Seville July 19, 2018

In the last months we started receiving a high volume of emails and contacts with questions regarding one of the research project that has been going on for 4 years in Spain about the NBIA's and, more specifically, about Braincure.

More contacts and questions about different subtypes of NBIA have continued to be received from different countries and therefore we update the situation.

Therefore, from ENACH Asociación we have thought it is convenient to inform about it.

Also the recent program of one of the Spanish public televisions for the World Day of Rare Diseases, which has focused on NBIA, synthesizes very well "where we come from and where we are".
It is available at Youtube with the title: ***Solidarios Canal Sur subENG*** or in the link https://youtu.be/mYPVHNUXFMY

BACKGROUND AND POSITIONING

Four years ago, a group of families, members of the ENACH Asociación, decided not to resign ourselves with the diagnosis of our children or with the absence of therapeutic options in the short-medium term. Then, we decided to entrust a group of experts in rare diseases, the search for drugs that were already in the pharmacy and that could be prescribed by any neurologist within their daily clinical practice. It was intended to avoid having to invest millions in the development of new drugs and having to wait for trials and other processes that would take years. The years that our children did not have.

Our target and **priority 1** was to find **drugs that could be found in the market** to treat **OUR children just now, not tomorrow.**

It is important to clarify that ENACH Asociación is focused on results, that´s why we support to Braincure research group and that´s why we was the first Alliance member that supported to Retrophin clearly and, we will continue. We will support to the new company CoA Therapeutics or any other potential/tangible option that could appear putting drugs over the table. Research that works in the long term must go on but, the families that are part of ENACH Asociacion, we have decided to prioritize and support economically in the short term.

As explained, Braincure, is funded by the families of ENACH Asociación looking for therapy options for our children and just now. **It is being doing with none external or public support**. In any case, we share all the information and status of the research in our Official Facebook and Website, and inform to the other Partners of the NBIA Alliance about developments. If what we do here can help others it will be a great satisfaction for us

BASIC RESEARCH

In the last quarter of 2014, ENACH Association commissioned Dr. Sanchez Alcázar, Principal Investigator of the BRAINCURE Project, to try **to find existing drugs that individually or in combination** with other drugs could be a therapeutic option for NBIA.

The choice of Dr. Sanchez Alcazar was because of his extensive experience in research on rare diseases. 138 papers of which **41 papers are of mitochondrial diseases**. **PKAN, PLAN, BPAN and MPAN are a mitochondrial diseases** and therefore we thought it a good choice. It is his CV: https://www.researchgate.net/profile/Jose_Sanchez-Alcazar

There were several reasons that guided ENACH Asociación in this direction:

-Developing a new drug takes years and has an unattainable cost for a small association that had been formed just 1 year earlier.

- The process from the moment the new drug is developed until it is available on the market can reach up to 10 years (European Medicines Agency authorizations, clinical trials, etc.). Our patients could not wait all that time.

-There were several groups worldwide working on different lines of research but we did not see that in the short-medium term, they could put on the table some specific therapeutic options.

-There was a biotech company that was finalizing the development of a drug for the conduct of a clinical trial in PKAN, Retrophin. We wanted to try to find a formula that could cover as many subtypes ENACH as possible.

Finally, inspired by how was therapeutically managed the AIDS crisis in the early 90s: Combined treatment, known as cocktail of drugs (ARVs) all existing ones. Patients who received those combined treatments showed remarkable improvement from the outset. To this day, AIDS is not cured but, it has managed to chronify.

It was decided to use a drug screening system. Look at this paper published in the prestigious NCBI: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058157/ . The pharmaceutical industry has been using screening for years to be more efficient in the search for molecules that can finally be a drug available in the market. **Are no necessary papers for doing a screening. The only required important thing is to have the right tool to do it.**

The project started and had before it a first major challenge, finding a system that would detect whether the drugs to be tested in cells (fibroblasts) from patients were working at the cellular level. To do this, BRAINCURE, developed a method (the tool) that allows to detect if the drugs tested could recover the cells into normality terms in several biomarkers **not only iron accumulation**. After several months of work, the tool, the screening, was set up.

After the development of the method, a screening of drugs started and, in a few weeks, the UPO001 (coded name) applied in certain doses in the fibroblasts of the patient PKAN number 1, restored in terms of normality the detected biomarkers found in the cellular pathophysiology. **It was getting to attack the origin of and not just an epiphenomenon like the iron accumulation.**

This could be a great advance for the treatment of our patients and therefore, ENACH Asociación, asked to Dr. Sanchez Alcazar to introduce this new strategy of approaching to the disease and the preliminary results to the other NBIA researchers at a symposium held in Munich in 2015.

The purpose of the request of the ENACH Asociacion to Dr. Sanchez was to connect the dots, to show this tool, this new potential avenue, even in the very initial phase, because it could be interesting for ALL our patients in time terms.

Many questions were asked and not all of them could be answered because of the very preliminary results.

Some refuted NBIA researchers took, this strategy, the screening system, as bad science due to is not following the traditional science model that takes years to find therapies for patients. To connect the dots in this scenario is very difficult and sad for the families.

However, one year later, other NBIA research groups, followed the same philosophy of screening. Therefore this new approach shared in Munich was not sterile.

From 2015 up to day, most of the questions done during that Symposium at Munich now have responses due to Braincure group are acquiring a high level of knowledge of the disease and its mechanisms, which is leading us to findings not previously described in the literature.

The Biobank of patient samples was growing and that led to BRAINCURE to one conclusion: The identified existing drugs and doses that worked in the sample of the patient 1 did not work or worse in other patient samples. This led to approach the project in a personalized manner, patient by patient.

Following this methodology, due to the high number of PLAN patients in Spain, we asked to Braincure to try in this subtype, with similar results than PKAN.

Later, it was diagnosed the first case of BPAN in our country and, all the families that are part of Enach Asociación decided that we should also include/support her.

Recently Braincure included MPAN as a potential research line.

CURRENT SITUATION OF BRAINCURE PROJECT BASIC RESEARCH

1º.-Have already been identified more drugs, either alone or in combination, they have given excellent response in cells, restoring them as at normal levels:

-PKAN: 13 drugs. Ongoing
-PLAN: 12 drugs. Ongoing
-BPAN: 3 drugs. Only preliminary results. Stopped because of lack of funding.
-MPAN: 3 drugs. Only preliminary results. Stopped because of lack of funding.

2º.-The fibroblasts obtained from PKAN and PLAN patients have been reprogrammed directly into neurons to validate the results obtained in fibroblasts in this other cellular model. The reprogramming system is direct, that is the newest technology.

Once Braincure identifies which drugs and in what doses works in each patient's fibroblasts, the results are introduced to the patient's neurologist so, that he/she decides whether or not to apply the treatment.

BRAINCURE research project is **authorized by the Ethics Committee of the Spanish public health system**, one of Top 5 best in the world.

About the safety for the patients because of the used drugs, it are of wide therapy draft and low toxicity even in high doses, and approved by the FDA and EMA (the European FDA)

At this point finish the research team of Dr. Sanchez Alcazar.

CLINIC TRANSFER

Once the neurologist is informed about the results of the screening in his patient, he/she is the one who decides whether to apply the treatment or not. In this sense it is necessary to explain that the detected drugs are in which any neurologist can indicate within their daily clinical practice, so we have that any situation of risk for the patient is filtered by his neurologist.

CURRENT SITUATION OF CLINICAL RESEARCH

-5 PKAN patients in treatment **with excellent results** monitored by the neurologists based on videos a scales. (Research line open)
-3 PKAN patients who are being incorporated with an improved cocktail. (Research line open)
-1 PLAN patient who has just started treatment. (Research line open)
-NO BPAN patients under treatment. (Research line STOPPED due to funding)
-NO MPAN patients under treatment. (Research line STOPPED due to funding)

- The preliminary PKAN clinical results at 6, 9 and 12 months will be handled in two parallel ways:

  - Presentation of results and details in the appropriate neurologist forums
  - Publication in medical-scientific journals.

- Additionally, Braincure Project includes an area of which there is a significant lack of literature. It is about the **neuropsychological aspect** of each of these NBIA groups.

CONCLUDING

We believe that it is good for our children that other therapeutic proposals arise. We need to have plan A, B, C, D, etc ... to see which one is the best, so we encourage families that wish to participate in the Retrophin trial for PKAN or other proposals to do so. Only with this philosophy can we reach the conclusion beforehand of which or what are the best options for patients

This the strategy and positioning of ENACH Asociación and will continue due to the results. If any family, consider that we could be useful for them, we will be really committed to help.

Antonio López

President and father of 2 PKAN patients
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