Three cases of scombroid syndrome in Italy: clinical and preventive considerations

M. Pallocci¹, A. Messineo¹, P. Passalacqua², C. Zanovello¹, M. Treglia¹, L. T. Marsella¹

¹Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy; ²Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy

Abstract

Background. Foodborne diseases are common sources of morbidity and mortality worldwide. Scombroid syndrome represents a particular condition since it is not directly related to the ingestion of spoiled food but is determined by high levels of histamine, a chemical mediator naturally produced within the human body under particular conditions. In these cases, histamine is formed as a result of the bacterial activity from histidine, an amino acid present at high levels in some fish species. The resulting symptomatology can range from mild symptoms such as headache and skin rash to more severe manifestations such as hypotension and coronary spasms. Reference regulations in Italy set maximum levels of histamine in food at 200 mg/kg.

Cases description. The cases described involve a family of three who, following the ingestion of a tuna dish, started to exhibit symptoms typical of an allergic reaction. In one case, hypotension, tachycardia, and electrocardiographic changes in the ST-tract suggestive of myocardial ischemia also appeared with negative myocardionecrosis enzyme dosage. All three cases experienced complete remission of symptoms in the absence of sequelae. Histamine concentrations in fish sampled three days later were 169 mg/kg.

Conclusion. The cases described emphasize the importance of proper differential diagnosis as well as the importance of implementing specific controls in food hygiene.

Keywords: foodborne disease, scombroid syndrome, histamine intoxication, case report

Introduction

Foodborne diseases are relatively common causes of morbidity and mortality globally. Nevertheless, too often some are poorly known or even underestimated. Histamine intoxication, known as the “scombroid syndrome,” is one of the most common fish ingestion intoxications in the US. In Europe and Italy, however, notices concerning this syndrome are few and underreported (1).

The scombroid syndrome is a type of food poisoning caused by the ingestion of altered fish products containing high levels of histamine, in the absence of organoleptic alterations (2). It is a chemical-type intoxication, characterized by symptoms that generally appear 10 minutes to 2 hours after consumption of fish that naturally contain high levels of histidine. Histidine is converted to histamine by the action of the histidine decarboxylase produced by bacteria, which grow and multiply if there are no inhibiting conditions (3). The symptoms are characterized usually by rash on the face, neck, and upper chest, flushing, sweating, nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, palpitations, oral burning sensation, metallic taste, and hypotension, and usually resolve within 24 hours. The syndrome may also take on the clinical features of an acute coronary syndrome (4).

In this context, some cases of allergic angina with normal coronary arteries, termed Kounis syndrome (KS), have been reported, which has been related to exposure to, among others, several foods, including fish and shellfish (5). The exact pathophysiological mechanism of KS remains poorly understood, as most of the related literature consists of case reports or case series. The main proposed pathophysiological mechanism is that of vasospasm, plaque rupture, and thrombosis, due to the rapid release of inflammatory mediators during a hypersensitivity reaction (6).

The cases described concern a family of three people who, as a result of contextual ingestion of tuna type Alalunga, manifested symptoms attributable to mackerel syndrome requiring hospitalization.

Case report

Case 1

The first case involves a young woman who about 35 minutes after finishing her meal suddenly manifested a major dyspneic crisis with bronchospasm, tachycardia, headache, diffuse itching, and erythema on the face and trunk.
associated with marked general discomfort. The father, a laboratory physician, interpreted such symptomatology as an “allergic reaction” and immediately intervened by administering corticosteroids (Phlebocortid), antihistaminic therapy and oxygen. The woman was conducted to the emergency room where dyspnea with skin rush spread over the entire body surface and conjunctivae, anxious state, and tachycardia (HR 101/min) were detected. The patient was placed under multiparametric monitoring and received oxygen therapy. Then diagnosed with “scombroid syndrome” and temporarily hospitalized, she was discharged eupneic and free of erythema after therapy at 10 p.m. the same day. However, the same, immediately after discharge suffered from an anxious depressive state that several months later was still present.

Case 2

The second case involves the father, a middle-aged man who about 30 minutes after accompanying his daughter to the hospital manifested malaise with severe gastralgia, nausea, and diffuse erythema on the trunk and back. Premedical chest pain associated with a hypotensive crisis (BP 70/40) also appeared, which was followed by cardiovascular collapse and loss of consciousness. The electrocardiogram showed a transient episode of atrioventricular block of the 2:1 type resolved spontaneously with transient ST-segment depression in the V4-V5 leads, while the echocardiogram showed good left ventricular systolic function. Blood tests were normal (there was no increase in markers of myocardial cytonecrosis) and coronarography was suggestive for coronary sclerosis in the absence of significant stenosis. At the discharge the diagnosis was transient myocardial ischemia in hypotensive crisis in the context of scombroid syndrome with an episode of paroxysmal atrial fibrillation. The patient was subsequently discharged and, at a follow-up visit several months later, reported no symptoms attributable to respiratory or cardiac disease.

Case 3

Within hours of the admission of the relatives, the son, who had remained asymptomatic in the emergency waiting room, also felt malaise, and flushing in his face and trunk, associated with tachycardia and profuse sweating. He was then admitted to the emergency department and underwent radiological and laboratory investigations that demonstrated a significant increase in white blood cells (16,180/μL) and marked increase in thyroid hormone FT4. He was discharged a few hours later with a diagnosis of agitation in possible food poisoning and hyperthyroidism and a prescription for antiallergic and antibiotic therapy.

The investigations of surveillance authorities

Following the hospital’s notification of the scombroid syndrome food poisoning to the surveillance authorities, an inspection was carried out 3 days later, which found poor hygienic conditions inside the restaurant. Several deficiencies in the Self-Hygiene and Sanitation Control Plan (HACCP) were noted, as well as the lack of recording the temperature of the refrigerators that had been off for a few hours due to a malfunction in the electrical system without any replacement generator set being activated. A tuna steak of the same origin and date as the one used for consumption in the intoxicants and stored in the refrigerator was also taken and underwent laboratory analysis that detected histamine levels of 169 mg/Kg.

Discussion

Scombroid syndrome is among the most common causes of seafood poisoning. First described in 1799 in Britain, it reemerged in the medical literature in the 1950s when outbreaks were reported in Japan (7). The fish involved are mainly red-fleshed fish species belonging to the families Scombridae (tuna, yellowfin tuna, skipjack or bonito, mackerel, mahi-mahi), but also Clupeidae (sardines, herring, cuttelfish, and anchovy) and fish species related to these that have been refrigerated or improperly stored after fishing. It has also occasionally been associated with the ingestion of certain types of cheese (8). Unlike ciguatera (9), which involves semi-pelagic fish species in tropical islands that feed on smaller “reef” fish and thus increase the toxicity of toxins ingested by them, mackerel syndrome can affect any type of fish if poorly preserved and containing high levels of histidine. Histidine is naturally found in many species of pelagic fish due to their need to buffer accumulated acid in their muscles, which is related to the ability of these fish species to swim for long distances.

If not properly maintained at a temperature ≤ 0°C immediately after fishing, Gram-negative bacteria, including Klebsiella pneumoniae, Proteus morganii, Serratia marcescens, and Enterobacter intermediate (10), present in fish gills and in the microbiota of the gastrointestinal tract convert histidine to histamine through the activity of histidine decarboxylase. Once formed, histamine is resistant to cooking, smoking, freezing, and canning (2). In order to prevent bacterial overgrowth and subsequent production of histamine, fish should be handled under the most hygienic conditions, and special attention should be paid to storage and thawing at low temperatures (no more than 6°C), avoiding interruption of the cold chain. It is very critical to provide refrigeration immediately after capture. Histamine is produced before fish spoilage can be detected through sensory characteristics (appearance, odor, taste), especially in the presence of “additives” that confer an apparent freshness to the fish but do not slow its degradation. These include cafodos (or cafados), a mixture of citric acid, sodium citrate and hydrogen peroxide (the latter is banned in fish products) a product whose use is not authorized in Italy (11). This product does not appear to be toxic by itself, at least at low concentrations; the greatest risk derived from its use is associated with the potential ingestion of the spoiled fish (12).

Histamine is a chemical mediator of allergic reactions, and the symptoms it causes are those that also occur during severe allergic reactions. However, there is no clear dose-response relationship between oral administration of histamine and ingested histamine levels in decomposed fish, the latter in some cases resulting in greater toxicity than an equivalent oral dose of pure histamine (13).
In this regard, other mediators have been proposed in recent years as being involved in the development of the syndrome, including cadaverine, putrescine, and cis-urocanic acid (14). Cis-urocanic acid has been recognized as a stimulating factor for mast cell degranulation, which is responsible for the release of endogenous histamine, increasing the total histamine concentration in fish tissues. It is indeed necessary to point out that although histamine is involved, it is not, from a pathophysiological point of view, a true allergic reaction to fish, which, instead, results from an IgE-mediated reaction and is independent from the preservation and integrity condition of the fish (15), so that individuals with previous toxicities will still be able to eat well-preserved fish without presenting any symptoms (13).

Normal levels of histamine in fresh fish are generally less than 0.1 mg/kg (16), although reference legislation in Italy (EC Reg. 854/04 and EC Reg. 2073/05) has set a maximum histamine content of 200 mg/Kg for fresh fish and 400 mg/kg for preserved products, it has been shown that even lower intakes can be dangerous for humans, especially in cases of histamine hypersensitivity, asthma, or heart disease (11,17). In this regard, it should be noted that in the US the maximum levels allowed by the FDA are 50 mg/Kg, significantly lower than the levels allowed in Italy (17). With reference to the cases presented, investigations by the competent agencies showed histamine levels below the legal limits, nevertheless the syndrome occurred in one case with cardiac symptoms, emphasizing the hazardous nature of the presence of histamine even below 200 mg/Kg. There are several reports of scombroid syndrome in the literature from all over the world. In Israel, 46 cases were reported from 2005 to 2007, 25% of which were symptomatic predominantly as a result of tuna consumption, with relatively rapid-onset (within 20 minutes) manifestations represented by flushing, gastrointestinal disorders, and headache; hypotension was reported in two cases (18). A literature review regarding histamine food poisoning considered 55 case reports in which there were a total of 103 cases involved in which the presence of histamine at high concentrations was reported (19).

Another outbreak of scombroid fish poisoning occurred in the French armed forces in Dakar, Senegal. Symptoms observed were hot flashes (85.9%), headache (83.1%), rapid/weak pulse (59.1%) and diarrhea (47.9%), the onset ranged from a few minutes to 3 hours after the meal. Most patients recovered quickly with antihistamines. No bacterial contamination was found in the leftover food, but the histamine concentration in tuna was found to be 4900 mg/kg, almost 50 times higher than the concentration allowed by European regulations (20). In terms of clinical presentation, in addition to the milder manifestations, cardiac symptoms have been reported in some cases characterized by chest pain, hypotension, and electrocardiographic changes in the ST-segment elevation, as in one of the three cases described in our work. Such cases have been associated to a coronary artery spasm. These are generally benign evolving situations, which, however, in some cases may require administration of fluids and circulatory supportive drugs due to the onset of hemodynamic failure (21). In terms of diagnosis, in addition to a proper history regarding the mode of onset of symptoms, histamine and N-methylhistamine can be measured in urine samples (22). Furthermore, new methods have recently been developed able to detect in a food sample the levels of histamine and the simultaneous presence of the responsible bacteria (23). The syndrome should be prevented through proper storage process and by strict adherence to the “cold chain” and the regulations stipulated in EU and National Food Protection Legislation (especially the HACCP plan).

Despite the relative benignity of scombroid syndrome, cases that evolve fatally or are characterised by severe symptoms are very rare, the reported data on the possibility of outbreaks of scombroid syndrome show that it presents numerous public health implications. Firstly, the need to correctly identify cases of scombroid syndrome as quickly as possible to set up a correct therapeutic strategy, but also to trace the source of intoxication and thus interrupt the food chain of transmission of the toxic substance and thus prevent an outbreak from forming or spreading. Maintaining high quality and control standards and the implementation of efficient monitoring and reporting systems based on a rapid and complete flow of information to ensure the correct detection of cases and to contain any outbreaks is therefore essential for preventive aims. To achieve these objectives, the surveillance of disease outbreaks in the territory appears to be essential. It is also considered advisable in this context for health authorities and hospitals to adopt dedicated protocols to provide an operational guiding tool for health workers involved in the management of such events.

**Conclusion**

Maintaining low storage temperatures and respecting the cold chain are essential elements in limiting bacterial growth and the occurrence of intoxications of the type described. In this perspective, even random power outages of refrigerators of a few hours can lead to the occurrence of even severe food poisoning. Furthermore, since it is infeasible to control millions of fish offered for sale every day in every country, the controls should be primarily carried out by the producers/sellers taking advantage of the method of self-control, especially if provided for by European and/or each country’s regulations (HACCP method). Another issue concerns the ability to correctly differentiate between allergic phenomena in general and preformed histamine poisoning syndrome, which should be the subject of a proper diagnosis. Firstly, Histamine content in the food and laboratory analysis combined with inspection of the places where the food is prepared and served constitute elements that need to be investigated in order to correctly reconstruct the dynamics of the events and also define a possible hypothesis of responsibility. It should also be noted that scombroid syndrome, due to the underlying mechanism, is also connected with international trade and long-distance transportation of this kind of food. In fact, if the fish is procured through a controlled fish center and/or in a marine area or through fishermen’s cooperatives, it is more difficult for the syndrome to occur, while it may be more frequent following long-distance transport when the cold chain may not be respected or in supplies from foreign wholesalers or in fish subject to weaker international controls.
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References

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