STUDY OF ACUTE PHASE ICTUS MECHANISMS THAT FAVOUR THE DEVELOPMENT OF EPILEPSY

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1. Project summary

The development of post-stroke epilepsy has an important impact on the patient, affecting both cognitive function and motor recovery. Therefore, the study of post-stroke epileptogenesis could help us to improve the quality of life of these patients. The present study aims to find clinical, radiological and blood biomarkers that are present during the acute phase of stroke within the different processes (inflammation, neuronal death, cell adhesion, astrocytic proliferation and angiogenesis) that may allow us to predict patients with a higher risk of developing post-stroke epilepsy. Understanding these mechanisms and processes will help us to better understand epileptogenesis. We evaluated 1,115 stroke patients (941 with ischaemic stroke and 174 with haemorrhagic stroke) previously included prospectively in the Stroke-Chip study, in which different markers were evaluated during the acute phase. These patients have been prospectively re-evaluated clinically, taking into account the time of seizure onset and the development of epilepsy. Clinical, radiological and blood biomarkers have been evaluated. In addition, a neuropsychological evaluation, brain MRI and a second blood sample were performed on a selected group of patients who developed epilepsy compared to a control group. With the blood samples of these patients, an exploratory study was carried out to discover new biomarkers.In this study we describe the specific clinical, radiological and serum biomarkers that are associated with the development of post-stroke epilepsy.

2. Results

Two biomarkers (NCAM and TNF-R1) have been discovered that may play an important role in the prediction of early-onset seizures. The combination of these biomarkers with the severity and type of stroke increases the risk of occurrence of these seizures. Three biomarkers associated with the development of post-stroke epilepsy have also been found in the long term. A low expression of the S100b and Hsc70 proteins, an overexpression of endostatin, together with stroke severity and history of early-onset seizures, predict the development of seizures during follow-up.

In an exploratory analysis (Discovery) to find differential expressions among 480 proteins, we observed that 9 proteins (CASP-8, TNFSF-14, STAMB, ENRAGE, EDA2R,

SIRT2, TGF-alpha, OSM and CLEC1B) had a clear low basal expression in patients who developed post-stroke epilepsy, some of them (TNFSF-14, CLEC1B and OSM) increasing significantly after the development of post-stroke epilepsy, and 2 proteins (SRC and STAI1) with a different profile of basal-follow-up expression increasing after the development of epilepsy and decreasing in controls.

3. Future clinical relevance

The identification of patients with an increased risk of developing seizures may help us to develop new lines of treatment for their prevention, thus improving patient management from the beginning. It also allows us to design new predictive scales for post-stroke epilepsy that combine these biomarkers with known clinical risk factors. This prevention will ultimately result in an improvement in the patient's quality of life and, consequently, in savings for the healthcare system. In addition, the identification of new biomarkers helps us to better understand the mechanisms involved in epileptogenesis, and allows us to create and develop new studies for further research in this area.

4. Scientific bibliography generated

From the results obtained in the research carried out in this project, the following papers have been published in indexed journals:

Abraira L, Giannini N, Santamarina E, Cazorla S, Bustamante A, Quintana M, Toledo M, Grau-López L, Jiménez M, Ciurans J, Becerra JL, Millán M, Cardona P, Terceño M, Zaragoza J, Cánovas D, Gasull T, Ustrell X, Rubiera M, Castellanos M, Dávalos A, Montaner J, Álvarez-Sabin J. Correlation of blood biomarkers with early-onset seizures after an acute stroke event. Epilepsy Behav. 2020 Mar;104(Pt B):106549. doi: 10.1016/j.yebeh.2019.106549. Epub 2019 Oct 31. Erratum in: Epilepsy Behav. 2020 May;106:107045. PMID: 31677998. Impact factor: 2.937.Q2.

Abraira L, Santamarina E, Cazorla S, Bustamante A, Quintana M, Toledo M, Fonseca E, Grau-López L, Jiménez M, Ciurans J, Luis Becerra J, Millán M, Hernández-Pérez M,

Cardona P, Terceño M, Zaragoza J, Cánovas D, Gasull T, Ustrell X, Rubiera M, Castellanos M, Montaner J, Álvarez-Sabín J. Blood biomarkers predictive of epilepsy after an acute stroke event. Epilepsia. 2020 Oct; 61(10):2244-2253. doi: 10.1111/epi.16648. Epub 2020 Aug 28. Impact factor:5.864. Q1.

Moreover, as a result of this research, Dr Laura Abraira del Fresno has completed her doctoral thesis entitled "Study of the mechanisms of the acute phase of stroke that predispose to the development of epilepsy", which has obtained a grade of Excellent Cum Laude. Thesis supervisors: Francisco Javier Salas Puig, Estevo Santamarina Pérez and José Álvarez Sabín. Universidad Autónoma de Barcelona, January 2021.
In addition, the results of this research have been disseminated in the following national and international congresses:

Abraira L.; Cazorla S.; Quintana M.; Bustamante A.; Grau L.; Ciurans J.; Jiménez M.; Martínez S.; Becerra J.L.; Millán M.; Toledo M.; Salas-Puig J.; Montaner J.; Rubiera M.; Álvarez-Sabin J.; Santamarina E. Estudio de los mecanismos de fase aguda del ictus que favorecen el desarrollo de epilepsia. LXX Reunión Anual de la Sociedad Española de Neurología, Noviembre 2018, Sevilla, España.

Abraira L, et al. Correlación entre marcadores sanguíneos y epilepsia post-ictus en pacientes con ictus isquémico agudo sin historia de crisis sintomáticas agudas.

LXXII Reunión Anual de la Sociedad Española de Neurología. 26 de Noviembre de 2020.

Abraira L, Quintana M, Fonseca E, Toledo M, Grau L, Ciurans J, Jimenez M, Becerra JL, Bustamante A, Penalba A, Montaner J, Alvarez-Sabin J, Santamarina E. Estudio exploratorio de biomarcadores sanguíneos en pacientes con epilepsia postictus. LXXIII Reunión Anual de la Sociedad Española de Neurologia. 22 noviembre-2 diciembre 2021.

Abraira L.; Cazorla S.; Quintana M.; Bustamante A.; Grau L.; Ciurans J.; Jiménez M.; Martínez S.; Becerra J.L.; Millán M.; Toledo M.; Salas-Puig.; Montaner J.; Rubiera M.; Álvarez-Sabin J.; Santamarina E. Correlation of blood biomarkers with early-onset seizures after an acute stroke event. Seizures & Stroke, 1st international congress on

*epilepsy in cerebrovascular disease, February 2019, Göteborg, Sweden. (Abstract No. 25) *Chosen as "Best poster"*

Abraira L.; Cazorla S.; Quintana M.; Bustamante A.; Grau L.; Ciurans J.; Jiménez M.; Martínez S.; Becerra J.L.; Millán M.; Toledo M.; Salas-Puig.; Montaner J.; Rubiera M.; Álvarez-Sabin J.; Santamarina E. Correlation of blood biomarkers with epilepsy development after an acute stroke event. Seizures & Stroke, 1st international congress on epilepsy in cerebrovascular disease, February 2019, Göteborg, Sweden. (Abstract No. 3)

Results will also be presented at the European Epilepsy Congress (14th ECE 2022) to be held in Switzerland next July:
Abraira L, Quintana M, Fonseca E, Toledo M, Grau-Lopez L, Ciurans J, Jiménez M, Becerra JL, Bustamante A, Penalba A, Montaner J, Alvarez Sabín J, Santamarina E. Exploratory study of blood biomarkers in patients with post-stroke epilepsy. 14th European Congress on Epileptology (ECE), 9-13 July 2022, Geneva, Switzerland.