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SPONTANEOUS EXTRACRANIAL CAROTID ATHEROSCLEROSIS EVOLUTION IN ASYMPTOMATIC INDIVIDUALS

A three-year prospective study

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ABSTRACT - *Objective:* To evaluate the spontaneous evolution of extracranial carotid atherosclerosis in asymptomatic patients who did not present the main risk factors associated to the disease. *Method:* A prospective study including patients of both genders, age ranging from 40 to 70 years, not presenting any signs and symptoms of cerebrovascular disease and without the main atherosclerosis risk factors were included. Patients who were using or had used medication during the follow-up period that could potentially influence in the spontaneous course of atherosclerosis were excluded. The evaluation of the plaque and degree of stenosis were acquired using mode B, 7.5 MHz Doppler ultrasonography (USG). The follow-up was carried out for 36 months, with clinical, neurological, and USG exams repeated in a period of 6 to 8 months. Ninety-six individuals (48 women) completed the study with the presence of plaque, and 52 (26 women) with a degree of stenosis. *Results:* As to the degree of stenosis, 25% of the patients had worsening, 69% remained stable and 6% improved. When only the presence or absence of plaque was considered, 20% showed worsening (plaque developed during follow-up), 7% improved (disappearance of plaque), and 73% remained stable. No differences were found between the male and female patients. *Conclusion:* These results confirm the dynamic characteristics of plaque. In asymptomatic individuals without specific treatment, spontaneous improvement may occur, however, rarely. These findings may contribute as an assessment criterion when a decision is to be made in high-risk patients.

KEY WORDS: atherosclerosis, carotid, stroke, plaque, stenosis.

Evolução espontânea da aterosclerose carotídea extra craniana em indivíduos assintomáticos: estudo prospectivo de três anos

RESUMO - *Objetivo*: avaliar a evolução espontânea da aterosclerose carotídea. *Método*: estudo prospectivo com pessoas de ambos os sexos, idade de 40 a 70 anos, sem sinais e sintomas de doença cerebrovascular e sem os principais fatores de risco para aterosclerose. Foram excluídos os doentes que estavam em uso ou os que, durante o período de acompanhamento, usaram medicações que potencialmente pudessem influir no curso espontâneo da aterosclerose. As avaliações da placa e do grau de estenose foram obtidas por ultrassonografia com Doppler (USG). Investigou-se separadamente a presença de placa e o grau de estenose. O seguimento foi feito por 36 meses, com exame clínico, neurológico e novo USG repetidos com intervalo de 6 a 8 meses. Completaram o estudo 96 indivíduos (48 mulheres) quanto à presença da placa e 52 (26 mulheres) quanto ao grau de estenose. *Resultados*: Quanto ao grau de estenose, 25% dos indivíduos pioraram, 69% permaneceram estáveis e 6% melhoraram. Quando se considerou apenas a presença ou ausência da placa, 20% pioraram (desenvolveram placa durante o seguimento), 7% melhoraram (desaparecimento da placa) e 73% permaneceram estáveis. Não houve diferença em relação ao sexo. *Conclusão*: Estes resultados confirmam as características dinâmicas da placa. Em indivíduos assintomáticos e sem tratamento específico, a melhora espontânea ocorre, porém é pequena. Estes dados podem contribuir para auxiliar na tomada de uma decisão, em doentes de alto risco.

PALAVRAS-CHAVE: aterosclerose, estenose, carótidas, doença cerebrovascular.

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Atherosclerosis of the carotid arteries is the main cause of stroke or transient ischemic attack (TIA) in adults[1]. It may provoke thrombosis and/or emboly usually related to serious obstructive processes. Atherosclerotic lesions may be found since infancy and worsen with aging[2]. The prevalence is low in the 40-year age range, and is present in approximately 80% in the groups over 60 years of age[3,4]. The process of this disease is dynamic, in constant evolution, with a possibility of accumulation of new elements in the atheroma, regression of the same, degeneration or tissue restructure, causing, as a final result, a tendency of progressive worsening[5,6]. This worsening can be seen as the increase of the plaque and/or in the degree of stenosis. The reduction of the plaque and/or in the degree of stenosis is currently one of the great challenges in the treatment and prevention of atherosclerotic diseases. Modification and stabilization of the plaque has been proposed as one of the benefits of the treatment with lipid reducers[7] and inhibitors of the angiotensin-converting enzyme (I-ACE)[8]. Recent studies[7,9] have demonstrated that plaque regression is related to the reduction of lipid content and that worsening is related to an increase in lipid content. In this process of evolution there is also a strong relationship to inflammatory and infectious events[5,10-12]. A likely small increase of the fibrotic components and atrophy of smooth muscle cells are factors that may be related to plaque regression[7,9]. Atherogenesis involves the tunica intima and begins through an endothelial dysfunction with progression to the subendothelial space[5,7,9]. Several studies have evaluated the regression of the plaques with lipids reduction[13,14] and blood pressure[8] and the role of drugs with antiinflammatory properties and endothelial remodeling[5,8,15,16]. There are studies that stress the importance of the role of the tunica media and of the tunica adventitia in atherogenesis, especially in the remodeling process of the vessel walls[7,9,17].

There is a direct relationship between the risk of stroke and the degree of stenosis, according the trials ACAS ("*Asymptomatic Carotid Atherosclerosis Study*")[18], NASCET ("*North American Symptomatic Carotid Endarterectomy Trial*")[19] and CSTCG ("*European Carotid Surgery Trialists Collaborative Group")*[20], though this is not the only element capable of triggering ischemic complications[5,7]. Currently, several atherogenic risk factors are known that, if controlled, may contribute to the reduction of disease incident, and slow down or improve its evolution. Few studies are dedicated to analyzing the spontaneous evolution of the plaque, independent of the presence of risk factors, its maintenance or correction.

This present study aims to address the following aspect: study the spontaneous evolution of carotid atherosclerosis, in patients without the classic risk factors, who do not use medication, that, theoretically, could interfere in the course of the disease.

METHOD

A prospective study realized in patients followed-up in the Cerebrovascular Disease Clinic of the Neurology Discipline of the Santa Casa de São Paulo-Faculty of Medical Sciences. Hospital admission of the patients occurred in the period between 05/1997 and 05/1999 and the study was concluded in 07/2002. Caucasian patients of both genders were included, with ages ranging from 40 to 70 years, not presenting carotid disease symptoms, without the main atherogenic risk factors: high blood pressure, dyslipidemia, diabetes, inactivity, and use of tobacco. Patients excluded were in continuous use, for more than three months, of anticoagulants, plaque antiaggregants, corticoids, anti-inflammatories, immunosuppresants, calcium channel blockers, anticonvulsants, anxiolytics, statins, fibrates, hypotensives, and/or free radical removers, because the prolonged use of these drugs could eventually alter the course of the atherosclerosis.

The plaques were analyzed using the measures of plaque thickness and degree of vessel stenosis, individually established by Doppler ultrasonography (USG) of the carotid arteries, using the SD-800 Phillips module, with a 7.5 Mhz linear transducer. The follow-up was done in a period of 36 months, with clinical, neurological, and USG exams repeated in a period of 6 to 8 months, for every patient. Patients who did not complete the 36-month follow-up were excluded, as well as those who developed disease during follow-up and used one or more of the drugs mentioned above for a period longer than 3 months, or who developed, in a persistent manner, for more than 3 months, one of the mentioned atherogenic risk factors. Within these criteria, 96 individuals completed the study with the presence or absence of plaque (measure), and 52 in relation to the degree of stenosis. Forty-four patients did not present stenosis in the first ultrasonography exam; these patients were not included in the stenosis degree analysis group. Consequently, this group was limited to 52 patients out of the entire patient group.

Because the evolution of atherosclerosis is slow, statistical analysis was done at the end of the follow-up period in order to avoid data overlapping from analyses of intermediate observations.

Atherosclerotic plaque evolution was evaluated using two factors after the 36-month period: proportion of indi-

viduals with clinical deterioration or evolution (increase) of the plaque, and the proportion of individuals with spontaneous improvement (reduction or disappearance of plaque). Regarding the degree of carotid stenosis, two variables were also considered after the 36-month period: the proportion of individuals with the increase of stenosis and the proportion of individuals with the reduction of stenosis.

Data were processed using the EPI-INFO v. 6.04b software and all of the estimations were calculated using a confidence interval (CI) of 95%.

The Ethics and Research Committee of the Santa Casa de São Paulo approved this study.

RESULTS

Comparisons between findings were done individually for every patient from the different exams undertaken throughout the 36-month follow-up period. Evaluation was done in a sequential manner, always from the individual patient, without associating the data between different patients. The first exam was considered as the basis for all of the comparisons and was the established control of each patient. From the results of the individual variations, percentages of improvement, deterioration, or stability were established for the entire study group. On average, each patient underwent 6 ultrasonography exams. For plaque measure evaluation, vessel wall thickening was considered.

As to the degree of stenosis (Table 1), the study showed that 25% worsened, 69% remained stable and 6% showed improvement in the degree of stenosis. When only the presence or absence of plaque was considered (Table 2), the findings were similar, 20% of the patients who did not have plaque in the beginning of the study developed plaque during follow-up (worsened), 7% of the patients had plaque disappearance during the 36 months of follow-up, and the remaining patients (73%) remained stable. There was no significant difference between men and women Table 3.

Table 1. Spontaneous evolution of stenosis degree after the 36-month follow-up in 52 asymptomatic patients.

Degree of Stenosis	Frequency	%	95% CI
Increase	13	25	14.5-39.2
Reduction	3	6	1.5-16.9
Total	52	100	

Table 2. Spontaneous evolution of the atherosclerotic plaque after the 36-month follow-up in 96 asymptomatic patients.

Plaque condition	Frequency	%	95% CI
Worsened	19	20	12.6-29.4
Improved	7	7	3.2-14.9
Total	96	100	

DISCUSSION

There are few studies in the specialized literature that evaluate the evolution of the atherosclerotic plaques of the carotid arteries in humans asymptomatic of cerebrovascular disease. Despite the fact of being an important parameter for making a clinical decision, there are few studies with this characteristic. Most of the studies were realized in coronaries or in symptomatic patients, different than the approach of this present study.

The analysis of the carotids was done using Doppler ultrasonography, which is a reliable diagnostic method, free from risk, and allowing a com-

Table 3. Comparative spontaneous evolution of the atherosclerotic plaque and stenosis degree in the carotid artery, between asymptomatic men and women after the 36-month follow-up.

	Condition of the plaque				Stenosis degree			
	Women		Men		Women		Men	
	N	%	N	%	N	%	N	%
Stable	35	36.5	35	36.5	18	34.6	18	34.6
Worsened	9	9.4	10	10.4	7	13.5	6	11.6
Improved	4	4.1	3	3.1	1	1.9	2	3.8
Total	48	50	48	50	26	50	26	50

Obs: In the statiscal analysis, the p value was not significant neither for the condition of the plaque nor the stenosis degree.

parative study with a good safety index[1,6]. Other methods that may be considered more precise, such as digital angiography, angio-resonance, and angio-tomography, have important limitations; such as high cost and procedure risk, that makes regular use not viable. The main parameters that are usually analyzed by ultrasonography are the presence of atherosclerotic plaque, its physico-chemical and morphological characteristics, and its degree of stenosis. The latter characteristic is one of the important elements used to determine the risk of the patients developing ischemic events, from plaque rupture and consequent thrombosis[18,19,20]. Other elements also of significant importance that contribute to the vulnerability of the plaque, its breaking and thrombosis are the constitution of the plaque, especially in relation to the amount of lipids and calcium, and the thickness of the fibrous cover[5,7]. Several inflammatory mechanisms have been implicated in the evolution of the plaques, such as macrophage and T-lymphocyte activation, which release cytokines (interleukins Iβ, 2, 6, 8), tumor necrosis factor, and interferon gamma, responsible for triggering reactions that bring about the escalation of atherosclerotic processes, that may provoke plaque destabilization[10]. Infections, especially from *Chlamydia pneumonia*, have also been associated to the appearance and/or worsening of atherosclerosis[11]. The association between lipid oxidation and atherogenesis and the progression of carotid atherosclerosis, in humans, has been much emphasized[2]. According to KAPS (*Kuopio Atherosclerosis Prevention Study),* the most important predictive factors for determining atherosclerotic progression are elevated serum levels of 7β-hydroxycholesterol, the major product of cholesterol oxidation in lipoproteins and cell membranes, lipid hydroxyperoxidase in the LDL, the oxidative susceptibility of the VLDL and LDL autoantibodies[2]. Drugs with anti-inflammatory action, including statins and the I-ACES, have been used with good expectations in plaque reduction[5,15,16].

The possible roles of these factors, which interact in the atherosclerotic evolution, were not a specific aim for evolution in this study. We tried to focus on the behavior of the plaque in the spontaneous evolution, which could be a base for prompt clinical decisions. In order to accomplish this, the presence of carotid plaque was evaluated and its degree of stenosis in asymptomatic individuals, without the classic risk factors for atherosclerosis. Plaque behavior and degree of stenosis were separately analyzed because both are important and should be individually analyzed as risk factors for cerebrovascular diseases. This methodological criterion might allow for the analysis of the spontaneous evolution of the degree of stenosis, regardless of the action of these factors. Symptomatic individuals were excluded because they present a great chance of presenting a vulnerable atherosclerotic plaque, with an increased risk of rupture and progression. Based on this same principle, patients undergoing drug therapy that could potentially alter the course of atherosclerosis were excluded. In this study, the age was limited between 40 and 70 years, with the goal of homogenizing the study group, because it is known that atherosclerosis is rare in individuals under the age of 40, and has accentuated progression in individuals over the age of 70 years[3,4]. We included only white patients, because it is known that atherosclerosis has different behavior in different races; furthermore, the inclusion of only one race had the goal of homogenizing the study group.

As to the degree of stenosis (Table 1), our results showed that 25% worsened during the period the study was conducted, 69% remained stable and 6% showed improvement in the degree of stenosis. When only the presence or absence of plaque was considered (Table 2), the findings were similar, being that 20% of the patients worsened 7% of the patients had plaque disappearance during the 36 months of follow-up, and the remaining patients (73%) remained stable. There was no significant difference between men and women (Table 3); however, it is important to emphasize that a few subgroups formed by this division are fairly small, not permitting a confident analysis of this finding, which would require a bigger study group. Hennerice et al.[6], using a methodology similar to the present study, found more optimistic results than in ours, verifying progression in 30% of the cases, stability in 51% of the cases, and improvement in 19% of the cases. Akins et al.[21], in a study about intracranial atherosclerotic evolution in 21 patients, using angiography, in a 26.7 month follow-up period, found results very similar to those of Hennerice et al.[6], concluding that, on average, 40% of the patients maintained a stable degree of stenosis, 20% had regression and 40% worsened. The differences of these findings may be associated to the specific genetic, environmental, and behavioral characteristics of our population, or may even be the consequence of different study methodologies.

The morphological and/or physical characteristics were not evaluated in this initial study, which would require an increased number of cases in order for sub-group division. It is known that calcified plaques are those that less regress, rarely ulcerating, and the soft plaques have greater variability and instability[6].

These results confirm the dynamic characteristics of the plaque and may be useful in aiding in the decision making process, especially in high-risk patients, in view of the necessity to choose between a therapeutic or a surgical approach. This information could be useful as a parameter for comparison in the follow-up of high-risk patients that could be candidates for intervention or surgical procedures.

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