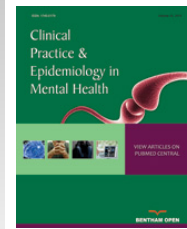




Clinical Practice & Epidemiology in Mental Health

Content list available at: www.benthamopen.com/CPEMH/

DOI: 10.2174/1745017901612010001



Quality of Life in Carotid Atherosclerosis: The Role of Co-morbid Mood Disorders

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Abstract:

Introduction/Objective:

To study in severe carotid atherosclerosis (CA): the frequency of mood disorders (MD); the impairment of quality of life (QoL); the role of co-morbid MD in such impairment.

Methods:

Case-control study. Cases: consecutive in-patients with CA (stenosis $\geq 50\%$). Controls: subjects with no diagnosis of CA randomized from a database of a community survey. Psychiatric diagnosis according to DSM-IV made by clinicians and semi-structured interview, QoL measured by the Short Form Health Survey (SF-12).

Results:

This is the first study on comorbidity on CA disease and MD in which psychiatric diagnoses are conducted by clinicians according to DSM-IV diagnostic criteria. Major Depressive Disorder (MDD) (17.4% vs 2.72%, $P < 0.0001$) but not Bipolar Disorders (BD) (4.3% vs 0.5%, $P = 0.99$) was higher in cases ($N=46$) than in controls ($N= 184$). SF-12 scores in cases were lower than in controls (30.56 ± 8.12 vs 36.81 ± 6.40 ; $p < 0.001$) with QoL comparable to serious chronic diseases of the central nervous system. The burden of a concomitant MDD or BD amplifies QoL impairment.

Conclusion:

Comorbid MD aggravates the impairment of QoL in CA. Unlike autoimmune diseases or degenerative diseases of the Central Nervous System, CA shows a strong risk of MDD than BD.

Keywords: Bipolar disorder, carotid atherosclerosis, major depressive disorder, mood disorders, quality of life.

INTRODUCTION

Carotid atherosclerosis is a leading public health issue. The atherosclerotic disease has been the first cause of death and morbidity in developed countries for the past decades, while recently the traditional risk factors for atherosclerotic and cardiovascular diseases have increased also in some developing countries like China and India. It is estimated that by 2020 cardiovascular diseases will be the major causes of morbidity and mortality also in most developing nations

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around the world [1]. Carotid atherosclerosis is a determinant of acute cerebrovascular events - *e.g.* stroke - and of early cognitive impairment [2]. The incidence of stroke in the US is about 800,000 identified events each year [3, 4].

Approximately one out of 10 subjects over 70 years of age in the community presents with Carotid Stenosis. Many of them are apparently asymptomatic, in the sense that these cases were not diagnosed for cardiovascular disease or acute vascular events [5]; prevalence is twofold in subjects at risk [6]. Elderly age, male sex, history of vascular disease, hypertension, hypercholesterolemia, metabolic diseases and diabetes mellitus, and history of smoking have been identified as predictors of atherosclerosis [7]. This means that adequate preventive measures could be implemented and, in the case of already manifested and identified significant stenosis, an appropriate intervention could prevent cerebral vascular attacks and stroke. In fact there are now standardized and safe enough methods to treat carotid stenosis: for many years the gold standard has been a surgical treatment with carotid endarterectomy (CEA), sided in the past two decades by endovascular stenting of carotid lesions (CAS), a valid alternative [8, 9]. Both treatments have shown similar effectiveness [10].

Prevention programs have encountered implementation difficulties and the appropriate surgical intervention is not well accepted by patients yet [11]. A better assessment of the damage caused by carotid atherosclerosis to the quality of life of people suffering from it could be useful to estimate the weight and the importance of appropriate prevention programs.

Another remarkable aspect requiring clarification is the role of comorbid depressive and mood disorders in treatment compliance and in the impairment of quality of life. Around 20% of patients with stroke were found comorbid with depression [12]. However all research on comorbidity of vascular (and cerebrovascular) diseases and depressive disorders published to date for the identification of cases of depression have adopted a questionnaire like the Center for Epidemiologic Studies Depression Scale (CES-D) [13] and not a structured clinical interview. The latter is considered the best method by the international standards of research in psychiatry [14 - 20].

A correct estimate of such comorbidity is a critical issue, because some researchers have found that concomitant depression is a determinant of poorer clinical outcomes, mortality, and risk of functional disabilities [21]. Coherently an effective treatment of depression was found to be associated with a better course of coronary heart disease, patient's adherence to interventions, and a decrease in acute events [22].

Evidence shows that the co-morbidity between depression and atherosclerosis can occur because people with depression have a high risk of developing atherosclerosis and, vice versa, because people with atherosclerosis - and with neuro-vascular diseases in particular - are at risk of depression [23]. A specific subtype of depression - called vascular depression - is characterized by: 1) onset in late life; 2) hyperintensities at brain Magnetic Resonance Imaging (MRI); 3) great neuropsychological impairment; 4) poor response to antidepressants especially when brain damage is associated with deficits in executive functioning [23, 24]. Despite the lively debate stimulated by this new diagnosis, so far researchers have not made an agreement on the diagnostic criteria of Vascular Depression. This concept is nevertheless an indicator of how the two disorders may be influencing their respective evolutionary paths [23].

The purpose of this work is to study the items listed below through standardized psychiatric diagnosis conducted by means of semi-structured interviews carried out by clinicians and a case control design:

- 1) The frequency of major depressive disorder and other mood disorders in severe carotid atherosclerosis and the risk compared to healthy controls;
- 2) The impairment of quality of life in people with carotid atherosclerosis;
- 3) The role played by mood disorders in the impairment of quality of life in people with carotid atherosclerosis.

METHODS

Design: Case-control Study

Subjects

Cases (Table 1) were inpatients with Carotid Atherosclerosis of the Thoracic and Vascular Surgery Clinic of the University Hospital of Cagliari, Italy, from July 2013 to May 2014.

The controls included subjects with no diagnosis of Carotid Atherosclerosis who were selected from a database used for an epidemiological survey in Italy [25]. The selection of sex- age- and residence-matched controls from the 3498-

subject database followed a randomized block design. A block was created for each case that included all eligible ages (± 2 years) and sex-matched controls drawn from the database. Four individuals per block were extracted for each case and were automatically excluded from the remaining blocks.

Psychiatric Diagnosis

The “Advanced Neuropsychiatric Tools and Assessment Schedule” (ANTAS) is a semi-structured clinical interview derived from the Structured Clinical Interview for DSM Disorders, non-patient version (SCID/NP-DSM-IV). It allows detecting and diagnosing psychiatric disorders [26]. The validity and reliability of the diagnoses derived from the ANTAS were tested against SCID. Agreement with SCID was found with mean Cohen’s K = 0.85 [25]. The interviews were carried out by clinicians with at least of experience in psychiatry. Bipolar Spectrum Disorders were screened by means of the Mood Disorder Questionnaire, Italian version [27].

Table 1. Demographic characteristics of the study sample.

	Cases (46)	Controls (184)
Age (mean \pm ds)	72.56 \pm 7.26	72.50 \pm 7.26
Gender		
m	30 (65.2 %)	120 (65.2%)
f	16 (34.8%)	64 (34.8%)

Diagnosis of Carotid Atherosclerosis

The diagnosis of carotid stenosis in the selected cases was performed through clinical examination, including Duplex ultrasound scanning of the epi-aortic trunks and Contrast Enhancement Computed Tomography (CECT) of the neck [28]. We included subjects with documented stenosis $\geq 50\%$, using ECST criteria. In controls, the presence of Carotid Atherosclerosis was excluded after a clinical interview and anamnesis, subjects with history of severe vascular disease, severe hypertension and diabetes mellitus were also excluded from controls.

Measure of Quality of Life

In both cases and controls the subject’s perception of their quality of life was measured by means of the Short Form Health Survey (SF-12) [29]. The SF-12 is widely used tool internationally; it measures the perception of quality of life according to specific dimensions: physical activity, health problems inducing limitation of physical activities and roles, emotional status, pain, general health, vitality, effectiveness of the social network, and mental health. The period of reference for the scoring is one month prior to evaluation. Higher scores on the SF-12 are associated with a higher quality of life.

Table 2. Quality of life and mood disorders in cases and controls.

	Cases (46)	Controls (184)	df	P	OR	CI 95%
SF12	30.56 \pm 8.12	36.81 \pm 6.40	F(1,228,229)=31.325	p<0.000		
MDQ	6 (13.0%)	5 (2.76%)	$\chi^2=8.76$ (1)	p=0.003	5.43	1.38 -21.82
MDD Lifetime	8 (17.4%)	5 (2.72 %)	$\chi^2=15.07$ (1)	p<0.0001	7.62	2.10 -28.66
Bipolar Disorder (BP1-BP2)	2 (4.3%)	1 (0.5%)	0.01 (2)	p=0.99	----	

1 df 2 with Yates’s correction

Analysis of Data and Measure of Attributable Burden in Worsening QoL

Comparison between means and standard deviations of SF-12 scores and other numerical data in the sample was carried out by means of ANOVA one-way statistics. According to previous published papers [30, 31] “Attributable Burden in Worsening QoL” means the difference between the SF-12 score of cases with Carotid Atherosclerosis and the SF-12 score of an age- and sex-matched sample without the disorder and drawn from the Italian database community survey [25]. A comparison on “Attributable Burden in Worsening QoL” was carried out comparing Carotid Atherosclerosis scores with other impairing health condition measures in studies that had drawn their controls from the same data base used in the preset study for controls, and where all cases were consecutive cases referring to units of the same University Hospital in the same city [30 - 34].

Ethical Aspects

The community survey and the program of a series of case controls on databank-based studies for controls were

approved by the ethical committee of the Italian National Health Institute (Rome). This study protocol was approved by the independent ethical committee of the Azienda Ospedaliero Universitaria of Cagliari, Italy. An informed consent form was signed by each candidate. The study did not imply any change of the scheduled treatment for patients, which is defined according to the clinical judgment and international guidelines and by the patients' decision to accept the treatment or not.

RESULTS

The sample of this research (see Table 1) consisted of 46 patients with carotid stenosis; it was composed of 30 men (65.2%) and 16 women (34.8%). It included 8 (17.39%) patients with Transitory Ischemic Attack, 4 (8.70%) with slight Stroke, 3 (6.52%) with a history of "drop-attack", and 31 (67.39%) with asymptomatic carotid disease.

The control group consisted of 184 subjects without a diagnosis of carotid stenosis, selected with the above-described matching technique. This technique creates a sample of controls that is perfectly homogeneous with the study cases in terms of gender and age variables.

Table 3. Burden Attributable to Carotid Atherosclerosis in worsening quality of life and comparison with other disease (studies were carried out with controls drawn from the same community study data bank, and cases were consecutive ones in wards of the same University Hospital).

Disorders	SF-12 (Mean±sd)	Attributable Burden [Sf-12 in standardized controls – SF-12 in cases]	Comparison with Carotid atherosclerosis	Comparison with Carotid atherosclerosis With Major Mood Dis
Major Depressive Disorder	33.8 ±9.2	5.6±3.6 (N=287)	DF 1,331,332; F= 0.978 p=0.32	Df 1,293,294; F=9.16 p=0.003
Multiple Sclerosis	29.5±7.3	7.0±3.5 (N=201)	DF 1,245,246; F= 1.642 p=0.201	Df 1,209,210; F=3.50 p=0.062
Wilson's Disease	33.8±9.0	4.4±1.7 (N=23)	DF 1,67,68; F=2.80 p=0.099	Df 1,31,32; F=8.49 p=0.003
Eating Disorders	34.9±6.2	4.4±6.6 (N=60)	DF 1,104,105; F= 2.374 p=0.126	Df 1,68,69; F=4.49 p=0.038
Panic Disorder	35.5±4.6	2.9±0.9 (N=123)	DF 1,167,168; F=49.751 p<0.0001	DF 1,131,132 F=76.78
Panic Disorder with Agoraphobia	34.5±6.1	4.2±2.4 (N=32)	DF 1,76,77; F=4.4 p=0.039	Df 1,40,42; F=10.92 p=0.002
Carotid Atherosclerosis	30.6±8.1	6.2±5.0 (N=46)		
Carotid Atherosclerosis with Major Mood Disorders (DDM or BP)	27.2±5.2	9.30±7.8 (N=10)		

Cases show a lifetime prevalence of manic/hypomanic episodes measured as positive at the screening (MDQ score > 7) and higher than in controls (13.0% vs 2.76% P = 0.003). Regarding the prevalence of Bipolar Disorder (BP 1/BP 2 according to DSM-IV) the difference between cases and controls did not reach statistical significance (4.3% vs 0.5%, P = 0.99) (Table 2).

The lifetime prevalence of Major Depressive Disorder, diagnosed according to DSM-IV criteria, was higher in cases than in controls (17.4% vs 2.72%, P <0.0001). Among cases, out of the six patients with co-morbid major depressive disorder four had had onset after the age of 60 (8.7%) as against one in the control group (0.5%).

The mean scores of SF12 in patients with carotid atherosclerosis (cases) were significantly lower than those of healthy controls (30.56 ± 8:12 vs 36.81 ± 6:40; p <0.001) (see Table 2).

The burden attributable to carotid atherosclerosis in worsening quality of life is comparable to that of serious chronic diseases of the central nervous system such as Wilson's disease and Multiple Sclerosis, and with severe psychiatric disorders like Major Depressive Disorder (Table 3). The burden of a concomitant major mood disorder (MDD or BD) amplifies quality of life impairment, patients with carotid atherosclerosis in comorbidity with a major mood disorder have a greater impairment than those who have major depression (DF 1,293,294; F=9.16 P=0.003) end ever than those with Wilson's disease (DF 1,31,32; F=8.49 p=0.003 (Table 3).

DISCUSSION

Our study found that carotid atherosclerosis is comorbid (lifetime) with Major Depressive Disorder in about 1 case out 5 with an approximate risk is about 6 times higher than the standardized sample without atherosclerosis disease.

This result is consistent with the prevalence of depression among patients with cerebrovascular disease or stroke, which oscillates between 15 and 25% [12]. As underlined in the introduction of this study we must consider that the research works carried out so far have adopted a questionnaire as the CES-D for the identification of cases of depression; they did not use structured clinical interviews carried out by clinicians. The latter is considered the best method available for psychiatric diagnosis in clinical patients and in community epidemiological samples [35, 36]. The use of this method in addition to screening questionnaires allows identifying "cases" according to international classification systems as DSM-IV. The use of CES-D was common of those studies that have found an association between carotid disease and depressive symptoms [15 - 20] as well as in the famous "Rotterdam Study" that did not find this association [14]. This is therefore the first study on comorbidity between mood disorders and carotid vascular disease in which psychiatric diagnoses are conducted by clinicians, through a semi-structured interview and in accordance with international diagnostic criteria. It is also the first study that allows a better approximation of the risk by means of a case-control model.

Our sample did not show a risk of DSM-IV Bipolar I or II Disorder that would be similar to the risk found for DSM-IV MDD, although patients with hypomanic episodes attributable to the bipolar spectrum - as measured with an instrument like the MDQ - tend to have a greater risk in the presence of carotid atherosclerosis. A vast literature on the association between vascular heart disease and bipolar disorder is available, often with a positive association ([37 - 39], and sometimes with no association at all [40]. Data in the literature related to vascular brain diseases are rare, but an association was proved by one study at least [41]. However the most important determinants of vascular disease such as diabetes, alcohol abuse and smoking were found more frequently in bipolar patients than in healthy controls [42]. The lack of homogeneity among the results and the fact that an association between atherosclerotic disease and bipolar disorder was not always found despite an increased presence of hypothetical risk factors in the studies, as in our case, could be explained by bipolar disorders' developing only belatedly vascular lesions [39]. Moreover the association between vascular and cerebrovascular disease and bipolar disorder would drastically shorten life expectancy, generating a bias in cross-sectional studies [41]. An alternative hypothesis is that the Bipolar Spectrum Disorders associated with vascular disease can present with unusual symptoms. Our study found an association with the broad area of the bipolar spectrum defined by positivity to MDQ, and not with the diagnosis of bipolar disorder according to DSM-IV. This might be supportive of the second hypothesis.

The finding that carotid disease has a higher risk of major depression than the risk of bipolar disorders is opposite to the finding on autoimmune diseases of the central nervous system like Multiple Sclerosis [43], or degenerative diseases with a genetic basis like Wilson's disease [32].

The measure of the subjective perception of quality of life in a done disorder is a construct of relevance in today's clinical practice and for public health issues, the subjective quality of life is adopted as a measure of outcome in diseases having a strong impact on the daily life of patients [44, 45]. Our study has detected that carotid atherosclerosis compromises quality of life when compared to people who do not have it, and its burden is comparable to that of serious chronic diseases of the central nervous system such as the aforementioned Wilson's disease and Multiple Sclerosis, and with severe psychiatric disorders like Major Depressive Disorder (Table 3). The burden of a concomitant major mood disorder (MDD or BD) amplifies quality of life impairment to the extent that people with carotid atherosclerosis in comorbidity with a major mood disorder have a greater impairment, at a statistically significant level, than those who have major depression only or a severe degenerative disease such as Wilson's disease. Only against Multiple Sclerosis does the difference reach the limits of statistical significance, although carotid atherosclerosis shows a greater impairment of quality of life still.

LIMITATIONS

The diagnosis of Carotid Atherosclerosis in the selected cases was made by clinicians by means of Doppler ultrasound scanning and CECT scan. In contrast, community controls reported to the interviewing clinicians a diagnosis of Carotid Atherosclerosis if they were aware of such a problem even if subjects with history of severe vascular disease, severe hypertension and diabetes mellitus were also excluded from controls

The risk of false negatives in the group of controls thus quite exists, although the hypothetical false negatives among the control group would reinforce the null hypothesis of no association between Mood Disorders and Carotid Atherosclerosis, and decrease the Attributable Burden to Carotid Atherosclerosis in impairing quality of life. This limitation therefore does not invalidate the results of the study, but we may only speculate that the association found may be rounded downward.

On the other hand the case-control design does not allow excluding the effect of Berkson's bias.

CONCLUSION

Mood Disorders are associated with the carotid vascular disease with a tight fit. Unlike autoimmune diseases or degenerative diseases of the Central Nervous System, carotid atherosclerosis shows a higher risk of MDD than of BD.

The combination with a mood disorder aggravates the impairment of quality of life to the extent that the attributable burden to these diseases in comorbidity is higher than the impairment caused by major depression or Wilson's disease only.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We are grateful to all the patients of the University Hospital of Cagliari for participating in the research. The research was supported by the University of Cagliari.

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Received: May 7, 2015

Revised: May 20, 2015

Accepted: May 20, 2015

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