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A Case of Localized Adrenergic Urticaria Mimicking an Allergic Reaction to a Sweat Chloride Test

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Summary. Adrenergic urticaria (AU) is a rare type of physical urticaria triggered by stress. It is frequently confused with IgE-mediated urticaria or other physical urticarias. This report describes a case of localized adrenergic urticaria triggered by a sweat chloride test in an adolescent male with multiple atopic disorders. A pruritic papular rash at the site of a sweat chloride test prompted an evaluation for allergic and physical urticarias using multiple skin test methods. A positive intradermal skin test to noradrenaline, which reproduced the rash observed during the sweat test, led to the diagnosis of adrenergic urticaria. This is the first case report describing an immediate adrenergic urticarial reaction to sweat chloride testing in a patient with other atopic disorders. *Pediatr Pulmonol.* 2009; 44:935–938. © 2009 Wiley-Liss, Inc.

Key words: cystic fibrosis; iontophoresis; pilocarpine; noradrenaline.

INTRODUCTION

Adrenergic urticaria (AU) was first described in 1985 by Shelley and Shelley.¹ It is a rare type of physical urticaria and to our knowledge this is the seventh case to be described in the literature. AU is triggered by stressful situations, not by changes in body temperature or exercise, as occurs with the more common cholinergic urticaria. AU presents with individual pin point lesions that are surrounded by a white halo, a result of blood vessel vasoconstriction. Reactions associated with sweat chloride testing have been reported in the literature, however, to our knowledge, this is the first case report investigating the etiology.^{2,3} We describe an atopic child with an immediate type sensitivity reaction to the quantitative pilocarpine iontophoresis sweat chloride test.

Despite the widespread use of mutational analysis for cystic fibrosis (CF), the measurement of elevated concentration of chloride in sweat remains the standard procedure for confirming the diagnosis of CF. This is because to date there are over 1,500 mutations of the CFTR gene responsible for CF and routine laboratory genetic testing panels will not identify all cases of CF. In addition, the results from mutational analysis may not be conclusive for a diagnosis of CF, due to the differentiation between CF causing mutations and yet unknown consequences of other CFTR mutations.⁴ A quantitative sweat chloride test is recommended for anyone having symptoms of CF;

anyone with a family history of CF and anyone identified at risk for CF based on newborn screening results.^{5,6}

A diagnostic sweat chloride test consists of three parts: sweat stimulation by pilocarpine iontophoresis, sweat collection onto gauze, filter paper or Macroduct coils and analysis of sweat for chloride concentration.⁷ Pilocarpine is delivered into the skin by a low-voltage electric current through the process of iontophoresis. Pilocarpine nitrate in either a gel or moistened pad is placed under the positive

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electrode; an electrolyte solution in a gel or moistened pad is placed under the negative electrode, and a current of 2–4 mA is applied for a maximum of 5 min. Following iontophoresis, it is expected that the skin corresponding to the area under the positive electrode be slightly erythematous. From this site sweat is then collected and quantitatively analyzed for chloride.

CASE REPORT

A 10-year-old boy was referred to the pulmonary clinic for evaluation of a chronic cough. His past medical history included premature birth at 34 weeks with no history of intubation, but requiring oxygen therapy for 14 days. He had a history of allergic rhinitis and asthma, with environmental allergies to cat and mold. He had past episodes of chronic sinusitis, but without other infections, including pneumonia. He also had a history of absence type seizures and an EEG performed demonstrated several areas of epileptiform activity. Over the last 2 years he had increasing cough with sputum production, as well as an increase in coughing with mild to moderate exertion with episodes of chest tightness and difficulty breathing with vigorous exercise. Of note, he also had a past episode of “collapse” during vigorous exercise. An evaluation by a cardiologist did not identify any abnormalities and an echocardiogram was interpreted as normal. He was diagnosed with exercise-induced bronchospasm by an exercise challenge and has been treated with Advair[®] and Singulair[®] with Albuterol pre-exertion and as needed. He has never been hospitalized, except shortly after birth for his prematurity, and has had no surgeries. His family history was significant for co-porphyrria and asthma in the mother, and chronic sinusitis, allergies, asthma and severe life-threatening cold-induced urticaria in his brother.

The pertinent findings on physical examination included swollen and erythematous turbinates, tonsils were moderately enlarged bilaterally and the skin was without dry patches or lesions. He had clear lung fields, no pathologic cardiac murmur and absent digital clubbing. The remainder of his physical examination was unremarkable.

Because of the history of chronic cough, he was referred for sweat chloride testing to rule out CF. The two electrodes were placed on the arm with one above the wrist and the other right above the antecubital fossa. Following iontophoresis he developed erythematous papules under both the positive and negative electrodes with confluent erythema between the two electrodes. It was reported that the iontophoresis had been extended due to problems getting the electric current started. The test was stopped and he was referred to an allergist for an evaluation. An extensive work-up was performed and included a total IgE of 271 IU/ml (2–15 IU/ml). An evaluation for an immediate IgE-mediated hypersensitiv-

ity to the components of the sweat test, pilocarpine (0.4%) and magnesium sulfate was performed by the percutaneous skin test method, the results of which were negative. He also underwent evaluation for physical urticarias, including cholinergic, adrenergic, heat and cold urticaria. Cholinergic urticaria was evaluated using percutaneous and intradermal testing to methacholine at a concentration of 0.1 mg/ml. Cold urticaria was assessed using an ice cube test applied to the forearm for 5 min and assessing for a reaction at the site at 10 min. Heat urticaria was assessed using applied heated cylinder of 51–52°C.⁸ Negative reactions occurred for all the tests. Adrenergic urticaria was assessed using percutaneous skin tests to adrenaline at concentrations of 0.001 and 0.01 mg/ml, and to noradrenaline at increasing concentrations of 0.5×10^{-6} , 0.5×10^{-5} , 0.5×10^{-3} , and 0.01 mg/ml, which were all negative. Testing to noradrenaline by the intradermal method was performed using the same concentrations, but was stopped at a noradrenaline concentration of 0.5×10^{-5} when the patient demonstrated an erythematous wheal with a surrounding white halo. The patient reported the rash was exactly the rash observed during the sweat chloride test, though with the presentation of multiple lesions. Based on the results of the various tests described above, the diagnosis of adrenergic urticaria was made. With reassurance that the patient did not have an immediate hypersensitivity to the chemicals used in the sweat test, and in a relaxed setting to avoid test anxiety, a repeat sweat test was performed without incident. The test was found to be within normal limits with a sweat chloride concentration of 23 mmol/L. The patient has not required medications to control his symptom of urticaria.

DISCUSSION

To our knowledge, this is the first case report describing adrenergic urticaria induced by a sweat chloride test. Our patient presented with classic erythematous papules surrounded by white halos. The lesions were reproducible with intradermal skin testing to noradrenaline at a concentration of 0.5×10^{-5} mg/ml. Diagnostic studies to evaluate other forms of physical urticarias, including cholinergic, heat, and cold urticaria, as well as an immediate-hypersensitivity to pilocarpine and magnesium sulfate were all negative. Repeat testing under relaxed conditions and without pre-treatment with antihistamines did not lead to a reoccurrence of the rash and the sweat chloride test was completed without incident, further demonstrating that direct current or mechanical pressure from the test were not the cause of the rash. This case report demonstrates the necessity to ascertain the etiology of cutaneous reactions during sweat chloride testing in order to determine the risk and appropriate prophylaxis to safely complete the sweat chloride test.

Previously, LeGrys and Retsch-Bogart² described an immediate cutaneous reaction to sweat chloride testing in which they were able to successfully complete retesting following predosing the patient with hydroxyzine hydrochloride. The urticarial reaction was suspected to be an immediate-hypersensitivity reaction to pilocarpine although no skin testing was performed for confirmation. Pilocarpine is a cholinergic agonist and clinically is used to treat xerostomia and glaucoma. Delayed hypersensitivity reactions to pilocarpine, in the form of contact dermatitis, have been described to ophthalmic pilocarpine solutions, and are typically confirmed through patch testing to the antigen in question.⁹⁻¹¹ IgE-mediated immediate-hypersensitivity reactions are identified by skin testing to the antigen in question or through the identification of IgE specific to the antigen in the blood through radioallergosorbent testing. There is the potential that IgE-mediated reactions can lead to systemic reactions, even with pre-treatment with an antihistamine. It is therefore advisable to evaluate the etiology of the rash and to make assessments of the risk for retesting. Though the urticarial reaction described by LeGrys and Retsch-Bogart may have been an immediate hypersensitivity reaction to pilocarpine, effectively suppressed with hydroxyzine, it is also possible that the rash was due to one of the physical urticarias and repeat testing without incident was due to the anxiolytic effects of hydroxyzine. Thus, it is unclear if the urticarial reaction was an IgE mediated immediate hypersensitivity reaction, or due to one of the physical urticarias.

Physical urticarias are induced by environmental stressors and include mechanical, solar, aquagenic, cold, heat [cholinergic (core body temperature increase) and localized heat urticaria] and adrenergic urticaria. Cholinergic and adrenergic urticaria both present with erythematous papules, but in cholinergic urticaria the papule is surrounded by erythema and in adrenergic urticaria the papule is surrounded by a white halo. Though the distinction between the two is quite clear, patients frequently are unable to describe their rashes or identify the inciting factor. Further confusing the issue, different forms of physical urticarias can coexist. Avoidance of the environmental stressor is key in the management of physical urticarias, thus making an accurate diagnosis critical.

There are a number of possible causes of a cutaneous reaction during a sweat test. Potential etiologies include an immediate sensitivity to the chemicals used in a sweat test, pilocarpine and magnesium sulfate, and the physical urticarias, notably adrenergic urticaria due to stress, heat (both cholinergic and localized heat), and mechanical pressure. As discussed above, the appearance of the rash can be helpful in identifying the etiology, though even cholinergic and adrenergic urticaria can develop large papules that resemble wheals. The localization of the rash

can also be very helpful in distinguishing the cause. A rash only in the area of contact with the pilocarpine solution would implicate an IgE-mediated immediate-hypersensitivity reaction, though the physical urticarias could also be an inciting factor. A rash at both the positive and negative electrodes, as occurred with our patient, suggests one of the physical urticarias. A rash outside the areas of contact with the electrodes also suggests a physical urticaria as the etiology. As several environmental triggers were implicated during our patient's sweat chloride test, testing to accurately identify the etiology was necessary. We employed a battery of skin tests previously reported in the literature to identify physical urticarias.^{1,12}

A limitation of this study is that evaluation of adrenergic urticaria has not been standardized and the sensitivity and specificity of skin testing is not known. Further, the skin tests were not performed in duplicate to confirm reproducibility. As anxiety is a cause of adrenergic urticaria, it is possible that baseline anxiety influences skin testing to noradrenaline and the concentration at which a positive reaction occurs. Indeed, our patient reacted to a smaller concentration of noradrenaline (0.5×10^{-5} mg/ml) compared to the investigation by Shelley and colleagues in which they found noradrenalin at concentrations of 3–10 ng in 2 ml saline (0.5×10^{-3} to 1.5×10^{-3} mg/ml) induced adrenergic urticarial lesions.

The mechanism of adrenergic urticaria is still unclear; however it is believed that it is triggered by noradrenalin and adrenaline. When AU was first described by Shelley, he demonstrated degranulated mast cells on electron microscopy, thereby showing that histamine was the ultimate mediator of adrenergic urticaria.¹ However, it is still unclear if noradrenalin alone or in combination with other factors is the stimulant that leads to the degranulation of mast cells. When Hausteiner described two patients with adrenergic urticaria and adrenergic pruritis, he demonstrated that the subjects had an increased baseline noradrenalin and adrenaline levels when compared to normal controls.¹³ The diagnosis of adrenergic urticaria to date has relied on intradermal skin testing with noradrenalin and the observation of the characteristic lesions. The most effective treatment of adrenergic urticaria is propranolol.¹

CONCLUSION

We describe the first case of adrenergic urticaria associated with sweat chloride testing in a patient with other atopic disorders. The lesions, though characteristic of adrenergic urticaria, were not initially identified due to unfamiliarity by observing medical personnel and the patient. Skin testing definitively identified the mechanism of adrenergic urticaria from multiple possible etiologies. A calm and relaxed atmosphere was provided for the

patient during repeat testing, and the sweat chloride test was completed without incident. Identification of cutaneous reactions during sweat chloride testing should be thoroughly evaluated for etiology and, if determined to be safe, repeat testing can be performed with appropriate prophylactic treatment.

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