS cases. The mean age was 59.8 years, with male cases (63%) predominating over females (37%). The mean interval duration between the initial onset of COVID-19 symptoms and the appearance of neurologic symptoms was 10.7 days. Fever preceded GBS symptoms in 17 (63%) patients. In 2 (7.4%) GBS patients, there were no preceding symptoms suggesting COVID-19 infection. Eleven patients were tested for anti-ganglioside antibodies, and only one returned positive for GD1b-IgG.[24] SARS-CoV-2 viral PCR was performed in cerebrospinal fluid (CSF) of 15 patients, and all were negative. On MRI, nerve root enhancement was observed in four, and bilateral facial nerve enhancement was seen in one patient.[21] Electrodiagnostic (EDX) testing was completed in 23 patients. Among them, 16 (69.6%) were found to reveal demyelinating, 6 (26%) axonal, and 1 (4.3%) mixed axonal and demyelinating features. Mechanical ventilation was administrated in 12 (44%) patients.

The most common immunotherapy was intravenous immunoglobulin (IVIG), administered in 24 (88.9%) patients; and plasmapheresis was used in 2 (7.4%). Hydroxychloroquine and/or antiviral therapies were added to treatment regimens in 7 (25.9%) cases. In regard to overall outcome, 16 (59.3%) patients showed clinical improvement or achieved full or near full recovery, 9 (33.3%) did not show significant improvement or had a worsening clinical status. Of the 16 patients who improved, all but 2 were treated with IVIG. For 2 (7.4%) patient outcomes were not reported.

Table 1: A list of published cases of Guillain-Barré syndrome associated with COVID-19

Author	Case #	Age/ Sex	Onset neurologic syndrome	Neurologic signs and symptoms	Cerebrospinal fluid	Antiganglioside antibody	Imaging	Electrodiagnostic test	Treatment	Outcome
Alberti[7]	1	71M	10 days after fever	Flaccid areflexic tetraparesis, respiratory failure	Protein 54 mg/dL; WBC: 9 cells/μL; negative SARS-COV-2 PCR	Not tested	CT brain normal	Demyelinating features	IVIG (0.4g/kg/day 5 days), LPV/r, HCQ	Died
Assini[8]	2*	55M	>20 days after anosmia, ageusia, fever, cough	Ptosis, dysphagia, dysphonia, hyporeflexia, respiratory failure	Protein normal, positive ologoclonal bands, negative SARS-COV-2 PCR	Negative	MRI spine normal	Demyelinating features	IVIG (0.4g/kg 5 days)	Complete remission
Assini[8]	3	60M	>20 days after fever, cough	Leg weakness, areflexia, dysautonomia, respiratory failure	Protein normal, positive ologoclonal bands negative SARS-COV-2 PCR	Negative	None	Axonal polyneuropathy	IVIG (0.4g/kg 5 days)	Remission of gastroparesis, improved leg strength
Camdessanche[9]	4	64M	11 days after fever, cough	Paresthesia, flaccid areflexic tetraparesis, respiratory failure	Protein:166 mg/dL; normal cell count	Negative	None	Demyelinating features	IVIG (0.4g/kg 5 days)	Unknown
Coen[10]	5	70M	10 days after cough, myalgia	Paresthesia, allodynia, flaccid areflexic tetraparesis, difficulty voiding, constipation	Albuminocytologic dissociation, normal IgG synthesis	Negative	MRI spine normal	Demyelinating features	IVIG (0.4g/kg 5 days)	Remission 5 days after treatment
Gutierrez-Ortiz[24]	6*	55M	5 days after cough, malaise, fever	diplopia, paresthesia, areflexia, ataxic gait, anosmia, ageusia	Protein 80 mg/dL, WBC normal, negative SARS-COV-2 PCR	GD1b-IgG (+)	None	Not done	IVIG (0.4g/kg 5 days)	Resolution of neurologic symptoms except anosmia, ageusia
Gutierrez-Ortiz[24]	7*	50M	3 days after diarrhea, fever	Diplopia, areflexia, ageusia	Protein 62 mg/dL, WBC 2 /μl	Not tested	None	Not done	No immunotherapy	Complete recovery in 2 weeks
Helbok[11]	8	68M	14 days after cough, myalgia, fever	Paresthesia, weakness, areflexia, respiratory difficulty	Protein 64 mg/dL; WBC normal; negative SARS-COV-2 PCR	Not tested	None	Demyelinating features	IVIG 30 g total followed by PLEX x 4	Remission in 4 weeks
Lascano[12]	9	52F	15 days after cough, fever, arthralgia	flaccid areflexic tetraplegia, dysautonomia	Protein 60 mg/dL; WBC 3 /μL; negative SARS-COV-2 PCR	Negative	MRI spine normal	Demyelinating features	IVIG (0.4g/kg for 5 days)	Walking with assistance at 5 weeks post treatment
Lascano[12]	10	63F	7 days after cough, odynophagia	Paresthesia, flaccid areflexic tetraparesis, respiratory failure	Protein 40 mg/dL; WBC 2 /μL	Not tested	None	Demyelinating features	IVIG (0.4g/kg for 5 days)	Remission of tetraparesis, persistent paresthesia 5 weeks post treatment
Lascano[12]	11	61F	22 days after cough, fever, odynophagia	Paresthesia, flaccid areflexic tetraparesis, facial and bulbar weakness, dysautonomia,	Protein 140 mg/dL; WBC 4 cells/μL; negative SARS-COV-2 PCR	Not tested	MRI revealing lumbosacral root enhancement	Demyelinating features	IVIG (0.4g/kg for 5 days)	Walking with assistance at 5 weeks post treatment
Oguz-Akarsu[13]	12	53F	no preceding illness	Paresthesia, dysarthria, areflexia, leg weakness	Protein 32.6 mg/dL; negative SARS-COV-2 PCR	Not tested	MRI showing thickening and hyperintensity of nerve roots	Demyelinating features	PLEX x 5 days; HCQ, AZM	Improved leg weakness in 2 weeks
Ottaviani[14]	13	66F	10 days after cough, fever	Tetraparesis, areflexia	Protein 108 mg/dL; WBC normal	Not tested	None	Mixed demyelinating/axonal	IVIG (0.4g/kg for 5 days); HCQ, LPV/r	Persistent respiratory and multi-organ failure
Padroni[16]	14	70F	24 days after cough, fever	Paresthesia, weakness, gait difficulty	Protein 48 mg/dL; WBC normal	Not tested	None	Demyelinating features	IVIG (0.4g/kg 5 days)	Worsening weakness, required mechanical ventilation
Rana[15]	15	54M	14 days after odynophagia, fever, chill	ophthalmoparesis, facial diplegia, tetraparesis, areflexia,	Not done	Not tested	MRI thoracic & lumbar spine normal	Demyelinating features	IVIG (0.4g/kg 5 days); HCQ, AZM	Improved partially

Table 1: A list of published cases of Guillain-Barré syndrome associated with COVID-19 (continued)

Author	Case #	Age/ Sex	Onset neurologic syndrome	Neurologic signs and symptoms	Cerebrospinal fluid	Antiganglioside antibody	Imaging	Electrodiagnostic test	Treatment	Outcome
				dysautonomia, respiratory failure						
Reyes Bueno[25]	16	51M	15 days after diarrhea, odynophagia, cough	Limb and back pain, leg weakness, areflexia	Protein 70 mg/dL, WBC 5 /µl	Negative	None	Demyelinating features,	IVIG (0.4g/kg 5 days)	Improvement in facial and limb paresis, diplopia, pain
Scheidl[17]	17	54F	14 days after anosmia, ageusia	Paresthesia, proximal weakness, areflexia	Protein 140 mg/dL; WBC normal	Not tested	MRI cervical spine normal	Demyelinating features	IVIG (0.4g/kg 5 days)	Near complete resolution
Sedaghat[18]	18	65M	14 days after cough, fever, dyspnea	Tetraparesis, areflexia	Not done	Not tested	MRI cervical spine unremarkable	Axonal polyneuropathy	IVIG (0.4g/kg 5 days); HCQ, LPV/r, AZM	Unknown
Su[19]	19	72M	7 days after diarrhea, anorexia, chill	Paresthesia, weakness, dysautonomia, respiratory failure	Protein 313 mg/dL; WBC 1 /µL; negative SARS-COV-2 PCR	Negative	CT brain normal	Demyelinating features	Unknown	No improvement. Required tracheostomy and gastrostomy
Otmani[20]	20	70F	3 days after cough, fever, dyspnea	Tetraparesis, areflexia	Protein100 mg/dl; negative SARS-CoV-2 PCR	Not tested	None	Axonal polyneuropathy	IVIG (2g/kg 5 days); HCQ, AZM	no significant improvement one week after treatment
Toscano[21]	21	77F	7 days after fever, cough, ageusia	Paresthesia, facial weakness, flaccid areflexic tetraplegia, respiratory failure	protein 101 mg/dl; WBC 4/µl; negative SARS-CoV-2 PCR	Negative	MRI lumbar spine reveal caudal nerve root enhancement	Axonal polyneuropathy	IVIG 2 cycles	persistence limb weakness, and dysphagia
Toscano[21]	22	23M	10 days after fever and pharyngitis	Facial diplegia, leg paresthesia, ataxia areflexia	protein 123 mg/dl; WBC normal; negative SARS-CoV-2 PCR	Not tested	MRI brain bilateral facial nerve enhancement; MRI spine normal	Axonal polyneuropathy	IVIG 1 cycle	Partial improvement
Toscano[21]	23	55M	10 days after fever, cough	Flaccid tetraparesis, facial weakness, areflexia, respiratory failure	protein 193 mg/dl; WBC normal; negative SARS-CoV-2 PCR	Negative	MRI brain normal; MRI lumbar spine reveal caudal nerve root enhancement	Axonal polyneuropathy	IVIG 2 cycles	Persistent respiratory failure and flaccid tetraplegia
Toscano[21]	24	76M	5 days after cough, hyposmia	Flaccid areflexic tetraparesis, ataxia	protein and WBC normal; negative SARS-CoV-2 PCR	Not tested	MRI brain and spine normal	Not done	IVIG 1 cycle	mild improvement
Toscano[21]	25	61M	7 days after cough, ageusia, anosmia	Facial weakness, flaccid areflexic paraplegia, respiratory failure	protein 40 mg/dl; WBC 3/µl; negative SARS-CoV-2 PCR	Negative	MRI spine normal	Demyelinating features	IVIG, PLEX	Remained tetraplegic and ventilated 4 weeks after neurologic onset,
Virani[22]	26	54M	10 days after fever, cough	Paresthesia, leg weakness, areflexia, respiratory failure	Not done	Not tested	MRI spine normal	Not done	IVIG (0.4g/kg 5 days); HCQ	Arm weakness resolved but leg weakness persisted
Zhao[23]	27	61F	No preceding illness	Decreased distal sensation, limb weakness, areflexia	protein 124 mg/dl; WBC normal	Not tested	None	Demyelinating features	IVIG 1 cycle; Arbidol, LPV/r	Resolved by day 30

***Cases classified as Miller Fisher syndrome.**
Abbreviations: WBC, white blood cell; IVIG, intravenous immunoglobulin; LPV/r, Lopinavir/Rotinavir; HCQ, hydroxychloroquine; PCR, polymerase chain reaction; PLEX, plasmapheresis; AZM, azithromycin.

Myopathy and hyperCKemia

Myopathy and hyperCKemia are frequently reported complications of COVID-19. A retrospective case series by Mao et al. [4] included 214 COVID-19 patients from Wuhan, China, and found 10.7% of patients had evidence of skeletal muscle injury, defined as muscle pain with creatine kinase (CK) levels of being >200 U/L. Of the 88 patients with severe infection, the incidence of skeletal muscle injury increased to 19.3%, compared to only 4.8% in 126 patients with mild infection. Zhang et al.[28] analyzed another group of 95 patients with COVID-19 in Wuhan and reported an incidence of 29.5% with hyperCKemia (defined as CK >200 U/L). Similarly, a higher incidence (43.8%) of hyperCKemia was observed in 32 patients with severe infection.[28] Romero-Sanchez et al.[29] analyzed a group of 841 patients hospitalized with COVID-19 in Spain. In their analysis, hyperCKemia was found in 73 (9.2%), and clinical evidence of myopathy was seen in 26 (3.1%) patients, 3 of which had EDX evidence of myopathy. Their patients may include cases of critical care myopathy, as a multivariate analysis reported longer ICU stay was the only independent predictor in the development of myopathy.[29] A few additional studies reported rhabdomyolysis in the setting of COVID-19. Jin et al.[30] described a 60-year-old man with CK of 11,842 U/L and elevated myoglobin of >12.00 mg/L. His clinical symptoms and CK improved with aggressive fluid therapy. Guan et al.[31] defined rhabdomyolysis as the presence of muscle pain, weakness and CK level that was 10 times the upper limit of normal and found a low incidence of 0.2% among 1099 patients.

Neuromuscular Junction Disorders

Patients with neuromuscular junction disorders such as myasthenia gravis (MG) are known to be vulnerable to infection leading to exacerbations.[32] Chronic immunosuppressive or immunomodulatory therapy and thymectomy also place these patients at increased risk for infections.[33] Concerns have been raised in that MG patients are at higher risk for contracting COVID-19 or developing exacerbations secondary to coronavirus infection.[34] To date, there are a total of 7 MG patients reported as having contracted COVID-19.[35,42,44] Table 2 outlines the clinical characteristics, treatment regimes, and outcomes of these patients. All 7 cases reside in the United States and all had generalized MG. Six were positive for acetylcholine receptor antibody, and one was positive for muscle specific tyrosine kinase antibody. Three patients required mechanical ventilation for respiratory failure, and one required significant supple-

Table 2: A list of myasthenia gravis patients with COVID-19.

Author	Age/sex	MGFA Class at COVID-19 diagnosis	Antibody status	Thymus status	MG treatment at time of infection	Signs and symptoms	MG and COVID-19 treatment	Outcome	MG course during COVID-19
Anand[35]	57M	1	AChR-Ab+	thymectomy	AZA 50 mg/day	sore throat, cough	AZA 50 mg daily, HCQ, AZM, TOZ	Required ventilation but extubated on day 7	No exacerbation
Anand[35]	64M	Remission	AChR-Ab+	thymectomy	MMF 1000 mg BID, Pred 5 mg QOD	cough, chill	Pred 10mg daily for 9 days then 5mg QOD, HCQ, AZM, CTX	Required ventilation then tracheostomy	No exacerbation
Anand[35]	90F	1	AChR-Ab+	No thymectomy	MMF 1000 mg BID, Pred 30 mg/day IVIG 0.8 g/kg monthly	shortness of breath, cough, fever	Pred 25mg daily for 6 days then 20mg daily, IVIG continued, HCQ, AZM, CTX	Required high flow oxygen therapy without need for ventilation	No exacerbation
Anand[35]	42F	2B	MuSK-Ab +	No thymectomy	Pred 5 mg alternating with 2.5 mg QOD	sore throat, myalgia, worsening dysphagia, neck weakness, diplopia	Pred 20mg daily, IVIG 2 g/kg	No respiratory support required	Exacerbation
Anand[35]	64F	1	AChR-Ab+	No thymectomy	MMF 750BID, Pred 15 mg/day	cough, night sweat, chill	Pred 15mg daily	No respiratory support required	No exacerbation
Delly[42]	56F	2B	AChR-Ab+	No thymectomy	Pyridostigmine 60mg QID, Pred 40mg/day, IVIG 1.3 g/kg every 2 weeks), HCQ 200mg BID for CTD	dyspnea, fever, myalgia, proximal limb weakness, respiratory failure	Pred 80mg daily, IVIG at 0.4 g/kg for 5 days then 0.65 g/kg for 2 days	Required ventilation then extubated on day 13	Exacerbation with crisis
Ramaswamy[44]	42F	2B	AChR-Ab+	Thymoma without thymectomy	MMF 1000 BID, pyridostigmine 60mg QID, Pred 30mg/day, PLEX q4week	fever, chill, cough, anosmia, ageusia	PLEX was held, home regime continued	No respiratory support required	No exacerbation

Abbreviations: MGFA, Myasthenia Gravis Foundation of America; MG, myasthenia gravis; AChR-Ab, acetylcholine receptor antibody; AZA, azathioprine; HCQ: hydroxychloroquine; AZM, azithromycin; TOZ, tocilizumab; MMF, mycophenolate mofetil; Pred, Prednisone; CTX, ceftriaxone; IVIG, intravenous immunoglobulin; MuSK-Ab, muscle specific tyrosine kinase antibody; CTD, connective tissue disease; PLEX, plasmapheresis.

mental oxygen. Two patients showed definite signs of MG exacerbation on examination, however, such an impression could have been hindered by the need for ventilation and sedation in COVID-19 patients with severe pulmonary dysfunction. Outcomes were fairly good in six patients, with only one patient remaining intubated at day 35.[35]

Acute Myelitis

So far there has been no case reports of a motor neuron disorder associated with COVID-19 infection. Two cases of myelitis have been reported [36,37]. Zhao et al.[36] described a 66-year-old man who developed lower extremity weakness with bowel and bladder incontinence followed by flaccid lower extremity paralysis, hyporeflexia, and a thoracic sensory level. Spinal cord imaging and CSF studies were not performed on this patient. He was treated empirically with IVIG and methylprednisolone, which led to some clinical improvement. Munz et al.[37] described a 60 year-old-man who presented with lower extremity weakness and bladder dysfunction 8 days after developing respiratory symptoms. CSF studies revealed a lymphocytic pleocytosis and negative SARS-CoV-2 PCR testing. MRI spine imaging revealed T2 hyperintensity in the thoracic spinal cord. He was treated with methylprednisolone which led to clinical improvement.

Management Considerations in Neuromuscular Patients Receiving Immunotherapy

Neuromuscular patients who are on immunosuppressive and immunomodulatory agents as well as those with respiratory and/or bulbar dysfunction secondary to neuromuscular disease should be considered high risk for severe COVID-19 infection and complications.[5,38] Patients should be encouraged to notify their healthcare provider immediately if there are signs suspicious for COVID-19 infection. Although there are currently no evidence-based guidelines for the management of neuromuscular disease in the current COVID-19 pandemic, there have been recommendations made by the French Rare Health Care for Neuromuscular disease Network (FILNEMUS) as well as recommendations made in a recent review article in Neurology by Guidon and Amato.[5,39] Proposed treatment strategies for initiating and managing immunosuppressants in neuromuscular patients are summarized in Table 3.

An MG expert panel has made recommendations for the management of MG patients during COVID-19, stating that therapy decisions should be individualized and made jointly with the patient's overall healthcare team.[34] The general recommendation for MG patients who contract COVID-19 is to continue current treatment, but cortico-

Table 3: Recommended adjustment of immunotherapy in neuromuscular patients.

Medication Class	Examples	Patients initiating treatment	Patients already on treatment
Corticosteroids	Prednisone, Methylprednisolone, Deflazacort	Treat at lowest effective dose	Continue therapy regimen If treated with intravenous corticosteroids, consider home infusion, intramuscular or oral dosing.
Immunosuppressive Therapy	Azathioprine, Mycophenolate mofetil, Methotrexate, Tacrolimus, Cyclosporine	Consider delaying initiation in stable patients with mild disease. Consider spacing-out lab monitoring	Continue therapy regimen
Immunomodulatory Therapy	IVIG/SCIG, Plasmapheresis	Consider initiating home infusions for immunoglobulin	Consider home infusions, reducing frequency in stable patients.
Cell depleting Therapy	Rituximab, Cyclophosphamide	Avoid initiating unless no alternative	Consider postponing infusions, spacing out dosing or switching to subcutaneous therapy
Complement Inhibitors	Eculizumab	Consider need for immunizations, exposure to facilities during infusions	Likely does not increase COVID-19 risk
Non-immunomodulatory infusions, gene therapy	Edaravone, Nusinersen/zolgensma, Patisiran/Inotersen, Lumizyme/myozyme	Consider initiating home infusions. SMA1&2 should not delay initiation of Nusinersen/Zolgensma. SMA3&4 could consider delay	Consider home infusions, risk of exposure in facilities versus risk of treatment interruption. Recommend not delaying Nusinersen/Zolgensma infusions in children, could consider delay in adolescent or adult patients.

Modified from Guido & Amato.[5]

steroid dosage may need to be increased as in stress-dose protocols.[34] If patients are hospitalized it is recommended that immune depleting agents be held, especially those that deplete B-cell lines that would directly impair development of antibody-mediated immunity to the novel coronavirus, but standard immunosuppressive agents such as azathioprine or mycophenolate mofetil may be continued, given their long wash-out period.[34] Additionally, it is important to be cautious with investigational treatments for COVID-19 in MG patients such as hydroxychloroquine and azithromycin as these have been associated with myasthenic worsening.[5,35]

Discussion

There is rapidly growing evidence that COVID-19 infection can be associated with neuromuscular complications, and thus neurologists and clinicians should be vigilant of these manifestations. The precise mechanism of coronavirus induced neurological and neuromuscular complications are not completely understood. Several theories have been postulated including neurotropic mechanisms of direct viral invasion of the peripheral nervous system versus immune mediated injury.[5,40] Both SARS-CoV-1 and SARS-CoV-2 use the angiotensin converting enzyme 2 (ACE2) to gain entry into the cells.[43] ACE2, which plays a critical role in the renin-angiotensin-aldosterone system, has been identified on a variety of human organs particularly lung epithelium and small intestine enterocytes, providing an entry point for the virus.[43] ACE2 receptors are also expressed in the nervous system including membranes of spinal cord neurons, as well as skeletal muscle.[4,36,43] There is speculation that ACE2 may serve as a mechanism for neurologic complications seen in COVID-19 leading to central nervous system involvement including acute myelitis.[4,36,37] However, it is unclear whether muscle symptoms described in COVID-19 are related to viral invasion via ACE2 located on skeletal muscle or due to the immune response causing up-regulation of cytokines leading to inflammation and muscle damage.[4] Future investigation as well as long-term follow up of patients with neuromuscular complications associated with COVID-19 will likely clarify our understanding and improve management strategies for these patients.

Apart from hyperCKemia and myalgia, GBS appears to be the most commonly described neuromuscular complication associated with COVID-19. It is speculated that there is an autoimmune reaction in which SARS-CoV-2 elicits an immune response targeting self-epitopes leading to nervous system involvement described as "molecular mimicry."[11,13,18] Such mechanisms have been previously proposed in bacterial or viral infections that commonly precede GBS (e.g., Campylobacter, cytomegalovirus, Epstein-Barr virus and Zika virus).[5,22,41] COVID-19 could have a para-infectious association with GBS rather than the more recognized post-infectious pattern classically reported. All 15 GBS patients reported had negative CSF SARS-CoV-2 PCR testing, arguing against direct viral invasion or intrathecal viral replication. Improvement with immunotherapy and perhaps the discovery of GD1b antibodies in one patient favor an immune mediated mechanism.

It is important to realize that preceding COVID-19 symptoms may not be evident prior to the onset of GBS in some patients.[13,23] These patients could be asymptomatic carriers, or they could have an overlapping COVID-19/GBS course. COVID-19 should be considered in the differential diagnosis for patients presenting with acute neurologic symptoms suggestive of GBS, even in cases without preceding respiratory distress.

A significant portion of patients with COVID-19 develop respiratory failure in need of long ICU stay. It will also be important to study an association of COVID-19 with the possible occurrence of critical illness myopathy and critical illness neuropathy common to patients who require intensive care management.

Finally, neuromuscular patients that are on immunosuppression or those with respiratory or bulbar dysfunction who should be considered as high risk for severe complications of COVID-19 should be judiciously monitored. At this time, recommendations for immunotherapy adjustment are mostly speculative. Data collection via large case series collection or disease registry is needed before evidence-based recommendations can be made.

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Rhabdomyolysis and COVID-19 Infection: Is It Due to Statin Use or Anti-TIF1-y Antibodies?

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ABSTRACT

Coronavirus disease 2019 (COVID-19), now a global pandemic, has infected millions of people and caused hundreds of thousands of deaths. Neurological presentation of the novel coronavirus includes headaches, seizures, myalgias, hyposmia, ageusia, etc. Guillain-Barre Syndrome (GBS) and its variant, Miller Fisher Syndrome, have been reported in COVID-19 patients presenting with lower limb weakness, paresthesia, facial diplegia, and ataxia. Most recently, large vessel occlusion strokes were seen in infected younger patients without vascular risk factors. We present a novel case of rhabdomyolysis associated with COVID-19 infection in a patient on atorvastatin, in whom we detected positive anti-transcriptional intermediary factor 1 gamma antibodies (anti-TIF1-y Ab). Bilateral upper and lower extremity weakness improved with aggressive fluid administration and intravenous immunoglobulin (IVIg) at 0.4mg/kg for a total of 5 days. Interrupting a strong cytokine response with IVIg early on during the disease may have led to rapid improvement.

Keywords: *COVID-19, SARS-CoV-2, rhabdomyolysis, myositis, inflammatory myopathy, anti-TIF1-y antibody.*

Background

Coronavirus disease 2019 (COVID-19), the disease caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has come a long way since it was first discovered in several patients in Wuhan, China on December 2019.[1] Now a global pandemic, it has infected millions of people and caused hundreds of thousands of deaths. Over a short span of time, the virus has revealed its nature, presenting with more than just severe respiratory symptoms. Neurological symptoms such as headaches, seizures, and loss of consciousness, hyposmia, myalgias, and ageusia have been reported to be associated with this novel virus.[2-6] In Italy, one of the most severely hit by the pandemic, five patients with COVID-19 presented with lower limb weakness and paresthesia, with one patient presenting with facial diplegia and ataxia, consistent with Guillain-Barre Syndrome (GBS)[7]. Miller Fisher syndrome, a variant of GBS, was described on a patient in Spain.[8] Most recently, large vessel occlusion strokes have been seen in younger patients with COVID-19 who did not have significant risk factors[9]. Indeed, this novel virus has caused a myriad of neurological symptoms, and neurologists are presented with the challenge of managing these patients without specific guidelines and with limited current data. We present a novel case of rhabdomyolysis associated with COVID-19 infection in a patient on atorvastatin, no rash but a positive anti-TIF1-y antibody titer found on myositis panel.

Case

A 69-year-old female was admitted to our hospital with a one-week history of progressive, severe arm and leg weakness and unsteadiness. She endorsed difficulty lifting her arms above her shoulders, with associated muscle pain. She had a recent normal mammogram. She also reported difficulty swallowing with both liquids and solid foods. She had a low grade fever at 99.1 F, tachycardia, as well as mild cough, which prompted a virus screen. Influenza A and B rapid testing were negative, but her PCR for SARS-CoV-2 came back positive. A computed tomography angiogram (CTA) scan of the chest was done, which revealed linear opacities involving the right upper lobe and both lower lobes, and several areas of minimal non rounded ground glass opacities involving the dependent aspects of both lobes. There was no evidence of pulmonary embolus. There were no physical or laboratory findings indicative of dehydration. Her inflammatory markers were elevated: D-dimer of 4,281 ng/mL (215-500 ng/mL), and C-reactive protein (CRP) of 1.6 mg/dL (0-0.3 mg/dL). Her creatinine kinase (CK) was elevated at 4,499 U/L (26-192 U/L), along with serum myoglobin at 2,132 ng/mL (13-17 ng/mL), and aldolase of 14.1 (1.5-8.1 U/L). She did not have any myoglobinuria, and her urine was negative for red blood cells (RBCs).

Neurology was consulted for her weakness and dysphagia. She was alert and oriented on initial examination, without dysarthria or aphasia noted, but her speech was hypophonic. Although there was no facial asymmetry nor ptosis at rest, she had some weakness of her facial musculature, with some air escaping when puffing cheeks. She had no trouble with eyelid closure. Bilateral shoulder flexors and the rest of her upper extremity proximal muscles were 3-/5 on manual

muscle testing, and 4+/5 distally for both wrists and fingers. Her hip flexors were bilaterally 3/5, and 4+ /5 on knee flexion, extension, as well as ankle dorsiflexion and plantarflexion bilaterally. She endorsed muscle pain on movement which may have somewhat influenced her effort during testing. Sensory examination was normal to light touch and temperature. Reflexes were 2 both for upper limbs, 1 for both knees, and were absent at the ankles bilaterally. She was able to walk with slow gait and with some assistance. MRI of her brain showed an incidental small meningioma with very minimal mass effect on the inferior frontal falx. Acetylcholine receptor antibody (Ab) and muscle specific antibody (MuSK) were both negative. Myositis panel was normal, except for anti-TIF1-y (p155/140) Ab (*Table 1*). She did not present with any rashes, nor does she have a history of cancer. As the patient was taking 40mg of atorvastatin for several years for dyslipidemia, 3-hydroxy-3-methylgutaryl coenzyme A reductase (HMGCR) Ab was obtained to evaluate for statin-associated autoimmune necrotizing myopathy (SANAM), which was negative. Atorvastatin was stopped on admission. Rheumatologic labs were also obtained and were negative, including ANA, Rheumatoid factor, ANCA vasculitis panel, RNP ab and anti-Smith ab.

Throughout the admission, the patient's respiratory status remained stable, her oxygen saturation levels well over 90% on room air. No antibiotics were given, and she was placed on IV fluids for her rhabdomyolysis. However, on Day 4 of admission, her CK levels continued to rise, reaching its peak of 5,456 (26-192) U/L, despite aggressive hydration and supportive care. She was then started empirically on immunoglobulin (IVIg) at 0.4mg/kg for 5 days. The day after the first dose, her CK started to trend down. She denied any side effects with the IVIg treatment. After completing her immunotherapy on Day 8 of admission, the patient noted subjective improvement of her lower extremity weakness. On Day 12 of admission, her hip flexors were 3+ to 4/5 bilaterally approximately, and she had increased range of motion on shoulder flexion and abduction. Functionally, her walking was better, and she had increased use of her arms without significant pain. Her CK on Day 12 was 2,617 (26-192) U/L. She was discharged on Day 21 of admission, and has a follow up visit in the neurology clinic.

Discussion

Our patient presented with the typical viral prodrome of myalgia and generalized muscle weakness while on chronic stable statin dosage. Rhabdomyolysis is not as widely reported with COVID-19 as myalgias. In fact, myalgia is a very common symptom in COVID-19, with up to 44% of confirmed cases in an institutional review of by Huang, et al.[5] However, Guan et al reported only 2 patients with rhabdomyolysis (muscle pain or muscle weakness, and CK > 10 times the upper limit of normal) out of 1099 with confirmed COVID-19 from 552 different hospitals in mainland China.[4] Beydon, et al presented another case in France, where the patient presented with myalgia and initial CK of 25,384 IU/L. MRI of the lower extremity showed muscle edema and their patient was treated with IV fluids.[10]

Lin, et al recently postulated that B lymphocyte reduction might occur during the early phase of severe COVID-19 infection, together with T lymphocyte reduction, as well as an increase in inflammatory cytokines and D-dimer.[11] This

Table 1: Myositis Panel

Antibody	Result
MI-2	Negative
PL-7 (threonyl-tRNA synthetase)	Negative
PL-12 (alanyl-tRNA synthetase)	Negative
P155/140 (TIF1-gamma)	Positive
EJ (glycyl-tRNA synthetase	Negative
Ku	Negative
SRP (Signal Recognition Particle)	Negative
OJ (isoleucyl-tRNA synthetase)	Negative
SAE (SUMO activating enzyme)	Negative
NXP-2 (Nuclear Matrix Protein 2)	Negative
MDA5 (CADM-140)	Negative

immune response is the basis for their recommendation to initiate high dose IVIg at 0.3-0.5g/kg per day for 5 days, to potentially interrupt the storm of inflammatory factors and enhance immune function.[11] While our patient in retrospect had milder COVID-19 disease, she was initially treated with IV fluids but continued to have an increase in CK levels. After receiving IVIg, her CK declined and her myalgia and weakness improved. While D-dimer was highly elevated, our patient was anticoagulated. She did not experience any thrombotic or other adverse event as a result of IVIg. The administration of IVIg in COVID-19 patients presenting with other neurological conditions has been shown to be safe and effective as well with concomitant anticoagulation. The five COVID-19 patients earlier mentioned with confirmed GBS from Italy all received IVIg. Two had a second course of IVIg, and one had subsequent plasma exchange (PLEX).[7] A Miller Fisher case with COVID-19 infection described in Spain recovered completely following IVIg treatment.[8]

We initially did not consider an autoimmune muscle injury mechanism in this case given negative serologies (ANA, RF, etc.) and swift response to IVIg. An interesting later finding in this case, however, was the presence of anti-TIF1-y antibody on myositis panel. Anti-TIF1-y ab is one of the autoantibodies associated with inflammatory myopathies, particularly in dermatomyositis. Adult dermatomyositis patients with anti-TIF1-y have a higher frequency of cancer, up to 70%, as compared to those who are antibody negative.[14] Our patient did not present with the typical skin lesions associated with dermatomyositis. She also did not have a history of cancer, no evidence of cancer on chest CT or prior mammogram. Masiak et al, in a single center study of 80 patients with a positive autoimmune inflammatory myopathy profile, 11 were positive for anti-TIFI-y antibodies, 6 were diagnosed with dermatomyositis, and 2 had a neoplasm. Interestingly, one patient in that study presented with rhabdomyolysis with severe muscular weakness.[12] Therefore, we suspect that the immune response may have contributed to our patient's rhabdomyolysis.

We hypothesize that the immune activation in the setting of milder COVID-19 infection may have resulted in this positive antibody titer. This complex infection triggers the recruitment of macrophages and monocytes, the release of cytokines and adaptive T and B cells to target cells.[15] Most cases of COVID-19 are mild, as was the case in our patient, and this inflammatory process is capable of resolving this infection. This is thought to be the result of a well-functioning immune system. We think that our patient who had a milder infection was able to generate an adequate immune response to COVID-19, part of which was the de novo production of anti-TIF1-y cross-reacting antibodies. Alternatively, that COVID-19 uncovered a predisposition to myositis in the setting of a mild infection cannot be excluded.

Our case report has several limitations including lack of outpatient follow up. In addition, electromyography and nerve conduction study (EMG/NCS) would have been a useful diagnostic tool to assist us in further characterization of the patient's muscle weakness. In addition, a muscle biopsy would also have been beneficial in describing the histopathological features. However, the limitations posed by isolation precautions, as well as strained health resources and organizational barriers due to the pandemic hindered us from performing any of these procedures.

In conclusion, rhabdomyolysis, as reported herein, is rare in the setting of acute COVID-19 infection. We cannot exclude that statin therapy may have triggered rhabdomyolysis. However, the elevation of anti-TIF1-y antibody titer suggests that COVID-19 infection has the potential to uncover or even trigger an autoimmune response targeting muscle. An international database is critically important to better capture rare neuromuscular complications of COVID-19 and to better characterize the acute and long-term neuromuscular sequelae of this pandemic.

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Transthyretin Familial Amyloid Polyneuropathy Mimicking Chronic Inflammatory Demyelinating Polyneuropathy

Familial Amyloid Polyneuropathy Case Report

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Introduction

Patients with typical Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) experience motor and sensory deficits that progress insidiously over a course of at least eight weeks, with diminished or absent reflexes.[1,2] There have been several revisions to the diagnostic criteria for CIDP over the years to aid clinicians in making this diagnosis, with variable sensitivity and specificity.[3-6] Given this, clinicians need to be aware of red flags that would lead one to consider an alternative diagnosis, such as Transthyretin Familial Amyloid Polyneuropathy (TTR-FAP).[7]

Systemic amyloidosis is caused by pathologic deposition of misfolded proteins, which leads to widespread tissue and organ damage. Amyloidosis can be genetic, acquired by primary hematological disorder, reactive, or related to natural aging.[8] FAP is the most common hereditary form of systemic amyloidosis, which is caused by mutations in TTR, and less commonly apolipoprotein A1, and gelsolin. TTR-FAP is inherited in an autosomal dominant fashion, but has variable penetrance.[9] Yet in late-onset cases, only one-third have a positive family history.[10] Transthyretin is primarily produced in the liver, but a small amount is made in the choroid plexus and retina. It functions to transport thyroxine and retinol binding protein, which incidentally is how the name transthyretin was derived. All known mutations are missense point mutations, that lead to the destabilization of the TTR tetramer and deposition of insoluble TTR oligomeric amyloid protein aggregates. This deposition can cause multiorgan dysfunction, affecting peripheral nerves, heart, liver, eyes, and leptomeninges. Phenotypic variation exists, however TTR-FAP classically presents as a length dependent neuropathy, predominantly small fiber sensory in early-onset cases, in patients prior to age 50. This group also tend to have prominent autonomic and cardiac dysfunction. Late-onset cases are more difficult to identify due to less prominent autonomic symptoms and in twenty percent of cases, a weakness pattern mimicking CIDP.[11]

Case Report

A 75-year-old right-handed female presented with a 5-year history of progressive extremity numbness and weakness. She first noticed numbness and tingling in her fingers and toes, that progressed to her mid arms and thighs. She also noticed imbalance and difficulty climbing stairs that progressed to weakness in her arms. She also reported unintentional weight loss, orthostasis, and difficulty emptying her bladder. She was previously diagnosed with CIDP, but failed to respond to corticosteroids or IVIG, and was recently placed on azathioprine at an outside clinic. There was no family history of neuropathy. Neurologic exam revealed symmetric moderate proximal and distal extremity weakness, with sparing of cranial and neck musculature. There was atrophy of distal extremities. On sensory examination, pinprick was diminished to elbows and knees, as well as impaired vibratory sense. Romberg was positive. Reflexes were absent to reduced throughout. Gait was wide-based and steppage.

Electrophysiological Findings

Electrodiagnostic testing showed a moderate mostly symmetric axonal and demyelinating sensorimotor peripheral polyneuropathy (Table 1). We identified > 30% temporal dispersion at left medial nerve (distal and proximal duration 5.4 ms and 7.1 ms, respectively), and increased distal CMAP duration of left ulnar nerve at the wrist (data not shown in the Table) was 7.3 ms. This value was considered prolonged per EFNS/PNS 2010 Criteria since it was ≥ 6.7 ms. In conjunction with the clinical presentation, fulfilled the criteria for definite CIDP based on EFNS 2010 criteria.

Additional Investigation

Cerebral spinal fluid protein was 73 mg/dL. Given refractoriness to two of the first line therapies for CIDP and due to the presence of mild autonomic symptoms, we evaluated the patient for CIDP mimics and suspected an alternate diagnosis. The patient underwent a sural nerve and vastus lateralis muscle biopsy. The nerve biopsy revealed severe loss of large caliber myelinated never fibers and am-

Table 1: Electrophysiologic Findings. Sensory nerve, motor nerve conduction studies, and need electromyography show asymmetric axonal demyelinating moderate peripheral polyneuropathy. There is left median nerve temporal dispersion along with increased distal CMAP duration of left ulnar nerve that fulfills EFNS 2010 criteria for CIDP. Rec: recruitment, mld: mild, mod: moderate, sev: severe, dec: decreased, ULN: Upper limit of normal, LLN: Lower limit of normal.

Sensory nerve conduction	*Peak Latency [ms] (ULN)*	*Amplitude [μV] (LLN)*	
Median.R to Index	6.0 (3.7)	9 (15.0)	
Ulnar.R to Digit V	2.9 (3.1)	6 (5.0)	
Radial.R to Anat Snuff Box	NR (2.8)	NR (10.0)	
Sural.R to Ankle	4.5 (4.5)	2 (3.0)	
Sural.L to Ankle	NR (4.5)	NR (3.0)	
Motor nerve conduction	*Onset Latency [ms] (ULN)*	*Amplitude [mV] (LLN)*	*Conduction Velocity [m/s] (LLN)*
Median.R to APB. Wrist Elbow	4.9 (4.5) 9.9	2.8 (4.5) 2.7	41 (49)
Ulnar.R to ADM Wrist B. Elbow A. Elbow	3.4 (3.6) 6.5 8.7	2.2 (5.0) 2.6 2.2	50 (50) 48
Peroneal.R to EDB. Ankle B. Fib Head A. Fib Head	4.3 (6.6) 12.0 15.0	0.4 (2.0) 0.3 0.3	36 (41) 40
Peroneal.R to TA. B. Fib Head A. Fib Head	3.2 (4.0) 6.3	1.5 (3.0) 1.3	37 (40)
Tibial.R to AH. Ankle Pop. Fossa	4.7 (6.0) 13.4	2.2 (4.0) 2.0	43 (57)
Median.L to APB. Wrist Elbow	4.4 (4.5) 8.6	4.8 (4.5) 3.4	50 (49)
Ulnar.L to ADM. Wrist B. Elbow A. Elbow	3.1 (3.6) 6.6 8.6	4.4 (5.0) 4.3 3.9	 52 (50) 50

Muscle	*Act*	*Fibs*	*PSW*	*Fasc*	*Poly*	*Amp*	*Dur*	*Rec*
Tibialis anterior. R	-	2+	2+	-	+	+	+	-
Gastroc Med H. R	-	2+	2+	-	+	+	+	mod dec
Vastus lateralis. R	-	1+	1+	-	-	+	+	sev dec
Gluteus medius. R	-	3+	3+	-	+	-	-	mld dec
Lumbar paraspinal; low. R	-	2+	2+	-				
1st dorsal interossei. R	-	3+	3+	-	+	-	-	mod dec
Biceps brachii. R	-	3+	3+	-	+	-	+	mod dec
Deltoid. R	-	3+	3+	-	+	+	+	mod dec
Extensor indicis proprius. R	-	2+	2+	-	+	+	+	mod dec
Triceps brachii. R	-	1+	1+	Few	+	+	+	mld dec

yloid deposition within the endoneurium by Thioflavin-S and Congo Red stains (not shown). The muscle biopsy identified clusters of atrophic myofibers. It also revealed amyloid deposition by Thioflavin S and Congo Red stains, and established this as transthyretin via immunohistochemical reaction (Figure 1). Genetic testing for TTR sequence confirmed a point mutation of A to G at position 3861 of allele 1. This mutation led to missense mutation of threonine to alanine at codon position 60, a known pathologic mutation.

To investigate for systemic involvement, an echocardiogram was preformed and demonstrated speckled myocardium, valvular thickening, and moderate concentric left ventricular hypertrophy consistent with amyloid deposition. She was evaluated by our liver transplantation team, but given her widespread disease involvement and age, she was not a candidate for liver transplant. She was started on diflunisal since at the time of her diagnosis, as neither antisense oligonucleotide therapy nor small interfering RNA was available. Genetic counselling was provided and she was lost to follow.

Discussion

This case highlights the importance of re-evaluation in patients who otherwise fit the diagnostic criteria for CIDP and are either refractory to first line therapies or have unusual manifestations (family history, dysautonomia, etc.). Additionally, this case displays some common clinical features and pitfalls of patients with late-onset TTR-FAP. TTR-FAP is a heterogenous disorder, with wide variation in age of onset, neurologic and systemic manifestations. In late-onset cases, the majority are without a positive family history. Therefore, a clinician needs a high index of suspicion, otherwise there can be significant delay in diagnosis. An accurate and timely diagnosis is particularly important

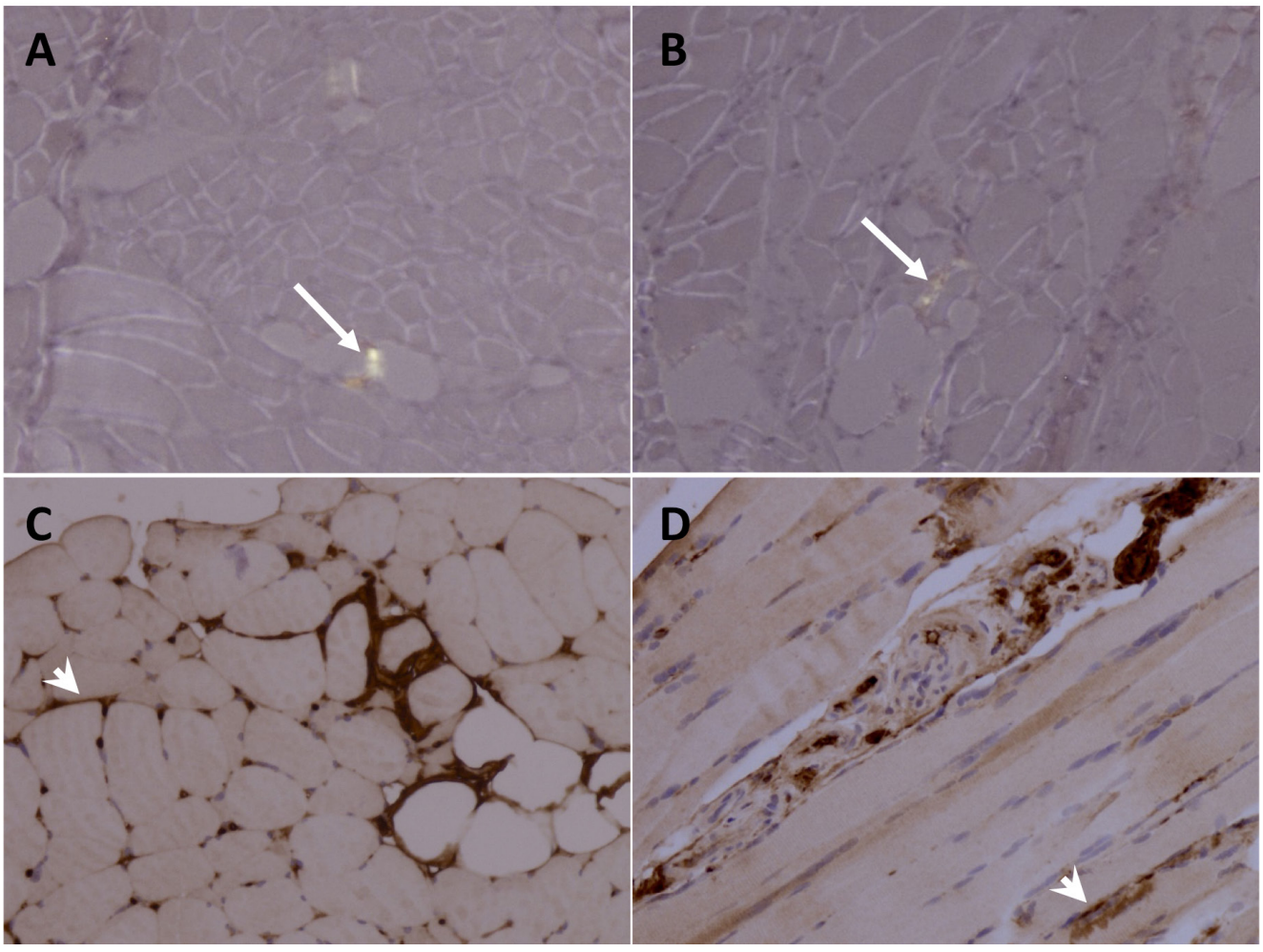

Figure 1. Vastus lateralis muscle biopsy sections. Small amyloid depositions are shown within blood vessel wall (A) and along muscle fiber surface (B) by Congo red stain under polarized light (arrow). Arrowheads in C and D show transthyretin antibody reaction, which identifies amyloid along muscle fiber surface (C) and within muscle cells (D).

since several treatment options are currently available for TTR-FAP.[12-15] In a study of patients presenting with sporadic onset in non-endemic areas, the mean time to diagnosis was four years.[11] In patients with autonomic dysfunction, cardiomyopathy, and lack of response to adequate therapy for CIDP, the diagnosis of TTR-FAP should be considered as to not delay clinical diagnosis, expose patient to unnecessary therapies, nor delay effective novel therapies. Recent expert consensus recommendations to improve diagnosis of TTR amyloidosis with polyneuropathy were published to avoid confusion with CIDP, idiopathic axonal polyneuropathy, lumbar spinal stenosis, and, more rarely, diabetic neuropathy and AL amyloidosis.[16] The challenge in recognition of TTR amyloidosis is more prominent in non-endemic areas, namely outside Portugal, Japan, Sweden, and Brazil. A high index of suspicion is required.

Currently used diagnostic criteria for CIDP are highly sensitive with 80 to 85% specificity. The PREDICT study was a multicenter randomized controlled trial of 6 monthly pulses of dexamethasone versus 8 months of daily prednisolone.[17] In this study, 10/39 (26%) were cured (>5 years off treatment) or in remission according to the CIDP Disease Activity Status scale after 1 or 2 courses of dexamethasone or prednisolone. Despite these CIDP patients being diagnosed by experts and using specified criteria, alternative diagnosis was found 7 out of 12 (58%) cases who did not respond to any therapy included 3 having hereditary neuropathy, 2 malignancy (lymphoma, plasmacytoma),1 TTR-FAP and 1 IgM paraprotein. This suggests a specificity of the ENMC diagnostic criteria for CIDP of 83%.[17,18] In another study, 44% of patients misdiagnosed as CIDP satisfied EFNS/PNS clinical criteria.[19] All of the CIDP misdiagnosis fell in the atypical CIDP group suggesting clinical criteria specificity of 80% (12/59 false positive). In addition, 15% of misdiagnosed patients satisfied EFNS/PNS electrodiagnostic criteria suggesting specificity of the electrodiagnostic criteria to be 93% (4/59 false positive).

While both CIDP and TTR-FAP can have autonomic involvement, these are milder in CIDP. For example, prominent sphincter dysfunction excludes CIDP according to the EFNS/PNS 2010 criteria.[3] In addition, certain features can help differentiate the two clinically. An echocardiogram or cardiac magnetic resonance imaging can be useful to identify evidence of an infiltrative cardiomyopathy, common in TTR-FAP and absent in CIDP. More recently, 99mTechnetium-pyrophosphate imaging (Tc-PYP) is thought to be more sensitive to detect amyloid deposits than other cardiac imaging modalities. In a study of 45 subjects (12 immunoglobulin light-chain amyloidosis [AL], 16 ATTR wild type, and 17 ATTR mutants), Tc-PYP cardiac imaging distinguished AL from ATTR cardiac amyloidosis.[20] Patients can have elevated CSF protein which can be supportive of the diagnosis of CIDP, however TTR-FAP rarely has an elevated CSF protein. In our case, the CSF protein (73) was > 60 mg/dl but many clinicians would consider this level expected for her age of 75. Lastly, 70%-90% of patients with CIDP respond to one or more of the standard therapies, which include corticosteroids, IVIG or plasma exchange.[21] Therefore, lack of treatment response should prompt re-evaluation of the diagnosis.

Recently, Lozeron and colleagues (2018) identified clinical features that could predict demyelinating TTR-FAP.[22] In their cohort, 13 of 84 patients (15%) of French ancestry had late-onset demyelinating TTR-FAP. They identified several suggestive features. Our patient had some of these features including dysautonomia, small fiber sensory loss above the wrists, and upper extremity weakness. Notably, our patient demonstrated sensory ataxia and did not have significant neuropathic pain, which differed from what was found in their demyelinating TTR-FAP cohort.[22]

Our patient was found to have T60A mutation. This mutation is thought to have originated in northwestern Ireland and has now become prevalent in the United States, which it is referred to as Appalachian amyloidosis.[23] It is estimated only 1% of patients worldwide with FAP have this mutation. A prospective study of sixty patients with the T60A mutation showed that a family history of amyloidosis was only present in 37%, median age of symptom onset was 63 years old, and the most common presenting symptom was cardiac.[24] Likewise, cardiomyopathy is nearly twice as common in patients with T60A mutation as compared patients with V30M mutation, the most common mutation worldwide.[23,25] These studies have also demonstrated a link between prevalent cardiac involvement with shorter mean survival. Additionally, non-V30M patients as compared to V30M group have a worse 5-year survival after orthotropic liver transplant. Even after liver transplant, progression of disease has been found to occur, which is thought to be due to wild-type TTR deposition onto existing pathologic amyloid deposits. Thus, the need for alternative therapies exits. Currently there are two TTR stabilizing drugs, tafamidis and diflunisal, and recently approved disease modifying drugs, inotersen and patisiran.[12-15]

Conclusion

Late-onset proximal and distal weakness, with or without autonomic features, that is refractory to adequate first line therapy for CIDP, despite negative family history should raise clinical suspicion for FAP.

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Progression of Charcot-Marie-Tooth Foot and Hand Deformities in a Family with CMT1A

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Keywords: *Charcot-Marie-Tooth, Hereditary Neuropathy, Neuropathy, Pes Cavus.*

Case Summary

A 6-year-old girl presented to our clinic with her mother and grandmother to establish care for Charcot-Marie-Tooth Type 1A (CMT1A), an autosomal dominantly inherited sensorimotor neuropathy due to PMP22 duplication. The progression of pes cavus, characterized by the increasing plantar concavity over time, and hammertoe deformities, due to the insidious atrophy of the intrinsic foot musculature, are observed in this family.[1] In addition to pedal deformities, our patient has ankle dorsiflexion weakness, requiring bilateral ankle-foot orthoses. Distal weakness and pes cavus deformity are the most common initial signs of CMT1A.

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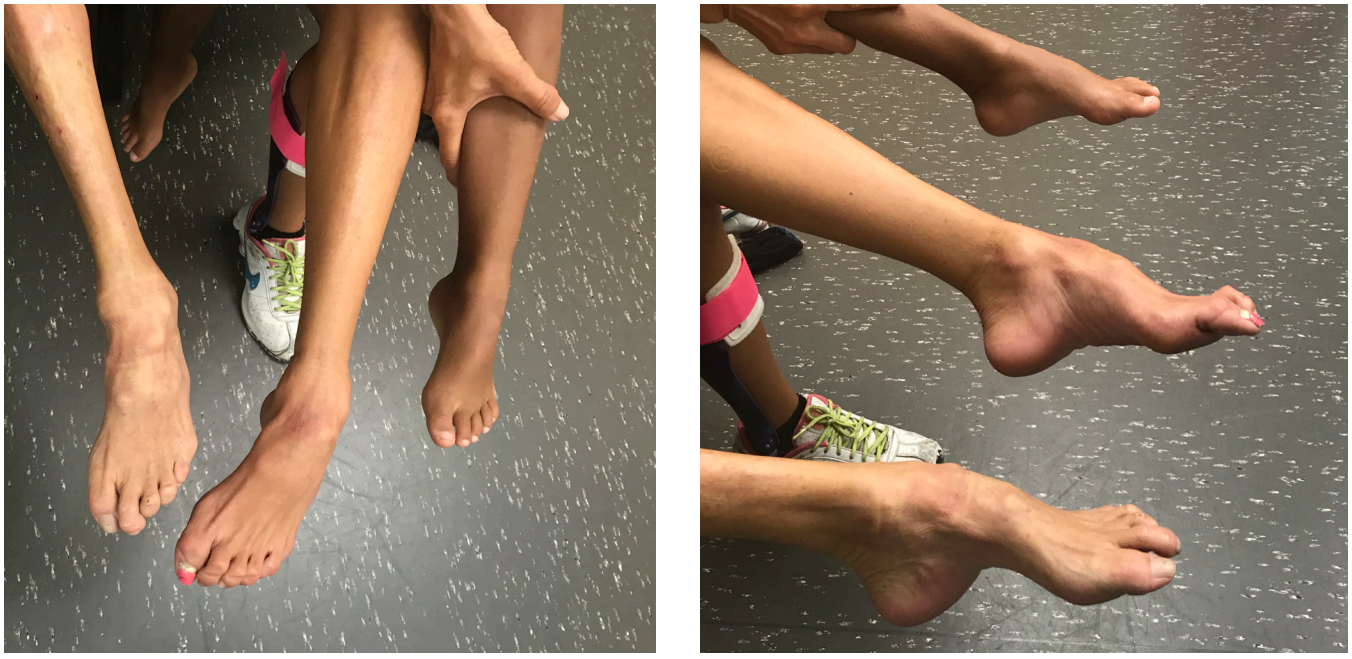

Figure 1 Legend

Progression of foot deformities in a family with CMT1A. A. The patient's feet (top) shows the onset of pes cavus and hammertoes, which become progressively more prominent in her 29-year-old mother (middle) and 50-year-old grandmother (bottom). B. The grandmother also has distal leg atrophy, resulting in stork-leg (or inverted champagne bottle) appearance.

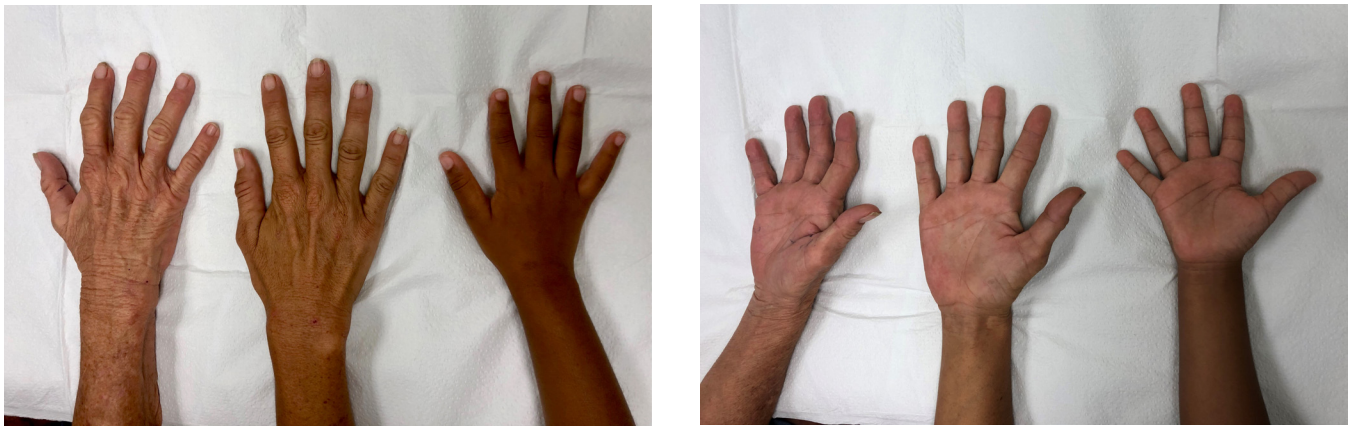

Figure 2 Legend

Progression of hand deformities in the same family. The patient's hand (top) demonstrates preserved intrinsic hand muscle bulk. Over time, there is loss of the dorsal interossei and lumbrical muscles in her mother (middle) and grandmother (bottom).

Comparative Effectiveness Study of Treatment of Sialorrhea in Patients with ALS

Richard J. Barohn, Byron Gajewski, Jeffrey Statland, Laura Herbelin, Russ Waitman, Kim Kimminau

Submitted to PCORI for the Assessment of Prevention Diagnosis and Treatment RFA, submitted 2014

Key words: *PCORI, ALS, Sialorrhea, Comparative Effectiveness*

Author/department/institution:
Richard J. Barohn MD
Department of Neurology
University of Kansas Medical Center
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Type of Grant: PCORI: Assessment of Prevention, Diagnosis and Treatment Options

Date Submitted: 2014

Date of Review: Spring 2015

Grant was: Not funded

Our team has been trying to get a comparative effectiveness grant from PCORI to determine which is the most effective therapy to manage excess saliva in ALS patients. Our attempts have not been successful. We have submitted the proposal in different forms several times. For this "proposed stuff" section we are publishing the version that got us closer to getting PCORI funding. In this application we proposed a four-arm study comparing glycopyrrolate 1 mg three times a day; amitriptyline 25 mg at bedtime; atropine 1% sublingual drops, 2 drops three times a day, and scopolamine transdermal patch (1.5 mg) every 72 hours. We proposed a Bayesian adaptive design with an approximate target of 125 patients in each group. Our primary endpoint was what we called a Patient Reported Saliva Management Scale (PRiSM) that was used in the study led by Carlayne Jackson of Myobloc in the Treatment of Sialorrhea in Patients with ALS (Muscle Nerve 2009:39:137-143). As in all PCORI projects we had a patient engagement group and we had our patient engagement faculty leader talks with groups of ALS patients and families about this study to get their input. They reemphasized what an important issue this is for ALS patients. The plan was to utilize the ALS clinic sites in the Greater Plains Collaborative which was one of the PCORnetworks that was led by Dr. Russ Waitman at the University of Kansas and included academic medical centers in the Midwest and Texas.

The reviewers of the grant clearly liked it and gave it an overall score of 26, which put the grant in the first quartile of PCORI studies in that round. Usually a 1st quartile study is funded. But some of the PCORI leaders did not think we could do such a study and on phone conversations insisted a four-arm Bayesian design study would be too difficult to perform and would likely not come up with a definitive answer. We provided additional information to PCORI but in the end the project was not selected for funding. Based on the feedback we resubmitted the project but with only 3 arms, and this time the score was 56! We kept trying by sending letters of intent to PCORI on future cycles but could never get approval to resubmit the project. The last two times we submitted letters of intent we changed the title to "SoPoDoP" – this stood for Shot or Patch or Pills or Drops and we included Botox as one of the 4 arms. We still think this is one of our best grant titles. But for this "proposed stuff" section we are publishing the grant that got the closest, almost funded, should have been funded score. We think this is still a major issue for ALS patients and that the PCORI structure would have been ideal to study this important clinical question. But we have given up trying to resubmit this project. We will leave it to some other neuromuscular clinical scientist to try again at some point. We hope the publication of this grant and the critiques will help that person or team, and we hope you all will enjoy reading our proposal.

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard J.

PCORI RESEARCH PLAN TEMPLATE

Please provide the information requested below. Detailed instructions are included in the Application Guidelines for this PFA.

RESEARCH STRATEGY

Describe your research strategy and plan, in detail, and demonstrate how your proposed study is responsive to this PFA. Include the relevant methodology standard citations (e.g., "PC-3"), as identified in the PCORI Methodology Report. Refer to the methodology report for explanations about the standards. The template shows where merit reviewers may expect to find information to evaluate each of the merit review criteria, which are delineated in the PFA. Do not exceed 20 pages. You may delete this instructional textbox.

A. Background

- *Describe the impact of the condition on the health of individuals and populations. (Criterion 1. Impact of the condition on the health of individuals and populations)*

ALS is a rapidly progressive and invariably fatal disease affecting motor nerves in the brain and spinal cord, and has a major impact on patients, their families, and communities. ALS is a rare disease. The incidence is 2 per 100,000, and the lifetime risk of ALS is 1 in 400. (1-5) The majority of cases are sporadic (85-90%). At any given time, approximately 21,000 people in the US have ALS, and sialorrhea (drooling) affects half of them. (6) The diagnosis of ALS is based on the El Escorial criteria, which define the key clinical and electrophysiologic signs of both upper and lower motor neuron dysfunction. (7,8) Weakness and atrophy begin either in bulbar, limb or respiratory muscles and spread to contiguous regions. Respiration is usually affected late in the disease. A number of clinical characteristics are associated with faster progression and poorer survival, including onset at an older age, initial bulbar dysfunction, greater medical comorbidities, and poor respiratory function. (9,10)

While the only treatment that has been proven to slow the progression of ALS is Riluzole, there are a number of symptomatic therapies available for ALS patients: these include management of drooling, pseudobulbar affect, use of gastrostomy for nutrition, and non-invasive ventilation (NIV) for breathing. (11,12) Focus groups with patients from the Greater Plains Cooperative (GCP) ALS specialty clinics identified drooling as a significant problem affecting quality of life. Drooling is fundamentally related to loss of the ability to swallow. Difficulty swallowing leads to pooling of saliva in the mouth, which patients interpret as an 'increase' in saliva. This pooling can lead to greater frequency of choking. Choking is a very frightening event to the patient as well as to their caregiver and family members, and can lead to aspiration pneumonia. Excessive drooling may result in discomfort and wetting clothing that requires constant management with a cloth, tissue or handkerchief to their mouth for absorption. This may make some patients feel infantilized, dependent on others and even humiliated or ostracized.

The American Academy of Neurology (AAN) has published practice parameter guidelines for symptom management in ALS, including drooling. (13,14) A number of anticholinergic drugs are used in ALS clinics to decrease sialorrhea. Based on the absence of published data, we conducted a survey to determine the most frequently prescribed medications for drooling in ALS (communication among 600 neuromuscular experts through a website founded by Richard Barohn, MD; Ricks Real Neuromuscular Friends; www.rrnmf.com): 53% of physicians prescribe glycopyrrolate; 26% amitriptyline; 18% using atropine sublingual drops; and 3% scopolamine patch. Additional treatments for drooling include botulism toxin and radiation therapy to salivary glands. (15,16) Although demonstrating some benefit, botulism toxin and radiation therapy are not ideal first line options for drooling because they are more invasive than medications with more severe potential side effects, they are often not covered by insurance, they require standardized technique, and are not universally available.

- Despite the wide use of anticholinergic drugs for drooling in ALS specialty clinics, no comparative effectiveness studies have been done to determine which medication is most effective for drooling with the fewest side effects.

The ALS clinical and research community have agreed on standard clinical measurement tools to assess outcomes, and using these tools, we envision that the GPC and selected sites from the Patient-centered Scalable National Network for Effectiveness Research (pSCANNER) can do comparative effectiveness studies in the symptomatic management of ALS. Standard functional and symptom scales include: the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R), ALS global quality of life scale, and the Patient Reported Saliva Management Scale (PRiSM). (16-19) These scales have largely been adopted by the GPC ALS clinics at this time, and because of the simplicity of the forms, the ease of creating REDCap surveys for the forms, and a commitment from Electronic Privacy Information Center (EPIC) to make them available to clinics in the electronic medical record (EMR), it is feasible to collect them in pragmatic studies in ALS.

ALS patients are seen in either an Amyotrophic Lateral Sclerosis Association (ALSA) or Muscular Dystrophy Association (MDA) sponsored clinics, usually at tertiary care centers. Very few ALS patients are followed by individual private practice neurologists for several reasons: the disease is rare and most neurologists only diagnose one patient every year or two, and the management and support of ALS patients and their families is complex and require a multidisciplinary health care team approach that is only available at ALSA or MDA sponsored clinics. In these clinics, in addition to physicians, there are Physical Therapists, Occupational Therapists, Respiratory Therapists, Speech Therapists, Social Workers, Equipment Vendors and Dieticians, and patients see multiple providers at every visit. Each site in the GPC and pSCANNER has an ALS clinic sponsored by one or both of these two organizations – so the ALS specialty clinics can be expected to capture the majority of ALS patients in these regions.

Most of the sites chosen for this study are also members of the ALS Research Group (ALSRG) which is an organization that educates the ALS research community on new developments. Recently the ALSRG has begun to work with an EPIC research group within EPIC Systems Corporation to embed standardized ALS research forms within the EMR at ALS clinic sites across the country that use EPIC. Dr. Barohn is a member of the ALSRG committee working on this project. The president of the ALSRG (Jonathan Katz, MD) and Director of Research Informatics at EPIC (Nancy Snider, PhD) have provided a letters of support for this study. It is anticipated that while most of the study will be managed in REDCap, we will allow patients to report outcomes using the EPIC standardized forms via their EMR patient-portal where available, or via a patient-portal to the EMR that invokes the REDCap survey. The simplicity of the forms and the familiarity with the ALS scales at most ALS specialty clinics makes this approach straight-forward and feasible to implement.

- *Identify gaps in evidence*

American Academy of Neurology has published guidelines for standard of care in ALS. (20) Over half of all ALS patients experience drooling, and approximately three-quarters of them could receive benefit from using oral/transdermal medications. (6) The most common agents used are scopolamine, amitriptyline, glycopyrrolate, and atropine. (6, 20) Published guidelines suggest there is a gap in care between available symptomatic treatments for drooling, and the frequency which these therapies are offered to patients. (20) One reason for this gap is limitations in guidance of which pharmacologic treatment to choose. Cholinergic muscarinic receptor antagonists or drugs with parasympathetic properties are the current first line standard of care for drooling. (21, 22) The major patient-support organizations for ALS (the MDA and ALSA) recommend these medications as a first line therapy for drooling. However, we cannot provide information regarding the comparative effectiveness of different drugs for patients or to the physicians treating them. Despite these agents demonstrating good efficacy for drooling in the majority of ALS patients, there is still a gap in their utilization, and a number of barriers to increasing their use in practice including: 1) no studies evaluating the comparative effectiveness of different anticholinergic agents; and 2) no studies evaluating the comparative safety profile of these drugs in ALS.

B. Significance

- *Describe the potential for the study to improve health care and outcomes. (Criterion 2. Potential for the study to improve health care and outcomes)*

- *Describe how the research is focused on questions that affect outcomes of interest to patients and their caregivers. (Criterion 4. Patient-centeredness)*

Given that there is not a cure for ALS, and there are limited symptomatic treatments, it is critical to devise effective study designs to test any drug that shows promise. Put simply, the more promising drugs that are studied and screened for effectiveness, the better the chance of finding ones that will ultimately benefit people with ALS.

This comparative effectiveness trial for drooling provides an ideal opportunity to use Patient Centered Outcome Research Network (PCORNet) methods and EMR-based infrastructure to conduct pragmatic trials in the clinic workflows. Eight of the sites in the GPC utilize the EPIC EMR with electronic patient-portals which allows close development of methods and infrastructure between the health information systems and research informatics teams. In addition all sites run REDCap. A large trial of the major drugs used for drooling in these clinics has the potential to have a major impact on patient care: 1) helping patients and physicians choose the best drugs to treat drooling; 2) helping choose drugs with the most favorable side effect profile; and 3) identifying any special groups who respond differentially to treatment. In addition as the GPC and pSCANNER sites included here represent a very large population of ALS patients – this study can directly impact prescribing practices, and then results of this study can be distributed throughout the clinics, the patients support organizations (MDA and ALSA), and patient groups, maximizing the ultimate impact. Effectively treating drooling can dramatically improve the quality of life for ALS patients.

Most ALS patients will have difficulties with drooling at some point during the course of their disease. Difficulties with drooling or drugs used for drooling was identified by patients and family members of being of vital importance during our patient and caregiver focus groups, as well as routinely expressed by patients in ALS specialty clinics. The following observations also support the impact of drooling in ALS:

- Drooling has a negative impact on the patient's interaction with the community. Patients ultimately have to resort to constantly placing a paper towel, tissue or handkerchief in their mouth to absorb the saliva. This produces an unpleasant odor and the patient may feel ostracized from community and friends.
- Drooling can lead to greater frequency of choking, which is very frightening event to the patients as well as to their caregivers and family members.
- Choking episodes can lead to aspiration pneumonia – pneumonia is one of the major reasons for hospital admissions in ALS patients (from the National Inpatient Sample, 1988-2002, over 17,000 ALS hospital admissions), and increases the risk of death during hospital admissions. (23)
- Non-invasive ventilation (NIV) has been shown to improve survival and quality of life in patients with ALS. (24) A common problem noted by patients is the inability to continue to use NIV when they have a pooling of saliva in the mouth.

C. Study Design or Approach

- *Research Design, Criterion 3 – technical merit*

State the specific aims

Difficulty swallowing can lead to problems managing saliva, leading to drooling in patients with ALS. This symptom is both a social and medical burden to the patient and their family and drooling can lead to choking episodes which can cause aspiration pneumonia. While there are medications for managing drooling in ALS, the best medication with the most tolerable side effects is unknown.

Specific Aim 1: To determine which of four standardly prescribed medications is best in controlling drooling. Patients will be randomized to receive one of the following: 1) scopolamine patch (1.5 mg) transdermal every 72 hours; 2) glycopyrrolate 1 mg three times a day; 3) amitriptyline 25 mg at bedtime; and 4) atropine 1% sublingual drops 2 drops three times a day.

Specific Aim 2: To determine the tolerability of each of the four treatments for drooling in patients using clinical and patient-generated information.
Secondary Aim 1: To better understand the response to drooling medications and side effect profiles for subgroups of patients with ALS (bulbar onset versus limb onset, men versus women, etc).
Secondary Aim 2: We will conduct a survey to understand the experience with medications for drooling of patients who cannot qualify or choose not to participate in this study, but still wish to share their experiences, as requested by patients and caregivers during our patient focus groups.

Describe the plan for developing a formal study protocol

Protocol Development Plan.
Our protocol development was a multistage process: 1) the first step was seeking out patient response in our GPC network of ALS specialty clinics; 2) our next step after identifying drooling as a topic of interest to patients was to conduct a poll on a major neuromuscular message board to find out the current pharmacological strategies for treating drooling (Ricks Real Neuromuscular Friends, www.rrnmf.com, survey > 600 neuromuscular specialists); 3) convoking a protocol focus group of patients and caregivers (see section Engagement Plan, Designing the Study); and 4) creating a protocol operations committee comprised of patient representatives, site PIs, statisticians, and patient organizations (MDA, ALSA). This group will meet throughout the coming months via email and phone calls to finalize the protocol proposed in this application.

In addition plans are in place to seek patient and family member feedback of the impact of being involved in the study in patient and caregiver meetings which will occur during the conduct of the study (see Engagement Plan, Conducting the Study).

Study Design
This study is designed as an open-label, randomly allocated four arm parallel group study.

Study Objective
To determine which of four treatments are most effective in the control of drooling in patients with ALS.

Describe how you will identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants.

Patients will be sought from all ALS referral sites participating in the GPC PCORNet Clinical Data Research Network (CDRN) and select pSCANNER sites. Together these hospitals cover 30 million patients and the ALS clinics see over 2,000 patients annually. ALS patients seen in these clinics represent the full spectrum of disease, with regards to gender, race, and socioeconomic status. Working together ALS specialty sites will expedite enrollment and serve as proof of concept that two CDRNs can work together to conduct important ALS research. In addition the study will be listed on clinicaltrials.gov and maintained during the conduct of the study. Patient support groups (MDA and ALSA) both regionally and nationally will be used to help identify eligible participants. Through prior efforts in the GPC, standardized searching criteria are in place to screen the EMR for eligible participants. Study visits will occur during routine clinical follow up, making the study easier for patients and family members. Data collection between study visits will be via the internet or telephone. Local coordinators or local clinic nurses have direct personal relationships with the patients involved in the study and will greatly help with retention and thorough collection of data.

Study Eligibility
Our goal is to be as inclusive as possible. Patients will be eligible if:
1) They are 18 years and older;
2) Have a clinical diagnosis of ALS made at one of the ALS specialty clinics in GPC or pSCANNER;

3) Suffer from drooling (score ≥2 on the salivation question on the ALSFRS-R);
4) Have no contraindication to taking anticholinergic medications;
5) Patients and their caregivers must be willing to complete the study and return for follow-up visits; and
6) Patients must give written informed consent before participating in this study.

Exclusion Criteria:
1) Inability to provide informed consent.

Describe how you will or have selected appropriate interventions and comparators

This comparative effectiveness project will determine the most effective treatment for drooling management in ALS patients. In particular, the adaptive design model used will allow us to efficiently identify the one or two most effective and best tolerated drugs. Doing so will directly impact patients who suffer from drooling, and allow clinics to provide information about effectiveness and side effects for each of the drugs.

Patients meeting the criteria will be randomized to receive either: a) Scopolamine patch (1.5 mg) every 72 hours; b) glycopyrrolate – 1 mg three times a day; c) amitriptyline – 25 mg at bedtime; or d) atropine 1% sublingual drops – 2 drops three times a day. These medications are currently being prescribed, but there has not been a head to head trial for determining which medication has the greatest effect or is the best tolerated.

Two additional procedures that have been used for drooling are myobloc (botulism toxin) and radiation of the salivary glands. We chose not to include myobloc or radiation of the salivary glands as a means of treatment for the following reasons: 1) Both myobloc and radiation to the salivary glands would typically be considered once people with ALS fail oral medications; 2) The study participants will need to pay for their medication in this study; 3) from experiences by the clinicians involved in this study, insurance companies do not routinely pay for these procedures; 4) The technique for performing the myobloc injections can be challenging and pose a significant risk if not performed correctly; and 5) the ability to perform myobloc injections may not be available at all of the study sites, or performed differently from site to site.

Study Conduct and Study Visits
This study has been specifically designed to reduce the burden and increase the participation and impact on ALS patients and their caregivers. The study itself is designed to run around routine clinical care visits. Much of the data captured will be contained in the medical record. The data collected between clinical visits will be telephone or by direct web-entry via a secured survey web portal (as preferred by patient participants). At the end of their initial study visit, patient participants will be randomized and will go home with a prescription for their study medication. This design was endorsed enthusiastically in our patient and patient/caregiver dyad focus/engagement group: both the patient-oriented nature of the questionnaire, design of essential elements of the study around routine clinical care visits, and the ability for monthly responses by web or telephone. We plan to convene a patient advocacy committee (PAC) to enhance the patient-centeredness by supplying vital information about the course of treatment being experienced and unique (or ubiquitous) problems facing these patients with respect to each treatment for drooling (See Patient Engagement Section). The PAC will be open to all patients enrolled in a specific arm once they complete the study. Patient/stakeholder engagement will include an integrated, team approach to developing the protocol, data forms and the database needed for the study.

Informed Consent and Baseline Visit: A person identified as a potential study participant will be given a consent form and allowed sufficient opportunity to read and ask questions. If they agree to participate, they will be asked to sign the consent form. They will then complete the questions in the ALSFRS-R and the ALS quality of life (QOL) instruments, as well as a survey as to effectiveness of prior drooling medications. If they meet inclusion/exclusion criteria, they will be randomized to one of the four arms. If the subject chooses to not participate in the study they will be offered the opportunity to

complete the drooling survey, instead, so their experiences can be captured. The drooling survey will include questions about: age, gender, age of symptom onset, site of onset, current areas affected, list of drooling medications, rank of the effectiveness of the medications, questions about botox and radiation, as well as effectiveness of those procedures.

Randomization:
The randomization schedule will be developed by the Department of Biostatistics at the University of Kansas Medical Center and incorporated into the GPC informatics methods that deliver consent and eligibility determination questionnaires. Subjects will be randomly assigned to one of the four treatment arms using the initial or updated randomization schedules described below in the "Procedures with Endpoint" section. Upon assignment, the local investigator will electronically receive the treatment arm prescription information to complete for the subject.

Month 1 and Month 2 Visits:
Subjects or their caregivers will complete the ALS QOL, ALSFRS-R and the Patient Reported Saliva Management Scale (PRiSM) – this can be entered by accessing questionnaires presented via the EMR Patient Portal (eg. MyChart for EPIC), or by a REDCap weblink.

Month 3 Visit:
The subjects will return in 3 months (+ 7 days) – this visit is designed to correspond to routine clinic follow up to reduce patient and caregiver burden. At that time, they will undergo the ALSFRS-R, complete the ALS Quality of Life Questionnaire, respond to the question in the drooling PRiSM scale 'Since the beginning of the medication, do you feel that the drooling is: 1. Markedly worse; 2. Slight worse; 3. Not at all different; 4. Slightly better; or 5. Markedly better.' Subjects will be asked if they stopped the medication because of intolerable side effects by answering the following question 'Have you stopped the medication that your doctor prescribed for controlling your excessive saliva?' If they answer yes, they will be asked when they stopped the medication. Any adverse events will be collected.

Adverse Events: An adverse event (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, laboratory or physiologic observations occurring in study participants. Information on adverse effects of medication and on inter-current events will be determined at each visit by direct questioning of the subjects, clinical examination, and laboratory tests. Tolerability will be determined by the ability to complete the study on the assigned experimental medication. AEs will be reported using NCI Common Terminology criteria for AEs (CTC version 4.0). AEs will be graded using the following scale: Grade 1 = mild, Grade 2 =moderate, Grade 3 = severe, Grade 4 = life-threatening, Grade 5 = death. A serious adverse event is defined as

1. Death;
2. Life-threatening (report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death);
3. Hospitalization (report if admission to the hospital or prolongation of a hospital stay results because of the adverse event);
4. Disability (report if the adverse event resulted in a significant; persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life;
5. Congenital anomaly (report if there are suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child);
6. Requires intervention to prevent permanent impairment or damage (report if you suspect that the use of a medical product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient).

Data Management

This study is proposed as the first pragmatic randomized controlled trial of our GPC PCORNet Clinical Data Research Network infrastructure. While combining sites from two CDRNs may seem technically challenging, in a rare disease like

ALS, the ability to draw from multiple sites across the Midwest and West coast is essential to gain the number of ALS participants required to answer the question of what is the best treatment for drooling. We have adopted a novel strategy to take advantage of existing infrastructure, and create a REDCap database so we can include sites not fully i2b2 compliant. The following organizational structure and resources will be used to carry out the project:

- IRB reciprocity agreements are already in place at the GPC sites
- IRB reciprocity will be in place at the pSCANNER sites prior to patient enrollment – implantation of IRB reciprocity at the GPC will help serve as a template for rolling this out at pSCANNER
- We will utilize a strategy where KUMC will serve as the central IRB for the GPC sites, and UCLA will serve as the central IRB for the pSCANNER sites
- All sites are ALS specialty clinic sites and have local patient lists
- All sites are MDA or ALSA certified clinics – and will have the national and local registries of patients available to help with recruitment for the study
- We can use already existing EMR search parameters to identify patients – the GPC has already demonstrated the ability to do this by creating an ALS patient survey
- Many GPC and pSCANNER ALS specialty sites already collect the ALSFRS-R during routine clinical care
- The PRiSM and global ALS QOL scales are simple scales used in most ALS trials, and will be familiar to all participating sites
- All outcomes for this study would be considered within the realm of routine standard of care
- Many EPIC sites will have the outcomes proposed for this study in their EMR – as they are being rolled out by EPIC central as a standard package for ALS specialty centers
- We will still use a REDCap data base for this study as not every site will have rolled out the new EPIC forms
- However we can use the EMR to: provide REDCap survey links via the secure patient-portals; or to directly capture outcomes for sites already running the standard EPIC forms.

The data collected for this study, either as part of routine care in the EMR, or via REDCap for this specific study, will be managed by the informatics teams at each GPC or pSCANNER site. The informed consent, questionnaires (eligibility/baseline, month 1,2, and 3), and adverse event data capture will be stored at each site of the GPC or pSCANNER on secure HIPAA certified servers as part of the electronic medical record system, or in a REDCap database. The site systems will reference a GPC web service that will deliver the randomization schedule (REDCap). Data will then be extracted as a HIPAA limited dataset from each site's i2b2 integrated data repository for trial monitoring and also after 100 subjects are enrolled to update the randomization schedule and at 13 week intervals as described in the analytic methods. The ALSFRS, the ALS QOL, and PRiSM questionnaires will be stored in the EMR or REDCap and abstracted at the end of the study period. After 100 subjects are enrolled analysis will be performed to update the randomization schedule, and at that time, data will be assessed for completeness, and reports created detailing missing data by site, and distributed to the local site coordinators for follow up.

Treatment Failures
Treatment failure will be defined as the following: did the subject stop the medication for any reason?

Analytic Methods

Overview
The primary aim of this study is to determine which intervention is most effective for drooling in ALS. We will perform a prospective randomized comparative effectiveness adaptive design study with those who have ALS. Four interventions will be tested. The following sections focus on different issues and detail how we determined power, sample size, and duration of this trial. Throughout we add information to help those less familiar with our design and analyses better understand what we did and plan to do with this study.

Sample Size Considerations:

This will be a pragmatic, open-label, randomly allocated four arm parallel group study.
Intervention: a)Scopolamine patch (1.5 mg) every 72 hours; b)glycopyrrolate – 1 mg three times a day; c)amitriptyline – 25 mg at bedtime; or d)atropine 1% sublingual drops – 2 drops three times a day.

Bayesian Adaptive Design:
(For adaptive and Bayesian trial designs, describe how you will address standards AT-1 to AT-5)
The first 80 subjects will be randomized 1:1:1:1, then response adaptive randomized to a total maximum number of subjects n=200. Using the Bayesian Adaptive Designs (BAD), at each interim analysis a decision will be made to either continue enrolling subjects or to stop the trial for results. The primary endpoint will be used to drive the adaptive randomization and stopping criteria. The endpoint will be %markedly better at three months (~12 weeks). We modify the CONSORT statement to report adaptive randomized clinical design (A-5).

Summary of the Bayesian Adaptive Design
The principle parameters that go into a Bayesian Adaptive Design are as follows:

- Begin interim analyses once 20 patients have been enrolled on each treatment
- Interim analyses occur every 13 weeks thereafter and data are used on all enrolled patients with 12 week data
- At each interim analysis stop for success if pr(intervention/arm is best) > .9 for some treatment after 100 patients have 12 week data
- Accrual rate is 2 patients/week
- The maximum number of patients enrolled with endpoints is n_{max}= 200
  - Update allocation probabilities based on information weighting
  - In the cases of no clear "winner" we will claim a "loser" treatment for interventions if pr(intervention/arm is best) < .01

Procedure with Endpoint
Patients will be randomized to one of four interventions with a maximum number of patients n_{max}= 200. Using a Bayesian Adaptive Design, at each interim analysis a decision will be made to either continue enrolling patients or to stop the trial for success (identification of best intervention). If patient enrollment continues, the randomization structure (i.e., how we randomize patients to each drug) will also be updated. The endpoint is used to drive the adaptive randomization and stopping criteria. The endpoint is the percentage of patients who report 'markedly better' on the drooling scale after 12 weeks. After we have endpoint data on 100 patients, the data will be analyzed and an updated randomization schedule will be used. Specifically, the arm, or intervention, that looks to be the best will get more participants allocated to it in this subsequent randomization. A new adaptive randomization schedule will be updated every 13 weeks, using up to date outcome data, until the trial is stopped. Early success stopping criteria will be if the probability of the maximum arm (i.e., the best intervention), measured by the percentage of patients 'markedly better' endpoint, is larger than 0.9. While this will halt new patient enrollment, we will confirm this finding with a subsequent analysis and evaluation after all data from all enrolled patients are obtained as some will still be actively in the study when the early stopping criterion is identified.

Virtual Participant Endpoint Response (Null and Alternative Hypotheses)
For the purposes of this investigation we looked at several virtual (or "pretend") responses to determine the power, sample size and time (duration) needed for our study. We created several scenarios for efficacy using six patterns (Table 1).

Table 1. Virtual response patterns for endpoint.

	1	2	3	4	
		Efficacy			
No Difference	0.10	0.10	0.10	0.10	all arms are equally efficacious
Best and 2nd Best	0.10	0.10	0.20	0.40	one arm is best, one is 2nd best
All Different	0.10	0.15	0.20	0.40	all have different efficacy
One Strong Best	0.10	0.10	0.10	0.40	one arm is much better

One Bad	0.10	0.40	0.40	0.40	one arm is a loser
One Modest Best	0.10	0.10	0.10	0.30	one arm is modestly better

Accrual (patient enrollment) Patterns

Accrual patterns are important to Bayesian adaptive designs and refer to how rapidly each site enrolls patients in the trial. We assume that the distribution of the accrual patterns follows a Poisson distribution with a mean, or average, number of patients accrued per week. The accrual patterns depend on two factors: (1) the number of sites actively enrolling patients in the trial, and (2) how fast the sites can enroll, which we assume is a constant for each. We expect to accrue an average of 2 patients/week. Determining this is important for identifying how long the trial will last.

Missing Data

All attempts will be made to collect any missing data points. Missing data will be identified during periodic data base reviews, and data reports. Sites or individuals with significant missing data points will be identified and coordinators can reach and out try and determine overcomable barriers to data collection on the individual level. The Bayesian model is less susceptible to missing data as the model weights the response based on the number of data points entered. In the scenario where missing data represents greater than 20% of expected data points for any given individual then a mixed model will be used to impute missing data.

Statistical Model

Of necessity the following is fairly technical, but it is needed to allow for appropriate statistical review and because it is the statistical model that will evaluate final determination of which intervention is "best". This is referred to as the arm of maximum efficacy. For this study the endpoint is $S_{EjT}|n_{jT}$~Bino(n_{jT} ,θ^e_j) for efficacy. In addition, we provide "weakly informative" priors, $\text{logit}\left(\theta_j^e\right) \sim N\left(0,100^2\right)$. Using the endpoint data and the prior probabilities, we then use Markov Chain Monte Carlo computations to obtain the Bayesian posterior distributions of $\left\{\theta_j^e \mid S_{EjT}\right\}$ the endpoint (i.e., efficacy) . The efficacy rate previously discussed is used for determining whether we have met our stopping criterion. Specifically, the rule is we will stop the trial if the probability of an arm (i.e., a intervention) having maximum utility is greater than 0.9. This may first be determined after enrolling 100 of the 200 potential patients. The function is θ^e_j and the arm (or intervention) having the maximum efficacy is $E_{\max} = \max\left(\theta_1^e, \theta_2^e, \theta_3^e, \theta_4^e\right)$. The stopping rule is mathematically $P(E_{max})>.9$). If a maximum utility arm (intervention) is not identified after 100 patients, this procedure and accrual will continue until a maximum arm is identified or we reach 200 enrolled patients.

Adaptive Randomization: Allocation

After the stopping rule is evaluated the next round of patients are randomized using a formula that takes advantage of the information gained from our analyses up to that point. Using this formula, each arm (or drug) is allocated for the next patients to be enrolled in the j^{th} arm proportional to $V_j^* = \sqrt{\frac{\Pr\left(\theta_j^e = E_{\max,T}\right) Var\left(\theta_j^e\right)}{n_j + 1}}$. This type of allocation tends to have more desirable properties then simply using $\Pr\left(\theta_j^e = E_{\max,T}\right)$. Using this approach will allow us to assign more patients to the most promising arm or intervention, and fewer patients to the least promising intervention.

Simulation Algorithm

The following steps summarize the algorithm (or rule) used to determine power, sample size, and duration of the trial. These are all necessary elements for establishing that the trial is of sufficient size and length to yield valid results. For this algorithm we used the "virtual patient responses" parameters (or simulated data) previously discussed. **Step 0:** Set the index for simulation iteration to be b=0. **Step 1:** Set b=b+1. **Step 2:** Simulate the initial observed data. **Step 3:** estimate

posterior parameters via simulation and calculate the stopping rule and the possible next allocation. **Step 4:** repeat steps 2 and 3 after collecting 13 more weeks of data. **Step 5:** evaluate all of the data after collecting all of the endpoints. **Step 6:** go to step 1 unless b=1000, then stop. We used this algorithm in a software package called FACTS™ (Fixed and Adaptive Clinical Trials Simulator) [65]. FACTS™ is very powerful and can handle a wide variety of models for exploring the operating characteristics of Bayesian clinical trials designs. It was developed by S. Berry, who co-authored the PCORI methods guidelines and wrote the Bayesian adaptive design portion of those guidelines. Dr. Berry is a consultant on this application and the University of Kansas Medical Center is the first academic institution with license to use FACTS™.

Power, Sample Size, and Trial Duration

We performed 6 sets of trial simulations based on the various efficacy (6 types) profiles that were shown in Table 1. Each set involved many trial simulations. These simulations resulted in identifying power (the probability of success) in two components—one for early success (i.e., being able to stop the trial early) and one for late success of the trial (i.e., after enrolling all 200 patients) (see Table 2). While some of these profiles/scenarios are very unlikely to occur, we include all in Table 2, ordered from most to least power. We highlight three combinations, or scenarios, here.

First (row #1 in Table 2), if there is one strong best drug in terms of efficacy, we estimated (identified) that 98% of the simulated trials had early success, 1% late success, and only 1% had incomplete results. Thus this simulation had 99% power. The average sample size of this trial scenario was 124. The average length of these simulated trials was 75 weeks. **Second (row #2 in Table 2),** if there is a best drug and second best drug in terms of efficacy, we estimated (identified) that 86% of the simulated trials had early success, 7% had late success, and 7% had incomplete results. This trial scenario had 93% power and the sample size of this trial scenario was on average 139. The average length of this trial scenario was 82 weeks. **Third**, we want to highlight a scenario in which there is one bad intervention and three that are very good. For this scenario, we estimated (identified) that 16% of the simulated trials had early success, 3% late success. The sample size of this scenario on average was 189 patients. The average length of the trials under this scenario was 112 weeks. The very nice property of this trial is that in this case we identify the correct loser 97% of the time. **Fourth**, we want to highlight the unlikely scenario that serves as our null hypothesis **(row #6 in Table 2)**. In this scenario there are no differences in efficacy among the interventions. Therefore, the extent to which this scenario is "successful" actually reflects our Type I error rate. For this scenario, we estimated (identified) that 3% of the simulated trials had early success, 1% late success. Thus this trial scenario produced an appropriate expected Type I error (α=.04, less than .05). The sample size of this scenario on average was 198 patients. The average length of the trials under this scenario was 117 weeks. Again, the trial characteristics of the rest of the virtual profiles, while unlikely to occur, are shown in Table 2 for completeness and ordered from most to least power. The first two scenarios (one strong best drug, and a best and second best drug) serve as our research hypothesis. We believe that they are the most likely scenarios and they have the requisite greater than 90% power.

Table 2. Simulated Trial Operating Characteristics.

Efficacy Profile	Average N	Probability of Success: Early	Probability of Success: Late	Power (Early+Late)	Average Time (weeks)
One Strong Best	**124**	**0.98**	**0.01**	**0.99**	**75**
A Best &2nd Best	**139**	**0.86**	**0.07**	**0.93**	**82**
All Different	144	0.82	0.08	0.90	85
One Modest Best	153	0.73	0.11	0.84	90
One Bad*	**189**	**0.16**	**0.03**	**0.19**	**112**
No Differences	**198**	**0.03**	**0.01**	**0.04**	**117**

*The proportion of times we say the bad arm is a loser=.97.

Describe planned sensitivity analyses to determine the impact of key assumptions. (IR-5)
We will model the endpoint as a Bayesian ordinal response and estimate the posterior probability of which drug is the best. This approach does not use a clinical definition of best but would be a good calculation to help inform treatment particularly if we don't find a definitive result on the binary outcome.

Heterogeneity of Response
A pre-specified subgroup analysis will estimate the additional effect of the best drug (as identified in the randomized trial) on patients that enter the trial with a better disease status (ALSFRS-R>30) versus patients that enter the trial with worse disease status (ALSFRS-R≤30). Additionally differential effects based on gender, race, and site of onset (bulbar versus limb-onset) will be determined. This estimate and testing of the interaction between initial disease status and treatment effect will use the data collected in both aims 1 and 2, providing approximately 50 patients in each of the four cells, which translates to a power of 81% (Type I error=.05) to detect a .4 point/month difference. Bayesian logistic regression will be used to analyze the main HTE.

Survey Analysis:
We will use descriptive statistics including means, medians, and interquartile ranges, or frequencies to describe the use of medications for drooling; a relative rank of effectiveness (0= not effective, 3=very effective); use of medications in combination; frequencies of procedures (botox or radiation of salivary glands) and relative effectiveness of these procedures. In addition we will compare responses based on gender, race, and site of symptom onset. Frequencies across group will be compared using the ChiSquare test, and ranked symptom effectiveness using Wilcoxon test for ranked or ordered data.

PATIENT OUTCOMES (PROJECTED)

Primary outcome measure: With direct input from patients we have chosen the Patient Reported Saliva Management Scale (PRiSM) as our primary outcome. This outcome has the advantage of being patient-reported and similar in design to global impression of change questionnaires. This measure is based on the patients' response to the following question: "Since the beginning the medication, do you feel that the drooling is: 1. Markedly worse; 2. Slightly worse; 3. Not at all different; 4. Slightly better; 5. Markedly better." 'Slightly better' or 'markedly better' implies a clinically meaningful improvement. This outcome was used successfully in a randomized controlled trial of botulinum toxin for sialorrhea management in ALS, and demonstrated responsiveness to treatment for drooling in ALS. (16) Secondary outcome measures include: a) ALSFRS-R, b) ALS quality of life question and c) proportion of patients stopping the medication because of intolerable side effects. Patients will be asked the following question: 'Have you stopped the medication that your doctor prescribed for controlling your excessive saliva?' The ALSFRS-R and the Global ALS QOL are standard outcomes used in most ALS clinical trials with considerable literature on their use. A change of 20% in the slope of decline of the ALSFRS-R is generally considered by patients and clinicians to be clinically significant. (25) Most importantly, patients reviewing these outcomes agreed that the questions were familiar to them and that the burden of completing the questionnaires would be minimal.

Reporting Plan

At completion of the study data will be analyzed per the plan in the statistical analysis section. Internal validity will be assessed by agreement between different scales, and by analysis of adverse events. In addition results of the study will be compared to results of the retrospective patient survey to look for consistency across responses for various drugs for drooling. In addition demographic information, site of symptom onset, and average ALSFRS scores will be compared to national demographic statistics for ALS. As patients will be recruited from many ALS specialty centers across the United States, we expect the population recruited for this study to be representative of the larger US ALS population.

D. Project Milestones and Timeline

- *Describe the projected outcomes and clearly articulate the goals to be accomplished during the research study*
- *Provide a timeline for completion of the research project within the proposed project duration*

This study is proposed as the first pragmatic randomized trial combining resources from both the GPC and pSCANNER. GPC has already linked their ALS specialty sites: 1) with IRB reciprocity in place; 2) ability to identify ALS patients using the EMR; and 3) ability to reach out to patients utilizing a ALS patient survey. pSCANNER will have IRB reciprocity in place by the time the grant is funded. We acknowledge the limitation that having standard data forms rolled out into every participating site EMR by the time the study is up and running may not be feasible. To get around that problem we have adopted the following plan to for data management: while we anticipate most of the study will be managed in REDCap, we will allow patients to report outcomes via EMR patient-portal that either invokes the REDCap survey or collects the same data in the EMR via EPIC standard ALS forms. This data is in turn will be integrated as a limited data set at the GPC level (managed by KUMC informatics under the direction of Dr. Waitman) to support this trial. While the data infrastructure is finalized, we will be holding monthly meetings with our protocol operations committee patient representatives with Kim Kimminau, PhD facilitating these meetings. We will finalize the protocol and submit to the IRBs: KU for GCP and UCLA for pSCANNER. Other sites will then provide IRB approval through IRB reciprocal arrangements developed for GPC and pSCANNER, respectively. We expect IRB approval by late spring early summer 2016. We anticipate enrolling in the first patient by September 2016. We anticipate that we should finish the study in two and a half years, leaving the last six months for dissemination of results and preparing the study manuscript.

Project Timeline (Add additional rows as needed)

Project Activity	Expected Completion Date
Year 1	
Linking the Electronic Medical Records of GPC and pSCANNER	September 2016
IRB approval at all sites completed	June 2016
Investigators training of protocol	July 2016
Year 2	
First patient	September 2016
25% enrollment	January 2017
50% enrollment	May 2017
Year 3	
75% enrollment	September 2017
Enrollment completed	December 2017
Paper written and published	September 2018

E. Patient Population

- *Describe the study population with respect to numbers of participants, age, gender, race, ethnicity, and clinical status as appropriate for the study.*

Amyotrophic lateral sclerosis has a median age of onset of 55 years with a male predominance of 1.5 to 1.(3, 26, 27) There is no racial or geographic predisposition except for an increased incidence on the Marianas Islands of Guam. The 14 ALS clinics represented by the GPC and pSCANNER for this study represent > 2000 ALS patients, and would be expected to be representative of the US population demographics for the Midwest and West coast. This population covers the spectrum from primary care networks serving rural and small communities to urban populations with significant African American and Hispanic representation.

Recruitment Plan

Total number of study participants expected to be screened:	1000
Total number of study participants expected to be eligible of those screened:	500
Target sample size (use same number stated in milestones):	200

Estimated Final Racial/Ethnic and Gender Enrollment Table

Race	Male (N)	Female (N)	Total (N)
American Indian/Alaska Native	1	0	1
Asian	6	4	10
Black/African American	16	13	29
Hawaiian/Pacific Islander	2	1	3
White	82	66	148
Multirace	5	4	9
Ethnicity	**Male (N)**	**Female (N)**	**Total (N)**
Hispanic (Latino/Latina)	19	14	33
Non-Hispanic	91	76	167

F. Research Team and Environment

- *Describe the capabilities of the research team to accomplish the goals of the proposed research project, and the appropriateness of the research environment to conduct the study.*

The GPC is a PCORNet Clinical Data Research Network (CDRN) composed of 10 leading medical centers repurposing the research programs and informatics infrastructures developed through Clinical and Translational Science Award (CTSA) initiatives. Partners are the University of Kansas Medical Center (KUMC), Children's Mercy Hospital, University of Iowa Healthcare, the University of Wisconsin-Madison, the Medical College of Wisconsin, and Marshfield Clinic, the University of Minnesota Academic Health Center, the University of Nebraska Medical Center, the University of Texas Health Sciences Center at San Antonio and the University of Texas Southwestern Medical Center. The GPC network brings together a diverse population of over 10 million people across 1300 miles covering 7 states with a combined area of 679,159 square miles. Of these, over 6 million have significant data maintained in electronic health records. This population covers the spectrum from primary care networks serving rural and small communities to urban populations with significant African American and Hispanic representation. ALS clinics at 8 of the ten medical centers in the GPC will be included in this study. The GPC selected ALS as the rare disease for which we could readily access all patients across our network and is working under the direction of Dr. Barohn to survey the GPC ALS population regarding their willingness to engage in research and provide feedback on patient-reported outcome measures.

Dr. Barohn has extensive clinical experience in the field of neuromuscular clinical trials. He currently is the PI on two active FDA-OPD R01 studies (ALS and myasthenia gravis). Dr. Barohn will serve as Principal Investigator throughout the implementation and conduct of the study. Dr. Barohn has been a leader in the Western ALS (WALS) Association (currently the treasurer), participated in the Northeast ALS (NEALS) Association and been on the executive committee in the ALS Research Group (ALSRG). He has participated in many ALS NIH trials and was instrumental in the development of the ALS Common Data Element Forms (ALSCDE). He sees ALS patients in both the ALSA clinic and MDA clinic.

Dr. Waitman (GPC principal investigator) is working with the informatics site leads to tailor existing electronic medical record systems, data repositories based upon the i2b2 software developed through the National Center for Biomedical Computing at Partners Healthcare System, data capture systems based on REDCap (Research Electronic Data Capture) developed by Vanderbilt University, and governance processes to support comparative effectiveness research in alignment with PCORNet objectives. The GPC complements considerable investments in electronic health records by our healthcare systems with existing NIH-funded technology (e.g., i2b2, REDCap) to provide a cost-effective common data model that promotes data transparency and interoperability. This includes:

1. Collecting Patient Reported Outcome Measures (PROM) standardized measures deployed using either EMR patient portals or data collection instruments for existing registry and research management systems such as REDCap.
2. Configuring comparative effectiveness trial components directly in the EMR (preferred) or integrate existing data capture and trial management systems.
3. Tailoring existing methods (a lightweight i2b2 plug-in) so each site's honest broker can extract limited data sets composed of EMR and PROM and securely transfer them to the GPC data store to support the conduct of the comparative effectiveness research (CER) trial monitoring and analysis.

pSCANNER is a CDRN network based on the West Coast. We have been in communication with the pSCANNER group and they are committed to participating (see letters of support). ALS specialty sites in pSCANNER agreeing to participate include University of California, San Diego; University of California, San Francisco; Cedars-Sinai; University of California, Davis, University of California, Irvine and University of California, Los Angeles and six senior investigators, which together bring an additional 600 potential ALS patients to this study. We believe that adding sites from this additional CDRN would expedite enrollment and serve as proof of concept that different CDRNs can work together to conduct a study.

This comparative effectiveness trial for drooling in ALS provides an ideal opportunity to use and provide feedback for PCORNet methods and EMR-based infrastructure to conduct pragmatic trials in the patient and clinic workflows. Eight sites in the GPC and five sites in pSCANNER will be included in this study. Furthermore, Dr. Gajewski is currently a co-investigator in the GPC methods core directed by Dr. Bradley Pollock (UCDavis) and works closely with the informatics teams developing infrastructure and also clinical investigators using the network. This trial and the team are well equipped to advance the conduct of pragmatic trials by integrating Bayesian Adaptive Designs within EMRs and clinical workflow.

We anticipate a total ALS population for this study of 2000 patients, approximately half will have difficulties with drooling (1000), and we anticipate one fifth of these might chose to participate in our study.

G. Engagement Plan

Describe the plan to engage patients and stakeholders meaningfully in the various phases of the proposed research. (Criterion 5. Patient and stakeholder engagement)

1. PLANNING THE STUDY: Describe how patient and stakeholder partners will participate in study planning and design.

To assess the importance of drooling and treatment from patients' perspectives we used two approaches. First, we asked GPC and pSCANNER network physicians to discuss the issue with their patients. Conversations yielded consistent findings that 1) drooling has substantial impact on patients' quality of life and 2) some of the medications prescribed work better than others. Using this information, we then convened a patient and patient/caregiver dyad focus group by phone (to reduce transportation and cost burden to participants). The patient facilitator prepared a number of broad questions to stimulate the conversation about the issue, being sensitive to different levels of comfort patients and caregivers have with the topic. Our clinics' and physicians' experience provided guidance to ensure that the facilitator's tone and approach were compassionate and sensitive to the possibility that patients' may be embarrassed or feel shame associated of their drooling. The focus group participants represented four different GPC sites. Five key findings from the focus group have helped to shape the approach and protocol for the study. First, patients shared enthusiastic support for the study and agreement that a better understanding of treatments for drooling in ALS would benefit patients. Second, there was general agreement that the inclusion and enrollment requirements suggested were reasonable. The patients and caregivers were passionate about ensuring that the study is available to as many patients as possible, and they discussed this topic at length. They fully understood that with greater participation, there will be more data, and more data might lead to improved therapies. Third, the participants said that they preferred to use their personal computers or tablets to input their own patient-reported outcomes. Their rationale for this preference was that their energy to share these important aspects of the study might not be highest during their clinical visits. In fact, patients, as well as caregivers, were unanimous in sharing how stressful and energy-draining additional study visits are for both of them. The participants went on to share a novel goal for the study. They asked the research team to consider having a survey to capture experiences with drooling treatments for patients who may not participate directly in the study. The group felt that there would be much to learn and that a survey would encourage patients and caregivers, even caregivers whose family member may have passed away, to share their experiences and possibly inform the research. Finally, the group overwhelming wants to stay involved through the study and to continue to advise and help in any way possible, especially in dissemination strategies that will assist the ALS community in learning about the study's findings. These individuals, along with additional patient and patient/caregiver dyads, will form the Patient Advisory Committee (see below).

Other stakeholders consulted and involved in developing the proposal include ALS clinics (MDA or ALSA sponsored clinics). These stakeholders promote the delivery of best care medicine, and they advocate for improved therapies, engagement and greater awareness of ALS. The clinics have a long tradition of responsiveness to patient and caregiver concerns, so their inclusion as key stakeholders ensures broad buy-in across the GPC and pSCANNER geographic areas and associated patient communities. Patient/stakeholder engagement will drive an integrated, team approach to developing the final study protocol, data forms and the database needed for the study.

Following the engagement of patients, physicians and advocacy stakeholders, we formed a Protocol Operations Committee (POC). This committee is composed of patients from the GPC and pSCANNER network (1 from each network), a physician from each participating site, patient advocate groups (MDA and ALSA), a statistician and an engagement facilitator. The purpose of the POC is to bring all points of view to the table and to facilitate co-learning, co-leading and collaboration. The engagement facilitator will use a variety of approaches (including World Café, Future Search, etc.) to ensure equal representation, respectful dialogue, and shared decision-making throughout the project.

2. CONDUCTING THE STUDY: Describe how patient and stakeholder partners will participate in the study conduct. (Enter your information here.)

We will create two committees for the conduct of this trial: a protocol operations committee (POC), and a patient advisory committee (PAC):

- Each committee will consist of a minimum of 2 patients (one from each network). The exception will be the PAC which will be composed of a minimum four patients and/or their caregivers from each network.
- The POC will review the protocol every six months to determine if the protocol needs to be modified.

- The PAC will meet via phone/webinar monthly to discuss the status of the study. They will be consulted regarding how best to recruit and retain patients. They will also be the first group with whom preliminary findings, patient-reported concerns and protocol modifications are shared or vetted for collaborative problem-solving.

A Data Safety Monitoring Committee will be established and meet after the first 80 subjects are enrolled and then whenever we have preliminary data to report. We will have a stakeholder member and a patient from each network on this committee.

Communication Committee will consist of the patient advocacy groups (MDA/ALSA) and patient partners involved in the POC or PAC who would like to volunteer. We will ask the patient advocacy groups to disseminate the information as we obtain information. This dissemination can be through their support groups, newsletters, meetings and sponsored clinics. We recognize that each of these groups have experience in different outreach strategies, and we will support the communications methods they recommend.

3. DISSEMINATING THE STUDY RESULTS: Describe how patient and stakeholder partners will be involved in plans to disseminate study findings and to ensure that findings are communicated in understandable, usable ways.
(Enter your information here.)

We will hold a monthly team meeting in which the status of study will be discussed. As mentioned above, members of the PAC, site investigators if needed, and DSMB members will be on these calls. The composition of these groups is such that we will have perspectives and input from patients, MDA, ALSA, the Center for Practical Bioethics and the Frontiers Community Partnership for Health program. During the course of this study, we will present on the status of the study at different scientific meetings, e.g. American Academy of Neurology meeting. We also will disseminate this information to the local and national chapters of both ALS patient advocacy groups, the PAC, and all investigators involved in the study. We will require each site to have a representative (investigators or coordinators) visit their local ALSA or MDA association patient meetings (if one exists) several times throughout the year. However, we will need to be mindful of what information may not be shared with patients participating in the study until all data have been collected. The patient representatives on our committees will be informed fully of the scientific reasons for this constraint and delay of release of some information. To the extent possible, we seek to include patients and patient/caregiver dyads on any of the dissemination activities they are interested and capable of joining. Rather than identify a specific patient or dyad to lead such efforts, opportunities to partner will happen throughout the project. This way, we will not overtax any individuals, but will rather encourage a vibrant and diverse patient/dyad engagement on a variety of dissemination activities.

Upon completion of this study, the trial results will be shared with Prize4Life (Prize4Life is a nonprofit organization dedicated to accelerating the discovery of treatments and cures for ALS, founded by a group of Harvard Business students after one of them contracted ALS). Patients and their caregivers from both the GPC and pSCANNER will assist in planning, conducting and disseminating the study results/findings. We will also disseminate the results through the MDA and ALSA. This can be done not only with information on their website, but the results can be conveyed to ALS patients and their clinicians which are all sponsored by MDA/ALSA. ALS patients in the US are all seen at designated MDA and ALSA clinics, thus they are linked to the community and provide a venue for information and implementation of new findings. Of course we will also disseminate the information to the physicians and health care providers by publishing the data and presenting it at national and international neurology meetings.

Within 6 months of completing the project, we will submit the final results for publication. Members of the committees will be able to proof and provide input to the paper. Prior to submission of the manuscript, it will be sent to all members of the PAC, the POC, the DSMB, and all investigators for content comment and suggestions. While the study participants cannot learn of the results of the study until the study is completed, the study will be complete at the time we submit the manuscript and thus may be shared. We fully expect and are planning to have patient/patient dyads be co-authors on these

publications.

The study Communication Committee is specifically designed to address dissemination of information from the sialorrhea project. Through issuing a regular newsletter, we will ensure that study participants are notified of the results of the study.

Once the data is published, Dr. Barohn, the site investigators, and our patient team members will present and discuss our study and its findings at annual scientific meetings (e.g. American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine), and at meetings of patients at the ALSA and MDA patient support groups. The Center for Practical Bioethics also will disseminate the information to health care professionals and at patient organizations involved in sialorrhea with which they collaborate. With respect to ensuring implementation of our findings in other settings, Dr. Barohn will request that the American Academy of Neurology initiate a practice parameter on the treatment of sialorrhea in ALS. Dr. Gary Gronseth, in the Department of Neurology at University of Kansas Medical Center, is the chair of the AAN Practice Parameter Committee and works closely with Dr. Barohn. Dissemination of this information will ultimately influence the practice of sialorrhea control for this population. Dr. Richard Dubinsky, also in the Department of Neurology at the University of Kansas Medical Center, chairs the American Academy of Neurology Committee to determine how the AAN Practice Parameters actually change neurologist's practice. Thus, once our findings are published and a AAN Practice parameter on the topic is completed, the AAN can study if practice has been altered regarding the management of sialorrhea for patients with ALS. We will further such implementation by additional publications and presentations to both clinician and patient groups. We recognize that sometimes patients with difficult to treat conditions are the ones to bring information about new treatments to their physicians. Our commitment to be proactive in disseminating our findings to patient groups will facilitate this route for implementing our findings in practice.

4. PRINCIPLES FOR ENGAGEMENT

- **Reciprocal Relationships:** *Describe the roles and decision-making authority of all research partners, including patient and stakeholder partners*.

A GPC IRB Authorization Agreement was created based upon a reciprocal deferral approach. In conjunction with this activity, Standard Operating Procedures (SOPS) were created to support the GPC's IRB reliance process. The GPC IRB Authorization Agreement has been executed by all ten sites within the network and is currently being utilized for both GPC specific studies/surveys as well as studies not directly utilizing the clinical data research network but involving GPC institutions. pSCANNER is currently in the process of completing a similar IRB agreement for their CDRN.

The GPC continues to have patient representatives involved in both governance and decision-making activities for the CDRN. These individuals have an equal vote and leadership role on committees as other members. Additionally, the GPC has convened a GPC-level Data Request Oversight Committee (DROC) that includes a patient representative. Health system leaders are similarly involved in governance and data oversight activities. The GPC invites participation by all stakeholders. It has established a level of trust through experience with patient and patient advocates from among their participating sites. Starting with the initial kickoff meeting, patient, patient/caregiver dyads, physicians, health system stakeholders and community organizations established an egalitarian-driven, open platform to discuss all aspects of the network's activities. The GPC's Patient/Community Engagement team meets monthly. In support of defining strategy and expectations in this area, a GPC Standard Operating Procedure for Patient Engagement has been developed and implemented. For this study, the processes and infrastructure developed for the GPC will contribute to the success of this study. pSCANNER has implemented similar processes and infrastructure which will further support successful execution. Attention to merging and blending lessons learned by pSCANNER activities with those of the GPC will happen by a facilitated webinar with an agenda to share lessons learned and values imbedded in each group's infrastructure. This will ensure that a common, collaborative framework, consistent with the values of both networks, guides and supports this project.

- **Co-learning:** *Describe plans to ensure that patient and stakeholder partners will understand the research process and that researchers will understand patient and stakeholder engagement and patient-centeredness.*
  (Enter your information here.)

For all phone calls with our patient and stakeholder partners, we will have a member of the research team available to answer questions and to facilitate if the group chooses. We will give explanations that can be easily understood and that accounts for various adult learning styles. For our researchers, we will hold investigator calls every three months until the first patient is enrolled and then monthly throughout the trial. We will encourage at least one each of the patient and stakeholder partners to participate in these phone calls as well. Each site will receive a DSMB report as when it is available.

We will establish at the onset of the project the common value of respect for everyone's comments and perspectives. The engagement facilitator(s) will be neutral mediators and will ensure fidelity to this approach. The facilitators will provide feedback to individuals if they violate this framework and will do so personally, on a case-by-case basis. If issues do not resolve, the facilitator(s) will bring the problem to the attention of the PI for personal attention. Further, engagement staff will offer online, in-service topics relevant to co-learning principles quarterly or more often at the team's request. This effort will ensure that the group is co-learning and modifying their approaches, if necessary, to remain patient and stakeholder-centric.

- **Partnership:** *Describe how the time and contributions of patient partners are valued and demonstrated in fair financial compensation, as well as reasonable and thoughtful time commitment requests.*

We will pay the patient partners who assist throughout this study $25 via gift card for their participation. We will recruit different members of our patient population to serve on committees to avoid overburdening any individual patient or patient/dyad partners. Phone calls will be scheduled using a group process to ensure highest levels of participation (i.e., Doodle poll) and conducted when it is convenient for the majority of participants. This may mean that calls occur after usual work hours. We will not require in person meetings due to the geographic distance among all stakeholder partners. We will encourage turning on and using camera features during GoToMeeting and other online venues to permit visual as well as auditory connections across the team.

- **Trust, Transparency, Honesty:** *Describe how major decisions are made inclusively and information is shared readily with all research partners, including patient and stakeholder partners; how patient and stakeholder partners and research partners express commitment to open and honest communication with one another; and how the study team commits to communicate study findings to the community studied, in a meaningful and usable way.*

Our patient partners' calls will be facilitated to ensure that all voices are heard and that everyone has a chance to participate. This is especially challenging because phone calls do not allow for visual cues that someone would like to speak. Further, some of the patient partners use assistance devices and require more time to compose and share their comments. Awareness of these issues and vigilance to make sure that everyone is included and given the chance to say (or share through typing a response, for example) will be honored and encouraged. Trust building requires the demonstration of how the value of participation plays out routinely and consistently. The trust building process has already yielded high participation and willingness to continue to work with the research team, so we expect this to continue. The investigators will always be available to answer questions and to fill in patient partners and stakeholders on the status of the study.

DISSEMINATION AND IMPLEMENTATION POTENTIAL

For detailed instructions, refer to the Application Guidelines for your PFA. Do not exceed two pages.

A. Describe the potential for disseminating and implementing the results of this research in other settings.

(Please also see PCORI Methodology Standard PC-4.)

We will hold a monthly team meeting in which the status of study will be discussed. As mentioned above, members of the PAC, site investigators if needed, and DSMB members will be on these calls. The composition of these groups is such that we will have perspectives and input from patients, MDA, ALSA, the Center for Practical Bioethics and the Frontiers Community Partnership for Health program. During the course of this study, we will present on the status of the study at different scientific meetings, e.g. American Academy of Neurology meeting. We also will disseminate this information to the local and national chapters of both ALS patient advocacy groups, the PAC, and all investigators involved in the study. We will require each site to have a representative (investigators or coordinators) visit their local ALSA or MDA association patient meetings (if one exists) several times throughout the year. However, we will need to be mindful of what information may not be shared with patients participating in the study until all data have been collected. The patient representatives on our committees will be informed fully of the scientific reasons for this constraint and delay of release of some information. To the extent possible, we seek to include patients and patient/caregiver dyads on any of the dissemination activities they are interested and capable of joining. Rather than identify a specific patient or dyad to lead such efforts, opportunities to partner will happen throughout the project. This way, we will not overtax any individuals, but will rather encourage a vibrant and diverse patient/dyad engagement on a variety of dissemination activities.

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Within 6 months of completing the project, we will submit the final results for publication. Members of the committees will be able to proof and provide input to the paper. Prior to submission of the manuscript, it will be sent to all members of the PAC, the POC, the DSMB, and all investigators for content comment and suggestions. While the study participants cannot learn of the results of the study until the study is completed, the study will be complete at the time we submit the manuscript and thus may be shared. We fully expect and are planning to have patient/patient dyads be co-authors on these publications.

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Once the data is published, Dr. Barohn, the site investigators, and our patient team members will present and discuss our study and its findings at annual scientific meetings (e.g. American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine), and at meetings of patients at the ALSA and MDA patient support groups. The Center for Practical Bioethics also will disseminate the information to health care professionals and at patient organizations involved in sialorrhea with which they collaborate. With respect to ensuring implementation of our findings in other settings, Dr. Barohn will request that the American Academy of Neurology initiate a practice parameter on the treatment of sialorrhea in ALS. Dr. Gary Gronseth, in the Department of Neurology at University of Kansas Medical

Center, is the chair of the AAN Practice Parameter Committee and works closely with Dr. Barohn. Dissemination of this information will ultimately influence the practice of sialorrhea control for this population. Dr. Richard Dubinsky, also in the Department of Neurology at the University of Kansas Medical Center, chairs the American Academy of Neurology Committee to determine how the AAN Practice Parameters actually change neurologist's practice. Thus, once our findings are published and a AAN Practice parameter on the topic is completed, the AAN can study if practice has been altered regarding the management of sialorrhea for patients with ALS. We will further such implementation by additional publications and presentations to both clinician and patient groups. We recognize that sometimes patients with difficult to treat conditions are the ones to bring information about new treatments to their physicians. Our commitment to be proactive in disseminating our findings to patient groups will facilitate this route for implementing our findings in practice.

B. Describe possible barriers to disseminating and implementing the results of this research in other settings.

Communication is the number one barrier to dissemination and implementation of study results. Communications must be open and frequent among all study members—investigators, their respective research teams, patient representatives, and study participants—and with other practicing clinicians and patients. We believe that our monthly phone calls and our organizational structure that includes a formal Communications Committee, will allow us to identify and solve any problems that might come up during the course of the study in a timely manner and will facilitate good communications within the study team during the conduct of the study. We specifically chose phone calls instead of in person meetings to allow quicker access to information and greater participation. With the number of investigators and patients involved in this study and the distance between the sites, an in person meeting would be difficult to schedule.

Through our monthly phone calls and our Communications Committee we also will be able to address any communication barriers related to recruiting patients for participation in the sialorrhea study. The support from our local association and the MDA and ALSA and our active involvement with the community engagement programs at our CTSA sites also will play a vital role in spreading the word about this study and for recruiting potential participants. Our requirement that study team member attend patient advocacy and support groups at the local level as well as the national level, will further enhance exposure about our study to those most interested in new options for ALSA.

C. Describe how you will make study results available to study participants after you complete your analyses.

After analysis of the data and once the paper is written, each site will contact their respective study participants and inform them of the results. This can be accomplished individually by phone call, letter, newsletters, webinar, and conference calls or in person when they return to clinic. Once the paper is published, a copy of the paper will be sent to all study participants. Each investigator may wish to hold an in-person meeting to discuss the results but due to the severity of the disease, this may not be a viable option for some study participants.

REPLICATION AND REPRODUCIBILITY OF RESEARCH AND DATA SHARING

For detailed instructions, refer to the Application Guidelines for your PFA. Do not exceed two pages.

A. Describe the ability to reproduce potentially important findings from this research in other data sets and populations.

Together the GPC and pSCANNER sites represent 14 major academic centers across the Midwest and West coast, and represent over 2000 ALS patients. A regional survey of Midwestern ALS patients included in ALSA clinics showed: of 1349 patients, 57% were male and 42% female for a male to female ratio of 1.3, which is similar to national averages. In addition approximately ¼ present with bulbar onset of symptoms, again closely matching larger epidemiological studies in the US. As an internal check we will also conduct a survey of past medication use for drooling, so patients who chose not to participate can still share their experience. We will be able to retrospectively determine if results from the prospective study match patient impression from the survey. The drugs chosen for this study are readily available and used in most ALS specialty clinics, to some degree. Once the results of this study are disseminated it will not be difficult for clinics to query patients to see how well our prospective study matches their clinical experience. But ultimately the true test of the results of this study, will be in how it instructs ALS specialty clinics in their prescribing practices. Our examination for heterogeneity of effect will help determine if there are differences in response related to gender, race, site of symptom onset, or severity of functional impairment.

B. Describe how you will make available, within 9 months of the end of the final year of funding, a complete, cleaned, de-identified copy of the final data set used in conducting the final analyses, or your data-sharing plan, including the method by which you will make this data set available, if requested.

This study is proposed as the first pragmatic randomized controlled trial of our GPC and pSCANNER PCORNet Clinical Data Research Network infrastructure. The data collected as part of routine care in the electronic medical record (EMR) is managed by the informatics teams at each GPC or pSCANNER site. This data is in turn integrated as a limited data set at the GPC level (managed by KUMC informatics under the direction of Dr. Waitman) to support this trial. Additionally, external investigators from either network may request access to the merged de-identified dataset through the GPC Data Request Oversight Committee in coordination with the Data Request Oversight Committees at each site. Upon approval, the investigator will be granted access to a secure REDCap database that holds the de-identified study data and relevant clinical data from the EMR.

C. Propose a budget to cover costs of your data-sharing plan, if requested. *These costs do not need to be included within the Budget Template.*

Not applicable

PROTECTION OF HUMAN SUBJECTS

For additional guidance, refer to Section 5.0, "Human Subjects Research Policy," of the Supplemental Grant Application Instructions for All Competing Applications and Progress Reports, from the U.S. Department of Health and Human Services. For detailed instructions, refer to the Application Guidelines for your PFA. Do not exceed five pages.

Describe the protection of human subjects who will be involved in your research.

The University of Kansas Medical Center will serve as Internal Review Board (IRB) of record for this study for all GPC sites, and UCLA for all pSCANNER sites. Each site must obtain approval from their IRB as well as from the IRB of record (KUMC/UCLA) before enrollment at their site can begin. This process will be followed carefully by the Research Institute Regulatory Affairs office at KUMC (Lindsey Hartke, BcS) to ensure that all sites comply.

Each consent form will contain the following information found from the National Institutes of Health (NIH) website (www.grants.nih.gov/grants/funding/phs398/phs398.doc). The components of the consent form must contain the following information (copied from the above website):

RESEARCH CONSENT FORM SAMPLE

Introduction

You are being asked to join a research study. Participating in research is different from getting standard medical care. The main purpose of research is to create new knowledge for the benefit of future patients and society in general. Research studies may or may not benefit the people who participate.

Research is voluntary, and you may change your mind at any time. There will be no penalty to you if you decide not to participate, or if you start the study and decide to stop early. Either way, you can still get medical care and services from the University of Kansas Medical Center (KUMC) or your study doctor.

This consent form explains what you will be asked to do if you are in the study. It also describes the possible risks and benefits. Please read it carefully and ask as many questions as you need to, before deciding about this research.

You can ask questions now or anytime during the study. The researchers will tell you if they receive any new information that might cause you to change your mind about participating.

This research study will take place at KUMC with Dr. Richard J. Barohn as the lead researcher. Participating sites and study doctors are listed on the first page of this document. About 15 people will be in the study at each study site. A total of about 200 people will be in the study at a minimum of 14 centers across the United States.

Why am I being asked to take part in this study?

You are being asked to take part in this study because you have Amyotrophic Lateral Sclerosis (ALS) and experience a symptom called drooling.

Why is this study being done?

ALS is a disorder that weakens motor strength and lung function. Rapid loss of nerve cells in the brain and spinal cord of ALS patients causes increasing weakness. Eventually, muscles don't work at all. Some drugs relieve symptoms of ALS. There is no cure for ALS.

While the only treatment that has slowed ALS is Riluzole, there are a number of symptomatic therapies available for ALS patients: these include management of drooling, pseudobulbar affect, use of gastrostomy for nutrition, and Non Invasive

Ventilation for breathing. Drooling is fundamentally related to loss of the ability to swallow. Difficulty swallowing leads to pooling of sialorrhea in the mouth, which you might interpret as on 'increase' in saliva. This pooling can lead to greater frequency in choking, and aspiration (where saliva goes down into your lungs).

By doing this study, researchers hope to determine which of four standardly prescribed medications is best in controlling drooling.

What is being tested in this study?
Difficulty swallowing can lead to problems managing saliva in patients with ALS. This symptom is both a social and medical burden. There are four drugs that will be tested in this study are a) Scopolamine patch; b) glycopyrrolate; c) amitriptyline and d) atropine 1% sublingual drops.

How long will I be in the study?
This study will last about 3 months.

What will I be asked to do?
There are two periods to this study:

Screening/Baseline Period: You may be asked questions to determine if you are eligible to participate in this study. If you are eligible and decide to participate, you will be given a prescription for one of the study drugs. You will also be asked to complete questionnaires about your functional status, your overall health, and amount of drooling.

Study Drug Period: In this period, you may take your assigned study drug for up to 3 months. You will be asked to complete questionnaires about your functional status, global health, and drooling during routine standard of care visits or over the internet or phone.

You will be randomly assigned (like drawing numbers from a hat) to one of the following four groups:

- **Group 1**: Scopolamine patch - 1.5 mg every 72 hours
- **Group 2**: glycopyrrolate – 1 mg three times a day
- **Group 3**: amitriptyline – 25 mg once a day at bedtime
- **Group 4:** atropine 1% sublingual drops – 2 drops 3 times a day

A computer will randomly assign you to a study group. If one drug shows little or no improvement in drooling the computer will start assigning more people to the groups that show better drooling management. No one on the study team will know which drug is better or worse until the study is over and all participants have completed the study. Information from questionnaires that all participants complete will help researchers come to a firm conclusion and write a truthful report about each drug and how well it worked or did not work for the control of drooling in patients with ALS.

The schedule of assessments is outlined below:

Screening/Baseline Visit (Month 0): You will be asked if you would like to participate in this study during a standard of care clinic visit. If you agree to participate, you will be asked to perform the procedures listed as part of research.

- You will be asked to read and sign this consent form. You will be given a copy of your consent form for your records.
- You will be asked questions about your medical history, age, race, ethnicity, date of birth as well as current and past medications you are taking. This includes prescriptions, over the counter medications, vitamins, supplements and herbs.
- You will be asked to take 3 questionnaires:
    - ALSFRS-R

  - ALS quality of life (QOL)
  - Patient Reported Saliva Management Scale (PRiSMS)
- You will be randomly assigned to a study group. You will be given a prescription and instructed how to take the study drug. The prescription you receive will last for the remainder of the study.
- This visit will last up to 1-2 hours.

Month 1 and 2: These visits will be completed at home on a computer using the Electronic Medical Record (EMR) Patient Portal unless you or the study staff feels a clinic visit is necessary due to complications. You will be asked to complete the same 3 questionnaires you completed during the screening/baseline Visit.

Month 3: You will be asked to come to the clinic for this visit. This is a standard of care visit for patients with ALS. During your standard of care visit you will be asked to complete the forms as listed above for research purposes.

Once the study has ended the study doctor will discuss future standard of care treatment options or you may choose to continue taking the medication you were receiving as part of this study.

What are the possible risks or discomforts?
The study drug may cause side effects or other problems. The researchers will be checking your medical information during the study to watch for side effects. However, you should tell the research team about anything that is bothering you or any changes in your health since the last visit. The researchers may be able to take steps to reduce side effects. You may experience none, some, or all of the side effects listed below. There may be other side effects or risks that are not yet known.

Risks of scopolamine patch, glycopyrrolate, amitriptyline and atropine drops:
- Dry mouth, blurred vision

Risks of scopolamine patch, glycopyrrolate and amitriptyline:
- Difficulty urinating

Risks of scopolamine patch and amitriptyline:
- Drowsiness

Risks of scopolamine patch:
- Disorientation, dilated pupils, confusion and hallucinations

Risks of glycopyrrolate:
- Decreased sweating, vision problems, loss of taste, headaches and nervousness

Risks of amitriptyline:
- Dizziness, constipation and weight gain

Risks of atropine:
- Intolerance to light and rapid heart beat

Questionnaires
There is a risk of feeling uncomfortable while answering some of the questions in the questionnaires. If you feel uncomfortable at any time you may skip a question or stop participating altogether.

Are there benefits to being in this study?
You may or may not benefit from this study. If your assigned study drug helps your pain, you may experience a benefit. Researchers hope that the information from this research study may be useful for managing sialorrhea in ALS.

Will it cost anything to be in the study?
There are no study-related medical services provided during this study. Research procedures such as questionnaires and pain scales will be collected during standard of care visits or research phone calls as described in this consent form.

The study drug will not be provided by this study. You or your insurance provider will be billed for the study drug you are prescribed. You should discuss the cost of these drugs with your pharmacy and/or insurance provider prior to deciding to participate in this study.

Your insurance may not cover some or all of the standard care services if you are part of a research study. You may want to talk to your insurance company and review your specific benefits and coverage before deciding to participate. You will be responsible for normal co-pays, deductibles and non-covered services that are not the responsibility of the study. Some procedures require Pre-Certification from your insurance company. Pre-Certification is not a guarantee of payment.

Will the researchers get paid for doing the study?
Your study doctor will receive payments from the Patient-Centered Outcomes Research Institute (PCORI) for conducting this study. Payments will be used for research purposes only.

More information about PCORI can be found on the following website: http://www.pcori.org/

What happens if I get hurt or sick during in the study?
If you have a serious side effect or other problem during this study, you should immediately contact your study doctor. Refer to the contact information on page 1 of this document.

Do I have to be in the study?
Being in research is voluntary. You can choose whether or not to participate. Even if you decide not to join the study, you can still come to your study doctor's clinic for services and treatment.

What other choices do I have?
You can choose not to be in the study. Instead of being in this study, you can receive treatments that are already used to treat ALS.

How will my privacy be protected?
The researchers will protect your information, as required by law. Absolute confidentiality cannot be guaranteed because persons outside the study team may need to look at your study records. Your health information is protected by a federal privacy law called HIPAA. By signing this consent form, you are giving permission for your study doctor and member of their study team to use and share your health information. If you decide not to sign the form, you cannot be in the study.

The researchers will only use and share information that is needed for the study. To do the study, they will collect health information from the study activities and from your medical record. You may be identified by information such as name, address, phone, date of birth, social security number, or other identifiers. Your health information will be used at KUMC by Dr. Richard J. Barohn, members of the research team, the medical records department of your hospital or clinic, the KUMC Research Institute and officials at KUMC who oversee research, including members of the KUMC Human Subjects Committee and other committees and offices that review and monitor research studies.
By signing this form, you are giving your study doctor and the research team permission to share information about you with outside persons or groups. Your information will be shared with the study team at KUMC, representatives of the Patient- Centered Outcomes Research Institute (PCORI), GAO (US Government Accountability Office), and other business partners who help with the study, the study's Data and Safety Monitoring Board, the study's Steering Committee, the study's Safety Committee, the U.S. Food and Drug Administration (FDA) and U.S. agencies that oversee human research (if a study audit is performed). These groups or agencies may make copies of study records for audit purposes. The purpose for using and sharing your information is to make sure the study is done properly and to evaluate the safety and effectiveness of the study drugs.

The HIPAA privacy law may not apply to everyone who receives your health information. Your information might not be

protected by HIPAA if persons outside your study site disclose it. In some cases, there may be other laws that protect your information from improper use.

While you are participating in this study, you may see and copy any study information that is placed in your study site medical record. However, some study information is kept only by the researcher. The records kept only by the researcher may not be available to you until the end of the study.

The researchers may publish the results of the study. If they do, they will only discuss group results. Your name will not be used in any publication or presentation about the study.

Can I stop being in the study?
You may stop being in the study at any time. Your decision to stop will not prevent you from getting treatment or services at the location you go to for this study. If you would be harmed by stopping the study drug suddenly, the researchers may ask you to gradually reduce the dose. You might be asked to come back for a final study visit.

You have the right to cancel your permission for researchers to use your health information. If you want to cancel your permission, please write to your study doctor using the address listed on the first page of this consent form. If you cancel permission to use your health information, you will be withdrawn from the study. The researchers will stop collecting any additional information about you about you unless they need information about a side effect of the study drug. They may use and share information that was gathered before they received your cancellation.

Could my participation be stopped early?
This study might be stopped, without your consent, by your study doctor, the sponsor or by the FDA. Your participation also might be stopped by your study doctor or by the sponsor if it is in your best interest or if you do not follow the study requirements.

Neither the sponsor nor your study doctor will be obligated to provide you with any study drug or treatment if the study is stopped early. Your study doctor will decide about future treatment, if it is needed.

Who can I talk to about the study?
Before you sign this form, your study doctor or other members of their study team should answer all your questions. You can talk to the researchers if you have any more questions, suggestions, concerns or complaints after signing this form.

CONSENT
Your study doctor or a member of their study team has given you information about this research study. They have explained what will be done and how long it will take. They explained any inconvenience, discomfort or risks that may be experienced during this study.

By signing this form, you say that you freely and voluntarily consent to participate in this research study. You have read the information and had your questions answered.

You will be given a signed copy of the consent form to keep for your records.

CONSORTIUM CONTRACTUAL ARRANGEMENTS

For detailed instructions, refer to the Application Guidelines for your PFA. Do not exceed five pages.

Describe the proposed research projects that will be performed by subcontracted organizations. Explain the strengths that these partners bring to the overall project.

GREATER PLAINS COLLABORATIVE

The Greater Plains Collaborative (GPC) is currently a partnership of ten medical centers located across seven states, the formation of which was driven by the initial PCORI vision of an integrated national data infrastructure to support practice-based outcomes and comparative effectiveness research.

The primary GPC organization (KUMC) and its subcontracting institutions each have well-established research programs as well as significant operational experience with both commercial EHR systems and informatics/data warehouse infrastructures. Additionally, the partners bring strong working relationships at both the localized level (between investigators and informatics/information technology organizations) as well as at the broader cross-institutional level. The subcontracting institutions within the collaborative each bring unique strengths and complimentary areas of expertise. The majority of sites are also CTSA sites or are participants in a CTSA consortium.

The following briefly describes each GPC partner site available to participate in this study (i.e. excludes Children's Mercy Hospital), their associated key personnel and their contribution to the consortium.

University of Iowa Healthcare, Iowa City, Iowa
University of Iowa Healthcare provides tertiary and quaternary-level patient care to the state of Iowa and the surrounding region as well as is a national leader in biomedical research. For the GPC partnership, University of Iowa Healthcare represents 1 hospital site, 12 clinic sites and 519,915 active patients with data in their EMR. The institution has a medical staff of 161 primary care providers and 1,047 specialty providers. The University of Iowa is both a CTSA site and is a NCI Designated Cancer Center. Gary Rosenthal, MD, is the Director of the University of Iowa Institute for Clinical and Translational Science (ICTS) is the Site PI. Dr. Rosenthal leads the GPC efforts around healthcare system and clinician engagement.

Medical College of Wisconsin (MCW), Milwaukee, Wisconsin
MCW is a private, freestanding medical school and graduate school of sciences located in Milwaukee, Wisconsin. For the partnership, MCW represents 4 hospitals and 189 clinics and brings 490,178 active patients with data in their EMR. The associated medical staff of MCW includes 406 primary care physicians and 2,293 specialty care providers. MCW is a CTSA site. MCW assumes the standard responsibilities as a member of the GPC under the leadership of Bradley Taylor, Chief Research Informatics Officer. Mr. Taylor contributes his expertise from over twenty years of experience in enterprise software solutions and engineering systems for whole genome sequencing. MCW provides GPC-wide expertise for the unstructured notes de-identification pipeline and Natural Language Processing (NLP).

University of Minnesota Academic Health Center, Minneapolis, Minnesota
The University of Minnesota (UMN) Academic Health Center (AHC) has partnered with one of the largest large care provider organizations in the state, Fairview Health Services, to create a secure link to data to support health research. Fairview Health Services, one of the largest healthcare providers in Minnesota, has 9 hospitals and 153 clinics and over 2.2 million patients with data in their EMR. The medical staff consists of 1,311 primary care providers and 2,814 specialty providers. The University of Minnesota is both a CTSA site and a NCI-Designated Cancer Center. The GPC partnership will benefit from the participation of the site leader, Connie Delaney, PhD, RN. Dr. Delaney is the Dean of the School of Nursing and also serves as the CTSA Biomedical and Health Informatics (BMHI) Director and as the

Acting Director for the Institute for Health Informatics (IHI). Additionally, Dr. Delaney an inaugural member of the Health Information Technology (HIT) Policy Committee of the U.S. Department of Health and Human Services and has conducted research and published extensively in the area of nursing data standards, nursing outcomes, their integration and alignment with other medical terminologies, and ultimate integration electronic health records and personal health records.

University of Nebraska Medical Center (UNMC), Omaha, Nebraska
The University of Nebraska Medical Center is Nebraska's only public academic health sciences center. With its associated Clinical Enterprise, Nebraska Medicine, it represents 2 hospitals and 28 clinic sites and brings 267,799 active patients within their EMR. Its medical staff consists of 240 primary care providers and 1,066 specialty providers. UNMC is both a COBRE IDeA award site and a NCI-Designated Cancer Center. In addition to standard partnership responsibilities, Dr. James McClay, the enterprise physician informaticist for UNMC, also plays a key role in the GPC. Dr. McClay provides informatics support to CER design and contributes to standards deployment across the GPC. Additionally, UNMC's Dr. James Campbell, CMIO, guides the management of terminology and the design of informatics methods and data collection instruments so that the GPC network can act as a feedback mechanism to measure Meaningful Use Stage 2 alignment at each site's healthcare systems.

University of Texas Health Sciences Center at San Antonio (UTHSCSA), San Antonio, Texas
UTHSCSA is the largest health sciences university in south Texas, serving both the San Antonio metropolitan area as well as the broader central and south regions of Texas. There are 36 affiliated clinics with 172,929 active patients in their EMR. Its medical staff includes 70 primary care providers and 339 specialty providers. UTHSCSA is both a CTSA site as well as a NCI-Designated Cancer Center. Alfredo Tirado-Ramos, PhD, Chief of the Clinical Informatics Research Division of the Department of Epidemiology and Biostatistics, has site leadership responsibility.

University of Texas – Southwestern Medical Center, Dallas, Texas
The University of Texas Southwestern Medical Center represents 2 hospitals and 51 clinic sites that serve the Dallas area. These hospitals and clinics bring 833,059 active patients with data in their EMR. The medical staff includes 180 primary care providers and 981 specialty providers. The institution is both a CTSA site as well as a NCI-Designated Cancer Center. UT Southwestern assumes the standard partnership responsibilities as a member of the GPC under the leadership of Lindsay Cowell, PhD. Dr. Cowell has expertise in the development of data standards and ontologies as well as experience in developing novel methods for representing and computing with biomedical knowledge, including in the context of EMR. Working with Dr. Cowell are members of the Academic Information Systems group which has extensive experience working with i2b2, REDCap, and other open source software. UT-SWMC represents a broad geography with a highly diverse patient population.

University of Wisconsin, Madison, Wisconsin
The University of Wisconsin – Madison and its affiliated University of Wisconsin Hospital and Clinics represent 1 hospital and 43 clinic sites for the partnership. The medical staff consists of 691 primary care providers and 743 specialty providers. Further, the University of has 416,106 active patients with data in their EMR. The University of Wisconsin – Madison has is both a CTSA site and a NCI Designated Cancer Center. Marc Drezner, MD, Site PI, leads the establishment of the network governance and centralized IRB processes for the GPC, specifically overseeing an Ethics, Regulatory and Contractual Processes committee. Dr. Drezner is Senior Associate Dean in the School of Medicine and Public Health and Executive Director of the NIH/CTSA-funded Institute for Clinical and Translational Research (ICTR) at the University of Wisconsin – Madison.

pSCANNER

pSCANNER (the patient-centered Scalable National Network for Effectiveness Research) is a stakeholder-governed federated network that uses a distributed architecture to integrate data from three networks covering over 21 million

patients in all 50 states: (1) VA Informatics and Computing Infrastructure (VINCI), with data from Veteran Health Administration's 151 inpatient and 909 ambulatory care and community-based outpatient clinics; (2) the University of California Research exchange (UC-ReX) network, with data from UC Davis, Irvine, Los Angeles, San Francisco, and San Diego; and (3) SCANNER, a consortium of UCSD, Tennessee VA, and three federally qualified health systems in the Los Angeles area supplemented with claims and health information exchange data, led by the University of Southern California. For this study, US Davis, UCLA , UC San Francisco and UC San Diego, will be the participating network sites.

California Pacific Medical Center

California Pacific Medical Center is one of the largest private, not-for-profit, academic medical centers in California and is a Sutter Health affiliate. As a tertiary referral center, the Medical Center provides a wide variety of services, including acute, post-acute and outpatient hospital care; home care and hospice services; preventive and complementary care and health education. The Forbes Norris MDA/ALS Research Center, located at California Pacific Medical Center has been at the forefront of neuromuscular disease research for over 25 years and is now one of the largest ALS clinical research centers in the United States. With one of the largest ALS patient populations, the Center carries on the legacy of its founder, Forbes H. Norris, M.D., a neurologist who was internationally renowned in the field of ALS research and clinical care. The Forbes Norris MDA/ALS Research Center is an ALS Association Center of Excellence, as well as one of six national Muscular Dystrophy Association ALS Centers dedicated to the treatment of ALS and related neuromuscular disorders.

PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard J.

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For detailed instructions, refer to the Application Guidelines for your PFA. Do not exceed 10 pages.

Following scholarly citation practice, list the source material cited in this Research Plan.

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PRINCIPAL INVESTIGATOR (LAST, FIRST, MIDDLE): Barohn, Richard J.

APPENDIX (optional)

For detailed instructions, refer to the Application Guidelines for your PFA. Do not exceed 10 pages.

PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE
SUMMARY STATEMENT
(Privileged Communication)

Principal Investigator: Richard Barohn, MD
Organization: University of Kansas Medical Center Research Institute, Inc.
Project Title: Comparative Effectiveness Study of Treatment of Sialorrhea in Patients with ALS
PCORI Funding Announcement: Assessment of Prevention, Diagnosis, and Treatment Options
Review Cycle: Spring 2015 Cycle
Request ID: SC15-1503-28249

AVERAGE OVERALL SCORE: 26

QUARTILE: 1

In-Person Review Discussion Notes:
Strengths:

- The proposed study is a straightforward comparative effectiveness research study. All four treatments being compared are efficacious.
- The Bayesian study design, which will ultimately enroll more patients into the most efficacious arm for maximum benefit, is very strong and compelling.
- The study will use existing PCORnet infrastructure.
- This is clearly a patient-centered study. Drooling restricts patients' ability to call for help and can lead to social isolation, diminishing quality of life.
- Potential for dissemination is high. The investigators are well established and the clinics involved have already adopted the standard scale.
- The study team recognizes that it is difficult for these patients to travel to their physician's office, so the study visits coincide with regular appointments. This is an excellent example of patient-centeredness. Reviewers also noted that the ability of participants to self-report through a portal demonstrates patient-centeredness.

Weaknesses:

- Patients will likely have already been on some sort of treatment for this symptom. Because the study design is open label, patients might already have notions of which treatment they prefer.
- The PRO saliva scale doesn't appear to have been previously validated, but this is a minor concern.
- Some reviewers were concerned that, because these potential participants are part of a tight-knit online community and the study design is open label, they could share information online

and introduce bias and confounding.
- Reviewers had some concerns about the medications:
  - The application does not discuss the half-life of the medications, and how long participants would be required to be off medications to allow for 'wash out' before taking their assigned study medication.
  - Drug carry over could result in side effects.
  - All proposed study medications have shown benefits with short-term use, but long-term efficacy of these medications has not been explored.
- The statistical analysis plan does not address how data collected at multiple time points will be analyzed.

Additional Comments:

- Reviewers were concerned that if patients must bear the cost of participation, recruitment might be a challenge. Other reviewers noted that most individuals with ALS are on Medicare, which does cover these medications, so insurance coverage should not be an issue.
- Some reviewers raised the possibility that IND approval would be necessary, because these medications are not proposed for this indication. Other reviewers noted that these medications are in widespread use, so it would not be necessary to obtain INDs. This needs to be clarified.
- It was unclear how local IRB approvals would affect the timeline.

The following reviewer critiques were completed prior to the in-person review and were not altered post-discussion.

Criterion 1: Impact of the condition on the health of individuals and populations

Reviewer 1:

Strengths:

- ALS is a progressive neurodegenerative disorder associated with extremely high burden for patients and caregivers.
- Sialorrhea affects half of patients with ALS.

Weaknesses:

- It is not clear that sialorrhea is the highest priority for patients with ALS. [*negligible weakness*]

Reviewer 2:

n/a

Reviewer 3:

n/a

Reviewer 4:

Strengths:

- Amyotrophic lateral sclerosis (ALS), sometimes called Lou Gehrig's disease, is a rare progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. However, about 10 percent of those with ALS survive for 10 or more years.
- Excessive saliva can be one of the most frustrating symptoms of ALS with sialorrhea affecting half of them. It can be life threatening, since it frequently causes choking, especially at mealtimes when saliva secretion is increased and chance of aspiration is greatest.

Weaknesses:

- None noted.

Criterion 2: Potential for the study to improve health care and outcomes

Reviewer 1:

Strengths:

- A survey conducted by the applicants documents considerable variation in use of treatments for sialorrhea in patients with ALS.
- Limited comparative effectiveness data exist to guide treatment selection for sialorrhea in patients with ALS. The treatments themselves have certain unpleasant side effects.
- The study will compare multiple treatment strategies.

Weaknesses:

- The application lacks sufficient information about the efficacy of the treatments under study in order to assess the potential impact of the proposed project. The applicants mention that the efficacy of the treatments is “high,” but, if this is true for all treatments under study, then the establishing the comparative effectiveness of these treatments may have limited impact if the differences in effectiveness are small. [*minor weakness*]

Reviewer 2:

Strengths:

- Combination of two CDRNs working together to conduct this important ALS gap in current knowledge.
- Preliminary data suggests drooling has a major, negative impact on quality of life for both patient and family.
- Clinical uncertainty in terms of best intervention with least harm (side effects) would have major impact on the ALS population and result in a change in clinical practice.
- Medical management of ALS patients is done through specialty clinics sponsored by the Muscular Dystrophy Association and the ALS Association. While the American Academy of Neurology has published practice parameters in ALS to include recommendations of anticholinergic medications, there is little consistency or regulatory in prescribing these medicines for patients.
- In addition, no studies have been done to compare effectiveness in these patients. Four specific medicines are generally used: scopolamine patch, glyycopyrrovate, amitriptyline and atropine. The GPC (Greater Plains Cooperative), a CDRN, has done considerable preliminary

work around surveying patients and their caregivers to understand if drooling presented a significant problem in management of ALS.

- In addition, through a website (www.rrnmf.com) commonly used by ALS physicians, surveys were conducted to understand if drooling was a topic of interest and learn what medicines were commonly prescribed.
- Wide variations in prescribing were evident as well as the frequency of recommendations. From these data, a significant gap in care was identified and plans made to attempt to address the gap.
- Positive results would be rapidly disseminated through publication, updating practice parameters, ALS clinics, and information to all patients. Identifying the most appropriate anticholinergic medicine with the most tolerable side effects would be of significant benefit to ALS patients.

Weaknesses:

- None noted.

Reviewer 3:

Strengths:

- Major: The proposal aims to generate practical information to guide patient with ALS choices and physician's recommendations regarding management of drooling. Four treatments for this condition will be compared in a randomized trial (1.5 mg scopolamine patch every 72h, glycopyrrolate 1m 3 times daily, amitriptyline 25 mg once daily at bedtime, and two atropine 1% sublingual drops three times daily).
- Major: The research is innovative in its approach, which uses adaptive clinical trial design to accommodate for the small number of patients with this rare disease and the number of treatments under examination.
- Major: Findings, whether positive or negative, have the potential to be disseminated both to patient and physician communities. The principal investigator and other researchers involved in the project are in leadership positions to influence the practice of sialorrhea control for patients with ALS.

Weaknesses:

- None noted.

Reviewer 4:

Strengths:

- There is a clear gap regarding the comparative effectiveness of selected treatment for drooling in patients with ALS. This application has a potential to identify the best medication in controlling drooling among four medications (scopolamine patch transdermal, glycopyrrolate, amitriptyline, atropine).
- The study will also determine the tolerability of each of the four treatments for drooling in patients from a four arm randomized controlled trial open label approach. The application has a potential to identify tolerability of each of the four treatments, choose drugs with the most favorable side effect profile, and identify subgroups who respond differentially to treatment.

- Positive findings could potentially be disseminated and implemented quickly within the medical community given proper health education of providers and patients, as well as caregivers.

Weaknesses:

- Proposed medications have been used with success for short periods in controlling drooling. A negligible weakness is that it is not clear if the proposed medications will illustrate its efficacy over longer periods.
- The drug riluzole (Rilutek) is the only medication approved by the Food and Drug Administration for ALS. The drug appears to slow the disease's progression in some people, perhaps by reducing levels of a chemical messenger in the brain (glutamate) that's often present in higher levels in people with ALS. The study needs to examine side effects and tolerability when medications are used with riluzole.

Criterion 3: Technical merit

Reviewer 1:

Strengths:

- A key strength of the study is that treatment assignment will be randomized.
- The use of a Bayesian Adaptive Design is innovative and the technical aspects are described in detail. The use of adaptive randomization will increase the probability that patients receive the most effective treatment during the course of the trial, which is good for patients and may enhance recruitment.
- The project will be conducted across multiple sites and will utilize the PCORnet infrastructure, which will increase the likelihood of successful implementation of the ambition study.

Weaknesses:

- It appears as though patients with prior treatment for sialorrhea will be included in the study, but it is not clear what impact this prior experience will have on the results of this open-label trial. [*minor weakness*]
- While patient input drove the selection of the Patient Reported Saliva Management Scale as the primary outcome, and while a prior randomized trial has used this tool, it appears that the measure has not yet been rigorously validated. [*negligible weakness*]

Reviewer 2:

n/a

Reviewer 3:

Strengths:

- Major: The ALS clinical and research communities have agreed on standard clinical measurement tools to assess outcomes, which the investigators envision will be used for the study.
- Major: The standard functional and symptom scales have largely been adopted by the GPC

ALS clinics and the investigators estimate that the corresponding forms will enable feasible data collection.

- Major: There is adequate access to patients to recruit the estimated 200 maximum needed to address the research aims. Patients will be recruited from all ALS referral sites participating in GPC PCORNet and select pSCANNER sites.
- Major: The research team has the necessary expertise to carry out the proposed study. The GPC is a PCORNet CDRN composed of 10 leading medical centers that will build on the resources developed through CTSA initiatives.
- Major: Collaboration with GPC ALS clinics and pSCANNER is expected to capture the majority of patients with ALS in the West and Mid-West.

Weaknesses:

- Minor: A clear plan to ensure future reproducibility of findings is not in place. This is a mild weakness to the extent that this is corrected.

Reviewer 4:

Strengths:

- The applicant proposed a pragmatic, four-arm, parallel, adaptive randomized clinical trial to identify the best treatment for sialorrhea in patients with ALS using a novel Bayesian adaptive design, in which a higher proportion of patients is likely to be randomized to the most effective treatment arm while generally using fewer total patients than an analogous trial with fixed randomization when identifying a superior treatment.
- This comparative effectiveness trial for drooling will use Patient Centered Outcome Research Network (PCORNet) methods and EMR-based infrastructure to conduct pragmatic trials in the clinic workflows, which will save time and cost due to the use of existing infrastructure.
- The applicants have extensive experience in implementing complex, large clinical trials.

Weaknesses:

- Measurement of outcomes occurs at specified time points such as months 1, 2 and 3. The applicants provided sample size estimation without incorporation of the outcome measurements at multiple time points.
- A moderate weakness is that statistical analysis plan does not incorporate the nature of the data collection such as measurement of outcomes at multiple time points.
- If ALS patients are already on medication for sialorrhea, they will be asked to switch based on the assigned treatment, which may cause adverse events and bias of the study results due to carryover effects of previous medication.

Criterion 4: Patient-centeredness

Reviewer 1:

Strengths:

- The proposal addresses several of PCORI's key patient-centered outcomes research questions.
- The primary outcome measure was guided by patient input.
- Other outcomes address health-related quality of life, which is inherently patient-centered.

Weaknesses:

- It is not clear whether the Patient Reported Saliva Management Scale is available in languages other than English and whether patients who cannot speak English will be included in the study. [*minor weakness*]

Reviewer 2:

Strengths:

- Patient centeredness is at the heart of this proposal as it begins with asking questions about drooling and its impact on quality of life of the patient and caregivers.
- It incorporates the patient voice in meaningful ways to understand how or if drooling is treated and with what medicines.
- It further investigates treating physicians, what medicines are recommended and with what frequency.
- The proposal includes patients and caregivers on protocol development as well as operations to understand how best to understand what medicine most effective and if there are subsets of patients that benefit from a particular approach. It also rules out myobloc and salivary radiation as these are invasive procedures which carry considerable risk and are not available at all ALS clinics. Typically myobloc and raditional of the salivary glands are utilized only when oral medication fails.
- This is a pragmatic study which incorporates patients in all aspects.
- Patients are able to participate in the study (based on inclusion criteria), also may elect not to participate, but rather share their experiences.
- Patients and their caregivers have been included throughout the design of the study, informing the project at each step.
- A positive outcome has the potential to improve the quality of life for patients with ALS, 50% of which suffer from constant drooling.

Weaknesses:

- The proposal does not evaluate 'last resort' therapies such as botox or radiation of salivary glands which may be considered for patients with drooling that does not respond to first-line therapy.

Reviewer 3:

Strengths:

- Moderate: The need to gain information about efficacy of treatments for drooling was identified by surveying patients in the Greater Plains Cooperative ALS specialty clinics and clinicians followed by focus groups of patients and caregivers.
- Major: The proposed study would address patients' options and benefits and harms of those options in the management of drooling in ALS. Study results would also empower patients by informing them on how to improve important outcomes affecting their quality of life.

Weaknesses:

- Minor: It is unclear how many patients were surveyed and the response rate to identify the proposed research question. It seems like the focus group of patients consulted to establish the need for the study was also small, so it is unclear whether the need for comparative effectiveness research on interventions to manage drooling would generalize to all or the majority of patients with ALS. This is a minor weakness considering that the applicants cite that published guidelines suggest a gap in care between available symptomatic treatments for drooling and the frequency at which these therapies are offered to patients and that over half of patients with ALS experience drooling.

Reviewer 4:

Strengths:

- The rationale behind the approach is based on patient comments collected by the researchers over years of treatment of Amyotrophic Lateral Sclerosis (ALS).
- The outcomes are all patient-centered. The primary outcome measures how they perceive their drooling compared to baseline on a 5-point scale.
- ALS patients will know what the benefits and side effects are, which will improve their chances of achieving their preferred outcomes.
- The study aims to improve management of disease and improvement in quality of life for ALS patients, which will benefit the patients and their caregivers/families.

Weaknesses:

- None noted.

Criterion 5: Patient and stakeholder engagement

Reviewer 1:

Strengths:

- Since the original submission, the applicants asked the physician networks to discuss the proposal with their patients. It appears as though secondary Aim 2 has been added, which will involve a survey to understand the experience with medications for drooling in patients who do not qualify for the study.
- The proposal mentions involvement of key stakeholders throughout the project.

Weaknesses:

- It does not appear that patient input played much of a role in the development of the original proposal and it does not appear that the discussions mentioned above led to meaningful modifications to the main study aims. [negligible *weakness*]
- Details of the selection and specific integration of patients and other stakeholders is vague. [*minor weakness*]

Reviewer 2:

Strengths:

- This proposal combines two CRDNs in a most efficient way and incorporates all stakeholders as partners in the process.
- The study plan, roles and responsibilities of all stakeholders and participants are well defined and thoughtfully described.
- It provides the opportunity to all patients/caregivers to participate to the degree they are able and willing, recognizing and reducing the burden of participation.
- It assigns equal value to all stakeholders and engages the community in the process to rapidly evaluate anticholinergic medicines.
- It recognizes that there may be differences in patients (onset of weakness), gender and other factors. Study conduct and analysis are well described.
- This is an important and thoughtful proposal that builds on existing relationships and is a trusted source for both patients and treating physicians.

Weaknesses:

- None noted.

Reviewer 3:

Strengths:

- Moderate: Patient input throughout the study will be sought through formation of a patient advocacy committee (PAC). Patient input was already taken into account to design the study and will continue to be engaged in particular for dissemination of the results and through monthly calls to discuss the study and provide input on how to recruit and retain patients.
- Major: There is transparency in the communications with patients. For example, the informed consent document discloses that the cost of the study drug will not be covered and must be covered by the patient or her insurance.
- Moderate: Input from various stakeholders will be taken into account throughout the study by forming a Protocol Operations Committee (POC), composed of patients, physicians, patient advocates, a statistician and an engagement facilitator. POC will review the protocol every six months.
- Moderate: There is clear delineation of roles for all stake holders. The research and its conduct are clearly driven by the expert investigators with patient input to ensure that the potential results align with patient needs. Similarly patients will make use of their strengths in knowledge dissemination and advice on subject recruitment.

Weaknesses:

- Moderate: It is unclear if participation in the study will be limited by willingness of insurance or patients to cover the cost of the study drugs.
- Moderate: Patient partner participation will be compensated with $25 gift cards. It is unclear if this compensation will be provided to all patients participating in the trial or whether this would be the compensation for participation in additional activities such as PAC. Engagement of PAC members as consultants would better compensate and recognize the contributions of these partners.

Reviewer 4:

Strengths:

- Stakeholders are part of ALS patient groups such as ALS Association, Muscular Dystrophy Association, American Academy of Neurology, which will be involved in dissemination and implementation of the study's results.
- Stakeholders were involved from the inception of the project through developing the research questions and providing feedback.
- Five key findings from the focus group have helped to shape the approach and protocol for the study.

Weaknesses:

- None noted.

Overall Comments

Reviewer 1:

This ambitious project will compare multiple treatment options for sialorrhea in patients with ALS across GPC and pSCANNER sites. Key strengths include randomized Bayesian Adaptive Design, the utilization of the PCORnet infrastructure, the focus on patient-centered outcomes, and the investigator team. The potential for significant impact is uncertain given the comparison of drugs that are already believed to be highly efficacious and because the study will not consider choking risk, which is described as a major consequence of sialorrhea. It is unclear whether the study will focus on only English-speaking patients.

Reviewer 2:

ALS patients and their caregivers are socially isolated by the level of weakness and functional loss. Compounding this, constant drooling affects 50% of the patients, presenting a social stigma based on the continuous need for wiping and the odor that occurs with constant saliva. Patients (and their caregivers) stop seeing friends and family, retreating to a life of isolation. Patients and caregivers life with the anxiety and threat of choking or aspiration, necessitating constant observation and care. Care is variable in rare disease because there is no available evidence. This proposal outlines a cogent approach with the potential to identify the most effective evidence-based approach to drooling. This would be rapidly implemented through the ALS clinics and delivered to patients who need and deserve help.

One weakness may be the out of pocket affordability of the intervention.

Reviewer 3:

The proposed research plan appears to have the necessary scientific rigor and expert involvement and resources to address a meaningful question with the potential to inform treatment choices of patients with ALS and drooling. A strength of the project is that it would build on the infrastructure created by PCORI and other federal grants (CTSAs) to address a patient-centered outcome research question. The input of patients has been taken into account to formulate a clinically meaningful research question and would continue to be engaged as the trial proceeds and as results are disseminated.

Reviewer 4:

The proposal deals with important questions for ALS patients and their caretakers. This study will benefit the ALS patients and caregivers since it will allow researchers to understand which medications for the treatment of sialorrhea are most effective. The applicants take advantage of a PCORNet CDRN, which will increase the likelihood of success. The applicants use the EPIC EMR which makes communication between all the teams less of a barrier. The application uses an innovative Bayesian adaptive design. The project is highly patient-centered, and the applicants have done an excellent job engaging the important stakeholders.

Proposed medications have been used with success for short periods in controlling drooling. However, it is not clear if the proposed medications will illustrate their efficacy over longer periods. The drug riluzole (Rilutek) is the only medication approved by the Food and Drug Administration for ALS. The study needs to examine side effects and tolerability when study medications are used with riluzole. If ALS patients are already on medication for sialorrhea, they will be asked to switch based on the assigned treatment, which may cause adverse events and bias of the study results due to carryover effects of previous medication. Measurement of outcomes occurs at specified time points such as months 1, 2 and 3. The applicants provided sample size estimation without incorporation of the outcome measurements at multiple time points. Statistical analysis plan does not incorporate the nature of the data collection such as measurement of outcomes at multiple time points.

Does the application have acceptable risks and/or adequate protections for human subjects?

Reviewer 1: Yes

Reviewer 2: Yes

The proposal has adequate protections for human subjects.

Reviewer 3: Yes

Institutional Review Board reciprocity agreements are in place to establish two central IRB oversight committees, which will hopefully ensure adequate protection of human subjects. The risks of participating in the study are presented in the sample informed consent attached to the application, and the risks of each drug to be tested are known. Adequate protections of patient data are also presented. There is also a well thought out data management plan to collect and maintain the data in HIPAA certified servers.

Reviewer 4: Yes

The application has acceptable risks and adequate protection for human subjects. The application appropriately described the possible risks for medications.

Health Sciences Research Day at University of Missouri, 2019

The 2019 Health Sciences Research Day was be held on Thursday, November 21, 2019. Organized and sponsored by the MU School of Medicine Research Council, Health Sciences Research Day also partners with the MU School of Medicine, MU Sinclair School of Nursing and MU School of Health Professions. This is an annual event where medical students, residents and other learners present the research they have done under the direction of a faculty mentor.

Some of these projects resulted in published papers already (Govindarajan R et al. RRNMF Neuromuscular Journal, 1(2), 3-6; Mehta T et al. RRNMF Neuromuscular Journal, 1(1); Digala LP, Clin Neurophysiol Pract. 2020;5:35-37) and one is under consideration for publication and manuscript is being written.

Raghav Govindarajan MD, FAAN
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Efficacy of botulinum toxin for treating cramp related pain in peripheral neuropathy

Tejas Mehta, Observer, Department of Neurology.
Richard Sommer, Department of Neurology
Raghav Govindarajan, MD, Department of Neurology

INTRODUCTION: Muscle cramps in peripheral neuropathy are the cause of constant distress and disability. Although several drugs have been used in its management, drug tolerability and inefficacy of these medications is a common concern. Botulinum toxin has been used to manage cramp induced pain in cases of diabetic neuropathy with significant improvement.

METHODS: This retrospective chart review included a total of ten patients with established diagnosis of polyneuropathy suffering from lower limb cramps. Comparison of pain score due to cramps before the administration, at 3-month, 6 month and 9 months follow up using the Wilcoxon test was done to assess the efficacy of botulinum toxin.

RESULTS: All patients enrolled in the study showed improvement of pain due to cramps assessed by visual pain analog scale with no adverse events. The improvement of pain score from before and at 3 months, 6 months and 9 months follow up was 1.6 ($p<0.05$), 2.7 ($p<0.05$) and 3.50 ($p = 0.05$).

CONCLUSION: Local BTX-A infiltration is likely efficacious and safe procedure for improving pain associated with cramps in patients with peripheral neuropathy of various etiologies.

Botulinum toxin for the treatment of lower limb cramp pain in patients with ALS

Tejas Mehta, MBBS, Observer, Department of Neurology
Richard Sommers, Department of Neurology
Raghav Govindarajan, MD, Department of Neurology

INTRODUCTION: Muscle cramps and pain associated with them can be seen in patients with amyotrophic lateral sclerosis (ALS) and are known to reduce the quality of life. Pharmacological treatment may not benefit all patients in treating these cramps. We assess the efficacy of Onabotulinum toxin A (BTX-A) in the treatment of lower limb cramps in patients with ALS.

METHODS: This retrospective chart review included a total of ten patients with ALS who suffered from pain due to lower limb cramps and were managed with BTX-A. Data including patient demographics, visual analog pain scale at different intervals during follow up, ALS functional rating scale and site of onset of ALS symptoms were documented. The pain score at baseline (before administration), at 3 month and at 6 months follow up were compared using Wilcoxon test to assess BTX-A's efficacy.

RESULTS: A significant improvement in average pain score due to cramps from baseline to the 6-month interval with a change of 3.1 ± 0.7 ($p<0.05$,95%CI) was seen on the pain scale. No adverse events were noted during or after administration of BTX-A.

CONCLUSION: Local BTX-A administration is an efficacious and safe procedure for improving pain associated with cramps in ALS.

Thickening Fraction as a Measure of Ultrasonographic Diaphragm Dysfunction in Amyotrophic Lateral Sclerosis

Presenter: Lakshmi P, Digala, Medical Graduate.
Lakshmi P. Digala, MBBS
Raghav Govindarajan, MD, Department of Neurology.

INTRODUCTION: Respiratory failure is the most common cause of death in ALS patients secondary to diaphragmatic dysfunction. In this case series of 3 ALS patients, we sought to determine the diaphragm dysfunction by measuring the diaphragm thickening fraction (DTf) and compared with the compound muscle action potential of diaphragm measured by phrenic nerve conduction studies.

METHODS: High-resolution linear US probe of 10 MHz (Philips Healthcare EPIQ 7 Ultrasound System Inc.) was used to measure the diaphragm thickness (DT) using B mode at the Zone of Apposition.

RESULTS: Diaphragm thickening fraction (DTf) is used to measure the extent of diaphragm dysfunction and as a predictive tool for extubation in patients on mechanical ventilation. In our patients, DTf (%) of <20% was predictive of diaphragm dysfunction as measured by the phrenic nerve conduction studies.

CONCLUSION: Critical illness polyneuropathy and myopathy are the cause of diaphragm dysfunction in mechanically ventilated patients. Similar mechanism of the secondary nerve (phrenic) and muscles (diaphragm) dysfunction due to death of anterior horn cell is seen in ALS patients. DTf (%) might serve as a useful surrogate marker to determine the diaphragm dysfunction even in the ALS patients.

Clinical Experience of Edaravone in Amyotrophic Lateral Sclerosis

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Tejas Mehta, Graduate Student
(Raghav Govindarajan, MD)
Department of Neurology

INTRODUCTION: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder affecting upper and lower motor neurons, resulting in progressive paralysis and death in 3-5 years. In May 2017, edaravone became the second FDA-approved medication for ALS. The therapy regimen is strenuous, requiring intravenous infusion daily for 14 days, followed by a 14-day treatment break. This cycle is repeated indefinitely until the patient chooses to discontinue the medication or dies as a result of his or her neurodegenerative disease.

METHODS: The current study investigated characteristics in a group of patients (n=7) with ALS who began and subsequently discontinued edaravone, compared to a group of patients (n=24) who have continued edaravone treatment for the duration of their disease. In addition, the study evaluated ALSFRS-R scores and FEV1/FVC ratio at different intervals during treatment.

RESULTS: The average patient age was 62.1 years, with a distribution of 18 males to 13 females. 18 patients had limb onset, 12 bulbar onset, and 1 diaphragmatic onset. 7 of the 31 patients discontinued treatment. The average age of patients who discontinued edaravone was 65.7 years, of whom which 3 had limb onset, 3 bulbar onset, and 1 diaphragmatic onset. Port complications were documented for 71.4 percent of patients who discontinued therapy. The remaining patients who discontinued reported no perceived benefit. Within the discontinuation cohort, there was a greater decline in ALSFRS-R scores and FEV1/FVC, compared to the continuation group.

CONCLUSION: When considering edaravone treatment physicians should balance the therapeutic effect, experience of adverse events, and patient perspective of benefit.

Factors Influencing the Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy

Amer Avdagic, M1
Raghav Govindarajan, MD
Department of Neurology

INTRODUCTION: Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a neurological disorder that leads to demyelination of peripheral nerves where the presentation for this disorder varies patient to patient. CIDP symptoms include loss of sensation, loss of reflexes, tingling and pain, and weakness. Criteria has been developed by the European Federation Neurological Society (EFNS) for guidelines in the diagnosis of this disorder. The objective of this study was to look at the relationship between the EFNS diagnostic criteria and whether patients that have the diagnosis of CIDP meet this criteria.

METHODS: We first completed data collection on the patient's diagnosed with CIDP and then the patients that were diagnosed but did not meet the criteria were analyzed to see what common outliers exist for this misdiagnosis.

RESULTS: This study looked at the relationship between the EFNS diagnostic criteria and symptoms present in the patients diagnosed with CIDP. The diagnostic criteria for the classic form of CIDP consists of progression for at least 2 months, weakness more than sensory symptoms, hyporeflexia, increased CSF protein, and nerve conduction evidence of a demyelinating neuropathy. There is evidence that has shown the over-diagnosis of a third to half of patients diagnosed with CIDP.

CONCLUSION: CIDP is a neurological disorder that varies in presentation making it difficult for accurate diagnosis. Criteria has been developed by the EFNS for guidelines in the diagnosis of this disorder. Overall this study investigated the factors that are involved in the false positive diagnosis of CIDP. Our data indicates the symptoms that increase the rate of misdiagnosis.