

## Background:

Transcranial brain parenchymal sonography (TCS) is an emerging technique based on the reflection and scattering of ultrasound waves through tissues of different acoustic impedance, used for the study and characterization of deep cerebral structures (substantia nigra, raphe nuclei, basal ganglia and ventricular system). Its main advantages are non-invasivity, rapid time of examination and low costs. In the last decades this technique has been extensively applied in the neurodegenerative spectrum, mostly as a valid supportive tool in the early diagnosis of Parkinson disease and in the differential diagnosis between idiopathic Parkinson disease and atypical or secondary parkinsonisms. Only few studies have so far applied TCS for the study of migraine patients, focusing mostly on brainstem raphe (a structure actively involved in central processing of noxious stimuli) with discordant results and involving only patients with episodic migraine. The aim of our study was to use TCS for the study of midbrain raphe nuclei in patients with episodic versus chronic migraine, and to assess possible associations between sonographic data and clinical characteristics of our patients.

## Methods:

35 migraine patients (20 episodic, 15 chronic) were enrolled at the outpatient clinic of Neurology Department of S. Giacomo Apostolo Hospital (Castelfranco Veneto-TV). As controls served 20 healthy age-matched subjects. Patients and controls underwent full clinical history and extensive neurological examination; diagnosis of migraine was made according to ICDH-3 criteria; TCS was performed by an expert sonographer through the transtemporal bone window, and midbrain raphe was divided according to international guidelines by a dichotomic two-point scale into two groups: normal (continuous raphe) or hypoechogenic (interrupted or invisible raphe). Statistical analysis was made by using Student's t test and ANOVA test in case of variables with normal distribution. For categorical variables, chi square test was used. In order to predict whether our clinical variables could have an effect on determining the type of raphe (normal or hypoechogenic) a logistic regression analysis was made.

## Results:

Clinical results: We documented a statistical differences between chronic migraineurs and episodic migraineurs for what concerns mean days of migraine/month ( $22.6 \pm 6.76$  versus  $4.10 \pm 2.51$ ;  $p < 0.001$ ) and mean number of migraine attacks/month ( $20.13 \pm 8.53$  versus  $2.55 \pm 1.55$ ;  $p < 0.001$ ), these data confirm the accuracy of our initial diagnosis. Chronic migraineurs showed a tendency towards a longer disease duration, although without statistical significance ( $p = 0.07$ ).-Figure 1.

Sonographic results: On a first analysis based exclusively on diagnostic category (episodic migraine/chronic migraine/controls) we observed an apparent significant difference between chronic and episodic migraineurs for what concerns echogenicity of mesencephalic raphe, chronic migraineurs displaying a higher prevalence of hypoechogenicity ( $p = 0.001$ )-Figure 4; no difference was evidenced between episodic migraineurs and controls.

We subsequently performed a logistic regression analysis in order to clearly evidence which clinical variables could have a role in determining raphe echogenicity; surprisingly, our study evidenced that an interrupted/absent (hypoechogenic) raphe is NOT related to migraine type ( $p = 0.196$ ), age, sex, or number of migraine attacks, or profile of analgesic consumption, while it is definitely related to disease duration ( $p = 0.033$ ).

## Discussion:

This is the first study to analyze patients with episodic versus chronic migraine by means of transcranial brain parenchymal sonography of raphe nuclei.

Brainstem raphe is a group of mostly serotonergic neurons clustered around the brainstem midline. They are divided into a rostral (midbrain, pons) group and a caudal (pons, medulla oblongata) group. Raphe nuclei with their serotonergic projections are actively involved in the processing of noxious stimuli and in the kindling of migraine attacks. In the past, functional neuroimaging techniques (PET studies) evidenced, during migraine attacks, higher concentrations of serotonin transporters (SERT) and activation of specific trunclal areas involved into serotonergic metabolism, corresponding to raphe nuclei. Hypoechogenicity of brainstem raphe is a well-known finding in depressive disorders, and corresponds histopathologically to a rarefaction of serotonergic neurons and a disruption of myelinated fibers passing through raphe nuclei.

Previous studies on brain parenchymal sonography and migraine selectively enrolled episodic migraineurs and yielded contrasting results, failing to demonstrate a distinct different pattern of raphe echogenicity between episodic migraineurs and controls; among migraineurs, those displaying an hypoechogenic raphe seemed to have a higher number of migraine attacks, longer disease duration and a pattern of analgesic consumption more oriented towards NSAID than to triptans.

Our study took into consideration both chronic and episodic migraineurs, evidencing that an hypoechogenic brainstem raphe is related uniquely to disease duration, independently of migraine type: patients with a longer history of disease, regardless of it being chronic or episodic, more frequently display an hypoechogenic raphe.

## Conclusion:

**Among migraineurs, patients with longer disease duration show a higher probability of manifesting an altered (hypoechogenic) brainstem raphe.**

**Hypoechogenicity could be determined by degenerative changes of raphe structures (as suggested by previous post-mortem and MRI studies) thus expressing a direct disease dependent effect; alternatively, raphe hypoechogenicity could point out a distinct subtype of patients, doomed (ab initio?) to have a long history of disease and a tendency towards chronicization.**

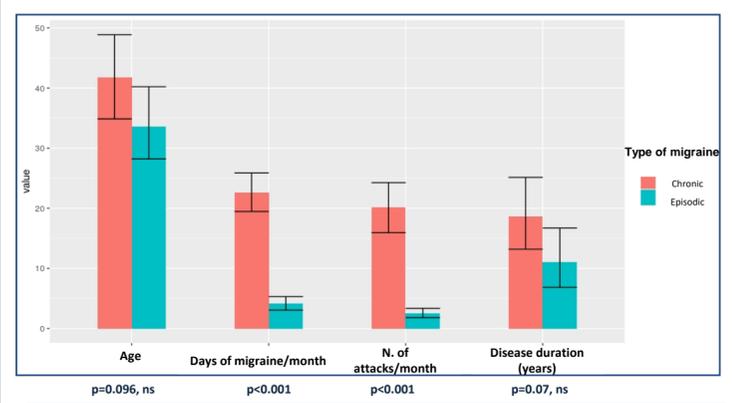


Figure 1: Clinical results: differences between episodic and chronic migraineurs

Figure 2: anatomical representation of brainstem raphe nuclei

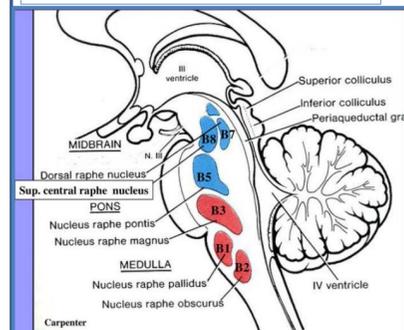
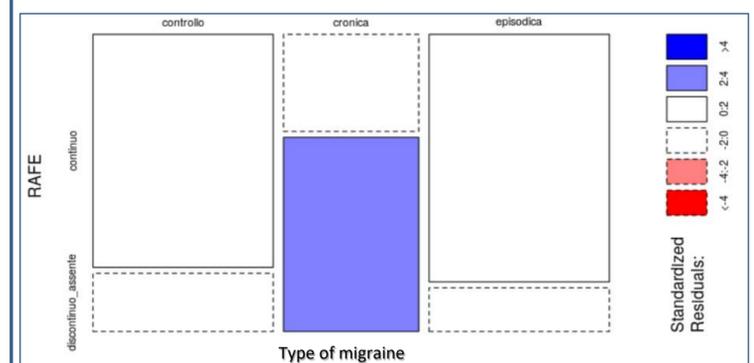


Figure 3: sonographic representation of mesencephalic raphe nuclei (NR): normal echogenicity (upper image) and hypoechogenicity (absent raphe)-lower image.



Episodic vs chronic migraine:  $p = 0.001$   
 Episodic migraine vs controls:  $p = ns$

Figure 4: At a first analysis, based only upon diagnostic category, a significant prevalence of hypoechogenic raphe was observed in chronic migraineurs. A subsequent logistic regression analysis, however, demonstrated that an hypoechogenic raphe is determined by disease duration and not by disease subtype.

## Acknowledgements:

Great thanks to my dear ex Colleagues of San Giacomo Apostolo Hospital, especially to Dr. Carla D'Ascenzo.