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Authors
Wen, S
Elias, PM
Wakefield, JS
et al.

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REVIEW ARTICLE

The link between cutaneous inflammation and cognitive impairment

S. Wen,[1] P.M. Elias,[2,3] J.S. Wakefield,[2,3] T.M. Mauro,[2,3] M.-Q. Man[1,2,3,*]

[1]Dermatology Hospital, Southern Medical University, Guangdong, China
[2]Dermatology Service, Veterans Affairs Medical Center San Francisco, San Francisco, California, USA
[3]Department of Dermatology, University of California San Francisco, San Francisco, California, USA
*Correspondence: M.-Q. Man. E-mail: mqman@hotmail.com

Abstract

Cognitive impairment is a symptom of neurological disorders, including dementia and Alzheimer's disease; and mild cognitive impairment can be a precursor of both disorders. Aged humans and animal models with other systemic disorders, such as cardiovascular diseases and diabetes, display a higher incidence of cognitive decline. Epidemiological studies have shown that the incidence of cognitive impairment also is higher in subjects with certain inflammatory skin disorders, including psoriasis and chronic eczematous dermatitis. Chronologically aged individuals exhibit increased cutaneous inflammation and elevated circulating cytokine levels, linked to alterations in epidermal function, which itself can induce cutaneous inflammation. Conversely, strategies that improve epidermal function can lower cytokine levels in both the skin and circulation. Thus, it seems likely that epidermal dysfunction could contribute, at least in part, to the development of chronic low-grade inflammation, also termed 'inflammaging', in the elderly. The evidence of cognitive impairment in patients with inflammatory dermatoses suggests a link between cutaneous inflammation and cognitive impairment. Because of the pathogenic role of epidermal dysfunction in ageing-associated cutaneous inflammation, improvements in epidermal function could be an alternative approach for mitigation of the ageing-associated decline in cognitive function.

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Conflicts of interest

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Introduction

Cognitive impairment (CI) is manifested by a number of neurological symptoms, including difficulties with memory, concentration and decision making, which impact the quality of patients' lives. Symptoms range from mild to severe, and the prevalence of cognitive impairment varies with age, education level and geographical location. For example, the prevalence of cognitive impairment without dementia in the USA is 22% in individuals aged 71 years or older.[1] The current estimated prevalence of CI is over 15% in subjects over 60 years of age, with this trend increasing from 2000 to 2019.[2–5] However, other studies revealed a decline in prevalence (11.8–8.9%) between 2008 and 2014.[6] A higher prevalence was observed in American Indian/Alaska natives (19.6%) and black Americans (13.2%) than in Asian or native Hawaiian/other Pacific Islanders (6.8%) in subjects ≥45 years old.[7] Moreover, education level correlates negatively with the prevalence of cognitive impairment.[6–8] People living in rural areas and/or lacking in challenging, physical and cognitive activities also displayed a higher prevalence of cognitive impairment.[6] The annual incidence of mild cognitive impairment (MCI) without dementia is 60–77 cases/1000 person-years in subjects aged 65 years or older in Italy and the USA.[8,9] In Australian subjects aged 70–90 years old, the incidence of MCI is 104.6 per 1000 person-years (95% CI, 81.6–

127.7), with a higher incidence in males than females (157 vs. 70 cases/1000 person-years).[10] Taken together, these various studies demonstrate that the prevalence of cognitive impairment can be associated with race, age, gender, education level and geographical location.

MCI can be the harbinger of dementia and/or Alzheimer's disease, because a substantial proportion of people with MCI develop Alzheimer's disease or dementia.[11] Dementia reflects severe cognitive impairment and is the most prominent clinical manifestation of Alzheimer's disease in up to 60%–80% of overall dementia cases. Annual progression rates of MCI to dementia and Alzheimer's disease are 22% and 29%, respectively.[12] The conversion rate of MCI to dementia was 23.8 per 100 person-years in subjects of an average age of 72.8 years old.[13] Yet, in this 1.2-year-follow-up study, 54% of MCI patients remained stable, while 17% returned to normal.[13] Similarly, a 3-year follow-up showed that 20% of subjects (23/105) with MCI progressed to dementia.[14] Both older subjects (mean age of 71 years old vs. 64 years old) and ApoE epsilon 4 carriers display an increased risk for progression from MCI to dementia. The odds ratio of progression from MCI to dementia is 6.72 ApoE epsilon 4 carriers vs. non-ApoE epsilon 4 carriers (95% CI = 2.93–11.9, $P = 0.001$).[15] Notably, up to 40% of Alzheimer's patients are ApoE epsilon 4 carriers.[16] Subjects with MCI that also exhibit a lower initial body mass index and associated weight loss have a higher risk of developing dementia.[17] Thus, a substantial portion of aged patients progress from MCI to dementia.

The aetiology of cognitive impairment is still uncertain. However, epidemiological studies demonstrate association of cognitive impairment with a number of other disorders, including cardiovascular diseases, diabetes mellitus, rheumatoid arthritis, asthma, osteoporosis and skin disorders,[18–21] although these associations are hotly debated.[22–26] In this review, we focus on the link between cognitive impairment and inflammatory skin disorders, and we discuss the possible role of cutaneous inflammation in cognitive impairment.

Inflammatory skin disorders

Psoriasis

Psoriasis, a common inflammatory dermatosis, is associated with many extracutaneous disorders such as cardiovascular diseases, diabetes and obesity.[27,28] Studies also show a link between cognitive impairment and psoriasis. Psoriatic patients exhibit higher rates of MCI (44% vs. 11% in the controls, $P = 0.002$), accompanied by reduction in the cortical thickness of parahippocampal and superior frontal gyri of the left hemisphere ($P < 0.05$, between psoriatic patients and normal controls),[29] the regions that regulate memory function. The Multivariate Forward Stepwise Regression Analysis showed that the association of MCI with psoriasis is independent of other factors such as age, gender, levels of education, smoking habit, hypertension, diabetes and hypercholesterolemia. Similarly, a 13 675-case study showed that the hazard ratio (HR) of vascular dementia was 1.73 (95% CI, 1.21–2.47) in psoriatic patients aged over 17 years old in Denmark.[30] However, others reported that psoriasis is primarily associated with non-vascular dementia (adjusted HR = 1.25, 95% CI, 1.07–1.45) in subjects aged over 40 years old in Taiwan.[31] Whether differences in patients' age and race contribute to these varying results is unknown. Moreover, individuals with a prior history of psoriasis also have a higher odds ratio (OR) of dementia than those without psoriasis (adjusted OR = 1.46, 95%CI 1.23–1.73, $P < 0.001$).[31] Plaque psoriasis-associated cognitive impairment is mainly in the domains of attention and concentration with mean Standardized Mini Mental Status Examination scores of 22.45,[32] while patients with psoriasis vulgaris mainly display cognitive deficits in visuospatial domain and executive functioning.[33,34] In addition, the prevalence of cognitive impairment of visuospatial function, denomination, naming and abstraction was higher in patients with psoriatic arthritis than in normal controls (92% vs. 58%).[35,36] This evidence suggests that the phenotype of psoriasis-associated cognitive impairment varies with subtypes of psoriasis. However, additional studies are needed to ascertain whether and how different subtypes of psoriasis affect different regions of the brain. The link between psoriasis and cognitive impairment is further supported by the reduced risk of cognitive impairment in psoriatic patients receiving systemic treatment vs. not receiving systemic treatment. A case–controlled study in over fifty thousand patients showed that the HR of Alzheimer's disease was lower in patients receiving systemic treatment (acitretin, methotrexate, cyclosporine and biological agents) of psoriasis vs. not receiving systemic treatment (incidence 6.5 vs. 3.7 per 1000 person-years, $P < 0.0001$; HR 0.988 vs. 1.098).[37] Interestingly, either systemic treatment of psoriasis for less than 90 days or phototherapy did not lower the risk of dementia. But systemic treatment of psoriasis for over 90 days significantly reduced HR of dementia (adjusted HR 0.66).[38] This line of evidence strongly suggests an association between cognitive impairment and psoriasis. However, Kridin, et al. reported that prevalence of dementia was lower in psoriatic patients than in the normal controls (1.6% vs. 1.8%; OR = 0.85, 95% CI 0.80–0.91).[39] A lower OR was observed in moderate-to-severe psoriatic patients (unadjusted OR 0.63, 95%CI 0.56–0.69),[39] probably because these patients all received systemic therapy. Cheng also reported that the incidence of dementia was similar between individuals with vs. without psoriasis, and that systemic treatments of psoriasis did not lower the risk for dementia.[40] In this study, The mean ages of the subjects in both groups were 60 years old, while early dementia starts at age of 50 years old. Thus, the incidence of dementia may not differ significantly in old subjects with vs. without psoriasis. Nevertheless, evidence does indicate a link between cognitive impairment and psoriasis.

Eczematous dermatitis

Various forms of eczematous dermatitis, including not only atopic dermatitis that persists into adulthood, but additionally, seborrheic dermatitis, xerotic eczema and stasis dermatitis, are common inflammatory skin disorders in adults, affecting ≈3% of adults worldwide.[41,42] Yet, an expanding literature indicates that eczematous dermatitis can be accompanied by systemic disorders.[43,44] Eczematous dermatitis is associated with an increase in both depression (HR = 1.16) and anxiety (HR = 1.17), and the former positively correlates with the severity of dermatitis.[43] A number of studies also describe declines in cognitive function in patients with eczematous dermatitis. For example, a study of 118 adult patients with atopic dermatitis showed that over 58% of patients had at least one or more symptoms of cognitive dysfunction in the prior 4 weeks.[45] A higher incidence of dementia was also found in a study of 1059 patients with atopic dermatitis compared to a cohort without atopic dermatitis (2.5% vs. 0.7%).[46] Moreover, the severity of cognitive dysfunction positively correlated with global atopic dermatitis severity.[45] Similarly, the prevalence of cognitive dysfunction such as memory impairment is higher in children with atopic dermatitis than those without atopic dermatitis (0.87% vs. 0.42%, $P < 0.001$).[47] For example, children with food allergies display a higher risk for memory impairment (8.70% vs. 6.56%, $P = 0.002$), while children with eczema have profound deficits in the domains of verbal comprehension and working memory compared with healthy controls.[48] Again, the more severe the atopic dermatitis, the higher HR for cognitive dysfunction is in children (HR = 2.07 for mild atopic dermatitis vs. 2.72 for severe atopic dermatitis).[49] Moreover, a history of atopy increases the risk for dementia by 16%, and the OR of eczema for Alzheimer's disease and dementia are 0.92 and 0.82, respectively. The onset of dementia in subjects with a history of atopy is earlier in males than in females.[50] When considered together, this evidence demonstrates that eczematous dermatitis can increase the risk of cognitive dysfunction.

Other inflammatory skin disorders

Evidence indicates that other inflammatory skin disorders are also associated with cognitive dysfunction. For instance, rosacea is common in subjects aged 45–60 years, with a rosacea prevalence of ≈5.5%.[51] Psychological disorders in rosacea patients include depression, anxiety and cognitive impairment.[52–55] HRs of dementia and Alzheimer's disease were 1.07 and 1.25, respectively, in patients with rosacea, with a higher HR in females than in males (1.28 vs. 1.16).[52] Moreover, a study on a small group of subjects showed that patients with prurigo nodularis displayed various degrees of cognitive impairment, ranging from MCI to Alzheimer's disease.[56] A higher incidence of dementia was observed in patients with vitiligo, an inflammatory skin condition with reduced stratum corneum hydration and delayed epidermal permeability barrier recovery,[57,58] than in normal controls (5.0 vs. 1.0 per 1000 person -years), with adjusted HR of 5.3.[59] However, a 10-year follow-up study showed that the rates of Alzheimer's disease were comparable between vitiligo and non-vitiligo subjects.[60] Thus, further studies are needed to assess the relationship between vitiligo and cognitive dysfunction.

Basis for the link between cutaneous inflammation and cognitive impairment

Cognitive impairment has long been considered as a natural phenomenon of ageing. However, a handful of evidence suggests a link between cognitive impairment (MCI, dementia and Alzheimer's disease) and inflammation. Studies showed that several cytokines participate in the pathogenesis of Alzheimer's disease-associated dementia. IL-1β can increase expression of inducible nitric oxide in astrocytes, consequently potentiating N-methyl-D-aspartate induced neurotoxicity, while TNF-α can increase production of amyloid-β, a key contributor to the development of Alzheimer's disease.[61,62] The pathogenic role of inflammation in dementia is also evidenced by co-localization of neuroinflammation and protein aggregation in frontotemporal dementia.[63]

Aged humans display elevated circulating levels of inflammatory cytokines, such as IL-6 and TNF-α, which are associated with increased risk of morbidity and mortality in the elderly,[64] as well as of vascular dementia and Alzheimer's disease.[65] Higher serum levels of IL-1β, IL-12 and TNF-α are associated with non-amnestic, multiple domain MCI, exhibiting impairments in multiple non-memory domains.[66] In Alzheimer's patients, serum levels of IL-6 and TNF-α positively correlate with the severity of cognitive dysfunction,[67] although one study showed that levels of some cytokines, such as IL-1β and IL-6, in cerebrospinal fluid negatively correlated with dementia severity scale.[68] Yet, the bulk of current evidence suggests critical role of inflammation in cognitive dysfunction.

The essential role of inflammation in cognitive dysfunction is also supported by several clinical observations. For example, use of non-steroidal anti-inflammatory drugs likely lowers the risk of cognitive dysfunction.[69–73] Likewise, glucocorticoids (potent immune suppressors) lowers the risk of dementia (HR = 0.81).[74] Similarly, administration of a TNF-α inhibitor reduces the risk of Alzheimer's disease with OR of 0.3 to 0.73.[75] Lee, et al. reported that treatments of an Alzheimer's patient with dapsone, another anti-inflammatory agent, reversed Alzheimer's disease to MCI.[76] In a murine model of Alzheimer's disease, intraperitoneal injections of an IL-1 receptor antibody for 6 months decreased pro-inflammatory cytokines and excessive microglial activity, accompanied by improvements in cognitive function.[77] Correspondingly, either knockout of the IL-1 receptor or administration of an IL-1 receptor antagonist accelerates memory recovery following hypoxia/reoxygenation in mice.[78]

However, several studies failed to demonstrate a benefit of non-steroidal anti-inflammatory drugs for cognitive impairment

in Alzheimer's disease,[79–81] possibly because some cognitive dysfunction in Alzheimer's disease is too severe; or that nonsteroidal anti-inflammatory drugs may not be potent enough to overcome abnormalities in the later stages of cognitive dysfunction. Studies also showed that anti-inflammatory agents that do not affect TNF levels fail to reduce the risk of Alzheimer's disease,[75] suggesting a critical role of TNF in this disease. Moreover, cognitive dysfunction can be caused by multiple pro-inflammatory cytokines. Inhibition of one cytokine may not suffice to mitigate cognitive decline, since other cytokines may still exert a pathological impact on the development of cognitive decline. Thus, the ideal anti-inflammatory candidates against cognitive decline should be those that can inhibit a wide spectrum of cytokines or reduce cytokine production at points of inflammation origin.

Ageing-associated epidermal dysfunction and inflammation

As humans get older, especially those over age of 65 years,[64] they generally display chronic low-grade inflammation, also termed 'inflammaging', even in the absence of an apparent inflammatory disorder. The causes of inflammaging have been widely speculated on and include cellular senescence, genetic susceptibility, microbiota, gut permeability and/or visceral obesity.[82] However, recent evidence suggests epidermal dysfunction can contribute to the elevated levels of pro-inflammatory cytokines in the circulation of the elderly.

Previous studies showed that disruption of the epidermal permeability barrier increases the production of pro-inflammatory cytokines and inflammatory infiltration in the skin.[83,84] Conversely, improvement in epidermal permeability barrier lowers expression levels of pro-inflammatory cytokines, such as IL-1α and TNF-α.[83–86] Moreover, expression levels of 11β-hydroxysteroid dehydrogenase type 1 are increased in the epidermis of aged skin compared to that of the young skin.[87] The increased 11β-hydroxysteroid dehydrogenase type 1 does not only cause epidermal permeability dysfunction[87] but also increases cytokine production in keratinocytes in response to stimuli.[88] In addition, stratum corneum hydration also regulates cutaneous inflammation. Low humidity increases epidermal IL-1α production[89] and dermal mast cell density,[90,91] while improvements in the epidermal permeability barrier and in stratum corneum hydration alleviate inflammatory symptoms in winter months.[92]

Stratum corneum pH can also influence cutaneous inflammation. Alkalinization of the stratum corneum activates serine proteases, inducing kallikrein 5 and protease-activated receptor 2, resulting in cutaneous inflammation. Conversely, acidification of the stratum corneum attenuates the development of cutaneous inflammation in both NC/Tnd mice and a murine model of hapten-induced atopic dermatitis.[93, 94]

Our recent work provides even more convincing evidence that epidermal dysfunction contributes to elevations in circulating levels of pro-inflammatory cytokines. In comparison to young mice, expression levels of pro-inflammatory cytokines are elevated in both the epidermis and the circulation of aged mice, while improvements in epidermal function with topical emollients lower cytokine levels in the epidermis and the circulation of aged mice and humans.[95,96] Correspondingly, a number of clinical observations show that improvements in epidermal function with a topical emollient can both attenuate and prevent the development of inflammatory skin disorders, such as atopic dermatitis and psoriasis,[97–101] which both display elevated circulating cytokine levels,[102–104] as well as a high incidence of cognitive impairment, as detailed above. Finally, a recent 3-year pilot clinical trial demonstrates that topical emollient eases the progression of cognitive impairment in aged humans.[105]

Perspectives

Aged individuals are predisposed to the development of cognitive dysfunction, which is likely linked to inflammaging. However, the origins of inflammation in the elderly remain obscure. Our recent studies suggest a possible pathogenic role for epidermal dysfunction in inflammaging, including the following observations: a) disruption of the epidermal permeability barrier increases expression levels of cytokines in both the skin and serum, without concurrent elevations of the same cytokines in the liver, accompanied by cutaneous inflammation in mice; b) disruption of epidermal permeability barrier in athymic mice, which lack T cells (a major source of cytokines), also results in increased cytokines in both the skin and serum; and c) improvements in epidermal function lower circulating levels of cytokines in both aged mice and humans.[95,96] In aged humans, epidermal functions, including epidermal permeability barrier homeostasis, stratum corneum pH and hydration, decline as early as age ≈50 years.[106] Defective epidermal function can increase the production of cutaneous cytokines, eventually resulting in an increase in circulating levels of cytokines, because of the vast size of the skin (≈15% of body weight). Consequently, sustained epidermal dysfunction can provoke significant elevations in circulating levels of pro-inflammatory cytokines. The increased inflammation in the circulation down-regulates expression levels of a tight junction protein (occludin 1), as well as vascular cell adhesion molecule 1 in the endothelial cells of the brain, leading to an increase in blood–brain permeability,[107] which is further associated with cognitive dysfunction in the elderly.[108–110] Thus, we hypothesize that age-associated cognitive decline is caused, at least in part, by sustained epidermal dysfunction, resulting in inflammaging, consequently leading to a disruption of the endothelial barrier and neural inflammation in the brain, eventually leading to the development of cognitive dysfunction (Fig. 1). Hence, improvements in epidermal function could inhibit inflammation at its origin (the skin) and could serve as a valuable approach in alleviating cognitive decline in the elderly. However, it is worth noting that not all skin care products are

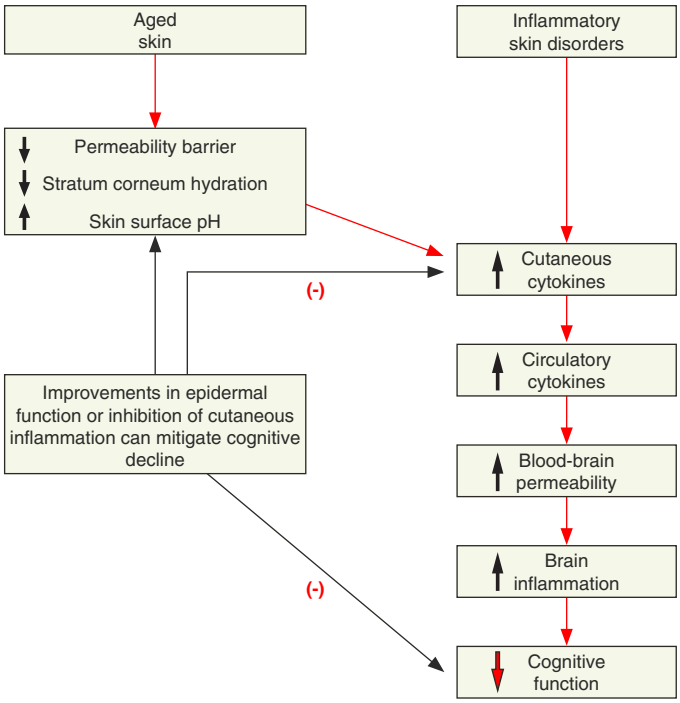

Figure 1 Schematic diagram showing the possible pathogenic role of epidermal dysfunction and inflammatory skin disorder in the development of cognitive impairment. Both epidermal dysfunction and inflammatory skin disorders can increase cytokine levels in the circulation. The increased circulating cytokines can increase blood–brain permeability, resulting in brain inflammation, consequently leading to the development of cognitive dysfunction. Thus, either improvement in epidermal function in the elderly or appropriate management of inflammatory skin disorders can possibly mitigate the decline in cognitive function.

beneficial. Depending on the ingredients (and the amount of each ingredient), some skin products can disrupt epidermal function.[111–113] Use of some of these products, especially for the long term, could in theory provoke deterioration in cognitive function.

In summary, both inflammatory skin disorders and epidermal dysfunction can increase circulating levels of pro-inflammatory cytokines, which can compromise blood–brain permeability barrier, resulting in inflammation in the brain, consequently leading to the development of cognitive dysfunction. While some forms of anti-inflammatory therapy can reduce the risk for cognitive dysfunction, improvements in epidermal function in the elderly could be an optimal approach to alleviate ageing-associated declines in cognitive function. Appropriate clinical trials are warranted to validate this hypothesis.

Authors' contributions

MMQ, conceptualization; MMQ and SW, literature search and draft; PEM and JSW, critical review and draft; TMM, critical review.

Data availability statement

Not applicable.

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