Outcomes in Primary Raynaud Phenomenon

A Meta-analysis of the Frequency, Rates, and Predictors of Transition to Secondary Diseases

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Objective: To summarize the current literature on the frequency, rates, types, and outcome predictors of secondary diseases that develop in patients with primary Raynaud phenomenon.

Methods: A structured MEDLINE literature search with the MeSH heading "Raynaud’s disease," which was crossed with (1) systemic sclerosis, (2) prognosis, (3) prospective studies, (4) follow-up studies, and (5) retrospective studies, was used to identify 910 articles for possible inclusion. Articles that identified patients with primary Raynaud phenomenon who were followed up and re-evaluated at the end of the study, and which used published classification criteria to assess the presence or absence of secondary disease were included. Patient-years of Raynaud disease, patient-years of follow-up, and rates and predictors of transition to secondary disease were calculated from the articles selected. The summary odds ratio and positive predictive value for evaluation criteria at entry were calculated from 2×2 tables generated for each variable.

Results: Ten articles identified a total of 639 patients with primary Raynaud phenomenon who were followed up for 2531 patient-years. Eighty-one patients (12.6%) developed a secondary disorder, 80 of which were connective-tissue diseases. Transitions occurred at a mean rate of 3.2 per 100 patient-years of observation. The mean time to develop a secondary disorder was 2.8 years from study entry and 10.4 years from the onset of Raynaud phenomenon. At entry, the best predictor of transition was an abnormal nailfold capillary pattern (positive predictive value, 47%). Antinuclear antibodies in these patients had a positive predictive value of only 30%.

Conclusion: Although a variety of clinical and serological abnormalities can be found in patients with primary Raynaud phenomenon, only a small percentage of them develop a connective-tissue disease.

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REVERSIBLE vasospasm of the extremities occurs either as an isolated symptom without underlying disorder (primary Raynaud phenomenon) or in association with another disorder or condition (secondary Raynaud phenomenon). Several of the more commonly recognized associations include the use of vibration tools, certain drugs (especially ergotamine tartrate), smoking, history of frostbite, environmental exposure to vinyl chloride, and, importantly, diseases of vascular or autoimmune origin. Secondary diseases are infrequently reported in patients identified through population-based surveys, where prevalence estimates of Raynaud phenomenon range from 3% to 22%. In contrast, secondary diseases are commonly found in cross-sectional studies of patients with Raynaud phenomenon who have sought medical attention. In 1 large series from a vascular surgery department, secondary diseases were found in more than 81% of patients seen. In another series from an immunology department, connective-tissue diseases were found in 49% of patients with Raynaud phenomenon when first seen, and evidence of associated diseases was found in an additional 17%. These frequency differences are likely influenced by population and referral bias, as well as the thoroughness with which these patients are evaluated, but they suggest that a high percentage of patients with primary Raynaud phenomenon do not seek medical attention for this condition.

Although patients diagnosed as having primary Raynaud phenomenon may eventually develop a secondary disorder, the frequency, rates, and types of diseases that evolve in these patients are not well established. In 1 large series, only 13 of 267 patients identified as initially having primary Raynaud phenomenon

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METHODS

SEARCH STRATEGY

Appropriate articles were identified by searching the National Library of Medicine MEDLINE and examining bibliographies of original articles and review articles retrieved. The National Library of Medicine search included articles published from January 1966 through June 1996. Five searches were carried out by means of the MeSH headings: (1) systemic sclerosis or circumscribed systemic sclerosis, (2) prognosis, (3) prospective studies, (4) follow-up studies, and (5) retrospective studies. This strategy identified 910 articles for which the titles and available abstracts were examined for possible inclusion. Articles not dealing with the study of patients with Raynaud phenomenon, or where Raynaud, Raynaud phenomenon, or Raynaud's phenomenon did not appear in the title, were excluded. Abstracts of the remaining articles, where available, were examined, and if the content appeared pertinent or the abstract was not available, the entire article was reviewed for possible inclusion. From these articles, those that (1) identified patients by the presence of Raynaud phenomenon, (2) evaluated and excluded at entry known secondary or associated causes of Raynaud phenomenon, (3) measured a clinical or laboratory variable at study entry, and (4) followed up and reevaluated patients at the end of the study were included. The use of classification criteria was included in the data analysis.21 One article that did not reference classification criteria for diagnosing secondary disease (the “gold standard”), and examination of patients at entry and follow-up. A maximum score of 100 was possible with this scale. For each analysis, transition rates of patients were compared from the “top” half and the “bottom” half of the scale.

QUALITY SCORE

Because there is no published quality-assessment scale appropriate for this type of review, an assessment tool was developed to judge the quality of the articles reviewed, with the use of a modification of scales published for evaluating diagnostic tests (Table 1).30 For each variable, a value of 0 (criterion not met) or 2 (criterion satisfied) was assigned and this value was multiplied by a previously assigned weighted value of 1, 3, or 5. Criteria given the highest weighting (value of 5) were exclusion of a preexisting disease at entry, detailed description of patients at follow-up whose disease evolved during the period of observation, the use of classification criteria for diagnosing secondary disease (the “gold standard”), and examination of patients at entry and follow-up. A maximum score of 100 was possible with this scale. For each analysis, transition rates of patients were compared from the “top” half and the “bottom” half of the scale.

DATA ANALYSIS

Numbers and types of transitions were derived from information reported in the 10 articles and included in the data analysis. Patient-years of follow-up and patient-years of Raynaud disease were calculated by multiplying the number of patients included in each study by the average duration of follow-up and average duration of Raynaud phenomenon for each study, respectively. Rates of transition were adjusted by patient-years of follow-up or patient-years of Raynaud phenomenon for each study, and expressed as transitions per 100 patient-years of follow-up or per 100 patient-years of Raynaud phenomenon. For each evaluation criterion reported by the authors to be present or absent at entry, a 2×2 table was constructed to tabulate whether the test or finding was associated with the eventual development of an associated disease. The summary positive and negative predictive values of these tests and findings were calculated from these tables. Summary odds ratios were calculated by means of a Mantel-Haenszel fixed-effects model, weighting individual studies by their variance.31 One half was added to each cell so that no value would equal 0.34 Kaplan-Meier curves and proportional hazard curves were generated by the statistical software program Stata.35

RESULTS

PATIENT SUMMARY

A total of 639 patients (82% were women and 18% were men) with primary Raynaud phenomenon were identified from 10 studies that satisfied the inclusion criteria outlined above (Table 2).22-31 The average age at onset of Raynaud phenomenon was 33.6 years (range, 22.6-45.7 years), and the average age at entry into the studies was 42.1 years (range, 35.3-52.7 years). Raynaud phenomenon had been present in these patients for a mean of 8.3 years (range, 4.4-21.3 years).
years) before study entry. The average length of study follow-up was 4.0 years (range, 2.1-6.5 years), for a total of 2531 patient-years of follow-up. The total duration of Raynaud phenomenon (duration of study plus duration of Raynaud phenomenon before entry) was 12.3 years (range, 8.4-28.3 years), or 7844 patient-years of Raynaud phenomenon.

TRANSITIONS

During follow-up, 12.6% of patients (81/639) developed a secondary disorder, 80 of which were connective-tissue diseases (Table 3). Two thirds (n=53) of these were systemic sclerosis. When adjusted for length of follow-up, transitions were infrequent, occurring at a mean rate of 3.2 (range, 0.8-7.0) per 100 patient-years of observation. The rate of transition when measured from the onset of Raynaud phenomenon was 1.4 (range, 0.4-1.9) transitions per 100 patient-years of symptomatic Raynaud phenomenon.

Six articles provided information about individual patients who developed secondary diseases in sufficient detail to allow generation of a 2 × 2 table.
detail to calculate survival curves. Three of these reported the time of transition from the onset of Raynaud phenomenon and the time from study entry (1 article presented the data in both fashions). The Kaplan-Meier curves for these patients are shown in the Figure. The mean time to develop a secondary disorder from onset of Raynaud phenomenon in 29 patients was 10.4 years (median, 7.8 years; range, 0.6-27.9 years), and the mean time to develop a secondary disorder calculated from entry into studies in 27 patients was 2.8 years (median, 2.3 years; range, 0.1-6.5 years). When calculated from entry into studies, the time to develop systemic sclerosis (mean, 3.2 years; median, 2.7 years) was longer than the time to develop a secondary disorder other than systemic sclerosis (mean, 1.3 years; median, 1.3 years; P=.03). However, when calculated from onset of Raynaud phenomenon, the time to develop systemic sclerosis (mean, 10.1 years; median, 10.7 years) compared with a secondary disorder other than systemic sclerosis (mean, 10.7 years; median, 7.5 years) was not different (P=.35).

PREDICTORS OF TRANSITION

Although all 10 studies measured 1 or more clinical or laboratory variables that potentially served as predic-

tors of clinical transition, there was considerable variation in what initial evaluation was performed. Nine of 10 measured antinuclear antibodies (ANAs), 6 looked at nailfold capillary pattern, 5 assessed digital ulcers or pits, 4 reported cutaneous features other than digital ulcers (puffy fingers, telangiectasias, or sclerodactyly), 4 assessed pulmonary function, and 4 assessed esophageal motility.

The odds ratios and the 95% confidence intervals for these measures are shown in Table 4. As independent variables, the odds ratios of all except digital ulcers were statistically significant (column 2). The types of assays (indirect immunofluorescence or immunoblotting) or substrates (rat liver or HEP-2 cells) used to measure the ANAs did not significantly alter the findings for ANA testing (data not shown). However, the odds ratio of abnormal pulmonary function and esophageal dysmotility (but not cutaneous lesions), when adjusted for the presence of either a positive ANA test result or abnormal nailfold capillary pattern, did not reach statistical significance (column 3). The odds ratio of an abnormal nailfold capillary pattern, adjusted for a positive ANA finding, retained its statistical significance, but the odds ratio of a positive ANA result, adjusted for an abnormal nailfold capillary pattern, was not statistically significant. The odds ratio for patients with both a positive ANA result and abnormal nailfold capillary pattern was 22.6 (95% confidence interval, 6.9-73.8). The odds ratio of developing a secondary disease for patients with any abnormality (compared with those who had no abnormality) was 29.7 (95% confidence interval, 15.2-58.1).

The unadjusted negative and positive predictive values for each variable reported in the 10 studies are shown in columns 4 and 5 of Table 4. All variables were better negative than positive predictors of the eventual development of a secondary disease, but the best positive predictor of transition (an abnormal nailfold capillary pattern) was only 47%.

ARTICLE QUALITY

The average rating of the articles reviewed was 77.1, and the average score of the highest 5 articles was 88. The use of classification criteria for diagnosis of transitions was the gold standard for study inclusion in this review,
Raynaud phenomenon is found frequently in the general population. For patients with no apparent secondary disorder who seek medical attention, slightly more than 1 in 10 will eventually develop a connective-tissue disorder. In contrast to observations made by Allen and Brown,12 these transitions can occur over many years: an average of 2.8 years from initial examination and an average of 10.4 years from the onset of Raynaud phenomenon. The best predictors of transition at entry are findings on physical examination: an abnormal nailfold capillary pattern and cutaneous findings of telangiectasias, puffy fingers, or sclerodactyly. The presence of dilated capillary loops and areas of avascularity in the nailbeds of patients with scleroderma and related disorders has been reported by several authors, and this study reemphasizes its importance as an early clinical finding.17-45 The sensitivity of ANAs in systemic sclerosis has been reviewed recently but, in this analysis, had a positive predictive value of only 30%.46 Abnormal pulmonary function, esophageal dysmotility, and digital pits or ulcers, when adjusted for the presence of a positive ANA finding or abnormal nailfold capillary pattern, were not statistically significant independent predictors of transition.

The generalizability of the findings in this analysis is limited by substantial variation in the rates of transition to secondary disease, even when adjusted for length of follow-up. Differences with respect to age at entry, duration of Raynaud phenomenon before study entry, and length of follow-up were apparent, but additional variables that could not be assessed are likely to include sex and ethnic variation, population and referral bias, and differences in standardized entry and assessment protocols. Among these, referral bias is likely to be significant. Six of the 10 studies reviewed were from immunology or rheumatology specialty centers, several with known interests in systemic sclerosis. Patients may have been referred to these specialists because of their physicians’ clinical suspicion of a secondary disorder, potentially overestimating the frequency with which a connective-tissue disease would develop in these patients.

In addition, there were no uniform entry criteria or standard evaluation protocols among the studies reviewed. Some articles may have contaminated their findings by including patients who at entry already had features of systemic sclerosis (puffy fingers, telangiectasias, or sclerodactyly). As these turned out to be strong predictors of transition, overestimation of the rates of transition is likely in these studies. Interestingly, however, the presence of digital ulcers, one of the classification criteria for systemic sclerosis, was not a good predictor of transition. The findings from larger, multicenter prospective studies with standard entry and evaluation criteria that include patients with Raynaud phenomenon may address these issues.17-48

The challenge a clinician often faces in classifying some patients with Raynaud phenomenon is not apparent in an analysis of this type. Of the 639 patients in this review, who were identified at entry as having primary Raynaud phenomenon, 262 had some clinical or laboratory abnormality identified at entry. However, only 76 of these 262 patients developed a classifiable connective-tissue disease during the period of follow-up (5 patients who developed a secondary disease had no abnormalities at entry). The remaining 186 subjects (approximately 30% of all patients studied) who had some identifiable abnormality in addition to their Raynaud phenomenon did not develop a secondary disorder. Authors described these conditions as “scleroderma spectrum” disorders, “possible,” “probable,” “suspected,” or “questionable” secondary Raynaud phenomenon, and “Group II” patients. This diversity of terminology illustrates the problems physicians can encounter in characterizing such patients. Difficulties in classifying and treating many patients who have incomplete features of connective-tissue diseases have been addressed, as has the limited usefulness of classification criteria in the clinical diagnosis and management of systemic sclerosis.49,50 Criteria proposed by LeRoy and Medsger42 may prove useful in categorizing these patients with indeterminate disease.

Despite these limitations, this study demonstrates that, in a clinical practice, the rate and frequency with which secondary disorders classifiable as connective-tissue diseases develop in patients with primary Raynaud phenomenon is low. The best predictors of transition are features seen on physical examination, especially abnormalities of the nailfold capillary bed. In addition to symptomatic treatment of these patients’ Raynaud phenomenon, careful serial physical examinations, reassurance, and watchful waiting may be the most effective strategy to care for these patients.

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REFERENCES