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Seizures induced by NSAID

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Key words: adverse reactions; nonsteroidal anti-inflammatory drugs; oral challenge; seizures.

● ADVERSE reactions to nonsteroidal anti-inflammatory drugs (NSAID) have been recognized for years. Such reactions include acute asthmatic attacks or perpetuation of ongoing asthma, initiation or perpetuation of chronic urticaria, and anaphylactic or anaphylactoid episodes (1).

In this paper, we report the case of an infrequent NSAID adverse effect confirmed by oral challenge test. This case illustrates indomethacin- and acetylsalicylic acid (ASA)-induced seizures.

A 65-year-old man without a remarkable neurologic and atopic medical history had an episode of seizures about 15 min after ingestion of one Inacid[®] tablet (indomethacin 50 mg). He had taken no other medication. The man complained of abdominal pain and rapid onset of profuse sweating, loss of consciousness, tonic extension of the arms, and turned up eyes, without urinary incontinence. The symptoms resolved within 3–4 min without

treatment, with slow return to complete lucidity: after seizure, the patient was confused, sleepy, and uncooperative for several minutes before full recovery. Results of physical examination were unremarkable, neurologic examination showed no abnormalities other than limited drowsiness. General analysis and kidney function were normal, as was computed tomography (CT) of brain, electroencephalogram (EEG), and Holter electrocardiogram.

During the allergologic evaluation, the patient was orally challenged, after giving written, informed consent. A single, nonchewable, 50-mg indomethacin tablet (regular-strength Inacid) was used. The patient repeated the previous clinical features 10 min after the ingestion of the tablet. He had no other symptoms. We also performed oral challenge with ASA, and diclofenac, with good tolerance.

The patient was followed up for 2 years, and during this time he received ASA on several occasions without difficulty. After this period of time, he presented a new episode of seizures, similar to those previously described, 10 min after ingestion of 500 mg ASA. General and neurologic examination, general analysis, kidney function, brain CT, and EEG were again normal. After discussion with him about adverse reactions to NSAID, a new challenge was undertaken only with salicylate and isonixin, with tolerance. The patient did not have any symptoms during or after the challenge. We did not perform oral challenge with AAS and other NSAID because informed consent was not given by the patient.

Many drugs are known to cause convulsions in many different circumstances. In order to focus on this problem properly, one must clearly distinguish between situations in

which this adverse effect is observed at therapeutic dosages and conditions in which seizures are part of the clinical picture of poisoning (2). In this particular case, the seizures developed after standard dosage of the drugs, and they were not followed by other symptoms. These features indicate NSAID to be the trigger factor.

Seizures have occasionally been reported during NSAID therapy: mefenamic acid (3), ibuprofen (4), and diclofenac (5) have been implicated. In all cases, the seizures have been induced by therapeutic dosage, but, in some cases, a number of pre-existing conditions also contribute to the adverse reaction, conditions which are related either to the disease or to concurrent medication with other drugs. However, the particular association of the drug administration with these concomitant factors does not fully explain the occurrence of seizures, because only in a few cases does this kind of association cause seizures. This observation leads to the conclusion that, in many cases, factors related to patients themselves are a major determinant affecting the occurrence of seizures. These factors are far from being clearly understood, but probably involve some form of predisposition to the seizure and a pharmacologic mechanism: in mice, it was shown that NSAID act on the convulsive threshold by inhibition of cerebral prostaglandin and thromboxane synthesis (6).

Adverse reactions to NSAID are usually thought to result from cyclooxygenase inhibition. The fact that two different NSAID were implicated in the adverse reaction observed in our patient suggests that an idiosyncratic mechanism could be implicated, possibly related to prostaglandin and/or thromboxane levels in the brain (6). However, other mechanisms might be implicated, the clarification of which should be aided by the increased attention to seizures after ingestion of NSAID that this case report suggests.

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Immediate urticaria to Euphorbiaceae

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Key words: allergy; dermatitis; *Euphorbia characias*.

• VARIOUS allergic disorders, ascribable exclusively to the *Hevea* genus, have long been described in relation to the *Euphorbiaceae* family. The *Hevea* genus is used in the extraction of latex, which is an important raw material in various products in daily use, such as gloves for housework, rubber for erasers, adhesive tape, and stickers; sports articles (balls, sailing accessories, and underwater masks); and medical and paramedical tools (surgical gloves, catheters, adhesive plasters, and dummies).

This natural latex induces IgE-mediated disorders that are moderately distressing, although in a few categories of workers the percentage of sensitization may be rather high, causing disorders of the respiratory tract with attacks of asthma and anaphylactic shock (1–3).

During a botany tutorial session on autochthonous flora, a few university students taking biological sciences (more precisely, seven students from the third year) developed severe immediate urticaria-type itchy allergy, at the site of contact, although the itch was also generalized in three cases of urticaria angioedema syndrome, after gathering a few specimens of *Euphorbia characias* L. No symptoms involving the airways were observed, because the latex was too dense to spread in the atmosphere.

E. characias L. is a plant of the Euphorbiaceae family that grows wild in Portugal and in the Mediterranean basin in dense monospecific populations at the edges of holm oak woods or secondary maquis, in heathland and pastures.

The plant has upright, pubescent stems that are bare in the lower parts and 6–12 cm tall. The lower leaves are

reflex, while the upper ones are upright, linear, and lance-shaped, often with revolute margins. The flowers form umbels of 20–22 radii, and have greenish, trapezoidal glands. When crushed, all parts of the plant emit a dense, white, particularly irritant latex that is often released into streams to poison the water and collect the fish.

Contact of this latex with the mucosa of the nose, mouth, and eyes causes severe irritation, although it never progresses to the most dangerous forms. Contact with the epidermis, however, does not cause any disorder.

Because of its particular hardness and climatic and environmental resistance, *E. characias* L. has been genetically improved through hybridization, in order to obtain particularly suitable strains that can be grown in gardens, in spite of their dangerous latex (4).

Previous studies have shown the presence of diterpenoids of the lathyrane and jatrophane types in *Euphorbias* (5, 6). These compounds,

however, were not active in irritancy tests.

The material collected in Sardinia and analyzed by us, on the other hand, contained diterpenoids unrelated to the ones previously found in this species (atisane, abietabes).

However, phorbol and ingenol derivatives, which are the most typical irritant compounds of spurge, could not be detected. We recently found diamine oxidase and peroxidase activity in the latex of *E. characias* samples collected in Sardinia (7, 8).

In other recent studies on *Hevea brasiliensis* Müller Arg., it was pointed out that allergic manifestations related to IgE-mediated sensitization are caused by the protein antigens of natural latex (9), whose most important allergens seem to be rubber elongation factor (10) and prohevein (11).

Therefore, the irritant action might be caused by the protein component in *Euphorbia* latex, particularly by diaminoxidase. This enzyme oxidizes putrescine and cadaverine at a fairly high rate and, although less efficiently, a few other related compounds, but not histamine, spermine, or spermidine.

The subjects with clinical manifestations of urticaria underwent a careful anamnesis that showed that they had been exposed to *Euphorbia* latex. They underwent prick tests, and their serum was found to be positive for specific IgE.

It is clear that subjects exposed to this plant either for professional reasons or by accidental contact, should be protected by pharmacologic prevention with antihistamines and barrier creams to be applied on the hands every 2 h, especially those who are exposed to *E. characias* and other latex-containing members of the *Euphorbiaceae* family for work and/or study.

In fact, it is likely that similar species may cause dangerous irritant clinical manifestations in predisposed and sensitized subjects.

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Contact with sap of *Euphorbia characias* L. can induce severe itchy urticaria with positive skin prick tests.