Clinical and Experimental Health Sciences

The Relationship Between Gluten Entheropathy and Nail Capileroscopy Findings and Disease Activation

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ABSTRACT

Objective: Nailfold Videocapilloroscopy (NVC) is an examination method that is used as an aid in the diagnosis, follow-up, and treatment strategy of rheumatic diseases such as systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and gives an idea about microcirculation by examining the vascular bed. It is a cheap, easily applicable, and quickly accessible method. Because of these features, we aimed to use the NVC method in patients with Gluten Enteropathy (GE) to determine whether this method will be a helpful technique in the diagnosis, activation decision, remission follow-up, and treatment strategy in patients with GE.

Methods: In this study, 67 patients diagnosed with GE (n=35 disease-active group (AGE), n=32 disease-related remission group (RGE), and control group (CG)-27 healthy people whose diagnosis of GE was ruled out were included in this study. Group and CG were divided into ten parameters in capillary pathologies (capillary density loss, dilated capillary, giant capillary, microhemorrhage, avascular area, tortuosity, branched capillary, disorganization, extravasation, angiogenesis). They were divided into two groups as RGE and compared with the results obtained from NVC measurements.

Results: When patients diagnosed with GE and CG were evaluated in terms of capillary disorder with NVC, While all of the patients with capillary disorders were in the GE group, no capillary disorders were found in the control group ($p<0.01$). When patients diagnosed with GE were divided into two groups (AGE and RGE), NVC measurements were compared; All patients with capillary disorders were found in the AGE group ($p<0.01$). Capillary density loss and/or avascular area were detected in 80.9% of patients with capillary disorders.

Conclucion: Our study found a statistically significant difference in NVC measurements between GE patients and CG ($p<0.01$). The fact that all patients with capillary disorders were in the active group in terms of the disease and no capillary disorders were detected in any patients in remission showed that this method could be used as an auxiliary technique in the diagnosis of GE, making the decision of activation or remission, monitoring the disease and determining treatment strategies.

1. INTRODUCTION

Gluten enteropathy (GE) is a disease that affects the small intestines. It progresses with chronic damage due to the inflammatory T cell response against the storage proteins called “gluten” in wheat, rye, barley, and oat (1). The clinical manifestations of this disease, which is also defined as celiac disease, are recurrent episodes of diarrhea and constipation, abdominal distention, abdominal pain, gastroesophageal reflux, weight loss, fatigue, anemia, osteoporosis, and malnutrition (2). The diagnosis combines clinical features, specific serological markers, endoscopic appearance, and biopsy results (3).

Nailfold Videocapilloroscopy (NVC) is an examination method used to diagnose rheumatic diseases such as systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and gives an idea in terms of microcirculation by examining the vascular bed. With NVC, the capillaries in the nail bed are enlarged approximately 200 times, and parameters such as capillary density loss, hemorrhage, avascular area, neogenesis, tortuosity, and disorganization are evaluated.

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This method is the best non-invasive technique used to evaluate microcirculation in vivo. It is an inexpensive, easily applicable method that guides the diagnosis, activation, remission, and even response to treatment of autoimmune diseases (4).

The pathogenesis of the extraintestinal manifestations of celiac disease is unknown. For example, some patients are faced with a clinic that leads to cirrhosis due to severe hepatotoxicity. The proposed mechanism in these patients was to find more hepatotoxins in the portal circulation. The presence of anti-tyroglobulin autoantibodies in liver biopsies supports this mechanism and suggests vascular-mediated organ damage (5). It has also been shown that celiac disease is associated with autoimmune diseases that cause microvascular damage, such as Sjögren's syndrome and systemic lupus erythematosus (6). In conclusion, although there is no study showing that celiac disease causes microvascular damage, it has suggested the possibility that this disease itself may cause damage to the microvascular bed by an unknown mechanism. This study was planned because capillaroscopy is the easiest method of examining the microvascular bed.

In this study, we aimed to determine whether there is a relationship between nail bed capillaroscopic findings of Celiac Disease, a systemic disease. We desired to see whether a Celiac disease helps decide on activation or remission with our results.

2. METHODS

2.1. Inclusion Criteria

Sixty-seven patients diagnosed with GE were included in the study. GE anti-tissue transglutaminase [a-TTG] sought positivity in these patients. Afterward, the small intestine biopsy taken by the endoscopic method was retrospectively scanned and evaluated histologically with the March-OberHuber classification. Patients in the Type 3 class with a high probability of GE biopsy findings based on intraepithelial lymphocyte increase (IEL), crypt hyperplasia, and villus shortening findings were included in the study (7,8).

Two groups were formed, the patient group with a diagnosis of GE, 35 patients with active disease (AGE), and 32 patients who met the criteria for remission (RGE). AGE's inclusion criteria were active clinical symptoms, positive a-TTG, and MOH type 3 class on endoscopic biopsy. All of the patients in this group were recruited from newly diagnosed patients. The patients in the RGE group were previously clinically positive, a-TTG positive, endoscopically in the MOH type 3 class, diagnosed with GE, had no clinical findings with a gluten-free diet, had negative autoantibodies, and lost typical pathological findings in endoscopic biopsy (MOH type 0, 1 and 2) patients are included. On the other hand, 27 non-smokers whose CG was admitted to the outpatient clinic of our hospital with nonspecific dyspeptic complaints, GE diagnosis was ruled out by serology and biopsy, without any systemic disease and pregnancy, were included.

2.2. Exclusion Criteria

In our study, patients younger than 16 years of age and older than 65 years, with any autoimmune disease such as systemic sclerosis, systemic sclerosis, systemic diseases such as hypertension, diabetes mellitus, chronic kidney failure, acute kidney failure, congestive heart failure, chronic lung diseases, malignancy, dilated cardiomyopathy. Patients with conditions or habits such as smoking and alcohol were not included in the study. Persons with congenital nail anomaly and anatomical defect or who lost a part of their finger in any way were also excluded from the study.

2.3. Methodology

NVC examination in all patients was performed by a VideoCap 3.0 videocapillaroscopy device and an experienced capillaroscopy specialist. The study was planned to be single-blind from the point of view of the capillaroscopist. Control capillaroscopy was designed one month later to demonstrate the reproducibility of the analysis. However, it could not be performed due to the possibility of changing the capillaroscopy of the patients under treatment and affecting the results. The biggest shortcoming of our study is the lack of reproducibility. NVC measurements were divided into ten parameters: dilated capillary, giant capillary, loss of capillary density, avascular area, disorganization, tortuosity, extravasation, microhemorrhage, branched capillary, and angiogenesis. Each individual to be examined for NVC was left in the test room at a temperature of 20-22˚C for at least 15 minutes before the procedure. The thickness of the standard capillary wall is 0.5 micrometer (µm), and its diameter is 4-9 µm (9). The diameter of the arterial column is 5-15 µm, and the diameter of the venular column is 7-18 µm. Dilated capillaries were defined as the arterial column diameter of the capillary larger than 15 µm or the venular column diameter more significant than 20 µm in NVC measurements. Capillaries with an arterial or venous column larger than 50 µm were defined as giant capillaries. Capillary density; is defined as the number of capillaries with a length of 1 millimeter (mm) in the distal row at each nail base (10). The presence of 9 to 13 capillaries per 1 mm in length was taken as a reference, and fewer than nine capillaries were accepted as a decrease in capillary density (11). The avascular area was considered two or more capillary reductions in different regions of the nail fold (10). Normal capillaries are straight like a hair or inverted u-shaped like a hairpin, and the deterioration of this architectural structure was considered disorganization. The term tortiotized was used for capillary folding. A hazy appearance on capillaroscopy due to extravasation of plasma from the damaged capillaries was accepted as extravasation. Bleeding outside the capillary due to capillary damage was considered a microhemorrhage. Capillaries with bush-like branches were deemed to be branched capillaries. Tortuosity in the capillary bed, branching, bush-type capillaries,

and anastomoses between capillaries were accepted as angiogenesis (11).

AGE, RGE, and C.G. were measured with our NVC device, and the relationship between the groups was investigated.

2.4. Statistical Analysis

AGE, RGE, and CG were measured with our NVC device, and all the patients investigated age, gender, and the relationship between them and NVC. The analysis tested compliance of numerical data with normal distribution with the ShaphiroWilk test. The Mann-Whitney U test was used to compare the non-normally distributed variables in the two groups. The relationship between categorical variables was tested with Chi-square. Descriptive statistics are given as mean ± standard deviation and median (25%-75%) for numerical variables and numbers (%) for categorical variables. Analytical measurements used SPSS 22.0 package program in the analysis, and $p<0.05$ was considered significant.

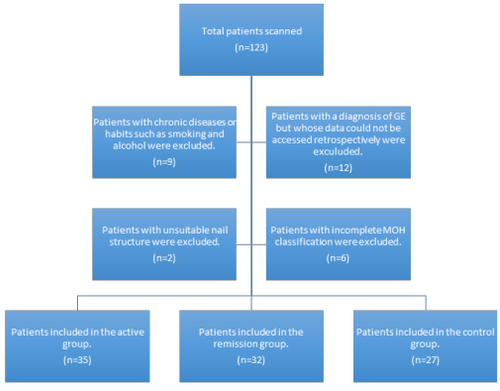
2.5. Ethics Approval

This study was carried out by T.C. It has been prepared with the approval of Gaziantep University Faculty of Medicine Ethics Committee with the number 300/2017.

3. RESULTS

The summary of the population included in our study is in table 1. The people included in the study consisted of 71.3% (n=67) patients with a diagnosis of GE, 28.7% (n=27) from CG, and a total of 94 people were included in the study. When GE and CG were compared in gender, 70.4% (n=19) of CG was female, and 70.1% (n=47) of GE was female. When GE and CG were compared in terms of gender and age, no statistically significant difference was found (female 70.1% vs. 70.4%, p=0.983, 27.64±10.06 years vs. 28.81±3.82 years, p=0.275).

Table 1. *Flowchart of the study population.*



Distribution of GE patients participating in the study according to the March-OberHuber classification; type 0: 40.3% (27), type 1: 4.5% (3), type 2: 3% (2), type 3a: 3% (2), type 3b: 6% (4), type 3c: 43.3% (29) was found (Figure 1). The patients with Type 0, 1 and 2 were in the RGE class, and the patients in Type 3 were in the AGE class.

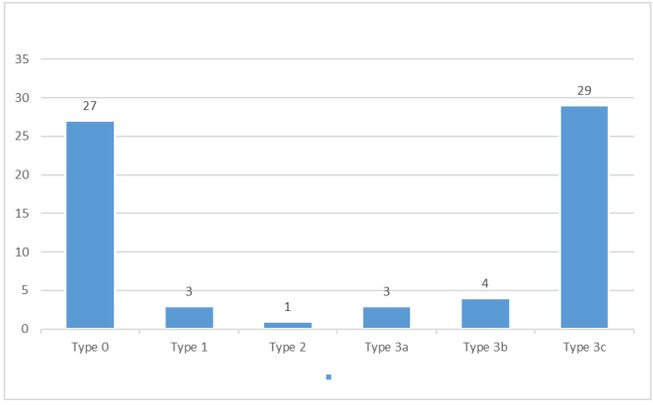


Figure 1. *Distribution of patients according to March-OberHuber classification*

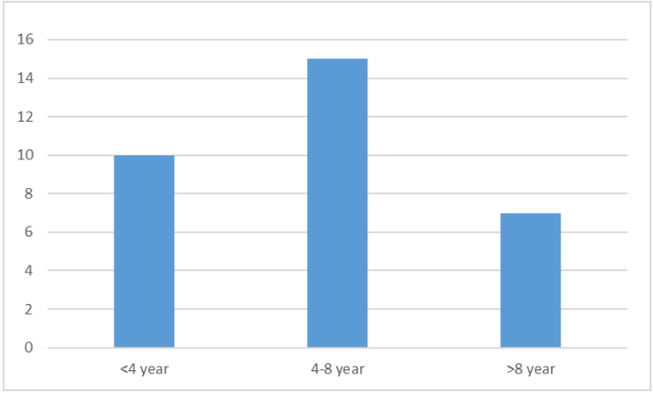


Figure 2. *Disease duration of the RGE group*

The distribution of the group in remission according to the years of follow-up; was determined as 31% (10) under four years, 47% (15 between 4 and 8 years), 22% (7) at eight years and above (Figure 2).

When the NVC measurement results of GE and CG were compared, the capillary disorder was found in 31.3% (21) of GE, and no pathology was detected in CG (p=0.001) (Table 2).

Table 2. *Capillary disorder comparison between GE and CG.*

PATIENT/CONTROL GROUP						
		GE (n=67)		CG (n=27)		p
Capillary Disorder	Negative	46	68,70%	27	100,00%	*0,001*
	Positive	21	31,30%	0	0,00%	

When GE was evaluated within itself, it was divided into two groups as AGE and RGE. No significant difference was found between AGE and RGE in evaluating gender and age (respectively; 71.4% female vs. 68.8% female, p=0.81, 28.80±11.05 years vs. 26.37±8, 85 years, p=0.355).

In NVC measurements made between AGE and RGE, the capillary disorder was detected in 60% (n=21) of AGE, and no capillary disease was detected in NVC measurements made in RGE. This result was statistically significant (Table 3).

Table 3. *Capillary disorder comparison between AGE and RGE.*

		GROUP				
		AGE (n=35)		RGE (n=32)		p
Capillary Disorder	Negative	14	40,00%	32	100,00%	*0,001*
	Positive	21	60,00%	0	0,00%	

Considering the subclasses of NVC measurements in AGE, capillary density loss and avascular area coexistence in 7 patients, density loss, dilated capillary and avascular area coexistence in 4 patients, density loss and dilated capillary coexistence in 2 patients, density loss, avascular area, and microhemorrhage coexistence in 1 patient were found. Also, loss of density in 2 patients, tortuosity in 2 patients, microhemorrhage in 1 patient, dilated capillary area in 1 patient, avascular location in 1 patient, and capillary disorder were detected in 21 patients in total. Giant capillaries, branching, disorganization, extravasation, and neogenesis were not seen in any patients.

4. DISCUSSION

During the development of GE disease, the duration of exposure to gluten and the onset and development of autoimmune disease is directly proportional (12). In the measurements we made in our study, all patients with capillary disorders were newly diagnosed and active in terms of the disease. This result shows that there is a significant relationship between capillary disorder and GE. While no capillary disorders were detected in our 32 patients in clinical, pathological, and complete laboratory remission, the detection of all patients with capillary disorders in the active patient group supports that gluten exposure is directly related to microvascular damage.

With the ingestion of gluten in GE, immunological events in which clinical findings occur due to the combination of gliadin peptides found in the small intestinal mucosa and HLA class II molecules begin. The tissue groups that show this reaction the most are HLA-DQ2 and HLA-DQ8 (13). It has been demonstrated that the 33-mer peptide in the structure of the gliadin molecule is the precursor molecule that initiates the inflammatory response in genetically predisposed individuals (14). This inflammatory response may also be causing damage at the capillary level. It is known that the level of serum a-TTG is related to the degree of villous atrophy (15). In the evaluation of these patients, it was determined that all 21 patients with capillary disorders were in the active AGE group, and antibody positivity was shown in all active patients. These results lead us to a significant relationship between the activity of the disease and the capillary disorder. The absence of capillary damage in any patient in remission supports this finding. As a result, it has been suggested that this method is a non-invasive and easy-to-apply helpful method that can be used in diagnosing GE, distinguishing active or remission disease, and monitoring the effectiveness of treatment.

In the NVC measurements we made in our study; We have classified capillary disorders into ten subclasses as capillary density loss, dilated capillary, giant capillary, microhemorrhage, tortuosity, avascular area, extravasation, branched capillary, disorganization, and neogenesis. In our measurements, capillary density loss in 76.2% (16) of patients with capillary disorders, an avascular area in 61.9% (13), dilated capillaries in 33.3% (7), and 9.5% (2) we detected microhemorrhage and tortuosities. In our measurements, capillary density loss in 76.2% (16) of patients with capillary disorders, the avascular area in 61.9% (13), dilated capillaries in 33.3% (7), and 9.5% (2) we detected microhemorrhage and tortuosities. In particular, loss of capillary density is seen in Raynaud's phenomenon and scleroderma. In contrast, the avascular area is seen in Wegener's disease, systemic lupus erythematosus, and scleroderma, and these two pathologies show direct tissue hypoxia (10,11). In our study, these two pathologies were detected together in 12 of our patients. When evaluated in total, we found that at least one of these two pathologies was present in 17 of 21 patients with capillary disorders (80.9% of patients with capillary disorders). This result suggested that the capillary disorder developing in the nail bed in GE disease was predominantly secondary to tissue hypoxia. These findings are similar to NVC findings seen in scleroderma. In a single-case publication presented by R.Thonhofer et al., it was found that an active scleroderma pattern was detected in the capillaroscopy measurement performed in a patient diagnosed with GE, and NVC measurements were found to improve with the removal of gluten from the diet (15). This single case presentation on this subject, which can be found in the literature review, supports the results of our study.

5. CONCLUSION

As a result of our study, it has been seen that NVC measurements are a proper method in diagnosing GE, predicting disease activation, and monitoring the response to treatment. Disruption of nail microarchitecture in active GE suggested that the disease may have systemic effects through immunological mechanisms. This finding may indicate that there are new pathways in the pathogenesis of the disease. These findings may contribute to elucidating the immunology of the disease.

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