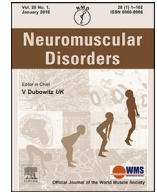




Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Patients' Forum

My trial and training journey in X-linked myotubular myopathy: mountains and valleys

1. Introduction

In this Patients' Forum, a patient with X-linked myotubular myopathy (XLMTM), describes the tremendous effects he has reached by very dedicated physical training with his physical therapist. He was motivated to start training when included in the Unite-CNM trial at the onset of the COVID-19 pandemic. It illustrates the potential of physical training in congenital myopathies, the importance of intrinsic motivation, and the need to standardize physical training during clinical trials. His testimonial is followed by a commentary of the (pediatric) neurologists, physical therapist and rehabilitation specialist that were involved in the clinical care and natural history study and clinical trial he participated in.

2. My trial and training journey

I would like to share my recent experience with physical training to encourage others and to raise awareness among clinicians performing clinical research.

I am a 23-year-old Dutchman who suffers from XLMTM, among a whole list of other things. As will become painfully evident in this piece, I am not a scientist or anyone with any credibility in the medical field beyond my personal life experience, though I am quite certain that by now I have spent more of my time in hospitals than some doctors.

Besides studying law, I am currently an active member of ZNM – Zusammen Stark! e.V., the Dutch-German-Austrian family association for centronuclear myopathies. I am part of the pharmaceutical contact group, which is in charge of maintaining dialogue with the pharmaceutical companies that have an interest in centronuclear myopathies. It is also ZNM – Zusammen Stark! e.V. for which I attended the EURODIS open academy summer school on Medicines Research & Development. I gained a lot of information about the legal and procedural side of drug development and built a strong network. This is very useful for our association today. With introductions out of the way, and the description of my medical history covered by my neurologist (see below) I will for my part just be sticking to my story, so let's get to it.

When I was younger, I never really saw much point to training, beyond some general maintenance exercises. I was never a particularly motivated child or teenager and saw exercise as

nothing more than daunting, painful, and exhausting. I welcomed every opportunity to skip my weekly physio exercise session.

Around late 2015 I was recruited for NatHis-CNM, a natural history study in Belgium with the hope that this would serve as a gateway for recruitment into one of the clinical trials that were up and coming in our disease. This eventually happened in late 2019 when I was recruited into the Unite-CNM trial by Dynacure.

I suppose that this was the first time the idea of training popped into my mind. My goal was to make the most of the opportunity. I thought that if I started working out long before the trial, this would be my baseline and I would be allowed to continue to do so during the trial, which would allow me to make the most of whatever muscle enhancing medicine they were injecting me with. I think it was 2017 or 2018 when I first started walking a few times a week. Back then I could walk 500 m comfortably, with a maximum walking radius of 1 km.

Quickly after I started my walking routine COVID-19 hit. Like many others I was very afraid of what getting COVID would mean, thinking that it might even be what kills me, as back then my lungs were operating at about 30 % capacity. I made the decision to go in full self-lockdown, staying in my room for about 15 months, until I could get my first vaccination. This fear however kicked my motivation into gear. As I doubled down on my workout sessions it took me about a year (2021) before I could walk 2 km with difficulty. Two km would later become my lax workout session as I kept adding to the regime. Aside from walking, I also started doing bicep, triceps, shoulder, and back exercises to my routine as well as adding a backpack with weight to some of my walks (ranging from 2 to 4 kg). Over those first months my increase in energy and physical strength were already becoming apparent. Which boosted my motivation even further. In 2021 my motivation would gain another boost as the dosing of the Unite-CNM trial could finally commence.

At the baseline visit of the trial, I filled out a goal attainment scale, where I had to decide what the study drug had to do for me to consider it effective. The goals I defined were impossibilities to achieve naturally in my life and included: lying in bed without having to use my inhaler for respiratory relief and being able to live my life without crippling exhaustion all the time. My more ludicrous goals included walking 5 km and getting up from prone without any form of aid. During the eight weeks of dosing, I kept on increasing my training. Six weeks into the trial I managed hit

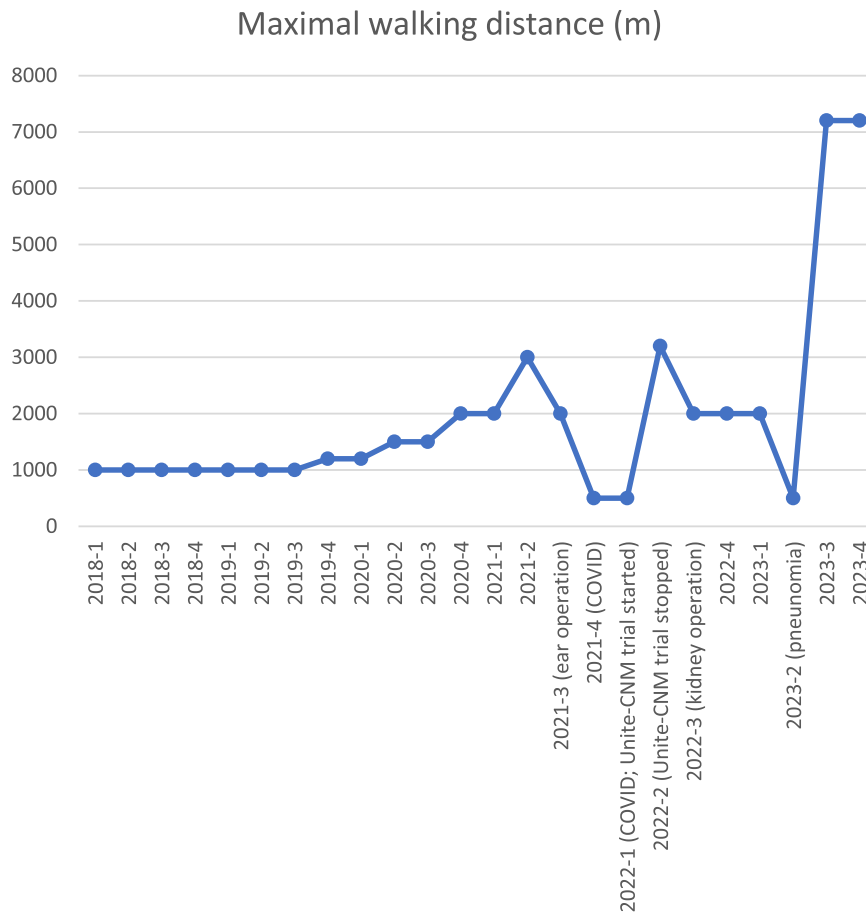


Fig. 1. Maximum walking distance in m in one walk, measured by the patient based on his notes and estimates, presented for each quarter.

my new record of 3 km, which was a huge victory, and one that, back then, I attributed to at least partly to the effects of the clinical trial, something that would later be disproven. In the first half of 2022, the trial was discontinued due to side effects in some of the patients enrolled. This was a major hit to my motivation and general mental health.

In that span of years, I had also lost most of the hearing in my left ear due to cholesteatoma, for which I had to have surgery. Surgery, after which I suffered from a bad and unexplainable case of postoperative cognitive dysfunction to a point where I couldn't find words and could barely finish a sentence for about two months. It was also around this time where I suffered my first bout of COVID which absolutely wrecked all the progress I had made. After my spell of covid I got back into the metaphorical saddle as I was determined to get back what I had lost. This proved useless as I got a second bout of COVID only a few months later. After recovering from my second run-in with COVID, when on vacation, I fell down some steps and broke my foot and damaged my ankle ligaments. On top of that I also received the news that the kidney stones that had been discovered back in 2012, had grown and would require me to undergo further surgery, something I had become more than a bit afraid of after having finally recovered from my brain issues.

Because of all this I was forced to quit two bachelor studies and for those three years, bit by bit, everything seemed to be slowly falling apart. Nevertheless, I kept up my training. After every setback I grabbed my bag and hit the road. In those years that was the only control I had over my own life, the only way to give myself a fighting chance in an ultimately unwinnable war.

Notable is also that in 2022 I finally conceded and got back in touch with my old physiotherapist. On top of my almost daily home workouts, I go there twice a week to use their gym under guidance for the exercises that are difficult for me to do alone. 2022 was also the year where I managed to improve my record ever so slightly to 3.3 km, this time without any placebo effect playing tricks on me in the back of my mind.

Whatever the case, my three years were capped off by bad pneumonia in the early spring of 2023, which saw me hospitalized for a week. By that time, I had already built up quite a bit with my training again, and even though it was the worst case of pneumonia I can remember, I managed to not lose my ability to walk for the first time.

I got back to training right away, even before I was out of the hospital, I had my parents sneak in my dumbbells so I could get right back to work. And so, with my oxygen mask still on my face, I started to work out. That summer I doubled my training again, incorporating a full range of body exercises and cardio workouts. I also did some research into diet and hydration and made a huge change there as well. Within two and a half months out of the hospital I set my new walking record at 7.2 km, this is a more than 100 % distance increase from the 1 km at which I started my training journey three years back (Fig. 1). For the first time in 18 years, I am also capable of getting up from being prone on the ground without any aid. My respiration over my years of consistent exercise has improved and my overall strength and energy have also increased considerably. Marking the attainment of all my trial goals to some extent, even blowing some out of the water outright. I have come to love the discomfort that

my training brings, and I know that those daily discomforts will soften the blow of the inevitable next setback. I am stunned every day at how much progress I have made, and catch myself telling people constantly that, if this had been the result of that drug tested in the clinical trial, I would have called it a miracle drug.

I also think it is important to note how much it has done for my mental health. I have always been a 'figure it out on your own' kind of guy, and even though talking about things is nice, my training has been my real therapy, my way to stick it to my dysfunctional body and take matters into my own hands. That and, I find it is hard to feel negative with all the endorphins in your brain pumping nonstop from constant exercise.

There is one final note I want to emphasize: I am doing this **out of my own motivation**, these results are those of three years hard disciplined work. Work you cannot commit to without an intrinsic motivation to do so. The last thing I want this piece to do is make the lives of children with muscle diseases even tougher by having their parents read this and force their children into some Olympic army bootcamp. I was a child with XLMTM not too long ago and know all too well that as a child with a disability your life is rough enough as is. But for those that have read this article and did not know this was even possible and want to do it, know these things: Motivation is temporary, Discipline is forever. Grit your teeth and get to work.

2.1. The (pediatric) neurologists' perspective (LS and NCV)

This patient is now a 23-year-old man with XLMTM, a rare form of congenital myopathy that affects 1/50,000 male newborn. [1] Recently, a gene therapy trial using an AAV8 vector carrying MTM gene demonstrated the possibility of very significant improvement in children, but unfortunately associated with a significant risk of fatal acute liver failure. [2] He was born after a full-term pregnancy. Postnatally, he was hypotonic and needed ICU support. His-first years were characterized by motor development delay, recurrent pneumonias, and failure to thrive for which nasogastric tube feeding was provided in childhood. Surgical correction of external eye movements for strabismus was performed at the age of 5 years, and an orchidopexy was performed at the age of 12 years.

XLMTM was diagnosed at the age of twelve with a muscle biopsy showing multiple centralized nuclei. DNA testing (age 12) showed a missense change in the MTM1 gene: c.1496G>T (p.(Trp499Leu)). This was classified as likely pathogenic, based on the evolutionary conserved amino acid and previous report of a mutation in the same codon. [3]

Other medical conditions diagnosed were hypercalciuria, urolithiasis, recurrent urinary tract infections, and migraine which were medically treated. Furthermore, asthma and osteoporosis were diagnosed and treated. Regular respiratory follow-up by the centre for home ventilation and the local pneumologist showed respiratory weakness (FVC 29 to 36 %) but no signs of nocturnal hypoventilation. At the age of 20, a cholesteatoma of his left ear was diagnosed, for which he was operated on at the age of 21 (endaural approach with chain reconstruction of left ear; general anesthesia, September 2021). At the age of 22 he was operated on because of urolithiasis (left ureterorenoscopy; general anesthesia, October 2022). He [had] suffered two episodes of COVID (November 2021; March 2022).

He attended regular elementary and secondary school and participated in social activities. With his parents, he has travelled to various countries, enjoying the exchange with various cultures. He started studying English at the age of 19, but the prospect of the physical challenges of being a teacher and physical

burden of studying at university in general made him change his career plans. His-plans to study law were delayed due to the consequences of the COVID pandemic, the burden of trial participation and intercurrent illnesses, but is currently going well.

At the age of 16, he was included in the natural history study in Belgium: Prospective Natural History Study of Patients With Myotubular Myopathy and Other CentroNuclear Myopathies (NatHis-CNM; NCT03351270). In comparison with other patients- he presented with a relatively mild form as he was able to walk independently and was overall pretty stable during the course of the study [4]

Subsequently, he was invited to participate in the Unite-CNM trial in Nijmegen, the Netherlands: Early Phase Human Drug Trial to Investigate Dynamin 101 (DYN101) in Patients \geq 16 Years With Centronuclear Myopathies (Unite-CNM; NCT04033159). Physical examination at baseline (early 2020, age 19) showed generalized muscle weakness, with shoulder abduction MRC2, elbow flexion and extension MRC3, and hip flexion and extension MRC2 and strength in lower legs MRC3. He could walk short distances without support but used an electric wheelchair for longer distances. The first dosing was planned in March 2020 but postponed because of the onset of the corona pandemic. He received the first dose in August 2020, as part of cohort SAD1. The multiple dosing phase started in January 2022 and was halted in April 2022.

The delay of the trial onset and the COVID pandemic initiated a strong urge in him to remain as fit as possible and was a good motivator for training. This has resulted in a dramatic increase in maximal walking distance. Functional improvements in daily life included an improved rising from a chair and stair climbing. Since part of the improvement took place during the trial participation, the patient initially understood this as a study drug effect. He was in the low-dose group and the increase reached afterwards was much larger, making this very unlikely. His-report illustrates the need to standardize physical training during clinical trials to prevent a bias.

2.2. The physical therapist perspective (CvG)

I graduated as a musculoskeletal therapist, profile manual therapy. This means that throughout the week I am mainly concerned with people who have issues with their musculoskeletal system. In addition, due to my personal sports interest, I often deal with sport-related injuries. As such, I have experience and knowledge of manual therapeutic treatments and exercise programs aimed at rehabilitation after such sports injuries. My expertise regarding neuromuscular disorders is however limited. Therefore, when this patient first came to our practice, my team and I considered other options. After discussing it, however, we decided to treat him. Firstly, he has a lot of experience and knowledge about his condition and is very capable of communicating what he can and cannot do. Furthermore, he is in touch with the specialized neuromuscular team in the hospital. Finally, he lives within walking distance of our practice and there is no other practice nearby.

I first met him when I started working at this practice in 2015. At this stage he was a teenager (15 to 17 years) and in our team we knew him as a recalcitrant young man who preferred talking to training, wasting as little energy as possible on physical exercise. We spent a lot of time trying to motivate him and get him to commit to the training program but ultimately with only little success. We managed to maintain his capabilities but did not make any improvement. The absence of long-term success resulted in his withdrawal from therapy after 2017. When good

results are not achieved and any growth or build-up is not noticed or seen, it becomes increasingly difficult to continue to motivate oneself to exert effort, this of course compounded by the fact that exerting such effort with a muscle condition is even more punishing.

At the end of 2022, he returned to our practice, but this time everything was different. He was 22 years old; he had matured and already started training years in advance, setting clear goals for himself. He took care of most of the exercises himself through exercise programs at home. These exercises mainly consisted of cardio fitness (long distance walking) and training of upper body strength (arms, shoulders, and chest). He was less able to train his legs and abdominal muscles (at home) as he liked to train them here in the practice with the help of apparatus under the trained eye of a therapist. This strategy quickly created a structure in which two exercises were performed twice a week and periodically increased, which was extra motivating. In addition, to maintain variety, I tried to come up with new exercises every week, with the leg muscles and abdominal muscle groups always in focus. We have now deviated from this initial plan and are also training arm muscles and do cardio here on a weekly basis, on top of the exercise he is doing at home. Though he had already started feeling the improvement in day-to-day life before he came to us, our systematic, twice a week hard session approach quickly accelerated this improvement. He has already achieved much more than he had initially hoped. All this makes him (and me as well) curious to see what else could be possible.

As a final note, it is important to report that his success, which has been leagues beyond what any of us expected, is mainly a result of the patients' attitude and mindset. The difference between the recent treatment period and that in 2017 is his intrinsic motivation. For this second period I did not have to motivate him at all, my only role has been to coach him. This is so much more satisfying for me as a therapist. His exercise allows him to improve his condition at a staggering rate, and this improvement in turn fuels motivation to work even harder. This is the seemingly self-sustaining loop of improvement he has made for himself.

2.3. The rehabilitation specialist's perspective (NBV)

Research into the effects of training in congenital myopathies is limited. A recent study in 16 patients with various other congenital myopathies revealed that the patients who were able to complete the training showed a significant improvement in VO₂max. Ten weeks of endurance training is safe and improves fitness in patients with congenital myopathies. However, nine patients dropped out of the training program. Fatigue was the major single reason. Alternative methods of training such as strength training or shorter training sessions at higher work intensities have not been explored in congenital myopathies yet [5].

Remarkably, this patient's perspective illustrates the importance of physical exercise for mental wellbeing [6,7].

Together, this patients' forum illustrates that regular sessions of exercise are beneficial for improving movement and muscle control, reducing risk of falls and injury, reducing symptoms, and associated co-morbidities, promoting independence, and improving quality of life by increasing self-efficacy. As such, it is a strong argument for the concept that exercise must be seen and prescribed as if it were medicine [8,9].

Conflict of interest

LS has received funding and compensation from Dynacure and Astellas. NV was PI of the Unite-CNM trial of Dynacure.

Declaration of competing interest

None.

CRediT authorship contribution statement

J. Van Tienen: Writing – original draft, Data curation, Conceptualization. **C. van Geenen:** Writing – original draft, Data curation. **N.B. Voet:** Writing – original draft. **L. Servais:** Writing – original draft, Data curation. **N.C. Voermans:** Writing – review & editing, Writing – original draft, Data curation, Conceptualization.

Acknowledgments

NV, NV and LS are member of the European Reference Network for rare neuromuscular diseases (EURO-NMD). We acknowledge the clinical study teams in Louvain (Belgium) and Nijmegen (the Netherlands) for their great efforts in performing the natural history study and clinical trial. We greatly appreciate the work of ZNM – Zusammen stark! e.V. for all the patients with centronuclear myopathies and their families in Europe, and of EURORDIS for empowering, partnering, and advocating for people living with a rare disease in Europe.

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