

Generalized urticaria caused by glycerin enema in an infant

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Glycerin is a trihydric alcohol with a molecular formula of $C_3H_8O_3$ and is used in cosmetic and non-cosmetic applications [1]. In cosmetics, glycerin is reported having function as a denaturant, fragrance ingredient, hair conditioning agent and so on. In non-cosmetics, glycerin is used in food packaging and is used in drugs, such as anorectal drug products, dermal protectants, in ophthalmic drug products, and in oral health-care products. Few cases of hypersensitivity to glycerin have been reported [2–5], and the substance is generally considered to be hypoallergenic because non-sensitizing based on previous reports [1]. Although the clinical picture of patients with allergy to glycerin and the utility of allergy testing for this condition are not fully understood, most patients with glycerin allergy present adult-onset contact eczema caused by creams or cosmetics containing glycerin. Herein, we reported an infant who presented generalized erythema and hives immediately after receiving a glycerin enema. Immunological contact urticaria was diagnosed by a skin prick test (SPT), basophil activating test (BAT), and drug provocation test (DPT). Informed consent to publish the details of the case was obtained from the patient's parents.

A female infant with a history of severe neonatal asphyxia (Apgar score 3 at 5 min), hypoxic ischemic encephalopathy, and infantile spasms started to receive glycerin

enemas (GLYCERIN ENEMA 50%; Kenei Pharmaceutical Co., Ltd., Osaka, Japan), not containing polyethylene glycol, daily to manage constipation from the neonatal period. When she was 8 months old, she experienced generalized erythema and hives without respiratory or gastrointestinal symptoms on two occasions immediately after receiving a glycerin enema (Fig 1). Neither she nor her family had a history of any other allergic disease (e.g., food allergy, bronchial asthma or atopic dermatitis).

A SPT with the 50% glycerin, the concentration described in a previous report [2], produced a wheal around 3 mm in diameter. Saline was negative, and histamine (Torii Pharmaceutical Co, Ltd, Tokyo, Japan) elicited wheals about 5 mm in diameter. BAT (BML, Tokyo, Japan) showing basophil activation > 5% is considered positive; in the present case, basophil activation was 6.5% (in 0.048 g/ mL of glycerin). Basophil activation was 0.7% and 21.1% in the negative and positive controls, respectively.

After obtaining written informed consent for a DPT, the patient was given 15 ml of a 50% glycerin enema solution under medical supervision. Thirty minutes afterwards, erythema and hives appeared on the chest and thighs without perianal skin symptoms. Based on the results of the allergy tests, glycerin enema-induced immunological contact urticaria was diagnosed. After the glycerin enemas and dietary glycerin were discontinued, the patient had no further allergic events.

Contact urticaria is a condition that is characterized by the immediate development of contact skin reactions, mainly consisting of wheals and flare [6]. The severity of contact urticaria can be classified into 4 stages, localized urticaria (stage 1), generalized urticaria (stage 2), extracutaneous involvement (stage 3) and generalized anaphylactoid reactions (stage 4) [6]. According to the classification, our case, presenting generalized urticaria, was considered stage 2 contact urticaria.

Of six, previously reported cases of glycerin hypersensitivity, five were of contact dermatitis, and only one case of an 81-year-old female patient was diagnosed as contact urticaria[2]. As in our case, this had required glycerin enemas on a regular basis to prevent constipation. Interestingly, both the latter patient and our patient had glycerin enema-induced immunological contact urticaria but no history of contact eczema and experienced no further allergic symptoms after discontinuing glycerin use. Glycerin in enema solutions is not absorbed by the rectal mucosa[7], but anorectal injuries incidental to frequent enema administration [8] may increase the risk of sensitization and even introduce antigens into the blood via the rectal venous plexus and contribute to general symptoms.

In clinical practice, skin tests are often used to determine whether immunological mechanisms are at work, and the DPT is considered the gold standard in the diagnosis of drug hypersensitivity, but these *in vivo* tests tend to be avoided as in a previously reported case in which an intradermal test and a DPT were avoided [2] due to the risk of triggering allergic symptoms, such as anaphylaxis. The utility of the BAT has been shown in patients with not only food but drug allergy, and the test might reduce the need for provocation tests[9]. Also, basophil activation triggered by diethyltoluamide has been reported in a patient with diethyltoluamide-induced contact urticaria[10]. The utility of BAT for diagnosing contact urticaria and glycerin allergy has not been established, but our patient showed basophil activation in response to glycerin; thus, BAT may be useful for diagnosing contact urticaria and reducing DPTs in patients with contact urticaria and can be expected to draw more attention in future clinical studies.

IgE-induced basophil degranulation has been well documented for several allergens.

However, with regard to pseudo-allergens like non-steroidal anti-inflammatory drugs, basophil activation does not seem to increase the expression of cell membrane markers [10]. The basophil response to glycerin seen on the BAT in the present patient may

suggest that the pathophysiology of the glycerin hypersensitivity reaction was IgE-mediated.

In conclusion, we experienced an infantile case of generalized urticaria caused by a glycerin enema solution. The present case report is the first to describe SPT, BAT, and DPT-proven, glycerin-induced immunological contact urticaria. Glycerin enema solution was found to be capable of causing an allergic reaction, and further investigation is needed to understand the pathophysiology of glycerin enema hypersensitivity and its difference to glycerin-induced contact dermatitis.

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Disclosure

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Figure**Figure 1.** Generalized urticaria appeared after administration of a glycerin enema.