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FAECAL INCONTINENCE AFTER ISCHAEMIC STROKE (FINISH STUDY): UNDERSTANDING THE PHYSIOPATHOLOGICAL MECHANISMS AND NEW FRONTIERS IN ITS TREATMENT

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1. Summary of the objectives and methodology

Stroke is a very common disease, being the leading cause of disability in developed countries, so its consequences have a significant socio-economic impact on health systems. One of them, fecal incontinence, also carries a very significant psychological burden for both patients and their caregivers, but there has been little scientific interest in knowing the magnitude of the problem and the mechanisms by which it occurs.

Therefore, the objectives proposed in the FINISH study were:

1. To study the prevalence of fecal incontinence in patients with stroke in the acute phase (the first 3 days) and at 3 months, evaluating for the first time the natural history of fecal incontinence in this context and identifying clinical and neuroimaging factors associated with its presentation and/or recovery.
2. To evaluate the existence of a pattern of common cerebral cortical activation in patients with ischemic stroke with persistent fecal incontinence after 3 months by performing a functional MRI study comparing these patients with a subgroup of patients with ischemic stroke without fecal incontinence

To achieve this, the following methodology was followed:
The study included all patients with acute stroke consecutively admitted to the stroke unit of the research center (Germans Trias i Pujol University Hospital, HUGTiP) less than 72 hours from the onset of symptoms, under 80 years, with no previous history of stroke, functionally independent in daily living activities prior to stroke (modified Rankin scale ≤2), and not suffering from fecal incontinence before admission.
One of the researchers in the project carried out a daily review of patients admitted to the stroke unit, checking the inclusion and exclusion criteria with a medical history addressed to the patient or family member in the event of lack of collaboration or alteration of language, and daily nursing records were reviewed to identify patients with fecal incontinence or continence. Once patients with fecal incontinence were identified, dedicated scales specific to the diagnosis and degree of incontinence were administered and continence studies were performed using anal ultrasound and rectal manometry in the digestive physiology office of our center. After 3 months, patients who were incontinent in the acute phase (the first 72 hours) were followed up in order

to identify those patients who had persistent fecal incontinence or recovered fecal incontinence.

Subsequently, patients with the subtype of ischemic stroke who had fecal incontinence were included in the second phase of the FINISH study together with a subgroup of patients who had suffered fecal incontinence after ischemic stroke and who had progressively regained continence, and another group of subjects with ischemic stroke who had not experienced fecal incontinence at any time, all of whom had similar clinical and demographic characteristics. Functional magnetic resonance imaging was performed according to a protocol for assessing the state of continence in both the sensory and motor control parts through the placement of a probe with a pressure sensor in the patient's anus and asking the patient to perform tasks (tightening/relaxing) with the anal sphincter. The purpose of the post-processing acquired MR functional brain images is to identify if there is a pattern of brain cortical involvement that is associated with the development of fecal incontinence after ischemic stroke.

2. Main results

Retrospective series published previously showed a high prevalence of fecal incontinence (FI) in stroke patients. Given the potential impact of this after-effect on patients' quality of life, we analyzed the current incidence of FI in acute stroke in a prospective series of patients without previous functional dependence admitted to the Acute Stroke Unit of the Germans Trias i Pujol Hospital, its evolution over time, and the characteristics of patients associated with the onset of FI. The FI was assessed by a multidisciplinary team trained using specific questionnaires at 72 ± 24 h (acute phase) and 90 ± 15 days (chronic phase). Demographic variables, relevant clinical history, stroke characteristics, mortality and functional status on the seventh day after stroke were collected.

During the period April 2018-December 2019, 743 patients were admitted, of whom 359 (48.3%) met the inclusion criteria of the FINISH study with a mean age of 65.9 ± 10 years and 64% men. Of those, 84.1% had ischemic stroke and 16.9% had hemorrhagic stroke. FI was identified in 23 patients (6.4%) at 72 ± 24 h and in 7

(1.9%) at 90 days ± 15 days after the onset of stroke. About 39% of patients with FI in the acute phase recovered in the chronic phase.

FI was more common in hemorrhagic strokes (18% vs. 5%, p 0.007) and in more severe strokes [average of the National Institutes of Health (NIHSS) Stroke Scale 18 (14-22) vs. 5 (3-13), p <0.0001]. No differences were found in the presentation of FI regarding age, sex, vascular risk factors, other comorbidities, or the affected hemisphere. Patients with neurological severity defined by an NIHSS ≥12 (AUC 0.81, 95% CI 0.71 to 0.89) were 17 times more likely to have FI (OR 16.9, 95% CI 4, 7-60.1) compared to patients with NIHSS <12, so the independent predictors associated with FI presentation were neurological severity at admission and hemorrhagic subtype of stroke. Patients with FI had a higher mortality rate (13% vs. 2.7%) and functional dependence (91% vs. 47%) at day 7 compared to patients without FI. No clinical features of the patients or of the stroke itself have been identified that are related to the persistence or recovery of FI in the chronic phase.

Therefore, the incidence of persistent FI in patients with acute stroke without previous functional dependence is currently lower than expected (2%), with an association with more severe stroke and hemorrhagic stroke. This is probably due to the clinical benefit of caring for patients in stroke units with trained teams and new brain reperfusion therapies. However, due to its impact on the quality of life of patients and their caregivers, it is necessary to deepen the knowledge of the underlying mechanisms that motivate this complication in order to address future therapeutic strategies.

The functional magnetic resonance imaging study after the application of a sensory and motor stimulus at the level of the patient's anus and the acquisition of functional brain images will provide us with information on the potential pathophysiological mechanisms of continence control at the central level and will make it possible to identify possible brain areas involved to address possible treatments that may improve or resolve persistent FI. We studied 23 patients and one healthy subject and began evaluating and interpreting the acquired images. The figure below shows the initial findings of activation of the cortical area after performing repetitive voluntary contractions with the external anal sphincter by a healthy subject (1A) and a patient with a stroke of the anterior artery territory (1B). It can be seen that the healthy

subject has bilateral activation of both paramedian primary motor cortices, while in the patient with stroke only the activation of the left motor cortex is observed.

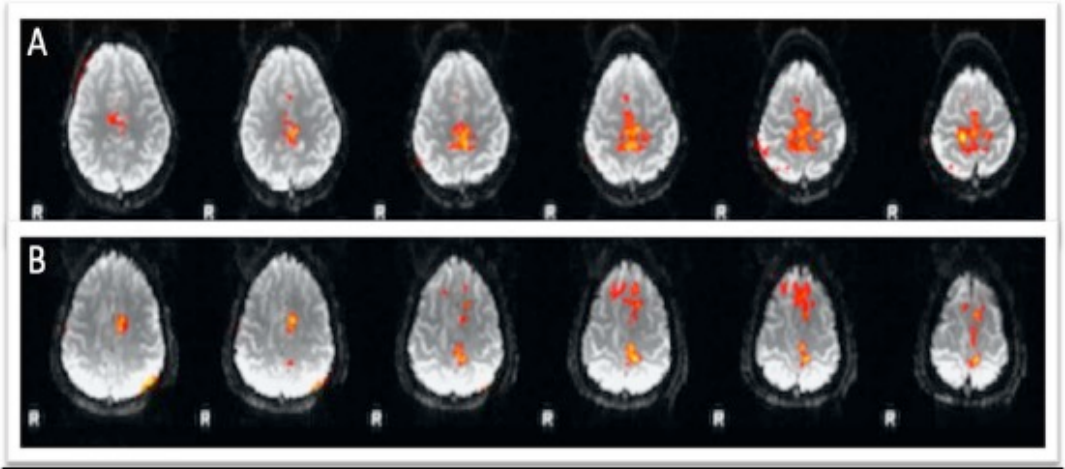

Figure 1. Pattern of cortical activation during repetitive voluntary contractions of external anal sphincter, preliminary data.

1A: Healthy subject. Bilateral activation of both paramedial primary motor cortex

1B: Right anterior cerebral artery stroke patient. Notice the unilateral left motor cortex activity during task.

3. Relevance and future implications

The results of this study in 2022, in the context of new advances in the treatment and stroke care protocols, make it possible to update the information on the different neurological after-effects that patients may suffer, specifically fecal incontinence, and therefore to be able to inform patients and relatives in advance about the possibility of suffering and/or recovering. Information and health education about the risk factors of suffering a stroke. and especially the way to face and treat the different after-effects that they suffer, are essential for the patient and their relatives to adapt to and overcome the paradigm changes in their day to day lives that this disease entails. Despite the relatively low frequency of fecal incontinence as an after-effect of definitive stroke, it has a very significant impact on patients' quality of life and on the burden of their caregivers. Therefore, the study has a direct implication in the preparation and needs of the patient and family when they return home, and indirectly in the management of healthcare resources.

In addition, if a specific cerebral cortical activation pattern is detected in incontinent patients with ischemic stroke, it will serve to begin to understand the

pathophysiological bases for which a patient can be fecally incontinent or continent after a stroke. This finding would make it possible to propose research on possible treatments that improve fecal incontinence in these patients. Sacral nerve stimulation is a therapeutic strategy used in the treatment of fecal incontinence due to other causes (for example, anal sphincter causes). Its potential neuromodulatory effect on cerebral cortical areas could be promising for patients with secondary fecal incontinence in stroke. Other neuromodulation systems, such as transcranial magnetic stimulation treatment applied to sensory brain areas if a specific cortical pattern is detected, could be of interest to evaluate in a clinical trial in patients with FI.

4. Generated scientific bibliography

The results of this project have been presented to the scientific community at two international conferences; the American Society of Colon and Rectal Surgeons Conference, Cleveland, USA in June 2019 and the European Stroke Organization, Vienna, in November 2020.

Results from the longitudinal study of current prevalence, natural history and factors associated with the presentation and persistence of fecal incontinence after stroke have been published in the Open Access journal, Frontiers of Neurology:

Current Incidence and Risk Factors of Fecal Incontinence After Acute Stroke Affecting Functionally Independent People
Lucente G, Corral J, Rodríguez-Esparragoza L, Castañero S, Ortizo H, Piqueras A, Broto J, Hernández-Pérez M, Domenech S, Martinez-Piñeiro A, Sierra J, Almendrote M, Parés D, Millán M.
Front Neurol. 2021 Nov 1;12:755432. doi: 10.3389/fneur.2021.755432. PMID: 34790163; PMCID: PMC8591097. Impact factor: 4. Views (March 2022): 1,139 in 4 months.

The analysis of the results of the performed functional MR is still under development. The obtained results will be described in a new manuscript that will be sent to an indexed journal.