ADVERSE REACTIONS TO FISH

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ABSTRACT
Adverse reactions to seafood and particularly fish are frequently encountered worldwide, including in Southern Africa. We present a case study of what is typically experienced in the domestic and clinical setting and describe the most frequent causes. This article gives a holistic outlook on adverse reactions to fish, other than allergy to fish, from a South African perspective. The review includes infection by and allergy to Anisakis, ‘iodine allergy’, histamine sensitivity, unabsorbable wax esters, ciguatera poisoning, heavy metal toxicity and bacterial contamination.

CASE STUDY
A 40-year-old man experienced a couple of episodes of acute, generalised urticaria within minutes of having a meal that included tuna. He had eaten tuna before on many occasions without any adverse reactions and therefore assumed that it was something else in the meal that had caused the reaction. He continued to eat tuna without experiencing urticaria every time. In total, he reacted three times after the initial reaction. This occurred over a period of 20 months and involved more or less the same amount of tuna every time. He did not react to physical contact with fish and did not eat canned tuna.

The patient had never shown any type of reaction to any other fish species. His wife, a dietitian, monitored his dietary intake carefully, trying to determine whether there was a correlation between his intake and the reactions.

Thought process
What could be possible causes for his reaction?

a. He was reacting to the tuna.
b. He was reacting to something else in the meal.
c. He was reacting to something in the environment while he was eating the meal.

His wife could not pick up any element in the meal other than tuna that was consistently associated with the reaction. No clues were indicated by the environment. Three out of the four reactions occurred after eating tuna in a specific restaurant, but he had also eaten tuna at that restaurant without any reaction.

Thought process
Could one react to tuna on one occasion and not the next? What type of reaction could it be: an allergy, intolerance or toxic reaction?

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Possibilities
Allergy
a. He was reacting to a heat-labile allergen in tuna. The fish may not have been cooked through on the occasions that he reacted to it.
b. The fish he was eating was not always tuna; i.e. he was truly allergic to tuna, but at the times he did not react to the ‘tuna’, he was eating another type of fish. (This, however, was not the case.)
c. The preparation method was not always the same (e.g. on some occasions spices were added, and these may have caused the reaction).

Intolerance
d. He reacted to histamine in tuna, as histamine intolerance can present with allergy-like symptoms. The fish may not have been stored properly on the occasions that he reacted, so that it had increased levels of histamine.

If the patient was sensitive to histamine and he had not reacted to other histamine-containing foods before, it would indicate that he reacted to a high dose of histamine. On the occasions that he reacted to tuna, the fish could have contained high levels of histamine (which is formed even in optimally stored tuna). But the restaurant owner claimed that the fish he served were freshly caught and served. This possibility was therefore excluded.

Toxic reaction
e. Whatever induced his reaction (e.g. bacteria or toxin) was ‘contaminating’ the fish and would therefore not always be present in tuna. But if he were reacting to a contaminant, then others eating the same meal in the restaurant would most likely also have been affected.

The patient’s total IgE and serum-specific IgE to tuna were measured. The total IgE was increased, but the IgE to tuna was normal.

What did this indicate?
Total IgE may be raised for a number of reasons, including sensitisation to one or more allergens. In this case, the allergen was not tuna. Allergic reactions to tuna may be mediated via IgE or cellular mechanisms. His wife decided to contact specialists in the field and was told to consider an allergy to Anisakis simplex. Allergy to this fish parasite is quite commonly found in Europe and Japan and is difficult to distinguish from regular allergy to fish. A serum-specific IgE test to this parasite was performed and a strong IgE response confirmed the diagnosis.

THE FISH PARASITE ANISAKIS
Allergy to fish has been widely discussed in the literature. There are, however, other factors relating to fish that can also cause an allergy, e.g. the fish parasite Anisakis. Anisakis or cod worm is a seafood-borne parasite that can cause two major problems in humans: infection (anisakiasis) and allergic reactions. Various studies have shown that up to 80% of fish samples can be infested by Anisakis simplex, the most common...
European Anisakis species. In Southern Africa the infestation rates for *Anisakis pegreffii* (our local species) are very high for species such as snoek, yellowtail or hake. The lifecycle of this parasite begins in the stomachs of whales and dolphins. Fertilised eggs from the female parasite are passed with the host’s faeces, and the eggs develop into larvae that hatch in seawater. These larvae infect minute crustaceans, in which they grow and become infective for the next set of hosts, which includes fish. Evidence exists that the nematode larvae move from the viscera to the flesh if the fish hosts are not gutted promptly after catching and if the cold-chain is broken.

The current international regulations on food fish and other fish products require the visual examination of the fish for visible parasites, and freezing at -35°C for >15 hours. This will definitely kill the worm; however, it has been demonstrated that certain *Anisakis* allergens are very stable against denaturation by heat or cold.

**Infection**

Humans become accidental hosts of the larvae by eating raw, undercooked or pickled fish, resulting in clinical symptoms. In a typical reaction, the worm penetrates the intestinal mucosa, and gastro-intestinal symptoms may occur in the first hour but can take up to 6 hours to develop. However, the worm is expelled after about 3 weeks by the immune system. During the time spent in humans, the worm releases a wide range of proteins, somatic and excretory, some of which seem to have immunological similarities to common allergens. Very probably during this period, sensitisation to *Anisakis*-derived allergens is taking place. The clinical manifestations vary from gastro-intestinal reactions to urticaria, angioedema and life-threatening anaphylactic shock and bronchoconstriction. It is not always easy to differentiate between infestation and an allergic reaction.

**Allergy**

During the period of infection, the immune system is exposed to a wide range of proteins. Therefore, allergic reactions to *Anisakis* mediated by IgE antibodies may be mistaken for a seafood allergy, as revealed by a study from Japan, where mackerel-induced urticaria was more often caused by *Anisakis* than by the fish itself. A study in Spain found that allergy to *Anisakis* was more frequent than fish allergy, and sensitisation much higher. Allergic reactions to this parasite should be suspected when allergic-like reactions occur after eating seafood, yet the results of serum-specific tests to seafood are negative. Reactions often occur intermittently after eating seafood rather than on every occasion. Allergic reactions are also experienced after handling infected fish and/or inhaling aerosolised allergens. Fig. 1 illustrates the clinical manifestations. Occupational exposure upon inhaling particles of *Anisakis simplex* (through cutting fish and inhaling fish flour) have been reported to cause conjunctivitis (perennial itching, burning and redness of the eyes, with increased tearing) and asthma. A study investigating these incidences in the South African context is currently being conducted by Dr M Jeebhay (School of Public Health, UCT), and colleagues.

Important measures to protect against infection with live parasites are deep-freezing the fish for an extended period or cooking at temperatures higher than 60°C for 10 minutes. However, this may not protect against reactions to the allergens in sensitised individuals. The heat-stability of *Anisakis* allergens has been demonstrated, although there have been reports of sensitised individuals (with a history of severe allergic disease to the parasite) who did not react to the dead larvae. The clinical reality is that sensitised individuals may react to cooked, frozen or canned fish.

It still remains unclear whether the development of *Anisakis* allergy requires prior exposure to living parasites, why some people vary in characteristics of *Anisakis* allergy symptoms, and which specific allergens are involved. A current study being conducted by Lopata and Brombacher (Division of Immunology, UCT) addresses these important clinical questions.

**IODINE**

Individuals may be led to believe that they are allergic to iodine, particularly after experiencing a reaction to iodated X-ray contrast media. To date, research has not confirmed that the condition ‘iodine allergy’ exists or that there is any cross-reactivity between the three sources of iodine, namely dietary iodine, iodated contrast media and povidone iodine. Research indicates that these patients should avoid the contrast media alone, and not dietary sources of iodine as well.

There are also, however, no reports in the literature that prove that adverse reactions to elemental iodine (in whatever form) do not occur. Either iodine allergy is very rare or does not exist, or the methodology used in studies examining iodine allergy was flawed.

To date, no relationship has been established between a sensitivity to iodine and seafood or fish allergy.

**HISTAMINE SENSITIVITY**

Histamine is a vaso-active amine that can induce allergy-like symptoms in sensitive individuals. The reactions, however, are not IgE-mediated but of an intolerance type.

Histamine may occur naturally at different concentrations in some foods such as fish, wine and cheese. The level present in fish can increase when fish is not properly refrigerated or if refrigeration is delayed (even though the fish is not rancid). The amino acid histidine (naturally present in fish) is converted by histidine decarboxylase to histamine at an optimal temperature of 20-30°C. However, certain histamine-producing bacteria have optimal temperature ranges far below 10°C. The longer the fish is not properly stored and remains ungutted, the higher the histamine content. Fish involved include mackerel, tuna, herring, sardines, marlin, anchovies and bluefish. Affected fish often have a metallic or peppery taste. The onset of symptoms is usually within a few minutes after ingestion of the food, and the duration of symptoms ranges from a few hours to 24 hours. Reactions that have been recorded to histamine are flushing, headache, dizziness, burning sensation in the mouth.
and throat, peppery taste, abdominal cramps, nausea, vomiting, diarrhoea, urticaria, generalised pruritus, sneezing, bronchospasm, asthma, respiratory distress, hypotension and eczema. A histamine reaction may often be indistinguishable from an allergy reaction. Histamine has also been implicated as an important mediator in certain types of headache that are thought to differ from migraine and tend to be located to one side of the head and face. Some studies have shown that histamine-intolerant individuals have a deficiency of the enzyme diamine oxidase, in the jejunal mucosa, resulting in diminished histamine degradation and absorption in the gastrointestinal tract. Up to 94 drugs have been shown to inhibit diamine oxidase, including dihydralazine, isoniazid, clavulanic acid, promethazine, verapamil and metoclopramide. Alcohol is seen as a histamine liberator; i.e. it can enhance the effect of histamine in sensitive individuals. In pregnancy we find the opposite effect, with diamine oxidase levels reaching up to 500-fold of normal values, giving the fetus increased protection against histamine poisoning. Histamine levels in freshly caught fish are less than 1 mg/100 g of fish, but if the fish is left at room temperature, this can increase to as much as 100 mg histamine/100 g of fish within 12 hours. Hazardous levels are thought to be 50 mg /100 g or more. But it is important to note that high levels of histamine do not necessarily occur in fish that are rancid. A recent study in the Western Cape (publication in preparation) by Lopata, Steinman and Morrom was undertaken as a result of frequent complaints of food retailers about allergy-like symptoms in customers consuming yellowtail. It was shown that ‘fresh’ fish samples, obtained from local fish markets, produced large amounts of histamine in as little as 1 day of storage at 4°C. Fish species implicated are yellowtail, tuna and snoek, and the levels of histamine seem to correlate with histidine content. The term ‘scombroid poisoning’ originates from the fact that spoiled fish from the family Scombroidae (e.g. tuna, mackerel and bonito) were originally implicated in incidents of this type of poisoning. In addition, it is not only fish that can cause histamine reactions, but also wine, cheese and sauerkraut. UNABSORbable wax esters in fish The passage of oil through the rectum has been observed following the ingestion of ‘butterfish’; this is simply a food idiosyncrasy. There have only been a few articles in the literature on this subject: 1 in a South African journal and 3 in a single issue of Communicable Diseases Intelligence in 2002. The latter journal reported 3 ‘outbreaks’ in Victoria, Australia. There had also been a similar communication from New South Wales in October 2001. Following media reports on this issue in Australia, there have been numerous additional reports (60 before 2002). One of the authors has, while lecturing, asked his audience of food manufacturers and scientists on several occasions how many of them have experienced this phenomenon. Around half would put up their hands. There is probably significant under-reporting of this condition, as the symptoms can be mild and short-lived. But for some affected individuals, they can be quite dramatic and embarrassing, as experienced on separate occasions by two of the authors. Also, the incidence is likely to increase as butterfish is eaten more commonly.
Wax esters consist of fatty acids esterified to similarly long-chain alcohols. Such compounds are found in animal, plant and microbial tissues, and they have a variety of functions such as energy storage, waterproofing and even echo-location. The ultimate source of the wax esters (or at least the fatty alcohol component) is likely to be zooplankton. However, most predators of zooplankton such as the herring, sardine and baleen whale do not accumulate wax esters. It has been presumed that these animals cannot metabolise the wax esters. Two wax-accumulating vertebrates are the coelacanth (Latimeria chalumnae) and the sperm whale.25

There are few data available to identify people susceptible to this type of oily diarrhoea. One study found no association between the development of the symptoms and body mass index, age or general health status. Researchers found, however, that individuals with bowel problems, malabsorption or pregnancy may be at increased risk. It is also possible that seasonal and geographic differences may influence the level of indigestible wax ester content in fish.24,30

There have been reports of toxic effects in experimental animals but not in humans. Although many who experience this phenomenon are concerned by its effects (including social embarrassment and having to throw away clothes soiled with the oil), the condition appears to be medically harmless with the quantities of fish that are normally consumed.25

Ciguatera poisoning is triggered by eating tropical reef fish that have fed on toxic algae, which produce neurotoxins called ciguatoxins. Ciguatoxins are lipid-soluble, heat-stable polyether toxins accumulated in the muscles of many subtropical and tropical marine finfish.31 Ciguatoxins are produced by Gambierdiscus toxicus, a marine dinoflagellate that lives on macro-algae. They arise from biotransformation of related toxins (gambieroxins) after ingestion by the fish. The toxins and their metabolites are concentrated upwards in the food chain when carnivorous fish prey on smaller herbivorous fish by eating the algae. More than 400 species of fish can be vectors of ciguatoxins. Examples are Spanish mackerel, red snapper, barracuda, sea bass, eels and kingfish. Ciguateric fish look, taste and smell normal, and the toxicity is not diminished by freezing or cooking. The detection of toxins in fish or toxin-exposed humans remains a problem.

Humans are exposed at the end of the food chain. The disease is characterised by gastro-intestinal, neurological and cardiovascular disturbances. There is no immunity, the toxins are cumulative, and symptoms may persist for months or years or recur periodically. While ciguatera is probably the most frequently reported seafood-related illness, with up to 50 000 victims annually, considerable under-reporting still occurs, which has implications for both the investigation and control of outbreaks.26,32
Ciguatera is most prevalent in sub-tropical and tropical Pacific and Indian Ocean regions, and in the tropical Caribbean. However, as reef fish are increasingly exported to other areas (alive, fresh or preserved), ciguatera occurs far from tropical oceans, and as a result has become a world health problem. There is very little information on ciguatera exposure on African coastlines. However, the factors which favour ciguatera, such as suitable water temperature, abundance of high-risk fish species, and the dependence of communities and subsistence fisheries on coastal fishing, pose a risk of ciguatera exposure.

HEAVY METAL TOXICITY

Although several metals can accumulate in fish, mercury is the most common. Mercury is a naturally occurring element, found in soil and rocks and also in lakes, streams and oceans. It is also released into the environment by human activities. The mercury in lakes, streams and oceans can be transformed by bacteria into methyl mercury, an organic and more toxic form. This form of mercury is the predominant form present in the flesh of fish, and humans are exposed to it when ingesting the fish. High levels of mercury can damage the nervous system, but the effects of trace amounts are not known. Long-term studies are being conducted to determine the effects of low levels of mercury, especially in young children.23,34

Since methyl mercury tends to concentrate or ‘biomagnify’ through the food chain, predator fish species tend to have higher levels than non-predator fish species. Some countries have set limits for the mercury content in seafood, e.g. 1.0 mg/kg for finfish that are known to contain high levels of mercury (such as swordfish, southern bluefin tuna, barramundi, ling, orange roughy, rays and shark), and 0.5 mg/kg for all other species of finfish, crustaceans and molluscs. In some countries the public is advised to limit consumption of shark, marlin, swordfish and fresh and frozen tuna to only once per week. Pregnant women, women of childbearing age and young children should limit their intake even more.33,34

BACTERIAL CONTAMINATION

Bacterial contamination of seafood can result in two types of reactions:

- a pharmacological reaction in sensitive individuals caused by the production of high levels of substances such as histamine and cadaverine (see ‘Histamine sensitivity’ above)
- bacterial food poisoning caused by bacteria such as *Salmonella* and *Listeria monocytogenes*, often present in fish harvested in waters containing untreated sewage.39

CONCLUSION

In conclusion, it is important for health professionals to differentiate allergy from other sporadic causes of adverse reaction to fish. An incorrect diagnosis of fish allergy may result in life-long avoidance of fish and other lifestyle changes that may not have been necessary at all.

REFERENCES

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