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Nailfold video capillaroscopy in Turner syndrome: a descriptive study

Videocapilaroscopia na síndrome de Turner: estudo descritivo

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Abstract

Background: An increased prevalence of impaired glucose homeostasis is reported in Turner syndrome. Endothelial changes are described in patients with insulin resistance, which may be present in patients with Turner syndrome. Video capillaroscopy is a noninvasive examination that allows assessment of vascular patency.

Objective: To describe the nailfold morphology of capillaries in Turner syndrome using video capillaroscopy.

Methods: Subjects were studied in a temperature-controlled room, 20 days after no nailfold manipulations. The capillaries were visualized by microscope connected to a television and computer and were studied and classified according to these patterns: loop distribution, papilla, avascular fields, edema, form, capillary limbs, flow and hemorrhagic extravasation.

Results: Fifty patients aged between 6-37 years with Turner syndrome were studied. Eighteen (36%) patients had normal capillaroscopy with hairpin pattern in loop distribution and no avascular fields. The papilla was ratified in 13 (26%) and enlarged in four (8%). Edema occurred in 22 (44%) cases. There were three (6%) macrocapillaries and three (6%) were branched. Tortuosity was present in five (10%) patients. Hemorrhagic extravasation occurred in one (2%) case. Flow was fast in seven (14%), granulous in five (10%) and slow in six (12%).

Conclusion: There was a high prevalence of nailfold capillaroscopy changes in Turner syndrome and the most prevalent alterations found were edema and ratified papilla.

Keywords: Turner syndrome, nailfold capillaroscopy, endothelium.

Resumo

Contexto: Estudos evidenciam distúrbios no metabolismo da glicose na síndrome de Turner. As alterações no endotélio estão descritas em pacientes com resistência insulínica, que pode ocorrer em pacientes com síndrome de Turner, e o estudo dos capilares pela videocapilaroscopia é um exame não-invasivo que permite avaliação da permeabilidade vascular.

Objetivo: Descrever a morfologia dos capilares na síndrome de Turner usando a videocapilaroscopia.

Método: As pacientes foram estudadas em sala com temperatura controlada, após 20 dias sem manipulação das cutículas. Os capilares foram visualizados por microscópio conectado à televisão e computador, sendo estudados de acordo com os seguintes parâmetros: distribuição de alças, papila, áreas desvascularizadas, edema, forma, tamanho, fluxo e hemorragia.

Resultados: Cinquenta pacientes com síndrome de Turner foram estudadas, com idades entre 6 e 37 anos. Dezoito (36%) tiveram exame normal com distribuição de alças com padrão em paliçada e sem áreas desvascularizadas. A papila foi retificada em 13 (26%) e alargada em quatro (8%). Edema ocorreu em 22 (44%) casos. Havia três (6%) capilares ectasiados e três (6%) eram ramificados. Tortuosidade estava presente em cinco (10%) pacientes. Hemorragia ocorreu em um (2%) caso. O fluxo foi rápido em sete (14%), granuloso em cinco (10%) e lento em seis (12%).

Conclusão: Houve uma maior prevalência de anormalidades na videocapilaroscopia na síndrome de Turner, e as alterações mais comuns foram edema e papila retificada.

Palavras-chave: Síndrome de Turner, videocapilaroscopia, endotélio.

Introduction

Turner syndrome (TS) is a relatively common chromosome disorder, caused by complete or partial X monosomy. TS affects approximately 1:2,000 female births and as many as 10% of spontaneous miscarriages have a 45,X karyotype.^{1,2} Gonadal dysgenesis and short

stature are two of the characteristic clinical features of this syndrome.¹⁻⁶

An increased prevalence of impaired glucose homeostasis and diabetes mellitus is reported in TS.⁷⁻¹⁰ Insulin resistance appears very early in the natural history of TS.¹⁰⁻¹⁴ This resistance seems to involve monoxidative

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Table 1 - Distribution of groups by karyotype and pubertal status

Variable	Group 1 (n = 18)	Group 2 (n = 32)	Total (n = 50)
Karyotype			
45,X	11 (61.1%)	16 (50%)	27
Mosaicism	7 (38.9%)	16 (50%)	23
Pubertal development			
Prepubertal	5 (27.8%)	11 (34.3%)	16
Spontaneous puberty	1 (5.5%)	5 (15.6%)	6
Postpubertal	13 (72.2%)	21 (65.7%)	34

pathways of glucose metabolism and is likely to predispose adults with TS to future development of diabetes.³⁻⁵

Endothelial disturbance is present in groups with increased risk for diabetes and insulin resistance.¹²⁻¹⁷ Human microcirculation can be studied in vivo using different methods, such as plethysmography and capillaroscopy.¹⁷⁻²³

The aim of this study is to describe the morphology of nailfold capillaries in patients with TS using video-capillaroscopy.

Methods

A descriptive cross-sectional study was carried out. Diagnosis of TS was confirmed by karyotype. Diabetic patients were excluded. This study was approved by the ethics committee of Universidade Federal do Rio de Janeiro. Subjects were studied in a temperature-controlled room in the morning following a night's fasting, 20 days after no nailfold manipulations. The subjects were comfortably seated in a chair with the observed hand at heart level with the forearm and hand bent at the elbow. All patients had their arm blood pressure measured in this position using the auscultatory method. Capillaries were visualized by microscope connected to a television monitor and computer. A few drops of immersion oil were spread on the observation area. Capillary morphology was studied in a magnification of 0.8 to 10.0 x by the same observer. The capillaries were classified in the following patterns: loop distribution, papilla, avascular fields, venous plexus, edema, form, capillary limbs, flow and hemorrhagic extravasation. The following capillary

characteristics were considered normal: hairpin loop distribution, normal papilla, absent avascular fields, absent edema, normal form of capillary limbs, continuous flow and no hemorrhagic extravasation. Patients were classified in three groups according to pubertal status: prepubertal, spontaneous puberty and postpubertal, and also according to karyotype by 45,X and mosaicism.

Results

Fifty patients with TS were studied, aged between 6-37 years. Patients' mean age was 17.2 ± 4.0 . The karyotype of 27 (54%) patients was 45,X and 23 (46%) were mosaic. Sixteen (32%) cases were prepubertal and 34 (68%) were postpubertal. Spontaneous puberty occurred in six (12%) patients and all continued to present regular menses.

Distribution of the presence of abnormalities by karyotype and pubertal status is presented in Table 1. Eighteen (36%) patients had normal capillaroscopy in all patterns (group 1) and 32 (64%) had abnormal capillaroscopy (group 2). Distribution of groups considering age and medication is presented in Table 2. Abnormality patterns are described in Tables 3 and 4. Number of abnormality patterns varied among patients. Eleven (22%) patients had only one abnormality, nine (18%) had two, seven (14%) had three, four (8%) had four and one (2%) had five abnormalities. All abnormalities are described in Table 5.

Discussion

Study of capillaries may express the status of vessel permeability and videocapillaroscopy is an easy and non-invasive method to study them. Since nailfold capillaries are parallel to the skin surface, they can be seen in

Table 2 - Distribution of groups by age and medication

Age	Group 1 (n = 18)					Group 2 (n = 32)				
	N	GH	GH + E	E	E + P	N	GH	GH + E	E	E + P
6-9	1 (100%)	2 (40%)	-	-	-	2 (33.4%)	3 (30%)	-	-	-
10-14	-	3 (60%)	-	-	-	2 (33.3%)	5 (50%)	-	-	-
15-19	-	-	1 (100%)	2 (100%)	4 (44.5%)	2 (33.3%)	2 (20%)	1 (100%)	-	3 (20%)
20-24	-	-	-	-	3 (33.3%)	-	-	-	-	4 (26.7%)
25-29	-	-	-	-	-	-	-	-	-	6 (40%)
30-34	-	-	-	-	2 (22.2%)	-	-	-	-	1 (6.6%)
>35	-	-	-	-	-	-	-	-	-	1 (6.7%)
Total	1	5	1	2	9	6	10	1	-	15

E = estrogen therapy; E + P = estrogen + progesterone therapy; GH = growth hormone therapy; GH + E = growth hormone therapy + estrogen therapy; N = no medication.

Table 3 - Distribution of capillary patterns in group 2

Capillary pattern	Group 2 - Abnormal (n = 32)	
	Normal	Abnormal
Loops	Hairpin - 31 (96.8%)	Mixed - 1 (3.2%)
Papilla	Normal - 15 (46.9%)	Ratified - 13 (40.6%) Enlarged - 4 (12.5%)
Avascular fields	Absent - 31 (96.8%)	Present - 1 (3.2%)
Edema	Absent - 10 (31.3%)	Present - 22 (68.7%)
Form	Normal - 26 (81.2%)	Branched - 3 (9.4%) Macrocapillaries - 3 (9.4%)
Capillary limbs	Normal - 27 (84.4%)	Tortuosity - 5 (15.6%)
Flow	Continuous - 14 (43.8%)	Fast - 7 (21.9%) Granulous - 5 (15.6%) Slow - 6 (18.7%)
Hemorrhagic extravasation	Absent - 31 (96.8%)	Present - 1 (3.2%)

full length by microscopy. This method only requires a period of about 20 days free of nailfold injuries. Cardiovascular complications are the main cause of increased mortality in TS. Ischemic heart disease risk factors

reported in TS include hypertension, diabetes mellitus, dyslipidemia, obesity and estrogen deficiency.^{4,12,13} Capillaroscopy allows visibility of the capillaries but a single capillary form is not pathognomonic of a given disease.

Table 4 - Distribution of abnormalities by age

Age	Papilla						Form						Flow														
	Ratified			Enlarged			Edema			Branched			Macrocapillary			Tortuosity			Fast			Granulosis			Slow		
	N	GH	E + P	N	GH	E + P	N	GH	E + P	N	GH	E + P	N	GH	E + P	N	GH	E + P	N	GH	E + P	N	GH	E + P	N	GH	E + P
6-9*	-	2	-	1	-	-	2	2	-	1	-	-	1	1	-	1	1	-	-	-	-	1	-	1	-	-	-
10-14	-	1	-	-	-	-	2	1	-	1	1	-	-	-	1	1	-	-	2	-	-	1	-	1	1	-	-
15-19	1	-	2	1	1	-	2	2	2	-	-	-	-	1	-	1	-	-	2	2	-	-	-	1	-	1	-
20-24 ⁺	-	-	2	-	-	1	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-
25-29	-	-	4	-	-	-	-	-	4	-	-	-	-	-	-	-	-	-	-	1	-	-	1	-	-	-	-
30-34 ⁺	-	-	1	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
> 35	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
Total	1	4	8	2	1	1	6	5	10	2	1	-	1	2	-	3	2	-	4	3	-	3	2	3	1	2	-

E + P = estrogen + progesterone therapy; GH = growth hormone therapy; N = no medication.
* One in GH therapy and had hemorrhagic extravasation.
† One in E + P therapy and had mixed loops.
‡ One in E + P therapy had avascular field.

Table 5 - Number of abnormalities at capillaroscopy

	Mixed loop	Enlarged papilla	Ratified papilla	Avascular field	Edema	Branched form	Macrocapillaries form	Tortuosity	Fast flow	Slow flow	Granulous flow	Hemorrhagic extravasation
Mixed loop												
Enlarged papilla												
Ratified papilla	1 (2%)		10 (20%)									
Avascular field			1 (2%)									
Edema	1 (2%)	4 (8%)	9 (18%)	1 (2%)	7 (14%)							
Branched form					3 (6%)							
Macro capillaries form		2 (4%)										
Tortuosity		2 (4%)			2 (4%)		1 (2%)					
Fast flow		1 (2%)	3 (6%)		1 (2%)				2 (4%)			
Slow flow		2 (4%)			4 (8%)							
Granulous Flow			2 (4%)								3 (6%)	
Hemorrhagic extravasation							1 (2%)					

Hairpin pattern is considered normal¹⁸⁻²¹ and most cases in our study presented this form of loops. Some authors^{18,19} referred that presence of the venous plexus may be normal or not, considering patient's age. This occurs during childhood and it is reported that the plexus disappears in adults. Venous plexus was absent in almost 90% of the patients, but was present in three (6%) adult patients. We are currently unable to define the significance of this presence. Tortuosity was present in 10% of cases. Leader¹⁸ considered that tortuosity may occur in adults, but any tortuosity must be considered abnormal in children. In our study, five patients had tortuosity. Two of them were children, prepubertal and using growth hormone and three were adolescents, without use of any medication and with development of spontaneous puberty. Diagnosis of tortuosity was performed using an article by Walls & Buchanan,²⁰ who consider tortuosity as being pathologic only if it is present in > 20% of capillaries studied. Tortuosity may represent diabetes^{24,25} or lupus erythematosus.²⁶ Diabetes was an exclusion criterion of our research, and none of our patients presented symptoms or signs suggestive of lupus disease. Edema was the most common abnormality observed followed by ratified papilla, and the association of edema and ratified papilla occurred in about 16% of the patients. Edema may represent trauma, especially in children, but it is not specific and is also reported in other pathologies, such as diabetes.²⁷⁻²⁹ We found edema in all ages and none of our patients indicated previous trauma. Trauma in children is more common than in other ages and may not be reported correctly as such by the child, whereas adolescents and adults may inform if there was any trauma event. Hands and fingers were examined before the nailfold capillaroscopy and none presented signs of injury.

Edema was observed mostly in older patients using estrogen and progesterone and in children using growth hormone, about 46 and 33%, respectively. Growth hormone therapy is associated with some collateral effects, including edema and is also correlated to insulin resistance, which can deteriorate endothelial function.³⁰ The same effect is reported with use of estrogens³¹ and the high prevalence found in this study may be explained by this collateral effect. On the other hand, estrogen receptors are present in vascular smooth muscle and endothelial cells and the use of estrogen therapy has a

favorable effect on cardiovascular hemodynamics in TS.^{32,33} Chan et al. studied the effects of hormone replacement therapy on endothelial function in women with TS using plethysmography. These authors analyzed the endothelium-dependent vasodilator factors, such as bradykinin and endothelium-independent vasodilator factors, such as nitric oxide, and referred that hormone replacement therapy improved endothelial function in patients with TS.³² In the literature, it is reported that progesterone may antagonize the beneficial effect of estrogen on the vasculature.³² In our study, patients using only estrogen therapy or estrogen plus progesterone had a high prevalence (18%) of edema and ratified papilla.

We found some cases with slow or granulous flow, which were abnormal and suggested some disturbance of the capillary circulation.^{19,21} Seven of our patients presented fast flow. There is no consensus about fast flow – some studies report this pattern to be normal,¹⁸ while others consider fast flow pathologic and associated with anemia.¹⁹ None of our patients had anemia. Presence of branched or macrocapillaries may indicate chronic diseases, such as dermatomyositis and scleroderma.^{21,27,28} When these patterns are present, other pathologies should be investigated. The papilla was enlarged in four cases in this study and all of them also presented edema. Three group 2 patients had macrocapillaries, one of whom also had tortuosity. Moura et al.²⁵ found that diabetic patients had more enlarged capillaries and tortuosity than the control group. This abnormality was also described in rheumatologic disease^{21,28} and other studies have described hemorrhagic extravasation.²¹ In our study, only one patient presented hemorrhagic extravasation and needed to be evaluated for rheumatologic disease. We compared our data with reports for healthy subjects or in some diseases, such as diabetes or lupus erythematosus,^{24-26,29} because for TS we did not find previous reports about vascular endothelium using videocapillaroscopy. We conclude that there is a high prevalence of alterations in nailfold capillaroscopy in TS and that edema and ratified papilla are the main alterations.

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