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Review

Cerebral magnetic resonance changes associated with fibromyalgia syndrome☆

Iñigo Murga[a,*], Virginia Guillen[a], José-Vicente Lafuente[a,b,c]

[a] LaNCE, Departamento de Neurociencia, Universidad del País Vasco, Leioa, Bizkaia, Spain
[b] Grupo de Nanoneurocirugía, Instituto de Investigación Sanitaria BioCruces, Barakaldo, Bizkaia, Spain
[c] Facultad de Ciencias de la Salud, Universidad Autónoma de Chile, Santiago de Chile, Chile

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ABSTRACT

Fibromyalgia syndrome is a chronic disease, of unknown origin, whose diagnostic criteria were established in 1990 by the American College of Rheumatology. New criteria were proposed in 2010 that have not yet been validated. It is characterized by a generalized chronic musculoskeletal pain, accompanied by hyperalgesia and allodynia, as well as other motor, vegetative, cognitive and affective symptoms and signs.

We have reviewed a set of studies with cerebral magnetic resonance (morphometry, connectivity and spectroscopy) that refer to changes in areas involved in pain processing.

Modifications in gray and white matter volume, as well as in levels of N-acetylaspartate, choline or glutamate, among other metabolites, have been observed in the hippocampus, insula, prefrontal and cingular cortex. Neuroradiological findings are nonspecific and similar to those found in other examples of chronic pain. An increase in the sample size and a standardized methodology would facilitate comparison, allowing the drawing of general conclusions.

Cambios en la resonancia magnética cerebral asociados al síndrome de fibromialgia

Palabras clave:
Síndrome de fibromialgia
Resonancia magnética cerebral
Morfometría
Espectroscopia
Conectividad

RESUMEN

El síndrome de fibromialgia es un trastorno crónico, de origen desconocido, cuyos criterios diagnósticos estableció en 1990 el Colegio Americano de Reumatología; en 2010 propuso unos criterios nuevos que aún no están validados. Se caracteriza por dolor musculoesquelético generalizado, crónico, acompañado de fenómenos de hiperalgesia y alodinia, así como otros síntomas y signos, motores, vegetativos, cognitivos y afectivos.

Revisamos un conjunto de estudios con resonancia magnética cerebral (morfometría, conectividad y espectroscopia) que refieren alteraciones en áreas de procesamiento del dolor.

Se observan cambios en el volumen de la sustancia gris y blanca, así como de los niveles de N-acetilaspartato, colina o glutamato, entre otros metabolitos, en hipocampo, ínsula, corteza prefrontal y cingular, principalmente. Los hallazgos neurorradiológicos son inespecíficos y superponibles a los de otros cuadros de dolor crónico, pero un aumento del tamaño muestral y una metodología estandarizada facilitaría la comparación entre series, permitiendo extraer conclusiones generalizables.

Introduction

Fibromyalgia syndrome (FMS) is characterized by widespread chronic musculoskeletal pain, of unknown etiology, with hyperalgesia and allodynia. It is accompanied by other symptoms, such as: fatigue, insomnia, paresthesias, swelling in the hands,

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* Corresponding author.
E-mail address: imurga005@ikasle.ehu.eus (I. Murga).

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neurovegetative changes, concentration problems, memory and mood disorders. Symptom intensity fluctuates throughout the natural course of FMS.

Diagnostic criteria for this syndrome were provided by the American College of Rheumatology in 1990,[1] although in 2010 this same organization proposed new criteria that have not been validated yet.

The World Health Organization[2] classifies FMS under the heading of diseases of the musculoskeletal system and connective tissue (code M79.7), and the International Association for the Study of Pain[3] has classified it under code X33.X8a.

In a study conducted in 5 European countries (France, Germany, Italy, Portugal and Spain), prevalence was 4.7%, and the female/male ratio was 3 to one.[4] Its high prevalence, the disability it causes and the frequency of long-term sick-leaves of these patients, make the economic cost be high, making it an increasingly important social and health problem.

The diagnosis is clinical. There is currently no specific analytical, imaging or anatomopathological test to verify this diagnosis. In the perception and experience of pain, various brain structures are included, such as the somatosensory cortex (primary and secondary), the cingulate gyrus (anterior region), the insula, thalamus, the posterior parietal cortex and the prefrontal cortex. All of them are involved in the so-called "pain network", a set of areas, structures and nuclei dealing with the perception, transmission and processing of the various sensory and affective components that constitute the experience of pain.

The quantitative study of anatomical and biochemical variables is an important strategy for the diagnosis, prognosis and follow-up of various diseases.[5] Many authors have shown, by using neuroimaging techniques, changes in volume, connectivity and metabolism of the brain areas involved in the "pain network" in FMS. The morphometric study of certain brain structures by using the voxel based morphometry technique, plus the identification of the variations in some metabolites by magnetic resonance spectroscopy (MRS), and the study of functional connectivity with the analysis of the blood-oxygenation-level dependent signal, are a very promising tool to elucidate the morphobiological component of various disorders, including FMS.

This paper is a critical review of the neuroimaging contribution to FMS. The ultimate aim is to find clues or evidence on indicators that might help determine the diagnosis and/or evolution of this condition.

Development

The diagnostic criteria followed in all the studies considered are those of the American College of Rheumatology.[1] However, so many and diverse inclusion-exclusion criteria between the different series makes it difficult to include them in a meta-analysis.

Changes in the size of brain structures

Voxel-based morphometry analyzes the anatomical regions of the brain such as the thalamus, insula, amygdala, hippocampus or cingulate gyrus. In all of them the size decreases,[6–9] only in one study the size increases in the basal nuclei, in the cerebellum and in the orbitofrontal cortex.[10]

Another method of study is the diffusion tensor imaging, which allows to evaluate microstructural changes through the analysis of the diffusion direction of hydrogen protons (water) in the tissue (anisotropy). This method requires further computational processing time, but the results are very sensitive to differences in shape and volume in small brain structures.[11] The imaging studies obtained by means of diffusion tensor show in the gray matter of both thalamus an anisotropy drop, as well as in the white matter tracts connecting them with the cortex, corresponding to changes in the microstructure of these anatomical areas[12] (Table 1). The thalamus plays a central role in the sensory-discriminative component of pain. Therefore, a detailed volumetric analysis of the different thalamic nuclei would be interesting.

Table 1
Analysis of brain morphometry and diffusion tensor by magnetic resonance imaging in fibromyalgia syndrome.

Related author	Result	Anatomical area
Kuchinad et al.[6]	↓ Gray matter	Posterior cingulate cortex (bilateral) Medial prefrontal cortex Insula (left) Parahippocampal gyrus (left)
Schmidt-Wilcke et al.[10]	↓ Gray matter	Upper temporal cortex (right) Insula (left) Thalamus (left post)
	↑ Gray matter	Orbitofrontal cortex (left) Striated nucleus (bilateral) Cerebellum (left)
Lutz et al.[12]	↓ Gray matter	Hippocampus (bilateral)
	↓ FA gray matter	Posterior thalamus (bilateral) Insula (bilateral)
	↑ FA gray matter	Anterior cingulate cortex (bilateral) Superior frontal cortex (bilateral) Postcentral gyrus (bilateral) Amygdala (bilateral) Hippocampus (bilateral)
	↑ FA white matter	Anterior cingulate cortex (bilateral) Superior frontal cortex (bilateral)
	↓ FA white matter	Talamocortical pathway (bilateral)
Wood et al.[7]	↓ Gray matter	Anterior cingulate cortex (left) Posterior cingulate cortex (right) Parahippocampal gyrus (bilateral)
Burgmer et al.[8]	↓ Gray matter	Anterior cingulate cortex (right) Lateral prefrontal cortex Amygdala (left)
Robinson et al.[9]	↓ Gray matter	Anterior cingulate cortex (left) Medial insula (left)

FA: fractional anisotropy.

Distribution of metabolites in various brain areas

MR spectroscopy allows *in vivo* determination of the level of various molecules in particular regions of the brain. We should consider the various normal metabolites depending on location, age and echo time used.[13]

The most common metabolites determined are: creatine (Cr), the basic compound of the energy metabolism of the brain, is a very stable metabolite, therefore, used as a reference for calculating the rates of others; N-acetylaspartate (NAA), is used as a marker neuronal density marker, although dynamic changes in their rates may reflect neuronal dysfunction rather than loss; Choline (Cho), a marker of phospholipid metabolism, reflects cell proliferation and is higher in tumor processes; lactate is the end product of anaerobic glycolysis, present in brain tissue at very low levels, which under normal conditions are not detectable by spectroscopy. Their presence is indicative of ischemia or infiltration by highly glycolytic cells, such as macrophages; Myo-inositol (MI), used as a glia marker; Glutamine (Gln) and glutamate (Glu), the latter being the most abundant excitatory amino acid in the brain acting as a neurotransmitter.[14] The changes in the relative concentration of these metabolites, plus the occurrence of others, which in normal circumstances are not present, are a reflection of the pathological changes occurring in a particular area of the brain parenchyma.[15]

This technique has important limitations, for example, the threshold of definition or discrimination of the equipment gathering the data, or the computer software used for its analysis. The