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Editorial

Scombroid Syndrome and Allergic Acute Coronary Events

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Introduction

Scombroid Syndrome (SS, also known as Scombrotoxism or Scombroid Ichthyotoxicosis) is a recently described pathology due to the consumption of altered fish flesh, in the absence of organoleptic abnormalities [1]. It is a particular type of Kounis Syndrome, a disease in which a cardiovascular event (a coronary vasospasm, a myocardial infarction or a stent thrombosis) occurs as the consequence of an allergic or hypersensitivity, anaphylactic or anaphylactoid insult [2]. This inflammatory basis has a first actor in mast cell [3,4]. Mast cell interacts and activates directly or indirectly other inflammation cells (macrophages, T lymphocytes) [4]. In hypersensitivity mast cells degranulation put in circulation several inflammatory mediators like histamine [4]. Histamine is a biogenic amine that has a major role in the inflammatory and allergic response [6]. Its effects include coronary vasoconstriction, induction of tissue factor expression, and platelets activation [6-8]. These effects justify the name of 'Histamine fish poisoning' with which SS is also known. Other inflammation mediators have a cardiovascular effect [2]: chemokines, enzymes such as the neutral proteases chymase, tryptase and cathepsin-D, cytokines, peptides, proteoglycans, growth factors and arachidonic-acid products such as leukotrienes, thromboxane, prostacyclin, PAF, and tumor necrosis factor. All the neutral proteases can activate metalloproteinases which degradate the collagen cap of the plaque, bringing to erosion and then rupture. Cathepsin-D and Chymase have a role in converting Angiotensin I in Angiotensin II, with a vasoconstrictor effect [9]. Vasoconstriction is induced also by leukotrienes [10]. Thromboxane has both a vasoconstrictor and a platelet aggregation mediator effect. All these mediators assume a particular relevance for patients with cardiovascular risk factors, especially for those with a methabolic syndrome [11]. They play also a role in the more general context of the Kounis Syndrome with Histamine playing a central role in SS [2,12].

We performed a systematic research on Pubmed using the key words 'Scombroid Syndrome' and 'Kounis Syndrome'. We found 251 articles but we selected only 23 articles of interest.

SS physiopathology is explained by the high level of Histamine in the altered fish flesh [13]. It is important to underline that freshly caught fish does not contain a sufficient quantity of histamine to determine symptoms [14,15]. The potential risk is linked to fish species (especially the Family of Scombridae, migratory pelagic species such as mackerel, tuna and tuna yellow-fin and non-migratory species such as menhaden and minnows) in which there is a high level of the amino acid histidine in its free form, physiologically present as a buffer system in their tissues, protecting them from the sudden increase of lactic acid [16-19]. A good maintenance of the cold chain prevents the decaboxylation by histidine decarboxylase, an enzyme present in some bacterial species, in histamine [20]. This process occurs typically in early stages of fish deterioration, in the absence of organoleptic abnormalities, when after fish death, there is no more defense against bacterial growth. An interesting hypothesis suggest that some substances present in fish, increase histamine toxicity in human, promote its absorption, or inhibit its inactivation by histamine N-methyltransferase and diamine oxidase [3,21,22]. There are some enhancers in the fish tissues (other amines like putrescine, cadaverine, tyramine, agmatine) which could play a role in the development of

symptoms [3,21-23]. These involve especially skin (common, especially rash localized to the face and neck, facial swelling, hives, conjunctival hyperemia and pruritus); gastrointestinal apparatus, very frequent but not specific (diarrhea, abdominal pain, nausea, vomiting); nervous system (headache, palpitations, tingling, troubles of the vision, tremors, weakness, feeling of heat) [2]. Have been described also hemodynamic symptoms [24] (hypotension and dizziness) and, in the most dangerous situations also cardiovascular events (coronary vasospasm, myocardial infarction, stent thrombosis) [2]. The last situation configures the Kounis Syndrome, with ECG changes, from ST-segment elevation or depression to of heart block (of any degree) and arrhythmias. Kovanen et al demonstrated that 2 days after an acute coronary event infiltrates of degranulated mast cells at the site of coronary atheromatous erosion or rupture were found. To date three types of Kounis Syndrome are described: Type I (coronary artery vasospasm without history of coronary artery disease); Type II (quiescent pre-existing atheromatous with a culprit vessel, in which inflammatory mediators can induce either coronary artery spasm or acute myocardial infarction); and Type III (coronary stent thrombosis with histological demonstration the presence of eosinophils and mast cells). The evolution from SS to Kounis Syndrome is a potentially risk for the patient life that the physician should remember.

Particular attention should be paid to those patients who arrive to the Emergency department with cardiovascular risk factors (arterial hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, previous myocardial infarction): their danger threshold is lower. According with Athyros et al [25], a new cardiovascular risk disease estimation could be helpful to better define an optimal management protocol and pharmacological approach. In fact several recent evidences justify higher level of alert in patients with a chronic activation of the inflammatory cascade, also in those with a not primitively heart disease [26]. The reason for this kind of approach is attributable on the central role of endothelium dysfunction between inflammatory mediators and atherosclerosis [27].

In this setting some improvement in symptoms has been reported with antihistamines treatment and possibly with steroids with resolution of hives in the Type I [28-30]. Nitrates, calcium channel blockers can be administrated to reduce the vasospasm, especially in Type II variant, but the administration of β -blockers may exaggerate coronary spasm due to unopposed activity of α-adrenergic receptors. Epinephrine in Kounis syndrome (typically the drug of choice in anaphylaxis) may aggravate ischemia and worsen coronary vasospasm, so only in severe cases should be administered a sulfite-free epinephrine intramuscularly (this route has faster onset of action with a more stable concentration than the subcutaneous one). Caution must be exercised with opioids, which, in Kounis syndrome, may cause massive mast-cell degranulation. Paracetamol is not recommended, especially by intravenous administration, because it might cause severe hypotension. In Type III variant is a protocol for myocardial infarction should be started, with urgent aspiration of intra stent thrombus [31-33]. There are emerging evidences that the flavonoid quercetin has a good efficacy in blocking mast cell cytokines in humans [34]. This interesting option could be effective in the prevention of Kounis syndrome as well as a diet containing natural flavonoids with mast cell inhibitors [35].

SS definitive diagnosis implies that allergic symptoms are present, an antihistaminic therapy is effective and the presence of high levels of histamine in the fishery product.

SS often does not show itself in a dangerous way but the physician of the Emergency Care unit should keep in mind that its evolution is not ever predictable and there is a potential risk of life if heart is involved, especially in atopic subjects and in those who develop an anaphylactic reaction with pre-existing cardiovascular risk factors. Recognize SS and its development in a Kounis Syndrome can save life to the patient. In this setting a new definition of the cardiovascular risk disease, with a combination of the emerging evidences about the role of quercetin and of the natural flavonids, may allow physicians to take early therapeutic decisions.

Abbreviations

SS-Scombroid Syndrome

Keywords: Acute Coronary Events; Vasospastic Allergic Angina; Allergic Myocardial Infarction; Allergic Stent Thrombosis; Scombroid Syndrome; Kounis Syndrome.

Declaration of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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