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ORIGINAL ARTICLE

Tumor Necrosis Factor alpha, prognosis and stroke subtype etiology

H. Flores-Cantú[a], F. Góngora-Rivera[b,*], F. Lavalle-González[c], J.Z. Villarreal-Pérez[c], D. Cantú-Sánchez[b], A. Anaya-Escamilla[b], H.J. Villarreal-Montemayor[b], H.J. Villarreal-Velázquez[b], GECEN collaborators[1]

[a] *Department of Internal Medicine at the ''Dr. Jose E. Gonzalez'' University Hospital of the Autonomous University of Nuevo León, Monterrey, Mexico*
[b] *Neurology Service at the ''Dr. Jose E. Gonzalez'' University Hospital of the Autonomous University of Nuevo León, Monterrey, Mexico*
[c] *Endocrinology Service at the ''Dr. Jose E. Gonzalez'' University Hospital of the Autonomous University of Nuevo León, Monterrey, Mexico*

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Abstract
Objective: To determine the relationship between TNF alpha and the etiology, localization, extension, intima media thickness, carotid atherosclerotic plaque, and outcome after an acute stroke.
Methods: We randomly selected 75 patients with acute strokes from a total of 253 patients that were admitted prospectively from May, 2008 to December, 2010. We analyzed TNF alpha levels and compared it with demographic data, clinical outcome upon hospital discharge, and at 3 months post discharge with neuroimaging studies. We used the Chi-square test, the *U*-Mann–Whiney test and the Cox logistic regression adjusted for age, gender and stroke extension.
Results: We included 47 men and 28 women. The most common etiologies were atherosclerotic (39%) and small vessel disease (27%). TNF alpha levels did not differ between atherosclerotic and cardioembolic stroke etiologies, except for the lacunar infarction, which had the lowest levels ($p = 0.048$), and did not correlate with a worse functional outcome upon hospital discharge ($p = 0.852$) or at 3 months following discharge ($p = 0.194$). Additionally, we found a positive relation between intima media thickness >1 mm and TNF alpha ($p = 0.004$). TNF alpha was not associated with the extension of the stroke by an ASPECTS score with CT or MRI ($p = 0.323$) or with the arterial territory involved ($p = 0.289$).

* Corresponding author at: Servicio de Neurología, Hospital Universitario José Eleuterio González, Universidad Autónoma de Nuevo León, Avenida Gonzalitos s/n, Col. Mitras Centro, C.P. 64460 Monterrey, Nuevo León, Mexico. Tel.: +52 81 8348 9266; fax: +52 81 8347 1059.
E-mail addresses: fernando.gongora@hotmail.com, fgongora@excite.com (F. Góngora-Rivera).
[1] Margarito Raúl Hinojosa-García, Meztli Artemisa Espinosa-Ortega and Helda Estrella Sánchez-Terán. Students Against Neurologic Diseases (GECEN by its Spanish acronym) of GESTIMED, School of Medicine at the Autonomous University of Nuevo Leon, Monterrey, Mexico.

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Conclusions: TNF alpha was not globally associated with functional outcome after acute stroke, just in the lacunar infarction, which has the lowest levels. We also found a positive relation between TNF alpha and intima-media thickness.

Introduction

Strokes are the most common cause of functional disability in adults[1] and the sixth leading cause of death in our country.[2] It is considered to be the second most common cause of death in the world, and its prevalence is increasing in developing countries due to increased life expectancy and changes in eating habits and lifestyle.[1]

A stroke may have different etiologies. Among them the most common are known to be large artery atherosclerosis, small vessel disease or lacunar type, and caused due to cardiac embolism.[3] Other less common causes are pro-thrombotic states of systemic diseases, primary or secondary cerebral vasculitis, and arterial dissection secondary to medications or harmful substances.[3] When a patient has two probable causes or there is a failure to clarify the etiology, it is defined as undetermined until the moment that its origin is detected. Up to 15–25% of strokes remain undetermined.[1]

Atherosclerosis is a more common cause, especially in adults older than 50 years.[3] Unfortunately, there are no reliable statistics on the prevalence of atherosclerotic carotid artery stenosis in strokes in our country. However, in other developed countries, it has been established that 35–50% of cases are caused by atherosclerosis of large vessels, such as the carotid artery, the thoracic aorta and the proximal intracranial vessels.[3]

The second most common cause of a stroke is a disease of the penetrating vessels by degeneration of the vascular wall or lipohyalinosis, with the consequent microangiopathy of the small cerebral vessels and infarcts of a more limited volume, usually less than 1.5 or 2.0 cm.[1] This disease is typical of patients with hypertension and/or chronic diabetes. The volume of injuries from a lacunar infarct is small; therefore, a lesser number of neurons are affected. However, its clinical consequences depend on the location of the lesion.

Thirdly, there is the cardio-embolic etiology. This may be due to an arrhythmic phenomenon, or an injury to the heart wall that conditions a focal myocardial dyskinesia and thus the formation of an intracavitary thrombus, as occurs after a heart attack.[3] Although more common in younger subjects, its diverse etiology makes it likely in the elderly as well. Strokes, as a consequence of an embolus from the heart, can hide a distal artery in the brain, and generally hide a vessel of great size, leading to a wide-reaching stroke.[3]

The etiology may vary according to the study population, which is what makes it important to emphasize the etiological definition of a stroke in all prospective cohorts of patients.

After a stroke, inflammatory phenomena as a result of the damage and its extent occur,[4] as well as others, which seek to limit the consequences of the lack of irrigation in the peripheral area of a stroke, known as the ischemic penumbra area.[5,6]

Among the molecules that have been defined to be associated with strokes, their extension and prognosis, are cytokines, such as IL-1, IL-6, and TNF alpha.[7] Some molecules increase in blood immediately and remain in the blood at high levels for several days. Their quantification may be a reflection of the degree of damage or the extent of the stroke, and may even help to etiologically differentiate the type of stroke.[5,6,8–10]

Tumor Necrosis Factor (TNF) alpha and Cerebral Vascular Disease (CVD)

TNF alpha is produced by brain cells, both neurons and microglia, after suffering ischemia.[11] It is involved in all stages of brain injury by stroke. Its pro-inflammatory effect appears to initially maintain cerebral flow in the periphery of the stroke and is proportional to stroke size.[5–9]

Many studies that have associated etiological subtype and functional prognosis following a stroke, but few who have studied TNF alpha as a pro-inflammatory cytokine cerebrospinal fluid and serum that can be associated with the size, clinical severity and etiology of a stroke.[4,6,8–10,12–14]

In a study of 123 stroke patients and 123 healthy controls, patients with cardioembolic CVD showed higher levels of TNF alpha plasma in plasma when compared with the other subtypes.[13] In a study of 36 patients with acute ischemic stroke at admission,it was found that concentrations of TNF alpha did not vary significantly from controls, but the amount of soluble TNF receptor type 1 in the first week correlated strongly with stroke size by CT at 5–7 days, as well as the mRS (modified Rankin Scale) at 3 and 12 months.[11]

There have only been a few studies on the behavior of TNF alpha in strokes, especially TNF alpha in acute strokes that emphasize the stroke etiological subtypes and clinical features.

Materials and methods

Patients

This is an analytical cross-sectional study nested in a prospective cohort of patients diagnosed with a stroke who were admitted to the Neurology Department at a tertiary level teaching hospital in Northeastern Mexico (*Intrahospital Registry of NeuroVascular Disease – iRENE-*) in the period of May, 2008 to December, 2010. The protocol was approved by the Ethics Committee; patients and/or family members signed a letter of consent.