**Following the International *SPATAX-PREPARE-ASG* meeting in Nice (Sept 20, 21 2019) a video meeting held on oct 29, 2019 (11-13h) has enabled a fruit full discussion between *SPATAX* organizers**
**(Prs Alexandra DÜRR (AD), Giovanni STEVANIN (GS), and Mrs Elodie PETIT, Clinical-Research Associate) and members of the *EUROHSP* Board of Directors, Marina ZAPPAROLI (MZ), President, Hermien REMMELINK (HR) vice President, & Jean BENARD (JB), Patients Scientific Advisor.**

***The 3 following issues had been addressed***

## HIGHLIGHTS OF THE *SPATAX-ERARE-PREPARE-ASG* MEETING 20-21 September 2019, Nice, France

**Prs AD & GS (as SPATAX Organizers):** The meeting organized by *SPATAX, Erare PREPARE_Ataxia and Ataxia Study Group* (ASG) on spastic paraparesis and ataxia in Nice (2019 September 20-21) gathered 160 scientists and patients from 21 countries from 4 continents. The 19 seminars *(S)*, 12 oral presentations (*OP*) from abstracts selection and the Abstracts *(A)* from 70 posters allowed many exchanges between researchers and to hear the voice of patients.

Regarding research on HSP, several results can be highlighted **(please, *to refer see Attached Program as well as Poster Booklet*):**

***https://spatax.files.wordpress.com/2019/10/booklet_2019-version-en-ligne.pdf***

### DIAGNOSIS

Diagnosis still improves with the novel generation of sequencing (NGS) according to the 2 works of Ashraf Yahia (*A2*) and Mélanie Papin (*A76*). Several genes are more frequent than expected such as SPG8 according to Cécilia Marelli (*A41*), but also KIF1A mutated cases (Mélanie Papin (*A76)* and Yosra Halleb (*A21*) works). There are more than 70 known causative genes but probably more if we consider the overlap of genes with other neurological diseases. There are more and more genes involved in spastic ataxia such as ARSACS, SPG7 and now POLR3A (Marc Corral-Juan (*A32)* and VPS13D (Christelle Durand (*A22*)). Interestingly, in the meeting one novel spastic ataxia gene was reported by Rebecca Schule (S), RNF170, which is involved in similar processes as other HSP genes related to the degradation of IP3 receptors (SPG18, SPG72 and also the SPG37 according to the work of Giovanni Stevanin also presented at the meeting, A78). Lipid metabolism is also the source of many disorders affecting the cerebellum or the pyramidal tract as pinpointed by Frederic Vaz (*S)* and Fanny Mochel (*S*). Indeed, Frédéric Vaz also reported a new HSP causative gene in this biological pathway, PCYT2, involved in phosphatydil ethanolamine synthesis. The clinical spectrum of several HSP entities expands also to other diseases such as the involvement of mutations of CYP2U1 in Pseudoxanthoma elasticum according to Christelle Durand (*A10*). PRUNE 1

was also reported as a novel gene causing HSP while already known in other disorders (Stefania Magri (*A73)*). Overlap with leukodystrophies is also frequent (Roberta LaPiana (*A34*)). New families mutated in KIF5A (Siri Lynne Rydning (A19), TFG (Simona Petrucci (*A40*). ARG1 (Liena Elsayed *(A46*) and FARS2 (Anna Meszarosova (*A42*) were also reported at the meeting with expanding phenotypes.

## FUNCTIONAL STUDIES

Functional studies on several genes pinpointed the defective autophagy in AP4 syndromes (Juan Bonifacio (*S*) and Alexandra Davies *(S*) but also in the cases of CAPN1 mutations (Chiara Vantaggio (A*22*) and defective recycling of lysosomes seems common to SPG11 (Frédéric Darios (*S),* Maxime Boutry (*A4*), Liriopé Toupenet (*A80)* and Typhaine Esteves (A*3*), SPG15 and probably SPG48 (Marianthi Breza (*A58*).

## THERAPY

Therapy was also discussed, including physiotherapy and exergames (Matthis Synofsik (*OP*) which clearly improve the quality of life if the patients are engaged in their use for the long-term, but the use of Botulimun toxin was debated since associated to variable tolerance and results according to the patient (Alexander Geurts and Fabricio Diniz, *see last round table*). Curative treatments are still not available but preclinical studies are under trial in animal models for some genetic entities and a clinical trial on SPG5. This latter trial aiming at reducing the toxicity of cholesterol derivatives was conducted in patients in Germany and France. However, while the results were successful in normalizing a biomarker in the blood, they were not satisfying in the brain yet, calling for treatment adaptation. Other therapies using Crisp-Cas9, stem cells or IPS are for the moment too risky at the human level, particularly for brain diseases. Modifying therapies based on the observation of various phenotypes associated to the same mutation even in the same family may also emerge in the near future: Francesca Sardina showed that early-onset SPG4 patients present levels of spastin lower than in controls and late-onset individuals of the same family and this might be the consequence of the regulation of spastin expression by HIPK2 (*A47*).

- Before therapy, natural history studies and registries of patients are crucial, and this was discussed by Rebecca Schule (S) that presented the *TreatHSP registry* and Alexandra Durr (S) that presented the *SPATAX- REDCap database*. Siri Lynne Rydning also presented a poster on the Norwegian cohort (*A18*). The clinical evaluation of HSP patient is very homogeneous for clinical signs (less evident for MRI) but there are ongoing studies on that aspect, Katiane Servehere (*A43*). Fatigue, well-being (Adam Lawrence (*A11* ) as well as speech patterns and cognitive functions (Lais Aleves Jacintho Scudeiro (*A64*) must also be evaluated and included in future registries. It is crucial that each country or center has its own registry with possible exchanges of data for specific projects between various research teams. The selection of patients for clinical trials is very strict and depends on the readout to measure and ages, clinical presentation etc, and not all patients can be eligible. However, making registries of all patients maximizes the chance to have access to the adequate patients to start such studies when available. An international call for patients mutated in SPG11 will be launched very soon. In France, Italy and Germany, SPG4 registries collect already

around 2000 patients just for a single entity so that rare disease are not so rare if we work together. It is also important to collect brain material (Brain donation at death) as most of the time therapeutic ideas come from neuropathological observations and, so far, this biological material is totally lacking in HSP research as compared to other neurological diseases such as Ataxia.

**Following this presentation, head to head discussion between SPATAX Organizers and EUROHSP Representants had continued in dealing with the two specific concerns as follows:**

## COMPATIBLE HSP REGISTRIES & FORTHCOMING CLINICAL TRIALS IN EUROPE

**MZ, HR ,JB** : From the SPATAX-PREPARE-ASG presentations, today several HSP networks stand up*, i.e.,*

1. SPATAX data base under the *Red Cap* software, worldwide accepted and used; it is compatible with everything and dedicated to HSP and ataxias; Spatax has about 800 SPG 4 HSPers in the database of which 30-40 % comes from outside France; in Italy a recent survey indicates 720 cases.
2. The National German Register, the *Treat'HSP network*, also open to other countries for HSP patients,
3. Some others National registers which are coming up such as the Italian register combining HSP & Ataxia.
4. So far we do not know about Registries of Spain, Portugal, UK, Norway, Denmark, Sweden, Greece, etc?? But they probably exist in several research teams such as the large national and pioneer cohort of Paula Coutinho in Portugal.

### ***Are all these databanks available for all institutions aiming at HSPs clinical trials ?***

**Pr AD** : All the data bases funding these networks may crisscross mutually, given that standardized items have been previously set up by the medical and scientific community. This data compatibility enables now foreseeing clinical trials. It is crucial that each country or center has its own registry with possible exchanges of data for specific projects between various research teams. Exchanges of clinical and genetic data between databases are feasible. The selection of patients for clinical trials is very strict and depends on the readout to measure treatment efficacy according to age, clinical presentation etc, Keep in mind that not all patients can be eligible. Also some limitations deserve to be considered on a case-by-case basis:

1. For clinical items, we need biomarkers, not only biomarkers of body fluids but also imaging data using MRI, -which stands up as an essential tool for evaluating treatment effect of neurological diseases-, MRI special acquisition may not be available everywhere, so far. For example, in HSP, it has been shown recently the presence of a specific change in the spinal cord volume. The constitution of a brain and spine post-mortem bank is essential for the researchers to deepen their findings.

Clinicians are now asking for the help of the different patient associations throughout Europe to help constituting this bank and raise patients awareness

2. In Europe, clinical research is based on a diversity of law. Indeed, each country has to comply to its law procedures and legal authorities. For instance, France should only include in a clinical trial patients with French as their mother tongue and who are affiliated to the French social security benefits. The different documents of the study have to be validated by the High authority on health and the ethical committee. All of this is essential to preserve patient safety. Safety as a medical level and also to secure its personal data.
3. From the patient, the signature of an informed consent is mandatory. Indeed, it is essential that the patient knows exactly what is done with the data collected during a specific study and that the research center respect the procedures.
4. Patient clinical characteristics dictates eligibility or not to enter into a clinical trial in order to preserve the patient safety
5. Clinical centers where trials are done must be affiliated to Health Ministry of each country given emergency requirements. That is a reason that patients can not be treated in some research institutes.
6. Size of patients cohort for clinical trial: from 20 individuals for a phase I (Toxicity assessment) to 300 for a phase III (just to give you a rough idea). However, those numbers depend on the study, the objectives, the treatment, the evaluation tools, etc
7.

**Prs AD & GS:** Very importantly, making registries of all patients maximizes the chance to have access to the adequate patients cohort to start such studies, when a therapeutic option is merging up. So, before the end of 2019, our *SPATAX* network will launch an International call to the SPG11 HSP patients asking about their willingness of participating to forthcoming natural history study and eventually in future clinical trials. This call will be sent using not only regular medical channel (from Reference & competence centers to the patient's Neurologist) but also National Associations to their members who may convince their clinician to participate. Moreover, this first SPG11 call will provide a proof of concept for forthcoming clinical trials regarding other genotypes such as SPG4, SPG8 etc....

**MZ, HR, JB**: We fully approve this proposal that will establish a very strong link between respective communities of clinicians and patients.

## EUROHSP ISSUES

## A) A Scientific , Medical *EUROHSP* Committes ?

In 2010 a EUROHSP Scientific Advisory (SA) was composed of 11 experts but, up to now, never had a meeting !

**JB :** The reason is that the main *raison d'être* of a SA is to validate scientific value of projects following a grant call. So far no common pot has been formed in the EUROHSP Federation ! To our knowledge only Italian Association *Vips Onlus* & *ASL-HSP France*

provides money specifically devoted to Research (around 50kE/year) and functions using their own National SA supporting essentially national research teams.
**Prs GS & AD**: you should form this unique SA at the European level rather than continuing with your national SA since we need to work together.

## B) A scientific & medical HSP, Rehabilitation, Genetics specialist as a mediator between patients and researchers, as a first step ?

**HR**: This is highly necessary ! **JB** : During *SPATAX*, I asked Dr Chantal TALLASKEN (Norway) she could play this role. We (Marina & Jean) must ask her officially.

## C) Grants from the European Commissions

**Pr GS :** We stress the fact that this year there was a European Grant Call for rare diseases but not including HSP and a call for neurodegenerative diseases again not including HSP. Why ? Ataxia and ALS research were included in both calls distributing several million euros, but HSP was not eligible. Because you, representants of E*UROHSP* Federation and your National HSP Associations are neither visible nor audible at the European level !

**PrAD:** To exist you have to use the ERN-RND network to get advocates with a strong voice towards Europe ( http://www.ern-rnd.eu/)

**MZ**: Lori RENNALINTON (Austria) and Giorgia TARTAGLIA (Italy) work at this issue.

## D) Others Advices from Prs DÜRR & STEVANIN

- **Pr AD** will sent us some information about variations of the spinal cord characteristics which are discovered in SPG11 and SPG4. We can use it to stimulate people to donate the body to a brainbank. We have to take care that HSP is known in the brainbank and that people with HSP know why it is so important.

**-Pr AD** mentioned that she got a new PhD student, she will do some research on the practical problems of HSP: incontinence, fatigue, cognition. She will also doing some research on the baclofen pump with 12 patients.

# EURO HSP
## European Federation of National Associations

**Austria - Denmark - France - Italy - Nertherlands**
**Norway - Spain - Switzerland - United Kingdom**


ALGHERO 2017


WIEN 2019

**To be the unified European Voice on behalf of HSPers**

## EURO HSP Mission

- Empower its members
- Promote patient Centric HSP Research
- Take collective action for HSPers to access accurate diagnosis and optimal treatment and care

### Strategic Goals

- ✓ Support member organisations
- ✓ Influence the HSP Research agenda towards patient-centric outcomes
- ✓ Secure the support of key researchers
- ✓ Achieve with Australian, US and TWS Foundations the unified worldwide voice for HSPers

### Specific Goals

- ✓ Through a harmonious European HSP registry, encourage pharmaceutical industry investments
- ✓ Via EURORDIS, press EU to make HSP a research priority
- ✓ Encourage SPATAX to utilize patient-voice when defining HSP Research priority
- ✓ Create a Patients - Researchers forum
- ✓ Develop a functional data base
- ✓ Coordinate with ERN-RND towards the best patient practices