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Letter to the Editor

Surge in iatrogenic botulism cases in Europe: Threat perceptions and salient countering measures

Dear Editor,

Germany notified five iatrogenic botulism cases involving botulin neurotoxin type A (BoNT/A) injection on 7 March 2023 in individuals that underwent medical procedures in Turkish health institutions. A total of 71 cases were reported in four European countries, namely, Turkey, Germany, Austria and Switzerland by 17 March 2023, majority of them linked to Turkish hospitals in Istanbul and Izmir (https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON450). As the article is in its final stage getting revised, 16 more cases from the European region were reported (www.ecdc.europa.eu/en/news-events/botulism-iatrogenic-update-cases-europe-march-2023#:~:text=Since%20late%20February%202023%20and,%2C%20and%20T%C3%BCrkiye%20) till March–April 2023 with a break-up of 14 cases from Germany, and one case each reported from France and Switzerland. Thus, the total number of reported/confirmed cases stands at 87 as the article undergoes through its final revision (Table 1). Although the genesis of the medical condition is allegedly attributed to specific Turkish cities, the reported cases show that such a situation could be transboundary and possibly global due to the unrestricted and relatively easy international travelling. If not contained and nipped at the bud the seemingly one-off instance may sooner or later go out of hand affecting a larger chunk of the global population. As per the available data, the present cases related to intragastric administration of botulin neurotoxin (BoNT) to lose weight (weight-loss medical care). The products used for the purpose were seized by the Turkish medicines and medical devices agency for both iatrogenicity and latrogenicity examination and evaluation. Thus, there is 'toxic' risk for travellers to Turkey especially for medical procedures involving injecting BoNT intragastrically (https://www.ecdc.europa.eu/sites/default/files/documents/Communicable-Disease-Threats-Report-10-Mar-2023.pdf). In 2022, WHO alerted with five falsified BoNT product batches in Jordan and Turkey (May), the UK and Kuwait (June), and Poland (July) (https://www.ecdc.europa.eu/sites/default/files/documents/Communicable-Disease-Threats-Report-10-Mar-2023.pdf). Whether these batches were used to treat any reported case is unclear. Iatrogenic botulism was previously reported in Egypt and Turkey, often linked to the counterfeit or unlicensed BoNT. Turkish investigations reported that licensed BoNT products were administered for a purpose other than the approved intended (off-label) use.

Botulin neurotoxin of *Clostridium* causes neuroparalytic botulism. Produced anaerobically by Clostridium (C. botulinum, C. baratii, C. butyricum, and C. sporogenes), botulin is a fatal neurotoxin [1,2]. Although could be life-threatening, botulism cases associated with natural, accidental or potentially deliberate sources of infection is relatively rare [1]. However, an Egyptian study reported that seven patients that were injected with 200–300 IU BoNT-A intramuscularly to treat for cerebral palsy, one for spastic dystonia and one for hyperhidrosis developed botulism [1]. As per health authorities there, the cases related to Neuroxin®, a highly concentrated unlicensed and imported BoNT-A preparation. These cases were in the middle-aged adults, mostly in women. The clinical symptoms ranged from mild to severe, observed as headache, fatigue, blurred vision, dizziness, bilateral ptosis, dyspnea, dysphagia, neck weakness, general muscle weakness and swollen tongue.

Complete recovery period from botulin usually is weeks to months. Critical cases would need botulin antitoxin treatment with hospitalisation, including intensive care (in ICUs). 5–10% cases are fatal in foodborne botulism (https://www.ecdc.europa.eu/en/news-events/botulism-cases-europe-following-medical-interventions-botulinum-neurotoxin). Information on iatrogenic botulism mortality is limited. More such yet to identify/report cases, particularly among the travellers to Turkey for medical treatment involving BoNTs, is also possible. Travellers to Istanbul and Izmir for intragastric BoNT treatment are encouraged to seek medical advice if they experience symptoms of weakness, difficulty in breathing and/or swallowing.

Botulin neurotoxin (BoNT) is critically lethal and occurs in eight (A to H) serotypes [3,4]. Of these, three (A, B and E) are most common in human ailments. BoNT blocks the neuronal function that could lead to muscular and respiratory paralysis. It inhibits acetylcholine release from the motor neuron (at the presynapse) at the neuromuscular junction paralysing the muscle depending on the dose [3]. An active BoNT has two disulphide-bond linked chains, one heavy (~100 kDa) and one light (~50 kDa). The BoNT/receptor complex becomes endocytotic with the selective and irreversible binding of the heavy chain to the high-affinity surface receptors at the presynapse of the cholinergic neuron. As intragastric BoNT treatment in the obese may have high risk, the European Centre for Disease Prevention and Control (ECDC) strongly advices against it (https://www.ecdc.europa.eu/en/news-events/botulism-cases-europe-following-medical-interventions-botulinum-neurotoxin).

Early administration of botulin antitoxin is recommended as it could accelerate recovery [1]. However, its early diagnosis and rapid administration of the botulin antitoxins is challenging. The diagnosis rests on BoNT injection in recent past and its clinical fallouts. Further, the diagnosis of the same in iatrogenic botulism cases could be still challenging due to extremely low dose of toxin used and the timing for serum sampling at a potentially suboptimal phase. Only a few diagnostic procedures with better sensitivity than the classical mouse bioassay are validated for use on clinical specimen. Thus mouse bioassay is still regarded as a reference to detect BoNT in clinical samples. As investigations to ascertain the cases and due notification are going on, the countries at risk need to remain vigilant.

Whether the reported events were due to therapeutic or procedural issues in the concerned hospitals or the administered product had an issue is yet unclear. Turkish investigations revealed that although the BoNT product that was administered was licensed but was administered for unapproved use. Thus, licensed BoNT products injected

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Table 1
The iatrogenic botulism cases (since late February 2023 to 30 March 2023).

Country	Iatrogenic botulism cases
Germany	30
Austria	01
France	01
Switzerland	02
Turkey	53

intragastrically to treat obesity are medically not approved for it. Investigation remains open to hypothesise the possible reasons of intoxication. Although the ongoing investigation looks at the product quality and safety, medical error, or a BoNT overdose to determine the cause of intoxication, investigation against the parties involved is also recommended. Collaborating with the ECDC and affected parties, the WHO is carrying out the investigation, risk assessment, information sharing and event response. Further, a statutory warning of toxic effects and the risks may be adequately tackled, depending on the product use pattern. Before the situation blows out of proportion, preventing additional cases by deciphering the genesis of the disease, detecting it rapidly, and differentiating the outbreak type as natural, accidental or potentially deliberate is recommended. As it appears, BoNT is undoubtedly a double-edged sword manifesting clinical symptoms if not handle carefully while providing advanced medical intervention options to treat critical or cosmetic medical cases. In light of this, a 360° approach to reduce its ineffects and enhance its utility in line with One Health model shall be a befitting social, technical and medicolegal strategy.

Declaration of competing interest

There are no conflicts to declare.

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