Prevalence of Raynaud Phenomenon and Nailfold Capillaroscopic Abnormalities in Fabry Disease

A Cross-Sectional Study

Samuel Deshayes, MD, Laurent Auboire, MD, Roland Jaussaud, MD, PhD, Olivier Lidove, MD, Jean-Jacques Parienti, MD, PhD, Nathalie Triclin, Bernard Imbert, MD, Boris Bienvenu, MD, PhD, and Achille Aouba, MD

Abstract: Fabry disease (FD) is a lysosomal disorder leading to progressive systemic involvement, including microvascular damage that leads to neurological and cardiovascular disorders. We hypothesize that the latter could be documented at an early stage by performing a microcirculation study with nailfold capillaroscopy and evaluation of Raynaud phenomenon.

The objective was to measure the prevalence of Raynaud phenomenon and nailfold capillaroscopic abnormalities in FD.

This cross-sectional study included a standardized questionnaire and a nailfold capillaroscopy that assessed previously reported patterns in FD (dystrophic and giant capillaries, avascular fields, irregular architecture, dilatation and density of capillaries, hemorrhage), and was conducted on 52 Fabry patients and 39 controls. Capillaroscopic photographs were reviewed by 2 independent blinded investigators.

Twelve Fabry patients (38%) suffered from Raynaud phenomenon, 5 were males (ie, 50% of male Fabry patients), compared with 2 controls (13%) (P < 0.001), of whom none were males (P < 0.001). Raynaud phenomenon was concomitant or before the occurrence of pain in the extremities in 42% of Fabry patients.

More ramified capillaries were significantly observed in Fabry patients (12/32, 38%) than in controls (5/29, 13%, P = 0.016).

Secondary Raynaud phenomenon should lead to screening for FD, especially in men. By extension, in high-risk populations for FD, the presence of Raynaud phenomenon and ramified capillaries should be assessed.

(Medicine 94(20):e780)

INTRODUCTION

Fabry disease (FD), secondary to a deficit in α-galactosidase A caused by abnormalities in the GLA gene, belongs to X-linked lysosomal disorders. The progressive accumulation of neutral glycosphingolipids, particularly globotriaosylceramide, within lysosomes leads to a multiorgan disease.1,2 The “classic” severe phenotype, including systemic involvement, has an estimated incidence of 1 in 117,000 in the general population.3 This figure is probably underestimated, as suggested by newborn screening and by the discovery of atypical variants with late-onset isolated renal or cardiac manifestations.4–7 A diagnosis is frequently delayed for many years because of nonspecific signs.8

Enzyme-replacement therapy is available and decreases morbidity,9–11 especially if it is started before the onset of complications, hence the importance of early screening of these patients. One of the earliest and common symptoms is pain in the extremities,1 classically attributed to neurologic involvement (small nerve fibers of the peripheral somatic and autonomic nerve systems).12–14 FD also induces vasculopathy of small vessels by accumulation of neutral glycosphingolipids in smooth muscular and endothelial cells, which affect the microcirculation.15,16 Raynaud phenomenon results from a disorder of vascular thermoregulatory control mechanisms, related to an increased sympathetic activity affecting the microcirculation and to endothelial dysfunction. This is more pronounced in the case of secondary Raynaud phenomenon.17

Although nailfold capillaroscopy assesses small vessels and Raynaud phenomenon is secondary to dysregulation of vascular homeostasis, little research has been done on these subjects in FD.

The first identification of dystrophic capillaries in FD occurred in 1993 with the description of 3 case reports,18 followed by another case report of ramified capillaries in 1994,19 and a study of 8 members of a family who had FD in 2006, which reported 37% of ramified capillaries.20 Wasik et al.21 in a matched case–control study with 25 Fabry patients (17 men, 8 women) in 2009, reported 72% of dystrophic capillaries, with a higher incidence of Raynaud phenomenon in Fabry patients, especially male patients (20%). Costanzo et al.22 in 2014, supported these results and reported 52.6% of dystrophic capillaries in a study of 19 Fabry patients, compared with 0% in 19 matched controls.

The objective of this study was to measure the prevalence of Raynaud phenomenon and nailfold capillaroscopic abnormalities in a larger cohort of Fabry patients.

DOI: 10.1097/MD.0000000000000780
METHODS

Patients
We performed a cross-sectional study during a patient-support association meeting. This meeting, organized by the FD French patients association in June 2013, brought together already diagnosed Fabry patients from all over France. Diagnoses were made by experienced clinicians in FD on patients presenting clinical signs or familial history of the disease with a biological confirmation (α-galactosidase activity with a genetic analysis of the α-galactosidase A gene for men, and excretion of urinary Gb3, α-galactosidase activity, and gene mutation analysis for women). The subjects fulfilled the following inclusion criteria: being aged ≥18 years, and had given their written informed consent after oral information was supplied by the investigators.

Data Collection
The subjects viewed a slideshow focusing on Raynaud phenomenon, describing its 3 phases with photographs. They then completed a standardized self-assessment questionnaire, including age, gender, medical history, cardiovascular risk factors, and manifestations of FD, enzyme-replacement therapy, and Raynaud phenomenon. They also underwent a nailfold capillaroscopy23 of the 3 last fingers of each hand (CapXview HD, Xport technologies, Craponne, France) to assess the following parameters, according to the previously reported patterns observed in FD:

1. dystrophic capillaries (particularly bushy and ramified capillaries),
2. avascular fields,
3. irregular architecture,
4. dilatation of capillaries,
5. giant capillaries,
6. hemorrhage, and
7. density of capillaries (per mm).

Two independent blinded reviewers assessed the capillaroscopic photographs. A consensus was reached regarding any differences. Accompanying persons constituted the control group.

This study was approved by the local ethics committee.

Data sets are available from the Dryad repository, at http://datadryad.org/ with the doi:10.5061/dryad.kq04t.

Data Analyses
Statistical analyses were performed using R 3.0.3 software. Categorical variables are reported as percentages and were compared using the χ² or Fisher exact test, according to expected frequencies. Continuous variables are expressed as their means ± standard deviations, and were analyzed using Student t test. A P value of <0.05 was considered statistically significant.

RESULTS
Seventy-one questionnaires were collected from 32 Fabry patients (45%) and 39 controls (55%). Concerning demographic data, sex ratio was statistically different, with more men in the control group (Table 1). Data regarding Raynaud phenomenon are presented in Table 2. Pain in the extremities was reported among 28 Fabry patients (88%) versus in none of the controls (p < 0.001). Patients with FD and Raynaud phenomenon all suffered from pain in the extremities, versus no pain in the controls (P = 0.011). Raynaud phenomenon was concomitant or before the occurrence of pain in the extremities in 42% of Fabry patients. Twenty-five of the 32 Fabry patients (78%) (10/10 males, 15/22 females) were receiving enzyme-replacement therapy. The only nailfold capillaroscopy parameter that was statistically different was a particular major dystrophic capillary pattern (Table 3, Figure 1).

DISCUSSION
This study reveals a higher incidence of Raynaud phenomenon in Fabry patients (38%) than in controls (5%), versus 3–22%24–26 in the general population. This figure is higher than the 15.3% reported in the study by Germain et al, who measured the prevalence of Raynaud phenomenon in Fabry patients.27 Among males, half of our Fabry patients had Raynaud phenomenon compared with none among the control group. According to the literature, the prevalence of Raynaud phenomenon varies from 0.5 to 16%26,28,29 in the general male population, and 2.5% to 22% in the general female population.26

| TABLE 1. Demographic and Clinical Characteristics of Fabry Patients and Controls |
|-----------------|-----------------|-----------------|
|                 | Fabry Patients  | Control Group   | P Value |
| n               | 32              | 39              |         |
| Age, mean ± SD  | 45.5 ± 13.8     | 48.2 ± 11.5     | 0.38    |
| Sex ratio (males/females) | 0.46 (10/22) | 1.6 (24/15) | 0.02 |
| Smoking, n (%)  | 1 (3)           | 4 (10)          | 0.37    |
| Hypertension, n (%) | 8 (25)       | 4 (10)          | 0.1     |
| Hyperlipidemia, n (%) | 4 (13)       | 4 (10)          | 1       |
| Diabetes, n (%)  | 1 (3)           | 3 (8)           | 0.63    |
| Enzyme-replacement therapy, n (%) | 25 (78) | N/A             | N/A     |
| Pain in the extremities, n (%) | 28 (88) | N/A             | N/A     |
| Cornea verticillata, n (%) | 22 (69) | N/A             | N/A     |
| Angiokeratoma, n (%) | 18 (56)       | N/A             | N/A     |
| Abnormal sweating, n (%) | 18 (56)       | N/A             | N/A     |
| Cardiac involvement, n (%) | 18 (56)       | N/A             | N/A     |
| Abdominal pain, n (%) | 17 (53)       | N/A             | N/A     |
| Hearing loss, n (%) | 15 (47)       | N/A             | N/A     |
| Unexplained fever, n (%) | 12 (38)       | N/A             | N/A     |
| Renal involvement, n (%) | 11 (34)       | N/A             | N/A     |
| Stroke, n (%) | 8 (25)           | N/A             | N/A     |

N/A = not applicable, SD = standard deviation.

| TABLE 2. Characteristics of Patients Suffering From RP |
|-----------------|-----------------|-----------------|
|                 | Fabry Patients  | Control Group   | P Value |
| Males with RP, n (%) | 5/10 (50) | 0/24 (0) | <0.001 |
| Females with RP, n (%) | 7/22 (32) | 2/15 (13) | 0.27 |
| Total with RP, n (%) | 12/32 (38) | 2/39 (5) | <0.001 |

P value of < 0.05 was considered statistically significant.
RP = Raynaud phenomenon.
Secondary Raynaud phenomenon in men is usually thought to be associated with chronic occupational exposure, especially in manual workers, which may explain the higher incidence of dystrophic capillaries in men. The high prevalence of Raynaud phenomenon in FD, hardly described so far, should be considered as a cause of secondary Raynaud phenomenon. By inducing small-fiber neuropathy (both autonomic and sensitive), endothelial dysfunction, smooth-muscle-cell proliferation, the accumulation of neutral glycosphingolipids may impair vascular tone and favor Raynaud phenomenon. Because Raynaud phenomenon is concomitant or before the occurrence of pain in the extremities in almost half of Fabry patients, this could be, at least in part, a causal factor of this pain.

Consistent with data in the literature, a significantly higher rate of ramified capillaries in Fabry patients was observed, particularly in males, which may reflect a more severe involvement of the microcirculation in the latter, as already identified for other involvements. In contrast, no significant difference was found regarding dystrophic capillaries as a whole. This discrepancy might be explained by the higher proportion of males, more susceptible to dystrophic capillaries, within our control group compared with the Fabry group, or it may have been because of improved microcirculation after treatment. Indeed, 78% of our Fabry patients were receiving enzyme-replacement therapy, compared with 0% in the other 2 published studies. López-Rodríguez et al, in their study of a family of 8 members who had FD (5 of them receiving enzyme-replacement therapy), noted that the 3 patients with a normal nailfold capillaroscopy were under treatment. It would be interesting to carry out a prospective study on the diagnostics of FD to monitor any associations between capillaroscopic abnormalities and enzyme-replacement therapy.

Angiokeratoma and tortuosity of the conjunctival and retinal blood vessels have been previously described. It now

### TABLE 3. Results of Nailfold Capillaroscopic Parameters

| Parameter                              | Fabry Patients (n = 32) | Control Group (n = 39) | P Value |
|----------------------------------------|------------------------|------------------------|---------|
| Dystrophic capillaries, n (%)          | Female/male            | 14 (64)/9 (90)         | 11 (73)/19 (79) | 0.73/0.65 |
|                                        | All/male               | 23 (72)                | 30 (77) | 0.63 |
| Bushy capillaries, n (%)               | Female/male            | 1 (5)/2 (20)           | 2 (13)/6 (25) | 0.56/1 |
|                                        | All/male               | 3 (9)                  | 8 (21) | 0.33 |
| Ramified capillaries, n (%)            | Female/male            | 6 (27)/6 (60)          | 3 (20)/2 (8) | 0.72/0.005 |
|                                        | All/male               | 12 (38)                | 5 (13) | 0.016 |
| Avascular fields, n (%)                | Female/male            | 2 (9)/1 (10)           | 1 (7)/0 (0) | 1/0.30 |
|                                        | All/male               | 3 (9)                  | 1 (3) | 0.33 |
| Irregular architecture, n (%)          | Female/male            | 5 (23)/3 (30)          | 2 (13)/2 (8) | 0.68/0.14 |
|                                        | All/male               | 8 (25)                 | 4 (10) | 0.10 |
| Hemorrhage, n (%)                      | Female/male            | 3 (14)/4 (40)          | 4 (27)/5 (21) | 0.41/0.40 |
|                                        | All/male               | 7 (22)                 | 9 (23) | 0.91 |
| Dilatation of capillaries, n (%)       | Female/male            | 8 (36)/7 (70)          | 9 (60)/10 (42) | 0.16/0.14 |
|                                        | All/male               | 15 (47)                | 19 (49) | 0.88 |
| Giant capillaries, n (%)               | Female/male            | 1 (5)/0 (0)            | 0 (0)/0 (0) | 1/1 |
|                                        | All/male               | 1 (3)                  | 0 (0) | 0.46 |
| Density of capillaries per mm, mean ± SD| Female/male            | 9.5 ± 1.92/8.8 ± 1.62  | 8.53 ± 1.64/9.42 ± 1.32 | 0.13/0.26 |
|                                        | All                    | 9.29 ± 1.83            | 9.08 ± 1.49 | 0.67 |

P value of < 0.05 was considered statistically significant. SD = standard deviation.

Secondary Raynaud phenomenon in men is usually thought to be associated with chronic occupational exposure, especially in manual workers, which may explain the higher incidence of dystrophic capillaries in men. The high prevalence of Raynaud–phenomenon in FD, hardly described so far, should be considered as a cause of secondary Raynaud phenomenon. By inducing small-fiber neuropathy (both autonomic and sensitive), endothelial dysfunction, smooth-muscle-cell proliferation, the accumulation of neutral glycosphingolipids may impair vascular tone and favor Raynaud phenomenon. Because Raynaud phenomenon is concomitant or before the occurrence of pain in the extremities in almost half of Fabry patients, this could be, at least in part, a causal factor of this pain.

Consistent with data in the literature, a significantly higher rate of ramified capillaries in Fabry patients was observed, particularly in males, which may reflect a more severe involvement of the microcirculation in the latter, as already identified for other involvements. In contrast, no significant difference was found regarding dystrophic capillaries as a whole. This discrepancy might be explained by the higher proportion of males, more susceptible to dystrophic capillaries, within our control group compared with the Fabry group, or it may have been because of improved microcirculation after treatment. Indeed, 78% of our Fabry patients were receiving enzyme-replacement therapy, compared with 0% in the other 2 published studies. López-Rodríguez et al, in their study of a family of 8 members who had FD (5 of them receiving enzyme-replacement therapy), noted that the 3 patients with a normal nailfold capillaroscopy were under treatment. It would be interesting to carry out a prospective study on the diagnostics of FD to monitor any associations between capillaroscopic abnormalities and enzyme-replacement therapy.

Angiokeratoma and tortuosity of the conjunctival and retinal blood vessels have been previously described. It now

![Figure 1. Capillaroscopic photographs of (A) ramified and (B) bushy capillaries (×50).](Image)
seems that dystrophic capillaries, observed by nailfold capillaroscopy, and newly reported vessel tortuosity, visible on the external surface of the upper eyelid, enrich Fabry vasculopathy of clinical examination. These clinical signs could improve screening of people in high-risk populations for FD (hyper- trophic cardiomyopathy, dialysis patients, stroke in young people). To our knowledge, this study is the third, but the largest, study to assess nailfold capillaroscopic abnormalities in FD. The control group was constituted of family members, sharing the same genetic and/or environmental factors, potential source of confounding factors. It was not matched on age and sex. Despite this, age was not statistically different between the 2 groups. The female predominance in our Fabry patients can be explained by a higher mortality and morbidity rate in male patients before the availability of enzyme-replacement therapy, imped ing their participation to meetings, and/or by a possible over-representation of females in the patient-support association meetings. This non-comparability of the control group regarding sex ratio is the main limitation of this study. Nevertheless, the predominance of males in the control group, more susceptible to dystrophic capillaries, could have revealed a more specific pattern of dystrophic capillaries in FD, namely ramified capillaries, not discovered hitherto. Moreover, the inhomogeneity of Fabry patients regarding enzyme-replacement therapy, unlike the other 2 studies, opens up new perspectives of studies that can explain some of the discrepancies encountered with previous data. Because this study was based on self-assessment questionnaire, no data on mutations were available. Therefore, no genophenotypic correlation could be done. We report the prevalence of Raynaud phenomenon and nailfold capillaroscopic abnormalities in French Fabry patients. Hence, our findings may not apply to other countries with different genetic and environmental factors.

CONCLUSION

Our data strengthen the fact that secondary Raynaud phenomenon should lead to screening for FD, especially in men. By extension, in high-risk populations for FD (ie, hypertrophic cardiomyopathy, dialysis patients, stroke in young people), the presence of ramified capillaries and Raynaud phenomenon should also be assessed.

ACKNOWLEDGMENTS

The authors thank all participants and the FD French support patient association (APMF).

The authors also thank Dr Erwan Floch, PharmD (France) for language correction of the manuscript.

Funding sources: None.

REFERENCES

1. Germain DP. Fabry disease. Orphanet J Rare Dis. 2010;5:30.

2. Tuttolomondo A, Pecoraro R, Simonetta I, et al. Anderson-Fabry disease: a multorgan disease. Curr Pharm Des. 2013;19:5974–5996.

3. Zarate YA, Hopkin RJ. Fabry’s disease. Lancet. 2008;372:1427–1435.

4. Spada M, Pagliardini S, Yasuda M, et al. High incidence of later-onset Fabry disease revealed by newborn screening. Am J Hum Genet. 2006;79:31–40.

5. Van der Tol L, Smid BE, Poorthuis BJHM, et al. A systematic review on screening for Fabry disease: prevalence of individuals with genetic variants of unknown significance. J Med Genet. 2014;51:1–9.

6. Linthorst GE, Bouwman MG, Wijburg FA, et al. Screening for Fabry disease in high-risk populations: a systematic review. J Med Genet. 2010;47:217–222.

7. Shi Q, Chen J, Pongmoragot J, et al. Prevalence of Fabry disease in stroke patients – a systematic review and meta-analysis. J Stroke Cerebrovasc Dis. 2014;23:985–992.

8. Lidove O, Kaminsky P, Hachulla E, et al. Fabry disease “The New Great Imposter”: results of the French Observatoire in Internal Medicine Departments (FIMeD). Clin Genet. 2012;81:571–577.

9. Mehta A, Beck M, Eyskens F, et al. Fabry disease: a review of current management strategies. QJM. 2010;103:641–659.

10. Lidove O, West ML, Pintos-Morell G, et al. Effects of enzyme replacement therapy in Fabry disease – a comprehensive review of the medical literature. Genet Med. 2010;12:668–679.

11. Rombach SM, Smid BE, Bouwman MG, et al. Long term enzyme replacement therapy for Fabry disease: effectiveness on kidney, heart and brain. Orphanet J Rare Dis. 2013;8:47.

12. Biegradable M, Linthorst GE, van Schaik IN, et al. Fabry disease: a rare cause of neuropathic pain. Curr Pain Headache Rep. 2013;17:365.

13. Bertelsen AK, Tondel C, Krohn J, et al. Small fibre neuropathy in Fabry disease. J Neurol. 2013;260:917–919.

14. Tuttolomondo A, Pecoraro R, Simonetta I, et al. Neurological complications of Anderson-Fabry disease. Curr Pharm Des. 2013;19:6014–6030.

15. Schiffmann R. Fabry disease. Pharmacol Ther. 2009;122:65–77.

16. Ro L-S, Liao M-F, Chen C-J, et al. Peripheral microcirculation dysfunction evaluated by computed tomography perfusion study in Fabry patients. Eur J Neurol. 2012;19:e4–e6.

17. Flavahan NA. A vascular mechanistic approach to understanding Raynaud phenomenon. Nat Rev Rheumatol. 2014doi:10.1038/nrrheum.2014.195.

18. Bolla G, Dissier P, Harle JR, et al. Le «Raynaud» de la maladie de Fabry. Intérêt de la capillaroscopie digitale. A propos de 3 cas. Rev Médecine Interne. 1993;14:488.

19. Jansen W, Lentner A, Genzel I. Capillary changes in angiokeratoma corporis diffusum Fabry. Inte´reˆt de la capillaroscopie digitale. A propos de 3 cas. Me´decine Interne. 1994;7:68–70.

20. López-Rodrı´guez M, Barbado-Herenda FJ, Torrijos-Eslava A, et al. Capillaroscopy in Fabry disease: study of a family. Indian J Hum Genet. 2006;12:23–25.

21. Wasik JS, Simon RW, Meier T, et al. Nailfold capillaroscopy: specific features in Fabry disease. Clin Hemorheol Microcirc. 2009;42:99–106.

22. Costanzo L, Bucceri S, Capranzano P, et al. Early cardiovascular remodelling in Fabry disease. J Inherit Metab Dis. 2014;37:109–116.

23. Société Française de Médecine Vasculaire (SFMV), Collège des Enseignants de Médecine Vasculaire (CEMV), Collège Français de Pathologie Vasculaire (CFPV), Société Française de Microcirculation. Atlas de capillaroscopie. Issy-les-Moulineaux, France: Elsevier Masson; 2013.

24. Herrick AL. The pathogenesis, diagnosis and treatment of Raynaud phenomenon. Nat Rev Rheumatol. 2014;10:1038/nrrheum.2014.195.

25. Gayraud M. Raynaud’s phenomenon. Joint Bone Spine. 2007;74:e1–e8.

26. De Angelis R, Salaffi F, Grassi W. Raynaud’s phenomenon: prevalence in an Italian population sample. Clin Rheumatol. 2006;25:506–510.
27. Germain D, Atanasiu O, Cordier A, Benistan K. Patients affected with Fabry disease have an increased prevalence of Raynaud’s phenomenon: an investigation of 222 patients (Abstract/Program 2367T). Presented at the 63rd Annual Meeting of The American Society of Human Genetics, October 23, 2013 in Boston, MA. Available at: http://www.ashg.org/2013meeting/abstracts/fulltext/f130122306.htm. Accessed 7th November 2014.

28. Prete M, Fatone MC, Favoino E, et al. Raynaud’s phenomenon: from molecular pathogenesis to therapy. *Autoimmun Rev.* 2014;13:655–667.

29. Block JA, Sequeira W. Raynaud’s phenomenon. *Lancet.* 2001;357:2042–2048.

30. Hoerth C, Kundi M, Katzenschlager R, et al. Qualitative and quantitative assessment of nailfold capillaries by capillaroscopy in healthy volunteers. *VASA.* 2012;41:19–26.

31. Lorenzen JM, Dietrich B, Fiedler J, et al. Pathologic endothelial response and impaired function of circulating angiogenic cells in patients with Fabry disease. *Basic Res Cardiol.* 2013;108:311.

32. Aerts JM, Groener JE, Kuiper S, et al. Elevated globotriaosylsphingosine is a hallmark of Fabry disease. *Proc Natl Acad Sci U S A.* 2008;105:2812–2817.

33. Michaud L. Vascular tortuosities of the upper eyelid: a new clinical finding in Fabry patient screening. *J Ophthalmol.* 2013;2013:207573.

34. Waldek S, Patel MR, Banikazemi M, et al. Life expectancy and cause of death in males and females with Fabry disease: findings from the Fabry Registry. *Genet Med.* 2009;11:790–796.

35. Owen JE, Goldstein MS, Lee JH, et al. Use of health-related and cancer-specific support groups among adult cancer survivors. *Cancer.* 2007;109:2580–2589.

36. Krizek C, Roberts C, Ragan R, et al. Gender and cancer support group participation. *Cancer Pract.* 1999;7:86–92.