The Importance of Networking in Pseudohypoparathyroidism: EuroPHP Network and Patient Support Associations

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Abstract

Pseudohypoparathyroidism is a rare endocrine disorder with an estimated prevalence of 1/100,000. It is characterized by hypocalcemia and hyperphosphatemia in the absence of vitamin D deficiency or impaired renal function. Research studies during the last 20 years have led to the identification of the molecular underlying cause of the disease, the characterization of the clinical and biochemical characteristics and the observation of an overlap between genetic and clinical manifestations.

The creation of networks both for specialists (including endocrinologists, pediatricians, dermatologists, geneticists, molecular biologists…) and patients support groups brings up the opportunity of research advance, synergism and common objectives for families and investigators, improving the quality of information about the disease and its outcome, that, at the end, will improve both the knowledge and life of the patients and their families.

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Pseudohypoparathyroidism

In Europe, a disease is considered to be rare when it affects 1 person per 2000 (i.e. if its prevalence is lower than 1/2,000). In this sense, pseudohypoparathyroidism should be classified as a very rare disease; even its exact prevalence is still unknown, recent studies have estimated it at 1/295,000 in Japan, at

1/150,000 in Italy (Orphanet ID 12935) and at of 1.1/100,000 in Denmark (1).

In fact, the first description of patients affected with pseudohypoparathyroidism (PHP) dates back to 1942, when Fuller Albright and colleagues reported some cases showing significantly reduced levels of plasmatic calcium with hyperphosphatemia that were associated with raised serum parathyroid hormone (PTH) levels and normal renal function. These individuals presented with a clinical phenotype, that was referred to as Albright's hereditary osteodystrophy (AHO), characterized by the presence of a constellation of specific somatic and developmental abnormalities including short stature, obesity, rounded face and brachydactyly (2).

In the following years, research efforts on this disease increased significantly permitting the identification of different PHP subtypes and additional clinical signs associated to PHP, such as ectopic subcutaneous ossifications and cognitive abnormalities of varying degrees. The main underlying pathophysiological mechanism was gradually identified as a defective activation of the cAMP signal transduction pathway by PTH secondary to molecular defects affecting the alpha subunit of the stimulatory G protein (Gsα) (3-9).

In 1990, the discovery of inactivating GNAS mutations, the gene encoding for Gsα, in patients with signs of AHO and with/without hormone resistance (clinical conditions named PHP1A and PseudoPHP, respectively) can be considered as a milestone in the research advance on PHP (10).

Further studies demonstrated that Gsα was predominantly maternally expressed in specific human tissues, including the proximal renal tubules, pituitary, gonads, and thyroid. The loss of parental-specific imprinting methylation pattern at GNAS differentially methylated regions (DMR) led to a PHP phenotype characterized by PTH resistance in absence of AHO features (a clinical condition named PHP1B) (11-16). Most GNAS methylation defects are sporadic, except for some familial cases in which deletions of maternal imprinting control elements (ICR) within *STX16* or *NESP55* upstream genes have been described and few cases of paternal uniparental isodisomy (UPD) (17-28).

Recently, other studies highlighted a clinical and molecular overlap between PHP subtypes. This includes GNAS imprinting defects in patients clinically diagnosed with PHP1A and lack of mutations in Gsα-coding exons (29-34), as well as novel causative molecular defects, such as complex deletions or inversion of the GNAS gene (35-39).

Despite a phenotype highly reminiscent of PHP, 15 to 30% of the patients lack GNAS genetic and epigenetic defects (32,40-42). In some of these patients, mutations in factors of the Gsα/cAMP cAMP- signalling pathway, including *PRKAR1A* (the regulatory subunit of the protein kinase A) and *PDE4D* (a phosphodiesterase), were discovered. These data confirmed the phenotypic overlap between PHP and Acrodysostosis (ACRDYS), a phenotypically related skeletal disorder that is difficult to distinguish from PHP only on the basis of clinical, biochemical and radiological features (43-53).

Moreover, paternally inherited GNAS mutations may lead to PPHP and/or to Progressive Osseous Heteroplasia (POH), in which ectopic subcutaneous ossifications progressively extend into deep connective tissues and skeletal muscles during childhood (54,55).

In conclusion, the clinical and molecular overlap between these different but closely related disorders represents a real challenge for clinicians as to differential diagnosis and genetic counselling. This strongly suggests that different classification models are necessary and it alters our previous understanding on how defects of the cAMP signalling cascade could cause AHO-related disorders (56,57).

The Importance of Networking: EuroPHP Network

To face this challenge, the EuroPHP network was created in 2011, to stimulate the research and interest upon PHP. It is composed of pediatricians, endocrinologists, geneticists, researchers and students, from different countries in Europe, including United Kingdom, France, Italy, Spain, Germany, Belgium and Turkey. All members of the EuroPHP network share a common interest for disorders in which the PTH/PTHrP signaling pathway is impaired. This network is funded by the ESPE Research Unit. This funding allows the EuroPHP members to financially support their collaboration, organize meetings and conferences as well as produce peer-reviewed publications. The main objectives of the EuroPHP network are to increase knowledge and awareness, to ameliorate diagnosis and care of PTH/PTHrP signaling related disorders as well as to improve the understanding of other imprinting disorders.

In fact, EuroPHP has initiated several studies, which were published in peer-rewiewed journals and/or presented at national and international congresses (39,58). In addition, EuroPHP has defined for the first time standards of quality of molecular diagnosis for epigenetic form of PHP (59).

Therefore, the EuroPHP network highlights the importance of networking to achieve advance in clinical, translational and scientific research of very rare diseases as PHP, The network aims at enlarging research area to imprinting disorders through its deep involvement in the European COST action BM1208 run by Pr. T. Eggermann The next challenge for the EuroPHP is to develop care-centered projects comprising guidelines for PHP.

The Role of the Patient Support Groups

Creating a patient support group for a rare disease is not an easy task. However, social networks can help to find more patients and more families with the same rare disease. We will share here the experience of different PHP patient support groups.

Spain: AEPHP (Spanish Association of Pseudohypoparathyroidism)

In 2014, six years after the PHP clinical diagnosis of his daughter, Juanfran Camacho was able to contact Guiomar Perez de Nanclares via Internet. They kept on contact by mail. Afterwards, Mr Camacho created a Facebook profile and a blog to try to contact other people affected by the same disease as his daughter, discuss and share experiences about it. By doing this, two more families were found and started to interact with Mr Camacho.

In March 2015, when the BM1208 Action organized the Bremen meeting for families, patients and experts in three imprinting diseases (Beckwith-Wiedemann syndrome, Silver Russell syndrome and pseudohypoparathyroidism), Dr Perez de Nanclares asked Mr Camacho to be the PHP patient representative for Spain. This is how the adventure of the "MAGIC Association" started and it is when we realize the importance of an interaction between medical experts and patients in order to understand better the disease. A Twitter account (@asociacion_php) was created as well as a Facebook page? (https://www.facebook.com/allbrightosteodistrofiahereditaria/?ref=hl) and a blog (http://asociacionespanolaphp.blogspot.com.es/). An e-mail address specific for the patients (asociacionpacientesphp@gmail.com) was also created and new patients genetically diagnosed with PHP were informed about this email address as well as about the possibility of joining a closed Facebook group (https://www.facebook.com/groups/1560679404213406/). When about ten families were contacted, we decided to create the Spanish Association for the study of PHP and we met in Madrid at the beginning of July 2015. Association regulation and representatives were established and the official recognition of the disease was asked to the Spanish Ministry of Interior.

The management of all the previously listed social networks is taken care by one patient representative and one expert on the disease. Recently AEPHP has decided to translate our Facebook publications in English since we have noticed that some families from abroad have also liked the page.

The AEPHP's main goal for this year is to increase it visibility so that other Spanish families can join them and receive information about different aspects of the disease as well as share experiences and doubts.

When asking to the AEPHP members about what the Association provides to them, they said: "Hope and a lot of support to fight everyday" (SPG); "Happiness and fear, relief and anxiety, because we know where we are but not where we go to, opposite feeling sometimes hard to control, but staying together gives you the strength we need to keep going" (JFK); "It helps me to understand the disease, so I can help my son, it brings hope to the families and gives as the opportunity to become active participants, making this rare disease as visible as possible, since visibility helps rare diseases a lot" (SGP); "It gives us the serenity of knowing that we are not alone any more"; "as a mother, it brings me illusion (maybe she means HOPE?), fear, responsibility and, more than anything, I want to learn how to fight with this disease, I want to listen to all professional experts and people as they can teach us a lot and; as a patient, it gives me freedom because I learnt the name of the terrible monster I have to fight against and having the name provides me security and excitement to face my diagnosis with no fear" (CHE).

Germany: Pseudohypoparathyreoidismus (Deutschsprachiger Raum und Europa)

Mr and Mrs Wichers' daughter, a single child of five years old, was diagnosed with PPHP. Initially her parents noticed calcifications on her skin, when she was about 1½ years old. They brought her to a dermatologist and he sent them to the Universitätsklinikum Münster, where a biopsy was performed and PseudoPHP was diagnosed. The whole family was tested and found negative for mutations associated with PHP, so Mr Wichers' daughter appeared to have a spontaneous mutation. Before the medical treatment started, she could not move or crawl. Physiotherapy and a special psychomotoric training program helped her to start walking.

A doctor at the UKM told Mr and Mrs Wichers' about a congress happening in Bremen in March 2015 on imprinting disorders and patients support groups. They received an official invitation to the congress but they could not participate. Mr Wichers then decided to join an US-American self-support group for PHP on Facebook. Subsequently, he decided to create a group on Facebook for German patients to be able to get in contact with other parents or adult patients to share experiences, worries and ideas. Dr Perez de Nanclares met Mr Alexander Wichers within the American Pseudohypoparathyrodism Support group (https://www.facebook.com/groups/436127013073176/) and Mrs Beatrice Voigt at the Bremen COST Meeting. In that occasion they exchanged facebook contacts, and by the end of May 2015 they decided to create a closed Facebook group (https://www.facebook.com/groups/1628847100685801/) to contact as many

German families as possible. The facebook German group has then become a European group.

Mr Wichers thinks that "exchanging is important, interesting, exciting, but also exhausting sometimes, as there are different types of PHP that people suffer from, different questions, and also different ways of thinking about the disorder. He continues "I have the impression that most people suffer from PHP1A. It is sometimes very difficult to moderate/mediate between the different group-members and to find a certain level of consensus in terms of meeting each-other in real life or dealing with the disorder in public".

At the moment, the association is focused on finding a place and a day for the first German PHP meeting.

France

A French patients' group was built in 2007 by two French families severely affected by the disease under the acronym of AFOHA (Association française d'ostéodystrophie d'Albright) (http://s209246221.onlinehome.fr/bienvenue-2/). This group gathers mainly patients affected with PHP1A and PPHP. They created a webpage to provide information, advices and help isolated families and patients. The website communicates with the reference center for rare disorders of the calcium and phosphate metabolism. The patients' association ensures several public manifestations such as the Facebook group (https://www.facebook.com/espoirpourlapseudohypoparathyroidie/?fref=nf) or the meeting with Association Handicap 73. In addition, AFOHA works thoroughly to promote actions for rare diseases together with the health and public authorities.

More recently, another patients' group was born to include disorders which are not represented in AFOHA yet share similar issues like POH or PHP type 1B. Its acronym is K20 for chromosome 20. Its main goal is to gain visibility for families and caregivers through a webpage and a Facebook group in order to share and combine forces. Both groups always worked in close interaction with the national reference center for rare diseases of the Calcium and Phosphate metabolism coordinated by A. Linglart and are involved in the larger OSCAR network of rare bone diseases (http://blog.filiere-oscar.fr/).

The Netherlands

Once being member of the German PHP group, Vanja De Mol, created a closed Dutch PHP support group at Facebook (https://m.facebook.com/groups/1375395566111282), with two families contacted by now and awaiting for many others. Within the group, they find support and friendship. "We are in it all together...as a parent or as a patient. And we are looking for recognition with each other".

Belgium

Stéphanie Fratta-Chermanne and his husband discovered the illness of their son when he was 1 year old, and felt that nobody knew this illness in Belgium, so they began to search, and found some explanations on the web. They discovered a person whose son also presented this illness and she invited them to join the Facebook American PHP group. But, as French speakers, they decided to create, a few years later, a new Facebook AHO group "AHO en français" (which means "AHO in French", https://www.facebook.com/groups/123047161220572). Within this group, French-speaking people from different countries share their experiences. There are people from Belgium, France, Luxembourg, Switzerland, Ile de la Réunion and Canada. They are only 27 members but "it helps. The youngest with PHP is 1 year-old and the older is 35. There are also a lot of mothers with PPHP. We discuss about our kids (the older discuss about themselves), about the illness, about the therapy, about hope…".

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Disclosure

The authors have nothing to disclose

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