Hyperechogenicity of the periaqueductal gray in migraine as a potential marker of progressive dysfunction: preliminary results

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- Background

The periaqueductal gray matter (PAG) is an anatomically heterogeneous, functionally diverse region of densely layered neurons surrounding the aqueduct of Sylvius. In positron emission tomography (PET) studies during migraine without aura, increased blood flow was measured in mesencephalic regions that possibly reflect PAG, dorsal raphe nuclei and locus ceruleus activation, raising the possibility of the existence of a brain stem generator of migraine attacks. Activation of these brain regions seems specific for migraine and not for facial pain or cluster headache.

It is widely accepted that the brainstem plays a significant role in migraine pathophysiology. The PAG is a substantial component of the descending pain modulatory network. Previous MRI studies by Welch group demonstrated that PAG iron levels are abnormally high in both episodic and chronic migraine, suggesting the hypothesis that iron accumulation may be a marker of progressive PAG dysfunction.

It has been found that PAG has the concentration of transferrin receptors than any brain region. Transferrin receptor density may be a marker of iron demand during oxidative metabolism and may be influenced by nociceptive function. Overexpression of transferrin receptors could lead to tissue iron accumulation and iron-catalized free radical cell damage, accentuated by repeated episodes of hyperoxia during migraine attacks with or without aura.

The increase in iron levels can be investigated with transcranial sonography (TCS) on account of heavy metal-induced hyperechogenicity.

TCS is a neuroimaging method which, in B-mode, can provide data on various brain structures and has been proven to be reliable and useful in detection basal ganglia alterations in several movement disorders ad multiple studies have shown echogenicity of the mesenchephalic midline-brainstem raphe to be significantly lower in patients with mood disorders.

- Objectives

The purpose of our study is to evaluate hyperechogenicity of PAG in patients with chronic migraine and Medication Overuse Headache (CM + MOH – group 1) and patients with episodic migraine (EM – group 2), according to the International Classification of Headache Disorders (ICHD III Beta version).

- Methods

Group 1 consisted in 10 patients, all female aged between 36 and 55 years; Group 2 consisted in 10 patients, 8 women and 2 men, aged between 45 and 59 **(table 1)**. The duration of illness was recorded for group 2 and the duration of CM, including previous years of EM was recorded for group 1. The subjects with EM referred a history of low frequency migraine attack per month.

TCS was performed by a single experienced investigator blinded to the clinical scores using a phased array ultrasound system equipped with a 2.0-2.5 MHz transducer according to standardized procedure developed in 2004 by the European Society of Neurosonology and Cerebral Hemodynamics (ESNCH). Using the transtemporal approach, the midbrain and diencephalic examination planes were visualized in axial section.

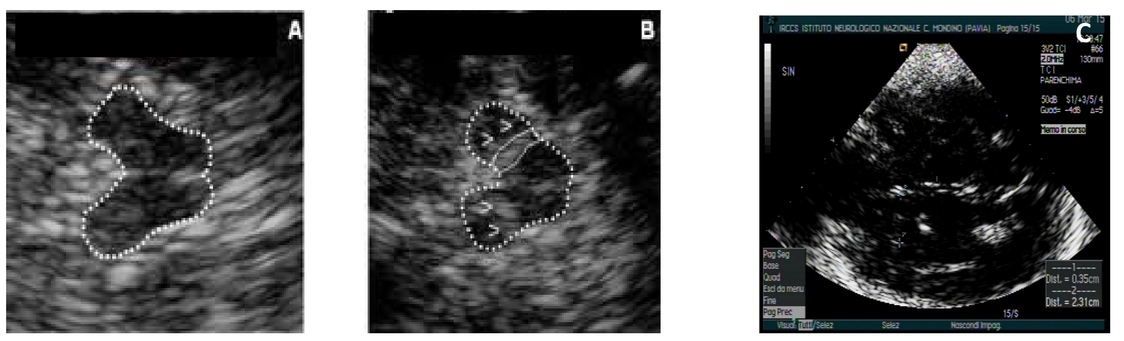
Echogenicities of raphe midbrain **(figure 1 A),** Substantia Nigra **(figure 1 B)** and PAG, thalami, lentiform nucleus (LN) and head of the caudate nucleus (CN) were examined and graded as hyperechogenic. The maximal width of the frontal horns of the side ventricles and the minimal transverse diameter of the third ventricle **(figure 1 C)** were measured on a standardized diencephalic examination plane. Hyperechogenicity was considered as the visually rated intensity of the ultrasound signal increase compared to the surrounding brain tissue. A standardized system setting was used for TCS **(table 2).**

All the patients underwent TCS: one patient from group 1 and one from group 2 were excluded for unsonable trantemporal window.

Table 1.	CM+MOH (group 1)	EM (group 2)
N° patients	10 (M/F: 0/10)	10 (M/F: 2/8)
Age range	36-55 years	45-59 years

Table 2 - Standardized system setting for TCS	
Transducer	20-35 Mhz
Penetration depth	14-16 cm
Dynamic range	45-55 dB
Contour amplification	Medium to high
Image brithness	Adapt as needed
Time gain compensation	Adapt as needed

Fig. 1 : A raphe midbrain, B Substantia Nigra , C Frontal horns of the side ventricles and the transverse diameter of the third ventricle



- Results

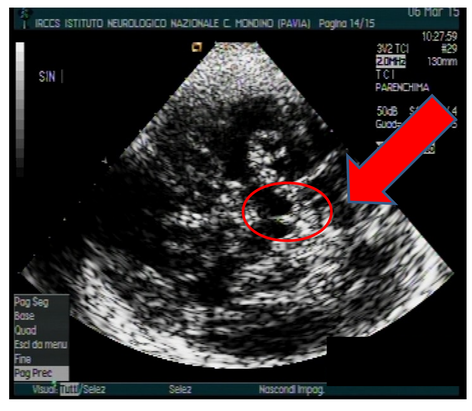
Mean PAG echogenicity was lower in patients with EM.

A clearcut increase in PAG hyperechogenicity was detected in 6/9 CM + MOH subjects and in only 1/9 EM **(Table 3 and figure 2)**.

Table 3.	EM	CM + MOH
PAG echogenicity *	1 + / 8 -	6 + / 3 -

* **+** hyperechogenicity / **-** hypoechogenicity

Fig. 2 – PAG in CM+MOH (example)



- Conclusion and Discussion

These preliminary findings support the possible occurrence of a progressive degeneration of PAG in migraine history evolution.

The possibility to reliably detect this degeneration with TCS could provide a low-cost, harmless, widely available tool. Evaluation on a larger population and a standardization using semiquantative visual assessments are needed to confirm the PAG dysfunction in chronic migraine and the reliability of TCS for screening purpose and to predict the evolution of the disease.

- References

1. Welch KMA et al. Periacqueductal grey matter disfunction in Migraine: cause or the burden of illness? Headache 2001; 41:629 -637

2. The International Classification of Headache Disorders, 3rd edition (beta version), 2013