Ocular symptoms and rosacea: A population-based study

Short title: Rosacea and ocular symptoms

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Key Message: Eye symptoms are common in subjects with rosacea. However, ocular rosacea is poorly recognized.

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Abbreviations:

NFBC66: Northern Finland Birth Cohort 1966 study

ETR: erythematoteleangiectatic

Abstract

Background

The symptoms of ocular rosacea are often non-specific and there is no dependable diagnostic test for the disease, which may cause difficulties in diagnostics. The aim of this study was to examine the association between clinical findings of rosacea and self-reported ocular symptoms in a general population of middle-aged subjects.

Methods

A clinical whole-body examination by a dermatologist was performed for 1,932 subjects belonging to the Northern Finland Birth Cohort 1966 Study. The presence of ocular symptoms was self-reported. The difference between rosacea and ocular symptoms was tested. Logistic regression analysis was used to identify associations between rosacea and ocular symptoms.

Results

The prevalence of rosacea was 15.1% (n=292); in the subjects with rosacea, erythematoteleangiectatic rosacea was found in 83.2% (n=242), papulopustular in 15.4% (n=45), ocular in 0.03% (n=1), and phymatic in 0.1% (n=3). Ocular symptoms in rosacea subjects were common, with dryness (32.3%), tearing (29.4%), foreign-body sensation (21.8%) and photophobia (20.5%) being the most common ones. Foreign body sensation was reported significantly more often in those with rosacea compared to those without ($p<0.04$). In logistic regression analyses, after adjusting, the subjects with rosacea had a 1.5-fold increased risk for decreased visual acuity in the dark (1.48, 95% CI 1.01–2.14) compared to those without rosacea.

Conclusion

Eye symptoms are common in subjects with rosacea. All patients with rosacea should be asked about ocular symptoms and both skin and eyelids should be examined even if the cutaneous findings are mild.

Introduction

Rosacea is a chronic relapsing facial skin disease with a high prevalence in fair-skinned Europeans(1). Rosacea affects both sexes with a slight female predominance(1). Rosacea is characterized by variable presentation: persistent facial erythema, papules, pustules, telangiectasia, and recurrent flushing. According to signs and symptoms, rosacea is divided into four subtypes: erythematoteleangiectatic (ETR), papulopustular, phymatous, and ocular rosacea(1). Even though there are many studies concerning the overall prevalence of rosacea, studies reporting the exact prevalence of different subtypes of rosacea are scarce. A recent systemic review reported that ETR type affects 70–80% of rosacea patients, being the most common subtype(2). The prevalence of ocular rosacea is estimated to be clearly lower, 1–8%(2).

Although rosacea is considered primarily a disease of the skin, eye involvement in rosacea patients has been reported to be relatively common(3-5). An epidemiological study from the UK (n=60,042 cases with rosacea) found that 20% of the patients with rosacea had at least one ocular symptom(6). In another study performed in an ophthalmology clinic, the prevalence of ocular signs in rosacea patients was over 80%(3). The diagnosis of ocular rosacea is based on clinical observation including one or more eye symptoms (such as foreign-body sensation, photophobia, blurred vision, redness and dryness of the eyes) or clinical signs (teleangiectases of the conjunctiva and lid margin, lid and periocular erythema, interpalpebral conjunctival hyperemia, blepharitis, meibomian gland dysfunction)(7, 8). However, the symptoms of ocular rosacea are often non-specific and an exact diagnostic test for ocular rosacea is lacking(7). Due to difficulties in diagnosing ocular rosacea it has been speculated that the disease is easily missed and underdiagnosed (9).

Because ocular rosacea is poorly recognized, there is a high need to increase knowledge about its presence. The aim of this study was to evaluate the prevalence of ocular symptoms in rosacea subjects in the general population of the Northern Finland Birth Cohort 1966 Study (NFBC1966) during the cohort's 46-year follow-up study (n=1,932).

Methods

Study design and population

The study population is part of the Northern Finland Birth Cohort 1966 study (NFBC 1966), which is a longitudinal research program in the two northernmost provinces of Finland. Initially, NFBC 1966 included all 12,058 children whose expected time of delivery was in the year 1966 (covering 48% of Finnish territory and 13.2% of the population in 1966). The whole NFBC has been evaluated regularly since birth by means of health questionnaires and clinical examinations.(10)

Between April 2012 and May 2013, study cases belonging to NFBC1966 from the Oulu area and surroundings (at 100 km distance including rural areas) participated in the multidisciplinary 46-year follow-up -study (n=1,932) including clinical examinations and several health questionnaires. A dermatological whole-body examination was part of the follow-up study.(11)

Dermatological examination

The skin examination began with visual observation of the whole skin and was performed by a specialist in dermatology or an experienced resident. The clinical skin examination has been described in detail previously(11). All skin diseases, including rosacea, were documented. Diagnosis and classification of rosacea was based on evaluation by a dermatologist at the study visit and on internationally accepted criteria. According to its clinical presentation, rosacea was classified using the following four subtypes: erythematotelangiectatic rosacea (ETR), papulopustular rosacea, phymatous rosacea, and ocular rosacea(1).

Ocular symptoms

The presence of ocular symptoms was evaluated separately in connection with the 46-year follow-up study by using multidisciplinary health questionnaires. Questions regarding ocular symptoms

were designed by ophthalmologists to find out ocular symptoms in general. Since these questions were symptom based validation of questions was not performed. The study subjects answered the following questions: “Have you had the following symptoms during the past two weeks?” 1) Foreign-body sensation in your eyes? 2) Tearing? 3) Photophobia? 4) Tenderness/pain in your eyes? 5) Blurred vision? or 6) Decreased visual acuity in the dark?

Statistical analyses

The overall prevalence of rosacea and self-reported ocular symptoms was calculated. A Chi-square-test was used to test the difference between rosacea and ocular symptoms. Logistic regression analysis was used to identify associations between rosacea and ocular symptoms. Adjustment was made for the following confounding factors: sex, socioeconomic status and physical activity. Crude and adjusted odds ratios (OR) with 95% confidence intervals (CI) were reported as measures of association. Statistical analyses were performed using SAS software package (version 9.4, SAS Institute, Inc.) and p-values <0.05 were considered statistically significant.

Results

In connection with the 46-year follow-up study of the whole birth cohort, altogether 3,181 cases living in the city of Oulu and surroundings were asked to attend a clinical examination including total body skin examination. Of them, 1,932 (60.7%) participated in the study and they formed the skin study population[7]. The baseline characteristics of the study population are shown in Table 1.

According to the clinical examination by dermatologists, the prevalence of rosacea was 15.1% (n=292). The subtypes of rosacea were divided as follows: ETR 83.2% (n=242), papulopustular 15.4% (n=45), ocular 0.03% (n=1), and phymatic rosacea 0.1% (n=3). The most common ocular symptoms in rosacea subjects were dryness (32.3%), tearing (29.4%), foreign-body sensation (21.8%) and photophobia (20.5%) (Table 2). Study cases with rosacea reported significantly more foreign body sensation in their eyes compared to those without rosacea ($p<0.04$). Subjects with rosacea had also more dryness, tearing, photophobia, eye tenderness/pain and decreased visual acuity in the dark than those without rosacea, but the difference did not reach statistical significance. In total, subjects with rosacea had more simultaneous eye symptoms (>2 eye symptoms) (n=105, 36%) than those without rosacea (n=493, 30.2%), but the difference was not statistically significant ($p=0.09$)(data not shown). In an adjusted model (adjusted by sex, SES, physical activity) the subjects with rosacea had a 1.5-fold risk for decreased visual acuity in the dark than those without rosacea (1.48 95% CI 1.01– 2.14). (Table 2)

Discussion

In this population-based study, we found that ocular symptoms were very common, reported in about one third of the patients with rosacea. The most common symptoms were dryness, tearing, foreign-body sensation and photophobia. However, during clinical examination performed by dermatologists ocular rosacea was rarely diagnosed among rosacea subjects and was only reported in one study case.

The prevalence of ocular rosacea has been reported to be 1–8%(2). However, the real prevalence of ocular rosacea is probably underestimated because of challenging diagnostics(5). According to the UK-based General Practice Research Database study (n=60,042) in which rosacea patients were examined by general practitioners, typical eye symptoms/findings were hordeolum (7.6%), conjunctivitis (4.1%), eye irritation/pain (3.2%), watery or dry eye (3.6%), and blepharitis (2.1%)(6). In a smaller study (n=100) performed in a dermatology clinic in Greece, one third of the rosacea patients had ophthalmologic findings, burning sensation, tearing, conjunctivitis and blepharitis being the most common of them(12). In the present study, up to 32% of the subjects reported eye symptoms, which is in line with previous findings (3, 6, 7, 12). Nevertheless, most of the previous studies of ocular rosacea have been conducted in ophthalmology clinics (4, 7, 13, 14) even though the disease should be discussed more from the dermatology perspective as well(9).

In the present study, ocular rosacea was poorly diagnosed by dermatologists: while every third subjects reported eye symptoms only 0.3% were diagnosed as having ocular rosacea. There are many speculative explanations why ocular rosacea is easily missed. In general, it is possible that patients with rosacea do not mention eye symptoms to the doctor, at least if they are not asked. Patients may also overlook the relationship between the ocular symptoms and their rosacea(9). Furthermore, according to a previous study, ocular symptoms have been quite poorly recognized by dermatologists, especially when compared to ophthalmologists(3). For dermatologists, it can be

difficult to distinguish ocular symptoms of rosacea from other eye disorders because no explicit diagnostic test for ocular rosacea is available and because the symptoms are often non-specific(3). In addition, it has been claimed that dermatologists are not accustomed to perform an ophthalmological evaluation even when patients with rosacea complain about vision problems(3). Furthermore, previous studies have reported that ocular symptoms do not correlate with the disease severity in the skin (14, 15)and thus, eye symptoms can be easily ignored in those with mild skin rosacea. In turn, the diagnosis of ocular rosacea may also be very challenging for ophthalmologists if the ocular signs are subtle: differential diagnostics from other ocular diseases with similar findings such as dry eyes may be difficult. In particular, if the ophthalmologist is unaware of the presence of cutaneous rosacea, ocular inflammation may be missclassified as some other ocular disease(4). Ocular signs and symptoms can also sometimes precede cutaneous ones(3).

Early diagnosis of ocular rosacea is important and enables accurate treatment of the disease and therefore the relief of symptoms. Eye involvement in rosacea is known to cause varying eye symptoms and remarkable discomfort, and in its most extreme state, the ocular disease may lead to sight-threatening complications(7). Even though severe endpoints such as recurrent erosion of the ocular surface, ulceration, and corneal perforation are considered rare in rosacea patients(6), also high prevalence of corneal manifestations has been reported (33%)(3-5).

The etiology of rosacea remains partly unclear(16). However, the inflammation is the major part of the pathophysiology(16). In ocular rosacea, the inflammation has been documented to be present in meibomian glands resembling the sebaceous glands that are inflamed in cutaneous rosacea(12). Dysfunction of the meibomian glands leads to abnormal lipid composition of the tear film and further to dry eye(12, 17). Consequently, dryness of the eye and recurrent chalazia often provide the first clue of ocular rosacea(12).

The main strength of the present study was the wide general population. Rosacea was diagnosed and classified by experienced dermatologists with optimal ability to differentiate rosacea from other

skin conditions. It is also noteworthy that due to the birth cohort's study design our study subjects were not asked to commit to this study because of their ocular symptoms or rosacea, which likely made for a more objective evaluation as ocular symptoms were enquired separately. The participation rate of the study was satisfactory (60.9%) and highly comparable with the participation rates in other cross-sectional European health examination surveys (18, 19). As a limitation, we admit that not all study cases invited chose to participate. In the 46-year follow-up study, participants were more often employed and from higher social class, more likely to be married and with children compared to non-participants(19). As another limitation, it would have been optimal to have an ophthalmologist's evaluation of all the study cases to verify more exactly the diagnosis of ocular rosacea that was now only found in one study subject.

In conclusion, eye symptoms seem to be common in subjects with rosacea, but ocular rosacea is easily missed by dermatologists. Ocular rosacea may cause varying degrees of ocular morbidity, increase emotional stress and lower the quality of life(7, 20). The need for early diagnosis of ocular involvement is crucial to optimize accurate management and prevent severe manifestations including vision loss. Based on our findings, we recommend that all patients with rosacea should be asked about ocular symptoms even in the case of mild cutaneous findings. Examination of rosacea patients should include the inspection of the eyes including inner eyelids. More collaboration between dermatologists and ophthalmologists is needed and severe cases of ocular rosacea should always be referred to an ophthalmologist.

Statements

Ethical aspects

The Ethical Committee of the Northern Ostrobothnia Hospital District approved the study (§94/2011), which was performed according to the principles of the Helsinki Declaration of 1983. The participants took part on a voluntary basis and signed an informed consent. The data were handled on group level only, personal information being replaced by identification codes resulting in complete anonymity.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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The study had no sponsors.

Author Contributions

SPS, LH, KT and JJ were involved in the study conception and design. SPS and LH provided study materials and collated data. All authors were involved in analysis and interpretation of the data. HV and JJ provided statistical expertise. SPS drafted the manuscript; LH and KT revised it critically for important intellectual content; all authors approved the final version. SPS and LH are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data sharing: The data that support the findings of this study are available from the Northern Finland Birth Cohort 1966 Study. Restrictions apply to the availability of these data, which were used under license for this study. Data are available at http://www.oulu.fi/nfbc/node/44315 with the permission of the Northern Finland Birth Cohort.

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Table 1 Baseline characteristics.

	No rosacea* N=1633 N (%)	Rosacea* N=292 N (%)	p-value#
Gender			<0.001
Male	799 (48.9)	94 (32.2)	
Female	834 (51.1)	198 (67.8)	
Rosacea subtypes			
Ertythematotelangiectatic		242 (82.3)	
Papulopustular		45 (15.4)	
Phymatic		3 (0.1)	
Ocular		1 (0.03)	
Education			0.147
Basic	45 (2.76)	8 (2.74)	
Secondary	942 (57.7)	186 (63.7)	
Tertiary	646 (39.6)	98 (33.6)	
Physical activity			0.010
Inactive	320 (20.4)	73 (25.6)	
Lightly active	598 (38.0)	123 (43.2)	
Active	601 (38.2)	81 (28.4)	
Very active	53 (3.37)	8 (2.81)	

*There is some missing data because all subjects did not answer the questionnaire or have denied the use of their data afterwards

#Statistical analyses were performed by Chi-Square test

Table 2 The association between rosacea and ocular symptoms

	No rosacea* N= 1633 N(%)	Rosacea* N=292 N(%)	Crude OR		p-value	Adjusted OR
Foreign-body sensation					0.039	
No	1318 (83.5%)	223 (78.2%)	Ref.	Ref.		
Yes	261 (16.5%)	62 (21.8%)	1.41 (1.02-1.91)	0.036		1.20 (0.86-1.64)
Tearing					0.873	
No	1128 (71.3%)	202 (70.6%				
Yes	454 (28.7%)	84 (29.4%)	1.03 (0.78-1.36)	0.813		0.90 (0.68- 1.19)
Photophobia					0.474	
No	1301 (82.3%)	225 (79.5%)				
Yes	279 (17.7%)	58 (20.5%)	1.20 (0.87-1.64)	0.257		0.99 (0.69- 1.40)
Tenderness/pain					1.000	
No	148 9(94.6%)	266(93.3%)				
Yes	85 (5.40%)	19 (6.67%)	1.26 (0.73-2.07)	0.392		1.08 (0.59- 1.84)
Blurred vision					1.000	
No	1413 (89.4%)	257 (89.5%)				
Yes	168 (10.6%)	30 (10.5%)	0.99 (0.64-1.47)	0.945		0.86 (0.54- 1.33)
Decreased visual in dark					0.067	
No	1378 (88.6%)	240 (84.5%)				
Yes	178 (11.4%)	44 (15.5%)	1.42 (0.98-2.02)	0.060		**1.48 (1.01- 2.14)**
Dryness					0.134	
No	1142 (72.3%)	193 (67.7%)				
Yes	438 (27.7%)	92 (32.3%)	1.24 (0.94-1.63)	0.119		1.01 (0.76- 1.34)

*There is some missing data because all subjects did not answer the questionnaire or have denied the use of their data afterwards