# NEURODEGENERATION WITH BRAIN IRON ACCUMULATION (NBIA) DISORDERS: CLINICAL EVALUATION AND GENETIC CHARACTERISATION THROUGH A SPANISH MULTICENTRE RESEARCH NETWORK

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## 1. Summary

Background/main objective: Neurodegeneration with brain iron accumulation (NBIA) is due to several genetic defects causing movement disorders and brain iron deposition in children, PKAN (pantothenate kinase associated neurodegeneration) being the most common one. Significant knowledge gaps concerning NBIA phenotype-genotype correlations and disease progression persist. Moreover, despite advances in the research of novel therapies for PKAN, validated international clinical rating scales to be used in clinical trials are lacking. We aim to identify and genetically characterize the Spanish population with NBIA and to design and validate a quantitative method for clinical assessment of PKAN patients.

Methodology: Cross-sectional observational multicentre study, with prospective NBIA patient recruitment through professional associations. Design of a disease rating scale for PKAN (PKAN-DRS) including four subscales: cognitive, behavioural, physical, and functional assessment. Validity and reliability: four independent examiners will rate PKAN patients three times within a one-month period using recorded videotapes. Sanger sequencing of NBIA genes and exome sequencing of unsolved families to search for new NBIA genes.

Expected results: To date, 46 NBIA patients have been identified at 14 centres in Spain but, with an estimated prevalence of 1-3 cases/million inhabitants, we plan to enrol 100 patients. The PKAN-DRS, will allow us to classify patients according to severity in different phenotypes, and to establish phenotype-genotype correlations. In all likelihood age at disease onset will inversely correlate with PKAN-DRS scores. We should be able to identify a genetic defect in most NBIA patients.

## 2. Results

We have identified 134 patients affected by neurodegenerative diseases with brain iron accumulation (NBIA) in the Spanish population. Given the number of patients identified for each genetic defect, we can predict an incidence of 0.81 cases per million inhabitants of pantothenate kinase deficiency (PKAN), and 0.36 cases per million

inhabitants of phospholipase A2 deficiency (PLA2G6), the two most frequent genetic defects in our population.

We have designed a scale for PKAN patients called PKAN-DRS, which we have used to evaluate 47 patients from Spain, Portugal, Greece and the United Kingdom. We have shown that all patients have dystonia (with predominance of axial and oromandibular involvement) and atypical parkinsonian signs (postural instability, bradycardia, rigidity). These neurological disorders, and intellectual disability, have a great impact on their disability. The scale also allowed the identification of a group of patients with the p.T528M mutation and a milder phenotype. Clinimetric studies demonstrated that the scale is a valid and reliable tool to quantify the severity of the disease in future clinical trials.

In 16 patients with PLA2G6, the second most frequent NBIA defect in our population, we have performed a semiquantitative analysis of brain anomalies showing that cerebral atrophy is a universal sign in all cases and cerebellar severity is a predictor of poor prognosis and loss of ambulation. In addition, we have described the natural history of the disease by identifying that cerebellar ataxia is an early onset sign of the disease, while dystonia and parkinsonism appear in advanced stages.
The identification and characterization of NBIA disorders in Spain allowed us to participate in the first international trial to evaluate the efficacy, safety and tolerability of a substitutive treatment with fosmetpantotenate (RE-024) in PKAN, having recruited 17 of the 80 total patients in this country.

We have created a Spanish register of NBIA patients with mutations referenced to a publication or to an rs code (available at: http://espinos.cipf.es/index.php/en/mutations-db). We have also incorporated the clinical and genetic data into the international registry created by the TIRCON consortium (Treat Iron-Related Childhood-Onset Neurodegeneration), and funded by the European Union (https://tircon.eu/nbia-network/nbia-registry-clinical-centres), to which we belong as a clinical centre.

We have collaborated with the Spanish Association of NBIA patients (https://www.enach.org/) in the recruitment of patients. We have empowered families, improving their knowledge about their disease and the most appropriate care to treat

their symptoms. We have also disseminated the advances in research on NBIA disorders and our results from this project. This has been possible with the organization of two meetings for patients and professionals on NBIA, held in 2015 (https://metabolicas.sjdhospitalbarcelona.org/noticia/primer-encuentro-asociacion-enach-espanola) and 2018 (https://www.vallhebron.com/es/agenda/del-genoma-la-medicina-de-precision-en-los-trastornos-del-movimiento-pediatricos-0), the first and last years of the project.

## 3. Future implications

1) We have empowered the association of patients with neurodegenerative diseases in our country, and they are the engine to continue research in Spain. The 134 patients with NBIA identified in this project are aware of their illness, the complications that they may present, their prognosis, and what are the most effective treatments to control their symptoms according to medical evidence and clinical practice guides prepared for these genetic defects.

(2) Families with genetically confirmed NBIA disorders may request genetic counselling in order to prevent the occurrence of future cases in their families through pre-implantation genetic diagnosis, or through therapeutic interruption of pregnancy. The patients themselves are also in the same situation as to be able to prevent their offspring from being affected. This practical application generates a great socio-economic impact since affected individuals represent a high economic and social cost.

(3) The population of PKAN patients in our country are participating in the first international clinical trial for PKAN that evaluates the efficacy of phosphopantothenate, and may continue to participate in future trials that are being developed.

(4) Future clinical trials may use the PKAN-DRS, which has been designed and validated with this project, to evaluate therapeutic efficacy.

## 4. Literature

We have published seven papers in journals that appear at Web of Science, with a total Impact Factor of 54.584 scores. These journals are in Decile 1 (two papers), Quartile 1 (one paper) and Quartile 2 (four papers).

**Original articles**

Tello C, Darling A, Lupo V, Ortez CI, Pérez-Dueñas B, Espinós C*. Twin-sisters with PLA2G6-associated neurodegeneration due to paternal isodisomy of the chromosome 22 following in vitro fertilization. Clin Genet 2017; 92: 117-8. **IF 3.512. Quartile 2.**

Darling A, Tello C, Martí MJ, Garrido C, Aguilera-Albesa S, Tomás-Vila M, Gastón I, Madruga M, González-Gutiérrez L, Ramos-Lizana J, Pujol M, Gavilán T, Tustin K, Lin JP, Zorzi G, Nardocci N, Martorell L, Lorenzo-Sanz G, Gutiérrez F, García PJ, Vela L, Hernández-Lahoz C, Ortigoza-Escobar JD, Moreira F, Coelho M, Correia L, Castro A, Ferreira J, Pires P, Costa C, Rego P, Magalhães M, Stamelou M, Rodríguez-Blázquez C, Martínez-Martín P, Lupo V, Stefanis L, Pons R, Espinós C, Temudo T, Pérez-Dueñas B. Clinical Rating Scale for Pantothenate Kinase-Associated Neurodegeneration: A Pilot Study. Mov Disord 2017; 32: 1620-30. **IF 8.324. Decile 1.**

Meyer E, Carss KJ, Rankin J, Nichols JM, Grozeva D, Joseph AP, Mencacci NE, Papandreou A, Ng J, Barral S, Ngoh A, Ben-Pazi H, Willemsen MA, Arkadir D, Barnicoat A, Bergman H, Bhate S, Boys A, Darin N, Foulds N, Gutowski N, Hills A, Houlden H, Hurst JA, Israel Z, Kaminska M, Limousin P, Lumsden D, McKee S, Misra S, Mohammed SS, Nakou V, Nicolai J, Nilsson M, Pall H, Peall KJ, Peters GB, Prabhakar P, Reuter MS, Rump P, Segel R, Sinnema M, Smith M, Turnpenny P, White SM, Wieczorek D, Wiethoff S, Wilson BT, Winter G, Wragg C, Pope S, Heales SJ, Morrogh D; UK10K Consortium.; Deciphering Developmental Disorders Study.; NIHR BioResource Rare Diseases Consortium., Pittman A, Carr LJ, Perez-Dueñas B, Lin JP, Reis A, Gahl WA, Toro C, Bhatia KP, Wood NW, Kamsteeg EJ, Chong WK, Gissen P, Topf M, Dale RC, Chubb JR, Raymond FL, Kurian MA. Mutations in the histone methyltransferase gene KMT2B cause complex early-onset dystonia. Nat Genet. 2017 Feb; 49(2):223-237. **IF 27.125. Decile 1.**

Darling A, Aguilera-Albesa S, Tello C, Serrano M, Tomás M, Camino-León R, Fernández-Ramos J, Jiménez-Escrig A, Poó P. O'Callaghan M, Ortez C, Nascimiento A, Candau Fernández Mesaque R, Madruga M, Arrabal L, Roldán S, Gómez-Martín H, Garrido C, Temudo T, Jou-Munoz C, Muchart J, Huisman TAGM, Poretti A, Lupo V, Espinós C, Pérez-Dueñas B. PLA2G6-associated neurodegeneration: New insights into brain abnormalities and disease progression. Parkinsonism Relat Disord 2018; doi: 10.1016/j.parkreldis.2018.10.013. **IF 4.721. Quartile 1.**

Marti-Sanchez L, Ortigoza-Escobar JD, Darling A, Villaronga M, Baide H, Molero-Luis M, Batllori M, Vanegas MI, Muchart J, Aquino L, Artuch R, Macaya A, Kurian MA, Dueñas P. Hypermanganesemia due to mutations in SLC39A14: further insights into Mn deposition in the central nervous system. Orphanet J Rare Dis. 2018 Jan 30;13(1):28. **IF 3.607. Quartile 2.**

Baide-Mairena H, Gaudó P, Marti-Sánchez L, Emperador S, Sánchez-Montanez A, Alonso-Luengo O, Correa M, Grau AM, Ortigoza-Escobar JD, Artuch R, Vázquez E, Del Toro M, Garrido-Pérez N, Ruiz-Pesini E, Montoya J, Bayona-Bafaluy MP, Pérez-Dueñas B. Mutations in the mitochondrial complex I assembly factor NDUFAF6 cause isolated bilateral striatal necrosis and progressive dystonia in childhood. Mol Genet Metab. 2019 Jan 5. **IF 3.774. Quartile 2.**

**Review**

Tello C[#], Darling A[#], Lupo V, Pérez-Dueñas B, Espinós C*. On the complexity of clinical and molecular bases of neurodegeneration with brain iron accumulation. Clin Genet 2018; 93: 731-40. *(Invited Review).* **IF 3.512. Quartile 2.**

**Book chapter**

Lupo V, Darling A, Tello C, Pérez-Dueñas C, Espinós C*. The role of oxidative damage in neurodegeneration with brain iron accumulation disorders. En: Reactive Oxygen Species Biology and Human Health. Taylor & Francis Books, Inc. Chapter 7, pp: 93-102, 2016. ISBN: 9781498735452.

Schneider SA, Espinós C, Pérez-Dueñas B. Syndromes of Neurodegeneration with Brain Iron Accumulation. En: Inherited Metabolic Movement Disorders: Recognition,

Understanding, Improving Outcomes. Darius Ebrahimi-Fakhari & Phillip L. Pearl. Chapter 16 (*under review*).