Epidemiology of Raynaud's Phenomenon

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Abbreviations

ANA	Anti-nuclear antibody
CI	Confidence interval
CTD	Connective tissue disease
DU	Digital ulceration
ESR	Erythrocyte sedimentation rate
GP	General practice
HAQ	Health assessment questionnaire
MCTD	Mixed connective tissue disease
ND	Not described
OR	Odds ratio
RA	Rheumatoid arthritis
RP	Raynaud's phenomenon
RR	Relative risk
SLE	Systemic lupus erythematosus
SSc	Systemic sclerosis
UK	United Kingdom
US	United States of America
VCM	Vinyl chloride monomer
VWF	Vibration white finger

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Key Points

1. The prevalence of RP in most studies in the general population is between 3 and 5 %.
2. Primary RP accounts for 80–90 % of cases.
3. The prevalence of primary RP ranges from 2 to 20 % in women and 1–12 % in men depending on geographic location, the population studied, the definition of RP used and the method of case ascertainment.
4. Risk factors differ between women and men.
5. Primary RP and RP secondary to autoimmune disease are more common in women than in men.
6. In men, the prevalence of RP increases with age and is more likely than in women to be secondary to occupational exposures such as vibration or atherosclerotic peripheral vascular disease.
7. Up to 50 % of subjects with primary RP have a family history of RP in first-degree relatives, particularly in women and in those with early onset RP.
8. The prevalence of secondary RP depends upon the underlying disease.
9. Progression to secondary RP occurs in 14–37 % of subjects with primary RP.

This chapter discusses the epidemiology firstly of primary Raynaud's phenomenon (RP) and then of the different forms of secondary RP. Points considered include incidence, prevalence, and risk factors. "Risk factors" encompass risk factors for development of RP, for progression

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from primary RP to systemic disease, and (in the patient with systemic sclerosis [SSc]-related RP) for progression to digital ulceration or gangrene.

Primary RP

Incidence and Prevalence of Primary RP

Most studies of RP in the general population report the prevalence to be between 3 and 5 % with primary RP accounting for 80–90 % of cases [1, 2]. The prevalence of primary RP varies according to geographic location and ranges from 2.1 % in a study of 2,155 people randomly selected from an Italian general practice to 11.5 % among 234 people from the electoral roll in New Zealand [3, 4] with the majority of studies reporting a prevalence of less than 5 % (Table 3.1). Rates as high as 21 % in women and 16 % in men were found in general practices in the UK [5]. A large study of 4,182 patients from the Framingham cohort in the USA followed for 16 years reported a prevalence of primary RP of 7.2 % [6]. In Turkey, the prevalence among medical students and hospital staff was 3.6 and 5.9 % among 768 patients attending a medical clinic [7, 8]. In Greece, 5.2 % of 500 randomly selected hospital employees had definite RP [9]. Despite the variation in prevalence, there has been no clear change over time.

The incidence of primary RP has not been widely studied. Suter et al. followed 1,358 healthy individuals in the Framingham Offspring study cohort for a mean 7 years and found an incidence of RP in 2.2 % of women and 1.5 % of men over this 7 year period [10].

Several factors contribute to variation in the rates reported. Most studies have sought to distinguish primary from secondary RP but not all have reported the definition of RP used or they have used differing definitions. The most commonly used definition was proposed by the UK Scleroderma Study Group:

- Definite RP: repeated episodes of biphasic colour changes upon cold exposure
- Possible RP: uniphasic colour changes plus numbness or paraesthesiae upon cold exposure
- No RP: no colour changes upon cold exposure [11]

A less rigorous definition of blanching of the fingers with sensory symptoms in response to cold was used for the UK general practice study, which may also explain the higher prevalence rates observed [5]. Others have used cold-induced single colour change or finger blanching with clear demarcation.

Some studies have assessed prevalence in people randomly selected from the general population. Others have only included people selected from limited populations such as patients attending a particular general practice, medical students or employees and hence are prone to selection bias. While the predominant racial groups have varied amongst studies, the prevalence rates in different racial groups are often not reported. Only one study directly compared two genetically different racial groups. Valter et al. reported a higher prevalence of RP in 4,341 Indo-Europeans compared with 5,248 Finno-Ugric people living in Estonia [12].

Methods of case ascertainment have also varied. Patient- or physician-led questionnaires, telephone interviews and face-to-face assessments with or without the aid of colour charts and photos depicting the triphasic colour response have all been used and may be susceptible to recall bias. Cold challenge testing is a more objective assessment of vasoreactivity but is impractical in population studies.

Risk Factors for Primary RP

Age

While the onset of primary RP can be at any age, it is three times more common in those aged less than 40 years by which time in one prospective study of 424 people with RP, 73 % had developed symptoms [13]. Many patients with RP who are less than 40 years of age have a family history of primary RP [14]. RP appearing after the age of 40 years is considered late onset. In these patients, a positive family history is less common and secondary RP is more likely than primary [13]. Only 3 % of cases develop after the age of 60 [13].

Table 3.1 Prevalence of primary Raynaud's phenomenon

Country	Mean temperatures	Population studied	Ascertainment and definition	Number of people	Prevalence of RP
UK, 1990 [5]	ND	2 groups >15 years of age: patients attending 1 of 5 GPs in London; postal questionnaire to randomly selected patients of 2 GPs	Questionnaire followed by clinical interview; RP if white colour change, precipitated by cold and sensory symptoms	1,532 (413 in postal survey, 1,119 attending GP)	Postal survey: 19 % of women, 11 % of men Questionnaire at GP: 21 % of women, 16 % of men
South Carolina, 1990 [30]	ND	South Carolina residents >18 years	Face-to-face physician interview	5,246	3.5 % of total population 4.3 % of women, 2.7 % of men
Japan, 1991 [31]	ND	Japanese residents	Face-to-face physician interview with aid of photographs	3,873 (1,998 women, 1,875 men)	2.2 % of women, 1.2 % of men
Netherlands, 1992 [32]	ND	508 patients attending a GP	Questionnaire	508	2.9 % of women, 0.5 % of men
USA and France, 1997 [18]	5 regions ranging from warm coastal climates to cold mountainous regions	10,149 randomly selected people in Charleston (USA) and France	Telephone interview followed by face-to-face interview, clinical examination	10,149	5.8–20.2 % of women, 4.1–12.7 % of men Higher rates in cooler regions
USA, 1997 [6]	ND	4,182 (Framingham Study)	Physician-led questionnaire	4,182	All RP: 9.6 % of women, 8.1 % of men Primary RP over 16 years follow-up: 7.2 %
Estonia, 1998 [12]	ND	9,589 people (5,248 Finno-Ugric Estonians; 4,341 Indo-European Slavs)	Questionnaire followed by physical examination	9,589	4.0 % (higher prevalence among Slavs)
USA, 1999 [33]	ND	2,196 randomly chosen African American people living in inner-city Baltimore	Questionnaire, face-to-face interview RP if cold sensitivity plus cold-induced white or blue colour change of fingers	2,196	3.8 %
Greece, 2000 [9]	6.5 °C in winter, 24.8 °C in summer	500 of 756 randomly selected from hospital employees; mean age 33.7 years	Physician-led questionnaire, clinical examination	500	5.2 % 6.4 % of women, 0.9 % of men
UK, 2000 [34]		12,907 of 22,194 randomly selected from GP registration list in England, Wales and Scotland, and from armed forces in Britain; aged 16–64 years	Questionnaire; determined rates of finger blanching with clear demarcation	12,907 (5,994 women, 6,913 men)	4.6 %

(continued)

Table 3.1 (continued)

Country	Mean temperatures	Population studied	Ascertainment and definition	Number of people	Prevalence of RP
Spain, 2001 [35]	11 °C in winter, 22.8 °C in summer	276 people attending a GP in Valencia; mean age 54.4 years No concurrent CTD	Questionnaire	276 (205 women, 71 men)	3.3 % 3.4 % of women, 2.8 % of men Triphasic colour changes: 0 %; pallor only: 100 % of men, 57.1 % of women Pallor/cyanosis: 42.9 % of women
Turkey, 2003 [8]	−10 to 15 °C; 10–37 °C in summer	768 people >18 years (358 women, 410 men) attending GP. Excluded if comorbidities including secondary RP. Mean age 29.21 ± 10.35 years	Questionnaire. Diagnostic criteria as per UK Scleroderma Study group	768 (358 women, 410 men)	Definite RP: 5.9 % (mean age 24.78 years), male:female = 55:45 Probable RP: 7.0 % (mean age 26.94 years)
USA, 2005 [10]	ND	1,358 of 1,525 patients contacted; mean age 53.5 years; (Framingham Offspring study cohort)	RP clinical diagnosis, did not require two colour changes	1,358	10.9 % of women, 7.8 % of men
Italy, 2006 [3]	5.6 °C in winter, 21.6 °C in summer	2,155 of 3,664 randomly selected from 16 GPs in central Italy; aged >18 years (mean age 57.8 years)	Questionnaire, clinical examination RP if experienced pallor and sensory change precipitated by cold	2,155	2.1 % total population Male:female = 88.8:11.2 3.4 % of women, 0.5 % of men Positive for at least 1 criterion of CTD: 4.3 % Subsequently diagnosed with CTD: 0.28 %
Turkey, 2008 [7]	−0.6 to 6.8 °C in winter, 17.2–31.6 °C in summer	1,414 of 1,533 healthy medical students and hospital staff at a hospital in the Edirne Province, northwestern Turkey. Mean age women 27.0 years, men 27.5 years	Questionnaire Diagnostic criteria as per UK Scleroderma Study group	1,414 (838 women, 576 men)	Definite RP: 3.6 %
New Zealand, 2009 [4]	Varied; subtropical to sub-Antarctic	234 of 350 people randomly selected from New Zealand electoral roll	Questionnaire Diagnostic criteria as per UK Scleroderma Study group	234	Definite RP: 11.5 %

ND not described, *GP* general practice, *CTD* connective tissue disease

Female Sex

The prevalence of primary RP is consistently higher in women compared with men, being up to four times more common [15, 16]. This is particularly true for people aged less than 40 years as women are more likely to develop RP at a younger age and the prevalence of RP increases with age in men, as occupational exposures and atherosclerotic disease become more prevalent [17]. Prevalence rates of RP in men only exceed those in women in the setting of occupational exposure to vibration and hand trauma (Chap. 9).

Risk profiles differ between men and women. Fraenkel et al. reported that twice as many women who had been widowed, divorced or separated had RP than those who were married or had never married, suggesting emotional stress may have a role, but this relationship was not observed in men [17]. They also found that alcohol use doubled the risk of developing RP in women but not in men, while smoking increased the risk of RP in men only (odds ratio [OR] 2.6, 95 % CI 1.1–6.3) [17]. In contrast, another study found no association with either alcohol or smoking [18]. In both sexes, a lower body mass index is associated with a higher risk of developing RP, perhaps due to greater sensitivity to cold temperatures [15]. Whether the increased prevalence of RP in women is related to hormonal factors is unknown [17].

Environmental Factors

Relatively few environmental risk factors have been identified and many studies are cross-sectional or do not control for other factors.

In addition to triggering attacks, colder climate may have an aetiologic role. Subjects who have ever lived in colder climates have a higher prevalence of primary RP [19]. Few studies have directly compared the prevalence in different climates [19, 20] but the prevalence is generally higher in cooler locations, with Maricq et al. reporting rates up to 20.2 % in women and 12.7 % in men in cool mountainous regions [19].

The association with occupational factors such as vibration injury in particular, is well known but occupational risks have not been examined in most population studies of primary RP. Exposure to solvents, for example in medical laboratories, is associated with a higher prevalence of RP with symptoms of RP occurring more commonly in the absence of cold [21].

Genetic Factors (Including for Secondary RP)

Up to 50 % of subjects with primary RP have a family history of RP in first-degree relatives, particularly in women and in those with early onset RP [22, 23]. This suggests a genetic susceptibility although shared environmental factors could also contribute. In a study of female twins in the UK, Cherkas et al. found the concordance rates for cold sensitivity, RP and severe RP were all higher among monozygotic than dizygotic twins with heritability of 53 %, 55 % and 53 % respectively. Moreover, a potential contribution from the shared environment for all three traits was rejected [24].

Frech et al. found the relative risk of RP in first-degree relatives of patients with SSc compared with first-degree relatives of controls was 6.38 (95 % CI: 3.4–11.8) with decreasing risk with more distant relationships [25] This was greater than the risk of having SSc (RR 3.07) or an autoimmune disease (RR 2.49) and suggests the vasculopathy of RP is a heritable condition related to the vasculopathy of SSc but large genetic studies in this area are lacking. Polymorphisms of various candidate vasoactive mediator genes were not associated with RP in a small study of 95 cases [23]. Genetic abnormalities in the expression of type I interferon that predispose to abnormal endothelial cell senescence and apoptosis have been linked to SSc vasculopathy [26]. Similarly, a type I interferon signature on gene expression profiling may be associated with RP. This occurs in the setting of biallelic loss of protein expression mutations in the gene for tartrate-resistant acid phosphatase associated with bone dysplasia and increased autoimmunity including RP [27]. A two stage microsatellite-based genome wide study of six multi-case families in 2000 identified the β subunit of the muscle acetylcholine receptor and the serotonin 1B and 1E receptors as possible candidate genes for RP susceptibility [27]. For many common diseases,

single-nucleotide polymorphism-based, genome-wide association studies have been performed to identify genetic risk variants with great success. Despite the supportive evidence for a genetic component to the development of RP, such an approach has not yet been utilised. This is perhaps due to the lack of a sufficiently large collection of suitable cases with DNA available, and/or to the cost of such a study.

Polymorphisms in clotting factors leading to increased microvascular thrombosis do not appear to be increased in patients with primary RP [28].

Genetic factors may also influence the predisposition to secondary RP related to environmental factors such as vinyl chloride monomer (VCM) induced RP. A case-control study of 58 subjects with RP from a population of 305 French workers with a history of VCM exposure, found no association between M1 and GST T1 genetic polymorphisms of glutathione S-transferases, involved in VCM metabolism, and RP when analysed separately but when combined, were significantly associated with RP when compared with other combinations of genotypes (OR = 2.1, 95 % CI = 1.1–3.8) [29]

Secondary RP

Incidence and Prevalence of Secondary RP

Secondary RP occurs less frequently in the general population than primary RP, with a variable prevalence that depends on the underlying disorder (Table 3.2). Only 10 % have a positive family history [36].

In a small study of 118 patients seen in a rheumatology clinic in Italy, patients were classified as primary RP (29.7 %), secondary RP (53.3 %) or a third group with features suggestive of an underlying autoimmune disease but who did not yet meet full diagnostic criteria (16.9 %) [37]. An autoimmune disease was the most common underlying diagnosis in the secondary RP group (42.3 %), with SSc being the most common (25.4 %) followed by RA (7.6 %), SLE (5.9 %) and Sjogren's syndrome (1.7 %). Other major causes included vibrating tools and atherosclerosis (both 2.5 %) [37].

Similarly, a multicentre study in Italy of 761 patients with RP found primary RP in 35.2 % and secondary RP in 64.8 % of patients. SSc was the most common autoimmune disease (28.4 %) followed by SLE (6.8 %) and RA (5 %) [38]. A large proportion of patients (82.5 %) classified as

Table 3.2 Secondary Raynaud's phenomenon

Autoimmune disease
Systemic sclerosis
Rheumatoid arthritis
Sjogren's syndrome
Systemic lupus erythematosus
Dermatomyositis
Polymyositis
Occlusive vascular diseases
Atherosclerosis and emboli
Thromboangiitis obliterans (Buerger's disease)
Haematologic disorders
Cryofibrinogenaemia
Cryoglobulinaemia
Paraproteinaemia
Polycythaemia
Cold agglutinin disease
Neurologic disorders
Intervertebral disc disease
Carpal tunnel syndrome
Thoracic outlet syndrome
Pulmonary hypertension
Drugs
Ergot
Bleomycin
Cisplatin
Clonidine
Beta blockers
Cyclosporin
Interferon- α
Nicotine
Amphetamines
Cocaine
Vibration-induced
Vascular trauma
Hypothenar Hammer hand syndrome
Cold injury

Table adapted from UpToDate, Harrisons Internal Medicine

having primary RP had isolated features consistent with potential future development of an autoimmune disease. Common features included arthralgia (56 %), painless swelling of fingers (23.9 %), dryness of the mouth (21.6 %), migraine headaches (20.5 %), dryness of the eyes (16.8 %) and arthritis (15.7 %). This highlights the limitations of classifying RP into purely primary and secondary subtypes [38].

The annual incidence of secondary RP in the general population is unknown but among 112 patients with RP (73 % with primary RP, 14.3 % with secondary RP and the remainder suspected RP) attending a rheumatology clinic, followed for 5 years, the annual incidence of a concomitant disease that indicated secondary RP was 1.4 % [39].

Aetiology of Secondary RP

Systemic Sclerosis

The most common cause of secondary RP is SSc with rates of >95 % reported [40, 41] although a retrospective study of 61 patients with SSc in Malaysia, found a lower prevalence of 82.6 % [42]. This may reflect a difference in ethnicity, warmer climate or be due to recall bias. In most cases, RP is the initial presenting symptom of SSc and may precede other symptoms by 10 years [43, 44].

Walker et al. found a mean age of onset of RP of 42.9 years old for both limited and diffuse SSc although time until the next disease manifestation was significantly longer for those with limited disease (5 years versus 1.9 years) [41]. Patients who were anti-centromere positive were also found to have a significantly longer duration until the next disease manifestation compared to those who were anti-Scl70 positive (6.5 years versus 2.4 years). Subsequent organ involvement also varied depending on the age of onset of RP. In those who developed RP prior to the mean age of 42.9 years there was a higher rate of digital ulcers, but a lower rate of pulmonary fibrosis, pulmonary hypertension, diastolic dysfunction and arterial hypertension [41]. Age of onset is unrelated to geographic location [45].

Other Autoimmune Diseases

The reported prevalence of RP in RA ranges from 0 to 63 % [46]. Hartmann et al. performed a meta-analysis of 28 studies with 3,730 patients and using a random effects model, the overall estimate of prevalence was 12.3 % [46]. The prevalence fell from 11.2 % in 1977 to 9.4 % in 2012 although the definitions of RP varied amongst studies [46].

Between 12.5 and 33 % of patients with primary Sjogren's syndrome have RP, with the majority of studies reporting a prevalence closer to 33 % [47–53]. RP precedes the onset of sicca symptoms in 31–47 % of patients [49, 51–53], for a mean of 2.1 years in one study [52]. Multiple studies have demonstrated the course of RP to be relatively benign in this setting, with no patients developing acral necrosis [48, 49, 51, 52]. Pharmacological treatment is required in around a third of patients [52]. This subgroup of patients has a higher frequency of extra-glandular features compared to those without RP [48, 49, 53].

RP occurs in 2.5–60 % of patients with SLE [54–56], and is the most common cutaneous manifestation that is not lupus-specific [55]. Furthermore, it is more common in those with cutaneous lupus compared to those without [55]. Choojitarom et al. reported RP in 19.4 % of patients without a prior history of thrombosis but with at least one type of antiphospholipid antibody [57]. These patients had a higher rate of subsequent arterial thrombosis compared to those without RP (54 % compared with 18.5 %). Patients with SLE are also more likely to develop digital gangrene if they have concurrent RP [58].

There are few studies of RP in the idiopathic inflammatory myopathies. The prevalence in 30 patients in Jordan was 26 % although the definition of RP used was not documented [59]. A review of patients with anti-synthetase syndrome reported RP in 50 % of those with anti-Jo-1 antibodies and 40–100 % of those with anti-PL-12 antibodies [60].

Most patients with MCTD have features of SSc and the prevalence of RP is around 85 % [61]. RP also occurs in 46–56 % of patients with undifferentiated connective tissue disease, especially if they are female, have abnormal nailfold capillary microscopic changes and positive anti-RNP antibodies

[62, 63]. Other autoantibodies associated with RP include anti-Ku antibodies (67–79 %) [64, 65] and anti-Ki (42.8 %) [66].

Other Systemic Diseases

Occlusion of larger arteries can cause RP in relatively young people. The prevalence of RP in atherosclerotic peripheral vascular disease has been estimated to be 2.4 % [67]. In 103 patients with RP and no underlying disease, angiography demonstrated atherosclerotic stenoses in 44 patients who had a mean age of 47 years (half of whom had dyslipidemia), peripheral emboli in eight and thromboangiitis obliterans in three patients [68]. A meta-analysis of eight studies with 851 patients with thromboangiitis obliterans estimated the prevalence of RP to be 28.1 % [69]. As this disease causes segmental occlusions in limb arteries, mostly in male smokers, RP typically affects only one or two digits and may lead to severe limb ischemia.

Although studies of RP and increased plasma viscosity have conflicting results, Monti et al. reported that 19.5 % of 913 patients with cryoglobulinaemia had RP [70] and was more frequent in essential cryoglobulinaemia (19.9 %) and cryoglobulinaemia associated with autoimmune disease (36.7 %). This compared with the prevalence of RP in cryoglobulinaemia secondary to other diseases such as chronic liver disease (4.6 %) and lymphoproliferative disease (13.5 %) [70]. Other systemic diseases associated with RP include hepatitis C infection (11.8–22 % of those affected have RP) including those without cryoglobulinaemia (3.5 %) [71], human immunodeficiency virus (17.4 %) [72] and primary biliary cirrhosis, with (28.6 %) or without (8.9 %) pulmonary hypertension [73].

Neurologic Diseases

Rarely, RP complicates compression of the spinal cord or nerve roots due to intervertebral disc disease or tumours, or distal nerve compression in the carpal tunnel. A meta-analysis of eight trials with 675 patients with carpal tunnel syndrome with prevalence of RP ranging from 0 to 60 % estimated the prevalence of RP to be 15.5 % [74].

Thoracic outlet syndrome refers to the obstruction of the neurovascular bundle at the base of the neck. Vascular symptoms develop in approximately 10 % of patients. This can be RP or a non-specific constellation of symptoms of arm weakness, numbness, swelling, cyanosis and cold sensation [75]. No studies have assessed the prevalence of RP alone. It is possible that thoracic outlet syndrome and hand-arm vibration syndrome are interrelated although this is yet to be fully elucidated [75].

Drugs (Chap. 10)

Multiple drugs have been associated with RP, with cisplatin being the best studied. A meta-analysis of 24 studies with 2,749 patients found a prevalence of 0–64.3 % with an overall estimated prevalence of 24 % [76]. The onset of RP can be delayed 3–6 months after completing cisplatin-based chemotherapy regimens and be persistent in 10–49 % of cases [77]. There is a higher prevalence in those who receive five or more cycles of cisplatin [78] or in combination with bleomycin [77].

Meta-analyses of patients taking β-blocker drugs and interferon showed an overall estimated prevalence of RP of 14.7 % and 13.6 % respectively [79, 80].

Occupational Exposure to Vibration (Chap. 9)

Multiple epidemiological studies have demonstrated the association between RP and occupational exposure to vibration. Initially, excessive vibration can cause slight changes in sensation in the fingers, and with continued exposure this progresses to vibration white finger (VWF), also called hand-arm vibration syndrome. VWF is often used interchangeably with RP but there are some important differences. While both can lead to well-demarcated pallor of the fingers in response to cold or emotion, most studies of VWF do not mandate the biphasic or triphasic colour change characteristic of RP. In VWF, symptoms occur exclusively in the areas that have been exposed to vibration, thus do not occur in the toes, and severity correlates with the

degree of exposure [81]. The majority of cases are male and occupational vibration exposure comprises approximately one third of cases of RP in men compared with less than 4 % for women [34].

Studies of forestry workers, mechanics, quarry drillers and shipyard workers have found prevalence rates of VWF of 9.5–26.6 % [82–84], 15 % [85], 30.2 % [86] and 71 % [87] respectively. Bozenzi et al. studied workers exposed to hand-transmitted vibration including grinders, mechanics, caulkers, foundry workers, construction workers, quarry drillers, forest workers and workers in shipyards [88]. The prevalence of VWF was 17.2 %, varying from 9 % for grinders to 51.6 % for foundry workers. One prospective study by Hagberg et al. estimated the incidence to be 13.6 per 1,000 years of exposure [89].

Petersen at al. followed patients with VWF over 1–13 years (mean 5.3 years) [90]. Interestingly, while perceived frequency of attacks remained unchanged in 46 % of cases and increased in 32 %, finger systolic pressure actually improved in 43 %. A less favourable outcome was associated with ongoing vibration exposure, smoking, concurrent vascular disease and an earlier age at initial diagnosis.

Hypothenar hammer syndrome is another occupation-related syndrome in which repeated episodes of hand and wrist trauma result in damage to the ulnar artery, leading to aneurysmal dilatation with resultant embolisation and segmental occlusion. This may present as RP but is usually unilateral and associated with digital ulcers in the areas supplied by the affected vessel in 42.6 % of patients [91, 92]. It accounts for 1.13–1.17 % of all cases of RP, with 93.6 % of all cases being male [92]. Carpentier et al. showed that 13 (36.1 %) of 36 men with known ulnar artery occlusion also had RP, which in 8 (61.5 %), occurred only in the hand ipsilateral to the occlusion. 53.8 % had significant exposure to vibrating tools and 75 % had a history of repetitive palmar trauma. No women were studied [93].

Risk and Prognostic Factors for Progression to Systemic Disease

True primary RP may remit with time. In the Framingham Offspring study, primary RP remitted in 64.1 % in women and 64 % in men [10]. For others, RP may be the first sign of a systemic disease or indicate risk for other conditions such as migraine, unexplained syncope and gangrene.

Almost 99 % of patients with primary RP who progress to secondary RP develop an autoimmune disease [44]. Up to 37.2 % of 3,035 people with primary RP followed prospectively for 4.8 years by Pavlov et al. developed a definite connective tissue disease [94]. Patients who present after the age of 40, with a shorter duration of RP or worsening attacks are at risk of progressing to an autoimmune disease [43, 94, 95]. Patients with features suggestive of an underlying autoimmune disease at baseline are at the highest risk of disease progression [43, 44, 95, 96]. In the study by Pavlov et al., a scleroderma pattern of nailfold capillaries was strongly associated with the subsequent development of SSc and other autoimmune diseases [97].

Hirschl et al. followed 236 patients with primary RP for a mean of 11.2 years [43]. The annual incidence of progressing to suspected secondary RP was 2 % and to confirmed secondary RP was 1 %. The mean duration from suspected secondary RP to confirmation of an autoimmune disease was 5 years. Features that were most predictive included antinuclear antigen (ANA) >1:320, raised erythrocyte sedimentation rate (ESR) and abnormal nailfold capillary microscopy. Koenig et al. followed 586 patients with RP for a median 4 years, with 13.6 % progressing to a confirmed autoimmune disease, 92.6 % of whom developed SSc [96]. Patients with SSc-specific autoantibodies and/or abnormal findings on nailfold capillaroscopy at baseline were at the highest risk, with 47 % having SSc at 5 years and estimates of 69 % at 10 years and 79 % at 15 years. An earlier meta-analysis of ten studies with 639 patients with primary RP

also estimated that 12.6 % of patients developed a secondary disease [44]. As found by Koenig et al., a normal nailfold capillary pattern, negative ANA and absence of swollen fingers, telangiectasiae and sclerodactyly at baseline had a high negative predictive value [44, 96].

RP as Risk Factor for Digital Ischemia, Gangrene and Auto-amputation

Digital ulceration (DU) is a significant clinical problem in SSc-related RP, occurring in 30–58 % of patients [98–102], especially in diffuse SSc [100, 103]. The Canadian Scleroderma Research Group (CSRG) found current DU in 8 % of patients (11.9 % of diffuse SSc and 5.1 % of limited SSc) [100]. The prevalence of current DU was even higher in the German Network for Systemic Sclerosis registry at 24.1 % [102]. As expected, a greater proportion of patients have evidence of previous DU; in the CSRG study, 53.1 % of patients had digital pitting scars, again more commonly in diffuse SSc (63.2 % versus 46.6 % in limited cutaneous SSc) [100].

Studies have consistently shown younger age at onset of RP to be a significant risk factor for the later development of DU in SSc [100, 102]. Other risk factors include male gender, a higher ESR, younger age at first non-RP symptom and anti-Scl-70 antibodies [100]. Patients with DU are more likely to have RP than those without (98 % versus 94 %) [103]. DU typically develop within 5 years of the first non-RP symptom [103] and 32 % of patients experience recurrent or prolonged DU lasting over 6 months [101, 102].

Moderate to severe pain occurs in all patients and may necessitate opioid medication or hospitalisation. Other complications include superficial infections in 50 %, osteomyelitis in 1 %, bone and/or tendon exposure in 43 % and gangrene [99, 101–103]. Ultimately these complications lead to surgical or auto-amputation in 7–20 % due to irreversible tissue loss [101, 102]. The rate of gangrene and/or amputation rises to 30 % in those with prolonged DU of at least 6 months' duration. In those who have required amputation, there is a 1–2 % likelihood of requiring further amputation in the immediate 6–12 months [100] (Chap. 21).

Because of the risk of developing DU and/or gangrene, SSc-related RP may require aggressive treatment. Other causes of RP rarely lead to DU. There are case reports of DU in the setting of SLE and RP has been identified as a risk factor for gangrene, which develops in 0.67 % of patients with SLE [58]. DU occurs more commonly in the setting of antiphospholipid syndrome [104].

RP as Risk Factor for Other Organ Manifestations

The association between primary RP and migraines [23, 105–107] especially if the duration of primary RP is prolonged (OR 2.1, 95 % CI: 1.4–3.3) [108], has been interpreted by some authors to indicate a generalised disorder of vascular tone (Chap. 16).

Headache is a common complaint in patients with SLE, with migraine and tension-type headaches being the two most common subtypes. Studies conflict as to whether RP increases the risk of headache in these patients [109–111]

A small series of three retrospective and eight prospective cases of unexplained recurrent syncope and RP reported that nine also suffered from concurrent migraine with aura [112]. In all patients, syncope resolved after treatment with nifedipine, suggesting a possible relationship between RP and syncope [112].

Morbidity and Function

Primary RP follows a relatively benign course with minimal impact on overall function and quality of life. In many studies, the majority of cases have never presented to the healthcare system previously [34].

The greatest impact of secondary RP on morbidity and function arises from complications from DU and ischemic necrosis, namely pain, infection, gangrene and amputation, with

resultant loss of hand function. Hospitalisations in turn can lead to extended leave from work, financial difficulties and additional stress placed on family members [103].

Negative psychological effects arise from pain, hospitalisation, loss of function and disfigurement that are associated with self-esteem issues and higher HAQ scores [100, 103]. Those with persistent DU have a higher degree of disability [101].

Expert Opinion

Many of the epidemiologic studies of RP have limitations, particularly the lack of standardisation of the many variables that make direct comparison between studies difficult and also lead to a range of reported prevalence rates, for example of primary RP. Ideally, the prevalence of primary RP should be determined from a study sample selected at random from the general population to eliminate selection bias, utilise a standardised definition of RP (such as the UK Scleroderma Study Group definition) with physician-led assessments and account for potential confounders such as climate, race and previous occupational exposures. This is not the case in the majority of studies.

Other risk factors for RP also warrant further investigation. Exposure to cold is often a necessary trigger for RP and it is perhaps surprising that there are only two trials that directly compare prevalence rates of primary RP in different climates. There are no such trials in secondary RP. Many studies assessing the prevalence of primary RP have not included occupational exposure within their questionnaires, which in turn may have led to falsely high prevalence rates of primary RP. Exposure to vibration tools poses a significant risk for the development of RP, and this needs to be separated from primary RP when assessing prevalence rates.

Despite the supportive evidence for a genetic component to the development of RP, SNP based genome wide association studies have not yet been performed. This is perhaps due to the lack of a sufficiently large collection of suitable cases with DNA available, and/or to the cost of such a study.

Studies assessing the prevalence of secondary RP are limited in number, with some causes lacking any trials at all, including multiple drug agents. Within the trials performed, wide variation in results is again seen, reflecting a lack of standardisation of confounders. In addition, there is a lack of trials assessing incidence, both of primary and secondary RP.

On a pragmatic note for the clinician, young female patients who have not developed any additional features 2 years after the onset of RP alone are at low risk for developing an autoimmune disease. Older patients and male patients with RP should be followed as vasospastic symptoms may predate systemic disease by as many as 20 years.

Conclusions

The prevalence of RP in the general population in most studies is between 3 and 5 % with primary RP accounting for 80–90 % of cases. The prevalence of primary RP ranges from 2 to 20 % in women and 1–12 % in men depending on geographic location, the population studied, the definition of RP used and the method of case ascertainment.

Risk factors differ between women and men. The onset of RP in women is more common at an early age and is associated with a family history of RP, suggesting genetic factors may play a role in women as may hormonal and emotional factors. RP secondary to autoimmune disease is also more common in women than in men. In contrast, the prevalence of RP in men increases with age and is more likely to be secondary to occupational exposures such as vibration or atherosclerotic peripheral vascular disease.

The prevalence of secondary RP is related to the underlying disease. Progression to secondary RP occurs in 14–37 % of patients with primary RP. Almost 99 % of patients who progress develop an autoimmune disease, most commonly SSc. Risk factors for progression include positive ANA, elevated ESR, SSc-specific autoantibodies and/or abnormal nailfold capillaroscopy.

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