ORIGINAL ARTICLE

Prevalence and risk of migraine in patients with rosacea: A population-based cohort study

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Background: Rosacea features increased neurovascular reactivity; migraine is a complex neurologic disorder characterized by recurrent episodes of headache associated with nausea and increased sensitivity to light and sound.

Objective: We evaluated the prevalence and risk of new-onset migraine in patients with rosacea.

Methods: All Danish individuals 18 years of age or older were linked in nationwide registers. Adjusted hazard ratios (HRs) were estimated by Cox regression.

Results: In the total cohort (n = 4,361,688), there were 49,475 patients with rosacea. Baseline prevalence of migraine was 7.3% and 12.1% in the reference population and in patients with rosacea, respectively. The fully adjusted HR of migraine was 1.31 (95% confidence interval 1.23-1.39) for patients with rosacea. Patients with phymatous rosacea (n = 594) had no increased risk of migraine (adjusted HR 0.45; 95% confidence interval 0.11-1.80), whereas patients with ocular rosacea (n = 6977) had a 69% increased risk (adjusted HR 1.69; 95% confidence interval 1.43-1.99). Notably, the risk was higher among patients age 50 years or older than in younger individuals, and the risk was only significant among women.

Limitations: We were unable to distinguish between migraine subtypes.

Conclusion: We found a significantly higher prevalence and risk of incident migraine especially in female patients with rosacea. These data add to the accumulating evidence for a link between rosacea and the central nervous system. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.08.055.)

Key words: epidemiology; headache; migraine; prevalence; risk; rosacea.

Rosacea is a chronic facial skin condition that predominately affects women[1,2] and light-skinned individuals.[3] The rosacea prevalence in Denmark is 5%,[4] and onset is typically after 30 years of age.[5] Rosacea was recently associated with several neurologic conditions including Parkinson disease,

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multiple sclerosis, and Alzheimer disease in Danish administrative health registries.[6-8] Moreover, neurogenic rosacea has been proposed as a clinical rosacea subtype, where patients may have a range of neurologic symptoms such as flushing, and paroxysmal burning and stinging pain from the skin.[9] More than 30 years ago, Tan and Cunliffe[10] suggested an association between rosacea and migraine; a complex neurologic disorder characterized by recurrent episodes of headache associated with nausea and increased sensitivity to light and sound.[11] A more recent study suggested an increased risk of rosacea in female patients with migraine, but not in men.[12] The relationship between migraine and rosacea remains unclear. We therefore examined the baseline prevalence and risk of new-onset migraine in patients with rosacea in a nationwide Danish cohort.

CAPSULE SUMMARY

- Few studies suggest co-occurrence of migraine and rosacea, but data are scarce and inconsistent.
- Prevalence and risk of new-onset migraine is significantly increased in rosacea patients.
- Increased focus on symptoms of migraine in patients with rosacea may be warranted.

METHODS

Data sources and study population

Study approval was obtained from the Danish Data Protection Agency (ref. 2007-58-0015, int. ref. GEH-2014-018, I-Suite 02736), and approval from an ethics committee is not required for register studies in Denmark. The study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[13]

We used nationwide Danish registries to collect data for this study. A tax-supported health care system gives all Danish citizens equal and universal access to health care services, including general practitioners and hospitals. All inpatient and outpatient hospital consultations are recorded in the Danish National Patient Register,[14] which used codes from the *International Classification of Diseases, Revision 8* until 1994, and from the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) thereafter. All pharmacy-dispensed medications are registered according to the international anatomical therapeutic chemical (ATC) classification in the Danish Registry of Medicinal Products Statistics.[15] Collection of proxy data on smoking history and alcohol abuse has been described elsewhere.[16,17] Tax-reported household income data are recorded by Statistics Denmark[18]; information on age, sex, and vital and migration status is available from the Civil Registration System.[19]

We identified all Danish adults (age ≥18 years) alive and residing in Denmark on January 1, 2008 (ie, study start). Subjects were followed up from study start until December 31, 2012; death; migration; or the occurrence of an end point, whichever came first. Patients were classified as having rosacea if they—before study start—received either a diagnosis of rosacea (*International Classification of Diseases, Revision 8* code 695.3 and *ICD-10* code L71) recorded in the Danish National Patient Register, or if they had dispensed at least 2 prescriptions of topical metronidazole (ATC code D06BX01), which is the preferred first-line treatment for rosacea and only very infrequently used for other skin conditions in Denmark. At least 2 prescriptions were required to ensure persistent medical therapy. Patients with rosacea were classified as having ocular rosacea if they had also claimed a prescription for hypromellose eye drops (ATC S01XA20), which is often used to treat xerophthalmia in rosacea, and we identified patients with rhinophyma by *ICD-10* code L71.1. The primary end point was the first occurrence of migraine, defined by initiation of treatment with antimigraine drugs (ATC code N02C and M01AG02), which also included nonsteroidal anti-inflammatory drugs used exclusively for migraine (ie, tolfenamic acid). The STROBE recommendations were followed.[20]

Statistical analysis

We described baseline characteristics with means and SD for continuous variables and frequencies and percentages for categorical variables. Baseline prevalence of migraine was determined as the percentage of individuals who had used antimigraine agents between January 1, 1995 (when the Danish Registry of Medicinal Products Statistics was established), and January 1, 2008 (study start date). SAS statistical software, Version 9.4 (SAS Institute Inc, Cary, NC), and STATA software, Version 13.0 (StataCorp, College Station, TX), were used to summarize incidence rates per 1000 person-years, and Cox regression models were performed to obtain hazard ratios (HRs) for the risk of incident migraine (for all individuals without migraine before study start). HRs for migraine were calculated as age- and