Assessing cardiovascular risk in ATM heterozygotes

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Summary

Objective: To evaluate the carotid intima-media complex (CIMC) thickness and lipid metabolism biomarkers associated with cardiovascular risk (CR) in parents of patients with ataxia-telangiectasia and verify an association with gender.
Method: A cross-sectional and controlled study with 29 ATM heterozygotes and 14 healthy controls. Biochemical tests and CIMC thickness measurement were performed.
Results: The mean CIMC measurement in heterozygous ATM was 0.72 ± 0.1 mm (minimum: 0.5 mm and maximum: 1.0 mm). Noticed high percentage of amounts above 75 percentile compared to the population referential (16 [76.2%]), without any significant statistical differences between the female and the male gender (11/15 [73.3%] vs. 5/6 [83.3%]; p=0.550). The comparison between heterozygous and controls, stratified by gender, showed that in heterozygous ATMs, women had higher concentrations of HDL-c compared to men, as well as higher values of hs-CRP in relation to the control women. In heterozygous ATMs, stratified by gender, the correlation between HDL-c and hs-CRP was inversely proportional and stronger among women, with a tendency to statistical significance.
Conclusion: Heterozygous ATMs did not differ from controls in relation to the biomarkers studied related to CR. However, most of them presented increased CIMC, independent predictor of death, risk for myocardial infarction and stroke, compared to the referential for the same age group. This finding suggests CR in the heterozygous ATM and shows to the need to monitor CIMC thickness and nutritional orientations.

Keywords: Ataxia Telangiectasia. Atherosclerosis. Carotid Intima-Media Thickness. Insulin Resistance. Heterozygote.

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Introduction

Ataxia-telangiectasia (A-T) is a rare autosomal recessive syndrome that affects 1:40,000 live births in the United States.[1] The classic symptoms, which gave rise to the name for the disorder, are ataxia (loss of motor coordination – onset in early childhood) and telangiectasias (venous capillaries dilated in the corners of the eyes and skin, occurring around 4-6 years of age).[2]

Caused by mutations of the *ATM* gene (ataxia telangiectasia mutated),[3,4] which is encoded on chromosome 11q22-23, the protein associated with this gene is composed of 3,056 amino acids, belongs to the PIKK (phosphatidylinositol 3-kinase-related kinases) superfamily,[4] and is involved in DNA damage-response regulation.[2,5]

The ATM protein follows several molecular events. Its absence or failure induces the collapse of several mechanisms related to the development of disorders, including cardiovascular (CV) diseases. These mechanisms are described in the literature by means of experimental studies[6-14] and, more recently, by virtue of increased patient survival in studies with humans.[15] The mechanisms involved in CV risk associated with ATM failure entail increased c-jun

N-terminal kinase (JNK, related to metabolic syndrome), insulin resistance, dyslipidemia, angiogenesis, myocyte apoptosis and oxidative stress.[6,8-13,16]

ATM heterozygotes, who carry a mutant allele to the A-T locus, account for from 1.4 to 2% of the population.[1,17] A systematic review and a recent meta-analysis showed that first-degree relatives, parents and grandparents of A-T patients have an increased risk of ischemic heart disease.[18]

A retrospective controlled cohort study was conducted over 28 years with grandparents of A-T patients, i.e. individuals having the mutation, with the purpose of describing mortality rates. A total of 405 grandparents (204 ATM heterozygotes, as assessed by genotyping, and 201 controls) were included. Compared to controls, ATM heterozygotes had a significantly higher risk of death (between 20 and 79 years RR 1.9, 95CI 1.3-2.8, p<0.001). On average, death occurred 7 to 8 years earlier among ATM heterozygotes. The relative risk of death from cancer and ischemic heart disease before age 80 was 2.6 (95CI 1.4-4.7, p=0.002) and 2.0 (95CI 1-4, p=0.062), respectively. With respect to ischemic heart disease, death among ATM heterozygotes occurred 11 years earlier than in the control group (p=0.006), which was not observed for cancer.[19]

Studies describing CV risk mechanisms in A-T carriers[20] and ATM heterozygotes,[8,12,13,15] conducted either in humans or involving animal experimentation — as well as the scarcity of studies identifying such risk by biochemical and imaging techniques — highlight the need to expand research in this field. The aim of our study was to describe the carotid intima-media complex (CIMC) thickness and lipid metabolism biomarkers associated with CV risk and then to check whether there is an association with gender.

Method

A prospective, controlled cross-sectional study evaluated 29 fathers and mothers of patients clinically diagnosed with A-T (herein referred to as ATM heterozygotes). The control group consisted of 14 age/sex-matched healthy volunteers.

The inclusion criteria for the parents were: having offspring diagnosed with A-T in accordance with the PAGID-ESID criteria[21,22] and consenting to participate in the study. The inclusion criteria for the control group were: consenting to participate in the study, being eutrophic and a non-smoker. The exclusion criterion for both groups was not meeting the abovementioned inclusion criteria.

The study was approved by the Research Ethics Committee of UNIFESP-EPM (No. 921407/2014), and all participants signed a free informed consent form.

Demographic and clinical data were collected by means of a standardized questionnaire. The level of physical activity was assessed by a short version of the International Physical Activity Questionnarie (IPAQ). The individual CV risk was assessed based on the Framingham score.[23]

The anthropometric evaluation was based on weight, height, skin folds (tricipital, subscapular, bicipital, and supra-iliac skin folds), and circumferences (neck, abdominal, and brachial). Neck circumference (NC) measurements were taken and classified according to Ben-Noun et al.[24,25] The waist-to-height ratio (WhR) was used as a marker of risk for coronary disease.[26] Food consumption was obtained with the aid of a 24-hour food recall (R24hs).[27]

The following biochemical markers were used: total cholesterol and fractions, triglycerides, fasting glycemia, AST, ALT, GGT, us-CRP, IL-6, PON1, Apo A-I and Apo B. The TC/HDL-c, LDL-c/HDL-c, and Apo B/Apo A-I ratios were calculated.[28,29]

A single examiner took all CIMC thickness measurements, and only from ATM heterozygotes. We used a Medison Accuvix V10 unit with a high-frequency linear transducer (6-12 MHz) and adjusted its focal area to the area of interest (posterior wall of the common carotid artery) and its gain so as to avoid artifacts inside the vessel and yield a 4x magnification. The cutoff point we adopted for percentile classification was an adapted table from the CAPS Study, by age group and gender.[30]

We then entered and consolidated the data in Excel® Office spreadsheets. For the analysis, we used the SPSS 24.0 (IBM®) statistical package. Categorical variables were presented as total numbers (%) and compared using the Chi-squared test or Fisher's exact test. Continuous variables were tested for their normality. Parameters were presented as mean±standard deviation and non-parametric as median (interquartile range). Because they are not parametric, triglycerides, interleukin-6 and Apo-B values were submitted to the logarithmic transformation for analysis. For bivariate comparison, we used Student's t-test and ANOVA for two or more stations, respectively. In order to evaluate the association between us-CRP and HDL-c, we used Pearson's correlation. For multivariate analysis involving BMI, us-CRP and gender, in turn, we used logistic binary regression, enter method. We adopted a significance level of 5%.

Results

The general traits found in the ATM heterozygote and control groups can be seen in Table 1. We can observe that there was no difference between the groups in terms of age (41.0±9.3 years versus 43.3±8.9 years, p=0.420), gender and years of formal education (Table 1).

No serious CV events, such as acute myocardial infarction or stroke in the family, were reported in either group. Other previous conditions preceding CVDs (dyslipidemia, obesity, HBP and diabetes) were cited by 16 (55%) and eight (57.1%) participants in the ATM heterozygote and control groups (p=0.583), respectively (Table 1). The smoking frequency and level of physical activity were similar between both groups (Table 1). Only two women in each group reported having reached menopause.

Dietary intake did not differ between groups for any of the items evaluated: total energy (2,031.0±718.6 kcal versus 2,210.5±627.2 kcal, p=0.449), protein % (15.9±3.9 versus 17.3±3.4, p=0.180), carbohydrate % (45.9±11.0 versus 44.9±8.4, p=0.787), fiber (20.5±10.5 g versus 24.1±17.2 g, p=0.680), cholesterol (296.8±55.8 versus 316.3±40.1 mg, p=0.320), total fat % (31.8±9.0 versus 37.7±7.8, p=0.245), saturated fat % (4.5±0.7 versus 4.7±0.9, p=0.418), monounsaturated fat % (2.3±0.4 versus 2.1±0.5, p=0.796) or polyunsaturated fat % (2.0±0.3 versus 2.8±0.9, p=0.329).

Mean CIMC measure in the ATM heterozygote group was 0.72±0.1 mm (minimum: 0.5 mm and maximum: 1.0 mm). We found a high percentage of values above the 75th percentile in comparison to the population reference (16 [76.2%]), with no statistically significant difference between females and males (11/15 [73.3%] versus 5/6 [83.3%]; p=0.550).

We found no difference between the ATM heterozygote and the controls while comparing the variables in a categorized manner with respect to nutritional status and body composition (Table 1). With regard to CVD risk factors, only HBP showed a trend to be more frequent in the ATM heterozygote group (62.0% versus 28.6%, p=0.055). We observed no differences regarding changes in lipid profile, fasting glycemia and MetS (Table 1).

TABLE 1 General characteristics of ATM heterozygotes and controls.

Variable		ATM H group (n=29)	Control group (n=14)	p-value
Sex	Female	21 (72.4%)	9 (64.3%)	0.726
Education	> 4 years	22 (24.1%)	12 (14.3%)	0.693
Family history	CVD	16 (55.2%)	8 (57.1%)	0.583
Use of oral contraceptives		4 (19.9%)	4 (44.4%)	0.195
Use of alcohol	Social	17 (70.8%)	7 (29.2%)	0.745
Smoking habit	Yes	3 (10.3%)	0 (0.0%)	0.539
Physical activity	Very active	8 (27.6%)	4 (28.6%)	0.615
	Active	15 (51.7%)	7 (50.0%)	
	Irregularly active A	3 (10.3%)	1 (7.1%)	
	Irregularly active B	1 (3.4%)	2 (15.3%)	
	Sedentary	2 (6.9%)	0 (0.0%)	
BMI	> 30 kg/m²	5 (17.2%)	0 (0.0%)	0.156
Abdominal circumference	> 0.5 cm/cm	19 (65.6%)	5 (35.7%)	0.102
Fat percentage	High	23 (79.3%)	10 (71.4%)	0.704
Neck circumference	High	10 (34.5%)	1 (7.1%)	0.071
Blood pressure	High	18 (62.1%)	4 (28.6%)	0.055
Total cholesterol	Inadequate	15 (51.7%)	6 (42.9%)	0.747
LDL-c	Inadequate	13 (44.8%)	5 (35.7%)	0.744
HDL-c	Low	4 (13.8%)	2 (14.3%)	0.649
Triglycerides	Inadequate	1 (3.6%)	2 (14.3%)	0.254
Non HDL-c	Inadequate	11 (37.9%)	3 (21.4%)	0.324
Apolipoprotein B	Inadequate	17 (60.7%)	12 (85.7%)	0.159
Fasting blood glucose	> 100 mg/dL	3 (10.7%)	1 (7.1%)	0.593
us-CRP	Increased	9 (32.1%)	1 (7.1%)	0.125
Metabolic syndrome	Yes	3 (10.7%)	1 (7.1%)	0.607

Level of significance of the Chi-square test or Fisher's exact test (p<0.05).
CVD: cardiovascular disease; BMI: body mass index; LDL-c: low-density lipoprotein cholesterol; HDL-c: high-density lipoprotein cholesterol; us-CRP: ultra-sensitive C-reactive protein.

Laboratory test results and anthropometric variables referring to bodily condition were also compared in a continuous fashion between groups. In the bivariate analysis, we found us-CRP to be higher in the ATM heterozygote group (2.24±2.30 versus 1.11±0.97 mg/dL, p=0.015). However, this difference did not hold in the multivariate analysis when we adjusted us-CRP values for BMI and gender (OR = 1.646, 95CI 0.75-3.62, p=0.214) (Table 2).

A comparison between both groups, stratified by gender, showed that females in the ATM heterozygote group had higher concentrations of HDL-c compared to men in the same group and higher values of us-CRP in women in the control group. The other laboratory variables and BMI did not show a statistically significant difference relative to gender.

In the ATM heterozygote group, stratified by gender, the correlation between HDL-c and us-CRP was inversely proportional and stronger among women, with a tendency to statistical significance (r = -0.318; p=0.083) (Chart 1).

TABLE 2 Odds ratio of ultra-sensitive C-reactive protein in the ATM heterozygote group adjusted for body mass index and gender.

Variable	B	β	95CI	p-value
us-CRP (mg/dL)	0.499	1.646	0.75-3.62	0.214
BMI (kg/m²)	0.459	1.583	1.11-2.25	0.011
Gender (female)	1.048	2.851	0.44-17.45	0.285
Age (years)	0.004	1.004	0.91-1.10	0.934

Variables in the model: BMI (kg/m²), age (years) and gender (p<0.05).
us-CRP: ultra-sensitive C-reactive protein.

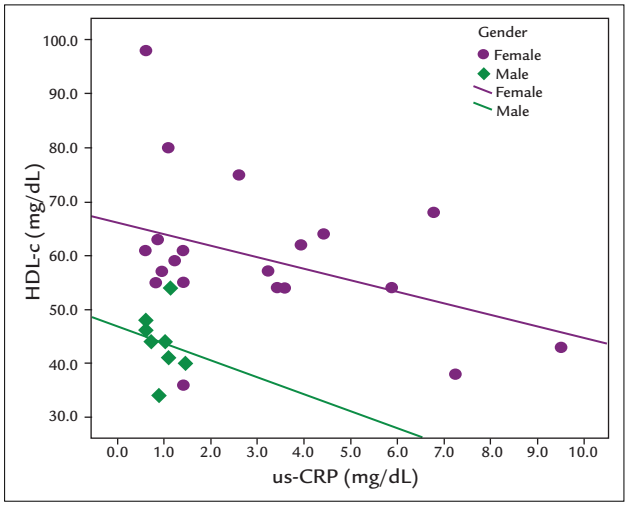

CHART 1 Correlation of HDL-c and us-CRP in the heterozygous ATM group by gender.

*Pearson's correlation (HDL-c and us-CRP)
Females (r = -0.397; p=0.083)
Males (r = -0.160; p=0.704)

Discussion

Our study was pioneer in analyzing CV risk based on the increase in CIMC thickness in heterozygous carriers of the ATM mutation. Specifically in females, there was also an increase in us-CRP compared to females in the control group. HDL-c concentrations were higher in females as compared to males.

A greater CIMC thickening was observed for both genders and was mostly classified as equal to or above the 75th percentile according to the reference value proposed by Lorenz et al. This indicates the existence of subclinical carotid atherosclerosis in this population.[30] A meta-analysis encompassing 15 studies showed that a 0.1-mm increase in CIMC was predictive of myocardial infarction (RR 1.15, 95CI 1.12-1.17) and stroke (RR 1.17, 95CI 1.16-1.21). A cohort of eight population-based studies (n = 37,197) with a follow-up of approximately five years demonstrated that a difference of only 0.1 mm in CIMC could increase the risk of myocardial infarction by 10% to 15% and stroke by 13% to 18%.[31] A study involving 3,067 participants from six cohorts showed that the increase in CIMC was positively associated with the risk of first infarction or stroke in individuals younger than 45 years, thus validating the use of this measurement in identifying risk, even in individuals whose age was similar to that which we studied.[32] A recent review article emphasizes the importance of the CIMC ultrasound evaluation procedure in identifying risk and as a means for predicting CV events.[33]

Some authors suggest that patients with the ATM mutation are at a high risk of diseases such as neoplasms and acute myocardial infarction.[19,34-37] A systematic review and recent meta-analysis concluded that there is no need to screen heterozygous carriers of the ATM mutation any differently than the general population for assessing CV risk. Still, it proposes that counseling towards healthy eating habits and lifestyle should be reinforced in that group.[18] The first publication addressing mortality from ischemic heart diseases in ATM heterozygotes dates from 1983.[38] Subsequently, other studies suggested a higher susceptibility to coronary atherosclerosis, MS and hypercholesterolemia.[8,12] Reduced MIRNI25B concentrations found in ATM heterozygotes resulting in overexpression of the CV susceptibility TNFS4 gene might be a possible causal explanation for this association.[15] In addition, studies with experimental animals have shown that ATM deficiency induces structural and functional changes following myocardial infarction, suggesting problems in remodeling, inflammation and apoptosis following ischemic events.[13]

A study conducted with grandparents of A-T patients undergoing genotyping in order to investigate the mutation showed an increase in the risk of death compared to

individuals from the same family not carrying the mutation. Compared to non-carriers, death from ischemic heart disease occurred 11 years earlier in carriers.[19]

The heterozygous ATM females in our study had higher us-CRP concentrations compared to the controls. Neutrophils isolated from A-T patients produce a greater amount of proinflammatory cytokines, which is an effect that can be partially explained by the increase in activation in p38MAP kinase.[39]

The association between increased CIMC and lower HDL-c concentrations suggests an even higher CV risk in male ATM heterozygotes. An observational cohort study (CANHEART – Cardiovascular Health in Ambulatory Care Research Team) of 631,762 Canadian individuals, mean age 57.2 years, reported that low HDL-c concentrations were associated with the risk of death from CVD in an independent fashion when compared to individuals with adequate HDL-c levels.[40] HDL-c can be converted from an anti-inflammatory particle to a pro-inflammatory particle in acute-phase situations of the inflammatory response. In this situation, HDL-c loses its antiatherogenic properties, becoming dysfunctional. Proinflammatory HDL particles are characterized by altered protein composition, namely increased levels of ceruloplasmin and serum amyloid A and reduced levels of Apo AI, paraoxonase and acetyl hydrolase PAF-AH (plasma platelet activating factor-acetylhydrolase).[41] Oxidative stress and inflammation (mechanisms accompanying ATM failure or absence) may contribute to the presence of dysfunctional HDL in ATM heterozygotes.

A study conducted with 13 A-T patients, offspring of the ATM heterozygotes assessed in our study, showed that triglycerides, total cholesterol and LDL-c and HDL-c concentrations were significantly higher in patients — and HDL-c concentrations were lower – when compared to healthy controls. The ratios associated with atherosclerosis (TC/HDL-c, LDL-c/HDL-c and Log TG/HDL-c) and non-HDL cholesterol (N-HDL-c) levels were also significantly higher in the group of patients.[42] There are no studies assessing the concordance between the changes in the lipid profile of patients and their parents, heterozygous carriers of the ATM mutation.

Studies in the literature suggest that healthy eating habits and an appropriate lifestyle should be reinforced among ATM heterozygotes.[18] In practice, this does not appear to be the case with these individuals, considering that we observed that their food consumption was similar to those in the control group. We found obesity in 17% of participants, increased abdominal circumference in 65.6%, metabolic syndrome in 11% and increased CIMC thickness, which is an early marker of atherosclerosis, in 76% of them. These findings indicate the need to effectively implement such counseling in the routine care given to those families.

Our study had some shortcomings: lack of genotyping for the ATM mutation, a transversal design, and lack of investigation of other biomarkers related to CV risk, such as lipoprotein a (Lpa), LCAT (lecithin cholesterol acetyltransferase) and adhesion molecules, i.e. ICAMs (intercellular adhesion molecules) and VCAM-1 (vascular cell adhesion molecule-1).

Conclusion

ATM heterozygotes did not differ from control individuals relative to the CV risk-related biomarkers that we studied. However, most of them had increased CIMC thickness, which is an independent predictor of death, risk of myocardial infarction and stroke, in comparison to reference values for the same age group. This finding suggests a CV risk in ATM heterozygotes and indicates the need for monitoring CIMC thickness, reinforcing nutritional counseling, and stimulating the practice of physical activity.

Resumo

Avaliação do risco cardiovascular de ATM heterozigotos

Objetivo: Avaliar a espessura do complexo médio-intimal da carótida (CMIC) e os biomarcadores do metabolismo lipídico associados ao risco cardiovascular (RC) em pais de pacientes com ataxia-telangiectasia (AT) e verificar associação com gênero.
Método: Estudo transversal prospectivo e controlado com 29 ATM heterozigotos e 14 controles saudáveis. Foram realizados exames bioquímicos e a espessura do CMIC por ultrassonografia.
Resultados: A média da medida do CMIC nos ATM heterozigotos foi de 0,72± 0,1 mm (mínimo: 0,5 mm e máximo: 1,0 mm). Observou-se elevado percentual de valores acima do percentil 75 em relação ao referencial populacional (16 [76,2%]), sem diferença estatisticamente significante entre o gênero feminino e o masculino (11/15 [73,3%] vs. 5/6 [83,3%]; p=0.550). A comparação entre os ATM heterozigotos e os controles, estratificados por gênero, mostrou que, nos ATM heterozigotos, as mulheres tinham maiores concentrações de HDL-c em comparação aos homens, e valores mais elevados de PCR-us em relação às mulheres controle. Nos ATM heterozigotos, estratificando segundo gênero, a correlação entre HDL-c e PCR-us foi inversamente proporcional e mais forte entre as mulheres, com tendência à significância estatística.

Conclusão: Os ATM heterozigotos não diferiram dos controles em relação aos biomarcadores estudados relacionados ao RC. Entretanto, a maioria deles apresentou aumento na espessura do CMIC, preditor independente de morte, risco para infarto do miocárdio e AVC, quando comparado ao referencial para a mesma faixa etária. Esse achado sugere RC nos ATM heterozigotos e aponta para a necessidade de monitoramento da espessura do CMIC e de orientações nutricionais.

Palavras-chave: Ataxia Telangiectasia. Aterosclerose. Espessura Íntima-Média Carotídea. Resistência à Insulina. Heterozigoto.

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