EUROHSP' SUM UP of the SPATAX 2019 MEETING
SEPT. 20-21, NICE, FRANCE

SPATAX is the network of hereditary SPAstic paraplegias (SP) and cerebellar ATAXias (CA)

Since 2000, clinical and genetic heterogeneity of these diseases have pushed clinicians and scientists working on these groups of diseases assembling the largest collections of families to constitute a clinical and genetic data base. SPATAX also includes major laboratories involved in the molecular basis of these disorders.The knowledge gained in the network will be immediatly applicable to patients to improve diagnosis , follow-up , appropriate genetic counselling, and to initiate clinical trials.

This 6th *SPATAX* meeting had been organized as a Satellite meeting of the International congress of Parkinson disease and Movement Disorders-MDS, sept 22-26.
The Scientific Committee of the meeting was composed of : Sylvia BOESCH (Austria), Alexandra DÜRR (France), Filippo SANTORELLI (Italie), Giovanni STEVANIN (France), Matthis SYNOFZIK (Germany), Chantal TALLASKEN (Norway), Bart Van de WARRENBURG (Netherlands).

The willingness of the organizers to fully involve patients in the meeting led to a preliminary short oral presentation of Marina ZAPPAROLI-MANZONI, President of the *EUROHSP* federation that gathers 10 National HSP Associations. In a few and very sensitive words of a Mum who cares her lovely teenager affected by HSP, Marina expresses to the researchers the expectations of all families coping with HSP.

This short sum up will focus specifically to the communications regarding HSP.

ORAL PRESENTATIONS

They were done as either Plenary Conference (30', n=12), Selected Abstracts (15', n=12), Invited Scientists (15', n=4) and Networks News (10', n=4). Abstracts displayed as regular posters (n=71) were presented during pauses and coffee breaks.

One may group plenary oral talks according to 3 essential issues :

- **Researches aiming at identifying altered molecular traits, including metabolic disorders that may direct to therapeutics**
- **Networks required for the development and validation of clinical and molecular biomarkers as outcomes parameters for clinical trials**
- **Therapy.**

RESEARCHES SEARCHING COMMON ALTERED MOLECULARS TRAITS, & METABOLIC DISORDERS

Given HSPs stand up as a group of highly heterogenous monogenic neurodegenerative diseases (> 80 identified « *SPG* » genes so far) , researchers investigate any molecular pathway that could be drugable : either a specific uncontroled pathway for a single SPG or a common one involving several *SPG,* see ataxia genotypes. In that respect the proeminent presentations were as follows :

- **Rebecca SCHÜLE (Germany)** ***IP3 Receptor Degradation – A Mutational Hotspot for Hereditary Ataxia and Motor Neuron Disease.***
  IP3 receptor appears to the authors as a drugable pathway (*Nature Communication*. In press)
- **Frederic VAZ (Netherlands)** ***Organellar proteomics to investigate the mechanism that underlies the neuronal pathology of AP-4 deficiency***
  Through a lipidomics approach this team showed that lipids are consistently remodeling through membranes of various cellular structures (mitochonfria, endoplasmic reticulum, cell membranes) and HSP phenotypes parralel lipid related disorders.
- On the same line of evidence, is the team of **Frédéric DARIOS (France*) From physiopathology to preclinical trials in SPG11***
  In deciphering the altered lysosomal metabolism of the the pre-clinical *SPG11-/-* mouse model, the team showed that the accumulation of gangliosides is a consequence of the impaired lysosome recycling. Consequently, a reduction of the gangliosides load is proposed as a potential role of therapy. Given molecular physiopathology pinpoints role of lipids for *SPG4* and *SPG3A*, it is suggested to also test such an approach for the two HSP leaders related to dominant transmission
- **Fanny MOCHEL** *Metabolic forms of neurodegenerative disorders*
  Working downstream the molecular physiopathological pathways , this team studies all metabolic disorders related to HSP , such as urea cycle, MTHFR, cholesterol, phospholipids remodeling… with the aim to detect biomarkers required for the follow up of any clinical trial.

- **Alexandra DAVIES (Germany) and Juan BONIFACINO (USA),** ***Novels insights into AP-4-Deficiency Syndrome***

  In using different approaches, both teams work on AP-4 deficiency involving various forms of HSP (*SPG47, SPG50, SPG51, SPG52*). These teams aim at identifying the mechanism that underlies the severe neuronal pathology of the deficiency of this adaptator protein complex

HSP NETWORKS NEWS

Besides two Ataxia Networks, Thomas KLOCKGETHER *(Germany)* SCA global and Matthis SYNOFIKS *(Germany)*ARCA global networks, two HSP Networks have been formed :

- **Rebecca SCHÜLE** ***(Germany) TreatHSP.net and the Alliance for Treatment in HSP and PLS (Primary Lateral Sclerosis)***

  The German ***Treat'HSP network*** gathers HSP registers, Biobank and OMICS registers. It involves research of pathways and identification of targets. This opens to preclinical trials and leads to trial outcome parameters and finally to clinical trials.
- **Alexandra DÜRR (France)** ***Spatax data base to set up a TransNational HSP network***

  The *SPATAX* data base has been collected for more than a decade with the participation of clinicians and scientists from various European Institutions involved in these neurological diseases. Today the *SPATAX* database (about 5000 patients files) displays standardized items. In using REDCAP tool (Research Electronic Data Capture), the ***Trans National HSP Network*** is ready to be shared for clinical studies . since it offers homogeneized items and files including patients consent for research, phenotype & genotype data as well as biobanks (DNAs, RNAs, biological fluids, tissues…). The *TransNational HSP network* will open towards clinical trials.

THERAPY

We had been unfortunate not hearing the talk of Mimoun AZZOUZ (UK) *Gene therapeutics for spastic paraplegia types 15 and 47* who could not attend the Meeting.

Regarding physical therapies for HSP, four speakers presented tha following studies

- **Lucy VINCENT** ***(France) Dance for ataxias and spastic paraplegias***

  Taking into account the brain spasticity, Dance represents an environmental enrichment-multiplication of sensoromotor activities. See « *click and dance.com »*
- **Matthis SYNOFZIK** ***(Germany) Exergames and physiotherapy***

  Exercices at home, with a SARA assessment improve the wellbeing and delays disease progression. See Synofzik *et al* 2012, *Neurology*

- **Alexander GEURTS *(Netherlands) Potential effects of botulinum toxin in patients with pure HSP***
  The team shows that Botox injections in calves, soleus and gastrocnemius muscles improve gait speed and gait width. And stresses the interest of home-based speech exercices.
- **Fabricio DINIZ DE LIMA (*Brazil) A double-blind, randomized, placebo-controlled, crossover trial of botulinum toxin type A in hereditary spastic paraplegia – the SPASTOX***
  In sharp contradiction with the GUERTS work, the Brazilian team does not find any positive effect of Botox for gait

POSTERS

PATIENTS POSTERS

- **Marina ZAPPAROLI & Jean BENARD : EuroHSP *mission and goals*** :
  The Federation of 10 National HSP Associations, the strategic goals and expectations
- **Adam LAWRENCE *How HSP affects wellbeing***
  This is a sum up of findings from 3 on-line surveys regarding symptoms and sleep.
- **Carina THURGOOD, The Maddy Foundation *Hereditay Spastic Paraplegia SPG15*** *(SPG15)*
  The condition of *SPG15* patients is presented as well as its relation with *SPG11* condition. Noteworthy,using the very first gene therapy approach for HSP is proposed using AAV dual vector on patients fibroblasts ; preclinal trial on mouse model is on going .

POSTERS PRIZES

- **Abstract 4 Alexandre Pierga / Maxime Boutry -** *Spatacsin's role in lysosome recycling and lipid clearance*
- **Abstract 31 Marc Corral-Juan -** *An unstable ATTTC repeat mutation within the Disabled 1 gene causes cerebellar Purkinje cell alterations, DAB1 RNA switch, and Reelin signalling dysregulation in Spinocerebellar ataxia type 37.*

POSTERS REGARDING HSP

The content of all posters of the *SPATAX* 2019 can be obtained at :
https://spatax.files.wordpress.com/2019/10/booklet_2019-version-en-ligne.pdf

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