MITOFUSIN 2:

NEUROPATHIES E MITOCHONDRIAL FUSION

Milan, 7th april 2014

The 1st International Conference entirely dedicated to CMT 2A

The first international Conference "Mitofusin 2: Neuropathy and Mitochondrial Fusion" was a success. This conference, entirely organized by "Association Mitofusin 2 Project", was made in order to bring forward the latest advances in research and to promote international cooperation between scientists. Almost 150 people (patients and delegates of other Associations regarding Charcot-Marie-Tooth disease as the Italians Acmt-Rete and Aicmt, and the french Cmt-France, doctors and researchers) came from many European countries to hear 13 highly professional and specialized scientific experts talking about most important aspects of mithocondrial protein MFN2 connected to peripheral neuropathy. From United States, by teleconference, Professor Michael E. Shy showed some very significant updates.

Furthermore, the conference was a moment of deep humanity and participation.
We would like to thank Professors Nereo Bresolin and Giacomo P. Comi (University of Milan) and their team (Dr Federica Rizzo in particular for her valuable and constant contribution) for having organized the scientific part of the event; the prominent experts for their important contribution ; all participants and in particular patients with their families for coming from far away, especially all the friends from France. A special thanks to our wonderful volunteers, to the many donors who have supported us, in particular Banca Intesa Private Banking and Dr Renzo

Jorio, president of Accor Hotels Italy; to the excellent interpreters and to Angelo Mascherpa, our photographer, who did a great job photographing event.

Above Professors Comi, Bresolin e Bonneau (from the left to the right)
Below the Scientific Programme of the Conference detached in two sessions

SESSION 1

Chairpersons:	Prof Bresolin N (Milan), Prof Bonneau P (Angers, FR)
9, 30-9,40	Prof Bresolin N (Milan) Introduction to genetic etiology of neurodegenerative diseases
9,40-10,00	Prof Comi GP (Milan) Mitofusin 2, fusion and mitochondrial dysfunctions
10,00-10,50	Prof Shy ME (Iowa City, USA) Hereditary neuropathies
10,50-11,10	Prof Moggio M (Milan) Neuropathology: the study of peripheral nerve in human being. Applications for MFN2 animal model
11,10-11,30	Dr Quattrini A (Milan) Neuropathology: the study of peripheral nerve in experimental models
11,30-11,50	Dr Pareyson D (Milan) Clinical features associated with MFN2 mutations
11,50-12,10	Prof Fabrizi GM (Veron) Pathogenic variants and polymorphisms in MFN2 gene
12,10-12,30	Prof Mostacciuolo ML (Padua) MFN2 gene mutations
12,30-13,00	DISCUSSION

SESSION 2

Chairpersons:	Prof Comi GP (Milan), Prof Mostacciuolo ML (Padua)
14,30-14,50	Prof Bonneau P (Angers, FR) mtDNA depletions in severe MFN2 patients
14,50-15,10	Dr Bergamin G (Padua) Zebrafish as MFN2 disease model
15,10-15,30	Dr Corti S (Milan) iPSCs derived from skin fibroblasts as a disease model
15,30-15,50	Dr Rizzo F (Milan) Gene expression modulation in MFN2 mouse model (MitoCharc1)
15,50-16,10	Dr D'Angelo Mg (Bosisio Parini) Neurorehabilitation and follow-up
16,10-16,45	DISCUSSION
16,45-17,15	Living with CMT, Role of patients Associations and their families Associazione Progetto Mitofusina 2 Onlus (Rignano sull'Arno, Turin)
17,15	CLOSING REMARKS

Summary

The conference started with words of praise for our Association. Professor Nereo Bresolin, Director of Centro Dino Ferrari-Milan University , who opened the works, talked about this conference as an important turning point in the panorama of non-profit Associations concerning rare diseases, hoping that it could be taken as a model by other organizations for any future action in this field.
Then he pointed out new methods of study which are being applied nowadays in the matter of neuromuscular and neurodegenerative diseases, illustrating the positive aspects and those who still need to be explored. He concluded his speech by describing recent studies on the functions of the many proteins involved in HMSN2 rare disease, explaining how these works are essential to more specifically understand what might be action area for any possible therapy.

Professors Comi, Bresolin e Bonneau, chairpersons during the speech of Professor Mostacciuolo.

After him, Professor Giacomo P. Comi explained how mitochondria work and, in particular, how Mitofusin2 work in mitochondrial fusion, a process essential for the proper functioning of the mitochondria and thus also of the cells.

On the right Professor Comi from Milan University making his speech "Mitofusin 2, neuropathies and mithocondrial fusion" on the stage.

Professor Bresolin introducing Professor Shy in teleconference

In teleconference from University of Iowa City, Department of Neurology, Professor Michael Shy outlined clinical features of CMT2A due to mutations of MFN2 gene. It has a rate of 20% over the axonal form of HMSN also called "Charcot -Marie-Tooth type 2". The age of onset can be either late or early, the earlier is the more severe form. In order to value, in an objective way, how much severe are the symptoms presented by patients, Prof. Shy has developed, with his team , an interesting *rating scale of disease*. He said this method of measure is working very well as much as the criteria of investigation (clinical and genetic engineering) which they are employing to reach a correct diagnosis for the disease. Then, he introduced the interesting therapeutic research carried out by his group, with the use of both stem cells and animal models of the disease. The teleconference was closed under the hope that a clinical study will be carried out through a collaboration between his department and our scientific Committee in the University of Milan, as well as a cooperation between our Association and the American Association CMTA, that supports their research.

Summary

Then took place Prof. Maurizio Moggio of Milan University. He talked about the importance of the biopsy of the nerve to provide important information about diagnosis.

Dr Angelo Quattrini of San Raffaele Hospital in Milan spoke about the study of peripheral nerve among experimental models, focusing on the pathogenesis in animal models of neuropathies. In particular, he described the study, carried out by him and his team in their laboratory, on the MPZ, a protein boundup with CMT.

Professor Moggio from Policlinico of Milan during his speech about peripheral nerve in human being

Dr Davide Pareyson of Carlo Besta Institute in Milan, outlined the clinical features of the different autosomal dominant forms of CMT caused by mutations of the protein MFN2: the types classified as CMT2A, CMT5, CMT6 and those of the rare and complex recessive forms, illustrating some of the cases they have studied. He pointed out the fact that we must distinguish the pathogenic mutations from the benign ones. He spoke about the importance of the REGISTER OF PEOPLE WITH CMT, just started up in Italy, inviting patients to join it.

Prof. Fabrizi of Verona University focused his speech on the description of the functional domains of proteins MFN1 and MFN2, in particular to the great number of mutations in the protein Mitofusin2, some of which do not seem to be pathogenic.

On the left Dr Pareyson from Besta Institut of Milan

Prof. Maria Luisa Mostacciuolo of Padua University of illustrated the different kind of mutations to which the gene MFN2 is subjected. The genetic survey, carried out with the new methodologies, is giving us a lot of new information, but we should consider also the cases related to large families of patients where patients and subjects are carrying the mutation but without disclosing the disease.

On the left Professor Mostacciuolo and on the right Professor Fabrizi

Summary

Dr Bergamin during his speech about Zebrafish as MFN2 disease model

Prof.Patrizia Bonneau from University Hospital of Angers, spoke about the depletion of mitochondrial DNA in patients with HMSN 2 severe forms. He illustrated a series of cases she analyzed : in some of them, patients had, in addition to neuropathy, other serious problems concerning the central nervous system. She stated that the function of Mitofusin 2 is very important, although entering into the study of its mutation is a bit as "opening Pandora's Box." He concluded by saying that it is very difficult to understand the disease by simply analyzing the patient from the clinical point of view.

Then, there was a little deflection from the program: Dr D'Urso, a very important neurofisiopatologist of Milan Policlinico Hospital, was invited on the stage by Professor Bresolin, to talk about the importance of a partnership between pathologists and neurophysiologists in order to reach a more precise diagnosis in this very difficult field.
After that, Dr Giorgia Bergamin from London showed her innovative experimental study carried out by observing a small freshwater fish, called Zebrafish, whose developing is extremely fast: for this reason is a good experimental model for the research on Mitofusin 2.

Very interesting was the intervention made among the audience by Professor Julius Geir Braathen, who came from Oslo, at the invitation of Professor Comi, to present his research on several interesting cases of CMT2A in Norway.

L'intervento del Professor Braathen from Akershus University Hospital

Soon after, Dr. Stefania Corti, head of Neural Stem Cell Lab of Milan University – Policlinico Ca'Granda Foundation, spoke about the ongoing studies in his laboratory (research supported also by our Association). She explained how to create stem cells from skin fibroblasts of patients affected by CMT2A.Then she illustrated the trials of cell transplantation in the mouse model of SMA, experiments which could be translated also to the mouse model of CMT2A.

Dr. Federica Rizzo , of Centro Dino Ferrari- University of Milan, showed the research project supported by our Association Mitofusin 2 Project It is based on the modulation of gene expression Mitofusin2, studied in order to reach a possible gene therapy for CMT2A (HMSN 2). The trials are carryed out "in vitro", but also "in vivo" experiments are currently ongoing on mouse models. They begin to give interesting results. Dr. Rizzo concluded his speech by thanking our Association for the financial and moral support to continue the project with enthusiasm.
And finally, Dr. Grazia D'An-

Dr Corti, from University of Milan, manager director of Neuralstem Cell Lab

Summary

gelo of Eugenio Medea Institute in Bosisio Parini, talked about care and rehabilitation for patients with Charcot-Marie-Tooth disease. She explained what are the different clinical signs which characterize this disease, talking about the professionals necessary for the total care of the patient, from neurologist to physical therapist, orthopedic surgeon and radiologist, without neglecting the importance of psychological support for the patient and the family. A very interesting point, which was introduced by the Doctor, was about respiratory weakness of diaphragm and other respiratory muscles. Furthermore, she spoke about some issues bound with HMSN , such as the involvement of nervous central system (cognitive and behavioral defects) or neuropathic pain. She doctor also suggested to pay attention to osteoporosis, caused by the reduction of mobility, especially in the case of patients on wheelchair, recommending the necessary checks .

The Conference ended with the speeches of some of the members of Association Mitofusin 2 Project. President Eleonora Bartolini outlined the aim and the activities of our non-profit organization; then Annamaria Tozzi, one of the founding member , spoke with so much intensity and emotion, about the story of her family and about the casual meeting with another family which led to the foundation of the Association. Then Luisa Porzio, another founding member along with her husband Paolo, website manager, spoke about her experience as a mother of a young girl with CMT2A. She underlined the importance of Internet communication as a useful way to reach a great number of patients worldwide , to begin international cooperation , to promote scientific research to find the cure.

The President then resumed the word to thank all the participants and to invite everyone to join and support our association.

Some charter members and some supporters of Mitofusin 2 Project Onlus

"The Conference has been an important turning point in the panorama of non- profit Associations concerning rare diseases. An hearfelt thanks to all the partecipants!"

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