







Clinical trial

# Clinical clues to identify patients with ocular rosacea – a Germany-wide epidemiologic analysis

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## Introduction

Rosacea is a chronic inflammatory disease of the facial skin with a complex etiology and a severe impact on life quality of affected individuals.<sup>1–3</sup> The disease may involve the eyes yet escape diagnosis for a long time, resulting in inappropriate treatment.<sup>4,5</sup> Many hypotheses have been proposed regarding the complex association of ocular and cutaneous lesions, but all are speculative.

Facial rosacea is usually recognized by transient erythema of the skin – a so-called flush – often triggered by physio- and psychological stress. Additionally, persistent erythema, papules,

## Abstract

**Background and objectives** Ocular rosacea is a special manifestation of rosacea with unknown etiology. Eye involvement in rosacea patients is surprisingly common; however, it is often underdiagnosed, resulting in inappropriate treatment. We aimed to provide an updated epidemiologic perspective on ocular rosacea in Germany to improve patient care.

**Patients and methods** Data of 777 rosacea patients were assessed using a detailed online questionnaire regarding ocular and skin symptoms, previous dermatological and ophthalmological consults, presence of type 1 hypersensitivities, and Demodex testing. All data were statistically analyzed.

**Results** Most patients reported ocular symptoms (399/777, 51.4%), including red eyes (179/399, 44.9%), itching (187/399, 46.9%), sty or chalazion (309/399, 77.4%), and dryness (108/399, 27.1%). Ocular rosacea was confirmed in 149/309 cases who consulted an ophthalmologist (48.2%). A total of 159/399 (39.8%) had no pre-existing allergies. Eye involvement was significantly associated with the presence of skin symptoms ( $P < 0.05$ ), impacting patients' general well-being and overall treatment satisfaction. About half of Demodex-positive patients (21/45, 46.7%) showed ocular symptoms.

**Conclusions** Eye involvement in rosacea patients was common, often presenting with unspecific symptoms.

and pustules as well as secondary clinical findings such as burning, itching, a feeling of warmth, and pain can occur.

Ocular manifestations of rosacea have received more attention throughout recent years but are still an underrecognized multidisciplinary challenge for dermatologists, ophthalmologists, and allergists.<sup>6</sup> Ophthalmic rosacea can affect the eyelids (blepharitis, chalazion, and meibomianitis), the conjunctiva (conjunctivitis and keratoconjunctivitis sicca), the iris (iritis and iridocyclitis), and the cornea (corneal thinning, ulceration, and superficial keratitis).<sup>4</sup> The severity of the disease is classified into mild, moderate, and severe.<sup>7</sup>

Patients suffering from ocular rosacea usually report immense subjective impairment with burning, tearing of eyes, and photophobia. The pathophysiology is not yet fully understood but likely imposes a multifactorial origin, including genetic predisposition, dysregulation of the innate and adapted immune system, neuroinflammatory mechanisms, ultraviolet irradiation, local inflammatory responses, dysregulation of the vascular and lymphatic systems, and skin-related microorganisms. Especially inflammation and secondary dysfunction of the Meibomian glands as well as the presence of *Demodex* mites seem to be strongly associated with ocular rosacea.<sup>8–10</sup>

At present, data on ocular rosacea is scarce, contributing to the low level of awareness among physicians and patients. To close this gap, an epidemiological assessment of ocular rosacea in Germany focusing on the clinical characteristics of patients was performed. This might serve as a basis to improve patient care and aid future research.

## Patients and methods

### Data collection

A detailed online questionnaire was designed using SoSci Survey software (Leiner, 2016, Version 3.1.06) developed by the Institute of Communication Science and Media Research at the Ludwig-Maximilian-University (LMU), Munich, Germany. Data of 777 rosacea patients from across Germany were anonymously assessed regarding their demographic data, rosacea-associated primary and secondary cutaneous symptoms, ocular symptoms, frequency and satisfaction with ophthalmologic and dermatologic consults, history of allergies, *Demodex* testing, and quality of life aspects.

### Ethics committee

The Ethics Committee of LMU Munich reviewed and approved the ethical safety of the study (UE No. 707-16).

### Statistical evaluation

All data were statistically analyzed with SPSS (Statistics® Version 26 IBM Inc., Armonk, NY, USA). The corresponding images were generated using BioRender.com (2020) and Inkscape 0.92. Significance testing (significance level  $\alpha = 0.05$ ) was performed using the Pearson  $\chi^2$  test and Fisher's exact test. The strength of each effect was determined by Cramer's V test.

## Results

### Patient population

The study population included 777 rosacea patients (637 females [82.0%] and 140 males [18.0%]) with a mean age of  $54 \pm 11.2$  years, distributed among Germany (Table 1).

### Ocular symptoms

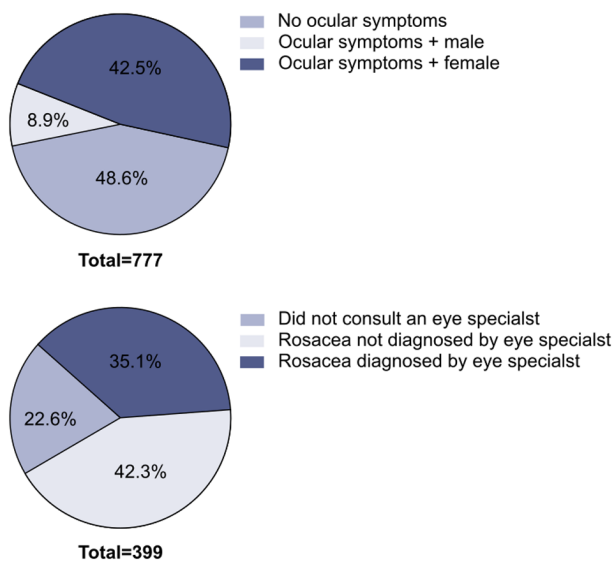
Half of patients reported ocular symptoms ( $n = 399/777$ ; 51.4%; 69 males, 330 females) with 77.4% previously consulting an

ophthalmologist ( $n = 309/399$ ). A subset of patients who consulted an ophthalmologist were diagnosed with ocular rosacea ( $n = 140/309$ ; 45.3%), Figure 1.

Most patients with ocular symptoms were between 60 and 80 years old ( $n = 121/215$ ; 56.3%). No patients over 80 years had ocular symptoms. The occurrence of initial symptoms is shown in Table 2.

**Table 1** Demographics of the patients included in this study

Age	Female	Male	<i>n</i>
21–30	5	1	6
31–40	67	12	79
41–50	190	23	213
51–60	227	33	260
61–70	109	45	154
71–80	37	24	61
81–90	2	2	4
>90	0	0	0
Total	637	140	777



**Figure 1** Pie charts of ocular symptoms (left) and their successful diagnosis by an ophthalmologist (right). Percentages derived from the total number indicated below each pie chart.

**Table 2** Timepoint when initial symptoms appeared

Timepoint of initial symptoms	<i>n</i>
Within the last year	7
1–2 years ago	13
2–4 years ago	52
4–10 years ago	130
Over 10 years ago	197
Total	399

*N* = number of individuals.

**Table 3** Complaints of patients with ocular symptoms

Type of eye complaints	Yes/No	n	%
Dry eyes	Yes	119	74.8
	No	40	25.2
Red eyes	Yes	83	52.2
	No	76	47.8
Itchy eyes	Yes	73	45.9
	No	86	54.1
Sty/Chalazion	Yes	36	22.6
	No	123	77.4
Other	Yes	25	15.7
	No	134	84.3
Total		399	399

N = number of individuals.

The main symptoms were dryness of eyes (74.8%), redness of eyes (52.2%), itchy sensation (45.9%), sty/chalazion (22.6%), or other complaints (15.7%) (Table 3).

### Type I hypersensitivities

Half of the patient cohort ( $n = 393/777$ ; 50.6%) had a type I hypersensitivity. More than half of these also suffered from ocular symptoms (225/393; 57.3%), the majority all year round (189/225; 84.0% summer + perennial), and few patients only perennial (36/225; 16.0%).

The most frequently reported allergy was against grass/pollen (215/777; 27.7%). Most patients with ocular symptoms (with and without allergy) presented perennial ocular symptoms (348/399; 87.2%), 39.8% of these without having an allergy (159/399). Most patients without an allergy also consulted an ophthalmologist (126/159; 79.2%). In half of these, rosacea was considered the main diagnosis (63/126; 50.0%).

Half of the patients with ocular symptoms had perennial ocular symptoms and no allergy against house dust mites/animal hair/mildew/other (197/399; 49.4%). From this group, 76.6% of patients consulted an ophthalmologist (151/197) who considered a rosacea diagnosis in half of them (73/151; 48.3%). Thirty-eight patients had perennial ocular symptoms with an allergy but no allergy against house dust mites/animal hair/mildew/other. Also in this group, most of the participants consulted an ophthalmologist (25/38, 65.8%). In 40.0% of these patients, the doctor considered a rosacea diagnosis (10/25).

Rosacea diagnosis was slightly higher if patients presented without an allergy (diagnosed in 50%) compared to patients with an allergy (diagnosed in 40%). Further analysis on whether symptoms appeared perennial or seasonal and their correlation with allergies and ophthalmology consults are presented in Figure 2.

### Association of eye problems with cutaneous manifestation and quality of life

Patients with self-reported ocular symptoms presented with significantly more cutaneous rosacea findings (Chi-square testing,

$P < 0.05$ ), felt less informed about their disease ( $P < 0.01$ ), were less satisfied with their dermatologic treatment ( $P < 0.01$ ), had a higher psychological distress ( $P < 0.05$ ), experienced more flushing ( $P < 0.01$ ), and had a lower quality of life ( $P < 0.001$ ) compared to patients without ocular symptoms. Additionally, a significant correlation between eye problems and skin type was observed, with dry to mixed skin conditions reporting more frequent ocular symptoms than normal and oily types (Table 4, chi-square testing,  $P < 0.01$ ).

### Demodex testing

A face swab for the detection of Demodex mite was performed in 11.1% of cases (86/777, 64 females and 22 males), all of them clinically presenting with both papules and pustules; 45/86 tested positive for Demodex mites (Demodex<sup>+</sup>: 52.3%; 30 females, 15 males). In addition, there was a highly significant association between Demodex testing and telangiectasia ( $P < 0.01$ ). In contrast, there was no significant difference regarding skin types ( $P = 0.228$ ), presence of secondary features ( $P = 0.585$ ), the appearance of pustules ( $P = 0.133$ ), nor the age of the patient ( $P = 0.825$ ).

### Demodex detection and correlation with ocular rosacea

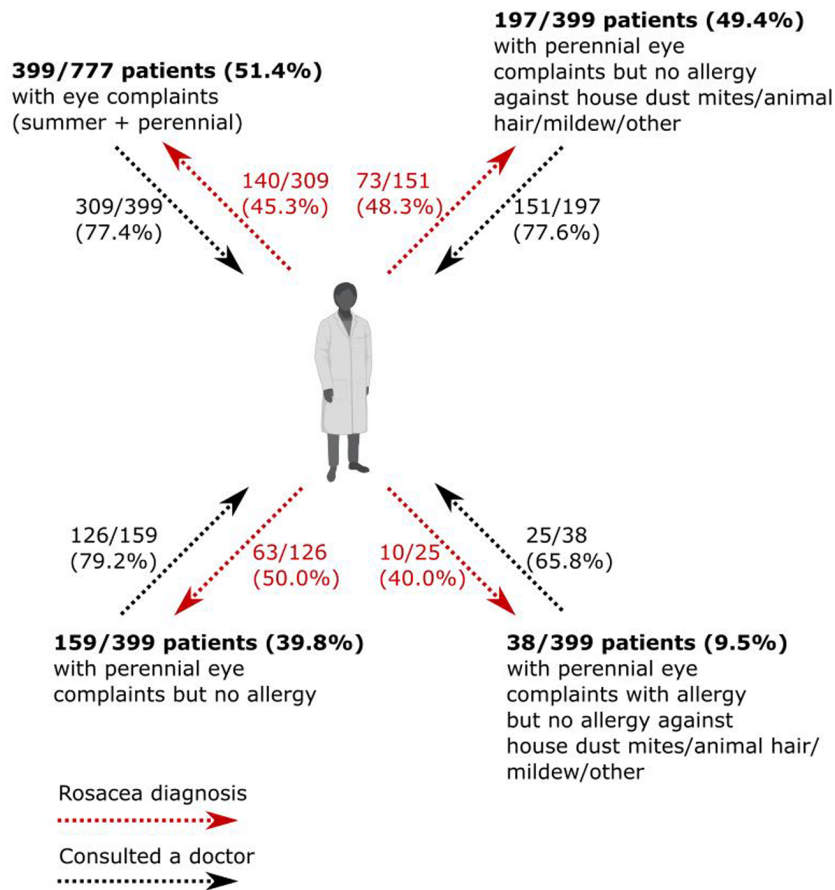
Forty of eighty-six patients who were tested for Demodex reported ocular symptoms (46.5%), out of which 21/40 tested positive (52.5%; Demodex<sup>+</sup>). There was a trend toward a significant association between the presence of telangiectasia and Demodex<sup>+</sup> ( $P = 0.097$ ). A higher percentage of men were Demodex<sup>+</sup> (68.2% vs. 46.9% women), also showing a trend toward significance ( $P = 0.08$ ). There was no difference between age and Demodex<sup>+</sup> ( $P = 0.533$ ). Moreover, there was no correlation between Demodex<sup>+</sup> and appearance of pustules ( $P = 0.386$ ), initial symptoms ( $P = 0.978$ ), or time since diagnosis ( $P = 0.313$ ).

Ophthalmologists diagnosed rosacea more likely in Demodex-tested patients (18/29; 62.1% vs. 122/280; 43.6%). Previous confirmation of Demodex positivity did not influence ophthalmologic diagnosis (9/16; 56.3% vs. 9/13; 69.2%) (Table 5).

### Discussion

To the best of our knowledge, this is the largest epidemiologic study on ocular rosacea in Germany which might have a substantial impact on the awareness of treating physicians and the care of suffering individuals. Since the prevalence of ocular rosacea remains unknown, studies on large patient cohorts are required.

Indeed, the present study revealed that half of the rosacea patients suffered from ocular symptoms (399/777, 51.4%), with 77.4% previously consulting an ophthalmologist (309/399). The diagnosis of ocular rosacea was confirmed in 45.3% of cases (149/309).



**Figure 2** Ophthalmology consults and rosacea diagnosis in patient groups with ocular symptoms and different allergy status. Black arrows show the percentage of patients that consulted a doctor with their complaints, and red arrows show the frequency of rosacea diagnosis by the doctor. Created with BioRender.com

**Table 4** Correlation between eye problems and skin appearance

		Normal skin	Greasy skin	Dry skin	Mixed skin	Total
Eye complaints	n	47	19	116	217	399
	%	11.8	4.8	29.1	54.4	100
No eye complaints	n	80	25	98	175	378
	%	21.2	6.6	25.9	46.3	100
Total	n	127	44	214	392	777
	%	16.3	5.7	27.5	50.5	100

Mixed skin = areas with either normal, greasy, or dry skin.

Since ocular symptoms are often unspecific as seen in our cohort and not intuitively linked to rosacea, we propose that all rosacea patients should be questioned regarding ocular symptoms and referred to an ophthalmologist for a thorough examination, e.g. including a Schirmer test assessing tear deficiency.<sup>11</sup> Erdur et al. identified that tear osmolarity was

**Table 5** Correlation between Demodex detection and rosacea diagnosis

		Rosacea diagnosis	
		Yes	No
Demodex	Tested	18	11
	Not tested	122	158
Demodex	Positive	9	7
	Negative	9	4

higher in patients with ocular rosacea compared to rosacea without ocular involvement and healthy controls.<sup>12</sup> The present study showed that “dryness of eyes” was a recurrent symptom in rosacea patients with ocular manifestation. For such patients, intense pulsed light (IPL) therapy showed excellent results in recent studies.<sup>13,14</sup> In addition, artificial tears with omega-3 fatty acids have been used to counteract ocular dryness.<sup>15-17</sup>

Palamar et al. used meibography to demonstrate that ocular rosacea patients had a significant reduction of meibomian gland

function associated with dry eyes.<sup>18</sup> The inadequate function of the Meibomian gland leads to an abnormal lipid composition of the tear film, which then causes thickened secretions, lower tear break-up time (TBUT), and consequently dryness of the ocular surface.

One of the most frequently discussed triggers of ocular rosacea remains Demodex mites.<sup>19–22</sup> However, the present study showed no statistically significant association between Demodex prevalence and ocular rosacea manifestation. Taking a deeper look into rosacea skin texture revealed an up to six times higher RNA level of Demodex mites on the skin surface.<sup>23</sup> These mites live in the Meibomian glands from which they can be isolated and are generally considered commensals; nevertheless, they can modulate the host's immune system, which includes disturbance of toll-like-receptor signaling.<sup>19,20,22</sup> Interestingly, the antimicrobial peptide (cathelicidin LL-37), synthesized by epithelial cells and infiltrating immune cells, requires proteolytic cleavage for its antimicrobial activity.<sup>24</sup> Rosacea skin is marked by enhanced protease activity but also antimicrobial effective LL-37 levels.<sup>24–26</sup> Enhanced protease activity and higher LL-37 levels may explain how Demodex mites trigger the immune system ultimately leading to typical rosacea symptoms, including ocular manifestation.

Even though it is well known that Demodex infection can be a challenging factor in rosacea,<sup>27</sup> patients with ocular rosacea symptoms are not frequently tested for Demodex prevalence, as seen in our cohort (86/777 participants; 11.1%). Also, since test results are very dependent on the investigator and can be false negative,<sup>28</sup> Demodex testing alone may not be sufficient to unravel the impact of these facultative pathogenic commensals. One study showed that Demodex infection can also be dosage dependent,<sup>29</sup> indicating that Demodex mites need to reach a certain density threshold before the immune system is alarmed.<sup>21</sup> Hence, Demodex-induced symptoms might be very dependent on individual immunologic mechanisms, and future investigations may identify a subgroup of patients that harbors genetic/immune alterations that make them particularly sensitive to Demodex mite infection, as done for papulopustular rosacea and rosacea-like demodicosis.<sup>30</sup>

As seen in different studies half of the patient cohort presented with type I hypersensitivity. Of note, 39.8% of patients that do not have an allergy presented ocular symptoms all year round. This clearly points out that Rosacea symptoms are not necessarily a consequence of allergic stimuli. The high number of patients with an allergy that consulted the ophthalmologist (76.6%) shows that those participants might be more sensitized to their symptoms and were motivated to go to the doctor despite knowing about their allergy. Indeed, in almost half of these participants, the ophthalmologist considered a rosacea diagnosis. We therefore recommend persons that know about their allergy but develop new symptoms to visit an ophthalmologist.

The results also show a significantly higher disease burden in patients with self-reported ocular symptoms. This might, on one hand, result from the fact that there is not only skin discomfort

but also impaired vision leading to even more limitations in daily life. On the other hand, most patients report their doctors to focus on the cutaneous or ocular rosacea, depending on the doctor's specialty, but rarely both (authors' observations).

In addition, the skin type influences the ocular involvement, with patients having a dry or mixed (mostly interpreted as generally dry skin with seborrhoea in the T-zone – forehead, nose, and chin) skin type report to have more ocular problems. As other authors report, dry skin is significantly linked to dry eyes,<sup>31</sup> which may result from sebstasis affecting not only the epidermal barrier but also the tear film composition. Additionally, patients' Demodex colonization might depend on sebum consistency, where seborrhoea and oily skin hinders mites to colonize the pilosebaceous unit (authors' observation, in publication).

The strength of the studies lies within the large patient cohort, including a wide range in patients' age and assessing many factors which might contribute to ocular rosacea. Future studies are needed to further elaborate on the mechanisms of rosacea development and the mode of action of mentioned risk factors. Here, immunological studies will be key to elucidate the exact triggers of this chronic inflammatory disease.

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