Neurological disorders associated with the consumption of shellfish : health professionals still unfamiliar with their diagnosis

he consumption of bivalve shellfish (mussels, oysters, etc.) can cause serious and even fatal neurological disorders due to the accumulation of natural toxins – whose levels are regulated – in their flesh. In June 2019, a specific case of poisoning associated with the consumption of mussels contaminated by paralytic toxins drew the attention of ANSES and the French Poison Control Centres (PCCs) to a possible lack of knowledge of poisoning with marine neurotoxins in other cases. A retrospective study of cases of shellfish poisoning recorded by the PCCs from 2012 to 2019, and of regulatory monitoring data for shellfish production areas, led to the identification of 15 probable cases of poisoning with neurotoxins. Prospective monitoring for shellfish poisoning causing neurological signs has since been introduced based on the PCCs national database.

Mussels, oysters, clams, scallops and other bivalve shellfish have a two-part shell containing the flesh of the marine mollusc.

These seafood products, which have long been part of the diet of human populations in coastal areas, are consumed throughout France and can cause poisoning.

These shellfish filter large amounts of water as they feed. They therefore absorb the contaminants contained in the water, such as pathogenic micro-organisms (bacteria, viruses), toxic microalgae, heavy metals and other (organic) pollutants, which accumulate in their flesh and can make them unfit for consumption.

More specifically, some species of phytoplankton (microscopic microalgae) produce toxins called phycotoxins; most of them cause digestive signs (diarrheic toxins), although others can be responsible for sometimes serious and even fatal neurological signs of rapid onset: this is the case of the paralytic toxins produced by algae of the genus *Alexandrium*, the best known of which are saxitoxin and its derivatives; there are also amnesic toxins, in particular domoic acid, produced by algae of the genus *Pseudo-nitzschia*, as well as toxins that have emerged more recently in Europe (pinnatoxins, brevetoxins, etc.). The toxins produced by shellfish are not destroyed by cooking. Levels of paralytic toxins – including saxitoxins – and domoic acid in seafood products

are regulated [1]. The thresholds are based on the consumption of "reasonable" amounts. Checks are organised in shellfish production areas. If the thresholds are exceeded, the health authorities temporarily close the shellfish production areas, or in the event of imports, withdraw the contaminated batches from the market, in order to protect the health of consumers.

In France, under the responsibility of the Directorate General for Food, there is a network (REPHYTOX) for monitoring regulated phycotoxins for which monitoring is mandatory (diarrheic toxins, saxitoxins and domoic acid) in shellfish from coastal production areas; it is supplemented by a network for monitoring emerging toxins (EMERGTOX[1]). Depending on the toxin in question, analyses are conducted by the laboratories of IFREMER[2] or by ANSES's National Reference Laboratory for marine biotoxins. Cases of shellfish contamination by saxitoxins were first observed in France in 1988; for domoic acid, the first cases of shellfish contamination date back to 2000 [2].

1.The EMERGTOX network also reinforces the monitoring of regulated toxins, in areas not yet affected by these toxins.
2. IFREMER: French Research Institute for Exploitation of the Sea.

An alert involving imported mussels drew ANSES's attention

In June 2019, RASFF informed the competent European authorities of two batches of mussels imported from Italy that were contaminated by saxitoxins. Although the levels of saxitoxins, measured as part of a self-check by the distributor, did not exceed the regulatory limits, the distributor had withdrawn the product from the market as a precautionary measure. Some batches had nonetheless been distributed and consumed. During the same period, a Poison Control Centre (PCC) informed ANSES of the case of an individual who had developed neurological signs potentially associated with the consumption of contaminated mussels [3]. This person had eaten a large quantity of mussels during two consecutive meals and within two hours of each of the meals, had experienced digestive problems, paraesthesia (or tingling) of the hands and feet, tremors and dizziness. They went to the emergency department and their symptoms spontaneously regressed. The causal relationship with the consumption of mussels was probable; the symptoms and the time to onset were consistent with the clinical picture expected with this type of poisoning. However, confirmation of this assumption met with two difficulties: the concentrations of saxitoxins measured in the mussels from the implicated batch (313 µg/kg mussel flesh) were below the regulatory threshold (800 µg/kg shellfish flesh); and no biological samples (blood, urine, etc.) had been collected to test for saxitoxins. It should be noted that these blood and urine analyses are not routinely performed by biology laboratories. The link between the symptoms and exposure to paralytic toxins was established thanks to the report received by RASFF from the product's distributor, which was not mandatory since the measured concentrations were below the regulatory limit.

A retrospective study of CAP data found cases of poisoning with marine neurotoxins that had gone unnoticed

This alert highlighted the probable under-diagnosis of cases of human poisoning with neurotoxic phycotoxins related to the consumption of shellfish. A retrospective study of cases of poisoning with bivalve shellfish recorded in the PCCs national database from 1 January 2012 to 31 December 2019 was therefore undertaken by ANSES, the PCCs' network and IFREMER. During this study period, 619 cases of food poisoning, all types of symptoms combined, were reported and split into 452 "files" (or shellfish meals, as one meal could be shared by several guests). Nineteen per cent of the meals involved collective food poisoning, with two to eight cases.

Fifty percent of the meals responsible for the poisoning included oysters; 33% included mussels, 11% scallops, 2% mussels and oysters, and the rest (4%) other shellfish.

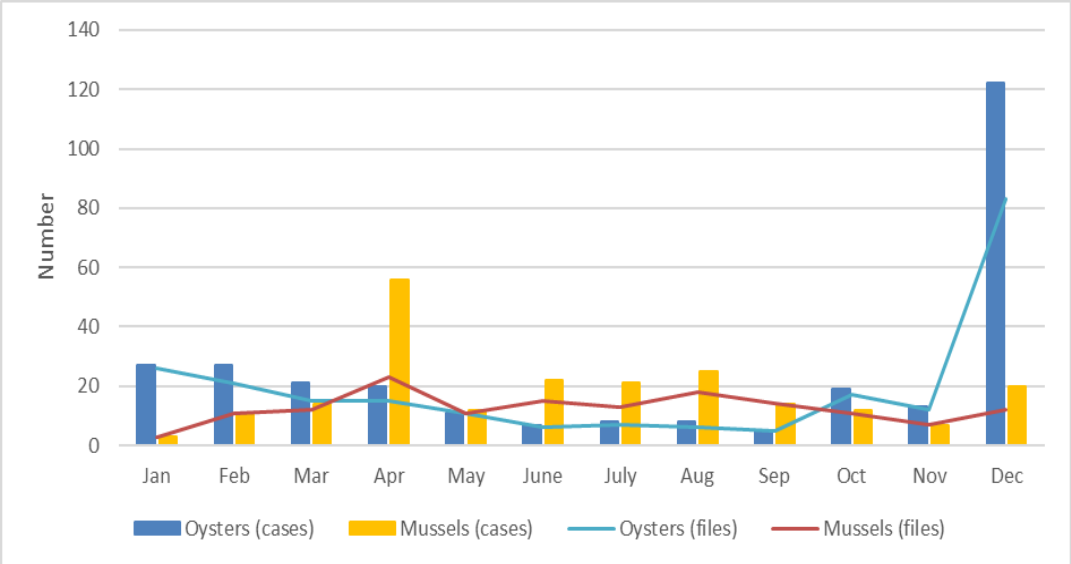

Figure 1: Monthly distribution of poisonings with oysters and mussels, all symptoms combined (number of cases and number of files or meals). January 2012 – December 2019 (Oysters: N cases=288 and N files=224; Mussels: N cases=217 and N files=150). Source: PCCs national database.

3.RASFF: Rapid Alert System for Food and Feed (alert system for EU Member States). RASFF alert notifications are sent when a food or feed on the market in the European Union may be contaminated, regardless of the agent (chemical, biological, etc.). The DGCCRF is RASFF's correspondent for France.

The monthly distribution of the cumulative number of poisoned individuals and meals involved over the 2012 to 2019 study period showed that oyster poisonings primarily occurred in December (42% of cases and 37% of oyster meals) and that mussel poisonings were most common in April (26% of cases and 15% of mussel meals) (Figure 1). However, poisonings with oysters and mussels could be observed all year long. Moreover, the large number of poisonings with oysters in December, added up over the 2012 to 2019 period, was partly due to several clustered cases of acute gastro-enteritis of viral origin (norovirus) that occurred in 2019 [4].

While, as expected, 88% of the poisoned individuals developed one or more digestive signs (vomiting for 61%, diarrhea for 47%, nausea for 27%, etc.), 22% (134 individuals) experienced at least one neurological sign (headaches for 10%, dizziness for 4%, paraesthesia for 3%, etc.), alone or combined with other symptoms. Three-quarters of the individuals who presented with at least one neurological sign also reported a digestive sign, which helped identify the possible food origin of the symptoms. The type of shellfish consumed (mussels, oysters, scallops, etc.) did not differ between the individuals who experienced a neurological sign and those who did not.

A PCC toxicologist thoroughly reread each of the 134 reports of cases where a neurological sign was mentioned, leading to the *a posteriori* identification of 15 cases that may have been due to the consumption of bivalve shellfish contaminated by a marine neurotoxin: 14 cases corresponded to a paralytic syndrome (suggestive of saxitoxins) and one to an amnesic syndrome (suggestive of domoic acid). No poisoning with other marine neurotoxins was suspected based on the available information.

The diagnosis was made retrospectively based on the coincidence between the described clinical signs, the report of shellfish contamination in monitored production areas (REPHYTOX) – or the RASFF notification – and the origin of the shellfish when this was known. No testing for marine neurotoxins (saxitoxins, domoic acid, etc.) was performed in the blood or urine of these 15 patients.

The 14 individuals with paralytic syndrome had shared 11 meals; 10 of them had eaten mussels, whether alone or combined with other shellfish (seven meals), while the others had eaten oysters, scallops or clams.

Six individuals had developed paraesthesia, affecting the hands and/or feet in four cases and the mouth in the two others. Five individuals had experienced muscle pain or cramps; two of these had also developed paraesthesia. Memory disorders had also been reported by family members of two individuals, raising the possibility of amnesic syndrome associated with paralytic syndrome.

While the severity of the reported symptoms was mild in 10 cases, four individuals experienced more severe or persistent neurological symptoms: bilateral paraesthesia of the hands and/or feet, ascending paraesthesia from the hand to arm, and associated muscle stiffness. The symptoms spontaneously regressed within 12 hours in the 11 cases where the clinical outcome was known.

Reading of the PCC files helped determine the origin of the consumed shellfish for six meals (eight individuals); this was retrospectively linked to a shellfish production area where high levels of saxitoxins, or even levels exceeding the regulatory threshold, had been identified for four meals; for the two others, it was linked to the RASFF alert notification from June 2019 for mussels imported from Italy.

Lastly, the 15th individual had developed memory disorders and severe mental confusion requiring them to be admitted to hospital in intensive care, following the consumption of dog cockles and whelks. The origin of the shellfish was known, and the REPHYTOX data for the production area from the same period showed levels of domoic acid above the regulatory threshold, suggesting amnesic syndrome. The patient recovered.

Measures should immediately be taken when a case is suspected!

Failure to diagnose neurotoxic syndrome, due to a lack of information about the shellfish involved, can be detrimental to the care of patients. First of all, any healthcare professional suspecting such poisoning should immediately contact a Poison Control Centre to optimise patient care. Following this study, the PCCs developed a specific questionnaire to collect all data necessary to determine, from the first call, the steps to be taken in the event of an individual reporting a neurological sign after consuming shellfish, so as to identify any suspected case. In this situation, it is necessary to investigate the clinical signs described in syndromes associated with marine neurotoxins, estimate the amount of shellfish ingested, and document their origin, place of purchase and production area. It is also important to ask the poisoned individuals to keep and freeze any meal leftovers, which may be used for subsequent analyses. The individual(s) should be referred to the emergency department for the collection of biological samples that may be stored (in particular for *a posteriori* testing for saxitoxins in urine) and will serve to confirm the poisoning.

It is essential to determine the origin of the shellfish to find information about potential toxins detected by REPHYTOX or RASFF notifications involving imported contaminated shellfish. These data contribute significantly to the diagnosis. It should be noted that from the time these toxins started to be monitored to the present day *(March 2021)*, there have been 19 RASFF notifications involving shellfish distributed in or imported into France and contaminated by paralytic toxins; 15 have involved amnesic toxins. When poisoning is associated with shellfish gathered by recreational harvesters in uncontrolled areas, it is essential to measure levels of toxins in unconsumed shellfish.

Lastly, in December 2020, ANSES and the PCCs introduced a system for the daily automatic monitoring of cases of shellfish poisoning recorded in the PCCs national database, to detect any suspected case the day following the call to the PCC. The aims are to launch investigations, alert the competent authorities, and inform the population as soon as possible.

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References

[1] Regulation (EC) No 854/2004 of the European Parliament and of the Council of 29 April 2004 laying down specific rules for the organisation of official controls on products of animal origin intended for human consumption.

[2] Belin, C., Soudant, D., & Amzil, Z. (2020). Three decades of data on phytoplankton and phycotoxins on the French coast: Lessons from REPHY and REPHYTOX. Harmful Algae, 101733. doi:https://doi.org/10.1016/j.hal.2019.101733

[3] N Delcourt, N Arnich, S Sinno-Tellier, N Franchitto. Mild paralytic shellfish poisoning (PSP) after ingestion of mussels contaminated below the European regulatory limit. Clin Toxicol. 2020 Jul 3;1-2.

[4] Toxi-infections alimentaires collectives suspectées d'être liées à la consommation de coquillages crus, bilan épidémiologique au 8 janvier 2020. *Santé publique France*. Online article. Updated on 10 January 2020. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-infectieuses-d-origine-alimentaire/toxi-infections-alimentaires-collectives/articles/toxi-infections-alimentaires-collectives-suspectees-d-etre-liees-a-la-consommation-de-coquillages-crus-bilan-epidemiologique-au-8-janvier-2020