9th World Congress on

Rare Diseases and Orphan Drugs

June 17-18, 2019 | Berlin, Germany

Poster

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Non-dystrophic myotonic disorders: Patients' insights on treatment access

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Background: Non-dystrophic myotonic (NDM) disorders are a heterogenous group of rare, genetic skeletal muscle chloride and sodium channelopathies with altered membrane excitability resulting in prolonged muscle contraction and delayed relaxation. Patients experience stiffness, pain, weakness, impaired mobility, fatigue, disability, falls, problems with speech, chewing and swallowing. Patients with NDM experience unpredictable frequency and severity of myotonic episodes, associated with life-long symptoms and negative impact on physical functioning and quality of life. Treatment has included unlicensed products such as mexiletine. This study sought to evaluate the awareness and access to mexiletine across Europe, and subsequent harm caused by limited treatment access. Following the study, mexiletine gained European marketing authorisation.

Method: A two-stage study ascertaining the level of access to mexiletine and benefits for those treated with mexiletine was developed and conducted in required languages. Healthcare experts and patient representatives were interviewed, followed by an online survey for patients and caregivers, in 13 countries.

Results: Online questionnaires were completed by 37 NDM patients, of whom 41% were currently taking mexiletine. Of those not taking mexiletine, 67% had never heard of mexiletine and 25% reported it not being available in their country. Treatment was required by 67% of patients to allow muscle warming before physical exertion and 50% to improve emotional well-being, and mexiletine drastically reduced frequency of falling in 44% of patients. Anxiety about future access to mexiletine affected 87% of patients. Disruption in mexiletine treatment harmed 85% of patients.

Conclusion: Mexiletine-treated patients experienced substantial benefits, while denied access resulted in substantial harm.

Biography

Carina Schulmann Schey is pursuing her PhD in the economics of orphan drugs and assessing alternative ways to adjudicate their value-add in the management of rare diseases. With a background as a Clinical Pharmacist with a special interest in rare diseases, she has published several peer-reviewed articles and abstracts in rare diseases. She sits on the expert judges' panel for the MassChallenge and on the scientific advisory panels for several charities, and as a Non-Executive Director for healthcare organizations.

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Notes:

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Rare oral soft tissue metastasis: An overview

Cinzia Casu and **Maria Giulia Nosotti**
President of AIRO RDH, Italy

Metastasis to the oral cavity is a rare event and constitutes 1% of all oral cavity malignancies. We would like to report the cases in the literature of rare oral soft tissue metastasis. We reported oral metastasis on the cheeks, on the lips, on the floor of the mouth, on soft palate and on the uvula. We had found only eight cases of oral metastasis on the lips searching on PubMed with the keywords "oral metastasis in lips", "lip metastasis". The primary malignant tumor that most frequently undergo metastasis at the labial level is certainly the renal tumor with five cases out of eight. In five cases the upper lip was affected, there was one case in which metastasis was present in both lips, and this is a very interesting data because the other malignant diseases are more frequent in the lower lip. We had found in Pubmed literature only seven cases of oral metastasis on the floor of the mouth with the keywords "oral metastasis in the floor of the mouth", "floor of the mouth metastasis"; we found only five cases of oral metastasis on the cheek with keywords "oral metastasis on the cheek". Oral lesion of 54 mm of maximum diameter was reported. We have searched cases of metastasis on the soft palate and on the uvula, with the key words " oral metastasis on soft palate" and "oral metastasis on uvula" and we have found respectively three and one (from the kidney) results. The malignant tumors that undergo metastasis at the soft palate were renal, bronchial and lung carcinomas. This overview underlines how this oral disease can sometimes be misunderstood, and the importance of regular checks in patients who already have a diagnosis of malignancy.

ORAL SITE INVOLVED	NUMBER OF CASES FOUND	PRIMARY SITE MOST INVOLVED
Lips	8	Kidney (5)
Floor of the mouth	7	Respiratory area (2), Liver (2)
Cheeks	5	Breast (1), Testis (1), Kidney (1), Stomach (1), not reported (1)
Soft palate	3	Kidney (1), Lung (1), Bronchial area (1)
Uvula	1	Kidney (1)

Table 1: Oral metastasis and Primary malignancy involved.

Recent Publications

1. Irani S (2016) Metastasis to the oral soft tissues: A review of 412 cases. J Int Soc Prev Community Dent. 6(5):393-401.
2. Irani S (2016) Pre-cancerous lesions in the oral and maxillofacial region: a literature review with special focus on etiopathogenesis. Iran J Pathol. 11(4):303-322.
3. Jatti D, Puri G, Aravinda K and Dheer D S (2015) An atypical metastasis of renal clear cell carcinoma to the upper lip: a case report. J Oral Maxillofac Surg. 73(2):371.e1-6.
4. Mintz S M and Radecki C (1988) Metastatic bronchial carcinoid tumor of the soft palate: report of a case. J Oral Maxillofac Surg. 46(6):516-8.
5. Lansigan N C Jr, Benisch B M and Sidoti J (1973) Renal carcinoma presenting as metastasis to uvula. Urology. 2(4):449-51.

Biography

Cinzia Casu has completed her Graduation in 2010. Currently, she is working at her Private Dental Practice in Cagliari, Italy. She had concluded a bienal Master's degree on Oral Surgery and Pathology at the University of Parma in 2015, and others courses of oral pathology. She is the author of several national and international articles and a monograph. She is the President of AIRO (Italian Academy of Oral Research). She is an Editorial Member of some international journals such as *Biology and Medicine Case Reports* and *Current Analysis on Dentistry*. She was a Speaker in Italian, European, and World congresses.

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Gene Silencing Approach for an orphan GNAO1-related neurodevelopmental disorder

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GNAO1 disorder is a fatal genetic neurodevelopmental disease characterized by epilepsy and movement impairment that begins in early infancy. GNAO1 gene is highly expressed in the brain and certain de novo mutations in this gene result in production of toxic protein that causes dysregulation in neuronal signaling. Currently no effective treatment is available for this pathology. Our aim at Marlin Biotech is to find gene therapy cure for GNAO1 disorder. Considering autosomal dominant condition of this disease, we suggest a strategy of allele-specific gene suppression that would selectively lower levels of abnormal protein in the brain neurons and leave functional protein unaffected. To test gene therapy approach *in vitro*, we developed an assay with expression of exogenous wild type or mutant (c.607 G>A) GNAO1 variants in cultured cells. We screened synthetic siRNA duplexes that target mutation site in GNAO1 RNA and downregulate expression of mutated gene through RNA interference (RNAi) pathway. Our data demonstrates that two RNAi effectors reduce accumulation of mutant GNAO1 transcripts in allele-specific manner. These results were confirmed at RNA and protein levels in heterozygous assay where both wild type and mutant GNAO1 variants were introduced into cells simultaneously in 1:1 ratio to mimic heterozygous condition of the patients. Taken together, our pilot experiments demonstrate the potential of allele-specific silencing approach for gene therapy of GNAO1-related neurodevelopmental disorder. Our next step is designing RNAi-based therapeutics for GNAO1 disorder that is compatible with delivery via adeno-associated virus (AAV) vectors to brain tissues. To validate beneficial effect of AAV-RNAi technology *in vivo*, we are also developing humanized mouse model of GNAO1 disorder using CRISPR/Cas9 technology.

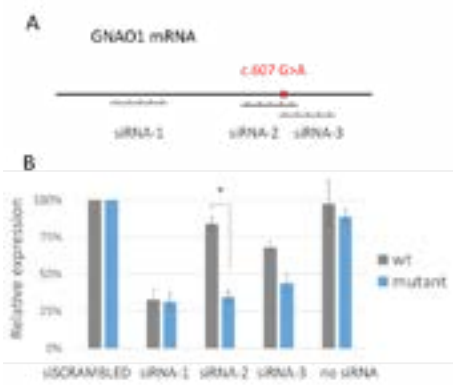

Figure 1: Allele-specific downregulation of mutant GNAO1 transcript by siRNA in cultured cells A. Position of selected siRNA target sequences in GNAO1 transcript is schematically shown. B. siRNAs targeting GNAO1 were screened in HEK293T cells expressing exogenous copies of mutant or wild type (wt) GNAO1 siRNA-1 served as positive control and reduced expression of both GNAO1 variants to ~30%.

Biography

Maryana Bardina has obtained her PhD in Molecular Virology at Lomonosov MSU, Moscow, Russia and completed training in viral vector design and gene suppression technologies at ICGEB, Trieste, Italy. She has joined Marlin Biotech in 2016 and developed methods for AAV production and purification. From November 2017, she leads the project on GNAO1 disorder aiming at finding gene therapy cure for this neurological disease.

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Accepted Abstracts

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Wyburn-Mason syndrome. Ever heard of it?

Dan Jeffries
Patient, Author and Advocate, Bristol, UK

Dan Jeffries has, and his insightful and entertaining talk explores what it's like living with one of the world's rarest medical conditions - and then finding out you have another one. Dan was diagnosed with Wyburn-Mason syndrome at four-years old. It is an exceptionally rare AVM (Artereovemous Malformation), situated around the midbrain and optic nerve. As a consequence, Dan is blind in his left eye. The AVM is untreatable and there are thought to be less than 100 reported cases in the past fifty years — worldwide. That works out to be about 1 in 70 million people. Pretty rare. And then, as he turned 30, Dan discovered that he had Acromegaly — a benign tumor in the pituitary gland. About 6 people per million are diagnosed with this unique and challenging condition that effects growth homrone and IGF-1 production, as well as impacting on vision, facial appearance, hands and feet, teeth, libido and more. Being Rare explores the early days of diagnosis, living with Wyburn-Mason syndrome and how things started to change during his twenties, leading to the bizarre discovery of Acromegaly — discovered by student doctors. Using an innovative slideshow, Dan is able to show key images, doctors notes and more, reflecting the methods used to tell his story in his published memoir, Me, Myself & Eye. Dan also explores the impact of living with rare conditions and how this can affect the individual on a day-to-day basis, as well as the empowerment it can bring too. "Dan's talk managed to be informative and entertaining, insightful and moving, educational and inspiring. You don't often find presentations that manage to combine all of those qualities! I left with a deeper understanding of what it is like to live with rare conditions, and also with a smile on my face!" - Pfizer UK.

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Integrated control and prevention of malaria (Anopheles stephensi) and dengue (Aedes aegypti) vectors with plant extracts through water, insecticides and BTI

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Mosquitoes act as life threatening disease vectors. Due to non-availability of vaccine and treatment for most of these diseases, the only solution is to control the mosquitoes. The continuous application of synthetic insecticides causes development of resistance in vector species, biological magnification of toxic substances through the food chain and adverse effects on environmental quality and non-target organisms including human health. So, under the Integrated Mosquito Management (IMM), emphasis is given on the application of alternative strategies in mosquito control such as use of insecticides, plant extracts and Bti. Mosquito larvae were collected from different habitats and brought for identification. After identification, Anopheles and Aedes mosquitoes were reared separately and treated with different plant extracts, growth regulators and Bti. Plant extracts through water and insecticides and Bti were tested in combination to test their efficacy against Anopheles and Aedes larvae. Again mortality data was collected and subjected to prohibit analysis to calculate LC_{50}. The least value of LC_{50} (162-398 ppm) observed with solution of water extracts, Bti and insecticides for Anopheles and Aedes larvae. By adopting these techniques we should able to manage the populations of Anopheles and Aedes in the environment.

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Ensuring patient centricity in rare disease drug development

Jennifer Mcnary
Fierce advocate, USA

Patient centricity is an often used but not always executed strategy in the current drug development landscape. It is known that patients and their caregivers are key stakeholders and potentially hold the greatest expertise in their own diseases; it is the responsibility of drug makers to enlist the help of these individuals to help ensure a successful pathway from pre-clinical development to the global market. During this presentation author will use her 17 years of experience as a caregiver to two rare disease patients and professional work as an Advocate and Consultant to demystify the concept of ensuring patient centricity in the rare disease drug development space. Participants should expect the following to be achieved: Exploring timelines and methods for seeking patient input into the drug development process at every stage, including endpoint selection, clinical trials, regulatory and commercial development; Learning best practices for working with patient, caregivers and advocacy groups to ensure a mutually beneficial relationship; Identification of ways to support and encourage the patient communities in your disease space; Development of strategies to tackle access issues within patient communities both pre and post drug approval.

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Primary hydatidosis of distal femur masquerating malignancy-a rare case

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Hydatidosis of bone is a very rare condition and its incidence as compared to other organs range from 0.5-4%. There is no typical clinical appearance and the image characteristics on Xray and CT are similar to those of tuberculosis, metastasis, giant cell tumour or bone cyst. Case Summary- A 53 year old female presented to the orthopaedics OPD of Safdarjung hospital with pain and swelling over her right knee region. Routine radiograph exhibited multiple lytic lesions with thinned out cortices and fracture of supracodylar region. A provisional clinical diagnosis of malignancy was made and fine needle aspiration was advised. Cytology was reported as suspicious of malignancy and histopathology was asked for confirmation. Biopsy was reported as Hydatid disease of bone. Early diagnosis is uncommon in primary hydatidosis of bone as it is not considered in the differential diagnosis of osteolytic lesion. Long term survival is possible with early diagnosis. This case is being presented due to its rarity.

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Lysosomal storage disorders-updates from India

Shashank Tyagi

Lysosomal Storage Disorder Support Society, India

Lysosomal Storage Disorders Support Society a first, not-for-profit and pan India organization is registered and headquartered in New Delhi, India, headed by a group of parents and patients of LSD who know what it's like to live with Lysosomal Storage Disorders. LSDSS was formed formally in year 2010 to address the unmet needs and create awareness that benefit patients with lysosomal disorders in India. LSDSS works for creating awareness for prevention, timely and accurate diagnosis, consultation, symptomatic care and treatment options amongst patients, physicians, care givers and hospitals across India. LSDSS is a prime force behind the formation of National Rare Disease Policy in India by approaching the Judiciary through legal cases. LSDSS is doing advocacy in Government of India at Central and State level for better implementation of National Rare Disease policy. LSDSS has been organizing Rare Disease Day every year since 2010 and have been conducting Continuing Medical Education programs, Medical Camps, Media Workshops besides observing International Gaucher Day, MPS Day, Pompe Day, from time to time in association with major hospitals in different parts of India. Currently, LSDSS has 685+ treatable LSD afflicted registered patients from different parts of India and 35+ Specialized Medical Genetics doctor's and LSD Expert group from all over India working in tandem with emphasizing on need of accurate diagnostics facilities available and scouting for more avenues to get treatment options for unmet needs of hundreds other children's. LSDSS is also a member of many reputed International Groups working on rare disorders and won PAL award in year 2011.

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