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Human poisonings by neurotoxic phycotoxins related to the consumption of shellfish: study of cases registered by the French Poison Control Centres from 2012 to 2019

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Abstract :

Context

In June 2019, a paralytic shellfish poisoning (PSP) case related to the consumption of mussels contaminated by saxitoxins at a concentration below the regulatory threshold came to the attention of the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). This pointed to probable undetected human cases of poisoning by neurotoxic phycotoxins.

Methods

We conducted a retrospective study of poisoning cases by bivalve shellfish (oysters, mussels and scallops) recorded by the French Poison Control Centres (PCC) from 2012 to 2019. All medical records were reviewed by a toxicologist.

Cases that could be related to neurotoxic phycotoxins were selected and described. Diagnosis was based on symptoms compatible with ingestion of contaminated shellfish and on contamination data for the shellfish production area (analysed by the French Research Institute for Exploitation of the Sea, Ifremer),

or notifications to the European Rapid Alert System for Food and Feed when the origin of the shellfish was known.

Results

Among the 619 shellfish poisoning cases recorded by the PCCs from 2012 to 2019, 22% (n = 134) had reported at least one neurological symptom (headache, dizziness or paraesthesia). Review of medical records for the 134 patients led to suspicion of 14 cases of PSP and one case of amnesic shellfish poisoning. Five patients experienced persistent neurological symptoms. Marine toxins were not tested for in the blood or urine of these patients.

Conclusion

This retrospective identification of cases strongly suspected of being related to neurotoxic phycotoxins led ANSES, PCCs and Ifremer to develop a specific questionnaire and to recommend actions to take when neurological symptoms related to shellfish consumption are reported to a PCC. Daily monitoring of shellfish poisoning cases registered in the national PCCs database was also implemented in order to rapidly detect any suspicious cases, alert the competent authorities, and warn the general population.

Keywords : Phycotoxins, poison control centre, shellfish, saxitoxin, epidemiology

Introduction

In June 2019, the Rapid Alert System for Feed and Food (RASFF) informed the competent European authorities of two batches of mussels imported from Italy that were contaminated by saxitoxin. During the same period, a Poison Control Centre (PCC) reported the case of a person who had developed neurological signs potentially associated with the consumption of contaminated mussels to the French National Agency for Food, Environmental and Occupational Health and Safety (ANSES), responsible for coordinating toxicovigilance in France (Delcourt *et al*., 2021). The symptoms and the time to onset were consistent with paralytic shellfish poisoning (PSP) according to the US Centers for Disease Control definition of PSP (McLaughlin *et al*., 2011). However, confirmation of this assumption met with two difficulties: the saxitoxin concentrations measured in the mussels from the implicated batch (313 µg eq STX kg^{-1} mussel flesh) were below the regulatory threshold (800 µg eq STX kg^{-1} shellfish flesh); no biological samples (blood, urine, etc.) had been collected to test for saxitoxin. The link between the symptoms and exposure to paralytic toxins was established based on the report received by the RASFF from the product distributor, which was not mandatory since the measured concentrations were below the regulatory limit. This alert highlights the probable under-diagnosis of human poisoning cases with neurotoxic phycotoxins, since the link between shellfish consumption and neurological signs is, depending on the situation, neither routinely sought nor established.

In this context, ANSES carried out a review of bivalve shellfish poisoning cases recorded by the French PCCs, looking for a link with environmental monitoring data when possible, specifically in order to identify those cases presenting neurological signs compatible with neurotoxic phycotoxins.

Material and Methods

Study design

This retrospective descriptive study was based on symptomatic poisoning cases related to the consumption of shellfish recorded by all of the French PCCs between the 1st of January 2012 and the 31st of December 2019.

Case definition

Cases were defined as symptomatic human poisoning in relation to bivalve mollusc consumption in France, regardless of symptomatology, registered by the PCCs. Cases of poisoning that occurred abroad, or with no causality between the suspected exposure agent and the symptoms, or without symptoms, were excluded from the study.

Data were extracted from the French PCC national database (SICAP), where all PCC cases, corresponding to "patients", are collected in medical records, corresponding to "events", each event (or shellfish meal in this study) containing either a single case or collective cases related to the same exposure. Among included cases, those with neurological symptoms were selected. A toxicologist reviewed all the medical records in which at least one neurological symptom was reported to specifically search for and describe cases that could be related to

neurotoxic phycotoxins, taking into account the type of symptoms and their time of onset after shellfish consumption. Cases with symptoms suggestive of an allergic reaction were excluded. The diagnosis was made retrospectively based on the clinical signs recorded, as well as, when the origin of the shellfish was known, co-occurrence with shellfish contamination reported in the monitored production areas (based on REPHYTOX database) or RASFF notification of imported products.

The REPHYTOX network, whose data are analysed by the French Research Institute for Exploitation of the Sea (Ifremer), under the authority of the Ministry of Agriculture and Food, collects samples from several hundred shellfish sites. This is sufficient to provide the authorities in charge of public health safety with information to make decisions on bans in harvesting areas.

Results and Discussion

Among the 727 cases coded as shellfish poisoning extracted from the SICAP during the study period, we included 619 patients, all types of symptoms combined, distributed in 452 events. In 19.5% of events, the number of patients per event was between two and eight. We excluded 108 cases unrelated to shellfish consumption, or with no causal link, or for which shellfish was consumed abroad. Fifty percent of the 452 included meals involved oysters, 33% mussels, 11% scallops, 2% mussels and oysters, and other shellfish for the remainder (4%).

Temporal distributions

As shown in figure 1, the annual trend of events (shellfish meals) remained steady from 2012 to 2017 and ranged from 58 to 42 during this period. The trend then increased gradually from 2018 to 2019, when 68 and 82 events were observed. The annual distribution of cases followed the same trend with more pronounced variations in numbers, since some events involved up to eight patients.

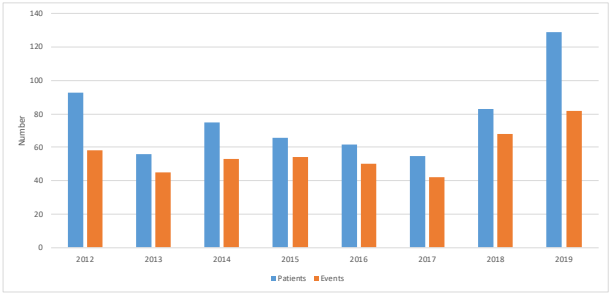

Fig. 1. Annual distribution of intoxicated patients and related events (shellfish meals). Data from January 2012 to December 2019. Source: SICAP.

We observed yearly seasonality in shellfish poisoning. Oyster poisoning showed winter seasonality, with a peak in December (representing 42% of patients and 37% of events) (Fig. 2). The seasonality of mussel poisoning was less pronounced, with poisoning occurring year-round.

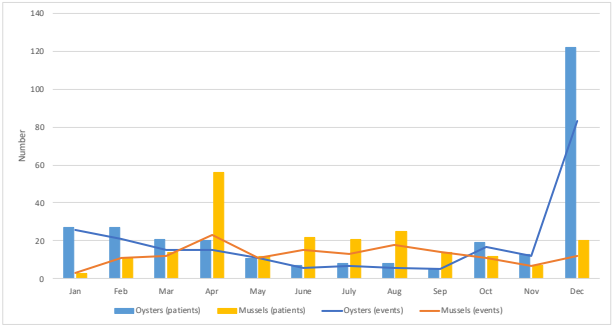

Fig. 2. Cumulative monthly distribution of intoxicated patients and related events (shellfish meals) with oysters and mussels. Data from January 2012 to December 2019. Source: SICAP.

Case description

Age of cases ranged from eight months to 93 years, with a mean age of 45.7 years ± 20.3 and a median age of 45 years (missing age for 8% of the 619 patients included). The sex ratio M/F was 0.7 (240/330).

While, as expected, 88% of the patients developed one or more digestive symptoms (vomiting for 61%, diarrhoea for 47%, and nausea for 27%), 22% (134 patients) experienced at least one neurological symptom (headache 10%, dizziness 4%, paraesthesia 3%), alone or combined with other symptoms. Three quarters of the patients who presented at least one neurological symptom also reported a digestive symptom, which helped identify the possible food origin of the symptoms.

Cases related to neurotoxic phycotoxins

Review of medical records for the 134 patients in whom a neurological sign was mentioned led to the *a posteriori* identification of 15 patients related to the consumption of bivalves contaminated by a neurotoxin phycotoxin. PSP was suspected for 14 patients and amnesic shellfish poisoning (ASP) for one patient. No poisoning with other marine neurotoxins (pinnatoxins, tetrodotoxins, or brevetoxins) was suspected based on the available information. Marine toxins (saxitoxin, domoic acid) were not tested for in the blood or urine of any of these patients.

The 14 patients with PSP had consumed 11 meals; 10 of them had eaten mussels, while the others had eaten oysters, scallops or clams. Six patients had developed paraesthesia, affecting their hands and/or their feet in four cases and the mouth in two cases; five patients had experienced muscle pain or cramps, two of these had also developed paraesthesia. Neurological symptoms occurred within 2 h and 30 min for half of the patients, and from 5 min to 72 h for all of them.

While the severity of the reported symptoms was mild (PSS1; Persson *et al*., 1998) in 10 cases, four patients experienced more severe or persistent neurological symptoms (PSS2): bilateral paraesthesia of the hands and/or the feet, ascending paraesthesia from the hand to the arm, and associated muscle stiffness. The symptoms spontaneously regressed within 12 h in the 11 patients where the clinical outcome was known.

The origin of the consumed shellfish was available in the medical record regarding six meals (eight cases). A specific episode of shellfish contamination in the harbour of the city of Brest, Brittany in 2012 was linked to one probable case of PSP. Similarly, other recurrent episodes of shellfish contamination in the Étang de Thau (lagoon on the Mediterranean coast) could have caused five cases of PSP from 2015 to 2016. Two other meals could be linked to the June 2019 RASFF alert notification concerning mussels imported from Italy.

Lastly, the 15th patient developed memory disorders and severe mental confusion (PSS3) following the consumption of dog cockles and whelks. As the origin of the shellfish was known, the REPHYTOX data from the same period showed concentrations of domoic acid above the regulatory threshold, suggesting ASP. The patient, who had been admitted to an intensive care unit, made a full recovery.

To our knowledge, this is the first time that human poisoning, recorded by the French PCCs, can be linked to contamination of

shellfish production areas, since the first recording of saxitoxin in shellfish production areas in France in 1988 and domoic acid in 1999.

However, the data should be interpreted with caution given that the cases collected by the PCCs are not exhaustive, and their representativeness remains unknown. People who present symptoms after a shellfish meal may consult a doctor or a pharmacist, go to the emergency department of a hospital, or choose self-medication, without calling a PCC.

Our 14 cases of PSP demonstrated the common findings of neurologic and gastrointestinal symptoms related to saxitoxin poisoning (Etheridge, 2010; Hurley *et al*., 2014). While four cases of PSP reported persistent neurological symptoms, no life-threatening cases or deaths occurred. Monitoring programs of shellfish poisoning by marine biotoxins have probably minimized the risk of severe human cases.

As toxicological assays of neurotoxins in human matrices (serum, urine) are currently not routinely performed by medical analysis laboratories, determination of the type and origin of the shellfish is essential in order to seek information on toxin concentrations detected by REPHYTOX or in RASFF notifications when shellfish have been imported.

ANSES, PCCs and Ifremer developed a specific guide to collect information when a person reports neurological signs after shellfish consumption and to recommend actions to take for further investigations. The patients should keep and freeze any meal leftovers for subsequent analyses. Measurement of toxin concentrations in unconsumed shellfish are key, especially when poisoning is associated with shellfish harvested from uncontrolled areas.

The suspected cases should be referred to the emergency department of a hospital, for collection of biological samples that may be frozen (in particular for *a posteriori* testing for marine toxins, even those not yet regulated in European countries such as pinnatoxins and brevetoxins). These samples will help to confirm the poisoning.

Daily automatic monitoring of cases of shellfish poisoning recorded in the PCC national database was also set up to detect any suspected case the day following the call to the PCC. The aims are to launch appropriate investigations, alert the competent authorities, and inform the population as soon as possible.

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