

The Use of Epicutaenous Patch Testing in the Evaluation of Gastrointestinal Disease

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Opinion statement

Traditionally, gastrointestinal (GI) diseases such as gastroesophageal reflux, gastritis, esophagitis, and irritable bowel syndrome (IBS) have not been thought of as hypersensitivity (allergy)-mediated illnesses; however, there has been growing research suggesting that food and environmental allergens may play a role in the development of GI illnesses, particularly those with refractory symptoms not responding to traditional therapies. The GI system and skin share similar components of the immune system and in some cases respond to foreign antigens in the same manner. With respect to confirmatory diagnostic testing, the skin is the more easily accessible organ compared to the gastrointestinal system. Patch testing is a well-established standardized non-invasive skin based test utilized for the evaluation of hypersensitivity reactions to antigenic triggers. There is growing evidence that patch testing may be helpful in the diagnostic evaluation of gastrointestinal manifestations of immune-mediated diseases. We predict that further utilization of the standard patch test in the diagnostic assessment of patients with GI symptomatology will prove useful for the identification of specific allergens and etiologic agents responsible for gastrointestinal type IV hypersensitivity reactions.

Introduction

Gastrointestinal diseases are estimated to affect 60 to 70 million Americans annually and are among the most common reasons for patients to seek healthcare in the USA [1]. Infectious diseases of

the GI system are one of the oldest known human ailments, and for the most part, their diagnosis and treatment are well established. Meanwhile, food allergies or sensitivities appear to be on the rise

worldwide, with self-reported prevalence in the USA and Europe of nearly 9 and 5.9 %, respectively [2, 3]. In many cases, while an association with an antigenic trigger can be demonstrated, there tends to be a lack of a direct causal link between antigen and disease. Gastrointestinal diseases such as gastroesophageal reflux, gastritis, esophagitis, and irritable bowel syndrome (IBS) are not traditionally thought of as hypersensitivity (allergy)-mediated illnesses; however, there has been growing evidence that food allergies and environmental allergens may play a role in the development of these diseases in a subset of patients with refractory symptoms not responding to traditional therapies.

The GI system and the skin share similar components of the immune system and in some cases respond to foreign invaders or allergy in a similar manner. It is for this reason that many human diseases can influence both the GI system and skin simultaneously or fluctuate back and forth between these distant sites. While the GI system is hard to access, the skin represents an easily accessible organ useful for the assessment of allergy. Patch testing is a non-invasive skin based test well established for the evaluation of hypersensitivity to antigenic triggers. In this review, we will explore the role of patch testing in the diagnostic workup for patients with GI illnesses.

The skin and the GI tract

Like the skin, the GI tract plays a similarly important role in allergen sensitization and provides unparalleled exposure to the external environment. The GI tract has an estimated 300 m² of surface area that is exposed to an estimated 70 to 100 g of non-self proteins daily [4]. Similar to skin, the integrity of the mucosal barrier in the GI tract is important for protection from sensitization. Factors that have been associated with sensitization to food include GI tract infection, disruption of native digestive processes (i.e., through the use of acid-neutralizing therapies), mucosal barrier disruption, and T cell regulatory dysfunction [4].

Many GI diseases have dermatologic manifestations; for instance, in Henoch-Schonlein Purpura (HSP), an IgA-mediated small vessel vasculitis, many patients will have abdominal pain, diarrhea, constipation, or rarely intussusception along with palpable purpura. In children, HSP is the most common systemic vasculitis and in nearly half of those with HSP the disease manifests after some sort of infection such as streptococcal throat infections or exposure to other triggers such as foods and medications. There are many neutrophilic diseases (driven by the infiltration of neutrophils), which lead to skin and GI manifestations and yet are thought to originate in the GI tract. Sweet's syndrome, acute febrile neutrophilic dermatosis, is a condition characterized by fever and erythematous skin and mucosal lesions with accompanied blister formation. There are multiple systemic diseases associated with Sweet's syndrome including inflammatory diseases, cancers, and infections of the GI system. Another neutrophilic dermatosis is bowel-associated dermatosis-arthritis syndrome in which patients present with a serum sickness-like syndrome consisting of fever, arthritis, and skin disease. In this instance, the manipulation of the GI tract by surgical intervention is the trigger for the disease and while the direct cause is not known, bacterial growth in the GI system and subsequent immune response is favored. Inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, can have many dermatologic manifestations such as pyoderma gangrenosum, erythema nodosum, or other skin

findings. And the final example is dermatitis herpetiformis (DH) in which patients get a blistering disease consisting of symmetric, pruritic, vesicles on the extensor arms and buttocks. Most patients with DH also have celiac disease—a gluten intolerance or allergy—that manifests as diarrhea, malabsorption, bloating, and weight loss [5]. The above diseases highlight the immunologic connection between the skin and the GI system and support why clinicians have effectively used the skin as a surrogate for the GI tract when examining for immunologic pathology or for testing possible reactivity to antigens. The most common test for exploring possible antigenic triggers in either the skin or the GI tract is patch testing.

Pathophysiology of type IV hypersensitivity

Patch testing is most commonly used in the investigation of type IV, delayed-type, hypersensitivity reactions, such as those seen in allergic contact dermatitis (ACD). For a patient to develop a type IV hypersensitivity, they must first be exposed to the allergen (sensitized) and then develop an immunologic response with the creation of immune memory. The individual is first sensitized to the allergen when the molecule (hapten) crosses the skin barrier and binds with endogenous proteins to form a protein-hapten complex. These complexes are taken up by antigen presenting cells, such as Langerhans cells and dermal dendritic cells, and are presented to naïve antigen-specific T cells either locally or after migrating to regional lymph nodes. Under the influence of IL-1, the naïve T cells differentiate and proliferate to form effector T cells, primarily the Th1 subtype. These effector T cells remain in the skin or, if selected in the lymph node, migrate back into the circulation and to the skin. Regardless of how they reside in the skin, upon re-exposure to antigen, these T cells are activated and through the release of cytokines induce an inflammatory response manifesting as ACD [6, 7]. Sensitization appears to occur more frequently in those with skin barrier dysfunction such as the elderly and those with atopic dermatitis, and indeed numerous recent studies have suggested that disruption of the skin may be a necessary first step to sensitization [8, 9].

Utility of skin based testing in GI disease

There are two distinct skin-based tests used to assess hypersensitivity reactions: prick testing and patch testing. Prick testing consists of the per-cutaneous introduction of a substance into the skin and the immediate measurement of histamine release. Food or air allergens, such as cat dander or dust mite, are typically tested by skin-prick test or by radioallergosorbent test (RAST) IgE levels.

Epicutaneous or skin patch testing, on the other hand, consists of the application of a substance onto the surface of the skin followed by monitoring for an immune response over days. Standard patch testing is generally used to identify triggers of ACD and involves the application of substances (e.g., fragrances, preservative) at standardized concentrations within chambers that are removed generally at 48 h. Readings are performed between 72 and 120 h. Another type of patch testing, atopy patch testing, involves standard patch

testing methodology utilizing intact protein allergens, usually food or air allergens (e.g., cow milk protein, dust mite) are used. While frequently used, atopy patch testing has discordant results in the literature [10]. Of note, atopy patch testing can be informative in rare cases where individuals react to protein allergens via patch testing but do not react with skin-prick or IgE testing.

There is growing evidence that food allergen sensitization may originate from exposure at sites distant from the GI tract such as the skin or nasal/respiratory mucosa. Observations in children with peanut allergy found that 72 % of peanut-allergic children reacted on their first known ingestion of peanuts, which implicates non-oral sensitization [11]. Furthermore, Chan et al. found that peripheral T cells isolated from peanut allergic patients expressed the skin-homing integrin cutaneous lymphocyte antigen (CLA+) rather than the gut-homing integrin $\alpha 4\beta 7+$, which suggests that peanut sensitization may actually originate from the skin [12].

Furthermore, mutations in fillagrin—a gene important in maintaining an intact skin barrier function—are highly prevalent in patients with atopic dermatitis and have also been linked to the GI disease eosinophilic esophagitis (EoE). Mutations in this gene have also been implicated in the increased risk of peanut allergy through decreased barrier function of the skin and impaired gut defenses [4]. In summary, given the parallels between the skin and GI tract, it is not surprising that food allergy, atopic diseases such as eczema and asthma, and GI diseases are intimately related [13].

Cudwoska et al. evaluated the diagnostic accuracy of the atopy patch test in the detection of delayed-type sensitization to various food allergens in children with digestive symptoms. They found a high sensitivity and specificity of atopy patch testing in children with cow's milk allergy (77 and 73 %, respectively). Thus, the combined atopy patch test and oral food challenge were determined to be essential for the avoidance of an unnecessary elimination [14]. In contrast, Costa et al. determined a lower sensitivity and specificity of atopy patch testing in children with cow's milk protein allergy (25 and 81.9 %, respectively). They determined that despite the operational difficulty and exposure risk, oral challenge is the best method for diagnosing cow's milk protein allergy [15].

Pfholer et al. revealed the usefulness of standard patch testing in a patient with probable contact allergic gastritis and nickel allergy. Delayed-type hypersensitivity against the components of the patient's artificial dentition appeared to be the cause of gastritis [16]. Picarelli et al. also found that nickel exposure via the gastrointestinal tract could induce diarrhea, abdominal pain, and swelling, known as allergic contact mucositis. These symptoms and mucosal lesions could be recognized by the oral mucosa patch test in 61.6 % of patients with intestinal symptoms to nickel. Skin lesions were only observed in 38.4 % of patients evaluated with the epicutaneous patch test. These findings point to the use of the oral mucosa patch test in identifying nickel-sensitive patients and could help identify patients whom could benefit from a low nickel diet [17].

Stierstorfer et al. sought to determine whether skin patch testing to certain foods and additives in IBS patients could identify food allergens responsible for the symptoms of IBS. Patch test-guided avoidance diets were subsequently undertaken to determine whether avoidance alleviated IBS symptoms. Thirty of the 51 participants showed at least 1 positive patch test result (garlic, nickel, isoeugenol were frequently positive) and 14 of the participants reported symptomatic improvement suggesting that allergic contact enteritis to ingested foods

or additives might contribute to IBS symptoms. Patch testing may be useful in identifying causative foods of IBS [18]. Liden et al. observed that cow's milk protein (CM) sensitivity was also related to irritable bowel syndrome in patients with primary Sjogren's syndrome. Of the 21 patients assessed, 8 patients had an increase in mucosal nitric oxide synthesis and myeloperoxidase, both signs of mucosal inflammatory reaction, after rectal CM challenge. These signs of milk sensitivity were not related to IgG/IgA antibodies to milk proteins. Interestingly, all patients who were sensitive to CM also suffered from IBS and reported improvement of intestinal symptoms on a cow's milk protein-free diet. The mucosal challenge to cow's milk protein also appears to be useful in the diagnosis and in establishing the treatment plan for patients with IBS [19].

While celiac disease would appear to be a perfect candidate for patch test based diagnosis, in celiac disease, the gluten patch test has not been found to be an efficient test for disease screening. Saneian et al. determined that the patch test could be useful in the diagnosis of disease if employed with the assessment of clinical symptoms and serologic/biopsy test results. They also suggested that a closer look at celiac disease should be considered if the gluten patch test is positive in patients with suspected celiac disease [20].

Atopy patch tests have also been recommended for the diagnosis of eosinophilic esophagitis in adults and children [21]. Sperger et al. observed that in over 75 % of patients with EoE symptoms, esophageal inflammation could be controlled with dietary elimination of foods. They reported that food allergens such as corn, wheat, and soy were identified most frequently with atopy patch testing whereas egg, milk, and soy were identified most frequently with skin prick testing. Skin prick and atopy patch testing were used to help identify trigger foods in most EoE patients [22]. Syrigou et al. also determined that the use of an elimination diet focused specifically on allergens identified in atopy patch tests (milk and egg were most common) resulted in improvement and resolution of symptoms and normal eosinophil levels after 12 months. An allergen-test driven elimination diet is thus an efficient complementary treatment to corticosteroids alone [23•]. One of the issues with the use of atopy patch testing and elimination diets in adults with EoE relates to the role that aeroallergens may play in the development of EoE in adults. It appears that aeroallergens (e.g., grass pollen and cross-reactive plant allergens) may play a larger role in the adult pathophysiology of EoE, and thus, the use of atopy patch testing and elimination diets is less clearly useful in adults as compared to children. Given these findings, Lin et al. still considers the usefulness of skin prick testing and atopy patch testing uncertain for food allergies in adults [24•].

While the usefulness of atopy patch tests, which mainly assesses food proteins as possible triggers, have been examined in GI diseases such as EoE, food proteins represent only a subset of the potential consumed triggers for this type IV hypersensitivity.

Humans consume numerous chemicals not present in traditional "food products" but are present in "consumed products" such as gum, mints, toothpaste, artificial flavors, and dyes. Furthermore, chemicals, such as propylene glycol, which are used frequently to preserve traditional food products are known to trigger IgE-type reactions. It is

important to consider the vast number of chemicals and additives we consume that would not be considered food. Therefore, these common chemicals, many of which are known to cause allergic contact dermatitis of the skin, represent a very probable set of triggers for GI type IV hypersensitivity reactions and yet are largely ignored. It is possible to test for these chemicals using standard patch test series such as food additives, baker's, and food dyes.

Researchers have begun to explore whether these consumed allergens might be previously unappreciated triggers for GI diseases with a defined type IV hypersensitivity-like reaction such as EoE and IBD [25]. Similar to atopy patch test-positive patients who are placed on food avoidance diets (e.g., cow's milk), we have placed patients with GI type IV hypersensitivity diseases who are positive to consumed allergens (e.g., food additives) on diets that restrict the consumption of these chemicals and have found clinically significant positive results (clinical observations, Weill Cornell Medical College, Department of Dermatology). Some of these diets are simple such as restrictions on gum and mint use or changes in toothpaste while some diets are more extensive when the reactive chemical is derived from plants (e.g., vanilla). As the number of patients assessed grows in number, it will become more clear if specific "consumed allergens" play a dominant role in GI type IV hypersensitivities.

Summary

Patch testing is gaining increasing recognition as a reliable way to identify the agents responsible for gastrointestinal reactions. These reactions are not limited to digestive symptoms in children such as cow's milk protein allergies, but also include allergic gastritis, celiac disease, GERD, and eosinophilic esophagitis in both children and adults. Broad elimination diets are usually the diagnostic and treatment method of choice in patients with gastrointestinal reactions; however, implementation and patient adherence is difficult. In addition to atopy patch testing, there may be a role for standard patch testing using consumed allergens commonly found in products. Avoidance of consumed allergens present in non-food products such as gums and mints might be a more obtainable goal as compared to broad food elimination diets. We predict that further utilization of the standard patch test in the diagnostic assessment of patients with GI disease will prove useful for the identification of specific allergens and etiologic agents responsible for gastrointestinal type IV hypersensitivity reactions. Future studies would be useful in further elucidating the role of standard epicutaneous patch testing in gastrointestinal disease.

Compliance with Ethical Standards

Conflict of Interest

Dr. Brienne D. Cressey, Ms. Cindy Parra, and Dr. Jonathan Hale Zippin declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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