Prospective Nailfold Capillaroscopy evaluation of Raynaud’s phenomenon in children and adolescents

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AVALIAÇÃO PROSPECTIVA DE CRIANÇAS E ADOLESCENTES COM FENÔMENO DE RAYNAUD ATRAVÉS DA CAPILAROSCOPIA PERIUNGUEAL

Objetivo: Avaliar prospectivamente os achados clínicos e de capilaroscopia perungueal de uma coorte de crianças e adolescentes com fenômeno de Raynaud sem critérios para doenças reumáticas auto-imunes.

Métodos: Foram incluídos 40 crianças e adolescentes com fenômeno de Raynaud. Cada paciente foi avaliado clinicamente e com exames laboratoriais incluindo a determinação de anticorpo antinuclear. Na mesma ocasião foi realizada avaliação capilaroscópica através de um microscópio óptico com aumentos de 10 e 16 vezes. Todos foram avaliados prospectivamente com tempo médio entre as avaliações de 1,6 anos.

Resultados: Dos 40 pacientes, 30 (75%) eram do sexo feminino, com média de idade de 14,6 anos e tempo médio de evolução de 4,2 anos. A média de idade do início dos sintomas foi de 10,4 anos e o tempo médio até o diagnóstico de 1,4 anos. Quatorze (35%) dos 40 pacientes apresentaram anticorpo antinuclear positivo. Cinco pacientes (12,5%) apresentaram alterações na capilaroscopia inicial: 4 microangiopatia inespecífica e 1 padrão esclerodermia. Três pacientes (7,5%) apresentaram alterações na capilaroscopia. Dois pacientes com padrão esclerodermia na capilaroscopia apresentaram durante a evolução doença mista do tecido conjuntivo e hipotireoidismo respectivamente. Em um paciente com capilaroscopia normal e presença de auto-anticorpos foi diagnosticado lúpus eritematoso sistêmico após 1 ano da avaliação inicial.

Conclusão: O fenômeno de Raynaud permanece como primário na maioria dos casos, entretanto a capilaroscopia perungueal e a determinação de auto-anticorpos são úteis para auxiliar na exclusão de doenças reumáticas ou outra doença auto-imune. Nenhuma outra criança teve diagnóstico de doença reumática auto-imune sistêmica durante a evolução.

Palavras-chave: Capilares; Microscopia; Criança; Adolescente; Fenômeno de Raynaud; Doenças do colágeno.

PROSPECTIVE NAILFOLD CAPILLAROSCOPY EVALUATION OF RAYNAUD’S PHENOMENON IN CHILDREN AND ADOLESCENTS

Objective: To evaluate prospectively the clinical features and nailfold capillaroscopy findings of a cohort of children and adolescents who presented Raynaud’s phenomenon (RP) without criteria for autoimmune rheumatic diseases.

Methods: 40 children and adolescents with isolated RP were included. Evidence of systemic autoimmune rheumatic diseases (SARD) was ruled out by thorough clinical and laboratory examination. Concomitantly we also performed wide-field nailfold capillaroscopy evaluation using an optical microscope with magnifications of 10 and 16X. All patients were prospectively re-evaluated within a mean interval time between evaluations of 1.6 years.

Results: Thirty (75%) out of 40 patients were female with a mean age of 14.6 years and mean follow-up time of 4.2 years. The mean age of disease onset was 10.4 years and the mean time until diagnosis was 1.4 years. Fourteen out of 40 patients (35%) presented antinuclear antibodies (ANA). Five (12.5%) patients had al-
tered nailfold capillaroscopy at first examination: four presented non-specific microangiopathy and one presented sclerodermia pattern. At the re-evaluation three patients (7.5%) presented nailfold capillaroscopy alterations (two sclerodermia pattern and one non-specific microangiopathy). The two patients who showed sclerodermia pattern at the nailfold capillaroscopy presented along the follow-up a diagnosis of mixed connective tissue disease and hypothyroidism, respectively. A girl with normal nailfold capillaroscopy and presence of autoantibodies was diagnosed with systemic lupus erythematosus after 1 year of initial evaluation. None of the other children presented diagnosis of SARD along the follow-up.

Conclusions: Primary Raynaud’s phenomenon remained the diagnosis in most cases in this series of children and adolescents presenting with initial RP complaint. Nailfold capillaroscopy and determination of autoantibodies were useful ancillary tools in the investigation of possible evolution towards SARD.

Keywords: Capillaroscopy; Adolescent; Child; Raynaud’s phenomenon; Autoimmune rheumatic diseases.

INTRODUCTION

Raynaud’s phenomenon (RP) is a vascular disorder characterized by episodic and reversible attacks of vasoconstriction with paleness of the extremities, followed by cyanosis and hyperemia, usually triggered by exposure to cold or emotional stress. Prevalence of RP in the general population ranges from 5 to 20%, and in children aged between 12 and 15 years, the described prevalence is estimated in up to 15%. Similarly to adults, it is more common in females and its prevalence increases with age5.

RP can be divided into primary or idiopathic, and secondary. Primary or idiopathic RP comprise up to 90% of RP cases and is characterized by symmetrical episodes, absence of tissue necrosis, ulceration or gangrene, absence of secondary causes (evaluated by anamnesis and physical evaluation) and of antinuclear antibodies (ANA), normal levels of acute phase markers, and no abnormality at nailfold capillaroscopy (NFC)6.

The main cause for secondary RP in children and adolescents is systemic autoimmune rheumatic diseases (SARD), among which the main members are systemic sclerosis (SSc) and mixed connective tissue disea-

se (MCTD)7,8. RP may represent the initial manifestation in a considerable number of SARD patients. Identification of secondary RP with support of NFC can actually lead to early diagnosis of such diseases, which are known to present an insidious development9-12. Laboratory examinations such as detection of autoantibodies (ANA, anti-topoisomerase-1 and anti-centromere) are also helpful for sclerodermia characterization. Literature reports estimate a 4% to 60% RP frequency in adult patients that developed SARD13-18. Enlarged and giant capillaries, avascular areas and irregular architecture at NFC examination were observed in adults with RP that developed SARD during a 6.5 year follow-up19. About 15 to 20% of adult patients with RP and without criteria for SARD, but possessing autoantibodies and/or NFC abnormalities, are at risk to develop some kind of SARD within a 10 year period15,16,20-22. Yet, these two important predictive factors in adults have not been properly studied in children.

Studies on children with RP suggest that NFC might distinguish patients with primary RP from those with RP secondary to SARD23,24. A prospective study with children and adolescents with RP showed that about 60% of those who developed diseases of systemic sclerosis group, presented sclerodermia (SD) pattern in average 6 months before the onset of the disease, highlighting the prospective value of NFC abnormalities regarding SARD development25.

In this study, we performed a prospective evaluation of a cohort of children and adolescents with RP without criteria for SARD and sought to understand the role of NFC and autoantibody determination in the early identification of secondary RP.

METHODS

Forty children and adolescents with RP were consecutively evaluated at the pediatric rheumatology outpatient clinic over the last 2 years. RP was defined as the presence of paleness, cyanosis or hyperemia at the nailfold bed conditions as to allow for NFC examination. Patients with SARD or other systemic diseases were excluded. All patients were prospectively evaluated in a mean time of 1.6 years (from 6 months to 2 years).

Anamnesis and physical evaluation were performed with emphasis on possible skin abnormalities (skin
thickness, Gottron’s sign, heliotrope, photosensitivity and nailfold hyperemia), calcinosis, digital infarcts, digital pitting, arthritis/arthralgia, muscle weakness, esophageal abnormalities (dysphagia), and pulmonary abnormalities (dyspnea, dry cough). RP was considered incomplete when one or two of the three consecutive phases (paleness, cyanosis and hyperemia) in the extremities of the fingers was absent.

Laboratory evaluation included blood cells count, testing for acute phase reactions (erythrocyte sedimentation rate – ESR and C-reactive protein test – CRP), muscle enzymes serum level (glutamic-oxaloacetic transaminase – GOT; glutamic-pyruvic transaminase – GPT; creatinekinase – CK; lactate dehydrogenase – LDH), autoantibodies (ANA; anti-double-stranded deoxyribonucleic antibodies – anti-DNA; extractable nuclear antigens – ENA; rheumatoid factor – RF; anti-topoisomerase-1 or anti-Scl 70; anti-polymyositis-scleroderma – anti-PM-Scl; anti-cardiolipin IgG and IgM); and hemolytic complement (CH100 and C2).

Capillaroscopic evaluation was performed by the same person (MTRAT) in an optical microscope with 10 and 16 times magnification, equipped with a graduated ruler attached to the right eyepiece to allow counting the number of capillary loops per millimeter in the distal row. Epi-illumination was provided by incandescent tungsten lamp with a green filter, so as to better highlight the capillaries against the tissue background. For optimal visualization of the capillary network, the periungual skin was overlaid with a transparent oleaginous agent. All hand fingers (with exception of the thumbs) were examined. The patients were advised not to touch or remove the cuticle (nailfold) during one whole month before the examination to allow optimal stretching of the capillary loops by the nailfold attached to the nail and to avoid micro traumas that could jeopardize the examination. The analysis and interpretation of the various microvascular phenomena were performed in a semiquantitative approach as proposed by Andrade et al., with focus on the number of capillaries per millimeter, number and extent of avascular areas, number of enlarged and giant capillary loops, and number and distribution of areas of microhemorrhage.

Enlarged capillaries were defined as those having 4 or more times the width of normal neighbor loops in the three limbs, ascendant, transition, and descendant. Giant capillaries were defined as aneurysm-looking loops with limbs about 10 times or more the width of normal neighbor loops. Morphological abnormalities were classified into three types: meandering, bushy, and bizarre capillaries. Meandering capillaries were defined as tortuous loops where the limbs were intertwined and crossed on themselves. Bushy capillaries were defined as those with small branches in different directions. Bizarre capillaries were those presenting with atypical structure, although not conforming to the types just described.

Capillary devascularization was estimated in two ways: 1) the number of capillary loops per millimeter allowed the detection of diffuse devascularization; and 2) the deletion score measured focal devascularization. The number of capillaries per millimeter was counted through the eyepiece with a graduated ruler. The final figure was the average of the linear density of capillaries in the fingers observed. Deletion areas were defined as the lack of two or more successive capillaries, or avascular areas measuring more than 3mm in extent. This system was adapted from Lee et al, and is graded as follows: Grade 0: No deletion areas; Grade 1: one or two discontinuous deletion areas; Grade 2: more than two discontinuous deletion areas; Grade 3: extensive and confluent deletion areas. The final degree corresponded to the mean of the figures ascribed for each finger.

Nailfold capillaroscopy was considered normal in the presence of a palisade of parallel capillary loops.

**FIGURE 1. Normal capillaroscopy (16 times magnification)**
without relevant morphological abnormalities and without deletion areas. (Figure 1) Non-specific microangiopathy was defined as the presence of enlarged capillaries and other morphological atypias without capillary deletion (Figure 2). The SD pattern was characterized by the presence of enlarged capillaries or giant capillaries and avascular lesions translating capillary deletion in a scenario of general distortion of the usual palisade array of capillary loops (Figure 3).

Intra and inter-observer variability was tested in 20% of the examined individuals. In order to evaluate the capillaroscopic findings we used the agreement between two observers (MTRAT/DGPP) by using Kappa ($k>0.80$).

All participants signed the informed consent term for participation in this study, which was previously approved by the ethics committee of Hospital São Paulo.

**RESULTS**

Our sample was composed of 40 patients: 75% females, 75% caucasians, with mean age of 14.6 years (ranging from 6 to 18 years) and mean follow-up time of 4.2 years (from 3 months to 12 years). Mean age of symptoms onset was 10.4 years (from 2 to 17 years) and mean age until diagnosis was 1.4 years (from 1 month to 8 years).

The majority of patients presented arthralgia (57.5%) on large joints (mainly on knees) and incomplete RP (80%) at the first evaluation. The most frequent manifestations were digital cyanosis and paleness. At the initial clinical examination, three patients presented acute arthritis in addition to RP, but only one of them had a positive ANA test. No patient presented fever, dysphagia, dyspnea, skin thickness, digital ulcers or digital pulp resorption. Fifteen patients (37.5%) used nifedipine as treatment for RP.

Clinical data and laboratory alterations at the initial evaluation of children and adolescents with RP are shown in Table I.

Initial laboratory examinations presented transitory lymphopenia and also mild alterations in the white blood cells count. No patient presented anemia (hemoglobin<11mg/dl), leukopenia (leukocytes <4000/mm³) or thrombocytopenia (platelets <100000/mm³). Some patients presented mild transient abnormalities in acute phase reactions (ESR and CRP). No patient presented GOT nor CK increase, but some patients presented subtle and transient increase in LDH and GPT serum levels. Anti-cardiolipin antibody was present in one patient at low levels and with no clinical relation to thromboembolism. Thirteen patients (32.5%) presented positive ANA: 7 at low titer (1/160) and/or with non-specific immunofluorescence pattern, and 3 of these presented negative ANA in the second evaluation; three other patients had positive ANA at high titer ($\geq1/1280$) with non-specific ANA pattern without progressing into some autoimmune disease during follow-up; and three patients had high titer...
ANA (1/1280) with nuclear speckled pattern. These three patients progressed into a secondary form of RP. Two of these (5%) ANA-positive patients at high titers (1/1280) and with speckled pattern also presented anti-RNP (ribonucleoprotein) antibodies in the first evaluation and a third one presented homogeneous ANA pattern (1/1280) and absence of anti-ENA antibodies during follow-up. No patient was positive for anti-DNA, RF, anti-topoisomerase-1 or anti-PM-Scl antibodies, and none had complement consumption.

Thirty-four out of the 40 patients initially evaluated presented normal NFC (85%), one had inconclusive result, four had non-specific microangiopathy and one presented SD pattern (Table 2). All patients were prospectively evaluated in a mean time of 1.6 years (from 6 months to 2 years) and three of them (7.5%) presented capillaroscopic abnormalities along the follow-up: one patient presented non-specific microangiopathy and two presented SD pattern. A 13-years old patient with SD pattern (mean deletion of 1.75, mean enlarged capillaries/finger of 2, and no giant capillaries) in the initial NFC remained with stable abnormalities two years later in the second NFC. She presented positive ANA with coarse speckled pattern at 1/1280 and progressed to mixed connective tissue disease (MCTD) two years after initial evaluation. The two other patients that presented abnormal NFC at the follow-up evaluation had a normal NFC at baseline: a 12 years old girl that changed into non-specific microangiopathy but did not develop any clinical evidence of SARD and remained with no autoantibodies after 1 year; and a 14-years old girl who developed full SD pattern (mean deletion of 2.8, mean enlarged capillaries/finger of 0.75 and no giant capillaries) with worsening of RP, presence of digital ulcers, diffuse hands edema, hypothyroidism, and nuclear homogeneous ANA at 1/1280 after 7 months of initial evaluation. An 11-years old girl that presented initially isolated RF, nuclear coarse speckled ANA at 1/1280, anti-RNP antibodies, and normal NFC, progressed to chronic arthritis, hemolytic anemia, anti-Sm antibodies, and was diagnosed as systemic lupus erythematosus (SLE) 1 year after initial evaluation. Thus, 3 (7.5%) out of 40 patients presented secondary RP along the follow-up investigation.

The capillaroscopic findings were fully concordant among the two observers and in intra-observer evaluation (kappa=1). No inferential statistical analysis was performed due to the small number of patients that progressed to secondary RP.

**DISCUSSION**

RP is still poorly described in pediatrics, with reported frequencies reaching up to 15% in children and adoles-

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**TABLE I. INITIAL CLINICAL AND LABORATORY DATA OF CHILDREN AND ADOLESCENTS WITH RAYNAUD’S PHENOMENON (N=40)**

<table>
<thead>
<tr>
<th>Data</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical data</strong></td>
<td></td>
</tr>
<tr>
<td>Incomplete RP</td>
<td>32 (80)</td>
</tr>
<tr>
<td>Complete RP</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>23 (57.5)</td>
</tr>
<tr>
<td>Skin Abnormalities*</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td><strong>Laboratorial data</strong></td>
<td></td>
</tr>
<tr>
<td>Acute phase reactions</td>
<td></td>
</tr>
<tr>
<td>ESR &gt; 25 mm/1st hour</td>
<td>5 (12.5)</td>
</tr>
<tr>
<td>CRP &gt; 0.6 mg/L</td>
<td>7 (17.5)</td>
</tr>
<tr>
<td>Muscle enzymes</td>
<td></td>
</tr>
<tr>
<td>GPT (&gt; 56 U/L)</td>
<td>1/37 (2.7)</td>
</tr>
<tr>
<td>LDH (&gt; 240 U/L)</td>
<td>3/37 (8.1)</td>
</tr>
<tr>
<td>Auto-antibodies</td>
<td></td>
</tr>
<tr>
<td>ANA Hep-2</td>
<td>13 (32.5)</td>
</tr>
<tr>
<td>Anti-ENA**</td>
<td>2 (5.0)</td>
</tr>
<tr>
<td>RF</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>ACL IgG/IgM</td>
<td>1 (2.5)/0(0)</td>
</tr>
</tbody>
</table>

*Skin abnormalities: livedo reticularis (N=5), photosensitivity (N=2).

**Discussion**

Table 1. Initial clinical and laboratory data of children and adolescents with Raynaud’s phenomenon (N=40)

**TABLE II. NAILFOLD CAPILLAROSCOPY OF CHILDREN AND ADOLESCENTS WITH RAYNAUD’S PHENOMENON IN TWO DIFFERENT OCCASIONS (N=40)**

<table>
<thead>
<tr>
<th>First Evaluation</th>
<th>Second Evaluation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (34)</td>
<td>Normal (37)</td>
</tr>
<tr>
<td>Non-specific</td>
<td>Non-specific</td>
</tr>
<tr>
<td>microangiopathy</td>
<td>microangiopathy</td>
</tr>
<tr>
<td>(4)</td>
<td>(1)</td>
</tr>
<tr>
<td>Inconclusive (1)</td>
<td>Inconclusive (0)</td>
</tr>
<tr>
<td>SD pattern (1)</td>
<td>SD pattern (2)</td>
</tr>
</tbody>
</table>

*Interval between examination: 6 months to 2 years (mean: 1.6 years)
The arrows represent the follow-up changes in the second evaluation of NFC.
cents\textsuperscript{1-2}. Its prevalence increases at adolescence with mean age at symptoms onset of 10 years, according to what was observed in our study, and it is also more frequent in females, as observed in 75\% of our sample\textsuperscript{1-3}. RP was incomplete in 80\% of our cases, challenging the diagnosis due to the lack of awareness by patients and physicians. Therefore, the diagnosis is usually delayed, like in our study, where we observed an interval of up to eight years (mean 1.4 years) between RP onset and diagnosis. In most cases, RP is defined as primary, as we found in 37/40 patients (92.5\% of cases)\textsuperscript{2}. It is known that primary RP is characterized as symmetrical attacks, absence of tissue necrosis, accral ulcers or gangrene, absence of ANA, normal acute phase reaction and normal NFC. In our 37 primary RP patients, only very few clinical and laboratory abnormalities were observed, and those were transient or had no clinical relevance. Although we had observed clinical complaints by a few patients, such as arthralgia or muscular weakness, those were only subjective and non-specific symptoms and the patients did not progress into any disease.

Even though we observed the presence of ANA in 13 patients (32.5\%), 10 presented low titer and/or non-specific patterns, and 3 (7.5\%) of them had negative results in the follow-up. Literature describes ANA presence in up to 12.6\% of healthy children and adolescents\textsuperscript{28}. A larger frequency of ANA in our sample suggests that these patients might not have primary RP and that longer follow-up period might show development of RP secondary to SARD in additional patients. These patients would have RP as a risk to develop such diseases. Nevertheless, in 3 patients (7.5\%), the presence of ANA at high titers and speckled pattern was a predictive factor to progress into SARD, also according to literature, which shows that about 15 to 20\% of adult patients with RP that have auto-antibodies and/or NFC abnormalities will develop some kind of SARD in up to 10 years\textsuperscript{15,16,19-22}.

Other laboratory abnormalities were also non-specific such as mild elevation in acute phase reactants, as well as abnormalities in red and white cell analysis, and elevation in serum muscular enzyme levels, which can be altered in several conditions. Since all abnormalities were transient, we believe that they were not pathologically meaningful.

Regarding NFC, it was normal for most cases, and those patients with non-specific microangiopathy (4 cases) in the first evaluation, had normal final findings in the follow-up. Non-specific microangiopathy is described as an elementary capillaroscopic abnormality that is able to progress to SD pattern or it might progress to normal NFC, as occurred with some of our patients in the second evaluation\textsuperscript{22-24}. However, 1 patient who initially did not present clinical features nor NFC abnormalities that could suggest SARD, presented NFC abnormalities during the follow-up, which were compatible to non-specific microangiopathy. This patient is still being clinically followed.

The prognostic value of NFC abnormalities has been described in adults and sporadically in children\textsuperscript{12,18,20,22,24,25,29}. The two patients from our sample with SD pattern developed clinical abnormalities that allowed them to be classified as secondary RP, suggesting that SD pattern probably represents a risk factor for SARD development in children. The first adolescent did not present any clinical abnormality at first examination, but already presented NFC abnormalities, ANA and anti-RNP antibodies. During the follow-up this patient developed digital ulcers, suggesting MCTD diagnose. In this regard, Duffy et al. studied NFC in 27 RP children (67\% with secondary RP) and suggested that presence of ANA concomitantly to NFC abnormalities were predictive factors to SARD development\textsuperscript{21}.

The second patient, however, presented a clear SD pattern in the second capillaroscopic evaluation, concomitantly with RP worsening, digital ulcers, diffuse hand edema, antinuclear antibodies (ANA) and hormonal thyroid alterations, with consequent hypothyroidism diagnosed 7 months after the initial evaluation. There are very scarce literature reports of hypothyroidism associated with secondary RP during childhood\textsuperscript{30-33}. In addition, the few reports of NFC abnormalities in hypothyroidism refer to capillary immaturity and a few giant capillaries although the vessels were not found to be tortuous and no SD pattern as in our patient’s NFC\textsuperscript{30-32}. For this reason, we cannot exclude the possibility that this patient might develop SARD in the future.

The patient that evolved with SLE 1 year after the initial evaluation presented normal NFC at both occasions. Studies in patients with SLE and RP suggest the detection of other changes needs higher magnification of 100 to 200 fold and 10 and 16 times magnification could not be enough to detect alterations\textsuperscript{34}. However NFC alterations were mild non-specific and characterized by long and tortuous loops, and sometimes small petechiae.

In a prospective study with mean follow-up period of 2 years, Pavlov-Dolijanovic et al. evaluated 250 chil-
Children and adolescents up to 20 years old with RP\(^{25}\). As we observed in our study, the majority presented normal NFC or non-specific findings (only 4% with SD pattern). Children and adolescents who developed scleroderma spectrum disorders showed definite SD pattern 6 months before the clinical expression of the disease. This evidences the prognostic value of NFC on SARD development. However, only 10 of the 59 patients who developed secondary RP presented NFC changes at baseline; this meaning that the majority of patients with systemic rheumatic diseases from this study did not have prior NFC alterations\(^{25}\). Due to the relevance of NFC in distinguishing primary from secondary RP in rheumatic diseases, this examination is recommended 6 monthly when RP is present\(^{10,25,35}\).

NFC has a few limitations indeed, such as dependency of skin transparency, and integrity of nailfold, in addition to the observer's subjectivity and his experience to achieve accurate results. In this regard, it should be emphasized that the SD pattern capillaroscopic definition in the present study was based on agreement of two experienced readers. Another limitation was that we did not perform videocapillaroscopy. Although, some authors claim that this exam is more accurate to discriminate giant or enlarged capillaries\(^{36,37}\), our group has recently demonstrated that conventional widefield NFC has equivalent accuracy for the detection and quantitation of the SD pattern\(^{38}\).

We conclude that clinical and laboratory examinations with NFC and ANA determination are essential to delineate the etiology of RP in children and adolescents. Although RP in childhood is most likely to represent primary RP, NFC and ANA are important tools in the investigation of these patients because they may detect early abnormalities that indicate seldomly unsuspected secondary RP and represent a risk factor for developing a SARD within months or years. Therefore, NFC is an important tool to predict the development of SARD. Due to the lack of studies with significant casuistic, multicenter prospective studies are needed in order to clarify more properly the NFC importance in children and adolescents with RP phenomenon.

ACKNOWLEDGMENTS
This project was supported by FAPESP process number: 07/55617-1

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Batalha, Portugal
8 a 9 Novembro 2013