CRANIOFACIAL PAIN CAN BE THE SOLE PRODROMAL SYMPTOM OF AN ACUTE MYOCARDIAL INFARCTION. AN INTERDISCIPLINARY STUDY

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ABSTRACT

We recently found craniofacial pain to be the sole symptom of an acute myocardial infarction (AMI) in 4% of patients. We hypothesized that this scenario is also true for symptoms of prodromal (pre-infarction) angina. We studied 326 consecutive patients who experienced myocardial ischemia. Intra-individual variability analyses with respect to ECG findings and pain characteristics were performed for those 150 patients who experienced at least one recurrent ischemic episode. AMI patients (n=113) were categorized into two subgroups: "abrupt onset" (n=81) and "prodromal angina" (n=32). Age, gender and risk factor comparisons were performed between groups. Craniofacial pain constituted the sole prodromal symptom of an AMI in 5% of patients. In those who experienced two ischemic episodes, women were more likely than men to experience craniofacial pain in both episodes ($p<0.01$). There was no statistically significant difference between episodes regarding either ECG findings or the use of the two typical pain quality descriptors "pressure" and "burning".

This study is to our knowledge the first to report that craniofacial pain can be the only symptom of a pre-infarction angina. Craniofacial pain constitutes the sole prodromal AMI symptom in one out of 20 AMI patients. Recognition of this atypical symptom presentation is low because research on prodromal AMI symptoms has to date studied only patients with chest pain. To avoid a potentially fatal misdiagnosis, awareness of this clinical presentation needs to be brought to the attention of clinicians, researchers and the general public.

Key words: *Myocardial infarction, myocardial ischemia, facial pain.*

EL DOLOR CRÁNEO-FACIAL PUEDE SER EL ÚNICO SÍNTOMA PRODRÓMICO DE UN INFARTO AGUDO DE MIOCARDIO. ESTUDIO INTERDISCIPLINARIO

RESUMEN

En un estudio previo encontramos que un dolor en la región cráneo-facial puede ser el único síntoma de un infarto agudo de miocardio (IAM) en el 4% de los casos. En el presente trabajo la hipótesis fue que este escenario es cierto también para la angina pre-infarto o angina prodrómica.

En el estudio se incluyeron 326 pacientes consecutivos con isquemia cardiaca sintomática. Se realizó un análisis intra-individual con respecto a características del dolor y hallazgos electrocardiográficos en los 150 pacientes que presentaron episodios recurrentes de isquemia cardiaca. Los pacientes con infarto agudo se categorizaron en dos grupos: "comienzo abrupto" (n=81) y "angina prodrómica" (n=32). Se realizaron comparaciones entre grupos con respecto a edad, género y factores de riesgo cardiovasculares. El dolor en la región cráneo-facial constituyó el único síntoma prodrómico (pre-infarto) de un IAM en el 5% de los casos. En aquellos pacientes que experimentaron dos episodios isquémicos, las mujeres tuvieron una mayor prevalencia de dolor cráneo-facial en los dos episodios ($p<0.01$). No se detectaron diferencias estadísticas entre episodios con respecto a hallazgos electrocardiográficos o al empleo de los descriptores verbales del dolor de origen cardíaco "opresivo" y "quemante".

Este es el primer estudio de investigación en documentar que el dolor en la región cráneo-facial puede ser el único síntoma de una angina pre-infarto. En efecto, esto ocurre en uno de cada 20 casos de IAM. El reconocimiento de esta presentación clínica es baja debido a que históricamente los criterios de inclusión de los estudios de angina pre-infarto incluyeron únicamente pacientes con dolor de pecho. Para evitar el error diagnóstico con consecuencias fatales para el paciente, es importante que esta información llegue tanto a los clínicos como al público en general.

Palabras clave: *Infarto de miocardio, isquemia cardiaca, dolor facial.*

INTRODUCTION

Coronary disease is the leading cause of death in developed countries, but its clinical and epidemiological characteristics are not fully understood[1]. Craniofacial pain as the sole symptom of myocardial ischemia has been overlooked as a research topic until recently, when we revealed a prevalence of this potentially fatal condition of 6% among angina patients[2]. We also found craniofacial pain to be the sole symptom in 4% of acute myocardial infarction (AMI) patients. Application of this percentage to the number of coronary heart disease patients in the US[3] indicates that more than 28,000 patients per year might experience craniofacial pain as the sole symptom of an AMI. The corresponding number for the UK would be 6,800[4] and for Sweden 750[5]. The risk of missed diagnosis and death in AMI patients without chest pain is high[6-9].

Overlooking variation in symptoms of a medical condition is likely to affect the results of decision-making models[10]. Most studies on variation in symptom presentation during myocardial ischemic episodes, including AMI, have been based on inter-individual comparisons. Only a few studies have focused on intra-individual variability and they have mainly been limited to ECG findings regarding the frequency and duration of transient ischemic episodes[11], alterations of autonomic nervous activity during angina[12] and the intra-individual variability in plasma levels of markers of cell damage[13]. Intra-individual variation in the presentation of craniofacial symptoms during recurrent acute ischemic episodes has not been investigated. Prodromal (pre-infarction) angina constitutes one or more acute myocardial ischemic episodes prior to an AMI, which can occur several hours, weeks or months before an AMI[14,15]. Prodromal angina was shown to be a strong predictor of improved survival and limited infarct size[16,17]. The physiological mechanism underlying the protective role of prodromal ischemia is known as "ischemic preconditioning"[18]. It was previously assumed that the window of protection of the preconditioning mechanism lasts only for a few days[19] but a recent clinical study suggests that it can last for weeks[20]. The inclusion criteria for clinical research on prodromal angina have specified patients with chest pain/discomfort with or without other symptoms [12,16,17,21-24].

The possibility of prodromal angina presenting as craniofacial pain alone has so far not been addressed. The aim of this study was to elucidate the prevalence of craniofacial pain as the sole symptom of prodromal angina and to analyze the intra-individual variations of pain characteristics and ECG findings in patients who experienced an AMI with prodromal symptoms.

MATERIAL AND METHODS

Study populations

Patients with a verified episode of myocardial ischemia were derived from 404 subjects who were consecutively admitted with signs and/or symptoms of myocardial ischemia to three cardiology units in Montevideo, Uruguay. Twenty patients could not be interviewed due to death or prompt dismissal for follow-up treatment elsewhere. The remaining 384 patients were examined and interviewed. Patients were excluded when myocardial ischemia was not verified (n= 25), craniofacial pain was due to a verified non-cardiac origin (n=18), ischemia was asymptomatic (n=9) or the patients had severe heart failure (n=3), psychiatric disorders or confusion (n=3). A total 326 patients met the criterion of having symptomatic myocardial ischemia, with or without AMI. Of these, 176 patients experienced only one symptomatic episode of myocardial ischemia, while 150 patients experienced at least two episodes within five months of each other. In the latter group of 150 patients, the last two episodes of symptomatic myocardial ischemia were included in the intra-individual variability analyses.

Two AMI subgroups were defined according to previous definitions[16,17]: "AMI with abrupt onset" and "AMI with prodromal angina". Fig. 1 illustrates patient subgroups with information on gender and age. Sample size calculations were made using the OpenEpi program. A minimum sample size of 73 AMI patients was needed to estimate the prevalence of craniofacial pain as the sole symptom of prodromal angina.

Data collection and analysis

Data were collected on demographic details, health history, risk factors, ECG findings and pain characteristics for each ischemic episode according to the methodology described in detail in our previous reports[2,25]. Myocardial ischemia and AMI were diagnosed by cardiologists according to

the American College of Cardiology definitions. Both ECG changes and biochemical marker evidence were analyzed. The locations of ECG findings (ST-segment elevation or depression) were categorized as anterior (leads V1 to V4), inferior (leads II, III, aVF) and lateral (leads I, aVL, V5 to V6) according to acknowledged criteria[26]. Ischemia related symptoms that were experienced within five months prior to the occurrence of an AMI were regarded as prodromal[14,15].

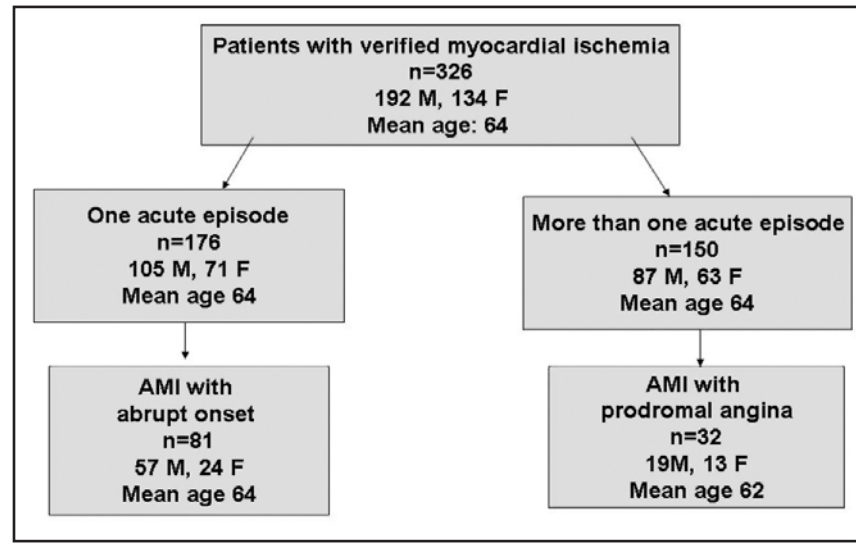

Fig. 1: Flowchart of patients and subgroups with information on age and gender. AMI: Acute myocardial infarction.

Age, gender and risk factor comparisons were performed between AMI groups. Intra-individual comparison was carried out in the patients with prodromal angina with respect to ECG findings, pain characteristics and effect of physical activity on pain.

Statistical analysis

The Wilcoxon test was used to compare mean ages between groups. Univariate chi-square analyses were used to assess gender differences between groups. A multivariate logistic regression model was used to assess possible associations between the presence of prodromes and craniofacial pain (dependent variables) and risk factors, age and gender.

McNemar's test was used to assess the significance of the differences between intra-individual episodes when the variable was dichotomous (e.g. AMI, pain relief at rest, etc). For intra-individual analysis of multinomial variables (e.g. quality of pain, site of ischemia) the Marginal Homogeneity test was used. The ¨coin¨ and ¨stats¨ packages of the R software were used to perform the statistical analysis[27,28]. The Wilcoxon signed-ranks test was used to analyze intra-individual variations in pain intensity.

Ethics approval

The Ethics Committees at the Universidad de la República and the Hospital Central de las Fuerzas Armadas, Uruguay, approved the study protocol. Informed consent was obtained from each patient included in the study.

RESULTS

Craniofacial pain as the sole prodromal symptom of an acute myocardial infarction (AMI).

AMIs were experienced by 120 patients, 81 from the "AMI with abrupt onset group" and 32 from the "AMI with prodromal angina group", with seven patients being excluded as they suffered recurrent AMIs.

Pain in the craniofacial area constituted the sole prodromal symptom of an AMI in 5% of patients (three men, three women, mean age 68 years). The pain locations reported by these patients were throat, right jaw, left jaw, left temporomandibular joint/ear, and mandibular molar teeth bilaterally.

All six patients with craniofacial pain as the sole prodromal symptom reported a difference in pain distribution between episodes. During the AMI all these patients again reported craniofacial pain but five of them also developed chest pain and one had back pain in addition to craniofacial pain. Only one of their clinicians had an early suspicion of a possible cardiac source of the prodromal facial pain. Five of these six patients reported that exercise aggravated the symptoms and that rest alleviated the pain. All six patients used the quality descriptors "pressure" and/or "burning" to describe the prodromal pain in the craniofacial areas. Prodromal craniofacial pain in combination with typical anginal locations (chest, arms, shoulders, etc) was experienced by another 12% (n=14) of the AMI patients.

Intra-individual symptom variability between myocardial ischemia episodes

Of the 150 patients who experienced at least two episodes of myocardial ischemia, four with prodromal angina had not sought medical care for their prodromal symptoms and were discarded from the intra-individual variation analysis of the location of ECG changes. The combination of pain quality descriptors reported by the patients generally changed significantly between the two ischemic episodes (p=0.01), although the quality descriptors "pressure" and "burning" remained the same. Pain intensity was higher during the AMI episodes (p< 0.001). The location of ischemia in the heart did not vary significantly between episodes, according to the ECG findings (p=0.32). Women were more likely than men to experience craniofacial pain in both ischemic episodes (P<0.01). No additional age or gender associations were found in the intra-individual analyses.

AMI with prodromal symptoms vs. AMI with abrupt onset.

No age or gender difference was found between groups. Patients in the prodromal angina group were more likely to be obese (p=0.026) and tended to have a family history of cardiovascular disease (p=0.05).

DISCUSSION

Prodromal angina and ischemic preconditioning has been shown to protect the myocardium, slow the process of cell death, limit the infarct size, and improve patient prognosis[18,22,29]. Prodromal angina pectoris, specifically, is a strong predictor of a smaller size infarct and lower mortality[17]; a meta-analysis showed that the occurrence of prodromal angina during the 24 hours before the onset of an AMI was associated with a 39% reduction of in-hospital mortality[30]. Studies of prodromal angina and its protective role have been largely limited to patients with chest pain symptoms and have not considered patients with prodromal craniofacial pain as the only symptom of cardiac ischemia[12,16,17,21-23].

Our study revealed that one in 20 AMI patients reported pain in the craniofacial structures as the only prodromal symptom. Considering that patients without chest pain during an AMI run a greater risk of death[7,31] and some of them therefore never reach the emergency room, it is highly plausible that our findings on prevalence constitute an underestimation. It was noticeable that patients with craniofacial pain as the only pre-infarction alert for the patient and the clinician consistently developed additional typical anginal symptoms during the AMI. It may be that the pathological changes occurring during the AMI episode released several chemical mediators and activated more nerve afferent fibers, inducing changes in the pain pattern.

It is generally believed that atypical presentation of an AMI is a well-known problem but clinical awareness appears low. Ninety percent of nurses and 100% of physicians from an Emergency Care Unit in North America stated that they had experience with atypical presentations of an AMI but 75% of nurses and 80% of clinicians reported that they do not look for atypical symptomatology in female patients[32]. Furthermore, during this same interview, pain in the craniofacial region was not cited by physicians or nurses as a symptom that would point to an AMI. In line with these findings, neither the patients with craniofacial pain as the sole prodromal symptom nor their clinicians recognized the cardiac origin of the pain in five out of the six patients included in our study. These findings point to the need for educational initiatives both for the general public and clinicians regarding this atypical AMI prodromal presentation.

In a previous study we showed that the quality descriptors "pressure" and "burning" were statistically associated with craniofacial pain induced by myocardial ischemia, with or without an AMI[25]. This study confirms that these pain descriptors were used also by patients in their reporting of pre-infarction craniofacial symptoms. The location of the prodromal craniofacial pain is also in line with our previous report regarding craniofacial pain locations during myocardial ischemia[2].

Orofacial location of pain is likely to cause the patient to seek a dentist, a general physician or an otorhinolaryngologist. The clinical information presented in this study regarding pain quality, aggravation by exercise and pain relief during rest, combined with the prevalence of these symptoms, should alert the clinician to consider the possibility of an AMI prodromal condition; failure to consider this possibility could have potentially fatal results.

This study is to our knowledge the first to report that craniofacial pain can be the only symptom precursor of an AMI. Its prevalence points to a

significant number of patients per year being at risk of misdiagnosis. The risk of overestimation of the prevalence is considered negligible since the sample size is well over the statistical calculations for minimum size. On the contrary, there is a risk of underestimation because a significant number of patients with atypical prodromals, i.e. those with craniofacial pain alone, never sought medical care and/or died before reaching the hospital.

In conclusion, craniofacial pain constituted the sole prodromal AMI symptom in one out of 20 AMI patients in our study. The explanation for the low recognition of this atypical symptom presentation is most likely that research on prodromal AMI symptoms has to date focused only on patients with chest pain as an inclusion criterion, regardless of other symptoms. To avoid a potentially fatal misdiagnosis, awareness of this clinical presentation of prodromal craniofacial pain alone needs to be conveyed to clinicians and the general public. Future research on prodromal AMI symptoms should also include patients without chest pain.

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