2nd International Meeting on Laminopathies

Bologna (IT), 6-8 April 2017
THIS IS NOT AN OFFICIAL REPORT, IT IS JUST A SUMMARY OF SOME OF THE CLINICAL LECTURES PRESENTED DURING THE MEETING.
The official and complete abstracts are available at:
https://media.wix.com/ugd/47c23e_4a0861eb9a344d3b8724446bba07643e.pdf

OPENING LECTURE

Giovanna Lattanzi, biologist, Bologna, Italy

Laminopathies are a group of diseases linked to mutations in LMNA gene, encoding lamin A/C, or in lamin partner genes.
Twenty-years research on laminopathies have shown that finding a cure for these disabling genetic diseases requires physiological lamin pathways to be unraveled. On the other hand, in search for pathogenetic mechanisms of laminopathies, translational research has provided new insights into lamin functions. Moreover, some potential therapeutic approaches have been proposed and tested in experimental models and clinical trials. In this scenario, multidisciplinary networks for the study and treatment of laminopathies were born in Italy and France.
The International Meeting on Laminopathies has been organized by these networks to provide an occasion to share knowledge among diverse specialists, from basic researchers to physicians, with the important contribution of patient experience and to pave the way to the creation of a European Network for Laminopathies.

MUSCULAR LAMINOPATHIES SESSION

Rabah Ben Yaou, neurologist, Paris, France

As for several other neuromuscular disorders, definite phenotype/genotype relations for laminopathies remain elusive, despite a remarkable progress that has been made in the description of the clinical and genetic spectrum of these diseases.
In France a web-based and freely available locus specific database was setup in 2013, aiming at gathering genetic and main clinical manifestations of cases reported with laminopathies. It is called OPALE, and it is dedicated not only to laminopathies but also to emerinopathies. Today there are at least 623 LMNA mutated patients identified in France. 244 of them had neuromuscular involvement of multiple faces that extends from elevated CPK to severe congenital muscular dystrophies, confirming the high phenotropic pleiotropy of laminopathies.

Lorenzo Maggi, neurologist, Milano, Italy

At present, no cure for laminopathies is available, but studies on potential therapeutic approaches to correct the genetic defect are in progress.
No data on laminopathies natural history through specific clinical evaluations have been reported
to date. That’s why he decided to start a study, aiming to develop a protocol for the clinical functional assessment of patients affected by laminopathies. The protocol includes a series of tests often used to describe other muscular diseases, but never, till now, used or at least published for laminopathies. (Ex: 6 minute walking test, timed 10 meter walk/run, rise from floor…).
Currently 22 patients have been evaluated. He and his group expect that this study will provide a tool for laminopathies assessment in clinical practice and in future therapeutical trials, thus improving management of these diseases and contributing to a better definition of laminopathies natural history.

**Agnieszka Madej-Pilarczyk**, neurologist, Warsaw, Poland

The Neuromuscular Unit in which this doctor works has registered 30 patients with EDMD1, 25 EDMD1 female carriers and 20 EDMD2 patients. Basing on clinical examination, diagnostic tests and histological and immuno-histochemical studies, she’s trying to characterize the natural course of the skeletal muscle disease. Additionally, she performed analysis of selected serum cardiovascular risk biomarkers, aiming to select the best ones for assessment of myocardial disease – in course.

**Ivana Dabaj**, pediatric neurologist, Paris, France

Corticosteroid therapy has shown a benefit in Duchenne muscular dystrophy, especially on skeletal muscle, scoliosis and respiration. She presented a series of 27 patients with CMD associated with LMNA mutation. The muscle biopsy was inflammatory in 16, and non-inflammatory in 9 patients. Important to mention that patients who responded to treatment do not always have inflammatory abnormalities on the biopsy. The positive effect of corticosteroids was clear in the first month in several patients. In non-responders, treatment was discontinued after 2 months of initiation. A prospective study is needed to determine the responders and the degree of benefit at the motor, respiratory, cardiac and orthopedic levels. She launched some before-after treatment videos and the improvement of these kids seemed incredible.

**Marion Main**, physiotherapist, London, UK

She works especially with kids with CMD and pointed the importance of physiotherapy to slow and correct as much as possible some of the malformations that the disease can give.

Asked about overexercise, Dr Main told us that we should’t obviously get totally exhausted, but said that aerobic exercise can be good. She meant the kind of exercise in which there’s increase in heart rhythm and respiratory acts. Not too much, not too poor!
Ivana Dabaj, pediatric neurologist, Paris, France

She presented some cases of CMD from an orthopedic point of view, showing treatments for scoliosis and neck contractures. When the neck contracture is extreme, there’s a treatment that can be done. The first phase consists in a HALO traction, followed by the fusion of the cervical spine, to solidify the work done with the traction. She exposed the case of a 36 years old male with CMD who could only look “at the roof” because of the neck contracture. With this treatment his neck returned straight, but of course was blocked.

During questions time we asked both Dr Dabaj and Dr Main what could be a treatment for the more mild neck contracture that adults have. Unfortunately the physiotherapist told us that the joint “gets used” to the contracture, so in adults it’s almost impossible to gain more grades of moving with physiotherapy. The neurologist told us that the surgery treatment should be done just in extreme cases because of the fusion of the cervical vertebrae.

CARDIOMYOPATHY SESSION

Vincenzo Russo, cardiologist, Napoli, Italy

In his center clinical practice, a high risk of sudden cardiac death for ventricular tachycardia-arrhythmias is not limited to EDMD2, but also occurs in EDMD1 and EDMD6 patients. Accordingly to their experience, they warmly recommend the presence of a cardiologist with high experience in electrophysiology as an essential part of the neuromuscular care team. Waiting for clear indications of guidelines and randomized clinical trials to solve important questions in this rare muscle disease group, they suggest that patients with EDMD perform:

· A 6-months interval cardiological evaluation
· A complete electrophysiological evaluation to assess the risk of sudden cardiac death and early detect the onset of conduction disorders and non-sustained ventricular tachycardia, through external loop recorder monitoring or implantable loop recorder
· An ICD implantation in all patients with permanent pacing indication for spontaneous or inducible ventricular arrhythmias
· An ICD-CRT implantation in patients who need an ICD implantation, but also have a left bundle branch block and depressed cardiac function.

Georgia Sarquella Brugada, pediatric cardiologist, Barcelona, Spain

She’s a cardiologist specialized in treatment of cardiac problems in kids with CMD associated with LMNA mutations. The key message from her presentation was that:

· Diastolic disfunction is very important and has a huge weight, even if systolic function is good
· Subcutaneous holter makes the difference. She recommends to implant one to record cardiac rhythm
· In low ejection fraction + arrhythmias, electrical storm can occur
· Early ICD implantation if non sustained ventricular tachycardia are seen
· Atrial arrhythmias, even non sustained, are dangerous
· Embolic events should be prevented. This is really important because pediatricians are not used to embolic events at all, so they may underestimate their weight.
Antoine Muchir, biologist, Paris, France

Although early initiation of treatments may delay the progression of dilated cardiomyopathy (DCM) and prolong the pre-transplantation phase of the disease, more-definitive therapies for DCM await better mechanistic understanding of the molecular basis for this disease to develop specific treatments.

Mouse models of LMNA cardiomyopathy have been created to decipher pathogenic mechanisms. The results of this study provide proof of principle for MAP kinase inhibition as a therapeutic option to prevent or delay the onset of LMNA cardiomyopathy. Pharmacological blockade of signaling in the MAP kinase cascade prevents left ventricular dilatation and deterioration in cardiac contractility. These studies clearly show that the abnormal activation involved is the pathophysiology of LMNA cardiomyopathy. These have helped to explain the pathogenesis of the disease as well as identify therapeutic targets for potential innovative pharmacological therapies, which will be tested using clinical candidates. This will provide the foundation for future clinical trials in human patients.

Giuseppe Boriani, cardiologist, Modena, Italy

The presence and severity of arrhythmic disturbances is usually not related to the presence and degree of neuromuscular impairment.

Since the most common clinical manifestations are lightheadedness, syncope, palpitations, ischemic stroke due to cardioembolism or even sudden death, risk stratification is the basis for prevention strategies that include use of cardiac implantable electrical devices. Clinical decision making has to consider the risk and benefit of brady-tachyarrhythmias, taking into account presence/absence of ventricular dysfunction, and the decision to implant a cardiac electrical device should consider the potential risks and benefits of device therapy, as well as the risk and consequences of potential device-related complications.

Giovanni Peretto, cardiologist, Milano, Italy

He analyzed the data coming from the Italian database. 164 patients with LMNA mutation from 13 Italian centers have been included.

99 patients displayed combined cardiological and neuromuscular defects, while 48 showed pure cardiac involvement. ICD was implanted in 47% of patients and appropriate shocks for ventricular tachycardia/fibrillation occurred in 38% of implanted patients. 14 patients required cardiac transplantation and 10 deceased.

In order to identify risk stratification markers, the occurrence of malignant ventricular arrhythmias, cardiac transplantation and death were considered endpoints. Multivariate analysis showed three independent predictors for the composite endpoint:

- Non sustained ventricular tachycardia
- Left ventricle ejection fraction < 50%
- Tendon retractions.

The identification of new risk stratification markers can lead to the elaboration of a risk score to improve especially the management of asymptomatic patients.