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An overview on immune system and migraine

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Abstract. – The pathogenesis of migraine is still unclear, but much evidence led us hypothesize that it can be associated with immune system modification, so that a role for cytokines has been suggested.

Cytokines are important mediators of the immune and inflammatory pathways and their receptors are widely express in Central Nervous System (CNS) by all cell types, including neurons, indicating that they can act on neuronal receptors.

Cytokines are now considered to be the pain mediators in neurovascular inflammation.

Furthermore cytokines may be a cause of the migraine pain: in fact an high levels of chemokines could stimulate the activation of trigeminal nerves, the release of vasoactive peptides or other biochemical mediators, such as Nitric Oxide, and then to cause inflammation.

In this scenario, many studies on humans have focused the attention on peripheral and central levels of cytokines, but data obtained are highly controversial.

Since at the moment there is not a conclusive evidence of the role played by cytokines in migraine, the Authors present and comment the latest reports regarding cytokine modification and the role of the immune system in migraine.

Key Words:

Migraine, Th1/Th2 cytokines, Nitric oxide.

Abbreviatons

MWoA: Migraine Without Aura
MWA: Migraine With Aura
NO: Nitric Oxide
iNOS: inducible Nitric Oxide Synthase
RANTES: Regulated on activated normal T-cell expressed, and secreted

Introduction

Migraine is the most common neurological disorder in Western population: it affects 6% of the male and 20% of the female population, so that it is considered as social pathology[1].

Serious unilateral headache, vomiting, nausea and photophobia usually characterize migraine attacks. About 30% patients have an aura period, characterized by visual, sensory and speech disturbances, before the headache starts.

Even if the mechanisms leading to the typical headache in migraine are still unknown, the etiology of migraine is surely multifactorial.

Various factors such as alcohol, smoking, nutrition, stress environmental changes, exercises and menstrual cycle, in women, have been all associated with migraine.

It is now admitted that the changes in the immune homeostasis could, in some ways, contribute to migraine.

Cytokines are small proteins produced by most cells in the body, which possess multiple biologic activities to promote cell-cell interaction. Several lines of evidences suggest that cytokines play an important role in several physiological and pathological settings such as immunology, inflammation and pain[2,3].

Cytokines have been shown to induce headache and many studies have examined cytokines levels in migraine patients but the results are very controversial.

One reason that could explain the different data could be that the cytokine assays have been measured in many cases only in the peripheral blood, in some cases ictally, in others interictally[4-6]. However a fluctuation of circulating cytokine levels in primary headaches is evident[7]. Recently, Perini et al[8] have measured a panel of pro- and anti-inflammatory cytokines (TNF-α, IL-1β, IL-2, IL-6 and IL-4, IL-10 respectively) in plasma of migraineurs in a time-locked relationship to the onset of attacks and during headache-free periods. They found neither significant differences between patients with and without aura; there were no differences in IL-6, IL-4 and IL-2 levels of patients outside and during the attacks and differences in IL serum levels between healthy subjects and patients were significant only

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for IL-10, being higher during attacks in comparison to controls and for TNF-α and IL-2 that were lower outside attacks than controls (Table I).

However, even if the cause of elevated cytokine levels during attacks is unknown, these data suggest that at least TNF-α, IL-1β and IL-10 may be involved in the pathogenesis of migraine attacks.

On the other hand, Fidan et al in 2006 in a study carried out in migraine patients during attacks and in attack-free periods did not found a significant difference in the serum levels of IL-1β, IL2, IFN-γ and TNF-α compared to those in healthy groups[9]. Whereas transitory increased levels of TNF-α and IL6 were observed in the internal jugular blood of MWoA patients. Both cytokines reached a peak at 1 hour from catheter insertion, and then tended to progressively decrease toward levels measured at baseline.

A higher level of these cytokines could stimulate the activation of trigeminal nerves and the release of vasoactive peptides and then to cause inflammation and therefore contribute to cause inflammation.

A slight increase in IL-1β was evident from 1 to 4 hours after catheter insertion and then decreased. Conversely, levels of IL-4 were reduced at the same times and its levels at the end of the attack returned to those detected at attack onset (Table II)[10].

An other clinical trial carried out by Ishizaki et al[11] in 2005 has focused the attention on an other particular cytokine: the Transforming Growth Factor Beta 1 (TGF-β1). This is a multifunctional proinflammatory cytokine involved in the modulation of cell growth, differentiation, and repairs following injury and immune-modulation[12].

The TGF-β1 serum levels in migraine were significantly higher than in controls but there were no any differences in the plasma levels between MWA and in MWoA and there was not correlation with age or duration of illness, or frequency of migraine headache.

Table I. Levels of serum cytokines in migraine patients and controls. The assay considered values obtained in healthy subjects (controls) and in patients during migraine attacks. Values are expressed as log 10(x+1) of pg/ml ± SD. (Perini et al.[8] modified).

Cytokine	Controls	Patients
IL-1β	0.72 ± 0.22	0.70 ± 0.11
IL-2	0.25 ± 0.36	0.06 ± 0.16**
IL-4	2.13 ± 0.19	2.09 ± 0.31
IL-6	0.66 ± 0.37	0.81 ± 0.32
IL-10	0.50 ± 0.22	0.68 ± 0.13**
TNF-α	1.71 ± 0.70	1.13 ± 0.91*

*$p < .05$ Outside attacks versus control; **$p < .004$ During attacks versus control.

Table II. Levels of jugular blood cytokines in migraine without aura patients: at the moment of catheter insertion (T = 0), after 4 hours of attack onset (T = 4h) and at the end of migraine attack (E.A.). Values are expressed as pg/ml ± SD. (Sarchielli et al.[10] modified).

Cytokine	T = 0	T = 4h	E.A.
IL-1b	18.00 ± 2.69	22.44 ± 3.66*	17.66 ± 2.43
IL-4	25.76 ± 3.07	12.85 ± 2.92**	22.44 ± 2.34#

*$p < .01$ versus T0; **$p < .001$ versus T0; #$p < .05$ versus T0

The most predominant systemic effects of TGF-β1 have been regarded as immunosuppressive properties and increases or decreases in the production of TGF-β1 have been reported in association with various diseases, including atherosclerosis, fibrotic disease, inflammatory bowel diseases and cancer[13-15].

TGF-β1 has been regarded as a platelet-derived cytokine and it has been demonstrated that human platelets contain pools of latent TGF-β1 and since many reports suggested that platelets play some role in migraine, we can hypothesize an effective involvement of TGF-β1 in headache pathogenesis[16].

Furthermore, a possible involvement of TGF-β1 has been notified in central fatigue or chronic fatigue syndrome and it has been proposed that excess exercise increases active TGF-β1 in brain, followed by the feeling of fatigue and decreasing motor activity[17]. Patients with migraine often complain of fatigue or lack of vigor during and between migraine episodes. These symptoms may relate to increased TGF-β1.

The study regarding chemokine could open a new window to understand migraine pathogenesis: in fact while MCP-1 and MIP-1a did not show any differences between migraine patients and controls, the serum level of RANTES effectively was significantly higher in the patients during attacks than other group[9]

It appears clear that some immunological changes take place during migraine and cytokines are considered to be the possible pain mediators in neuro-vascular inflammation and so they may cause the generation of migraine pain: they can also induce sterile inflammation of meningeal blood vessels in migraine[18] but at nowadays the immunological disorders in migraine have not been well defined yet. The more accredited hypothesis indicates that some change in TH2 type cytokines can play a role in the etiology of migraine. In fact while TH1 lymphocytes release IL-2, IFN-γ and

Table III. The most relevant cytokines related to migraine.

Cytokine	Main source	Target cells
IL-1 (α-β)	Monocytes/macrophages B-Lymphocytes Dendritic cells Endothelial cells	TH-Lymphocytes B-Lymphocytes NK-Macrophages Neutrophils Endothelial cells
IL-2	TH1-Lymphocytes	T-Lymphocytes NK
IL-4	TH2-Lymphocytes Mast cells NK	B-Lymphocytes
IL-6	Monocytes/macrophages TH2-Lymphocytes Bone Marrow stoma cells	Plasma cells B-Lymphocytes
IL-10	TH2-Lymphocytes	Macrophages
TNF-α (Tumour Necrosis Factor-α)	Macrophages Mast cells	Tumour cells Granulocytes
TGF-β (Transforming Growth Factor-β)	Platelets Macrophages Lymphocytes Mast cells	Monocytes/Macrophages

*$p < .05$ Outside attacks versus control; **$p < .004$ During attacks versus control.

lymphotoxin, Th2 release IL-4, IL5 and IL-10 and an unbalance between TH1/TH2 cytokines may influence the spreading of pain producing processes in migraine (Tables III and IV).

In a study carried out by Martelletti et al in 1998[19] it has been demonstrated that TH1 subset is lowered in MWoA patients in respect to controls whereas IL-4 serum levels were higher.

Nitric Oxide (Figure 1), a small gaseous molecule extremely versatile, seems to be involved not only in the modulation of TH1/TH2 subset[20] but also in the activation of cycloxygenase type 2 enzyme that is responsible for the synthesis of prostaglandins[21]. In MWA peripheral monocytes spontaneously release "in vitro" detectable amounts of NO and serum level of nitric oxide are much higher in patients than in controls; in patients monocytes the release of PGE2 is higher than in healthy subjects.

Finally most of the pro-inflammatory cytokines, such as IFN-γ, IL-1β and TNF-α are potent inducers of NO release by monocytes.

Recently, it has been reported[22] that the increased production of NO by monocytes of MWoA patients can be due to an up-regulation in iNOS expression secondary to the transient increase in NF-Kb activity. This observation is extremely important: in fact the activation of NF-Kb is linked to the induction of genes encoding for pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) and cycloxygenase expression.

At the light of these observations it is highly possible that TH1/TH2 cytokines may influence the spreading of pain-producing processes in migraine. On the other hand it is very often impossible to detect a real change in the levels of many cytokines, maybe because most of them have a very short life in serum and are quickly degraded and the serum clearance of cytokines is very rapid, sometimes in the order of minutes.

Some Authors[23] suggest that the urine collections could be used for the detection of cytokine concentrations: in fact while cytokine fluctuation are often transient and undetectable in serum, urine samples reflect a mean value within 24h could be more affordable.

Table IV. Identification and main properties of TH1/TH2 cytokines.

	TH 1	TH 2
Macrophage activation	+ + +	– – –
Selectin ligands	+ +	–
Receptors for IFN-γ	– – –	+ +
Receptors for IL-12	++	– –

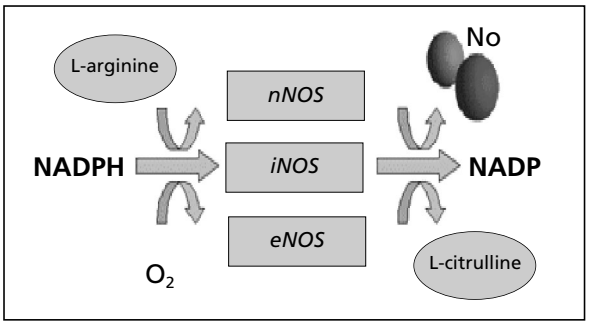

Figure 1. Nitric Oxide (NO) is produced by conversion of L-Arginine to Citrulline by a family of NO synthases: two constitutive isoforms: the neuronal (nNOS) and the endothelial (eNOS) and by the inducible one (iNOS).

We however conclude that about migraine and cytokines we are on long way on the basis of the latest researches, the immune system is securely involved.

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