Headache secondary to autoimmune disorder

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Background- Headaches are divided into primary (without an underlying cause) and secondary, those caused by other pathological conditions including inflammatory and autoimmune disorders.

Introduction - Headache has been suggested to be a neurological manifestation of many immunological/autoimmune disorders, both those primarily involving the central nervous system(CNS), such as multiple sclerosis, and those systemic, such as systemic lupus erythematosus.

Over the last decades, researchers have focused their attention on better understanding possible links between headache and autoimmune disorders. Both at epidemiological and pathophysiological levels, headache and in particular migraine, and autoimmune disorders seem to share common features:

• Epidemiologically, most autoimmune disorders are more frequent in females; likewise, almost all primary headache forms are more commonly diagnosed in females too.

• The onset of both headache and immunological/autoimmune disorders are generally at young ages.

• In terms of pathophysiology, in primary headaches, and mainly in the migraine context, the role of both neuroinflammation and immune system derangement has been increasingly acknowledged in the last decades, further supporting the view of a link of these conditions with immunological disorders.

Discussion - Neuroinflammation and Headache:

Contribution of neuroinflammation in the pathophysiology of several painful conditions, including migraine, is widely accepted. Also neuroinflammatory mechanisms have also been described in the context of several disorders causing secondary headache, such as post-traumatic stress disorder, chronic stress and traumatic brain injury.

Trigemino-vascular system (TVS) and headache

Role of TVS in primary headache has been well described .TVS activation, typically induces a local neurogenic inflammation involving dural and pial vessels which causes :

1. A plasma protein extravasation due to an increased meningeal vascular permeability

2. The activation of immune cells (mast cells and perhaps macrophages, localized near the dural afferents). Activated mast cells in turn produce several mediators including serotonin, histamine, arachidonic acid products, pro-inflammatory cytokines and chemokines.

• The upregulation of pro-inflammatory cytokines—specifically IL-1ß—in activated microglia has also been shown in the Trigeminal Nucleus Caudalis (TNC) .

• Neuroinflammatory events involving activated microglia and astrocytes also occur in the course of cortical spreading depression (CSD), which is considered the pathophysiological substrate of migraine with aura.

Pathophysiological links between primary headache and autoimmune disorders

A significant increase in the peripheral levels of pro-inflammatory cytokines such TNF-α, IL-1β, IL-6 have been found in migraine patients, both in interictal and ictal periods. Like in several autoimmune diseases, an impairment in natural killer (NK) cells, as well as a significant increase in the CD4+ lymphocyte and a decrease in the CD8+ lymphocyte subsets, was observed in migraine patients

Even for cluster headache (CH), some evidence supports a role for immunological dysfunctions in the pathogenesis of this disorder. Little is known in the role of a derangement of the immune system in tension-type headache.

Headache in different autoimmune disorders

A. **Vasculitides**: wide group of complex immunological diseases characterized by a relevant inflammation of blood vessel walls. An association between headache and vasculitides has not been definitely established, with some relevant exceptions (e.g. GCA). Systemic vasculitides can also cause secondary headache, and Behçet's syndrome seems to be one of the most strongly associated with headache. Other types of vasculitides, including polyarteritis nodosa and Takayasu's arteritis , can also involve CNS and cause headache.

B. **Connective tissue disorders**

1. **Systemic lupus erythematosus (SLE)** is a chronic systemic autoimmune disease, affecting the joints and multiple organs including nervous system. Neuropsychiatric symptoms affect about half of the patients with SLE which can also be among the earliest manifestations of SLE. Specifically, headache has been reported as the most frequent symptom of neuropsychiatric SLE. The role of headache in SLE has been recognized by the inclusion in the SLE Disease Activity Index (SLEDAI) of 'lupus headache' as a descriptor, defined as a severe, persistent headache which is often of migraine type and unresponsive to analgesia. Concerning tension type headache in patients with SLE, some investigations have revealed a higher prevalence of TTH compared to migraine.

2. **Sjögren's syndrome (SS):** Several epidemiological studies, as well as pathophysiological and histopathological research, have emphasized the involvement of the Peripheral Nervous System in SS, whereas the CNS involvement has not been fully defined. neurological onset may sometimes precede both the clinical appearance of systemic symptoms and the immunological diagnosis by many years. Thus, a SS should always be considered in patients with relatively non-specific

neurological symptoms, such as headaches, associated with sicca syndrome. Among CNS manifestations of primary SS, headache seems to be one of the most common; the most frequent type of headache observed in a cohort of SS patients fulfilled the criteria for migraine without aura. Some researchers have also reported the higher incidence of dry eye in migraine patients. Therefore the relation between SS and migraine might be bi-directional. In summary, headache in pSS has been suggested to be related to an 'autoimmune endotheliitis' which directly alters biochemical and humoral markers, in turn inducing perivascular inflammation that fosters vasomotor dysfunction.

3. **Raynaud's disease**: a possible endothelial dysfunction of the cerebral microcirculation or a potential inflammation-mediated shift of the neurovascular coupling which possibly accounts for both headache (especially migraine) and Raynaud phenomenon.

4. **Scleroderma**: Nervous system involvement in scleroderma has been increasingly recognized and an association between migraine and systemic scleroderma (SSc) has been suggested. In largest study of Neurologic involvement in scleroderma (182 cases), most frequent symptom was headache.

5. **Rheumatoid arthritis (RA):** In a questionnaire survey of migraine patients in Denmark, the prevalence of RA was significantly higher in migraineurs compared to patients without migraine. Indeed, serotonergic dysfunction has been implicated in the pathogeneses of both RA and migraine.

6. **Antiphospholipid syndrome (APS):** can be accompanied by additional clinical features, including valvular lesions, migraine, Raynaud's phenomenon, livedo reticularis, arterial hypertension and autonomic disturbances, such as postural tachycardia syndrome, neurocardiogenic syncope and orthostatic hypotension. Among neurological complications, recurrent headaches are quite prevalent in APS patients. Migraine is the most common type of headache and the most frequent neurological manifestation of APS. In fact, one study reported that migraine was the most common clinical, not only neurological, manifestation of APS.

Conclusion - Over the last three decades, evidence has been moving towards a possible confirmation of the comorbidity of headache with almost all autoimmune disorders. Most of the headache in autoimmune disorders fulfill the ICHD-3 criteria for migraine, which might be a consequence of general inflammatory mechanisms involving meningeal vessels and activating trigeminal terminals. Autoimmune disorders and headache tend to worsen each other. Several autoimmune disorders during active phases can exacerbate headache, in particular migraine, will make the treatment of headache very difficult, unless the underlying autoimmune disorder is properly managed first.