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Allergic contact dermatitis in patients with frontal fibrosing alopecia: An international multi-center study

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Abstract

Frontal fibrosing alopecia (FFA) mainly affects the anterior hairline and eyebrows and its etiology and associated factors remain obscure. The aim of this study was to evaluate the allergic contact dermatitis with patch test in patients with FFA. In this prospective study, 20 patients with FFA and 24 age and sex-matched healthy individuals were evaluated with patch testing. Diagnosis was made histologically, clinically and based on dermoscopic findings. Demographic data, age of onset, disease duration and FFA severity index are evaluated in all patients. Positive patch test reaction to one or more allergen was observed in 65% of patients while it was 37.5% in control group ($P = .003$). There was a significant difference between age ($P = .006$) and positive patch test results. No statistical significant difference was observed in the results of patch testing and disease duration ($P = .519$), menopausal status ($P = .085$), and FFA severity index ($P = .573$). Our findings suggest an association between FFA and allergic contact dermatitis. The utility of patch testing in FFA patients can explore the role of allergic etiology and may have an enormous impact on the diagnostic potential and quality of life of these patients.

KEYWORDS

allergen, allergic contact dermatitis, frontal fibrosing alopecia, patch test

1 | INTRODUCTION

Frontal fibrosing alopecia (FFA) is an irreversible scarring cicatricial alopecia, manifesting as atrophic and band-like recession of symmetric fronto-temporal and fronto-parietal hairline. FFA has been reported mainly in premenopausal women and rarely in men.¹⁻⁵ It is considered a variant of lichen planopilaris (LPP) and is frequently associated with the presence of perifollicular erythema and scaling in the affected area. The pathogenesis of FFA is poorly understood. Contact allergy represents an important differential diagnosis to skin diseases of the face and scalp. Potent allergens may lead to severe reactions on the face, hair or scalp.⁶⁻⁸ Patch test is the standard procedure used to diagnose contact allergy resulting from type IV hypersensitivity. It is gold standard for identification of allergens responsible for allergic contact dermatitis (ACD). Early diagnosis and treatment of ACD is associated with decreased costs to the health care system and improved quality of life and disease course.⁹⁻¹¹ T-cells are critical effectors for hypersensitivity reactions in ACD and on the other hand, it has been implicated that autoimmune mechanisms involving T1 helper cells play role in the pathogenesis of FFA.^{12,13} To date, there is no distinct study on evaluation of ACD with patch test in patients with FFA and comparing it with a healthy control group. Thus, our study aimed at evaluating the frequency of patch test positivity and possible link between delayed type hypersensitivity and FFA and comparing with a healthy matched group.

2 | MATERIALS AND METHODS

This was a prospective multi-center international study conducted on 20 FFA patients and 24 age and sex-matched individuals who were referred to skin clinic for other dermatologic diseases without autoimmune etiologies selected through simple random sampling after obtaining ethics approval from the institutional review board. Diagnosis was made based on the typical clinical presentation, characteristic trichoscopic findings (absence of follicular openings, follicular hyperkeratosis, perifollicular erythema, and follicular plugs) and histopathology. Patients with other concomitant scarring or non-scarring alopecia were excluded from the study. All the participants provided oral and written informed consent. Patch tests were performed on all study patients. At baseline, demographic data, history disease onset age, disease duration and FFA severity index (FFASI) were noted.¹⁴ Patch testing (North American standard series approved by ICDRG) results were evaluated in all patients. The sites of patches were examined on day 2 (D2) and day 4 (D4), according to International Contact Dermatitis Research Group (ICDRG) guidelines.¹⁵ The scoring of the patch test reactions was applied according to ICDRG recommendations as defined in the Table 1.^{16,17} A positive allergic reaction was defined as being at least grade 1+ according to ICDRG.¹⁵ In patients, where the patch had no skin contact upon patch test reading or had been removed prior to testing due to known contact sensitization, it was regarded as missing data.

TABLE 1 Notation of patch testing according to ICDRG

Symbol	Morphology	Interpretation
–	No reaction	Negative
+	Erythema, infiltration and possibly discrete papules	Weak positive
++	Erythema, infiltration, papules and vesicles	Strong positive
+++	Erythema, infiltration and confluent vesicles	Extreme positive
Ir	Different types of reactions (soap effect, vesicles, blister and necrosis)	Irritant reaction

2.1 | Statistical analysis

Data were analyzed using SPSS software package for statistical science (IBM SPSS Statistics for Windows, Version 22.0.0.0; SPSS Inc., Chicago, Illinois). Descriptive statistics (mean, SD and range for continuous variables, and frequency and percentage for qualitative variables) were used to describe patient's demographic and clinical features and also patch test results. Pearson's and Spearman's correlations were used for normality and nonparametric variables respectively. The proportion of patch test positivity and intragroup analysis was assessed using paired *T* test. *P* value <.05 was considered as statistically significant.

3 | RESULTS

Twenty patients with FFA were patch tested, of which 95% (19/20) and 5% (1/20) were females and male, respectively. In healthy group, 24 people were evaluated and 21 (87.5%) of them were female and three individuals (12.5%) were male. The mean age of case and control group was 39.70 ± 10.69 and 41.24 ± 11.34 years, respectively ($P = .024$). In case and control group, 42.1% (8/19) and 42.8% (9/21) were postmenopausal ($P = .28$). A positive family history of FFA was observed in 20% (5/20) of patients. The total duration of disease was 25.95 ± 20.11 months (range from 3-60 months). The mean FFA severity index (FFASI) was 12.15 ± 3.67 (range from 5.2 to 17.9). The basic characteristic information of study groups are shown in Table 2. Positive patch test reaction to one or more allergen was observed in 65% (13/20) in case group while it was 37.5% in control group ($P = .003$) (Figure 1). Among the cases, at least one 2+ and 3+ patch test reaction was observed in 10% (2/20) and 5% (1/20) of patients while it was 1 (4%) and 0 (0%) in control group ($P = .021$). Patients with positive patch test results had a mean age of 44.23 ± 7.73 while it was 42.16 ± 7.02 in control group ($P = .028$). Mean disease duration of patients with positive patch test was 28.15 ± 22.73 and mean FFASI score was 12.7 ± 3.83 (Figure 2). Patients and healthy individuals with negative patch test results had a mean age of 31.29 ± 10.73 and 32.39 ± 9.83 , respectively ($P = .02$). Mean disease duration was 21.86 ± 14.77 and mean FFASI score was 11.5 ± 4.18 . There was a significant difference between age

TABLE 2 Basic demographic information for study groups

Categories			Cases	Control	P
Gender	Male		1 (5%)	3 (12.5%)	.12
	Female		19 (95%)	21 (87.5%)	
Age	Range	19-30	5 (25%)		.34
		31-40	5 (25%)		
		41-50	8 (40%)		
		51-58	2 (10%)		
	Mean $\pm$ SD (years)		39.70 $\pm$ 10.69	41.24 $\pm$ 11.34	.24
Marital status	Single		3 (15%)	4 (16.7%)	.32
	Married		17 (85%)	20 (83.3%)	
Family history of FFA	Yes		4 (20%)	—	
Disease duration	Range (months)		3–60		
	Mean $\pm$ SD (months)		25.95 $\pm$ 20.11		
Menopausal status	Postmenopausal		8 (42.1%)	9 (42.8%)	.28
	Premenopausal		11 (57.9%)	12 (57.2%)	
Frontal fibrosing alopecia severity index (FFASI)	Mean $\pm$ SD		12.15 $\pm$ 3.67		
	Range		5.2–17.9		

**FIGURE 1** Clinical picture and patch test result in a 23-year-old patient with frontal fibrosing alopecia

($P = .006$) with positive patch test results in case group. There was no statistically significant difference between the results of patch testing and disease duration ($P = .519$), menopausal status ($P = .085$), positive family history of FFA ($P = .660$) and FFASI ($P = .573$) in case group. The most common allergens encountered in the case group were cobalt (II) chloride hexahydrate 35% (7/20), nickel (II) sulfate

hexahydrate 25% (5/20) and potassium dichromate 15% (3/20) and they were the same in control group with different order that is, cobalt (II) chloride hexahydrate 33.3% (8/24), potassium dichromate 20.8% (5/24) and nickel (II) sulfate hexahydrate 16.6% (4/24). Figure 3 demonstrates classic characteristics of two patients with FFA in our study.

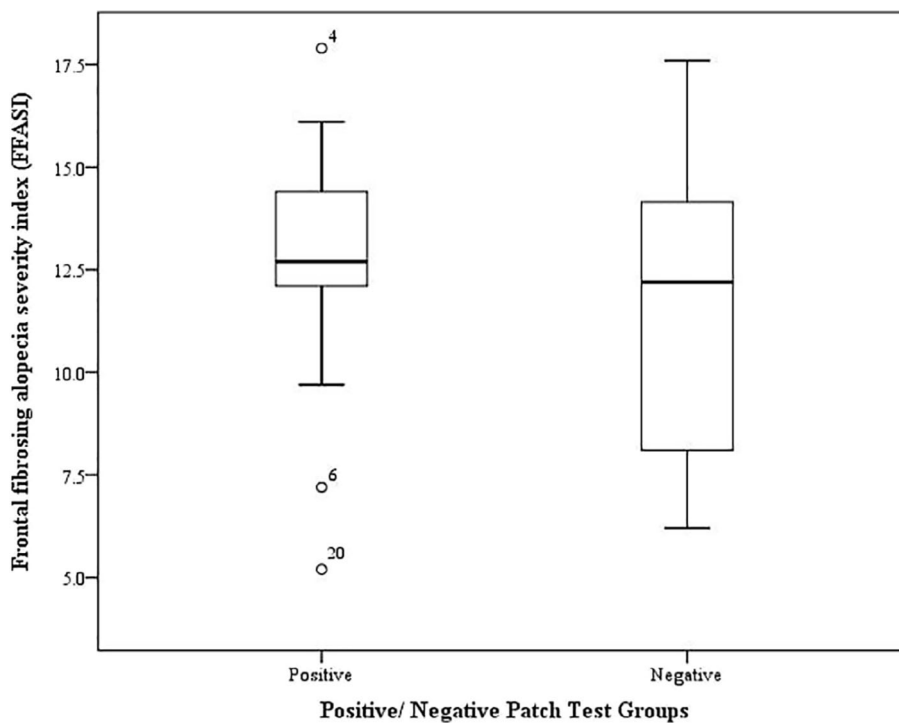


FIGURE 2 The mean frontal fibrosing alopecia severity index (FFASI) among patients with positive and negative patch test results

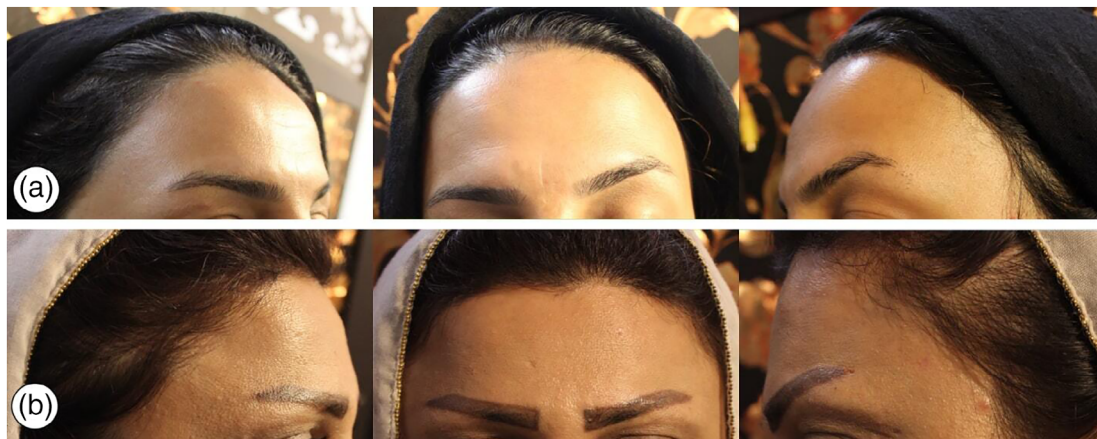


FIGURE 3 Classic features of frontal fibrosing alopecia (FFA) patients in two patients; band of frontoparietal hair recession and partial/complete eyebrow loss. A, 30-year-old female with 2 cm hairline recession, partial eyebrows loss, mild perifollicular inflammation and hyperkeratosis with FFASI score of 15.3. B, Small frontotemporal hairline recession, partial loss of eyebrows and mild perifollicular hyperkeratosis with FFASI score of 12.1 in a 34-year-old female with FFA. FFASI, frontal fibrosing alopecia severity index

4 | DISCUSSION

FFA, an uncommon variant of LPP, is a scarring alopecia manifests with the band of a receding frontal and temporo-parietal hairline.¹⁸ Eyebrow loss is one of the most frequent findings in FFA patients which presents in more than three fourth of patients in majority of studies and may be the first sign of the disease onset.^{19,20} As FFA is considered a lymphocytic scarring alopecia, the follicular hair units are targeted with inflammation and replaced by fibrosis due to the presence of inflammatory cells.²¹ Although hormonal, genetic, autoimmune, inflammatory and environmental factors seem to be involved in

the pathogenesis of FFA, their exact mechanism for disease progression is not well known.²² Some autoimmune diseases such as thyroid disorder or vitiligo have been associated with FFA²³ but so far, no link has been identified between ACD and FFA. ACDs results from specific immune responses against exposure to previously sensitized allergens, which subsequently can cause tissue damage.²⁴ The gold standard and method of choice for the diagnosis of ACD is patch testing. To date there has been no study with evaluation of patch testing in FFA patients and comparing it with healthy control group, thus our work is the first study in which the prevalence of sensitized allergens among FFA patients were surveyed and compared with healthy

individuals. T-cells are important effectors for hypersensitivity reactions in ACD. In addition, T1 helper cells play an important role in the pathogenesis of FFA. In this regard these two diseases may have mutual pathogenesis. FFA is a rare dermatologic disease; however, its prevalence is increasing worldwide. It affects predominantly the postmenopausal women, but in our study, 57.9% (11/19) of premenopausal women were affected. In a clinical review of 20 black patients from South Africa conducted by Dlova et al., 73% women were premenopausal, which was consistent with our study. The mean age of disease onset in our study was approximately 40 years (19 to 58 years), which was similar to Dlova et al. study.²⁵ In concordance with the previous studies, age-group of 50 to 60 years (6th decade) was mostly affected with FFA.²⁶⁻²⁸ Twenty percent (4/20) of patients had a positive family history of FFA; two of them were sisters, one cited her father and other case cited her mother to be affected with FFA. Positive family history in previous studies ranged from 0.9% (1/103 patients with FFA) in the study of Saceda-Corrado et al²⁹ to 39% (7/18 patients with FFA) in Callender et al study.³⁰

In this work, the severity of disease was evaluated based on FFASI score which provided a quantitative FFA severity including extent of alopecia, signs of local inflammation and patient's symptoms.¹⁴ In our study, the mean FFASI score was a bit higher among patients with positive patch test result than negative ones, but there was no significant difference in terms of FFASI score between these two groups. Cobalt (II) chloride hexahydrate was the most frequent allergen among FFA patients with positive patch test results, accounting for 65% of individuals. Cobalt (II) chloride hexahydrate is a metal commonly found in jewelry, keys, dental and orthopedic implants and also can be found in hair ornaments, eye-shadow, spray paints and wood stains.³¹ Doms-Gossens et al conducted a follow-up study on 100 patients with ACD due to cobalt, nickel and potassium dichromate exposure. In their study, nickel sulfate was the most common sensitizer especially among women, and on the other hand, cobalt hypersensitivity was accompanied by allergic reaction to nickel and potassium dichromate.³² Nickel sulfate has been responsible for a large proportion of ACD in the general population.³³ The prevalence of nickel sulfate allergy was 8.6% (range 0.7%-27.8%) in the general population and nickel was an important cause of ACD in Thyssen et al study.³⁴ In our study, the nickel (II) sulfate allergy prevalence was 25% among FFA patients. The patch test results and allergen analysis revealed that majority of patients with FFA suffered from ACD which was mostly caused by cobalt, nickel and potassium dichromate. A previous study stated that cobalt and nickel are common causes of ACD. It has been proposed that contamination with these metals may be of relevance to the causation/chronicity of dermatitis.³⁵ In their study, Aldoori and colleagues evaluated the leave-on facial skin care products and sunscreens and demonstrated that there is an association between FFA and the use of facial skin care products including facial skin care ones.³⁶ In contrast, Rocha and colleagues in another study assessed the photopatch and patch testing in 63 patients with FFA and did not demonstrate an association of FFA with photoallergy to several cosmetic-related substances.³⁷

5 | CONCLUSION

This study demonstrated that a large number of FFA patients had ACD. The hypothesis of the link between ACD and FFA may be of interest for the future research to find out more about the possible etiopathogenesis of FFA. This study also found that FFA has a potential to appear in younger adults and even with a high rate in premenopausal women (Figure 2A).

6 | LIMITATION

The number of study population is the main limitation of the study however due to low prevalence of FFA, it might be acceptable. More studies with larger study population can be done to evaluate the relationship between FFA and ACD.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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REFERENCES

- Banka N, Mubki T, Bunagan MJK, McElwee K, Shapiro J. Frontal fibrosing alopecia: a retrospective clinical review of 62 patients with treatment outcome and long-term follow-up. *Int J Dermatol*. 2014;53(11):1324-1330.
- Kossard S. Postmenopausal frontal fibrosing alopecia: scarring alopecia in a pattern distribution. *Arch Dermatol*. 1994;130(6):770-774.
- Lee JY, Hong JS, Lee SH, Lee AY. Successful treatment of frontal fibrosing alopecia with alitretinoin. *Dermatol Ther*. 2019 Sep;32(5):e13037.
- Özcan D, Tunçer Vural A, Özen Ö. Platelet-rich plasma for treatment resistant frontal fibrosing alopecia: a case report. *Dermatol Ther*. 2019 Sep;32(5):e13072.
- Vañó-Galván S, Molina-Ruiz AM, Serrano-Falcón C, et al. Frontal fibrosing alopecia: a multicenter review of 355 patients. *J Am Acad Dermatol*. 2014;70(4):670-678.
- Koch L, Aberer W. Allergic contact dermatitis of the scalp. *Der Hautarzt; Zeitschrift für Dermatologie, Venerologie, und verwandte Gebiete*. 2017;68(6):466-471.
- Schnuch A, Szliska C, Uter W. Facial allergic contact dermatitis. Data from the IVDK and review of literature. *Der Hautarzt; Zeitschrift für Dermatologie, Venerologie, und verwandte Gebiete*. 2009;60(1):13-21.
- Yang CC, Khanna T, Sallee B, Christiano AM, Bordone LA. Tofacitinib for the treatment of lichen planopilaris: a case series. *Dermatol Ther*. 2018;31(6):e12656.
- Dickel H, Altmeyer P, Brasch J. "New" techniques for more sensitive patch testing? *Journal der Deutschen Dermatologischen Gesellschaft*. 2011;9(11):889-896.
- Johansen JD, Aalto-Korte K, Agner T, et al. European Society of Contact Dermatitis guideline for diagnostic patch testing—recommendations on best practice. *Contact Dermatitis*. 2015;73(4):195-221.

11. Kadyk DL, McCarter K, Achen F, Belsito DV. Quality of life in patients with allergic contact dermatitis. *J Am Acad Dermatol*. 2003;49(6):1037-1048.
12. Gober MD, Gaspari AA. Allergic contact dermatitis. *Curr Dir Autoimmun*. 2008;10:1-26.
13. Ma SA, Imadojemu S, Beer K, Seykora JT. Inflammatory features of frontal fibrosing alopecia. *J Cutan Pathol*. 2017 Aug;44(8):672-676.
14. Saceda-Corralo D, Moreno-Arrones ÓM, Fonda-Pascual P, et al. Development and validation of the frontal fibrosing alopecia severity score. *J Am Acad Dermatol*. 2018b;78(3):522-529.
15. Wilkinson D. Terminology of contact dermatitis. *Acta Derm Venereol*. 1970;50:287-292.
16. Davis MD, Scalf LA, Yiannias JA, et al. Changing trends and allergens in the patch test standard series: a Mayo Clinic 5-year retrospective review, January 1, 2001, through December 31, 2005. *Arch Dermatol*. 2008;144(1):67-72.
17. Wetter DA, Davis MD, Yiannias JA, et al. Patch test results from the Mayo Clinic contact dermatitis group, 1998-2000. *J Am Acad Dermatol*. 2005;53(3):416-421.
18. Gameza VA, Deleuran M. Frontal fibrosing alopecia is a variant of lichen planopilaris. *Ugeskr Laeger*. 2015;177(2A):32-33.
19. Ladizinski B, Bazakas A, Selim MA, Olsen EA. Frontal fibrosing alopecia: a retrospective review of 19 patients seen at Duke University. *J Am Acad Dermatol*. 2013;68(5):749-755.
20. Samrao A, Chew AL, Price V. Frontal fibrosing alopecia: a clinical review of 36 patients. *Br J Dermatol*. 2010;163(6):1296-1300.
21. Olsen EA, Bergfeld WF, Cotsarelis G, et al. Summary of north American hair research society (NAHRS)-sponsored workshop on Cicatricial alopecia, Duke University medical center, February 10 and 11, 2001. *J Am Acad Dermatol*. 2003;48(1):103-110.
22. MacDonald A, Clark C, Holmes S. Frontal fibrosing alopecia: a review of 60 cases. *J Am Acad Dermatol*. 2012;67(5):955-961.
23. Miteva M, Aber C, Torres F, Tosti A. Frontal fibrosing alopecia occurring on scalp vitiligo: report of four cases. *Br J Dermatol*. 2011;165(2):445-447.
24. Martins LE, Reis VM. Immunopathology of allergic contact dermatitis. *An Bras Dermatol*. 2011;86(3):419-433.
25. Dlova N, Jordaan H, Skenjane A, Khoza N, Tosti A. Frontal fibrosing alopecia: a clinical review of 20 black patients from South Africa. *Br J Dermatol*. 2013;169(4):939-941.
26. Moreno-Ramírez D, Camacho Martinez F. Frontal fibrosing alopecia: a survey in 16 patients. *J Eur Acad Dermatol Venereol*. 2005;19(6):700-705.
27. Tan K, Messenger A. Frontal fibrosing alopecia: clinical presentations and prognosis. *Br J Dermatol*. 2009;160(1):75-79.
28. Tosti A, Piraccini BM, Iorizzo M, Misciali C. Frontal fibrosing alopecia in postmenopausal women. *J Am Acad Dermatol*. 2005;52(1):55-60.
29. Saceda-Corralo D, Fernández-Crehuet P, Fonda-Pascual P, Pindado-Ortega C, Moreno-Arrones OM, Vañó-Galván S. Clinical description of frontal fibrosing alopecia with concomitant lichen planopilaris. *Skin Appendage Disord*. 2018a;4(2):105-107.
30. Callender VD, Reid SD, Obayan O, McClellan L, Sperling L. Diagnostic clues to frontal fibrosing alopecia in patients of African descent. *J Clin Aesthet Dermatol*. 2016;9(4):45-51.
31. Hindsén M, Persson L, Gruvberger B. Allergic contact dermatitis from cobalt in jewellery. *Contact Dermatitis*. 2005;53(6):350-351.
32. Dooms-Goossens A, Ceuterick A, Vanmaele N, Degreef H. Follow-up study of patients with contact dermatitis caused by chromates, nickel, and cobalt. *Dermatology*. 1980;160(4):249-260.
33. Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from Northern Norway. *Contact Dermatitis*. 2007;56(1):10-15.
34. Thyssen JP, Linneberg A, Menné T, Johansen JD. The epidemiology of contact allergy in the general population—prevalence and main findings. *Contact Dermatitis*. 2007;57(5):287-299.
35. Basketter DA, Angelini G, Ingber A, Kern PS, Menné T. Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium. *Contact Dermatitis*. 2003;49(1):1-7.
36. Aldoori N, Dobson K, Holden CR, McDonagh AJ, Harries M, Messenger AG. Frontal fibrosing alopecia: possible association with leave-on facial skin care products and sunscreens; a questionnaire study. *Br J Dermatol*. 2016;175(4):762-767.
37. Rocha VB, Donati A, Contin LA, et al. Photopatch and patch testing in 63 patients with frontal fibrosing alopecia: a case series. *Br J Dermatol*. 2018;179(6):1402-1403.

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