

# The Role of Immune System Dysfunction in Co-Existence of Neurological Disorders in Psoriasis

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Psoriasis is an immune-mediated disease mostly characterized by red, scaly skin patches. Various systemic manifestations were also recognized in psoriasis including neurological disorders such as stroke, multiple sclerosis (MS), seizures, migraine, and Parkinson's disease (PD) (1).

*Question: How can psoriasis be associated with wide range of neurological disorders?*

*Idea: Immune system dysfunction may justify the link between neurological disorders with psoriasis.*

Immune system dysregulation may provide a link between neurological disorders with psoriasis. However, the role of non-immunological factors should not be underestimated. Overall, the underlying mechanisms for this correlation can be a cause or effect, a shared risk factor, side effects of treatment, or even a coincidental event. Cytokines are a group of small soluble proteins with a major role in cell signaling in the immune system but also increasingly recognized in the nervous system and skin with inflammatory and anti-inflammatory effects. Dendritic cells (DCs) play a crucial role in the first stage of the pathophysiological process in psoriasis; followed by T-helper (Th) 1 and 17 cells. Immunological triggers can induce the production of interleukin (IL)6, IL12 and IL23 from DCs. IL6 and IL23 can activate Th17 while IL12 can differentiate Th1. IL6 can inhibit the differentiation of T regulatory cells which have significant roles in immunosuppression (2). Th1 and Th17 are responsible for the production of different cytokines; such as TNF $\alpha$ , IFN $\gamma$ , and IL17 which are known to be the main factors in the pathogenesis of psoriasis (3). They can lead to differentiation and excessive proliferation of keratinocytes in skin. Increased levels of other pro-inflammatory cytokines have also been reported in psoriatic lesions; including IL6, IL8,

IL12, and IL18. Notably, elevated levels of pro-inflammatory agents were reported in sera of cases with psoriasis too (4).

The role of immune system in the pathophysiology of different neurological disorders have been investigated in many studies. Inflammatory processes can increase the incidence of stroke via various mechanisms; including thrombosis, vasculitis, and atherosclerosis. A leading cause of an ischemic stroke of the cerebral artery is atherosclerosis. The role of pro-inflammatory mediators in atherogenesis has been widely investigated in prior studies. Increased risk of cerebrovascular diseases in individuals with autoimmune disorders provides further support for the role of inflammation in the occurrence of atherosclerosis (5).

Recent evidence demonstrated increased inductions of differentiation and expansion of Th17 cells in MS. Various associated cytokines of Th17 cells such as TNF $\alpha$ , IL1, IL6, and IL17 are critical in MS occurrence (6). In other words, elevated levels of these mediators are considered as important factors in the pathogenesis of psoriasis and MS which can somewhat explain their co-occurrence.

Immunohistochemical analysis of resected epileptogenic brain tissue of animal models or human with drug-resistant epilepsy indicated high levels of cytokines in these tissues as compared to control groups (7,8). Elevated levels of pro-inflammatory agents were also reported in different types of provoked and unprovoked seizures; including febrile seizure, epileptic syndromes like West syndrome, temporal lobe epilepsy and epilepsy with unknown origin (9). The effects of anti-inflammatory medications in epilepsy improvement provided another support for the role of immune system dysfunction in epilepsy occurrence (10). Cytokines may

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increase the risk of seizure as the result of their direct impacts on CNS and decreasing blood-brain barrier (BBB) functions.

It is now recognized that a small 140 amino acid protein, called  $\alpha$ -synuclein, is a central component to the pathogenesis of PD. Misfolded  $\alpha$ -synuclein leads to activation of innate and adaptive immune systems which cause PD occurrence. Considering innate immune system, it is important to mention that a group of the pattern recognition receptors known as toll-like receptors (TLRs) may play a critical role in PD presentation. It appears that  $\alpha$ -synuclein can increase the activation of TLRs which leads to the production of different pro-inflammatory cytokines (11,12). These cytokines disrupt BBB function leading to the entry of neurotoxic agents and initiation of multiple neurodegenerative pathways. Of interest, increased activation of TLRs was also described due to psoriasis which may induce the same inflammatory pathways as  $\alpha$ -synuclein does (13).

Elevated levels of cytokines were also associated with the presence of migraine. It seems that psoriasis and migraine have shared pathogenic pathways. Leptin, which is known as a pro-inflammatory adipokine, can indirectly activate Th1 cells and induce the production of cytokines. High level of leptin was reported in migraine and psoriasis (14).

Psoriasis is associated with different other comorbid conditions such as metabolic syndrome, hypertension, and psychiatric disorders. The increased risk of occurrence of neurological disorders can be justified by these comorbidities. Furthermore, the presence of one neurological disorder in individuals can also lead to the occurrence of other neurological disorders. Shared risk factors including common genetic predisposition and an environmental trigger can also somewhat justify this link. Different genetic predispositions were described for psoriasis. These known genes span an array of functions that involve different aspects of both adaptive and innate immune systems. Genetic mutations were also described in various neurological disorders too. Future trials should investigate if there are common mutations between psoriasis and its neurological conditions.

Retinoids, methotrexate, cyclosporine, and biologic treatments such as TNF inhibitors are the known systemic treatments of psoriasis. Neurotoxicity may occur during the use of these medications. Stroke and seizures were reported after using methotrexate, and PD was reported during the use of infliximab.

### Conclusion and future direction

In clinical care, comorbidities continue to be under-

recognized and under-treated. Psoriasis significantly affects the quality of life of people, and its different comorbid conditions can greatly impact the life and mental health of these individuals. Identification of neurological disorders and trying to realize the underlying mechanisms for this link can help us to understand the pathophysiology of these diseases. Antibodies against neuronal surface antigens were identified in different systemic autoimmune disorders such as systemic lupus erythematosus. On the other side, emerging evidence indicated that these autoantibodies might play a significant role in the presentation of different neurological disorders; such as epilepsy (15). To date, no study investigated the presence of these antibodies in psoriasis cases. Such trials may provide greater supports for the role of immune system dysfunction as the etiology of the co-existence of neurological disorders in psoriasis.

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