

Generalised Urticaria in a Young Woman treated with Clomipramine and after Ingestion of Codfish

A Case Report

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We report a case of generalized dermatitis and itch induced by a possible drug-food interaction in a young woman who was consuming clomipramine for Obsessive Compulsive Disorder (OCD). A 33-year-old woman affected by anxiety symptoms presented to our observation for a clinical evaluation. After psychiatric evaluation, the diagnosis of OCD was performed according to DSM-IV-TR and a pharmacological treatment with clomipramine (75–100 mg/day) plus alprazolam (0.5 mg/day) was started. About one month later, the patient developed a severe generalized urticaria with intense itch. A new anamnesis revealed that on the day before the development of the skin rash, no other drug was consumed and the patient had eaten codfish; clomipramine was then gradually discontinued and changed into paroxetine (30 mg/day). At the moment the patient does not show any OCD related symptom and any adverse event to paroxetine treatment has been recorded. We postulate a possible interaction between clomipramine and codfish ingestion. Allergic potential of clomipramine was investigated, while clomipramine de-challenge induced a decrease of the skin rash, the drug re-challenge performed one month later did not induce any adverse event. In contrast, when the combined re-challenge of codfish and clomipramine was performed urticaria was newly observed. The Naranjo Probability Scale Score suggested a probable causal relationship between drug-food interaction and the skin rash. In conclusion, we suggest evaluating also the complete risk of drug-food interaction occurring on clomipramine treatment.

Introduction

Food-drug interactions have been reported to occur for a large variety of drugs. The causes of these interactions are mainly divided into pharmacodynamic and pharmacokinetic processes. Among the latter, drug metabolism plays a crucial role in drug interactions [9]. A metabolic food-drug interaction occurs when a

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certain food is able to change the activity of a drug-metabolizing enzyme, or when a drug is able to modify some metabolic pathways necessary for the food processing [9]. We report a case of generalized urticaria diagnosed in a young woman undergoing treatment with clomipramine, after ingestion of codfish.

Case

A 33-year-old woman (weight: 48 kg; height 155 cm), without any medical history of adverse drug reactions and with adequate renal and hepatic functions was admitted on December 2004 to the Psychiatric Unit of the "Mater Domini" University Hospital of Catanzaro for both the insurgence of anxiety symptoms and recurrent ideas concerning home-cleaning.

The patient was a housewife, without a history of allergic, autoimmune or rheumatologic diseases in her sons or parents. There was no history of alcohol or other drug abuse, and no significant past medical or surgical events. After psychiatric evaluation, the diagnosis of obsessive-compulsive disorder (OCD) was made according to DSM-IV-TR and treatment with clomipramine (75 mg/day) plus alprazolam (0.5 mg/day) were started. About one month later (12th January 2005) the patient was newly evaluated for the persistence of OCD related symptoms; therefore, clinicians increased the clomipramine doses to 100 mg/day. After seven days, a severe and generalized skin rash extended on trunk and arms with intense itch was observed.

On examination, her blood pressure was 110/70 mm Hg, heart rate 65 beats/min, respiratory rate 18 breaths/min and temperature 36.2 °C. No peripheral lymph nodes were observed. Cardiovascular, abdominal and respiratory relieves were normal. Blood chemical tests did not reveal any abnormality. Tests for hepatitis virus (HAV, HBV, HCV), Epstein-Barr virus (EBV), HIV, cytomegalovirus, and autoimmune serological manifestations (antimicrobial antibody, antismooth muscle antibodies, liver-kidney microsomal antibodies, thyroid peroxidase antibodies, and anti-double-stranded DNA) were negative.

Local examination of skin rash revealed papular eruption associated with itching and an increase in local skin temperature in most of body regions, especially on the trunk and all over the arms, but without regional positive lymph nodes.

On 20th January 2005, a steroid based pharmacological therapy was started without any significant improvement of symptoms. Then, on 24th January 2005, a new anamnesis excluded a recent history of allergic manifestations, related to drugs, herbal supplements, or contacts with chemical agents, but it revealed that on the day before the development of skin rash the patient ate codfish. The patient assessed that in the past the same food has always been well tolerated. At the beginning, considering the insurgence of skin rash as a well-known drug-own adverse event, clomipramine was gradually dismissed and changed to paroxetine (30 mg/day). About few days following the beginning of paroxetine (2nd February 2005) a new clinical evaluation showed a complete decrease in skin manifestations but also a lesser efficacy in the control of OCD symptoms. In agreement with the patient, we decided to further investigate the possible drug-food

interaction, and on 15th March 2005 the patient ate codfish during paroxetine treatment without any clinical manifestation. In order to evaluate the cause of skin rash, on 5th April 2005 clomipramine (100 mg/day) re-challenge was performed but no adverse event was registered, until on 12th May 2005 the patient ate again codfish during clomipramine treatment developing urticaria; therefore treatment with clomipramine was gradually dismissed and changed to paroxetine. In order to evaluate the relationship between the skin eruption and drug-food interaction, the Naranjo adverse probability scale was applied [14]. The Naranjo score estimates the probable relationship between drug-food interaction and skin manifestations. At the moment the patient does not show any OCD related symptom and any adverse event to paroxetine treatment has been recorded.

Discussion

In this paper we report a case of a young woman affected by OCD, who, during treatment with clomipramine, developed generalized skin rash manifestation, presumably induced by an interaction with codfish.

Clomipramine, a tricyclic antidepressant, is a potent serotonin reuptake inhibitor and may affect dopaminergic neurotransmission. The drug is well absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism induced by several isoforms of cytochrome P450 [2,4,12,27]. Clomipramine liver metabolism develops several metabolites; the major metabolite is nor-clomipramine, a potent noradrenaline reuptake inhibitor. Multiple controlled studies demonstrated clomipramine's efficacy in the treatment of OCD [6,8,22,23]. Interactions between clomipramine and barbiturates, haloperidol, monoamine oxidase inhibitors, and cigarette smoking have been documented [7]. The most common adverse effects of clomipramine are the well described anticholinergic effects; others include nausea, grand male seizures, and hepatic, urologic or cardiovascular reactions [5,10].

Moreover, clomipramine could be able to induce allergic reaction in about 1 % of treated patients. In our study we excluded that the allergic reaction was induced by clomipramine treatment alone. In fact, in our patient acute clomipramine de-challenge induced a decrease in skin eruption, while the drug re-challenge with clomipramine alone did not produce any adverse reaction.

Food is the most common eliciting factor of anaphylactic reactions and furthermore a rising prevalence of food hypersensitivity has been reported during the last decade [17]. Several papers documented that fish represent the most frequent elicitor of food allergy or anaphylaxis [18,19]. In particular, Gad C1, the major codfish allergen represents a typically digestion-resistant food antigen [1], which exhibit resistance to heating and proteolysis [3,21]. In agreement a recent paper has shown that codfish allergens are among the most frequent elicitors of severe IgE-mediated food-adverse reactions [26], since a very low frequency (0.2%) of allergic reaction after exposure to codfish has been reported [11,15].

It is well described that under physiologic gastric condition (pH < 2.5) codfish proteins are degraded completely within one minute. An increase of the pH from 2.5 to 2.75 abrogated the diges-

tion of cod proteins completely [25,26]. Therefore, under these conditions, the digestion of the fish proteins might be abolished and intact allergenic proteins might be absorbed inducing generalized allergic symptoms [20,24].

Previously it has been shown in experimental models that tricyclic drugs, used as antidepressants (such as desmethylinipramine), have been known to act as gastric antisecretory agents [16]. In agreement, we postulate that, at least in our patient, clomipramine is also able to elicit an increase in gastric pH, and able to induce a decrease in the acid degradation of codfish allergens; the elevation of codfish allergens levels could be related to the skin manifestation.

Previously it has been described that a cross-reactivity to different fish species exists in clinically codfish-allergic adults [11]. In contrast, our patient developed this reaction only after ingestion of codfish during clomipramine treatment; in fact the ingestion of other fish during clomipramine treatment did not induce any effect.

Finally, several dietary compounds or other constituents that are added during the meal preparation and are known to be digestible food antigens could be also able to induce allergy [28]. However we exclude their involvement because our patient consumed them during the overall period, moreover these aliments are mainly elicitors of local symptoms as an oral allergy syndrome [13].

It is important to remark that the adverse reaction showed a clinical improvement after clomipramine discontinuation and that alprazolam dosage has always remained unchanged. While adding alprazolam during paroxetine treatment, the codfish re-challenge did not cause any adverse skin manifestations.

Since the patient had neither past history nor a family history of skin manifestations, using Naranjo probability scale, we obtained a score of 6 indicating a probable relationship between skin eruption and drug-food interaction in the young woman.

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