Image of the Quayside in Newcastle , UK. The city where the GNEM-DMP curation team are based.

Thank you all for the support and your contribution to the GNEM-DMP. With your help, the project keeps improving and growing which could not be done without your continued contribution. 2016 has been a great year and we have made huge progress. We hope that 2017 will bring us further good news and scientific breakthrough.

In this 6th Edition of the GNEM-DMP Newsletter:

To join the GNE Patient Registry please visit: www.gnem-dmp.com
For more information on the GNEM-DMP contact: GNEM@treat-nmd.eu
For more information about Ultragenyx Pharmaceutical Inc. please visit: www.ultragenyx.com/patients/gnem
For more information about TREAT-NMD please visit: www.treat-nmd.eu

MRCC-UX001-00016

NEUROMUSCULAR DISEASE FOUNDATION
JOIN THE GLOBAL EFFORT TO CURE NEUROMUSCULAR DISEASES

NDF's ANNUAL GNE MYOPATHY (HIBM) SYMPOSIUM

AUGUST 31st- Sept 1st, 2016 @UCLA

Approximately 40 people including GNE myopathy patients, caregivers, NDF board members, scientists and healthcare providers came together on 31 August 2016 in Los Angeles for the annual symposium. Day 1 Morning Period was live streamed via the NDF Facebook page and featured the following presentations:

- *Dr. Madhuri Hegde from Emory Genetics gave a presentation which focused on DNA testing & mutation analysis in GNE myopathy.*

- *Dr. Andy Kogelnik from the Open Medicine Institute (OPI) discussed "Precision Medicine, Collaboration and Genomics in the Digital Age" highlighting OPI's capabilities to collect & test samples from around the world.*

- *Dr. Stan Krolczyk from Ultragenyx gave an overview of the design for two ongoing Ultragenyx studies: phase 2 and phase 3, which aim to determine the safety and effectiveness of aceneuramic acid (sialic acid) extended-release in ambulant GNE patients.*

- *Dr. Marjan Huizing from the National Institutes of Health (NIH) discussed the clinical studies of ManNAc, noting that the Phase 3 study recruitment is projected to start in 2017.*

- *NDF announced a collaboration with Dr. Jerry Mendell of Nationwide Children's Hospital in Columbus, OH to start pre-Investigational New Drug work in the area of gene therapy targeting GNE Myopathy.*

- *Dr. Carmen Bertoni gave an overview presentation on gene therapy and gene editing.*

Day 1 Afternoon Period hosted break-out sessions for scientists; these were moderated by Dr. John Hakimi. The patient sessions were led by Gretchen Kubacky, PsyD. and the caregivers sessions were led by Judy Clingman, MFT.

Day 2 Morning/Afternoon Period of the symposium featured adaptive yoga instruction, massage, stretching, and nutrition workshops by Mark Clements and Zamia Cohen.

For more information about NDF please visit:
www.curehibm.org

GNE Myopathy Patient Advocacy Summit - Barcelona, Spain

On 1 October 2016 in Barcelona, Spain, Ultragenyx hosted a patient advocacy summit which brought together patients, caregivers and patient advocacy organisations.

The aim of the summit was twofold; firstly, for patients to share their knowledge and experience to provide a better understanding of the needs of a GNE myopathy patient. And secondly, to help establish networks so that more advocacy groups become better connected and involved with supporting patients and families.

There were patient representatives from the following countries and regions: Northern Ireland, UK, The Netherlands, Reunion Islands, Spain, Japan, Germany, and Italy as well as the following patient advocacy organizations: Neuromuscular Disease Foundation (NDF) in the US, Patients Association for Distal Myopathies (PADM) in Japan, Associazione Gli Equilibristi in Italy, and Federación de Enfermedades Neuromusculare (ASEM) in Spain.

Dr. Behin from the Centre de Reference de Pathologie Neuromusculaire in Paris presented on the current understanding of GNE myopathy. Mónica Suárez Felgueroso gave an overview of Federación ASEM activities for patients with neuromuscular disease in Spain. Yuriko Oda discussed the establishment and growth of PADM which serves 100 people with GNE myopathy in Japan who meet six times per year.

The patients in attendance at the summit felt there was immense value in being connected to other GNE myopathy patients and families, it provided a welcome opportunity to share experiences and offer support to others who shared the same rare disease. Patients spoke about their own personal journeys during the day, detailing the challenges that patients, family and caregivers face when living with the disease. Namely, the difficulties in identifying financial grants (for things such as home adaptations etc.) and accessing additional care /support services and how this varies in each country.

This meeting was part of ongoing collaborations between patients, patient organisations and industry, in an effort to encourage GNE myopathy patients and their families to connect with neuromuscular patient advocacy groups. This increased level of open communication connectivity/relationship/ partnership between patient & patient organisations, will in turn lead to patients receiving the correct care and support. Please contact patientadvocacy@ultragenyx.com for additional information.

As a participant in the GNEM-DMP registry you will be automatically notified about upcoming events such as the patient advocacy summit. If you have a diagnosis of GNE myopathy (also known as HIBM, DMRV, QSM, Nonaka Myopathy or IBM Type 2) but are not yet registered, you can do so by going to the study website (www.gnem-dmp.com) and following a simple few steps to complete registration.

The History of GNE myopathy - A timeline of key events so far

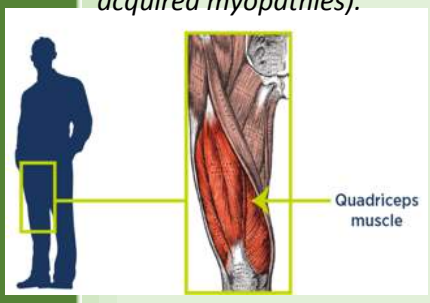
Introduction from the editor: Dr Zohar Argov is a world renowned Neurologist and Professor *(Emeritus)* of Hadassah-Hebrew University Medical Centre in Jerusalem, Israel, with a long-standing interest in muscle disorders. He first described GNE myopathy (referring to it at the time as Quadriceps-sparing or Inclusion body myopathy) in Jewish patients in 1984. Dr Argov is also a Special Medical Advisor to the CEO at Bioblast Pharma and is leading research programmes to develop better therapies for rare disease. In 2014 Dr Argov published his personal review of the history and current status of GNE myopathy, that spans his 35 year career in the neuromuscular field that started from a bedside observation of a patient, to where we are today.

Dr Zohar Argov

The journey of the identification of GNE myopathy begins in 1979, after Dr Argov returned from Newcastle upon Tyne (A city in the United Kingdom where the GNEM-DMP curation team are based) where he had undertaken a World Health Organisation (WHO) sponsored fellowship at the Muscular Dystrophy Laboratories under Lord John Walton and Professor Frank Mastaglia. The timeline below looks at key points in the discovery and development of GNE myopathy from the perspective of Dr Argov.

Adapted from; myopathy: a personal trip from bedside observation to therapeutic trials, Zohar Argov, Acta Myol. 2014 Oct; 33(2): 107–110.

1979 *Soon after Dr Argov's return to Israel (following his WHO fellowship in the U.K), he met a hospitalised man in his 60's, who he had observed sitting in his wheelchair, playing with his granddaughter. The man, sat in a wheelchair, was able to extend his legs straight forward (horizontally) whilst supporting the weight of his granddaughter, who was sitting on the lower part of the leg (near the ankles). Dr Argov noted that this was a very unusual activity for a person with a progressive myopathy, as these actions required major strength in the quadriceps (usually the muscle first involved in many muscular dystrophies and acquired myopathies).*



Location of quadriceps muscles on human body

1982 *Three years on from the first discovery of this unique syndrome, Dr Argov had identified 9 patients with what had by now being termed quadriceps sparing myopathy (QSM). All patients identified were of Jewish Iranian (Persian) origin and all had both 1) adult onset myopathy and 2) a biopsy that showed various numbers of muscle fibres contained 'rimmed vacuoles' (an area of vacuoles' (an area of pathological changes of muscle fibres). This was reported in an abstract at an Israeli-Italian joint meeting in Tiberias (Israel).*

The Islamic Republic of Iran is a sovereign state in Western Asia

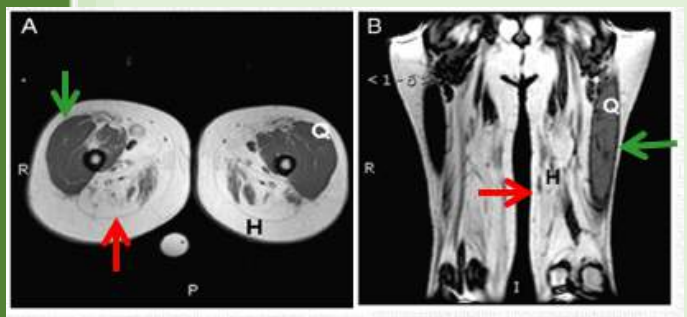
1984 *Dr Argov published his findings in a special issue (known as a festschrift) of the Journal of Neurological Sciences (honouring the departure of Lord Walton from Newcastle to Oxford). By 1984 27 patients had been diagnosed with QSM. Over the next two decades there were reports of patients presenting at clinics around the world with a similar disorder and because of similarities between QSM and sporadic inclusion body myopathy (IBM2) the disease began to carry the name hereditary inclusion body myopathy (HIBM). Almost simultaneously Dr Ikuya Nonaka identified and published a report on Japanese patients with a new distal myopathy. Later two conditions were linked together under one disease name.*

Lord John Walton of Detchant (16 September 1922 – 21 April 2016) was a British neuroscientist, academic, and life peer who sat in the House of Lords

1995 *The understanding that HIBM was not only a unique clinical diagnosis, but was in fact a well-defined genetic disease in itself, came from work carried by Dr Stella Mitrani-Rosenbaum, who was at this point in charge of the Molecular Diagnostics Unit at Hadassah Hebrew University Medical Centre, Israel. Dr Argov continues to work with Dr Mitrani-Rosenbaum, who by 1995 had been successful in linking the disease known as Persian-Jewish QSM, to a specific genetic defect in the genome (chromosome 9).*

Dr Stella Mitrani-Rosenbaum. Principal Investigator, Goldyne Savad Institute of Gene Therapy

1996 *As a direct result of Dr Stella Mitrani-Rosenbaum's work, a special meeting in Napoli, Italy took place in which the diagnostic criteria (the set standards which define the disease as HIBM based upon the specific genetic characteristics) for this recessive myopathy was set by a group of experts from around the world and published in a special issue of the Italian journal; Acta Myologica.*



Green-spared (Quadriceps)
Red- atrophic (Posterior an d medial compartment)

2001 *Iris Eisenberg, a PhD student in Prof Mitrani-Rosenbaum's laboratory identified mutations in the gene encoding named 'N-acetylglucosamine epimerase/N-acetylmannosamine kinase' (termed GNE) as the disease causing defect. This discovery was instrumental in determining, that the disease termed distal myopathy with rimmed vacuoles (DMRV) or Nonaka's myopathy in Japan, was in fact the same condition as HIBM. Following the gene discovery, the clinical description of patients with 'HIBM/DMRV' from numerous countries world-wide could now be confirmed by genetic molecular testing (to date there are more than 150 disease-causing mutations).*

2014 *Since Dr Argov's initial discovery in 1979, there have been multiple historic names for the disorder that continue to be used by research groups worldwide today. This has become increasingly confusing for clinicians, patients and researchers therefore a consortium (including Dr Argov) proposed to rename the disorder 'GNE myopathy'. The hope is that this name will eventually become the only term used for the condition around the world.*

Other names for GNE myopathy

While most commonly called GNE myopathy or Hereditary Inclusion Body Myopathy (HIBM), the muscle disease may also be referred to as :

- Distal Myopathy with Rimmed Vacuoles (DMRV)
- Quadriceps Sparing Myopathy (QSM)
- Hereditary Inclusion Body Myopathy Type 2 (HIBM2)
- Inclusion Body Myopathy Type 2 (IBM2)
- Nonaka Myopathy

2016 *Dr Argov continues working closely with researchers and patients' organizations devoted to develop treatment for GNE myopathy. He was the Principle Investigator on the Phase 2, Randomized, Controlled Aceneuramic Acid Extended Release Study.*

Dr Argov also consults for Ultragenyx, who currently run an advance therapy trial in this condition. With this he hopes that a 'corridor observation' in 1979 will lead soon to therapy.

Ultragenyx Announces Withdrawal of Marketing Authorization Application for Aceneuramic Acid Prolonged Release (Ace-ER) in the European Union

On November 11, 2016 – Ultragenyx Pharmaceutical Inc. announced that it had withdrawn its conditional Marketing Authorization Application (MAA) from the European Medicines Agency (EMA) for Aceneuramic Acid Prolonged Release (Ace-ER) for the treatment of adult patients with GNE myopathy. Conditional approval is a designation used in the European Union that allows medications for serious disorders to be made available to patients while the confirmatory studies are completed.The conditional MAA was based on data from the company's Phase 2 study, which was not initially designed as a registrational study. During the Committee for Medicinal Products for Human Use (CHMP) meeting, the CHMP indicated that the Phase 2 study was encouraging but did not provide a sufficient amount of evidence to support an approval at this time. Ultragenyx intends to obtain additional efficacy data from its fully-enrolled global phase 3 study to confirm the effects of Ace-ER, and plans to submit an MAA for full approval after data from this study are available in the second half of 2017. There are no consequences for patients currently participating in Ace-ER studies. ***"Our Phase 3 study is on track and is designed to confirm the encouraging results seen in the Phase 2 study through a larger trial with a primary endpoint and a placebo period that lasts for the full 48-week duration of the study,"*** said Emil D. Kakkis, M.D., Ph.D., Chief Executive Officer and President of Ultragenyx. ***"We are committed to bringing this potential therapy to patients affected by this progressive and debilitating muscle disease."***

Press Release in Full: (www.ir.ultragenyx.com/releasedetail.cfm?ReleaseID=998999)

If you have any questions about this announcement please contact the study team at gnem@treat-nmd.eu

Food Choices and Good Health

Introduction

Having a rare neuromuscular condition such as GNE myopathy impacts upon certain aspects of everyday life over time. Adults of all ages have varying nutrition and physical activity needs as their lives and body changes, maintaining healthy habits is an important way to maintain good health and allows you to feel the best. People with GNE myopathy have the same dietary requirements as the rest of the population. It is often asked in clinic what is a healthy diet? To try and answer this we have put together this short guide, which you may find useful - please note this is not medical advice.

The benefits of eating a healthy balanced diet and having a stable body weight are well documented it helps to maximise both mental and physical wellbeing. It can prevent malnutrition in all forms: obesity, overweight and underweight and helps protect against non-communicable diseases, including diabetes, heart disease , stroke, certain cancers and osteoporosis.

You may want to know where you fall in the weight range to determine whether or not you would like to modify your diet, to either gain/lose, or maintain weight with reducing mobility. A common measure used by health professionals to determine this is body mass index (BMI: weight (kg)/ height (m)^2) whilst this is useful for some, there may be a more reliable measure, like waist circumference, for people who rely frequently upon mobility aids[2]. Please consult your clinician or specialist dietitian who will be able to advise what is most appropriate for you.

Figure 1: The Eatwell Guide

What is a healthy balanced diet?

Maintaining healthy body weight in the most simplistic terms means you must expend as much energy as you consume. If you want to lose weight you must expend more energy than you consume. If you wish to gain weight you must eat more energy than you expend.

The Eatwell guide3 (fig 1) is a visual aid to describe the proportions of the five main food groups that should be eaten over the course of the day to be able to achieve a healthy diet. It is provided by Public Health England based on extensive research from a number of scientific committees (COMA, SACN) in the aim to disseminate nutritional information principally to the UK population[4]. Advice may differ slightly country to country but generally the key nutrition recommendations promoted are the same globally and are in line with that recommended by the World Health Organisation[5,6,7,8,9].

The key nutrition messages are:

Focus on variety, nutrient dense foods across and within all food groups (Fig 1 and Table 1) to meet needs within calorie limits. Nutrient dense foods are those which are very rich in vitamins minerals and other substances that have positive health effect with little or no solid fats and added sugars, refined starches and sodium. They are ideally in their natural form to retain important substance like dietary fibre. Other important key recommendations not listed in the table below but are echoed globally include: • Reduce SALT intake to less than 5g/day • Be physically active within your own abilities.

Table 1: Key Nutritional Recommendations

Base your meals around starchy
Carbohydrates

Starchy wholegrain carbohydrates should make up just over one third of the food you eat. They include **root vegetables, bread, rice, pasta, cereals and millet**. Choose wholegrain varieties (or eat potatoes with their skins on) when you can: they contain more fibre, and can help you feel full for longer.

Eat a rainbow of FRUIT & VEGETABLES
a minimum of **5 portions per day**

Two** pieces of **fruit
A portion is usually around 80g, for dried fruit a smaller portion is advised due to the concentrated sugar content (30g/small handful) and
One 150ml glass of fruit juice

Three portions of vegetables
One potion constitutes 80g or three heaped tablespoons of vegetables

Include **dairy** sources or ***dairy substitutes which are rich in calcium***

Include cheese, yoghurt and fromage frais in your diet. These offer a rich source of dietary calcium, protein and vitamin. Some dairy food can be high in fat and saturated fat, you can choose lower fat varieties.
Recommended portions are:
Cheese matchbox size (30g)
Small yoghurt
1/3 pint of milk
For those who are lactose intolerant other non-dairy sources of calcium are:
•fortified juices, cereals and breads,
•Tinned sardines and salmon with bones, broccoli and spring greens (Kale, bok choy, collard).
•Soy products tofu made with calcium sulphate, soy yoghurt and tempeh.

PROTEIN

Lean Meat: remove excess fat and skin from red meat and poultry, avoid frying where possible. Red meat should ideally be limited to two times per week. Processed meats (ham sausage frankfurters and deli meats) are very high in salt and should be eaten sparingly.

Pulses / Legumes (beans/peas and lentils): Beans and peas are also part of the vegetable group they provide a great source of protein are very low in fat and naturally high in fibre.

Seafood: Try to include two portions of fish per week one of which should be oily (kipper, tuna, mackerel, salmon, herring, anchovies) (140g)

Oils and spreads

Choose unsaturated oils and spreads (olive, sunflower, rapeseed or vegetable oils) and try to avoid the saturated / trans fats varieties such as butter, ghee and vanaspati. Never eliminate fat from the diet, but as it is very energy dense limit portion sizes to 5g/ 1 teaspoon.

Sugar

It is recommended adults eat no more than 30g (7 cubes) of sugar per day, on average people in the UK eat 2 to 3 times this amount. It can be difficult to know how much sugar is contained within foods so checking labels is important. It is generally advised to limit heavily packaged foods in the diet, this usually refers to confectionery, cakes biscuits sugary drinks.

Hydration

(est 240ml per glass)

Limit **alcohol**

intake to 14 units of alcohol per week and have at least two alcohol free days per week

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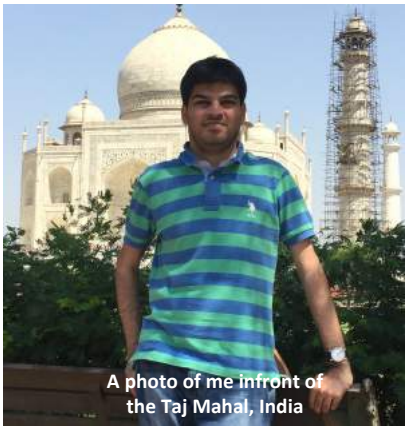
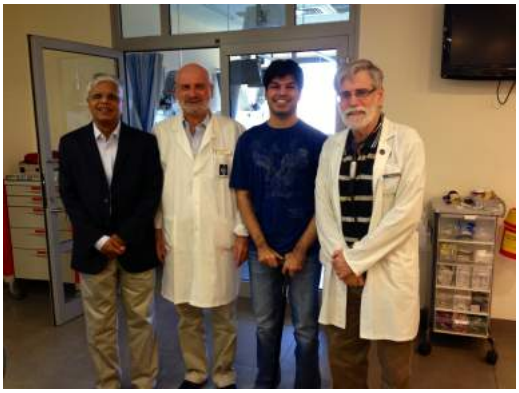
My Story So Far - Rushabh Desai


A photo of me infront of the Taj Mahal, India

Rushabh Desai is from India and in 2011 was diagnosed with the muscle wasting condition GNE myopathy, also known as Hereditary Inclusion Body Myopathy (HIBM). He is currently participating in the GNEM-DMP International Registry and is also involved in collaborating, educating and raising awareness of this rare disease across the world. Below, Rushabh talks about living with the condition and shares some stories about himself – please note Rushabh's experiences are his own and not representative of all study patients.

It seems just like yesterday that I was in my last year of study at University, unaware that what lay ahead was going to change the entire course of my life. I knew something strange was happening with my body but just couldn't figure out what it was. Right from my childhood I was very healthy and active in sports. During my university days, before the onset of this disease I was extremely good at swimming and gym work, thus when my friends questioned me "Why I walked strangely" I could not accept that things could go wrong with my body and chose to ignore it and not consult a doctor.


My father, Prof Argov, myself and Prof Caraco at the Hadassah Hospital clinical site in Jerusalem, Israel

During a picnic with my friends (aged 20) while playing a sport I suddenly noticed I was having difficulties running. My abnormal walking and running pattern was quite noticeable by now, which alarmed my mother who took me to see a doctor. After going to several doctors and going through various tests my parents were told that I have a muscle disease, but were not sure which one. My parents, acting in my best interest, hid the news from me so that I could complete my graduation.

After my misdiagnosis in India I went to the Institute of Myology in Paris in 2010 to see Dr Anthony Behin for a more accurate diagnosis. My diagnosis came as a shock to me. I was completely confused, shattered and in tears that I had a rare muscle disease which has no cure. For a 21 year old at that time, the agony and frustration just seemed to be expressed beyond words and all my dreams seemed broken in fraction of seconds.

Soon after my diagnosis I convinced myself that there was no point in crying. I started searching for more information about GNE myopathy on the internet and started getting in touch with patient groups and scientist around the world, to understand more about disease. In 2012 I was relieved to hear the start of the placebo-controlled study to evaluate sialic acid clinical trials that was being run by Ultragenyx. With the support of my parents I landed in the U.S and was enrolled at the University of California, Los Angeles (UCLA) trial site.

During this time many people in my community asked me what had happened to me. At first I didn't want to share my weakness due to embarrassment, as I knew they would not understand its complexity - but running away was not the solution. I started travelling and connecting with different patient groups and scientists throughout the world, understanding them and sharing my experience on various platforms has helped me express and accept myself in a much better way.

It has been quite a journey and I have been very fortunate to have met and received the guidance of top researchers/ scientists around the world working on GNE myopathy. This has brought a sense of responsibility and I look to help and guide other patients and to work towards collaborating, educating and raising awareness of this rare disease with a shear goal of reaching to a cure. With this common goal a few patients, their families and myself formed an organisation named "GNE Myopathy International" (www.gne-myopathy.org) in India to help and support various aspects pertaining to GNE myopathy.


Me with Dr Emil Kakkis CEO of Ultragenyx in early 2012

Since the onset of this disease back in 2008, a lot has changed and a lot is still yet to change in the future. Each day has brought a new set of challenges in my life and a lot more is yet to come. There are days where I have lost faith and there will be many more such days to come. In this adverse journey one thing I will refuse to let this disease change is my drive to fully cherish the gift of life and to push my abilities to grow in the best manner. Today I manage to work full time as an Investment Analyst at a listed financial company in India and I take each day as it comes. I choose to focus on what I can do and not on what I can't.


Paragliding over the Mediterranean Sea in Israel

Thank you for taking out your time to read my story!

Rushabh Desai

GNE Myopathy International