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NEWS, VIEWS, AND REVIEWS

Beyond the Brain: Understanding the Dermatologic Associations of Neurodegenerative Diseases

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INTRODUCTION

Neurodegenerative disorders are a prevalent cause of morbidity, often carrying substantial physical and psychosocial burden. Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common neurodegenerative disorders, and both have manifestations that extend beyond the nervous system.[1] Emerging evidence has identified possible inflammatory, genetic, and biologic mechanisms linking PD and AD to a range of dermatologic diseases. Awareness of associations between cutaneous and neurologic disorders may help physicians recognize comorbid skin disease and inform dermatologic care for patients with mobility or cognitive challenges. This review explores the relationship between neurodegenerative disorders and the skin, highlighting possible mechanisms and practical considerations for dermatologists caring for patients with neurologic disease.

Parkinson's Disease

PD occurs due to the progressive loss of dopaminergic neurons in the substantia nigra, resulting in motor symptoms such as resting tremor, bradykinesia, and shuffling-like gait.[1] A hallmark of PD is the abnormal accumulation of phosphorylated alpha-synuclein proteins. Phosphorylated alpha-synuclein can deposit in the brainstem, contributing to the motor symptoms observed in PD. This protein is also believed to deposit in peripheral cutaneous nerve fibers.[2] A growing body of literature is emerging in favor of using skin biopsies to support the diagnostic evaluation of PD, as opposed to solely relying on clinical observation and symptoms.[3] Punch biopsies of the skin have demonstrated high sensitivity and specificity for detecting the presence of phosphorylated alpha-synuclein.[2] A recent multi-center study demonstrated that 92.7% of participants with PD tested positive for phosphorylated alpha-synuclein on skin biopsy vs only 3.3% of control participants.[4] Dermatologists may therefore play a collaborative role in supporting neurology colleagues when diagnosing PD.

Additionally, a potential bidirectional relationship has been proposed between PD and cutaneous melanoma. A recent retrospective cohort study demonstrated that veterans with melanoma had a 47% higher risk of PD compared to veterans without melanoma (adjusted HR 1.47; CI 1.37-1.57).[5] Conversely, a cohort study with 333,990 participants found that males over age 65 with PD had a 2.8 times higher risk than those without PD to develop melanoma (HR 2.825; CI 1.395-5.721).[6] Several mechanisms have been theorized to support this relationship, though current understanding remains inconclusive.[7] One proposed theory suggests that alpha-synuclein can interfere with activation of tyrosinase, a key enzyme in melanogenesis. Suppression of tyrosinase activity can potentially increase the skin's susceptibility to ultraviolet-induced DNA damage.[7] Other theories have implicated levodopa, a medication used in the management of PD that also serves as a precursor in melanogenesis. Although the shared role of levodopa in melanin synthesis and the treatment of PD has prompted hypotheses, current evidence does not identify levodopa as a driving factor of melanoma.[7] However, given the relationship between PD and melanoma, the American Parkinson Disease Association recommends annual skin checks for patients with PD.[8]

Seborrheic dermatitis is also commonly associated with PD, affecting an estimated 18% to 59% of patients with PD as compared to roughly 4% of the general population.[9] Interestingly, seborrheic dermatitis may precede the diagnosis of PD. A retrospective case-control study identified an increased association between seborrheic dermatitis and PD up to 15 years before PD diagnosis (OR 1.47; CI 1.43-1.51). Alpha-synuclein has been proposed as a potential link for these conditions. Alpha-synuclein can accumulate in peripheral autonomic nerve fibers, which also innervate the sebaceous glands. Dysfunction of these fibers due to alpha-synuclein accumulation may alter sebum production, creating a favorable environment for the development of seborrheic dermatitis.[9]

Alzheimer's Disease

AD is characterized by progressive memory loss and executive dysfunction due to an aberrant accumulation of amyloid plaques and neurofibrillary tangles within the brain.[1] AD has been associated with psoriasis, with a cohort study revealing that subjects with psoriasis had a 13% higher incidence of AD than subjects without psoriasis (HR 1.13; CI 1.10-1.16).[10] However, a clear relationship between the conditions has not been established. Inflammatory signaling has been proposed as a shared mechanism, with a study conducted in mice with transgenic AD demonstrating decreased cerebral amyloid following inhibition of IL-12 and IL-23 signaling. Inhibition of IL-12 and IL-23 signaling is also a key tenet of psoriasis treatment, suggesting potential for a shared inflammatory pathway between the conditions.[11] Genetic overlap may also contribute to this connection, with a genome-wide association study revealing a shared single nucleotide polymorphism near the HLA-DRB5 gene.[12] Further evidence is necessary to elucidate a pathophysiologic relationship between psoriasis and AD.

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AD has also been associated with bullous pemphigoid (BP), with a meta-analysis demonstrating an increased risk of all forms of dementia in patients with BP (HR 1.41; CI 1.20-1.66).[13] In patients over the age of 80, those with BP had 40% higher odds of AD compared to those without BP (adjusted OR 1.40; CI 1.10-1.78).[14] While no mechanistic link has been identified between AD and BP, researchers have proposed a cross-reactive autoimmune response to the epidermal adhesion molecules BP180 and BP230. BP180 and BP230 are the targets of autoimmune activity in BP, and homologues of these proteins have been identified as present within the nervous system. However, the evidence supporting this postulated mechanism remains conflicting, warranting further investigation.[14]

Practical Considerations

The overlap between dermatologic and neurologic conditions has important implications for interdisciplinary care. From a neurology standpoint, awareness of the cutaneous associations of neurodegenerative diseases can allow for prompt recognition and referral to dermatology for appropriate management. From a dermatology standpoint, it is crucial to be mindful of mobility and cognitive status when working with patients who have PD and AD, respectively.

When working with patients with neurodegenerative disorders, it can be helpful to assess their ability to complete self-skin examinations at home. If conducting self-examinations is of concern, increasing the frequency of dermatology visits may be considered based on shared decision-making between the patient and provider.[15] Additionally, if topical medications are prescribed for patients with movement disorders, it is important to assess the ability of the patient to reach affected areas. If application of topical treatments presents a challenge, oral medications should be more strongly considered if appropriate.[15] Dermatologists should also be cognizant of the complexity of medication regimens when working with patients experiencing dementia. Close collaboration between dermatologists, patients, and their caregivers is crucial to establish an effective and manageable care plan.[16]

Future Directions

PD and AD have meaningful cutaneous manifestations that warrant awareness from both neurologists and dermatologists. While the relationship between neurodegenerative disorders and associated skin conditions has been well characterized by epidemiologic data, emerging research continues to identify potential pathophysiologic connections. Thus, additional studies should investigate possible underlying mechanisms and employ longitudinal, prospective designs to clarify directionality and causality of these associations. Establishing a deeper understanding of the overlap between neurodegenerative and dermatologic conditions can help inform screening guidelines, identify therapeutic targets, and facilitate streamlined interdisciplinary management for patients.

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