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Scombroid Fish Poisoning

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1. CLASSIFICATION AND IDENTIFICATION

Scombroid fish poisoning, otherwise known as histamine fish poisoning (HFP), is the most common seafood poisoning in the United States related to the improper storage of fish *(1)*. Because of misdiagnosis and other factors, HFP is undoubtedly underreported *(2)*. Enteric bacteria (*Escherichia coli, Proteus morganii, Morganella morganii,* and *Proteus vulgaris*) act on the flesh of the poorly maintained fish to produce elevated histamine levels (as well as other bioactive amines) through the breakdown of the amino acid histadine *(3,4)*. These organisms are part of the normal flora of certain fish and not thought to be the contaminants *(5)*. Histamine production is correlated to the histadine content of fish, bacterial histadine decarboxylase, and environmental factors *(6)*. Histadine levels vary from 1 g/kg in herring to as much as 15 g/kg in tuna *(7)*. Unspoiled, fresh fish do contain small amounts of histamine (<0.1 mg/100 g *[8]*), but do not cause HFP.

2. RESERVOIRS

The vast majority of fish causing HFP are members of the families Scombroidae and Scomberesocidae (hence the name scombroid fish poisoning), which include tuna, mackerel, skipjack, bonita, suary, and seerfish. Several nonscombroid fish are also linked to HFP, including bluefish, mahi-mahi, herring, sardines, and anchovies *(9)*. These fish are nontoxic when afresh, can still appear very normal with the development of toxicity, and have no putrid odor *(10)*. Other species that have also been affected are of little concern because they are not commonly eaten. The fish that are affected are thought to be related closely to specific endogenous bacteria. Interestingly, dark meat, a major component of the muscle of these fish, seems to be more affected. Improper storage of the fish at insufficient low temperatures appears to initiate the bacterial growth. Freezing, cooking, smoking, curing, or canning does not eliminate the potential toxins but destroys the bacteria that produce the toxins *(9)*.

3. FOODBORNE OUTBREAKS

Outbreaks are worldwide and are found in places where potentially spoiled, improperly handled scombroid-like fish species are eaten. Of note is that HFP occurs with the ingestion of canned tuna, a mainstay of the American diet. Hence, wherever a can of tuna are sent creates the potential for HFP. Recreational fishermen tend to have less

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stringent habits and regulations for storing their catch and are hence more likely to end up with fish capable of producing HFP. The Board of Health in New York City reports approx 70 cases of HFP per year, seen in emergency rooms or clinics, but clearly there are many more cases which are attested to a simple virus or food allergy (Dr. Herbert Schaumberg, personal communications). Last spring, there were 20 unreported HFP cases at Albert Einstein Medical Center alone after the Pediatric Department's farewell to the residents' banquet (Dr. Herbert Schaumberg, personal communications).

4. PATHOGENICITY (VIRULENCE FACTORS)

HFP is generally associated with high histamine levels (>50 mg/100 g) in spoiled fish that have high histadine content *(9)*. Histamine is endogenous to mast cells and basophils usually only having an effect when released in large amounts in response to an allergic reaction. Histamine has cell membrane receptors principally in skin, hematological, gastrointestinal, and respiratory systems *(11)*. Interestingly, consuming spoiled fish with histamine is more poisonous than taking an equivalent amount of pure histamine orally *(12)*, suggesting that there are other "scombroid toxins" acting with histamine *(13,14)*. The histamine-potentiator hypothesis is based on the observation that absorption, metabolism, and/or potency of one biogenic amine might be altered in the presence of another amine *(12,15)*. The biogenic amines putrescine and cadaverine are found in large quantities in toxic fish *(12)* and in significantly lower levels in nontoxic fish *(16)*. These amines, when given in higher ratios relative to histamine in toxic fish, have been shown to potentiate the effect of histamine in laboratory animals *(17)*. Some amines, such as cadaverine and putrescine along with a number of other tested chemicals found in spoiled tuna, may competitively inhibit diamine oxidase (DAO), the main histamine catabolizing enzyme in the intestinal tract, and histamine methyl transferase (HMT) *(18,19)*. The toxicity of histamine can be potentiated by cadaverine *(15)* and putrescine *(20)* in guinea pigs. A number of drugs inhibit DAO including iproniazid, isoniazid, pargyline, aminoguanidine, phenelzine, and tranylcypromine, which could predispose one to HFP *(21)*. Serotonin, tryptamine, and phenformin are good competitive inhibitors, whereas cimetidine and pheniprazine are noncompetitive inhibitors. Other antihistaminic drugs such as promethazine are less powerful inhibitors. Certain foods can inhibit DAO (alcohol and tyramine-containing foods such as strong cheeses) likely predisposing one to HFP as well *(12,22)*. HMT is inhibited by analogs of methylmethionine such as adenosyl-homocysteine, antimalarial drugs, and numerous agonists and antagonists of histamine receptors *(12)*. It should be noted that histamine has been implicated in the pathogenesis of migraine *(23,24)*, the intolerance of which may be based on a deficiency in the DAO enzyme *(25)*. A diet excluding alcohol and tyramine-containing foods is helpful for many patients with histamine-induced headaches. Regarding this fact, a worse reaction to HFP is expected if someone ingests wine with scombroid-laden fish, although no published data confirm this idea.

The "barrier disruption hypothesis," first proposed by Parrot and Nicot *(20)*, states that potentiators might interfere with mucin, which is known to bind histamine, thought to be an essential event in preventing the intestinal absorption of histamine and hence increases histamine absorption *(26,27)*. It has also been postulated that histamine may be released endogenously by an unknown scombroid toxin *(28)*. Urocanic acid, an imidazole compound and a histadine metabolite of spoiling fish, has been

shown to induce histamine in vivo in mice *(29)* and to degranulate mast cells in human skin organ cultures *(30)*. The role of endogenous histamine release in HFP has not been established *(31)*.

A recent publication describes the sensitive polymerase chain reaction technique for detecting *M. morganii*, which was found to be present in fresh fish including mackerel, sardine, and albacore. The gill and skin were the main harbor sites of the bacterium in this study *(32)*. Conventional culturing techniques did not detect the bacterium. This study demonstrates that histamine-forming bacteria are endogenous to these fish and are likely to proliferate under the suitable conditions. These findings also emphasize the importance of proper handling of fish, including refrigeration, to prevent HFP.

5. CLINICAL CHARACTERISTICS

Fish affected by scombroid tastes "peppery," which is thought to be related to elevated histamine levels. Headache, a burning sensation in mouth and oropharynx, and nausea are common neurological symptoms of HFP *(4,33)*. Other symptoms include diffuse erythema (especially flushing of the head, neck, and upper torso), headache, vomiting, diarrhea, and abdominal cramping *(33–36)*. Occasional arrhythmias, hypotension, bronchospasm, and cardiovascular collapse also occur *(37,38)*. Anxiety has also been reported as a prominent symptom with HFP *(39,40)*. Generally, HFP is not a life-threatening condition, but in those patients with serious preexisting conditions, notable respiratory and cardiac complications do occur *(38,40)*. The symptoms of HFP usually last for 8–12 h *(33)* and can come on within minutes of ingestion of a toxic meal *(33,41)*.

With HFP, there is a remarkably wide spectrum of clinical symptoms (mild to severe). Symptoms can be confused with *Salmonella* infection *(40)* as well as food allergy *(4)*. The usual HFP-associated fish species cause HFP much more frequently than they cause true allergic reaction *(12)*. The clinical setting of the poisoning shows evidence to the etiology as if only one person is affected by a meal when several individuals have eaten the same fish, sheds doubt on the diagnosis of HFP. Nevertheless, the concentration of the histamine may not be evenly distributed through the fish and, hence, not everyone who eats the fish will necessarily get sick. In fact, food allergies to most of the common fish involved with HFP are rare.

Although the diagnosis can be confirmed by detecting histamine in contaminated fish, remnants of the meal, or similar fish from the same source *(12,17)* as well as other biogenic amines *(16)* and urocanic acid *(42,43)*, the diagnosis is normally made by the history and clinical presentation. There are numerous methods for the detection of histadine-decarboxylating bacteria that can be performed with specific media that are selective for this enzyme *(4,44,45)* although some of these media have given false positive results *(45)*. The biochemical methods for detecting histamine and other biogenic amines are extensive as well as controversial and are well outlined by Lehane and Olley *(31)*. Measurement of plasma histamine levels is not routinely available in most community-based hospitals. Measuring human serum levels requires that histamine is measured within 4 h of the ingestion of the fish *(46)*.

Other diagnoses to be considered with HFP are severe migraine, intracranial hemorrhage, and pheochromocytoma *(36)*. HFP may resemble an immunoglobulin E (IgE)-mediated allergic reaction; however, HFP is a foodborne intoxication related to elevated histamine levels, and therefore the patient can safely eat the same type of fish again with impunity.

6. CHOICE OF TREATMENT

HFP is self limited, and the need for long-term therapy is usually unnecessary *(3,12)*. HFP exposure responds to corticosteroids, charcoal, and histamine blockers *(4,41,47)*. The H2 blocker cimetidine at 300 mg iv has been effective in HFP *(41,47)*. There is a rational basis for blocking H1 and H2 receptors (H2 receptors are found in human blood vessels) *(3)* to minimize the vascular effects of histamine. Therefore, the addition of the H1 blocker diphenhydramine at 50 mg im, in addition to a H2 blocker, is recommended *(3)*. At least some case reports have not shown diphenhydramine hydrochloride 25–50 mg po or iv by itself to be effective as a treatment option *(41)*. In severe cases, aggressive symptomatic care is required including intravenous fluids and possibly steroid therapy *(41)*. Adrenaline, which is often helpful in allergic reactions, is of little benefit in HFP *(48)*.

7. RESISTANCE EPIDEMIOLOGY

Because HFP is a consequence of improper handling/storage of fish and there are effective testing methods to identify toxic fish, prevention and control of outbreaks are possible. Contamination with histidine-decarboxylating bacteria can occur immediately after the fish are caught on the fishing vessel, in the processing plant, in the distribution of the fish, and also with the consumer, such as at home or in a restaurant *(12)*. Key to the prevention of HFP is proper cooling of fish immediately after they have been caught *(31,49)*. Interestingly, most HFP in the United States results from the improper handling of fish by recreational fishermen who often neither have the knowledge nor the proper equipment to cool the fish properly *(50)*.

Many countries have set limits for the maximum-permitted levels of histamine in fish. The amount of histamine produced is a function of the fish type, the part of the fish sampled, temperature, and the types of bacteria found on the fish *(51)*. Normal fish has less than 100 ppm of histamine (1 mg/100 g of flesh). Although the toxic dose and symptoms of HFP are variable *(4,12,52)*, illness usually occurs at levels of 1000 ppm (100 mg/100 g of flesh), but lower levels (20 mg/100 g of flesh) can also cause illness in some individuals *(3)*.

8. SUMMARY AND CONCLUSIONS

HFP is a common form of fish poisoning that is often mistaken for allergic reactions. The affected Scombroidae and Scomberesocidae family fish are commonly eaten and poisonings can occur most anywhere in the civilized world. The mechanism of HFP is primarily related to the ingestion of high levels of histamine, but other related compounds and drug interactions are involved to produce the syndrome. Although HFP is not a fatal intoxication, it can be debilitating. HFP is easily recognized with a proper clinical history and foresight to its existence, and can be managed successfully with histamine blockers and supportive care. It is also an easily preventable poisoning through the proper regulation and handling of fish.

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