RRNMF NEUROMUSCULAR JOURNAL
Letter from the Founding Facilitator

The purpose of creating RRNMF Neuromuscular Journal was to build a venue for our colleagues in the field of neuromuscular medicine to have a hassle free and easy way to get published in a journal devoted to neuromuscular disorders. I wanted to have a journal that costs no money to run and that did not charge authors a fee for publishing their papers and no subscription fee.

We also wanted it to be completely on-line and open access. In addition, I wanted the authors to own the contents of what they wrote. I did not want the journal to have any copyright or ownership of what was published. I wanted healthcare researchers/authors to be in control of the journal and not a publisher or a society.

Of course, I did not want this to be a predatory open access journal that charged excessive fees to publish and preyed on susceptible young investigators who were under pressure to publish at any cost. And I wanted it to be a fun journal that we all could enjoy and not have to worry that the editor or editorial board or reviewers would insist that you make minor and unnecessary changes to your manuscript. I wanted to avoid "gotcha" reviewer and editor comments. We are doing peer review, but it will really be looking at the overall big picture of what your manuscript is about and what you are trying to say and not nit-picking the manuscript apart which happens in so many ways in many journals in the review and editing process.

The new technology to do journal publishing digitally with tools we have in the University of Kansas Libraries Digital Publishing Services unit has allowed us to do this at this point in time.

This is a part of KU Libraries (not the KU Press which is a different unit that publishes hard copy books). KU Libraries provides a Journal Management System that allows online journal publishing. The Library has purchased software from a company called OJS. I became aware of the capability at KU only a couple of years ago through meeting Marianne Reed who is the Digital Initiatives Manager. I had been exploring fee for service open access publishing vendors but then I found out this is available at KU for free! All it takes is a KU faculty member who wants to start a journal and who is willing to put together a team of colleagues who would help. The Library provides a project manager to assist the Faculty with online publishing. The Faculty and his/her colleagues (which do not have to be from KU) are the "editors and editorial staff". KU Libraries has over 40 digital journals. The only other medical one is the Kansas Journal of Medicine which we are patterning much of our organization after. Go to journals.ku.edu to see the entire list and from this website you can click to go on any of the journals, including RRNMF Neuromuscular Journal. Also, you can go directly to our journal by using journals.ku.edu/RRNMF.

Being able to publish in this way is truly part of the computer revolution in communication that began in the middle of the last century but is now having even a greater impact every day. The computer revolution has changed everything we do as a species and how we communicate. I am old enough to have started my academic career prior to the computer revolution when we sent typed manuscripts (yes on a real typewriter) and mailed them to a journal (with postage stamps). The editor would return it with red pencil marks that he did himself for you to make revisions. I recall the first time I bought a portable electronic typewriter as a resident (1983-1986) in which I could program a template for the history and physical and I used this because my handwriting was so bad. These early "computers" evolved quickly to desk and laptops. We all moved on to typing our manuscripts on desk and laptops in the 1980s, but we still mailed them into the journal office and they still came back with red pencil marks to correct. I have all my old submitted manuscripts from Drs Robert Daroff and Lewis Rowland (from the journal *Neurology*) with their pencil corrections which I cherish. In the appendix I am attaching my first article that was accepted into *Neurology* that was edited by Dr. Daroff (lightly!) and our snail mail correspondence. This was our Myoshi Myopathy clinical paper. Dr. Miller insisted we not call the disorder by someone's name so the title was shortened to Autosomal Recessive Distal Dystrophy in the galley state (1). Finally, journals moved to online submissions and the process went full electronic in the late 1990s. So, this computer revolution in publishing did not take long to evolve.

Now the process has become less expensive and streamlined and software programs are available so nonprofit institutions like the University of Kansas can purchase them to make it available to their faculty who want to start their own academic journals.

I see this as part of the evolution of our human species that has a continuing drive and need to communicate ideas. What this journal is about is facilitating IDEAS to be seen by others in an evolving communication format that is part of this new revolutionary era of communication via online technology. Our human ancestors began walking about 2 million years ago. Mankind/homo sapiens seem to have evolved probably 200,000 to 300,000 years ago. These early humans lived in hunter-gatherer societies. All communication was in small tribes, around the fire and in caves. Food was free by being part of the clan. Tribes moved around a lot and there were no permanent settlements. But even these early humans wanted to communicate ideas and we have evidence of this in paleolithic cave drawings. The earliest cave drawings in Europe date from 17,000 to 30,000 years ago in France and Spain. Picasso apparently said after seeing the amazing animal cave paintings in the Lascaux Cave in France, "They've invented everything". Recently, even earlier cave paintings were discovered in Borneo, Indonesia from 44,000 years ago. (2) The Indonesian drawings

showed wild pigs and buffalo and also part human /part animal figures that had snouts and tails. These animal-human figures are thought to indicate that the early humans who created them could conceive of things that did not exist in the natural world. Cave drawings are thought to represent the beginning of creative thinking. This is the dawn of the IDEA Revolution. It has also been called the "Cognitive Revolution". (3)

The Agricultural Revolution occurred about 10,000 years ago. Humans moved from hunter-gatherer nomadic clans to cities and they had to grow food in farms to support the growing masses of people. The populations exploded. The food had to be locked up. People had to pay for the food. Religion develops to give people an explanation of "what the heck is happening" and allowed people to believe that if their life is difficult now they should not worry as it will be better after they die in the afterlife, or that a supernatural being has got their back. For a wonderful easy-to-read discussion about this march through various revolutions and the impact of the agricultural and other revolutions see *Sapiens: A Brief History of Humankind* by Yuval Noah Harari (nonfiction) and the series of novels by Daniel Quinn which tells this story in a unique way. (3,4,5,6)

A number of civilizations emerged around the planet. The earliest cities and civilizations were formed in what is now Iraq in Mesopotamia and written language called cuneiform was probably invented somewhere around 3200 BC in Sumer. The development of writing I believe was the First Communication Revolution. In Babylon the Code of Hammurabi was written in 1754 BC, one of the earliest deciphered writings of significant length. Other civilizations emerged in Egypt, Indus River Valley, Asia, Persia and the Minoans in Crete with their own language and written alphabets. The Minoans developed a language that was then widely disseminated by the Phoenicians and became the forerunner of Greek. The Mayans in Mesoamerica developed their own writing system independently perhaps as early as 500 BC. Eventually, western civilization evolved in classical Greece and Rome. Paper was developed in China between 100 BC and 100 CE, a major advance in communication, which I consider the Second Communication Revolution. Paper had immense consequences to the book world. Books could now be carried by hand and no longer had to be transported in multiple individuals / sections on parchment.

Following the fall of the Roman Empire things went dark in the west for a thousand years. The Third Communication Revolution occurred with the development of the movable type and printing press by Johannes Gutenberg around 1440. Immediately ideas could be easily communicated in books and other paper products. The rate limiting step was being able to read. The printing press facilitated the blossoming of the Renaissance in art and science (which had begun a century earlier) with the re-emergence of classic Greek and Roman works and the development of new ideas that could be easily printed and disseminated in books.

The Enlightenment Revolution in the 1700s promoted individual freedom to lead our lives and furthered ideas in rational science and in social behavior. The Industrial Revolution began in the early 1800s with the development of machines that made things easier to do. It also allowed people to move even more often and faster to the cities. It also locked more of the food up as well. From the mid-1800s to the mid-1900s there was another revolution in science-the Postindustrial Scientific Revolution. Machines that had been developed now allowed scientists to make new discoveries in every sphere of science culminating in the understanding of the cell and the universe, along with amazing breakthroughs in medical knowledge and treatments. Surgery was possible, new drugs were developed that actually worked and DNA was discovered unlocking the secrets of life. The years between revolutions became shorter and shorter. We moved quickly from the postindustrial scientific revolution to the current Computer Revolution of the last half of the 20th century, the Fourth Communication Revolution, which has led to RRNMF Neuromuscular Journal.

This new journal is an outgrowth of our website RRN-MF. I used to communicate with my close colleagues by snail-mail. At one point there were about six of us in a BBC - Barohn Book Club and I would actually mail books that I thought would be of interest to my friends. Then came emails. For years in the 1990s I resisted the use of email and had my secretary in Dallas print my emails and I would write my response in long hand and she would type it out and respond to the email for me. I just did not want to waste my time getting on a computer everyday to do emails. But when I moved to Kansas City and the University of Kansas in 2001, for the first three months I did not have a secretary. So, I was thrown into the deep water and had to begin doing emails myself.

My life has never been the same and I am not sure it is better for emails. But as a result of me learning how to do my own emails, in the early 2000s we began a chain email group that was the original BBC plus others, and we kept adding more neuromuscular doctors. The initial BBC and email chain crew as I recall was Jon Katz, Dave Saperstein, Carlayne Jackson, Tony Amato, John Kissel. We would email each other about cases that were challenging with difficult diagnosis and treatment issues. Todd Levine joined shortly after along with Tahseen Mozaffar and Aziz Shaibani. We called this growing group Rick's Real Neuromuscular Friends. In 2013 the opportunity came up to start a website with the help of the company Nufactor, Inc. who supplied us a webmaster. We created the RRNMF website so we could bring more neuromuscular doctors and health care professionals into the conversation. This has expanded so that now there are more than 2,000 health care providers and researchers interested in neuromuscular disease that are part of this unique communication vehicle. The website RRNMF.com is the portal to enter this electronic conversation. The RRNMF website also has other features like Sur-

veys, Grand Rounds presentations, Journal Club, but the highlight are the many cases discussed in the Forum. But the website did not have a true journal feature. Therefore, this new RRNMF Neuromuscular Journal is the next extension of electronic communication efforts in this space. We hope many of the cases that are posted on the RRNMF website get converted to case reports or case series for the journal. And we would like to see many of the ideas discussed on the RRNMF website get developed into New Discoveries/New Stuff (new original articles), Looking Back and Looking Forward at Stuff (review articles), Proposed Stuff (grants that have been submitted), What's on Your Mind? (Commentaries and Other Stuff), Meeting Stuff and Visual Stuff.

I am calling the journal leadership Facilitators rather than Editors to set a positive tone. The Facilitators will provide peer review for your submitted manuscripts. We do not plan to be overly critical about every punctuation or formatting style you choose or be argumentative about the point you are trying to make. We want to facilitate the process so you can get your manuscript published and so other neuromuscular researchers and health care providers can be aware of what's on your mind. We of course will offer constructive facilitation.

If you want to become an Associate Facilitator, send me an email or give me a call and we can discuss. We want to be inclusive, but I want to add Facilitators who get the spirit of what we are trying to do in order to promote publishing neuromuscular ideas.

Impact factor is not a concern of ours in creating this new journal. Marianne Reed assures me that articles published in the KU digital press series are easily searchable on Google Scholar which will index our papers within a week or two of publication. The current KU digital journals get thousands of hits annually on Google Scholar. Web of Science is another index and at least one KU Digital Journal is now indexed on Web of Science. We may eventually apply to get indexed by Web of Science. We know there is a lot of interest by authors to have their paper indexed in PubMed. We will get there. The Kansas Journal of Medicine is indexed in PubMed. There is a threshold of papers a journal has to have published before we can apply PubMed to begin getting indexed. It appears that once we have published 26 papers and have been in operation for a year, we can do that.

But even if we are not in PubMed at this time, I do not see that as a major issue. Our goal is to simply disseminate ideas in the field of neuromuscular disorders in an open access, free publishing format. If we are successful (and I am sure we will be) then issues like PubMed and perhaps even impact factor will take care of themselves. In the meantime, you will have to decide which of your ideas you want to publish in this new journal versus the other neuromuscular journals we all currently use to publish our work (Neurology; Muscle and Nerve; Journal of Clinical Neuromuscular Disease, JAMA Neurology, etc.). I trust that you will all have a pretty good idea which of these journals you want to shoot for as you contemplate your publication journey. We know it is not likely you will send a manuscript that you want to be published in Annals of Neurology or New England Journal of Medicine to RRNMF Neuromuscular Journal. But I am confident we will get our share.

So, enjoy this inaugural issue of RRNMF Neuromuscular Journal and please submit manuscripts. We plan to publish this approximately every other month at this time. Maybe at some point it will be monthly if we get a lot of submissions. The interesting thing about electronic journals is that you can publish an issue whenever you want and either often or as infrequent. But we will of course try to be consistent on publishing issues.

I want to thank Marianne Reed who for over a year has walked me through this new process of communicating ideas. I also want to thank Amanda Sebok my Executive Assistant who has helped me a great deal to get this journal launched. And also, thanks to the initial Facilitator team that bounced all these ideas around for over a year: Todd Levine, Jon Katz, Mazen Dimachkie, Mamatha Pasnoor and Laura Herbelin.

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APPENDIX

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Edited

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Miyoshi Myopathy

(Autosomal Recessive Distal Dystrophy)

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ABSTRACT

We describe five new cases of Miyoshi myopathy and emphasize the distinctive clinical and laboratory features of this distal muscular dystrophy. Symptoms began at age 15-25, the gastrocnemius muscles were selectively involved, and creating kinase was elevated more than 10 times normal. The EMG showed abundant brief motor units with numerous fibrillations. Dystrophic features without vacuoles were best seen in the biceps femoris muscle. Asymptomatic creatine kinase elevation was ~~observed~~ present years prior to the development of weakness. The disorder appears to be inherited in an autosomal recessive pattern. Miyoshi myopathy can be distinguished from other distal muscular dystrophies. We propose a new classification for the distal muscular dystrophies.

Introduction

Patients with primarily distal weakness and histologic evidence for muscular dystrophy are rare and may be difficult to classify (1). Welander described the first large series of distal myopathy (2) and, since then, there have been a number of reports describing other forms (3-12). Miyoshi and others have described an autosomal recessive myopathy with early adult onset, early involvement of gastrocnemius muscles, and markedly elevated creatine kinase (13-16). These Japanese reports remained unnoticed in the Western medical literature until recently (17-21). We describe five new cases of Miyoshi's myopathy and propose a classification system for the distal myopathies.

Case Reports (Table 1)

Case 1

A 27 year old male complained of a two year history of slowly progressive leg weakness. He had difficulty running and could not stand on his toes. He could rise from a chair without difficulty. He had no pain, sensory symptoms, cramps, or fasciculation. The patient had previously been on active duty in the U. S. Air Force for six years and had no difficulty with running or walking (including the annual 1.5 mile run).

The family history was negative, although we were not able to examine his parents or a 20 year old sister.

On physical examination, the abnormalities were restricted to the legs. The gastrocnemius muscles were atrophic but without fasciculation. Strength in the lower extremities (MRC scale 0-5) (22) revealed 5 knee extension, ankle

dorsiflexion, eversion, and inversion; 4+ hip flexion, abduction, and extension; 4 knee flexion; 4- ankle plantar flexion. Sensory testing and strength in other muscles was normal. Muscle stretch reflexes were normal except for absent ankle jerks. He could not walk on his toes, but could heel walk normally. He could rise from a chair and from squatting without difficulty.

Laboratory evaluation: creatine kinase (CK) was 10,050 IU/L (normal up to 195 IU/L); erythrocyte sedimentation rate (Westergren) was normal (2mm/hr). Motor and sensory nerve conduction studies were normal. Despite the absent ankle jerks and atrophic gastrocnemius muscles, an H reflex with a normal latency (27.5 msec) was easily obtained over the soleus muscle. Concentric needle electromyographic (EMG) examination in the lower extremities revealed grade 2+ fibrillation potentials [0 to 4 grading system(23)] in the medial gastrocnemius, biceps femoris; grade 1+ in the vastus lateralis and tensor fascia lata; and no fibrillations in the anterior tibialis or lumbosacral paraspinous muscles. Numerous polyphasic motor units were present in weak muscles, with units ranging from 4 to 15 msec in duration and 100uv to 2 mv in amplitude. Motor unit recruitment was full at minimal effort in weak (grade 4) lower extremity muscles except for the gastrocnemius. In this muscle many areas were devoid of voluntary motor units. In the upper extremity the deltoid and triceps muscles were normal; the biceps muscle had 1+ fibrillations, occasional polyphasic units, and normal recruitment, with the distal arm and hand muscles being normal. A CT scan and myelogram of the lumbosacral spine were normal.

A vastus lateralis muscle biopsy revealed a slight increase in variability of fiber size, ranging from 15 to 60 microns in diameter (fig 1). Rare atrophic angular fibers were seen. Three necrotic fibers were present; one was engulfed

by mononuclear inflammatory cells. No central nuclei were present and there was

no increase in connective tissue. Because the changes observed were minimal, a

lateral gastrocnemius muscle biopsy was performed. The muscle was pale and

resisted excision. On light microscopy, the muscle was replaced almost entirely

by connective tissue with only a few islands of small (4 to 25 microns) muscle

fibers (fig 2). A third muscle biopsy, from the biceps femoris, revealed

changes intermediate from the previous two specimens (fig 3-4). There was

marked variation in fiber size (4 to 120 microns). Atrophic fibers were of both

round and angular configurations and some stained darkly with the NADH stain. In

several areas, the angular fibers were seen in small collections. Approximately

thirty necrotic fibers, often undergoing phagocytosis by mononuclear

inflammatory cells were present. Central nuclei occurred in 10% of muscle

fibers, and fiber splitting was present. Connective tissue was increased. No

vacuoles were present. With the ATPase stains, a normal distribution of fiber

types were seen, without type grouping. While a few of the features noted above

suggested slight neuropathic changes, the overall biopsy pattern was most

consistent with a muscular dystrophy.

Prednisone was instituted at 100 mg daily for two weeks, then 100 mg. every

other day. After three months there was no improvement and the CK remained

between 6,000 and 10,000. Over the last year off Prednisone, there has been

moderate progression.

Case 2

A 20 year old female gave a one year history of difficulty standing on her

toes, walking up stairs, and rising from a deep knee bend. Her symptoms were

particularly apparent while, when horseback riding, she was unable to plantar flex her ankles to get her toes down into the stirrups. The symptoms evolved gradually over many months. There was no pain or sensory loss. The patient had previously been active physically and had been a high school cheerleader.

The family history was negative. Three brothers and both parents were living and well.

There was no facial or upper extremity weakness or atrophy. The gastrocnemius muscles were atrophic with normal bulk of the extensor digitorum brevis, peroneal and anterior tibial muscles. Muscle strength testing revealed grade 5 hip flexors and abductors; grade 4+ knee extension and knee flexion, grade 4+ ankle dorsiflexion and grade 4 ankle plantar flexion. Muscle stretch reflexes in the arms were normal, the knee jerks were depressed and the ankle jerks were absent. She could not walk on her heels or toes and there was a Gower's sign.

Serum CK was 9,440 IU/L (normal less than 89 IU/L). Nerve conduction studies were normal. EMG of the medial gastrocnemius and anterior tibialis revealed 1+ fibrillation potentials. Other details were unavailable.

A muscle biopsy of the lateral gastrocnemius showed marked fibrosis and remaining muscle fibers were small and round, with some necrotic fibers. Biopsy of the vastus lateralis revealed only minimal changes, with an occasional degenerating or necrotic fiber.

Over the next two years no objective change in strength or CK was noted although the patient complained of progressive weakness.

Case 3

A 24 year old *man* male complained of a seven year history of weakness in his calves. Initially there was aching and cramping in the calves and he subsequently developed great difficulty walking on his toes, and to a much lessor extent on his heels. Over the next five years he noted a gradual worsening of the distal lower extremity strength and progressive wasting of his calves. More recently he had difficulty walking up stairs and getting out of low seats. Six months before our evaluation he began noticing symptoms of weakness and aching in his arms, particularly of the triceps and extensor muscles of the forearm.

The past medical history was notable for juvenile diabetes mellitus for which he had required insulin for nine years, with good serum glucose control ranging from 130 to 150 mg/dl. A glycosylated hemoglobin was 7.9% (normal less than 8%). The family history was negative for muscle weakness or wasting.

On examination, there was marked atrophy of the legs with prominent extensor digitorum brevis muscles. No atrophy was noted in the upper extremities. Strength was normal in the arms except for grade 4 elbow and finger extensors. In the legs, hip flexion and knee extension were slightly weak but hip abduction and knee flexion were normal. Distally, there was a gradation of weakness, with the ankle plantar flexors being the weakest (4-), ankle dorsiflexors were 4, and ankle everters were 4+. Tendon reflexes were normal except for absent ankle jerks. The sensory exam showed only minimal vibration loss at the toes.

The CK ranged from 4,000 to 7,050 IU/L over several years. Nerve conduction studies were normal. The EMG revealed fibrillation potentials in the

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medial gastrocnemius (3+), anterior tibialis (1+), and peroneus longus (1+), and none in the vastus lateralis, lumbar paraspinous muscles, triceps or deltoid. Motor units in the gastrocnemius were polyphasic, brief, and low amplitude, but in the anterior tibialis and peroneus longus there were both long and short duration polyphasic units. Motor units were normal in the vastus lateralis, triceps and deltoid. The recruitment pattern was full in weak muscles.

Biopsy of the medial gastrocnemius revealed that much of the muscle specimen had been replaced by connective tissue. Of the remaining fibers, there was a marked variability in size, ranging from 4 to 80 microns in diameter. Some of the atrophic fibers formed small clusters. Occasional necrotic fibers but no inflammatory cells were seen. Fibers with internal nuclei and split fibers were present. Subsequently, a biceps femoris biopsy was performed. As in Case 1, while there was some increase in the endomysial connective tissue, it was not as severe as in the gastrocnemius biopsy. Muscle fiber size varied from 4 to 140 microns. There were over 50 necrotic fibers singly and in groups, many undergoing phagocytosis by macrophages and lymphocytes. Many of the smaller fibers occurred in groups of up to 15 fibers. These small fibers frequently stained intensely with NADH oxidative stain. Fiber splitting was present. No type grouping was seen with the ATPass stains. No vacuoles were present.

The patient was given azathioprine (2.5 mg/kg) for three months and Prednisone, 60 mg./day, was added for a further three months with no benefit. Weakness has progressed during the last year of follow-up, but the patient remains ambulatory without assistance.

Case 4

A 24 year old female [woman] complained of weakness of eight years duration. At the age of 17 she noted "tired" legs and difficulty rising from a squat. The CK ranged from 3,000 to 8,000 IU/L (normal less than 188 IU/L). A muscle biopsy of the vastus lateralis showed the possibility of polymyositis and led to treatment with Prednisone (60 mg./day), and then methotrexate (25 mg./week intravenously) over the next three years without benefit.

The patient was one of four siblings. A 21 year old brother had a similar pattern of weakness and has been previously described (21). His CK was found to be elevated (4,000 to 7,000 IU/L) for eight years prior to the first development of gastrocnemius weakness at age 23. A quadriceps muscle biopsy showed mild myopathic changes but a gastrocnemius biopsy revealed marked replacement by dense connective tissue. Two other brothers and both parents are alive and well.

At age 24, she had atrophy and wasting of the gastrocnemius muscles. Strength testing in the arms was normal except for shoulder abductors (4+), wrist flexors (4+) and interossei (4-). Hip and knee flexors were mildly weak (4+). Ankle dorsiflexion was normal; ankle inversion and eversion were grade 5 on the right and 4 on the left, and plantar flexion was grade 2 bilaterally. Extensor hallucis longus was grade 5 and flexor hallucis longus was grade 3. Tendon reflexes were normal except for absent ankle jerks.

CK was 2,258 IU/L (normal less than 195 IU/L). Nerve conduction studies were normal. EMG revealed 2+ fibrillation potentials in the left rectus femoris, with 1+ fibrillation in the vastus medialis, medial gastrocnemius and anterior tibialis. In all of these muscles, motor unit potentials were

polyphasic with reduced amplitude and duration. The recruitment patterns were full even in very weak muscles.

Vastus lateralis muscle biopsy revealed fiber size variability and scattered necrotic fibers. Occasionally the necrotic fibers were surrounded and engulfed by mononuclear inflammatory cells. Fibers with central nuclei were present. No clusters of atrophic fibers were seen and there were no vacuoles. Endomysial connective tissue was not increased.

The patient is still ambulatory without assistance but there has been significant progression over the last three years of follow-up.

Case 5

A 15 year old ~~female~~ girl was found to have an asymptomatic elevation of CK to 3,650 IU/L during routine blood tests prior to tonsillectomy. The family history was unremarkable, with three siblings and both parents free of neuromuscular symptoms or signs. Her neurologic examination was normal. Laboratory investigations included normal thyroid function and nerve conduction studies. EMG revealed no fibrillations and motor units ranged from 3 to 8 msec. in duration without polyphasia and with normal recruitment in distal and proximal upper and lower extremity muscles. A vastus lateralis muscle biopsy showed muscle fiber size variability from 20 to 80 microns with a rare scattered necrotic fibers and without inflammatory cells. Internal nuclei were seen in 10% of fibers. Endomysial connective tissue was not increased.

The patient remained normal for the next three years but her CK ranged from 5000 to 10,000 IU/L. At age 17 she first noted pain in her calf muscles after exercise. At age 19 she complained of poor exercise tolerance. A repeat vastus lateralis biopsy revealed muscle fiber size variation ranging from 5 to 125

micrometers with occasional (30%) internal nuclei. There were fifty necrotic fibers, a few undergoing phagocytosis. Atrophic fibers were both angular and rounded and were randomly distributed. Connective tissue was moderately increased. The NADH reaction showed ten dark angulated fibers but otherwise fibers had a normal intramyofibrillar network. Phosphorylase and myoadenylate deaminase were present.

She continued to complain of aching in her calves after exercise and at age 18 her calves first appeared thin and she had difficulty hopping and walking on her toes. Her ankle reflexes became diminished. By age 20 there was marked gastrocnemius wasting, inability to toe walk, and absent ankle jerks. She had difficulty climbing stairs and was unable to wear high-heeled shoes. Her CK remained 50 to 100 times normal.

Discussion

The five cases described above show the characteristic clinical and laboratory features of the autosomal recessive distal muscular dystrophy first reported by Miyoshi (13-17) and later by others (Table 2) (18-21). The salient clinical features of this disorder are: 1) Onset between age 15 and 25; 2) early and predominant involvement of the gastrocnemius muscles with relative sparing of the anterior tibialis; 3) elevation of serum creatine kinase, 10 to 150 times normal; 4) biopsy evidence of a chronic active myopathy without vacuoles; and 5) probable autosomal recessive inheritance, although sporadic cases are common. The course is steadily progressive. All five of our patients worsened during follow-up although they all remained ambulatory. There was no response to immunosuppressive therapy with corticosteroids or antimetabolites in the three patients treated.

These features characterize our five cases and those of Miyoshi (17 cases) (17), Nonaka, et al. (4 cases) (20), and three recent cases described by Galassi, et al. (21) (Table 2). Kuhn, et al. (18) reported two brothers with similar clinical features but the only muscle biopsy reported was of the vastus lateralis, which showed only slight changes. Biopsies of this muscle in our patients were also slightly abnormal.

Several points regarding the muscle biopsy deserve mention. The slight myopathic changes noted in biopsy of the vastus lateralis generally consist of rare scattered necrotic muscle fibers, occasionally being engulfed by inflammatory cells, with slight muscle size variability. However, most of the muscle fibers in the vastus lateralis biopsies are normal and the connective tissue is only minimally increased. Biopsy of the gastrocnemius muscle on the other hand shows severe fibrosis often with only a few remaining small, round fibers, or so called "end-stage muscle." Biopsies from the biceps femoris muscle showed the most representative changes. There was marked fiber size variability, with both hypertrophy and atrophy. Many muscle fibers were in various stages of necrosis and phagocytosis. In one case, these changes were interpreted as inflammatory myopathy (case 4 above). However, there were no inflammatory cells in the perimysial connective tissue, around blood vessels or in the endomysial connective tissue except when associated with necrotic fibers. Connective tissue proliferation was scant in the vastus lateralis, intermediate in the biceps femoris, and severe in the gastrocnemius. Small angular fibers formed clusters, often staining darkly with the NADH stain, reminiscent of a neuropathic process; however, the other histologic features, along with the characteristic changes in the vastus lateralis and gastrocnemius muscles, as

well as the characteristic clinical and electrodiagnostic findings, clearly indicate this is a primary muscle disease.

There is only one report of an autopsied case (17). In this patient the gastrocnemius was nearly totally replaced by fat; the anterior tibialis and biceps femoris had moderate dystrophic changes, and other proximal limb muscles were only minimally affected. Anterior horn cells and peripheral nerves were normal. Because of the wide range of biopsy changes in different muscles, we recommend biopsy of the biceps femoris.

The EMG findings are characteristic of a chronic myopathy. Modest numbers of fibrillation potentials were present in all patients, except case 5 who was studied before she was symptomatic. In general, motor unit potentials were brief in duration, low amplitude and polyphasic. In some patients (cases 1 and 3), a second population of polyphasic motor units was observed with longer durations, as has been reported in other dystrophies (24) and in chronic inflammatory myopathies (25). The recruitment pattern was full in weak muscles and thus characteristic of a primary muscle disease. An exception to this was occasionally seen in the very weak gastrocnemius muscles which, when severely replaced by connective tissue, showed a reduced recruitment pattern with the few remaining units firing very rapidly.

In Case 5, marked CK elevation preceded clinical evidence of gastrocnemius weakness by several years. This presymptomatic "hyper-CK-emia" was also described by Galassi, et al. (21) in two of their three cases. The first symptoms were aching in the calves with exercise (cases 3 and 5), or a tired, weak feeling in the legs (cases 1, 2, and 4). The earliest signs were the inability to toe walk and depression or loss of ankle tendon reflexes.

Gastrocnemius atrophy developed later.

Several of the clinical and laboratory features of this form of distal myopathy resemble those of inclusion body myositis (IBM) (26-30). In IBM, distal weakness is usually prominent, and the EMG and muscle biopsy have features resembling a neuropathic process (29). However, there are important differences that distinguish IBM and Miyoshi myopathy. In IBM, the distal muscle weakness almost always involves finger flexors and the quadriceps; the gastrocnemius muscle is not preferentially involved. The serum CK is only slightly increased in IBM. Finally, the muscle biopsy in IBM contains characteristic rimmed vacuoles and 15-18 nm filaments either within the nuclei or at the edge of the vacuoles on electron microscopy.

In 1986, Markesbery and Griggs (1) proposed a classification scheme for hereditary distal myopathies: (1) late adult onset autosomal dominant distal myopathy of Welander with onset in the hands; (2) late adult onset autosomal dominant distal myopathy with onset in the legs; (3) early adult onset autosomal recessive or sporadic distal myopathy with onset in the hands or legs. With the characterization of Miyoshi myopathy, this latter category must now be further subdivided (Table 3) as discussed below.

The most familiar late onset form was described by Welander (2). It is an autosomal dominant distal myopathy with onset in the 5th decade, and weakness beginning in the hands. Distal leg involvement occurs in the anterior compartment. The CK is either normal or mildly increased. The histologic changes noted by Welander, and later by Edstrom (29), ranged from mild myopathic changes to severe fibrosis, and vacuoles were observed in some cases.

The other form of late adult onset autosomal dominant distal myopathy

begins in the legs and has been reported in non-Scandinavian patients (3,4). The anterior compartment muscles are most affected and the CK is normal or mildly elevated. Muscle biopsy reveals a vacuolar myopathy.

It is now clear that there are two distinct types of early adult onset distal myopathies with autosomal recessive inheritance. One usually begins in the anterior compartment (5-12), although rarely it begins in the hands. The CK tends to be moderately elevated (<10 times normal) and the muscle biopsy reveals a severe vacuolar myopathy; the prognosis is generally good with a relatively benign course in most patients (12).

By contrast, the condition described herein as well as by Miyoshi and others can now be classified as a separate early adult onset distal muscular dystrophy (13-21) (Table 3). As described above, these patients present with gastrocnemius weakness and atrophy, markedly elevated CK (10 to 150 times normal), a dystrophic biopsy without vacuoles and a more rapidly progressive course with greater disability.

The observations on treatment with corticosteroids and azathioprine or methotrexate in our patients are uncontrolled. Nonetheless, the objective evidence of worsening in our cases makes it unlikely that patients with Miyoshi myopathy will respond to immunosuppressive treatment, despite the recent results described in Duchenne's dystrophy (32).

Thus, the muscular dystrophies with predominantly distal involvement include at least four separate disorders, each with distinctive clinical and laboratory features, and each probably reflecting different gene lesions.

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Table 1: SUMMARY OF CLINICAL DATA

CASE	SEX	AGE AT ONSET	EARLY GASTROC WEAKNESS	SERUM CK(IU/L)	BIOPSY	EMG
1	M	25	+	10,050	G – end stage/fibrosis VL – minimal myopathy BF – intermediate; dystophy	MUP – poly, brief REC – full FIBS – +
2	F	19	+	9,440	G – end stage/fibrosis VL – minimal myopathy	MUP – poly REC – full FIBS – +
3	M	17	+	7,050	G – end stage/fibrosis BF – severe dystrophy	MUP – poly, brief REC – full FIBS – +
4	F	16	+	8,000	VL – minimal myopathy	MUP – poly, brief REC – full FIBS – +
5	F	15	+*	11,040	VL – minimal myopathy	Normal**

G = gastrocnemius
VL = vastus lateralis
BF = biceps Femoris

MUP – motor unit potential
poly – polyphasic
REC – recruitment
FIBS – fibrillations

* – At age 22, 7 years after high CK noted

** – When clinically asymptomatic at age 15

Table 2: DISTAL MYOPATHY OF MIYOSHI: Literature Summary

AUTHOR	# PATIENTS	SEX	AGE AT ONSET	CREATINE KINASE	GASTROCNEMIUS WEAKNESS
1. Miyoshi et al. (1967/1986)	17	8 M 9 F	12-30	20 to 100 X Normal	17/17
2. Kuhn, et al. (1981)	2	2 M	17;20	25 X Normal	2/2
3. Alderson, et al. (1985)	1	1 M	19	12 X Normal	1/1
4. Nonaker, et al. (1985)	4	2 M 2 F	21;29 17;28	40-100 X Normal	4/4
5. Galasi, et al. (1987)	3	3 M	15;18;19	62-153 X Normal	3/3
6. Barohn, et al. (1991)	5	2 M 3 F	17;25 15;16;19	30-150 X Normal	5/5

TABLE 3

CLASSIFICATION OF DISTAL MYOPATHIES

Late adult onset (Welander Myopathy) - Type I (refs 2,31)

    Autosomal dominant

    Onset in hands

    Later leg involvement in anterior compartment

    CK normal or slightly increased

    Biopsy-variable; vacuolar myopathy in some cases

Late adult onset - Type II (refs 3,4)

    Autosomal dominant

    Onset in legs - anterior compartment

    CK normal or slightly increased

    Biopsy - vacuolar myopathy

Early adult onset - Type I (refs 5-12)

    Autosomal recessive or sporadic

    Onset legs - anterior compartment

    CK - increased, usually <10 X normal

    Biopsy - vacuolar myopathy

Early adult onset (Miyoshi Myopathy) - Type II (refs 13-21)

    Autosomal recessive or sporadic

    Onset legs - posterior compartment

    CK - increased 10 to 150 X normal

    Biopsy - dystrophy without vacuoles

        gastrocnemius often "end-stage"

LEGENDS

Figure 1. Case 1. Vastus lateralis. Muscle fiber size variability with one necrotic fiber. Hematoxylin and eosin, X 376.

Figure 2. Case 1. Lateral gastrocnemius. A. Marked muscle fiber loss with small atrophic fibers and replacement of muscle by dense connective tissue and fat. Hematoxylin and eosin, X 53. B. Higher magnification of an adjacent area shows muscle fiber size variability and central nuclei and dense connective tissue. Hematoxylin and eosin, X 376.

Figure 3. Case 1. Biceps femoris. Intermediate changes compared to Figures 1 & 2, with variable muscle fiber size, hypertrophic and small round fibers. Hematoxylin and eosin, X 376.

Figure 4. Case 3. Distal tapering with posterior compartment (gastrocnemius) atrophy.