EURO HSP
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HSP RESEARCH, STATE OF ART

INTRODUCTION

Hereditary Spastic paraplegia (HSP) stand up as a set of rare neurodegenerative diseases that affect the cortico-spinal tract.

HSPs share common invalidating symptoms : lower limbs weakness & spasticity, and possibly urinary disorders. HSPs, with a global prevalence of about 5/100 000, are orphan of treatment. Efficacy of symptomatic therapies (physiotherapy, drugs against spasticity) are transient and really unsatisfactory.

Following the two last decades of basic research, thanks to the growing use of next generation of DNA sequencing techniques, HSPs appear as a group of monogenic diseases which display a huge genetic heterogenenity. Indeed, so far, ***more than 70 genes (so called SPG), and related encoded proteins (with in suffix) , have been identified as causative of these conditions, one of them when mutated being able to lead a HSP form***.

But so far, altbeit intensive genetic studies ***about 50% of HSPers, are still deprived of genetic diagnosis*****.**

The most common affected HSP forms are respectively

- ⇨ **SPG4/spastin & SPG3A/Atlastin** for dominant transmission
- ⇨ **SPG11/Spastacin & SPG7/ Paraplegin** for recessive transmission

Whatever the mode of family transmission (dominant or recessive), animal models mimicking HSP disease have revealed ***several pathophysiological mechanisms at work in the cortico-spinal neurons*** **i**ncluding intracellular trafficking, defective mitochondria functions, changes to endoplasmic reticulum shaping, abnormal lipid metabolism, lysosome physiology, autophagy, myelinisation , and developpment.

Today current HSP research studies follow 2 distinct paths **:**

1. **<u>Basic research</u> aiming at genetic diagnosis & treating the cause**
2. **<u>Clinical research aimaing at improving quality of life</u>**

Most efforts and money are essentially devoted to Basic Research

🗐 ***Listing of 2018 and 2019 HSP publications, including Basic and Quality of life, see 2 Attached Docs : HSP Pubs 2018 & HSP Pubs 2019***

HSP BASIC RESEARCH

One can delineate 3 types of approaches

- ⇨ ***GENETICS***
  - **a) Identification of new causative genes, through exomes sequencing**
  - **b) Finding pathological variants of the identified genes**

- ⇨ ***SEARCH OF PATHOLOGICAL CAUSATIVE MECHANISM OF EACH HSP FORM*** **to lead to a targeted treatment in using preclinical animal models**

- ⇨ ***FINDING METABOLIC ABNORMALITIES HSP RELATED***
  - **a) Blood abnormal cholesterol metabolite for SPG5**
  - **b) Accumulation of sphingolipids for SPG11**

  They are the two first examples.

  These blood metabolites may be used as specific biomarkers of a HSP form and lead to the pending question : does abnormal or excess of metabolite determine the cortico-spinal neurons defect ? If so, therapy would consist in correcting the body level of these metabolites.

OBJECTIVES & ISSUES OF CURRENT BASIC HSP RESEARCHES

- ⇨ **GENETICS** : **Identification of the causative SPG gene in all HSPer families** in order to :
  - a) ***Discriminate in any family who is affected or not*** ?
  - b) ***Propose in vitro fecondation, pre-implantatory or prenatal strategies*** for next generation
  - c) ***Propose a specific treatment*** : either genetic, *i.e.*, gene therapy (correction or replacement of the defective gene) or using targeted chemical treatment against the defective HSP protein

- ⇨ **CAUSATIVE TREATMENT**
  - ***a) Specific treatment devoted to a HSP form***
  - b) ***General treatment that could fit to several HSP forms***

At the moment, several HSP forms elicit a number of cellular dysfunctions that complicates identification of the primary dysfunction or the dysfunction of the greatest relevance for the form of HSP Interestingly and hopefully, several common pathways relating to membrane dynamics are affected in multiple HSPs ; this occurrence suggests to developp therapies targeting these common pathways.(Boutry *et al, Current Neurology and Neurosciences Reports*, 2019, 19 :18). But today no such an approach is ongoing, unfortunately !

- ⇨ ***Improvement of physical activity***
- ⇨ ***Treatment of Spasticity and urinary dysfunctions***

As shown in the 2018 & 2019 publications, clinical research undertaken to alleviate HSP symptoms (spasticity, pain, fatigue) is very poor !

NATIONAL PATIENTS ASSOCIATIONS & HSP RESEARCH PROMOTION

■ REALISTIC FACTS & ISSUES

⇨ One of the *raison d'etre* of all National Associations composing EUROHSP is to inform HSPers about current research development. But a very few research leaders are ready to give time for popularizing to Patients Associations the main trends of research they follow. Researchers wait essentially for money from our Associations.

⇨ Two Associations (French and Italian) devote most of their income (charity actions, generous gifts, some regional grants and memberships fees) to support HSP research. Following a 2018' survey in our *EUROHSP* Federation, only French *ASL-HSP France* and Italian *A.I.Vi.P.S* Associations are able organizing every year a call of grants supervised by a consistent Scientifc Comittee ; these 2 associations offer to research projects 50-60 000 € / each year. Usually 2 or 3 research projects of 15kE in each country can be supplied per year . But up to now, these grants are exclusively offered to national HSP research teams ; indeed the Association administration committee members (in France at least !) do not accept to widespread collective money to a foreign team.

⇨ On a medical and scientific point of view, HSPs are related to others rare neurodegenerative conditions such as Cerebellar Ataxias and Friedreich and form a continuous pathological spectrum. Based on this evidence, the SPATAX network has been launched.

⇨ A very few teams are specifically involved in HSPs researches given this very rare group of diseases

⇨ Researchers are always looking for money to undertake projects ; they face difficulties to get important grants from National medical research organizations, given rare diseases such as HSP are not a national health cause compared to common diseases. To give an order of idea, average cost of one predoctoral research fellow weights 25 000^{E} per year (salary, materials and chemical supplies) ; a small team of 4 persons needs to find every year an average of at least 125kE. For research teams, the only way to get grant from National Research organisations is to present a project the results of which may pinpoint a new biological mechanism able to be extended to other diseases.

Thus small HSP association like our National Associations with a punctual grant of 15-20kE can only help a team to start a new project or to finish it !

⇨ The high genetic heterogeneity (>70 SPG genes identified) and the multiplicity of sustained pathophysiological mechanisms constitute a huge obstacle to get over.

REALISTIC INTERACTIONS HSPERS ⇔ RESEARCHERS
JEAN'S PROPOSALS

1) For Italy & France Associations, to launch grant calls indicating ours expectations for European research projects dealing with the most frequent forms of HSP : SPG4, SPG3A, SPG11 & SPG7

2) For each Association to interact with its reseachers of the country to give a yearly state of art of ongoing European projects

3) During the Spatax meeting sept 20-21 in Nice and the special short common conference Researchers-HSPers (only 30 minutes !!!) to push researchers to build a common European research project that we Associations will support freely (or for those Associations that support research to participate finantially to the European funding)

4) To participate as patients to any European HSP research project. Indeed European Scientific Commissions now ask researchers to inform the patients Associations and to obtain their agreement. That's now been established. It's a real progress : patients are included in any medical project. In this regard, I come back to the 2018 project *Omics approaches to unify hereditary spastic paraplegias* set by a worldwide consortium (Canada, France, Germany, Netherlands) coordinated by Pr STEVANIN in response to a Grant Call from *E-Rare Joint Translational European Community.* This project was not selected but will be presented again in 2019.

   May I kindly remind the difficulties I got from some Associations to give allowance of putting their logo to a covering letter (attached doc) without giving 1 euro !!! *(see Attached doc5 in pdf*)