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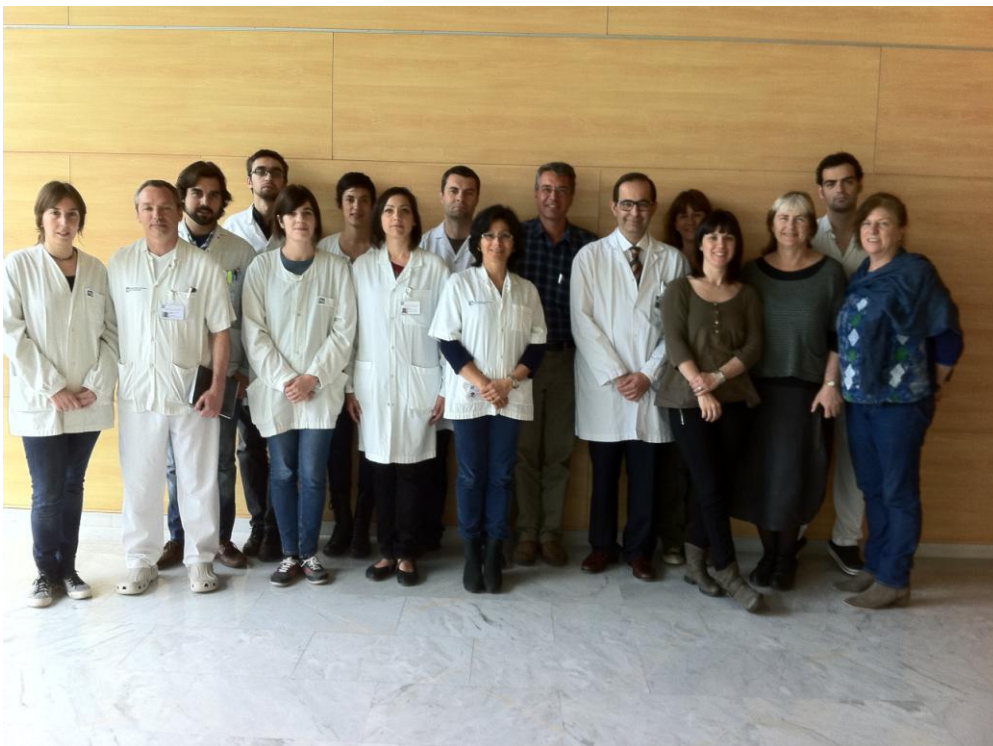
Acquired spinal cord and brain injuries



EFFECT OF AFFERENT OROPHARYNGEAL PHARMACOLOGICAL AND ELECTRICAL STIMULATION ON SWALLOW RESPONSE AND ON ACTIVATION OF HUMAN CORTEX IN STROKE PATIENTS WITH OROPHARYNGEAL DYSPHAGIA (OD). A RANDOMIZED CONTROLLED TRIAL

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1. Global project summary

This project includes three groups of studies. The first ones are finalist papers presented at the 5th Jornada del Pla de Salut de Catalunya, in Sitges, 27th November 2015 and also as oral presentations in the 2nd congress of *European Stroke Organization Conference*, Barcelona 11th May 2016. We described a high incidence of oropharyngeal dysphagia (OD) (45.1%) in post-stroke patients by using a clinical test previously developed and validated by our group, and we found a close association with age and stroke severity. OD significantly impacts on hospital length of stay, early complications such as respiratory infections and mortality during hospital stay, and patient functional status, institutionalization and survival during the first year after stroke.

The second group includes three studies, published or pending publication, which describe the pathophysiology and mechanisms of post-stroke OD. The first one describes the biomechanical aspects of deglutition and the impaired swallow response assessed by videofluoroscopy where delayed laryngeal vestibule closure is considered the main cause of aspirations, and the stroke neurotopographical factors associated with unsafe swallowing function. Then, we studied and characterized the cortical impairments associated with loss of pharyngeal sensitivity also linked to the pathophysiology of post-stroke OD. The last study describes the prevalence and complications associated with impaired cough reflex response in this phenotype of stroke patients.

The third group of studies, most of them published in scientific journals with high impact factor (first quartile/decile) compares the effect of various therapeutic strategies. The first one evaluates the effect of compensatory strategies based on the modification of bolus viscosity by using thickeners, and shows an important reduction in the prevalence of aspirations without any changes in swallowing function (compensatory mechanism). The results of pharyngeal electrical stimulations were neutral, although this technique improved swallowing function, the improvements were similar in the active and sham groups. However, both surface electrical stimulation (at sensory and motor level) and pharmacological treatments with TRPV1 and TRPVA1 agonists showed an important positive effect on impaired safety of swallow in post-

stroke patients and were safe treatments that promote the recovery of swallowing dysfunction.

To conclude, the results of this project funded by La Marató de TV3 allow us to recommend: a) the implementation of systematic screening and treatment programs for post-stroke OD to improve patients' outcome, and b) to change the paradigm of treatment from compensatory to neurorehabilitation strategies that allow and promote the recovery of swallowing function.

2. Results

Studies performed during the project:

A. Incidence, prevalence and complications of post-stroke OD.

1. Incidence, risk factors and complications of OD in patients with stroke (during hospital admission, at 3 months and one year).

B. Physiopathology and mechanisms of post-stroke OD.

2. Impairments in oropharyngeal swallow response assessed by videofluoroscopy.

Biomechanical study of aspirations

3. Spatiotemporal characteristics of the pharyngeal event-related potential in stroke patients with oropharyngeal dysfunction

4. Cough reflex attenuation and swallowing dysfunction in sub-acute post-stroke patients: Prevalence, risk factors and clinical outcome

C. Efficacy and safety of new neurorehabilitative treatments vs compensatory strategies for the management of post-stroke OD patients. Mechanism of action:

5. Compensatory strategies: A comparative study between modified starch and xanthan gum thickeners in post-stroke oropharyngeal dysphagia.

6. Transcutaneous electrical stimulation: Effect of surface sensory and motor electrical stimulation on chronic post-stroke oropharyngeal dysphagia

7. Intrapharyngeal electrical stimulation: Pharyngeal electrical stimulation for treatment of dysphagia in subacute stroke: A randomized controlled trial

8. Pharmacological stimulation by using TRPV1 and TRPA1 agonists

The results of each study

1. INCIDENCE, RISK FACTORS AND EVOLUTION OF OD IN PATIENTS WITH STROKE (DURING HOSPITAL ADMISSION, AT 3 MONTHS AND ONE YEAR).

Background. The incidence and the natural history of post-stroke oropharyngeal dysphagia (OD) are not fully understood nowadays. This is partly due to variability between studies regarding the selection criteria of patients, diagnostic methods of dysphagia and time over which the patient is evaluated. Despite the severity of associated complications, post-stroke OD is underdiagnosed and undertreated.

Objectives. To determine the incidence, risk factors and complications associated with post stroke OD.

Methods. We performed a prospective observational study on 403 consecutive patients with acute stroke admitted to a general hospital. We used a validated clinical test, the Volume-Viscosity Test (VVST) to diagnose post-stroke OD. We collected demographic data, functional status and clinical variables of stroke in order to assess risk factors for presenting OD. Then, on discharge and at three months, we evaluated functional scores and nutritional status, mortality, respiratory infection, the length of hospital stay and readmissions to analyse the influence of OD on these variables. We conducted a multivariate logistic regression analysis to determine the risk factors for OD on admission and for each outcome variable.

Results. The incidence of OD on admission was 45.06%. The results of the multivariate analysis showed that independent risk factors for OD were age, National Institutes of Health Stroke Scale (NIHSS) >6, the volume of the lesion and prior stroke. As outcome variables, we observed that, on discharge, OD was an independent risk factor for not returning home, for high mortality risk and significantly increased hospital stay. We also found that it was clearly associated with systemic complications (especially respiratory infections) and neurological complications during hospitalization but usually associated with other prognostic factors (such as the severity of the stroke and the volume of the injury). During the first year post-stroke, we demonstrated that OD was an independent risk factor of mortality with a Hazard Ratio (HR) of 4.7 and of worse functional status. Respiratory infections were also an independent risk factor of mortality during the first three months with an HR of 3.8. However, risk of death associated with the modified Rankin Scale (mRS) (0.2) and the volume of the lesion

(1.005) were also statistically significant independent factors of mortality during the first year of follow up, but at much lower rates than the risk of death associated with OD or respiratory infection.

Conclusions. The incidence of OD post-stroke is high and is associated with age, stroke severity and various clinical variables (level of consciousness, aphasia and dysarthria) and has a significant impact on length of stay, in-hospital complications and outcome at discharge and on functional status and mortality during the first year of follow up. Our results suggest that the implementation of systematic screening programs and early management of OD could significantly improve the outcome of post-stroke patients with OD.

2. IMPAIRMENTS IN OROPHARYNGEAL SWALLOW RESPONSE ASSESSED BY VIDEOFLUOROSCOPY. BIOMECHANICAL STUDY OF ASPIRATIONS

Background. Oropharyngeal dysphagia (OD) is a main complaint following stroke and it remains in the sub-chronic post-stroke stage. OD is associated with nutritional and respiratory complications and with a poorer functional status and higher risk of institutionalization at discharge and mortality.

Objectives. To describe those demographical, clinical, neurontopographical and videofluoroscopic risk factors associated with impairments on safety of swallow and to characterize the oropharyngeal swallow response (OSR) aspects linked with impaired safety of swallow in post-stroke patients (PSP).

Methods. PSP were screened for OD at least 3 months after stroke by using the clinical test volume-viscosity swallow test (VVST). Those PSP with clinical signs of impaired swallowing were further reassessed by videofluoroscopy (VFS). Demographical, clinical, neurontopographical and videofluoroscopic data was compared between those PSP with confirmed unsafe swallow (penetration-aspiration scale, PAS \geq 2) and safe swallow (PAS \leq 2).

Results. 73 PSP were included (76.7 \pm 9.3 years, 53.4% male), 97.3% confirmed signs of impaired safety of swallow in the VFS study (1.4% impaired safety, 20.6% impaired efficacy and 75.3% both impairments). The main signs significantly associated with unsafe swallow were age, severity of stroke according to the National Institutes of Health Stroke Severity (NIHSS), left-side stroke and total artery cerebral infarction (TACI). In addition, those PSP with impaired safety of swallow presented a poorer functional and nutritional status. A delayed OSR mainly linked with a delayed laryngeal

vestibule closure and upper oesophageal sphincter opening was detected in PSP with unsafe swallow. Also, PSP showed a reduce propulsion bolus force.

Conclusions. There are several demographic, clinical and neurontopographical factors associated with impaired safety of swallow in PSP. In addition, delayed times to airway protection and poorer propulsion forces had been associated with unsafe swallow in PSP.

3. SPATIOTEMPORAL CHARACTERISTICS OF THE PHARYNGEAL EVENT-RELATED POTENTIAL IN STROKE PATIENTS WITH OROPHARYNGEAL DYSFUNCTION

Objective: Oropharyngeal dysphagia (OD) is a highly prevalent symptom after stroke people. Appropriate oropharyngeal sensory feedback is essential for safe and efficient swallowing. However, pharyngeal sensitivity decreases with advancing age and could play a fundamental role in the physiopathology of post-stroke swallowing dysfunction. We aimed to characterize pharyngeal sensitivity and cortical response to a pharyngeal electrical stimulus in healthy volunteers (HV) and post-stroke patients with and without OD.

Design: 10 young HV, 10 older post-stroke patients without OD and 20 post-stroke patients with OD were studied by EEG through 32 scalp electrodes. Pharyngeal event-related potentials (ERP) were assessed following electrical stimulation of the pharyngeal wall. Sensory and tolerance thresholds to the electrical stimulus and latency, amplitude and scalp current density of each ERP component were analysed and compared. An ERP source localization study was also performed using the sLORETA software.

Results: Post-stroke patients (with and without OD) presented an increased sensory threshold to pharyngeal electrical stimulation compared to young HV. The cortical activation of older HV in response to pharyngeal electrical stimulus was reduced compared to young HV. PSP patients with OD also presented disturbances to the pharyngocortical connection together with disrupted pattern of cortical activation.

Conclusion: The main finding of our study is that post-stroke patients present a decline in pharyngeal sensory function, more severe in older patients with OD. This sensorial impairment might be a critical pathophysiological element and a potential target for treatment of swallowing dysfunction in older patients.

4. COUGH REFLEX ATTENUATION AND SWALLOWING DYSFUNCTION IN SUB-ACUTE POST-STROKE PATIENTS: PREVALENCE, RISK FACTORS AND CLINICAL OUTCOME

Background. Both cough and swallowing impairments in post-stroke patients (PSP) have been associated to increased risk for respiratory complications.

Aims. To assess the prevalence of alterations in protective cough responses in subacute PSP and their association with oropharyngeal dysphagia (OD), clinical and neurotopographic stroke factors and clinical outcomes.

Methods. Three-months after stroke, the cough reflex test (CRT) was performed by nebulizing incremental citric acid concentrations (7.8-1000mM) to determine the concentration that elicited two and five coughs; and OD was assessed by the volume-viscosity swallow test. Clinical and neurotopographic stroke risk factors and complications (readmissions, respiratory infections, institutionalization and mortality) were assessed within 3-12-months.

Results. We included 225 PSP. Prevalence of impaired CRT was 5.8%, that of OD was 40.4% (20.4% with impaired safety of swallow) and only 1.8% showed both impairments. No specific risk factors associated with impaired CRT were found, however, haemorrhagic, wide circulation infarction (TACI) and brainstem strokes delayed the cough response. Besides, OD was associated with age, TACI and poor functional and nutritional status. PSP outcome was unaffected by impaired CRT but OD and impaired safety of swallow increased institutionalization, respiratory infections and mortality with the poorest outcome for those with both dysfunctions.

Conclusions. Prevalence of subacute post-stroke OD and swallow safety impairments is much higher than CRT attenuation, and risk factors strongly differ suggesting that the swallow response receives a stronger cortical control than the cough reflex. OD impacts on PSP clinical outcome more severely than impaired cough being the poorest prognosis for patients with both airway protective dysfunctions.

5. A COMPARATIVE STUDY BETWEEN MODIFIED STARCH AND XANTHAN GUM THICKENERS IN POST-STROKE OROPHARYNGEAL DYSPHAGIA.

Background. Thickeners are used in post-stroke oropharyngeal dysphagia (OD) as a compensatory therapeutic strategy against aspirations.

Aims. To compare the therapeutic effects of modified starch (MS) and xanthan gum (XG) thickeners on swallow safety and efficacy in chronic post-stroke OD patients using clinical and videofluoroscopic (VFS) assessment.

Methods. Patients were studied by clinical assessment (volume-viscosity swallow test, V-VST) and VFS using 3 volumes (5, 10, 20mL) and 3 viscosities (liquid, nectar and spoon thick), comparing MS and XG.

Results. We studied 122 patients (46MS, 76XG). A) V-VST showed both thickeners similarly improved safety of swallow. Prevalence of safe swallowing significantly increased with enhanced viscosity ($P < 0.001$ vs liquid), MS: 47.83% at liquid, 84.93% at nectar, and 92.96% at spoon thick; XG, 55.31% at liquid, 77.78% at nectar and 97.84% at spoon thick. Patients on MS reported higher prevalence of pharyngeal residue at spoon thick viscosities. B) VFS: increasing bolus viscosity with either thickener increased prevalence of safe swallows ($P < 0.001$ vs liquid), MS: 30.25% liquid, 61.07% nectar, and 92.64% spoon thick; XG: 29.12% liquid, 71.30% nectar and 89.91% spoon thick. Penetration-Aspiration Scale score was significantly reduced with increased viscosity with both thickeners. MS increased oral and pharyngeal residues at nectar and spoon-thick viscosities but XG did not. Timing of airway protection mechanisms and bolus velocity were not affected by either thickener.

Conclusion. Increasing bolus viscosity with MS and XG thickeners strongly and similarly improved safety of swallow in chronic post-stroke OD by a compensatory mechanism; in contrast only MS thickeners increased oropharyngeal residue.

6. EFFECT OF SURFACE SENSORY AND MOTOR ELECTRICAL STIMULATION ON CHRONIC POST-STROKE OROPHARYNGEAL DYSPHAGIA

Background Chronic post-stroke oropharyngeal dysphagia (OD) is a common condition, leading to severe complications, including death. Treatments for chronic post-stroke dysphagia are scarce. The aim of our study was to assess and compare the efficacy and safety of treatment with surface electrical stimulation at sensory and motor intensities in patients with chronic post-stroke dysphagia.

Methods Twenty chronic post-stroke patients with OD were randomly assigned to: a) sensory electrical stimulation (treatment intensity: 75% of motor threshold) or b) motor electrical stimulation (treatment intensity: motor threshold). Patients were treated during 10 days, 1 hour per day. Videofluoroscopy was performed at the beginning and end of the study to assess signs of impaired efficacy and safety of swallow and timing of swallow response.

Key Results Patients presented advanced age (74.95 ± 2.18), 75% were men. The mean days post-stroke was 336.26 ± 89.6 . After sensory stimulation, the number of unsafe swallows was reduced by 66.7% ($P < 0.001$), the laryngeal vestibule closure

time by 22.94% ($P=0.027$) and maximal vertical hyoid extension time by 18.6% ($P=0.036$). After motor stimulation, the number of unsafe swallows was reduced by 62.5% ($P=0.002$), the laryngeal vestibule closure time by 38.26% ($P=0.009$) and maximal vertical hyoid extension time by 24.8% ($P=0.008$). Moreover, the motor stimulus reduced the pharyngeal residue by 66.7%, ($P=0.002$), the upper oesophageal sphincter opening time by 39.39% ($P=0.009$) and increased bolus propulsion force by 211.1% ($P=0.008$). No serious adverse events were detected during the treatment.

Conclusions & Inferences Surface electrical stimulation is a safe and effective treatment for chronic post-stroke dysphagic patients.

7. PHARYNGEAL ELECTRICAL STIMULATION FOR TREATMENT OF DYSPHAGIA IN SUBACUTE STROKE: A RANDOMISED CONTROLLED TRIAL

Background. Dysphagia is common after stroke, associated with increased death and dependency, and treatment options are limited. Pharyngeal electrical stimulation (PES) is a novel treatment for post-stroke dysphagia that has shown promise in three pilot randomised controlled trials.

Methods. We randomly assigned 162 patients with a recent ischaemic or haemorrhagic stroke and dysphagia, defined as a penetration aspiration score (PAS) of 3 or greater on video fluoroscopy, to 3 daily treatments with pharyngeal electrical stimulation or sham treatment. The primary outcome was swallowing safety, assessed using the PAS, at 2 weeks. Secondary outcomes included dysphagia severity, function, quality of life and serious adverse events at 12 weeks.

Results. In randomised patients, the mean age was 74 years, male 58%, ischaemic stroke 89%, PAS 4.8. The mean treatment current was 14.8 (7.9) mA, and duration 9.9 (1.2) minutes per session; based on prior data, 45 (58.4%) of patients randomised to PES appeared to receive suboptimal stimulation. The PAS at 2 weeks, adjusted for baseline, did not differ between the randomised groups: PES 3.7 (2.0) vs sham 3.6 (1.9), $p=0.60$. Similarly, the secondary outcomes did not differ including clinical swallowing and functional outcome. No serious adverse device-related events occurred.

Conclusions. In patients with sub-acute stroke and dysphagia, pharyngeal electrical stimulation was safe but did not improve dysphagia. Undertreatment of patients receiving PES may have contributed to the neutral result.

3. Publications

Under review

N. Vilardell, L. Rofes, W.V. Nascimento, D. Muriano, E. Palomeras, P. Clavé. PREVALENCE AND RISK FACTORS FOR COUGH IMPAIRMENTS AND SWALLOWING DYSFUNCTION IN SUBACUTE POST-STROKE PATIENTS. *Neurogastroenterology and Motility*. Submitted.

Christopher Cabib, Omar Ortega, 2, Hatice Kumru, Ernest Palomeras, Natalia Vilardell, Daniel Alvarez-Berdugo, Desirée Muriana, Laia Rofes, Rosa Terré, Fermín Mearin, Pere Clavé. NEUROREHABILITATION STRATEGIES FOR POST-STROKE OROPHARYNGEAL DYSPHAGIA: FROM COMPENSATION TO THE RECOVERY OF SWALLOWING FUNCTION. *Annals New York Academy of Sciences*. R1

Laia Rofes, Omar Ortega, Natàlia Vilardell, Lluís Mundet, Pere Clavé. Spatiotemporal characteristics of the pharyngeal event-related potential in stroke patients with oropharyngeal dysfunction. *Neurogastroenterology and Motility*. R1.

Accepted articles

Philip Bath, Polly Scutt, Jo Love, Pere Clave, David Cohen, Rainer Dziewas, Helle Iversen, Christian Ledl, Suzanne Ragab, Hassan Soda. Anushka Warusevitane, Virginie Woisard, Shaheen Hamdy. Pharyngeal electrical stimulation for treatment of dysphagia in subacute stroke: a randomised controlled trial. Manuscript number: STROKE/2015/012455

Published articles

1: Vilardell N, Rofes L, Arreola V, Speyer R, Clavé P. A Comparative Study Between Modified Starch and Xanthan Gum Thickeners in Post-Stroke Oropharyngeal Dysphagia. *Dysphagia*. 2015 Nov 25. [Epub ahead of print] PubMed PMID: 26607158.

2: Alvarez-Berdugo D, Rofes L, Farré R, Casamitjana JF, Enrique A, Chamizo J, Padrón A, Navarro X, Clavé P. Localization and expression of TRPV1 and TRPA1 in the human oropharynx and larynx. *Neurogastroenterol Motil*. 2016 Jan;28(1):91-100. doi: 10.1111/nmo.12701. Epub 2015 Nov 4. PubMed PMID: 26530852.

- 3: Clavé P, Shaker R. Dysphagia: current reality and scope of the problem. *Nat Rev Gastroenterol Hepatol*. 2015 May;12(5):259-70. doi: 10.1038/nrgastro.2015.49. Epub 2015 Apr 7. Review. PubMed PMID: 25850008.
- 4: Rofes L, Arreola V, Martin A, Clavé P. Effect of oral piperine on the swallow response of patients with oropharyngeal dysphagia. *J Gastroenterol*. 2014 Dec;49(12):1517-23. doi: 10.1007/s00535-013-0920-0. Epub 2013 Dec 11. PubMed PMID: 24326980.
5. Alvarez-Berdugo D, Jiménez M, Clavé P, Rofes L. Pharmacodynamics of TRPV1 agonists in a bioassay using human PC-3 cells. *ScientificWorldJournal*. 2014 Feb 2;2014:184526. doi: 10.1155/2014/184526. eCollection 2014. PubMed PMID: 24688365; PubMed Central PMCID: PMC3929291.
- 6: Rofes L, Arreola V, Martin A, Clavé P. Natural capsaicinoids improve swallow response in older patients with oropharyngeal dysphagia. *Gut*. 2013 Sep;62(9):1280-7. doi: 10.1136/gutjnl-2011-300753. Epub 2012 Jun 21. PubMed PMID: 22722616.
- 7: Rofes L, Arreola V, López I, Martin A, Sebastián M, Ciurana A, Clavé P. Effect of surface sensory and motor electrical stimulation on chronic poststroke oropharyngeal dysfunction. *Neurogastroenterol Motil*. 2013 Nov;25(11):888-e701. doi: 10.1111/nmo.12211. Epub 2013 Aug 12. PubMed PMID: 23937476.
- 8: Rofes L, Vilardell N, Clavé P. Post-stroke dysphagia: progress at last. *Neurogastroenterol Motil*. 2013 Apr;25(4):278-82. doi: 10.1111/nmo.12112. Epub 2013 Mar 11. Review. PubMed PMID: 23480388.
- 9: Position Statements of the ESSD: Screening, Diagnosis and Treatment of Oropharyngeal Dysphagia in Stroke Patients. *Dysphagia*. DOI 10.1007/s00455-013-9455-z.
- 10: Rofes L, Clavé P, Ouyang A, Scharitzer M, Pokieser P, Vilardell N, Ortega O. Neurogenic [corrected] and oropharyngeal dysphagia. *Ann N Y Acad Sci*. 2013 Oct;1300:1-10. doi: 10.1111/nyas.12234. Review. Erratum in: *Ann N Y Acad Sci*. 2013 Nov;1303:105. PubMed PMID: 24117630.

Doctoral Thesis

1) Desirée Muriana. Neuróloga. Factors de risc clínics, fisiopatològics i topogràfics per al desenvolupament de disfàgia orofaríngia en pacients amb ictus. Directors: Pere Clavé i Ernest Palomeras. Departament de Medicina UAB. Línia de Recerca: Medicina. Alteracions de la Motilitat Digestiva Humana. Neurologia. Acabada. Pendent de defensa el 3 de Juny de 2016.

2) Natàlia Vilardell. Farmacéutica. Efecte de l'estimulació sensorial aferent de l'orofaringe en la resposta de la deglució i en l'activació cortical en pacients amb ictus i disfàgia orofaríngia. Director. Pere Clavé, Tutor: Carlos Guarner Aguilar. Línia de Recerca: Medicina UAB. Alteracions de la Motilitat Digestiva Humana. Acabada la fase de camp, en fase d'anàlisi. Pendent de defnsa Q3, 2016.