Intrafamilial Transmission of Rosacea Spanning Six Generations: A Retrospective Observational Study

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J Clin Aesthet Dermatol. 2022;15(2):35–39.

Rosacea hereditary predisposition has been hypothesized based on family inheritance and twin concordance. Currently, information concerning intrafamilial rosacea transmission are still limited to few generations. The aim of our study was to assess data on rosacea intrafamilial transmission spanning six generations. One-hundred and thirty patients affected by rosacea who visited our acne and rosacea clinic from June 2018 to June 2019 were consecutively enrolled in this study. During clinical evaluation, an accurate anamnesis, including familiarity across six generations, which included vertical, horizontal, and combined transmission, was performed. Affected relatives were clinically evaluated, and in those in which clinical consultation was not feasible, clinical photos were obtained. The results showed that 64 of 130 patients (49.2%) were positive for at least a family member with rosacea. In addition, 90 affected relatives (69.2%) were identified by extending the familial investigation to the whole kindred, finding a percentage of familiarity (69.2%) higher than that reported in the literature (30-50%) with a 1:1.4. ratio of patients positive for familiarity/affected relative. Our study contributes to add knowledge about intrafamilial involvement in rosacea. Extending the search to all potential affected parents and offspring of rosacea patients can promote early diagnosis along with the adoption of correct therapeutic interventions and educational programs to prevent the exposure to triggering or exacerbating factors.
KEY WORDS: Rosacea, familiarity, intrafamilial, transmission

Rosacea is a common, chronic, relapsing inflammatory skin disease of the face with a negative impact on quality of life.[1,2] It encompasses a wide clinical spectrum (e.g., transient/persistent erythema, telangiectasia, papules/pustules, edema, phymatous changes and ocular symptoms), and uncomfortable symptoms (e.g., flushing, pain, burning, dryness).[3] Typically, rosacea can be divided into four subtypes: erythematotelangiectatic (ET), papulopustular (PP), phyma, and ocular.[4] In clinical practice different combinations of some subtype/cutaneous symptoms (phenotypes) are often seen and a classification based on phenotypes has recently been proposed.[5-7] Data from epidemiologic studies on the incidence and prevalence of rosacea are estimated to be 1.65 per 1,000 person-years (1.92 female/1.34 male) and 5 to 46 percent of the adult population.[8,9] Rosacea usually occurs after the third decade of life; however, pediatric forms can be observed.[8] Recent studies indicate that rosacea can affect not only fair-skinned people (Fitzpatrick Skin Types I–II), but all skin phototypes.[10]

The physiopathology of rosacea is multifactorial and still unclear; several factors, such as genetic susceptibility, positive family history, immune/neurovascular dysregulation, vascular and neuronal dysfunction, and local proliferation of skin commensals, are involved.[11–14]

In particular, the genetic component is not well understood but a hereditary predisposition has been hypothesized due to a higher prevalence among Northern Europeans (particularly the Celtic population),[15] family inheritance,[16-19] twin concordance,[20,21] and associations with autoimmune disorders.[22-24]

In addition, up to one-third of patients with rosacea have a marked increased positive family history.[17] However, information regarding defined genetic bases or inheritance are lacking, whereas epidemiologic data concerning intrafamilial rosacea transmission are limited to few generations. A further limit of the available studies is also the lack of clinical information, with results obtained by self-administered questionnaires or online surveys only.[18, 24]

The aim of our study was to assess data on rosacea intrafamilial transmission spanning six generations.

METHODS

Study population. All naïve patients affected by rosacea seen at our acne and rosacea Clinic from June 2018 to June 2019 were consecutively enrolled in this study. During the visit, demographic and lifestyle characteristics, anamnestic and clinical data (according to ROSCO

FUNDING: No additional funding was provided for this article.
DISCLOSURES: The authors declare they have no conflict of interest.
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TABLE 1. Demographic, anamnestic, clinical, and lifestyle data of patients with rosacea (n=130), of probands* (n=64) and affected relatives (n=90)

DEMOGRPAHICS AND DISEASE CHARACTERISTICS	PATIENTS WITH ROSACEA (N=130)	PROBANDS (N=64)	RELATIVES WITH ROSACEA (N=90)
Sex (n)	F93/M37	F43/M21	F56/M34
Age (mean, yrs)	49.3±16.5	49.6±18.6	52.3±18.5
Skin phototype, n (F/M)			
Phototype I	14 (F9/M5)	7 (F4/M3)	13(F8/M5)
Phototype II	69 (F56/M13)	33 (F26/M7)	45 (F31/M14)
Phototype III	40 (F27/M13)	20 (F12/M8)	25 (F14/M11)
Phototype IV	7 (F1/M6)	4 (F1/M3)	7 (F3/M4)
Body Mass Index, n (F/M)			
Normal weight	85 (F57/M28)	45 (F29/M16)	57 (F35/M22)
Underweight	7 (F6/M1)	3 (F2/M1)	6 (F5/M1)
Overweight	38 (F30/M8)	16 (F12/M4)	27 (F16/M11)
Smokers	32 (F14/M18)	13 (F5/M8)	--
Drinkers	9 (F4/M5)	8 (F3/M5)	12 (F3/M9)
Positive family history	64 (F43/M21)	64 (F43/M21)	90 (F56/M34)
Disease duration	9.7±11	9.8±10.6	12.3±13.4
Phenotype of rosacea, n (F/M)			
Centrofacial erythema +/- telangiectasias	49 (F36/M13)	26 (F18/M8)	45 (F28/M17)
Centrofacial erythema +/- telangiectasias + papules and pustules	67 (F55/M12)	28 (F23/M5)	32 (F26/M6)
Phymatous changes	5 (M5)	1 (M1)	3 (M3)
Ocular manifestations	9 (F2/M7)	9 (F2/M7)	10 (F2/M8)
Disease Severity, n (F/M)			
Mild	45 (F37/M8)	21 (F18//M3)	39 (F27//M12)
Moderate	70 (F45/M25)	35 (F21/M14)	42 (F25/M17)
Severe	15 (F11/M 4)	8 (F4/M 4)	9 (F4/M5)

*Rosacea patient reporting at least one affected relative
M: Male; F: Female

recommendations), including severity grade were collected.[5, 25] Queries on familiarity and interfamilial transmission up to six generations were performed. Based on the results the following modalities were considered: horizontal transmission that encompasses all family members who do not directly descend from the proband (defined as a subject with at least one family member with rosacea); vertical transmission that included all family members who directly descend from the proband in a ascending and/or descending trend. Combined transmission of both horizontal and vertical transmission was also considered (Figure 1). In the majority of cases, affected relatives were all clinically examined (including children) and for those not available for consultation, photos were obtained.

The study was performed in accordance with the ethical principles originating from the Declaration of Helsinki 1996 and Good Clinical Practices. The protocol was approved by the internal institutional review board of our hospital. A written informed consent was obtained from each patient before study procedures were started.

Statistical analysis. Data were analyzed through statistical software SPSS statistical software package (D.B. IV). The quantitative data are reported as mean ± standard deviation (SD), while the qualitative ones are expressed in number and percentage. Pearson's chi-squared test were utilized for continuous and categorical variables. The statistical significance was set at $p \leq 0.05$.

RESULTS

One-hundred and thirty adult patients (37 males/93 females; mean age 49.3±18.6 years; range 18–85 years) were consecutively enrolled. Demographic characteristics and anamnestic data are reported in Table 1. Fixed centrofacial erythema +/-telangiectasias+ papules/pustules lesions was the predominant phenotype in 67 (51.5%) followed by fixed centrofacial erythema+/- telangiectasias in 49 (37.8%), phymatous changes in 5 (6.9%) or ocular manifestations in 9 (3.8%). Overall rosacea severity was mild in 45 (34.6%) cases, moderate in 70 (53.8%) and severe in 15 (11.6%) (Table 1). Among these patients, a statistically significant association was found between fixed centrofacial erythema +/- telangiectasias + papules and pustules phenotype and female gender (p=0.0001); phymatous changes with male sex (p=0.0001), normal weight (p=0.009), and smoking (p=0.026); ocular symptoms with alcohol consumption (p=0.01).

With regard to familiarity, 64 probands out of 130 patients (49.2%) were positive for at least one family member. Among probands, 28 (43.8%) were affected by fixed centrofacial erythema+/- telangiectasias, 26 (40.6%) by fixed centrofacial erythema +/- telangiectasias + papules/pustules, and (14%) and 1 (1.6%) by ocular manifestations or phymatous changes respectively (Table 1). Severity rate was mild in 21 (32.8%), moderate in 35 (54.7%) and severe in 8 (12.5%) subjects (Table 1). A statistically significant association was found between familial rosacea and fixed centrofacial erythema +/- telangiectasias + papules/pustules lesions (p=0.005) and alcohol consumption (p=0.01).

In the probands group after an accurate familial anamnestic investigation of the whole kindred, 90 affected relatives (69.2%) were identified (Tables 1 and 2). Of these, 45 (50%) showed fixed centrofacial erythema +/- telangiectasias, 32 (35.5%) fixed centrofacial erythema +/- telangiectasias + papules/pustules, and 10 (11%) and 3 (3.5%) ocular manifestations or phymatous changes respectively (Table 1). Severity rate was mild in 39 (43.4%), moderate in 42 (46.6%) and severe in 9 (10%) subjects (Table 1). A statistically significant association was found between phymatous changes and male gender (p=0.0001).

Concerning the mode of rosacea inheritance, vertical transmission was recorded in 45 (70.3%) probands, horizontal in 11 (17.2%)

and combined in 8 (12.5%) (Figure 2).

Considering ascending, descending, and ascending/descending vertical transmission, 56 subjects were identified. Ascending transmission accounted for 45, descending for 7 and ascending/descending for 4 relatives. Overall, in the vertical transmission group maternal lineage was predominant compared to paternal (29/45.3% vs 21/32.9%) (Table 2).

In the horizontal transmission group of 13 relatives two pairs of fraternal twins were observed, and 21 relatives were involved in combined horizontal/vertical transmission.

TABLE 2. Probands and the corresponding affected family members spanning six generations

PROBANDS	AFFECTED FAMILY MEMBERS (DEGREE OF KINSHIP)	AFFECTED FAMILY MEMBERS (N)
14	1 (Mother)	14
8	1 (Father)	8
5	1 (Sister)	5
4	1 (Daughter)	4
3	2 (Mother + Maternal Grandmother)	6
3	1 (Paternal Grandfather)	3
3	2 (Father + Paternal Grandfather)	6
2	1 (Brother)	2
2	1 (Maternal Grandfather)	2
2	1 (Maternal Great-Grandmother)	2
2	2 (Father + Sister)	4
1	4 (Father + Paternal Grandfather +2 Brothers)	4
1	3 (Father+ 2 Paternal Aunts)	3
1	3 (Mother + Maternal Grandfather + Paternal Aunt)	3
1	3 (Mother + Father + Paternal Grandmother)	3
1	3 (Father + Paternal Grandmother + Sister)	3
1	2 (Daughter + Son)	2
1	2 (Father + Brother)	2
1	2 (Mother +Brother)	2
1	2 (Mother + Daughter)	2
1	2 (Father + Daughter)	2
1	3 (Brother)	3
1	1 (Son)	1
1	1 (Maternal Cousin)	1
1	1 (Sororal Niece)	1
1	1 (Maternal Uncle)	1
1	1 (Paternal Grandmother)	1
total=64		total=90

DISCUSSION

Genetic studies of rosacea indicated that approximately half of the factors implicated in the pathophysiology of rosacea are genetic, the remaining being environmental.[17] A survey study on a cohort-based of 275 twin pairs with rosacea (233 homozygous vs 42 heterozygous) aimed to assess the relevance of genetic and environmental influences (including life time ultraviolet radiation exposure, smoking, and alcohol consumption) on the disease estimated that their contribution accounted for 46% and 54% respectively.[20] The appearance of rosacea in one of two homozygous twins suggests that environmental factors may have played a role since one of them lived from childhood in a metropolitan area, while the other, affected by rosacea, lived in the countryside.[21] On the other hand, the role of genetic factors has been sustained by the finding of the same type/severity at disease onset in monozygotic twin pairs compared to heterozygote ones.[20]

It has been observed that familial inheritance plays a role in up to 50% of patients who show a positive family history for rosacea when compared to the healthy population (OR 4.31; 95% CI: 2.34-7.92; $p<0.0001$).[9,7,19] Regarding studies on rosacea transmitted over generations, an online 2008 survey from the National Rosacea Society (NRS) conducted on 600 rosacea patients (42% of Irish, German or English origin) showed that almost 52 percent of the interviewees reported to have at least one family member affected.[18]

Nevertheless, the mechanisms that underlie the familial transmission of rosacea in several members of the same family have not been well defined, due to deaths, limited family contact and lack of objective diagnosis provided by a clinician. In addition, family history for rosacea is sporadically mentioned in the patient medical history and little, if any, information about the involved relatives, the transmission modality and subtype/severity is rarely available.

In our series of 130 patients, 64 (49.2%) reported to have at least one affected family member. Interestingly, after extending the search up to six generations, the number of relatives affected was 90 (69.2%) and the diagnosis in all cases was confirmed by clinical or photos examination. Our data on familial involvement turns out to be higher than that reported in the literature, usually ranging up to 50 percent and a more accurate intrafamilial investigation can explain such difference.

Among intrafamilial modalities, vertical transmission through maternal lineage was predominant when compared with the paternal one (42.1% vs. 34.37%) or with combined or horizontal (62.2% vs. 23.3% vs 14.5%) (Figure 2). Interestingly, 12 elderly relatives (69±10 years) affected by mild fixed centrofacial erythema +/- telangiectasias believed they were affected by a form of familial "complexion" rather than a specific disease, and therefore never sought medical advice.

Our sample was limited to 130 patients, but some considerations can be made. It was a novel, non-sponsored study aimed at evaluating epidemiologic data of intrafamilial transmission of rosacea up to six generations, a subject not previously explored. It consisted of an accurate screening of a high number of rosacea patients' relatives (up to 600) with positive familiarity for rosacea implying their clinical evaluation or, when not possible, photo evaluation.

CONCLUSION

Based on our data, the prevalence of familial rosacea was 69.2 percent, with a ratio patients

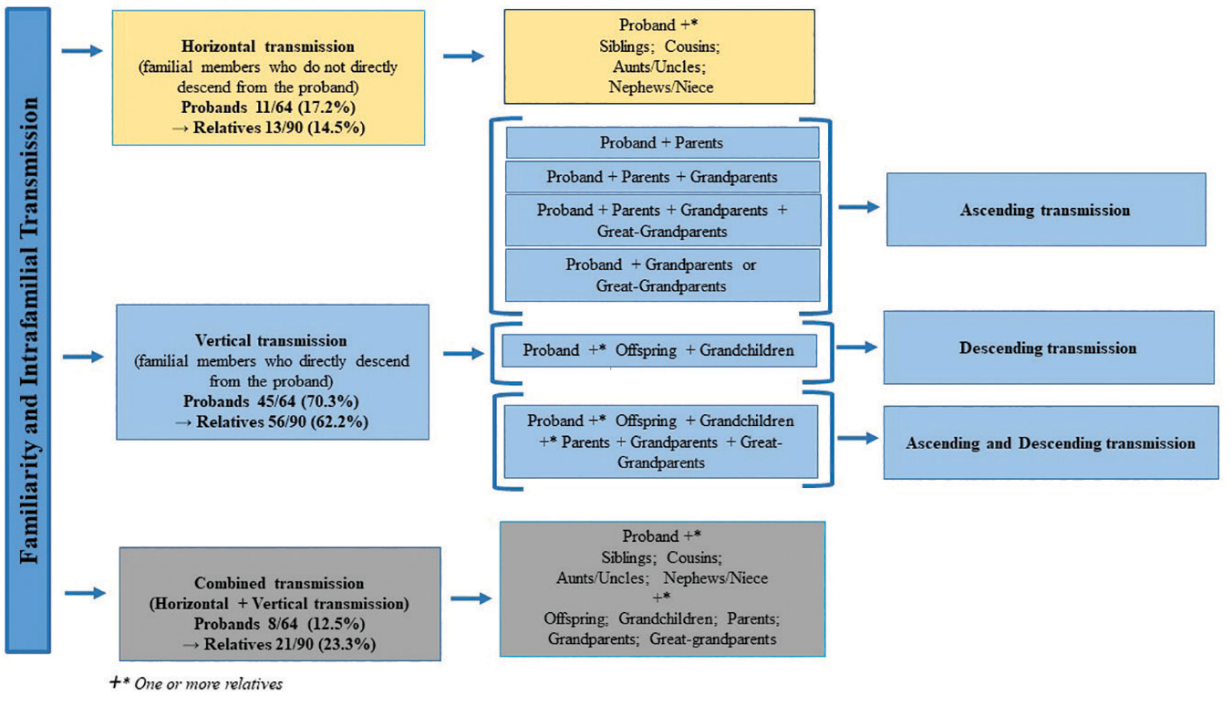

FIGURE 1. Study design and results.

FIGURE 2. Intrafamilial vertical transmission of rosacea through paternal lineage showing the proband (center), her father (right) and the paternal grandfather (left); the black-and-white photo in the upper left corner highlights grandfather's facial features at a younger age, when rhynophyma was not yet detectable.

positive for familiarity/affected relatives equal to 1:1.4. We believe that the prevalence of rosacea familiarity is underestimated and that a more accurate investigation among multiple family generations is advisable. Extending the search to all potential affected parents or offspring of rosacea patients with a positive family history can promote early diagnosis aimed at the adoption of correct therapeutic intervention and educational programs to prevent the exposure to triggering or exacerbating factors. Further Genome Wide Associations (GWAS) studies are however needed to better investigate specific genetic factors associated to familial rosacea risk, and to identify links between the gene variants and the expressed rosacea phenotype.

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