Increased risk of migraine in patients with psoriasis: A Danish nationwide cohort study

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Background: Psoriasis and migraine are common conditions with potential overlap of pathophysiological mechanisms. Both these diseases have been associated with increased cardiovascular risk but little is known about their interplay.

Objective: We sought to investigate the link between psoriasis, and the risk of new-onset migraine, in a nationwide cohort of the Danish population.

Methods: Data on all Danish citizens aged 18 years or older from January 1, 1997, to December 31, 2011, were linked at individual-level in nationwide registers. Incidence rates per 1000 person-years were calculated and crude and adjusted incidence rate ratios were estimated by Poisson regression models.

Results: The study comprised a total of 5,379,859 individuals, including 53,006 and 6831 patients with mild and severe psoriasis, respectively, and 6243 patients with psoriatic arthritis. Fully adjusted incidence rate ratios for migraine were 1.37 (95% confidence interval 1.30-1.45), 1.55 (95% confidence interval 1.29-1.86), and 1.92 (95% confidence interval 1.65-2.22) for mild psoriasis, severe psoriasis, and psoriatic arthritis, respectively. Stratification for sex revealed increased risk of migraine in both male and female patients.

Limitations: We were unable to distinguish between subtypes of migraine, eg, migraine with and without aura.

Conclusions: Psoriasis was associated with a disease severity-dependent increased risk of migraine independent of measured confounders. Further studies are warranted to determine the effects of antipsoriatic treatment on this association, and whether migraine modifies the psoriasis-associated risk of cardiovascular disease. (J Am Acad Dermatol 2015;73:829-35.)

Key words: epidemiology; headache; inflammation; migraine; psoriasis.

Psoriasis is a common T-helper-1 and -17 cell-mediated chronic inflammatory disease, affecting more than 2% to 3% of Europeans and up to 9% of individuals in some Nordic countries.[1] Increasing evidence suggest that psoriasis is associated with a variety of medical comorbidities, including ischemic heart disease, stroke, hypertension, dyslipidemia, type 2 diabetes mellitus, and obesity.[2,3] In addition to the direct medical costs as a result of treatment of the disease, patients with

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psoriasis often experience loss of work productivity and sick days, and frequently experience significant impairment of their physical, psychological, and social functioning.[3,4] Migraine is a chronic intermittent neurovascular pain disorder with increasing prevalence, currently affecting more than 12% of the Danish population.[5] Although the exact origin is not fully understood, migraine has been attributed to episodes of local sterile meningeal inflammation and hypersensitization of pain pathways, and proinflammatory mediators that contribute to the pathogenesis of psoriasis, such as tumor necrosis factor-alfa, can promote migraine, eg, by sensitization of meningeal nociceptors and peripheral nerve endings through activation of p38 mitogen-activated protein kinases, and increased dural mechanosensitivity.[6-8]

CAPSULE SUMMARY

- Psoriasis and migraine are each associated with cardiovascular disease.
- Psoriasis may be an independent risk factor for migraine.
- Increased focus on symptoms of migraine in patients with psoriasis may be warranted.

An association between migraine and cardiovascular disease has been established, and migraine with aura is associated with a 2-fold increased risk of ischemic stroke.[9] Indeed, like psoriasis and other inflammatory conditions, migraine appears to be associated with systemic endothelial dysfunction.[4,10-12] To our knowledge, only very few studies have described the association between psoriasis and migraine, and results are inconsistent.[3,13] We therefore investigated impact of psoriasis and psoriatic arthritis on the risk of new-onset migraine in a nationwide cohort of the Danish population.

METHODS

Study approval was obtained from the Danish Data Protection Agency (reference 2007-58-0015, internal reference GEH-2014-018, I-Suite 02736), and approval from an ethics committee is not required for register studies in Denmark. All Danish citizens have free, equal, and universal health care access, and individual-level linkage is possible among the nationwide administrative registries. Information on morbidity was obtained from the Danish National Patient Register, in which information on hospital admissions, procedures and diagnosis has been recorded since 1978. Data are recorded using *International Classification of Diseases, Revision 8* (*ICD-8*) codes from 1978 to 1994 and *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) codes from 1994 to present (*International Classification of Diseases, Ninth Revision* was never used in Denmark).[14] Hospital procedures (including hospital-based pharmacologic treatment, eg, with biological therapy) are coded in the Danish National Patient Register as treatment procedure (Sundhedsvæsenets Klassifikations System/Health Authority Classification System [SKS]) codes. Detailed and accurate information on all drugs dispensed from pharmacies are recorded in the Danish Registry of Medicinal Products Statistics according the international Anatomical Therapeutical Chemical (ATC) classification.[15]

The cohort comprised all Danish citizens aged 18 years or older from January 1, 1997, to December 31, 2011, and followed up until migration, death from any cause, or the occurrence of migraine, whichever came first. Patients with a history of psoriasis or migraine were excluded before study inclusion to accurately determine the temporal relationship between onset of psoriasis and risk of migraine, and ensure correct risk-time allocation. Patients with psoriasis were identified when they dispensed their second prescription of topical vitamin-D derivatives (ATC D05AX), which is the favored first-line treatment for psoriasis in Denmark, or by their first inpatient or outpatient consultation for psoriasis (*ICD-8* 696.10, 696.19, and *ICD-10* L40) or psoriatic arthritis (*ICD-8* 696.09 and *ICD-10* M070-M073), respectively. Patients were classified as having mild disease from onset of psoriasis and until they fulfilled the criteria for severe disease, if appropriate. Severe psoriasis was defined as receiving systemic treatment consistent with severe disease, ie, treatment with biological drugs, cyclosporine, hydroxyurea, psoralens, retinoids, or methotrexate, respectively. The primary end point was the first dispensed prescription of antimigraine drugs (ATC N02C) recorded in the Danish Registry of Medicinal Products Statistics.

Pharmacologic treatment, medical comorbidities, and socioeconomic status

Baseline comorbidity and pharmacologic treatment as described in Table I were defined up to 5 years, and 6 months before study inclusion, respectively, by use of ATC and *ICD* codes. Hypertension was defined by an algorithm, as previously described and validated with a positive predictive value of greater than 80%.[16] Diabetes was defined by either a hospital diagnosis or use of