Original Article

Value of the BIOCHIP Mosaic-based Indirect Immunofluorescent Technique in the Diagnosis of Dermatitis Herpetiformis among Patients with Chronic Pruritus

Burçin C. Bozca, Derya Mutlu[1], Soner Uzun

Department of Dermatology and Venereology, [1]Department of Medical Microbiology, Akdeniz University School of Medicine, Antalya, Turkey

Abstract

Background: The BIOCHIP mosaic-based indirect immunofluorescence technique is a practical, standardized test, and it has been used successfully in the diagnosis of autoimmune bullous dermatosis in recent years. **Objectives:** The study aimed to examine the diagnostic value of the BIOCHIP to identify dermatitis herpetiformis (DH) in patients with chronic pruritus (CP). **Materials and Methods:** This single-center case–control study included patients who applied to a dermatology clinic between July 2020 and December 2020. The diagnosis of DH was confirmed by direct immunofluorescence (DIF) test. In cases without DIF positivity, the diagnosis was established with a complete response to a long-term gluten-free diet and/or a swift response to dapsone treatment. All analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). The diagnostic performance of the variables was evaluated using receiver operating characteristic (ROC) curve analysis. *P* values < 0.05 were considered statistically significant. **Results:** GAF 3X (gliadin analog fusion peptide), as measured by the BIOCHIP method, had an area under the ROC curve of 0.854 (95% confidence interval: 0.688–1.000) for DH diagnosis with sensitivity, specificity, positive predictive, and negative predictive values of 72.73%, 100%, 100%, and 93.62%, respectively, demonstrating an overall accuracy of 94.55%. **Conclusion:** DH could be determined with nearly excellent accuracy by BIOCHIP GAF 3X analysis among patients with CP. BIOCHIP-based determination of GAF 3X was found to be superior to Enzyme-Linked ImmunoSorbent Assay (ELISA)-based determination of GAF 3X.

Keywords: BIOCHIP, dermatitis herpetiformis, gliadin analog fusion peptide

Introduction

Dermatitis herpetiformis (DH) is a disease characterized by symmetrical polymorphic lesions on the extensor faces of extremities and the sacrum. It is closely associated with celiac disease and responds positively to a gluten-free diet.[1] As such, DH is considered the specific cutaneous manifestation of celiac disease.[2] Pruritus is the main finding, and its absence should prompt a reevaluation of the diagnosis.[3] The disease usually begins with erythematous papules and urticarial plaques with vesicles, which may merge into small, tense bullae with serohemorrhagic content that demonstrates a centrifugal growth pattern.[4,5] Epidermal transglutaminase (eTG) is the primary autoantigen of DH.[6] Although a relationship between DH and different human leukocyte antigen (HLA) subtypes has been found in other studies, the strongest association was reported between HLA-DQ2 and HLA-DQ8.[7]

In the latest version of the European Guidelines on the Management of Pruritus,[8] it is recommended to perform an indirect immunofluorescence test (IIF) in addition to skin biopsy and a direct immunofluorescence test (DIF) to diagnose autoimmune bullous diseases (ABD) in the presence of itchy dermatoses with chronic pruritus (CP). Although DIF is the gold standard for diagnosing DH, it

Submission: 06-08-2022 **Revision:** 18-10-2022
Acceptance: 30-09-2022 **Web Publication:** 28-11-2022

Access this article online

Quick Response Code:

Website: www.tjdonline.org

DOI: 10.4103/tjd.tjd_101_22

Address for correspondence: Dr. Burçin Cansu Bozca, Department of Dermatology and Venereology, Akdeniz University School of Medicine, Antalya, Turkey.
E-mail: bozcacansu@gmail.com

How to cite this article: Bozca BC, Mutlu D, Uzun S. Value of the BIOCHIP mosaic-based indirect immunofluorescent technique in the diagnosis of dermatitis herpetiformis among patients with chronic pruritus. Turk J Dermatol 2022;16:125-30.

requires a skin biopsy, an invasive procedure. Alternative and less-invasive diagnostic methods may be needed in some patients at an advanced age who have comorbidities that may impair wound healing or bleeding control or those who do not wish to undergo the procedure.

The BIOCHIP mosaic-based IIF technique (EUROIMMUNE, Lubeck, Germany) is a developed, practical, standardized, and fast test compared with the DIF. Previous studies have shown that the BIOCHIP technique is efficient in diagnosing and screening pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid (BP).[9-11]

In this study, we aimed to investigate the diagnostic value of the BIOCHIP technique in the identification of DH among patients admitted to the hospital with CP.

Materials and Methods

This single-center, case–control study included patients older than 18 with pruritus defined as CP between July 2020 and December 2020. Upon the Ethics Committee's approval (ethics approval number: KAEK/1072019), patients who met the inclusion criteria were given detailed information about the purpose and scope of the study, and individuals who agreed to participate signed a written consent form for study inclusion.

Patients who presented with the complaint of widespread body itching (chronic generalized pruritus) for more than 6 weeks, with or without visible lesions on the skin secondary to scratching, were included in the study. Those younger than 18 years of age and those who could not or did not provide informed consent were excluded. Patients with localized pruritus, those diagnosed with scabies, and individuals who reported pruritus for less than 6 weeks were omitted. We confirmed the diagnosis of DH in cases whose clinical manifestations were compatible with DH and were positive for DIF. In patients whose clinical manifestations were typical for DH but negative for DIF, we established the diagnosis with a swift response to dapsone treatment and a response to a long-term gluten-free diet, which criteria support the diagnosis specified in the current European S2k guideline.[12] Patients were divided into three groups for the final diagnosis: CP (not grouped as either prurigo nodularis [PN] or DH), PN, and DH.

Peripheral venous blood samples taken from the patients for routine examinations were centrifuged, and a part of the serum was stored at −24°C until analyses were performed. The BIOCHIP mosaic-based IIF technique (Dermatology Mosaic 11, EUROIMMUNE, Lubeck, Germany) was used to detect autoantibodies in the serum. The same serum samples were also evaluated with an Enzyme-Linked ImmunoSorbent Assay (ELISA). The patient's demographic data, clinical characteristics, treatment responses, duration of a gluten-free diet, time of dapsone use, and the results of physical examinations were recorded. In addition, to evaluate the severity and characteristics of pruritus in patients with CP, a 12-item pruritus severity score[13] was used. The total scale score ranges from 3 (minimal pruritus) to 22 (the most severe pruritus), and higher scores indicate more severe itching.[13]

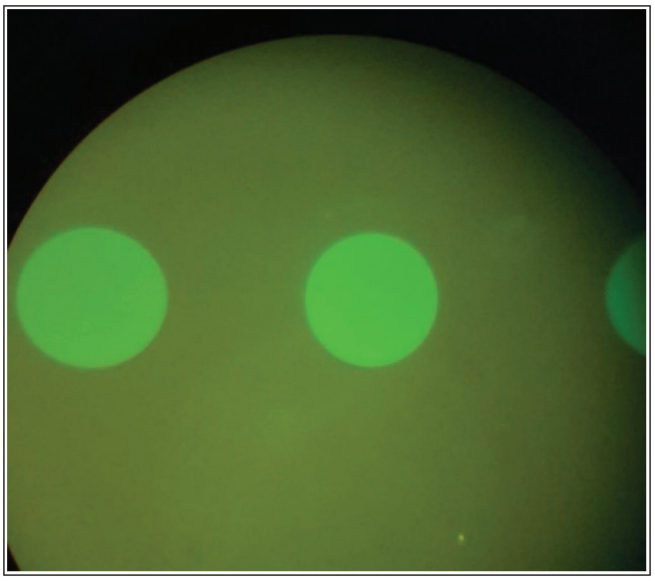

Figure 1: GAF 3X positivity in BIOCHIP, "full moon view"

BIOCHIP technique was applied as stated in previous publications.[10,11] All tests were evaluated by the same researcher (SU). The evaluating investigator did not know the diagnosis of the patients or whether the evaluated BIOCHIP technique was incubated with patient serum or control group serum. Case and control sera were compared with positive controls and evaluated on the same slide. In BIOCHIP, fluorescence prominence in the form of a full moon in the GAF 3X (gliadin analog fusion peptide) area was assessed as positive [Figure 1]; the full moon appearing as a silhouette was classified as a weak positive area that seemed completely dark was classified as negative. The accumulation of fluorescence material in intrahepatic sinusoids in the area of the liver endomysium was evaluated as positive [Figure 2].

Measurements were performed using the microwell ELISA method for anti-gliadin (GAF 3X) IgA, anti-gliadin (GAF 3X) IgG, tissue transglutaminase (tTG) IgA, tTG IgG, anti-BP 180 NC16A-4X IgG, anti-BP 230 IgG in line with the manufacturer's (EUROIMMUN, Lubeck, Germany) recommendations.

All analyses were performed using SPSS version 21 (SPSS Inc., Chicago, IL, USA). The Shapiro–Wilk test evaluated whether variables were normally distributed. Data are shown as the median (minimum–maximum) for continuous variables according to whether the variable was normally distributed and the frequency (percentage) for categorical variables. Non-normally distributed variables were analyzed using the Mann–Whitney U test or Kruskal–Wallis test, depending on the number of groups being compared. Corrections for multiple pairwise comparisons were performed using the Bonferroni correction method.

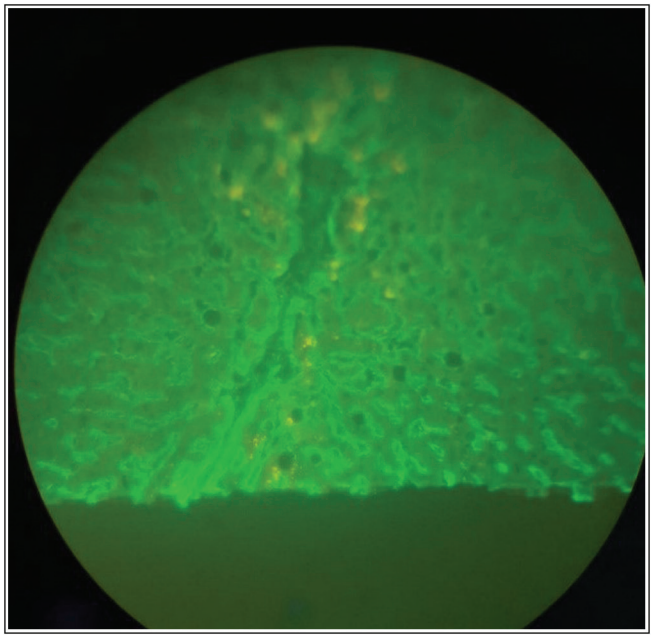

Figure 2: Liver endomysium positivity in BIOCHIP

Categorical variables were analyzed using Chi-square tests. The diagnostic performance of the variables was evaluated using receiver operating characteristic (ROC) curve analysis. *P* values < 0.05 were considered statistically significant.

Results

The study group consisted of 25 (40.86%) males and 30 (59.14%) females; 32 patients were in the CP group, 12 were in the PN group, and 11 were in the DH group. The ages of the patients ranged from 18 to 79, with a mean of 52.67 ± 15.99 years. There were no differences between the three groups regarding age, sex distribution, and age at onset of CP. The frequency of patients without any lesions was significantly higher in the CP group ($P < 0.001$). The localization of lesions showed that patients with DH had a higher frequency of having lesions in the scalp, elbow, and knee than in other groups ($P = 0.016$, $P = 0.009$, and $P = 0.018$, respectively). In contrast, lesions in the arm and lower leg were more frequent among those with PN ($P = 0.025$ and 0.003, respectively). The 12-item pruritus severity score results were similar in all three groups [Table 1].

Table 1: Summary of individual and lesion characteristics according to the group

	Groups			*P*
	CP	PN	DH	
n	32	12	11	N/A
Age	55 (18–78)	57.5 (27–79)	36 (24–76)	0.058
Sex				
Female	19 (59.38%)	5 (41.67%)	6 (54.55%)	0.576
Male	13 (40.63%)	7 (58.33%)	5 (45.45%)	
Age at onset	50.5 (15–78)	47.5 (20–77)	36 (15–75)	0.174
Duration of disease (months)	14.5 (2–300)	18 (3–600)	12 (10–24)	0.755
Lesions at onset				
No lesion	9 (28.13%)	0 (0.00%)	0 (0.00%)	<0.001
Excoriation	15 (46.88%)	0 (0.00%)	5 (45.45%)	
Excoriated papule	8 (25.00%)	1 (8.33%)	3 (27.27%)	
Excoriated nodule	0 (0.00%)	11 (91.67%)	0 (0.00%)	
Herpetiform lesion	0 (0.00%)	0 (0.00%)	3 (27.27%)	
Lesion location				
Scalp	1 (3.13%)[a]	0 (0.00%)[a]	3 (27.27%)[b]	0.016
Arm	12 (37.50%)[a]	10 (83.33%)[b]	6 (54.55%)[ab]	0.025
Elbow	4 (12.50%)[a]	0 (0.00%)[a]	5 (45.45%)[b]	0.009
Chest	5 (15.63%)	4 (33.33%)	2 (18.18%)	0.419
Abdomen	5 (15.63%)	0 (0.00%)	1 (9.09%)	0.326
Back	8 (25.00%)	5 (41.67%)	4 (36.36%)	0.515
Thigh	4 (12.50%)	5 (41.67%)	1 (9.09%)	0.056
Knee	4 (12.50%)[a]	3 (25.00%)[ab]	6 (54.55%)[b]	0.018
Lower leg	11 (34.38%)[a]	11 (91.67%)[b]	6 (54.55%)[a]	0.003
Gluteal area	7 (21.88%)	1 (8.33%)	3 (27.27%)	0.483
12-item pruritus severity score	16 (6–21)	17 (10–21)	15 (8–22)	0.433

N/A = not available

Data are shown as the median (minimum–maximum) for continuous variables according to the normality of the distribution and as frequency (percentage) for categorical variables

[ab]The same letters denote a lack of statistically significant differences between groups

Table 2: Measurements of performance to discriminate patients with DH from other patients

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)	AUC (95.0% CI)	*P*
BIOCHIP GAF 3X	72.73	100.00	94.55	100.00	93.62	0.854 (0.688–1.000)	<0.001
BIOCHIP liver (endomysium)	27.27	100.00	85.45	100.00	84.62	0.636 (0.429–0.844)	0.165
ELISA GAF 3X IgA	72.73	95.45	90.91	80.00	93.33	0.841 (0.678–1.000)	0.001
ELISA GAF 3X IgG	45.45	100.00	89.09	100.00	88.00	0.727 (0.527–0.928)	0.021
ELISA tTG IgA	63.64	97.73	90.91	87.50	91.49	0.807 (0.627–0.986)	0.002
ELISA tTG IgG	9.09	100.00	81.82	100.00	81.48	0.545 (0.345–0.746)	0.643
ELISA eTG	30.00	100.00	73.08	100.00	69.57	0.650 (0.417–0.883)	0.206

AUC = area under the receiver operating characteristic curve, CI = confidence interval, NPV = negative predictive value, PPV = positive predictive value

The HLA-DQ2 compatibility frequency was higher in the DH group than in the other groups ($P < 0.001$); however, a significant difference was not observed for HLA-DQ8 compatibility. Although DIF positivity was observed in four (44%) patients with DH, while only a single patient in the CP and PN groups had DIF positivity, the difference between groups was not significant ($P = 0.066$). Linear IgA accumulation was detected in the basement membrane of the patient, who was DIF positive in the CP group, and the ELISA was evaluated as negative. Treatment could not be applied because the patient did not return for a follow-up visit. In the PN group, the presence of autoantibodies against BP180 NC16A-4X and BP230 was confirmed by BIOCHIP and ELISA in the patient with DIF positivity. The patient has been diagnosed with PN-like bullous BP. BIOCHIP GAF 3X positivity occurred significantly more frequently in the DH group than in the other groups ($P < 0.001$). There were no differences in the anti-BP180 NC16A-4X, anti BP230, monkey esophagus, salt-split skin test, or rat bladder. Even though a significant difference was observed for liver (endomysium) positivity, only three patients (27%) in the DH group demonstrated positive results ($P = 0.002$). ELISA GAF 3X IgA and GAF 3X IgG positivity and ELISA tTG IgA positivity occurred significantly more frequently in patients with DH ($P < 0.001$ for all). Desmoglein-1 and -3 positivity were not identified in any patients, whereas the remaining parameters did not show statistically significant differences.

ROC analysis was performed to assess whether any parameters could distinguish patients with DH from the remainder of the study group. We found the BIOCHIP GAF 3X, ELISA GAF 3X IgA, ELISA GAF 3X IgG, and tTG IgA parameters had discriminatory values for DH. GAF 3X, as measured by the BIOCHIP method, had an area under the ROC curve of 0.854 (95% confidence interval: 0.688–1.000) for DH diagnosis with sensitivity, specificity, positive predictive, and negative predictive values of 72.73%, 100%, 100%, and 93.62%, respectively, demonstrating an overall accuracy of 94.55% [Table 2].

Discussion

The BIOCHIP technique provides a differential diagnosis between different ABD subtypes from a single serum sample containing multiple antigenic structures (in separate windows) in a single incubation area.[14] In the current study, we examined the diagnostic value of the BIOCHIP technique in the diagnosis of DH in patients with CP. Our findings showed that the BIOCHIP technique and ELISA methods could diagnose DH.

Previous studies have predicted that 85% of DH patients have HLA-DQ2 and 15% have HLA-DQ8 alleles. These alleles have been shown to demonstrate a high negative predictive value for the disease; therefore, their negativity can be used to rule out the disease.[7] We also found higher HLA-DQ2 compatibility frequency in patients with DH; however, it was identified in only six of the 11 patients. This may be due to the low sensitivity of the HLA test used in our center. In DH, autoantibodies specific to celiac disease, especially against naive gliadin, are lower than in the celiac disease; thus, the value of these tests in DH diagnosis may be limited. It has been reported that detecting autoantibodies targeting deamidated gliadin fragments, especially GAF 3X, is produced under the influence of tTG in the small intestines' inflammation environment in celiac patients, which may be more helpful for diagnosis.[15] This is because it has been reported that the use of GAF 3X as a substrate is superior to the use of naive gliadin, tTG, and endomysium in detecting DH. These findings are supported by the fact that, for DH diagnosis, GAF 3X IgA sensitivity was reported to be 84%, and GAF 3X IgG sensitivity was said to be 80% using an ELISA.[16] In another study, it was reported that the value of detection of GAF 3X with the BIOCHIP technique in the diagnosis of DH was highly similar to results obtained with DIF.[17] In the present study, GAF 3X detection with the BIOCHIP technique had 94.55% accuracy for DH diagnosis among patients with CP, whereas DIF was positive in only four of the 11 patients. Although it is necessary to diagnose nonspecific pathology cases and rule out other ABD group diseases via DIF, this method is invasive. It is also expensive because of the large number of antibodies required. In addition, positivity rates may vary depending on (1) whether appropriate laboratory standardization is performed between centers and (2) the level of experience of the examiner. However, the BIOCHIP technique is highly standardized and requires

minimal serum and is a minimally invasive procedure. It also enables rapid examination of many patients simultaneously, increasing consistency and efficiency. DIF-negative DH cases, a well-established phenomenon, are another disadvantage of DIF. According to our findings, we believe that detecting autoantibodies against GAF 3X via the BIOCHIP technique can usher in a new and practical approach to diagnosing DH. It should be noted that, although the GAF 3X assessment was very accurate, endomysium positivity (via BIOCHIP) was present in only three of the 11 patients, and ROC analysis did not demonstrate statistical significance. These values were lower than the sensitivity rates (52%–100%) reported previously in the literature.[18-20]

In the ELISA analysis of DH, the sensitivity and specificity of GAF 3X IgA were 72.73% and 95.45%, whereas these values were 45.45% and 100% for GAF 3X IgG, respectively. In a previous study, the sensitivities of ELISA GAF 3X IgA and IgG were reported to be 84% and 80%, respectively.[16] Our study found a similar sensitivity for GAF 3X IgA, but a lower sensitivity for GAF 3X IgG. In previous studies, the sensitivity of tTG IgA for DH was between 47% and 95%, with a specificity often higher than 90%.[18-20] In our study, the sensitivity and specificity of tTG IgA for DH detection were 63.64% and 97.73%, respectively. In contrast, tTG IgG did not provide a discriminatory value (a 9.09% sensitivity value, even though specificity was 100.0%). Our findings conflicted with a recent study, which found that eTG autoantigen was specific for DH.[6] In the current study, eTG was not found to have a discriminatory role in DH diagnosis. Previously, the sensitivity of eTG was reported to be between 52% and 100%, whereas it was found to have a sensitivity more significant than 90% according to an ELISA.[21,22] The test's specificity was excellent (100%) in this study, but sensitivity was only 30%. A limited number of studies have assessed eTG via an ELISA because eTG ELISA is not standard in all laboratories. Although the lack of significance in ROC analysis for eTG may be associated with the relatively low number of patients included in the analysis, we believe that this result is valuable in increasing awareness that eTG results may not be as accurate as previous publications suggest.

The most significant limitation of our study is the low sensitivity of DIF at our center. Therefore, in some patients who are DIF-negative but whose clinical characteristics are compatible with DH, the diagnosis of DH was confirmed by the response to a long-term gluten-free di*et al*one or a gluten-free diet and dapsone therapy. However, as included in the latest European S2k guideline of DH,[12] the response to the gluten-free diet and/or dapsone treatment is a new supportive diagnostic criterion for DH in patients whose clinical findings are thought to be compatible with DH with negative DIF results. It can aid in diagnosing response to treatment in centers where DIF has low sensitivity due to technical implementation, such as our center. Another limitation is that the research was not population-based and was conducted at a single center with a limited number of cases who had initially applied with CP; thus, these data do not demonstrate the efficacy of the BIOCHIP technique in identifying DH in the general population.

In a conclusion, DH could be determined with nearly excellent accuracy by BIOCHIP GAF 3X analysis among patients with CP. It is also noteworthy that ELISA methods had approximately 90% accuracy for identifying DH, even though our results suggest that the BIOCHIP-based determination of GAF 3X was superior. The 100% positive predictive value of the BIOCHIP GAF 3X measurement may be paired with HLA analyses (which have been established to be excellent for screening purposes) to confirm/exclude diagnosis in DIF negative with suspected clinical features of DH. Studies involving a higher number of patients, preferably with a more extended follow-up period, are needed to completely identify the role of the BIOCHIP technique in DH screening.

Acknowledgments

The funders had no role in the study design, data collection, and analysis, the decision to publish, or the preparation of the article. No additional external funding was received for this study.

Financial support and sponsorship

This study was supported by the "Research Projects Support Scholarship" based on the decision of the Turkish Dermatology Association.

Conflicts of interest

There are no conflicts of interest.

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