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Association between Primary Raynaud's Phenomenon and Migraine: Prevalence and Clinical Predictors

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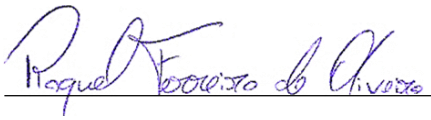

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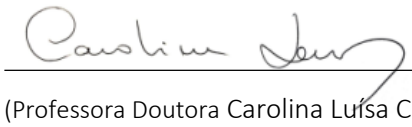

(Professora Doutora Carolina Luísa Cardoso Lemos)

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To my family
*and Rui***.**

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A todos vocês, agradeço-vos do fundo do meu ser,
Raquel Ferreira de Oliveira

RESUMO

Introdução: A Enxaqueca e o Fenómeno de Raynaud Primário partilham fatores precipitantes e de risco, assim como mecanismos genéticos e imunológicos. A sua associação tem sido amplamente demonstrada, mas nunca o foi na população portuguesa.

Objetivos: Pretendeu-se identificar a existência e a prevalência da associação entre Enxaqueca e Fenómeno de Raynaud Primário na população portuguesa, bem como fatores clínicos ou demográficos preditores desta associação.

Metodologia: Entrevistaram-se 70 doentes observados por enxaqueca na consulta de Cefaleias e 19 doentes observados na consulta de Raynaud e Capilaroscopia do Centro Hospitalar Universitário do Porto, entre julho de 2019 e fevereiro de 2020, utilizando um inquérito estandardizado sobre dados demográficos e clínicos e que permitia o diagnóstico e caracterização de Enxaqueca e de Fenómeno de Raynaud.

Resultados: Os resultados deste estudo indicam uma prevalência da associação entre Enxaqueca e Fenómeno de Raynaud na população estudada de 18.5 a 55.6%, dependendo do critério usado para o diagnóstico de Fenómeno de Raynaud. A prevalência de Fenómeno de Raynaud na população com enxaqueca e de enxaqueca na população com Fenómeno de Raynaud são significativamente superiores às descritas na população geral, e a prevalência da associação é significativamente superior à estimada na população geral ($P < 0.001$). Na população com diagnóstico prévio de enxaqueca, o menor uso de paracetamol como tratamento da fase aguda e uma menor prevalência de vómitos durante os episódios associaram-se positivamente com o diagnóstico de Fenómeno de Raynaud. O sexo feminino está associado ao diagnóstico de enxaqueca nos doentes com Fenómeno de Raynaud.

Conclusões: Este estudo evidencia uma associação entre Enxaqueca e Fenómeno de Raynaud na população estudada. No entanto, não parecem existir preditores clínicos e demográficos suficientemente eficazes para identificar os doentes com esta associação. Urge assim sensibilizar os clínicos para este facto, de modo a melhor identificar e cuidar destes doentes.

Recomendações: Estudos com amostras maiores e efetuados ao nível nos Cuidados de Saúde Primários poderão contribuir para melhor clarificar estes achados.

PALAVRAS-CHAVE: Fenómeno de Raynaud, Fenómeno de Raynaud/epidemiologia, Fenómeno de Raynaud/diagnóstico, Enxaqueca, Enxaqueca/epidemiologia, Prevalência

ABSTRACT

Introduction: Migraine and Raynaud's Phenomenon share triggers and risk factors, as well as genetic and immunological mechanisms. This association has been vastly demonstrated, but it has never been demonstrated in Portugal.

Objectives: Identifying the existence and prevalence of the association between Migraine and Primary Raynaud's Phenomenon in the Portuguese population, as well as clinical or demographic predictors of this association.

Methods: We interviewed 70 patients from the Migraine consult and 19 patients from the Raynaud and Capillaroscopy consult from Centro Hospitalar Universitário do Porto, between July 2019 and February 2020, using a standardized questionnaire about demographic and clinical data, and that allowed the diagnosis and characterization of Migraine and Raynaud's Phenomenon.

Results: The results of this study indicate a prevalence of the association between Migraine and Raynaud's Phenomenon of 18.5 to 55.6%, depending on the criterion used for the diagnosis of Raynaud's Phenomenon. The prevalence of Raynaud's Phenomenon in the migraine population and of migraine in the Raynaud's Phenomenon population are significantly higher than those reported in the general population, and the prevalence of the association is significantly higher than what is estimated in the general population ($P < 0.001$). In the population from the Migraine consult, lesser use of paracetamol as acute-phase treatment and a lower prevalence of vomiting during the headache episodes were associated with Raynaud's Phenomenon diagnosis. Female sex was associated with migraine diagnosis in the patients with Raynaud's Phenomenon.

Conclusions: This study shows an association between Migraine and Raynaud's Phenomenon in the studied population. However, there do not seem to exist strong enough clinical or demographic predictors to accurately identify the patients with this association. As such, it urges to sensitize the physicians for this, in order to better identify and care for these patients.

Recommendations: Studies with larger samples and conducted in the Primary Care could contribute to better clarify these results.

KEYWORDS: Raynaud Disease, Raynaud Disease/epidemiology, Raynaud Disease/diagnosis, Migraine Disorders, Migraine Disorders/epidemiology, Prevalence

ABBREVIATIONS LIST

ANA	Anti-nuclear antibody
CHUP	Centro Hospitalar Universitário do Porto
COX	Cyclooxygenase
GP	General Practitioner
IHS	International Headache Society
IQR	Interquartile Range
NSAIDs	Non-steroidal anti-inflammatory drugs
PPV	Positive Predictive Value
PRP	Primary Raynaud Phenomenon
RP	Raynaud Phenomenon
SD	Standard Deviation
SRP	Secondary Raynaud Phenomenon

INDEX

TABLES LIST

FIGURES LIST

INTRODUCTION

Raynaud's Phenomenon (RP) is a common condition characterized by transient vasospastic ischemia of the extremities, which results in shifting discoloration of the skin, most commonly pallor (white) followed by cyanosis (blue) and reperfusion (red), although the three stages are not necessary for diagnosis[1, 2]. The episodes are characteristically triggered by cold, but there are other important triggers, such as emotional stress and relative shifts in temperature[2]. The prevalence of RP in the general population is estimated in the 3 to 5% range, being higher in women than in men[3]. Primary RP (PRP) is a benign functional vascular disease that accounts for 80-90% of the cases, while secondary RP (SRP) is associated with a systemic condition, usually connective tissue diseases, but also some drugs and occupational exposures[1, 3, 4]. The pathophysiology is complex, involving neuronal and vascular mechanisms, functional and intravascular factors, and, in SRP, structural abnormalities[1, 5].

Migraine is a common neurological disorder characterized by recurring headaches, typically unilateral, pulsatile, with moderate to severe intensity, and a duration of 4 to 72 hours. They are frequently associated with symptoms such as nausea, vomiting, photophobia, and phonophobia, and are aggravated or caused by routine physical activity[6]. About one-third of the patients have a reversible neurological symptom complex called "aura", most commonly consisting of visual disturbances that occur before the headache[6, 7]. Common triggers are stress, fasting, weather changes, and menses[8]. Annual prevalence of migraine in the general population is around 12% and is higher in women[7]. Its pathophysiology is also complex. Current evidence suggests that the headache stage depends on the activation and sensitization of trigeminal nociceptors innervating the large meningeal blood vessels, superimposed on a dysfunctional regulation of cortical excitability[9].

The association between PRP and migraine has been vastly demonstrated[10-14], with a pooled odds ratio of 4.02 (95% CI 2.62 to 6.17) for the development of migraine in patients with PRP[15]. There is also a described association between these two entities and common immunological and genetic factors, such as the methyltetrahydrofolate reductase T677 allele[16] and *TREX1* RVCL-S mutations[17, 18]. The prevalence of migraine also seems to be proportional to the duration of RP[16]. All these observations, together with the facts that both are more prevalent in females and have common triggers, suggest similar pathophysiological mechanisms[12] and a common underlying genetic disturbance of the vascular tonus regulation[19].

This association, to our knowledge, has never been demonstrated in Portugal. Thus, with this study, we intended to verify if there is an association between Primary Raynaud Phenomenon and Migraine in the Portuguese population, as well as clinical or demographic factors that allow us to

predict this association. This could give us further insight into the pathophysiology of these entities and help us to determine the best management strategy for patients with this association. As a secondary goal, we intended to compare different diagnostic criteria of RP.

METHODS

a) Study design and population

We conducted a cross-sectional observational study at Centro Hospitalar Universitário do Porto (CHUP) on the adult patients followed at the Migraine consult from July 2019 to January 2020 or the Raynaud and Capillaroscopy consult from November 2019 to February 2020 of CHUP, to ensure the patients had at least one of the pathologies under study. Exclusion criteria were pediatric age (<18 years old) and Secondary Raynaud's Phenomenon.

b) Data collection

The patients were interviewed using a standardized questionnaire, which included demographic data, medical and surgical history, and questions allowing for the diagnosis and characterization of migraine and RP, such as frequency and characteristics of the episodes, triggers, age of onset, and treatments used.

The diagnosis of migraine was established according to the International Headache Society (IHS) criteria[6], using a questionnaire based on the one developed by Pereira-Monteiro and colleagues[20]. RP was diagnosed according to the criteria of Miller *et al*.[21], the International Consensus Criteria for the Diagnosis of Raynaud's Phenomenon[22], the 1993 criteria of UK Scleroderma Study Group[23] and the criteria of Maricq *et al*[24], independently (criteria A, B, C, and D, respectively) and in association (criteria A+D, B+D, C+D). The results obtained with each of these criteria were then compared, due to the absence of gold standard criteria for the diagnosis of RP: positive predictive value (PPV) was estimated as the percentage of patients diagnosed with RP by a specialist (either before the study or on the consult after the interview) within those who scored positive with each criterion, and the proportion of patients who were identified by each criterion within those with RP diagnosed by a specialist was calculated. Specificity and sensitivity were not determined, due to the design of the study not providing true negatives according to a gold standard. The subjects diagnosed with RP were given the choice of being referred to the Raynaud and Capillaroscopy consult to perform a nailfold capillaroscopy and rule out the possibility of SRP[25]. PRP was considered if the patient had no history of systemic diseases, namely connective tissue diseases, a physical examination negative for findings suggestive of secondary causes, a normal capillaroscopy, and, when available, a negative or low titer anti-nuclear antibody (ANA)[22].

Subjects diagnosed with either of the pathologies were given an informative brochure about the diseases. All the subjects signed an informed consent allowing for the collection, analysis, and publication of the anonymous data. This study was approved by the ethics committee of CHUP (ref: 2019.096(077-DEFI/079-CE)).

c) Analysis

Continuous variables were described as mean ± standard deviation (SD) if they were normally distributed according to the Shapiro-Wilk test, or if not, as median (interquartile range, IQR). Categorical variables were described with frequency and percentage (%).

Chi-square tests were performed to compare the prevalence between study groups and with the general population, and independent variable t-tests or Mann-Whitney tests were performed to assess continuous variables that were normally distributed or not, respectively. A *P* value of <0.05 was considered statistically significant. Data were analyzed using SPSS version 26.0.

RESULTS

a) Study population

The study population consisted of 89 patients, mostly female (84 [94.4%]), with a mean age of 43.5 ± 14.0 years old. 70 patients were followed at the Migraine consult, while 19 were followed at the Raynaud and Capillaroscopy consult (Table I).

All the patients recruited from the Raynaud and Capillaroscopy consult had PRP, whereas the patients from the Migraine consult who scored positive in at least one of the diagnostic criteria for RP were offered a Capillaroscopy consult, to classify them as either primary or secondary RP. None of them had known underlying autoimmune disorders at the time of the interview.

b) Association between migraine and RP

The prevalence of the association between migraine and RP varied between 18.5 and 55.6%, depending on the criteria used for the diagnosis of RP (Figure 1). Of the patients with the association, 24 (53.3%) were so far classified as PRP after observation by a specialist and a nailfold capillaroscopy examination, using criterion A for the diagnosis of RP. However, currently, the nailfold capillaroscopy examinations have been suspended, due to the SARS-CoV-2 pandemic. As such, it is not possible yet to classify every patient from the Migraine consult found to have RP, and this percentage cannot be regarded as the final result.

Of the patients presenting with the association, 5 (11.1%) referred temporal correlation between the episodes of migraine and RP.

c) Subpopulation from the Migraine consult

In the group of patients from the Migraine consult, 10 to 35 (14.3 to 50.0%) were diagnosed with RP depending on the criteria used (Figure 1). Of those, 9 were thus far observed by a specialist in a Raynaud and Capillaroscopy consult and were submitted to nailfold capillaroscopy. After the observation, 6 were classified as PRP, and 1 patient was considered by the specialist not to have RP, despite scoring positive in every criterion except for B and B+D. The remaining 2 patients were classified as SRP based on a scleroderma pattern in the nailfold capillaroscopy and were referred to the Autoimmune Diseases consult for further investigation.

Only 4 patients from the Migraine consult had a previous diagnosis of RP, which means that up to 88.6% of the patients with RP in this population were not previously aware of their condition.

Regarding potential predictors of the association between these two conditions, patients with RP used less paracetamol as acute-phase treatment (9 [25.7%] vs 20 [57.1%], $P = 0.008$) and had a smaller prevalence of vomiting with migraine episodes (16 [45.7%] vs 24 [70.6%], $P = 0.036$) than patients without RP. None of the remaining demographic and clinical characteristics were statistically significant when comparing patients with or without RP (Table II). This assessment was not yet made for patients who were classified as PRP, due to the low number of patients observed by nailfold capillaroscopy until now.

The prevalence of patients with RP was not significantly higher in patients who used triptans for the treatment of migraine, compared to those who did not use said medication (21 [44.7%] vs 14 [60.9%], $P = 0.203$). Likewise, the frequency of RP attacks did not differ between those two groups in a statistically significant manner ($P = 0.468$). The same comparison was not made for the use of beta-blockers or ergotamine, since only 4 and 5 patients, respectively, used those medications.

d) Subpopulation from the Raynaud and Capillaroscopy consult

In the group of patients from the Raynaud and Capillaroscopy consult, 11 out of 19 (57.9%) of the patients were diagnosed with migraine according to the IHS criteria[6] (Figure 1). Most of those (8 [72.3%]) already had a previous diagnosis of migraine.

Patients with migraine disorder were more frequently females than patients without migraine disorder (11 [100.0%] vs 5 [62.5%], $P = 0.027$). No other demographic or clinical factor was significantly associated with the diagnosis of migraine in this population (Table III).

Regarding the capillaroscopy findings, 8 (42.1%) of the patients both with and without migraine presented with unspecific, non-pathological changes, namely a granular blood flow, minor morphologic changes, dilated capillaries with preserved relationship between the arteriolar and venular limbs, or a visible venous plexus. However, none of the findings was significantly associated with the diagnosis of migraine (Table III).

e) Comparison between subpopulations

We compared the characteristics of migraine and RP in patients from either consult who had the association between RP and migraine.

Patients from the Migraine Consult had longer migraines (27 [77.1%] vs 4 [40.0%] patients reported a duration of days, *P* = 0.025), which were more intense (27 [77.1%] vs 3 [30.0%] patients reported severe intensity, *P* = 0.010), more likely to be aggravated by physical activity (31 [91.2%] vs 5 [55.6%], *P* = 0.010), accompanied by osmophobia (28 [80.0%] vs 3 [30.0%], *P* = 0.003) and nausea (31 [88.6%] vs 4 [40.0%], *P* = 0.001), and precipitated by prolonged fasting (21 [63.6%] vs 2 [20.0%], *P* = 0.015). Patients from the Migraine Consult also used less paracetamol (9 [25.7%] vs 8 [80.0%], *P* = 0.002) and more triptans (21 [60.0%] vs 0 [0.0%], *P* = 0.001) as acute-phase treatment.

Patients from the Raynaud and Capillaroscopy Consult reported less frequently weather changes as a precipitating factor for the RP episodes (3 [30.0%] vs 21 [65.6%], *P* = 0.047).

None of the other characteristics of either condition were significantly different between the two subpopulations.

f) Comparison between RP diagnostic criteria

Regarding the comparison between the criteria used for the diagnosis of RP, criterion A had an estimated PPV of 96.3%, criterion B of 100.0%, criterion C of 94.1%, criterion D of 94.4%, criterion A+D of 94.1%, criterion B+D of 100.0% and criterion C+D of 93.3%. Criteria B and B+D detected 43.5% of the patients with a specialists' diagnosis of RP, while criterion A detected 91.3%; the remaining criteria were able to detect between 60.9 and 73.9% of those patients (Table IV).

However, once more, we must consider that these values may change once every patient from the Migraine consult identified as having RP is observed by a specialist.

DISCUSSION

a) Prevalence of the association between RP and migraine

The prevalence of migraine in the Portuguese population is estimated to be 16.7%[26, 27]. The true prevalence of RP in the general population is difficult to ascertain due to the use of different diagnostic criteria. To our knowledge, in Portugal, only one study of the prevalence of RP was published, which used the 1993 UK Scleroderma Study Group criteria (our criterion C), and estimated the prevalence of RP to be 4.5%[28]. Therefore, the prevalence of the association between these two conditions in the general population, if it were a random occurrence, should be estimated at around 0.8%. The prevalence of the association found in our study (33.3%, using criterion C) was much higher (*P* < 0.001), suggesting that the association is not a mere chance phenomenon.

Considering only the population of the Migraine consult, the prevalence of RP found (30.0%) is also higher than in the general population ($P < 0.001$) when comparing using the same diagnostic criterion used in the study of Bertão *et al*.[28]. However, the mentioned study did not distinguish between primary and secondary RP. Currently, we cannot accurately determine the prevalence of PRP in the migraine population of our study, until all patients from the migraine consult with RP are evaluated in a Capillaroscopy consult. Nevertheless, the prevalence of PRP in the general population reported in the international literature is of 4.85%[15], whereas its prevalence in the migraine population of our study is expected to be higher than that, since it currently is estimated as 8.6% (6 patients out of 70), using criteria A for the diagnosis of RP, and it is likely to be higher after all patients are assessed by a specialist and with capillaroscopies, considering that 80-90% of the patients with RP in the general population are estimated to have PRP[29]. It would be interesting to assess if the proportion of patients with PRP is the same as in the general population, which could suggest that migraine might be associated with RP itself, and not only with the underlying conditions of SRP, in either a positive or negative fashion.

Of the patients diagnosed with RP in the Migraine consult, 88.6% were diagnosed *de novo* with this condition. This high percentage reveals a possible lack of awareness to RP by the neurologists and other physicians that may have contacted with these patients. However, it has been reported that only 4% of people can confidently identify the symptoms of RP[30], and only a few of the patients with RP have visited their general practitioner (GP) about this[30, 31]. Therefore, the lack of awareness can also be attributed to the patients, who do not identify their symptoms as worthy to discuss with their GP or may not even identify their symptoms at all. In fact, during the collection of data for this study, many patients said they had difficulty identifying the symptoms because they do not usually look at their hands. It is therefore important to raise awareness to RP both in the medical community and in the general public.

Similarly, considering only the population of the Raynaud and Capillaroscopy consult, the prevalence of Migraine found was 57.9%, also higher than the stated prevalence in the general population (16.7%[32]) ($P < 0.001$), further sustaining the association between PRP and migraine.

As can be seen, there is a strong association between these two conditions in our populations, which is in line with what is described in the literature[10-17].

Despite the widespread recommendation that patients with RP should avoid triptans[33, 34], given their mechanism of action as vasoconstrictors, we did not find a statistically significant difference in the prevalence of RP or frequency of attacks between patients who used triptans and those who did not. This goes in line with the recent findings that triptans do not induce vasoconstriction in the extremities nor RP[35] and the notion that triptans can be safely used in migraine patients with RP[36].

This is highly relevant since triptans are a useful acute-phase treatment for patients with migraine and should not be withheld without proper reasoning.

b) Prevalence of RP in patients with Migraine and clinical predictors

In our study, the prevalence of RP in patients with migraine was 50.0% according to criteria A, which is higher than what is reported in the literature (26.0%[10]) using the same criterion. Since the study by Zahavi *et al*.[10] also used the Miller criteria for the diagnosis of RP (our criterion A), we cannot attribute this difference to the use of different diagnostic criteria. However, the mentioned study excluded patients with SRP, which we could not yet do, as previously stated, due to the SARS-CoV-2 pandemic, and can be the reason for this difference, at least partially.

The only predictors we found for the association between RP and migraine in the population of the Migraine consult were a smaller prevalence of paracetamol use as acute-phase treatment and vomiting during the headache episodes.

Paracetamol is regarded as a useful first-line treatment for individuals with migraine headaches that do not cause severe disability[37]. Since the patients with and without RP did not differ in terms of intensity or frequency of headache, it does not seem likely that patients with RP do not use paracetamol because of a lack of efficiency due to higher disability. However, we should take in consideration the fact that our population sometimes prefers to use non-steroidal anti-inflammatory drugs (NSAIDs) instead of paracetamol, due to a misbelief that paracetamol is less effective because it is so widely used, which could in part explain why some migraineurs elect not to use paracetamol as acute-phase treatment. Notwithstanding, paracetamol seems to act mainly by central inhibition of prostaglandin synthesis[38], which are involved in migraine pathogenesis, namely vasodilating prostaglandins such as prostaglandin E_2, prostaglandin I_2, and prostaglandin D_2[39]. Additionally, the pathophysiology of RP seems to encompass a limitation in the endothelium-dependent vasodilation by the action of vasoconstrictor products of the cyclooxygenase (COX) pathway[40], as well as reduced production or action of endogenous prostacyclins[4, 41, 42]. If this endothelium dysfunction, proposed in the pathophysiology of RP, is not limited to the vascular bed of the fingers but is rather a generalized dysfunction, it could be proposed that, in patients with migraine and RP, the production of vasodilating prostaglandins is of less significance for the pathophysiology of migraine, and that paracetamol would not be as efficient as in other patients because the prostaglandin levels in these patients would be lower than in other migraineurs, thus justifying the less frequent use of this drug. At the same time, the use of NSAIDs did not differ between the two groups of patients. Despite NSAIDs also blocking the production of prostaglandins, their main mechanism of action in migraine seems to be the inhibition of neurogenic inflammation and the reversal of central sensitization associated with migraine[39], and thus could still be efficient

in these patients, even if the vasodilating prostaglandin levels are lower. Further research, prospectively comparing the response of patients with and without RP to acute-phase treatment for migraine headaches with paracetamol, and understanding if the prostaglandin system is affected in these patients, could contribute to our knowledge regarding the pathophysiology of these two conditions, and on how to better treat these patients.

Vomiting is a common symptom in migraine sufferers related to autonomic nervous system dysfunction[43]. It is reported to be more common in patients with young age, female sex, family history of migraine, abdominal pain, and photophobia/phonophobia[44]. However, none of these factors (besides abdominal pain, which was not evaluated in the present study) differed statistically between the patients with and without RP, and therefore are not able to explain the lower prevalence of vomiting in the patients with RP. Since the other migraine symptoms related to autonomic nervous system dysfunction, such as nausea, eyelid edema, conjunctival injection, lacrimation, nasal congestion, and ptosis[43] did not differ as well between the two groups, it seems unlikely that this difference is due to an alteration in the autonomic nervous system function, though there is also dysautonomia involved in the pathophysiology of RP[45].

Despite this discussion, the only two predictors found are insufficient to accurately identify migraineurs who might have RP, further emphasizing the need to screen patients with migraine disorder, to early identify the patients with RP and classify them as PRP or SRP.

c) Prevalence of Migraine in patients with RP and clinical predictors

In our study, the prevalence of migraine in patients from the Raynaud and Capillaroscopy consult was 57.9%. The prevalence of migraine in patients with RP has been reported as between 46.2%[12] and 61.0%[13], which is in line with the prevalence found in our study.

Only female sex was identified as a potential predictor of the association between RP and migraine. Both RP and migraine are more prevalent in women[7, 12, 15], and it is therefore easily understandable why the association would also be more prevalent in the female sex. We did not find this correlation in the Migraine consult population, though this is most likely because only 2 out of 70 patients from that population were men, preventing such comparisons.

Once more, this predictor is not enough to identify patients with RP who might have migraine disorder but suggests particular attention should be paid to the possibility of this association in female patients.

Duration of RP has been reported to be longer in patients with migraine than in patients without migraine[16], but our study did not replicate this finding.

We reported that 42.1% of the patients from the Raynaud consult had unspecific findings in the capillaroscopy. This is to be expected since the capillaroscopic pattern in healthy subjects is

characterized by a great variety of findings[46]. The fact that these changes were similar between patients with and without migraine suggests that migraine does not contribute to structural abnormalities of the peripheral capillaries. However, our sample consisted of only 19 patients. Future studies, with larger sample sizes, could help to better determine whether there is a specific capillaroscopic pattern in patients with migraine disorder, as occurs in Diabetes Mellitus [47, 48].

d) Comparison between subpopulations

When comparing the two subpopulations from either consult, we verified that patients with both migraine and RP from the Migraine Consult had longer and more intense headaches, which were more likely to be aggravated by physical activity, accompanied by osmophobia and nausea, and precipitated by prolonged fasting. Overall, this suggests that patients from the Migraine Consult had more severe migraine headaches, which is to be expected since this is a specialist consult in a tertiary hospital, to which only patients in need of specialist care by a Neurologist are referred. Patients with migraine disorder from the Raynaud and Capillaroscopy consult had less severe headaches, which could likely be monitored by their GPs. These patients also used paracetamol more frequently as acute-phase treatment for their headaches, which, in this instance, may be attributed to the lesser disability they experienced compared to patients from the Migraine Consult. This may also justify why they used fewer triptans. Nonetheless, a known diagnosis of RP in the patients from the Raynaud and Capillaroscopy Consult may also contribute to this fact, as physicians may have purposely avoided using triptans[33, 34], with paracetamol and NSAIDs as the most common alternatives, justifying why these patients use more paracetamol. Again, a prospective study of the efficacy of the acute-phase treatments for migraine in the population with the association could be of the utmost importance regarding how to better care for these patients.

e) Temporal correlation between episodes of migraine and RP

Only 5 (11.1%) patients with the association referred temporal correlation between the episodes of migraine and RP. Likewise, it has been reported that RP is temporally associated with the headache attack in 16-21% of the patients[10, 13]. This lack of significant temporal association could likely be due to different precipitating factors for each of the disorders, even if they share similar pathophysiologic mechanisms, as well as a lack of awareness by the patients if these episodes occur simultaneously.

f) RP diagnostic criteria

Regarding the comparison between the RP diagnostic criteria, although criteria B and B+D showed the highest PPV (100.0%), they detected only 43.5% of the patients with a previous diagnosis of RP,

and consequently are not appropriate for screening, as they are expected to miss many diagnoses. On the other hand, criterion A (proposed by Miller *et al*.[21]), with a PPV of 96.2% and which identified 91.3% of the patients with a previous diagnosis of RP, was considered the most balanced of these criteria for the screening of RP. The remaining criteria, despite overall showing a high PPV, were not as balanced as criterion A, as they failed to identify a considerable proportion of the patients with a previous diagnosis of RP.

Furthermore, even though the addition of color charts might improve the diagnostic ability by increasing its reliability[24] and lessening the frequency of false positives[49], it seems to decrease the PPV and possibly the sensitivity, as criterion A+D identified fewer patients with a previous diagnosis of RP than criterion A alone. As such, the use of color charts does not seem necessary for the diagnosis of RP, which is in line with the opinion of the experts on the latest Consensus for the diagnosis of RP[22]. Nonetheless, the color charts seemed useful to some patients who, upon seeing the examples in the photographs, acknowledged they did indeed have those color changes, despite not being able to do so before. Considering this, showing photographs of real RP events to patients might be a useful adjunct to the diagnosis, even if they are not a part of the criteria themselves. It is, however, worth mentioning that many patients had difficulties discerning the colors presented in the photographs, since the photographs used by the criteria of Maricq[24] have a low resolution by the current standards of digital photography, and were taken only in American-white population, which hinders the comparison for black patients. As such, it might be useful to develop a new atlas of RP events to show the patients when diagnosing RP, with different degrees of blanching and cyanosis, and with people of different skin color.

g) Limitations and Future studies

This study has some limitations. The answers to the questionnaire are bound to recall bias, which could influence the results. This was addressed by ensuring the research questions were worded carefully and that the interviewees were allowed enough time for an adequate recall. Nevertheless, many patients who did not know about RP previously to the questionnaire admitted to not be certain of the answer to some questions, because they do not usually notice them, which could have led to the underestimation of precipitating factors or accompanying symptoms. Likewise, the patients who did not know about RP were deemed as unreliable sources for the family history of RP, which could similarly be underestimated in both groups from the Migraine consult.

Patients from the Migraine consult were classified as PRP or SRP based on age at onset, evolution and characteristics of RP and capillaroscopy findings, but their ANA titer was not evaluated unless they were referred to the Autoimmune Diseases consult for probable SRP. However, patients

classified as PRP should also have their ANA titer tested, to complete their evaluation and rule out early systemic sclerosis[22, 50].

The number of patients from the Raynaud and Capillaroscopy consult was low. In fact, only 19 patients with PRP presented to this consult from November 2019 to February 2020. This could also have influenced the results, as the patients could have been referred for having more intense RP, which consequently would not represent the true scope of patients with RP. Likewise, patients from the Migraine consult were shown to have more severe headaches than patients from the Raynaud and Capillaroscopy consult, and they likely did not represent the true scope of patients with migraine. Therefore, it could be interesting to perform a similar study in Primary Care, to identify the true prevalence of this association in the general population.

In any case, this shows that few patients with PRP are referred to a capillaroscopy consult, even though every RP patient should have at least one capillaroscopy performed, to distinguish between PRP and SRP[51]. Furthermore, it is estimated that around 1% of the patients with PRP transition to SRP every year[52]. Similarly, only 11.4% of the patients from the Migraine Consult who had RP had been previously diagnosed with this condition. These findings are alarming because they demonstrate suboptimal care to these patients, who have not received proper advice regarding how to manage their RP. As such, it urges to sensitize Primary Care physicians, who are closest to these patients, to the importance of performing capillaroscopies in patients with RP, to identify SRP early on the course of the underlying diseases, and thus providing the most adequate care for them. Likewise, identifying patients with RP in a Migraine consult might be a useful tool for early detection of possible SRP and underlying autoimmune disorders, improving the care given to these patients and their quality of life.

In fact, a protocol could be proposed between the Migraine and Raynaud and Capillaroscopy consults, such as the one proposed in Figure 2, in order to identify patients with this association and better care for them, while also allowing to further study and understand this population. Patients from the Migraine consult would be screened for RP using the Miller criteria[21] and, if they screened positive, would have their ANA titers measured and be referred to a Raynaud and Capillaroscopy consult; the specialist at the Raynaud and Capillaroscopy consult would confirm the diagnosis and then decide if the patient should be referred to the Autoimmune Diseases consult, maintain capillaroscopic follow-up or be discharged. On the other hand, patients from the Raynaud and Capillaroscopy consult would be screened for migraine using ID-Migraine, a reliable and validated screening tool[53]. If positive, they would be referred to the Migraine consult, where the specialist would confirm the diagnosis and decide if they benefit from a specialist approach or if they should be monitored by their GP.

Conclusions

This study shows a strong association between Migraine and Raynaud Phenomenon in our population, supporting previous suggestions that these disorders may share a common pathogenic mechanism. Despite the association being more common in migraineurs who use less paracetamol as acute-phase treatment and with less prevalence of vomiting with the headache episodes, and in patients with RP of the female sex, these are not satisfactory predictors of the association. As such, it urges to sensitize physicians who may contact these patients for this association, so they can be identified and given the most adequate care. Further research, with larger sample sizes and in Primary Care, might contribute to better characterizing this population and understanding the pathophysiology behind this association.

This study was accepted for presentation in the Reunião Nacional de Cefaleias 2020, as an Oral Communication.

TABLES

Table I. Characteristics of the patient population.

	Total (n=89)	Migraine consult (n=70)	Raynaud consult (n=19)
Age (mean ± SD), years	43.5 ± 14.0	44.0 ± 12.9	41.8 ± 18.0
Female sex, n (%)	84 (94.4)	68 (97.1)	16 (84.2)
Previous diagnosis of migraine, n (%)	78 (87.6)	70 (100.0)	8 (42.1)
Previous diagnosis of RP, n (%)	23 (25.8)	4 (5.7)	19 (100.0)

Abbreviations: RP – Raynaud Phenomenon.

Table II. Characteristics of the patients from the Migraine Consult (n=70).

	Without RP (n=35)	With RP (n=35)	*P*
Female sex, n (%)	34 (97.1)	34 (97.1)	1.000
Age, mean ± SD	46.2 ± 12.9	41.7 ± 12.6	0.144
Family history of migraine, n (%)	18 (51.4)	18 (52.9)	0.900
Family burden of migraine, median (IQR)	1.0 (0.0-2.5)	1.0 (0.0-3.0)	0.945
Family history of RP, n (%)	0 (0.0)	4 (44.4)	0.078
Family burden of RP, median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.364
Working with chemicals, n (%)	5 (14.3)	5 (14.3)	1.000
Working with vibration machines, n (%)	3 (8.6)	0 (0.0)	0.077
Working with refrigeration systems, n (%)	0 (0.0)	1 (2.9)	0.314
Thyroid disease, n (%)	8 (23.5)	14 (40.0)	0.142
Beta-blocker, n (%)	5 (14.3)	4 (11.4)	0.721
Oral contraception, n (%)	11 (32.4)	13 (37.19	0.676
Vasoconstrictors, n (%)	2 (5.7)	0 (0.0)	0.151
Frequency of headaches, n (%)			0.692
Daily	9 (25.7)	12 (34.3)	
Weekly	18 (51.4)	17 (48.6)	
Monthly	5 (14.3)	5 (14.3)	
Annual	3 (8.6)	1 (2.9)	
Age of onset of migraine, mean ± SD	19.9 ± 11.5	20.9 ± 9.4	0.695
Duration of migraine (years), mean ± SD	26.3 ± 16.0	20.8 ± 14.5	0.136
Characteristics of headache, n (%)			
Pulsatile/throbbing	28 (80.0)	29 (82.9)	0.759
Stabbing	13 (37.1)	19 (54.3)	0.150
Burning	12 (34.3)	11 (31.4)	0.799
Pressure	27 (77.1)	26 (74.3)	0.780
Intensity of headache, n (%)			0.601
Light	0 (0.0)	1 (2.9)	
Moderate	7 (20.0)	7 (20.0)	
Severe	28 (50.9)	27 (49.1)	
Accompanying symptoms, n (%)			
Photophobia	30 (85.7)	34 (97.1)	0.088
Phonophobia	34 (97.1)	34 (97.1)	1.000
Osmophobia	26 (74.3)	28 (80.0)	0.569
Nausea	33 (94.3)	31 (88.6)	0.393
Vomiting	24 (70.6)	16 (45.7)	0.036
Conjunctival injection	17 (51.5)	14 (42.4)	0.459
Nasal congestion	8 (23.5)	8 (25.0)	0.889
Palpebral edema	22 (66.7)	20 (60.6)	0.609
Facial sweating	12 (35.3)	16 (47.1)	0.324
Miosis / ptosis	15 (45.5)	15 (48.1)	0.912
Agitation	18 (51.4)	22 (62.9)	0.334
Aura, n (%)	11 (31.4)	13 (38.2)	0.553
Precipitating factors, n (%)			
Stress	29 (85.3)	30 (85.7)	0.960
Prolonged fasting	21 (63.6)	21 (60.0)	0.758
Weather changes	12 (37.5)	17 (51.5)	0.256
Menstruation	21 (67.7)	23 (70.0)	0.559
Acute phase treatment, n (%)			
Paracetamol	20 (57.1)	9 (25.7)	0.008

NSAIDs	19 (54.3)	20 (57.1)	0.810
Opioids	1 (2.9)	0 (0.0)	0.314
Ergotamines	3 (8.6)	2 (5.7)	0.643
Triptans	26 (74.3)	21 (60.0)	0.203
Prophylactic treatment, n (%)			
Beta-blockers	1 (2.9)	3 (8.6)	0.303
Calcium channel blockers	0 (0.0)	1 (2.9)	0.314
Antiepileptics	12 (34.3)	15 (42.9)	0.461
Botulin toxin	2 (5.7)	1 (2.9)	0.555
Antidepressants	11 (31.4)	8 (22.9)	0.420

Footnote: Comparisons were made to the patients without RP.

Abbreviations: NA – Non-appliable; NSAIDs – Non-steroid anti-inflammatory drugs; PRP – Primary Raynaud Phenomenon; RP – Raynaud Phenomenon.

Table III. Characteristics of the patients from the Raynaud and Capillaroscopy Consult (n=19).

	Without migraine (n=8)	With migraine (n=11)	*P*
Female sex, n (%)	5 (62.5)	11 (100.0)	0.027
Age, mean ± SD	40.8 ± 23.9	42.6 ± 13.4	0.832
Family history of migraine, n (%)	1 (12.5)	6 (54.5)	0.061
Family burden of migraine, median (IQR)	0.0 (0.0-0.0)	1.0 (0.0-1.0)	0.109
Family history of RP, n (%)	1 (12.5)	4 (36.4)	0.243
Family burden of RP, median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.395
Working with chemicals, n (%)	0 (0.0)	3 (27.3)	0.107
Working with vibration machines, n (%)	0 (0.0)	1 (9.1)	0.381
Working with refrigeration systems, n (%)	0 (0.0)	2 (18.2)	0.202
Thyroid disease, n (%)	0 (0.0)	3 (27.3)	0.107
Beta-blocker, n (%)	1 (12.5)	3 (27.3)	0.435
Oral contraception, n (%)	1 (12.5)	4 (36.4)	0.243
Vasoconstrictors, n (%)	0 (0.0)	0 (0.0)	NA
Color changes, n (%)			
White	7 (87.5)	9 (81.8)	0.737
Blue	6 (75.0)	7 (63.6)	0.599
Red	7 (87.5)	7 (63.6)	0.243
Biphasic color changes, n (%)	6 (75.0)	6 (54.5)	0.361
Triphasic color changes, n (%)	4 (50.0)	2 (18.2)	0.141
Frequency of episodes, n (%)			0.136
Daily	4 (50.0)	1 (9.1)	
Weekly	2 (25.0)	5 (45.5)	
Monthly	2 (25.0)	5 (45.5)	
Seasonality of episodes, n (%)			0.960
Winter	5 (62.5)	7 (63.6)	
All year	3 (37.5)	3 (37.4)	
Age of onset (years), mean ± SD	34.5 ± 25.6	33.6 ± 15.2	0.928
Duration of RP (years), median (IQR)	5.5 (2.0-9.8)	3.0 (2.0-18.0)	0.968
Sites affected, n (%)			
Fingers	8 (100.0)	11 (100.0)	NA
Nose	2 (25.0)	0 (0.0)	0.131
Toes	3 (37.5)	4 (50.0)	0.614
Breast areola	0 (0.0)	0 (0.0)	NA
Ear lobe	2 (25.0)	1 (12.5)	0.522
Tongue	0 (0.0)	0 (0.0)	NA
Well-demarcated border between affected and unaffected skin, n (%)	5 (71.4)	4 (44.4)	0.280
Accompanying symptoms, n (%)			
Paresthesia	6 (75.0)	9 (81.8)	0.719
Numbness	5 (62.5)	6 (54.5)	0.729
Throbbing	2 (25.0)	7 (63.5)	0.096
Sweating	1 (12.5)	3 (27.3)	0.435
Precipitating factors, n (%)			
Cold	7 (87.5)	11 (100.0)	0.228
Emotional stress	0 (0.0)	2 (18.2)	0.202
Weather changes	2 (25.0)	3 (27.3)	0.912
Sleep	0 (0.0)	0 (0.0)	NA
Alcohol	0 (0.0)	0 (0.0)	NA

Tobacco	0 (0.0)	0 (0.0)	NA
Caffeine	0 (0.0)	0 (0.0)	NA
Cold water/air	7 (87.5)	4 (44.4)	0.064
Menses	1 (20.0)	1 (10.0)	0.591
Capillaroscopy findings, n (%)			
Normal	4 (50.0)	6 (54.5)	0.845
Non-specific changes	4 (50.0)	4 (44.5)	
Granular flow	1 (12.5)	2 (18.2)	0.737
Capillary ectasia	5 (62.5)	4 (36.3)	0.260
Minor morphologic changes	1 (12.5)	3 (27.30)	0.435
Visible venous plexus	0 (0.0)	1 (9.1)	0.381

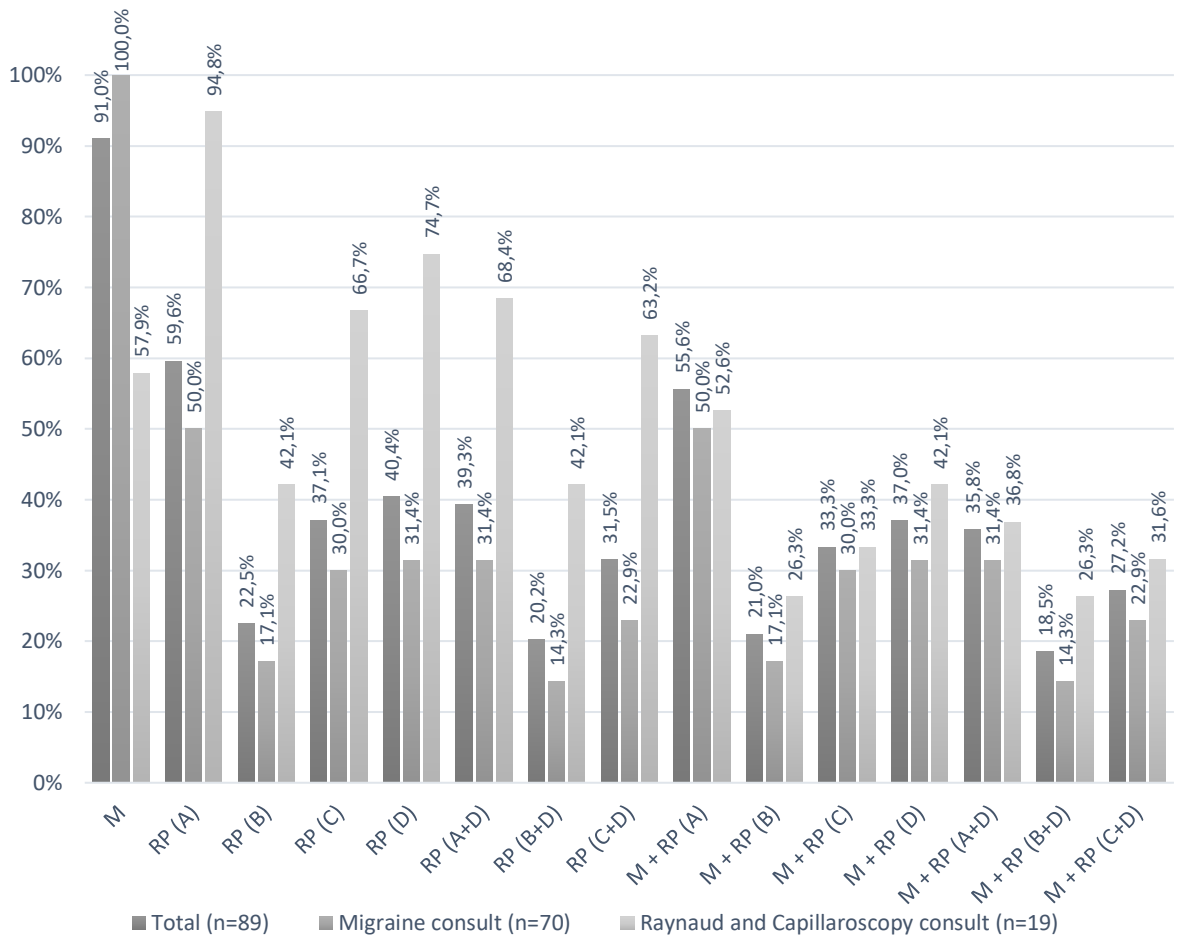
Abbreviations: NA – Non-appliable.

Table IV. Comparison between the diagnostic criteria of RP.

	Criterion A	Criterion B	Criterion C	Criterion D	Criterion A+D	Criterion B+D	Criterion C+D
Patients with previous diagnosis (n=23) who scored positive, n (%)	21 (91.3)	10 (43.5)	14 (60.9)	17 (73.9)	16 (69.6)	10 (43.5)	14 (60.9)
PPV (%)	96.3	100.0	94.1	94.4	94.1	100.0	93.3

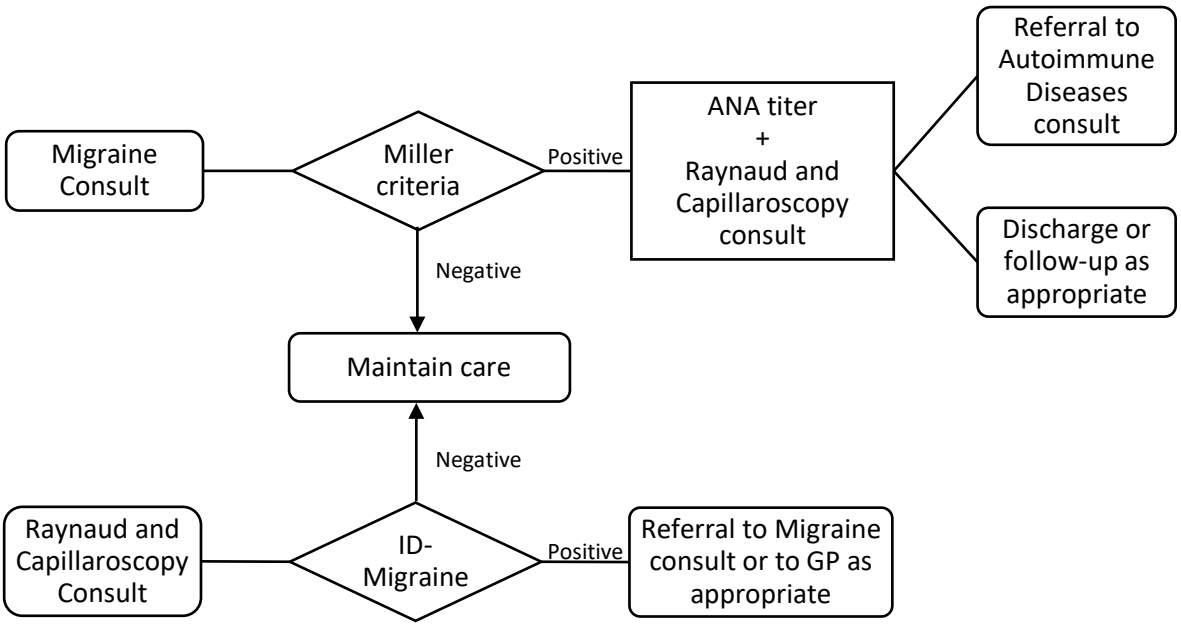
Abbreviations: PPV – positive predictive value.

FIGURES



Abbreviations: A – Criterion A; B – Criterion B; C – Criterion C; D – Criterion D; M – Migraine; RP – Raynaud phenomenon.

Figure 1. Prevalence of migraine and RP.



Abbreviations: ANA – anti-nuclear antibodies; GP – General Practitioner; RP – Raynaud Phenomenon.

Figure 2. Proposed protocol between the Migraine and Raynaud and Capillaroscopy consults.

APPENDIX

1 – Questionnaire

Identificação e Dados sociodemográficos													
Nº estudo													
Data													
Local													
Sexo	Feminino		Masculino										
Data de nascimento													
Estado civil	Casado(a)		Solteiro(a)		Viúvo(a)								
	União de facto		Divorciado(a)		Não especificado (NE)								
Atividade profissional													
	Com químicos?	Sim		Não		NE							
	Com máquinas com vibração?	Sim		Não		NE							
	Com sistemas de refrigeração?	Sim		Não		NE							
Antecedentes médico-cirúrgicos													
Comorbilidades	*Patologia tiroideia*	Sim		Não		NE							
Medicação crónica	*β-bloqueador*	Sim		Não		NE							
	Contracetivo oral	Sim		Não		NE							
	Vasoconstritores	Sim		Não		NE							
Antecedentes cirúrgicos	*Próteses de silicone*	Sim		Não		NE							
História familiar	*Enxaqueca*	Sim		Não		NE		Parentesco					
	Fenómeno de Raynaud	Sim		Não		NE		Parentesco					

ENXAQUECA												
Diagnóstico prévio	Sim				Não				NE			
Cefaleias Frequentes	Sim				Não				NE			
≥5 episódios cefaleias	Sim				Não				NE			
Frequência das cefaleias	Diária				Semanal				Mensal			
	Anual				NA							
≥15 dias / mês	Sim				Não				NE			
Idade 1º episódio												
Duração	Segundos				Minutos				Horas			
	Dias				Meses				Anos			
	Contínua (remissão < 3 meses)				Contínua (remissão > 3 meses)				NA			
Duração ≥4h	Sim		Não		NE		NA					
Caráter: *Pulsátil*	Sim		Não		NE		NA					
Picada/ Facada/Punhalada	Sim		Não		NE		NA					
Queimor / Ardor	Sim		Não		NE		NA					
Peso / Pressão	Sim		Não		NE		NA					
Moedeira	Sim		Não		NE		NA					
Intensidade	Ligeira		Moderada		Severa		NA					
Agravada por atividade física de rotina	Sim		Não		NE		NA					
Sintomas associados: *Fotofobia*	Sim		Não		NE		NA					
Fonofobia	Sim		Não		NE		NA					
Osmofobia	Sim		Não		NE		NA					
Náuseas	Sim		Não		NE		NA					
vómitos	Sim		Não		NE		NA					
Lacrimejo / Injeção conjuntival	Sim		Não		NE		NA					
Congestão nasal / rinorreia	Sim		Não		NE		NA					
Edema palpebral	Sim		Não		NE		NA					
Sudorese facial / frontal	Sim		Não		NE		NA					
Miose / Ptose	Sim		Não		NE		NA					
Agitação / Inquietação	Sim		Não		NE		NA					
Outros sintomas												
Localização Predominante	Hemicrania		Orbital		Frontal		Temporal					
	Parietal		Occipital		Nucal		Vértex					
	Facial		Malar		Mandibular		Temporo-mandibular					
	Otomastalgia		NA		Outra							
Unilateralidade	Sim		Não		NE		NA					
Presença de aura	Sim		Não		NE		NA					
Manifestações da aura: *Visuais*	Sim		Não		NE		NA					
Sensitivas	Sim		Não		NE		NA					
Auditivas	Sim		Não		NE		NA					
Gustativas	Sim		Não		NE		NA					
Motoras	Sim		Não		NE		NA					
Linguagem	Sim		Não		NE		NA					
Outras												

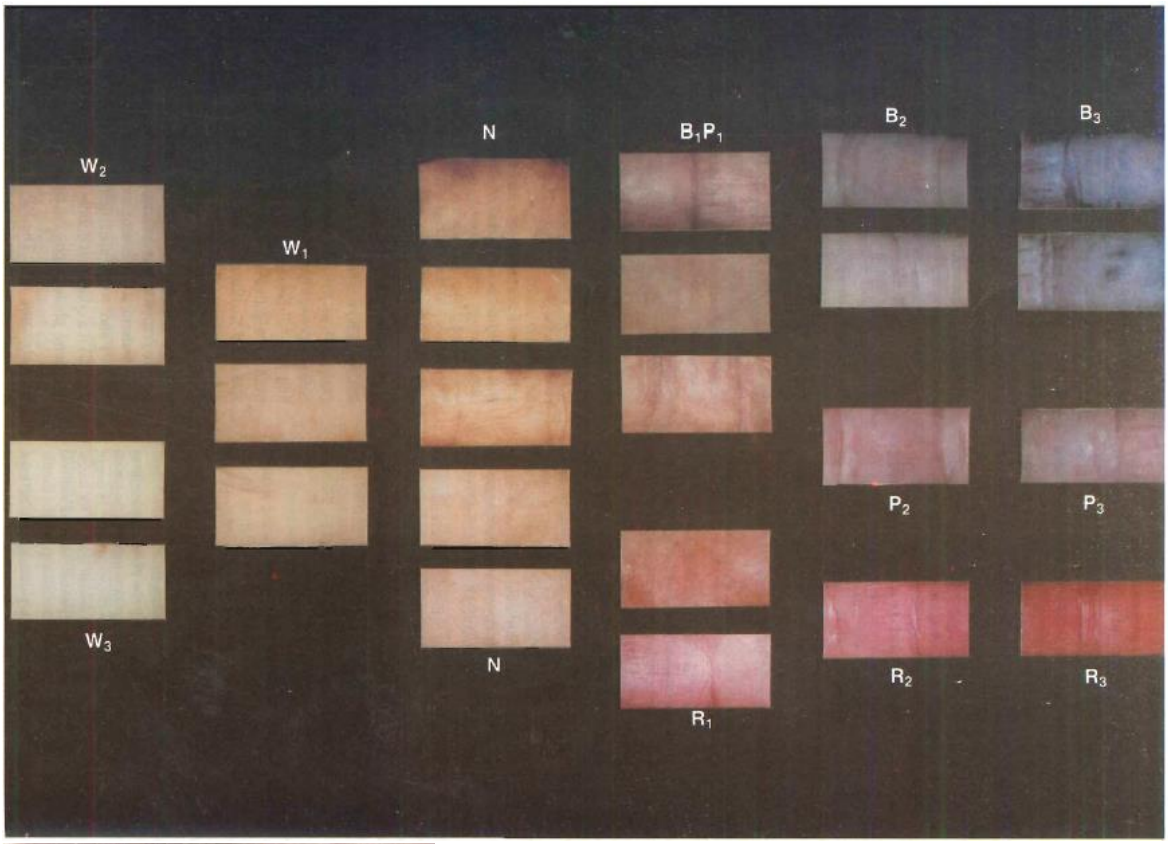
Características das manifestações da aura: *≥1 sintoma evolui em ≥5 min*	Sim		Não		NE		NA	
≥2 sintomas sucessivos	Sim		Não		NE		NA	
Duração cada sintoma 5-60 min	Sim		Não		NE		NA	
≥1 sintoma unilateral	Sim		Não		NE		NA	
≥1 sintoma positivo	Sim		Não		NE		NA	
Cefaleia segue-se em ≤60 min	Sim		Não		NE		NA	
Distribuição das cefaleias *Circadiana*	Dia		Noite		Sem distribuição reconhecida		NA	
Hormonal	Catamenial		Ovulação		Sem distribuição reconhecida		NA	
Sazonal	Primavera		Outono		Sem distribuição reconhecida		NA	
Fatores precipitantes *Stress emocional*	Sim		Não		NE		NA	
Jejum prolongado	Sim		Não		NE		NA	
Alterações climatéricas	Sim		Não		NE		NA	
Menstruação	Sim		Não		NE		NA	
Outros								
Fatores aliviantes *Escuro*	Sim		Não		NE		NA	
Outros								
Correlação temporal com os episódios Raynaud	Sim		Não		NE		NA	
Tratamentos fase aguda *Analgésicos*	Sim		Não		NE		NA	
AINEs	Sim		Não		NE		NA	
Opioides	Sim		Não		NE		NA	
Ansiolíticos	Sim		Não		NE		NA	
Triptanos	Sim		Não		NE		NA	
Outros								
Tratamentos profiláticos *ß-bloqueadores*	Sim		Não		NE		NA	
Bloq. Canais cálcio	Sim		Não		NE		NA	
Antiepiléticos	Sim		Não		NE		NA	
Toxina botulínica	Sim		Não		NE		NA	
Outros								

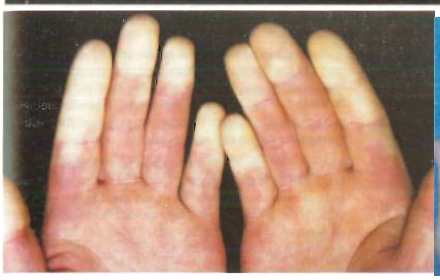
Fenómeno de Raynaud												
Diagnóstico prévio de Raynaud			Sim			Não			NE			
Dedos invulgarmente sensíveis ao frio			Sim			Não			NE			
Alterações de cor nos dedos das mãos com o frio			Sim			Não			NE			
Palidez acentuada												
Azulado			Sim			Não			NE			
Vermelho			Sim			Não			NE			
Bifásicas			Sim			Não			NE			
Trifásicas			Sim			Não			NE			
Escala de cores de Maricq												
Branco	W_1		W_2			W_3			NE			
Azulado	B_1 / P_1		B_2 / P_2			B_3 / P_3			NE			
Vermelho	R_1		R_2			R_3			NE			
Fotografia 1	Sim		Não			NE						
Fotografia 2	Sim		Não			NE						
Fotografia 3	Sim		Não			NE						
Locais afetados	Sim		Não			NE			NA			
Dedos das mãos												
Nariz	Sim		Não			NE			NA			
Pés	Sim		Não			NE			NA			
Aréolas mamárias	Sim		Não			NE			NA			
Lobos auriculares	Sim		Não			NE			NA			
Língua	Sim		Não			NE			NA			
Demarcação clara pele afetada vs. não afetada	Sim		Não			NE			NA			
Fatores precipitantes	Sim		Não			NE			NA			
Frio												
Stress emocional	Sim		Não			NE			NA			
Emoção forte	Sim		Não			NE			NA			
Alterações climatéricas	Sim		Não			NE			NA			
Sono	Sim		Não			NE			NA			
Consumo de álcool	Sim		Não			NE			NA			
Consumo de tabaco	Sim		Não			NE			NA			
Consumo de cafeína	Sim		Não			NE			NA			
Cataménios	Sim		Não			NE			NA			
Água / Ar frios	Sim		Não			NE			NA			
Outros												
Lateralidade dos episódios	Direita		Esquerda			Bilateral						
	NE		NA									
Frequência dos episódios	Diária		Semanal			Mensal						
	NE		NA									
Sintomas locais	Sim		Não			NE			NA			
Parestesias												
Entorpecimento	Sim		Não			NE			NA			
Latejar	Sim		Não			NE			NA			
Sudorese	Sim		Não			NE			NA			
Outros												
Lesões locais	Sim		Não			NE			NA			
Traumatismos severos prévios												
Úlceras ponta dos dedos	Sim		Não			NE			NA			
Cicatriz escavada	Sim		Não			NE			NA			
Correlação temporal com enxaqueca	Sim		Não			NE			NA			
Idade no 1º episódio												

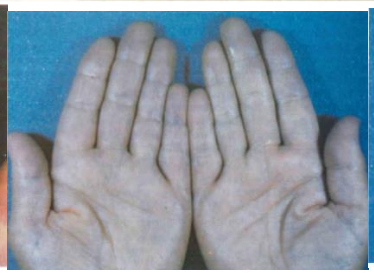
Se depois da análise deste questionário se considerar que é necessário, deseja receber a **convocatória para uma consulta e realização de exames no Hospital de Santo António?**

Sim ☐ Não ☐

Nome	
Morada	
Código Postal	
Telefone	
Telemóvel	
Email	







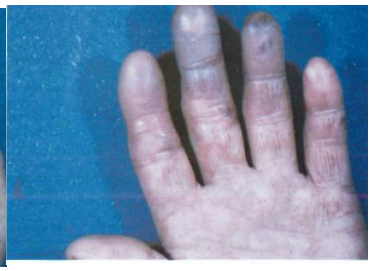


Figura 1 *Figura 2* *Figura 3*

In: Maricq HT, Weinrich M. Diagnosis of Raynaud's Phenomenon Assisted by Color Charts. Journal of Rheumatology 1988;15:454-9.

2 – Informed Consent

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

centro hospitalar do Porto

O presente Termo de Consentimento Informado está incluído num estudo de investigação intitulado ***Association between Primary Raynaud's Phenomenon and Migraine: Prevalence and Clinical Predictors*** para a Tese de Mestrado em Medicina de uma aluna do Instituto de Ciências Biomédicas Abel Salazar (ICBAS) / Hospital Geral de Santo António - Centro Hospitalar Universitário do Porto (HGSA-CHUP), no âmbito da Unidade Curricular Dissertação / Projeto / Estágio.

TERMO DE CONSENTIMENTO INFORMADO

Eu, abaixo-assinado:

Fui informado(a) de que o Estudo de Investigação acima mencionado se destina a estudar a associação entre Enxaqueca e Fenómeno de Raynaud.

Sei que neste estudo está previsto responder a um inquérito e que, caso se detete que tenho uma destas entidades clínicas, poderei ser convocado(a) para uma consulta no Hospital Geral de Santo António do Centro Hospitalar Universitário do Porto, onde poderei comparecer, se assim o desejar. Nessa consulta, serei observado(a) por um médico especialista e poderei realizar alguns exames e análises para melhor esclarecimento da situação.

Foi-me garantido que todos os dados relativos à identificação dos Participantes neste estudo são confidenciais e que será mantido o anonimato.

Sei que posso recusar-me a participar ou interromper a qualquer momento a participação no estudo, sem nenhum tipo de penalização por este facto.

Compreendi a informação que me foi dada, tive oportunidade de fazer perguntas e as minhas dúvidas foram esclarecidas.

Aceito participar de livre vontade no estudo acima mencionado.

Também autorizo a divulgação dos resultados obtidos no meio científico, garantindo o anonimato.

Nome do Participante no estudo:

_____

Data Assinatura

___/___/_____ _____

Nome do Aluno: Raquel Ferreira de Oliveira

Data Assinatura

___/___/_____ _____

Para qualquer esclarecimento adicional, contactar: estudo.enxaqueca.raynaud@gmail.com.

3 – Information about the study

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

centro hospitalar do Porto

Esta informação está incluída num estudo de investigação intitulado *Associação entre Fenómeno de Raynaud Primário e Enxaqueca: Prevalência e Preditores Clínicos* para a Tese de Mestrado em Medicina de uma aluna do Instituto de Ciências Biomédicas Abel Salazar (ICBAS) / Hospital Geral de Santo António - Centro Hospitalar Universitário do Porto (HGSA-CHUP), no âmbito da Tese de Mestrado em Medicina da aluna Raquel Oliveira. **A sua colaboração é importante e agradecemos desde já a sua disponibilidade.**

INFORMAÇÃO ACERCA DO ESTUDO

O Fenómeno de Raynaud é um distúrbio da vasculatura das extremidades que se manifesta por alteração da cor dos dedos das mãos provocada pelo frio ou *stress emocional*.

A Enxaqueca é um distúrbio neurológico que se caracteriza por dores de cabeça recorrentes, unilaterais, intensas, latejantes, agravadas por atividade física habitual, que se podem associar a sintomas como intolerância à luz e ao ruído.

Assim, este estudo tem como objetivo a determinação da prevalência da associação entre Fenómeno de Raynaud Primário e Enxaqueca na população portuguesa, bem como a identificação de preditores clínicos desta associação.

A sua participação neste estudo é **voluntária**. Não acarreta riscos de saúde para si, e caso deseje não participar ou desistir do estudo em qualquer momento, essa decisão não lhe trará qualquer tipo de penalização. Poderá interromper a sua participação a qualquer momento. Antes de participar, deve esclarecer todas as suas dúvidas. Se concordar, ser-lhe-ão colocadas algumas questões.

Caso se detete que sofre de Fenómeno de Raynaud ou Enxaqueca, ser-lhe-á entregue um panfleto informativo acerca da condição em questão, e será aconselhado(a) a transmitir a informação ao seu médico assistente. Se se detetar que sofre de Fenómeno de Raynaud, pode optar por vir a ser convocado(a) para uma consulta no Hospital Geral de Santo António onde, se desejar, será observado(a) e realizará alguns exames e análises para excluir patologias sistémicas às quais este fenómeno pode estar associado. Para isso, é necessário que se identifique e forneça os dados para posterior contacto; caso opte por responder ao inquérito anonimamente, o que pode fazer, não poderá ser convocado(a) para esta consulta. Se desejar comparecer à consulta, as despesas de deslocação serão da sua responsabilidade.

A confidencialidade dos seus dados será garantida, e estes não serão usados para outros fins. Na eventualidade de publicação ou divulgação dos resultados dos estudos no meio científico, será garantido o seu anonimato.

4 – Informative Brochure on Raynaud Phenomenon

5 – Informative Brochure on Migraine

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