

Allergic Purpura

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Low Level Laser Therapy in Children's Allergic Purpura

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ABSTRACT

Patients with allergic purpura have characteristic purpuric skin rash and some of the following clinical manifestations may be present: migratory polyarthralgias or polyarthritis, colicky abdominal pain, nephritis. Because until now there is no satisfactory treatment, we applied low level laser therapy (LLLT) in order to compare it with the classical therapy. Thirty-one children (2-16 years of age) have been included in the study and treated at debut of the disease. They were randomly divided: group A - (15 children) received LLLT; group B (16 children) was administrated classical therapy. Two GaAlAs diode lasers in red and infrared region (670 nm and 830 nm) were used. The density of energy (4 - 10 J/cm²), irradiating frequency (2.4 Hz) - was applied one session daily, using scanning technique under a special treatment protocol on cutaneous purpuric areas (21 sessions). Very good results were obtained in laser group. In the control group, after an apparent improvement, subsequent exacerbations and remissions were present, and three children developed chronic renal disease. The results prove that LLLT is acting as a triggering factor, which induces systemic effects through the circulation, followed by a response of the children's entire immune system. That is why LLLT is a very promising modality of treatment for the allergic diseases in children.

INTRODUCTION

Allergic purpura or anaphylactoid purpura is characterized by vasculitis of the small vessels, particularly those of the skin, gastrointestinal tract and kidney, which is most often manifested as a nonthrombocytopenic purpura, arthritis, nephritis, and abdominal pain. Heberden described for the first time this syndrome before 1800. In the 1830s, Schönlein described the typical rash and joint manifestations, and in 1870s Henoch recognized the gastrointestinal and renal manifestations. Osler pointed out the similarity between this disease and the hypersensitivity reactions, erythema multiforme and serum sickness.¹

The skin rash is often urticarial initially and then progresses to a macular-papular appearance that transforms into a diagnostic symmetric purpuric skin rash distributed on the ankles, buttocks, and elbows. The visceral lesions are less easily recognized but are more serious. The primary manifestations are due to vasculitis of the small blood vessels. Immune complexes (IgA with complement, IgG, or IgM) have been found in the serum and associated with blood vessel walls of the kidney, intestine, and skin.

The etiology is unknown. Suspected though not proved inciting antigens include group A β -hemolytic streptococci and other bacteria, viruses, drugs, foods, and insect bites.

The syndrome may occur at any age; it is more common in children than in adults, with most cases occurring in early childhood (2-8 yr. of age).

Approximately two-thirds of patients develop migratory polyarthralgias or polyarthritis, primarily of the ankles and knees. Abdominal colic – due to hemorrhage and edema primarily of the small intestine - occurs in about half of those affected. Twenty-five to fifty percent of those affected develop renal involvement. Hematuria alone is never the presenting complaint for purpura but usually manifests in the second to third week of illness.²

Conventional treatment

There is no specific and no satisfactory treatment. Therapeutic management is primarily supportive with close observation for signs of renal or gastrointestinal manifestations. In the rare instance in which a specific allergen can be proved the patient should avoid the antigen. When the disease follows a bacterial infection, particularly streptococcal illness, the organism should be eliminated and, if the disease recurs, prophylaxis considered. If culture for group A β -hemolytic streptococcus is positive or if the ASLO titer is elevated, penicillin should be given in full therapeutic doses for 10 days.

Symptomatic treatment is indicated for arthritis, rash, edema, fever, and malaise. Nonsteroidal anti-inflammatory drugs usually alleviate these self-limited discomforts. Intestinal hemorrhage, obstruction, intussusception, or perforation may be life threatening in the acute phase; these complications may be managed by the early use of corticosteroids. Therapy with prednisone, 1-2 mg/kg/24 hr, is often associated with dramatic improvement. Corticosteroid therapy is also indicated for the rare patient with central nervous system manifestations.

Corticosteroid therapy may provide symptomatic relief for severe gastrointestinal or joint manifestations but does not alter skin or renal manifestations. Acute renal failure should be managed in the same way as acute glomerulonephritis. Therapy for severe nephritis with corticosteroids, azathioprine and cyclophosphamide remains experimental, rarely justified.³

Prognosis

The prognosis for recovery is generally good, though symptoms frequently (25-50%) recur over a period of several months. In-patients who develop renal manifestations, microscopic hematuria may persist for years, and progression to renal failure occasionally occurs. Rarely death occurs from severe gastrointestinal complications, acute renal failure, or central nervous system involvement.⁴

Low Level Laser Therapy - A new modality of Treatment

Although it has been employed in the medical purposes from early sixties of the 20th Century, LLLT is still undergoing thorough scientific and clinical investigations. Three basic effects of LLLT (e.g., biostimulative-regenerative, analgesic and anti-inflammatory effect) haven't been challenged but fulfilled with effects of laser irradiation on the immune circulatory and hematological system, as well as promising effect of laser light on the oncological patients. Additionally, LLLT appear to have a virustatic and bacteriostatic effect.⁵

The first application of LLLT was completed on dermatological disorders like skin ulcers in early sixties. In the meantime, the range of dermatological indications for LLLT has increased.⁶

In order to reduce the suffering of children with allergic purpura we applied low level laser therapy for its *biomodulation* action on the entire immune system. This therapeutic modality was previously proven to have a benefic effect on blood circulation. That is why we thought that LLL could regenerate the microcirculation in the skin, affected by this disease. In the end, analyzing the obtained results for the LLL-treated patients, our presumption proved to be true.

METHODS

Patients and Study Design

Thirty-one children (2-16 years of age) were suffering from allergic purpura at debut of the disease. They were included in a two-year long study and randomly divided as follows: Group A - 15 children (5 girls and 10 boys, mean age 7.13 yr.) were applied LLLT. Group B - including 16 children (5 girls and 11 boys, mean age 7.0 yr.), was administrated classical therapy. Exclusion criterion for the both groups was the presence of any renal involvement. Also, patients were excluded if they had a history of chronic allergic purpura. They have been checked for an eventual previous upper respiratory infection, even streptococcal; allergy or drug sensitivity, as triggering factors for allergic purpura. The accurate diagnosis of allergic purpura was confirmed by the clinical manifestations of the disease and laboratory tests results. Basic demographic information and clinical characteristics before initializing the treatment are presented in Table 1.

Table 1. Demographic information and initial clinical characteristics.

Characteristics	Group A - LLLT (n=15)	Group B (n=16)
Sex: Boys:	66.7% (10)	68.8% (11)

Girls:	33.3% (5)	31.2% (5)
Average Age at Onset	7.13	7.0
Purpuric Rash	15 (100%)	16 (100%)
Fever	13 (86.7%)	14 (87.5%)
Angioedema	8 (53.3%)	6 (37.5%)
Arthritis	15 (100%)	12 (75%)
Abdominal Pain	12 (80%)	11 (68.7%)
Nephritis	0	0
Laboratory Findings (%)		
Hb (<10 g/dl)	9 (60%)	10 (62.5%)
Platelet count (> 400 x 10 ⁹ / L)	4 (26.7%)	5 (31.3%)
Leukocyte count (> 15.5 x 10 ⁹ / L)	11 (73.3%)	11 (68.7%)
Neutrophils-“segs” (> 62%)	11 (73.3%)	11 (68.7%)
ESR (>15 mm/h)	12 (80%)	12 (75%)
C Reactive Protein (> 0,75 mg/dl)	14 (93.3%)	14 (87.5%)
Serum IgA (>160 ui/l)	5 (33.3%)	4 (25%)
CH ₅₀ (> 125 CH ₅₀ u.)	6 (40%)	7 (43.8%)
CIC (> 20 mgeq/ml.)	5 (33.3%)	6 (37.5%)
c-ANCA (> 10 ui/ml)	3 (20%)	3 (18.8%)
p-ANCA (> 6 ui/ml)	3 (20%)	3 (18.8%)
Urinary Sediment - Hematuria	-	-

Plausible Triggering Factors for Allergic Purpura

Because the etiology of allergic purpura remains uncertain and some specialists tend to think that the disease often follows an upper respiratory infection, sometimes streptococcal, we checked each patient for an eventual upper respiratory infection. We also looked for allergy or drug sensitivity as triggering factors for allergic purpura and for the critical role played by immunoglobuline A in the immunopathogenesis of this disease (see Table 1), trying to place a particular emphasis on new information about the etiology, immunopathogenesis, and treatment of allergic purpura.

Our patients' clinical data concerning the association of group A β -hemolytic streptococcal infection, bacterial infection, allergy or drug sensitivity, and allergic purpura are presented in Table 2.

Table 2. Plausible Triggering Factors for allergic purpura.

Plausible Triggering Factors	Group A (n=15)	Group B (n=16)
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Group A - b - hemolytic Streptococci	4 (26.7 %)	3 (18.8 %)
Group B - b - hemolytic Streptococci	2 (13.3 %)	2 (12.5 %)
Respiratory infection (bacteria, viruses)	3 (20 %)	4 (25 %)
Drugs (Aspirin, Biseptol)	3 (20 %)	2 (12.5 %)
Foods	2 (13.3 %)	2 (12.5 %)

Disease evaluation Scores

In order to evaluate the clinical severity at presentation and status at follow-up, each patient was categorized according to the original criteria defined in Table 3. As such, each patient was assigned a total score that was calculated summing the separate scores assessed for each clinical manifestation (see Table 3).

Table 3. Clinical severity scoring system.

Clinical Manifestations	Status	Score
Purpuric Rash	Absent	0
	Urticaria	1
	Erythema	2
	Maculopapular Lesions and Petechial Lesions	3
	Larger Hemorrhages (<i>Palpable Purpura</i>)	4
Areas Affected by Purpuric Rash	Absent	0
	Lower Extremities	1
	Lower Extremities + Buttocks + Elbows	2
	Extended to Upper Extremities	3
	Extended to Upper Trunk and Face	4
Angioedema	Absent	0
	Dorsal Surfaces of Feet	1
	Dorsal Surfaces of Feet and Hands	2
	Extended to Scalp	3
	Scalp + Eyelids + Lips + Ears	4
Fever	36,5 °C	0
	36,5 - 38,0 °C	1
	38,0 - 39,0 °C	2
	39,0 - 40,0 °C	3
	> 40 °C	4
Arthritis	Absent	0
	Polyarthralgias	1
	Single Joint	2
	Several Joints	3
Abdominal Manifestations	Absent	0

	Nausea	1
	Vomiting	2
	Recurrent Colicky Midabdominal Pain	3
	Blood and Mucus in Stool because of Hemorrhage and Edema of the Small Intestine	4
Renal Involvement	Absent	0
	Hematuria	1
	Proteinuria	2
	Chronic Renal Disease	3

Skin and Renal Biopsies

For skin biopsy a fresh but well-developed lesion from skin should be selected for removal. The selection of primary lesions is extremely important to obtain an accurate diagnosis. The site of the biopsy should have relatively low risk for damage to underlying dermal structures. *Lidocaine (Xylocaine)* 1 or 2 %, with or without epinephrine, should be injected intradermally after cleansing of the site. The biopsy should be made at the proper depth in order that all three layers (epidermis, dermis, and subcutis) can be examined.⁷ The biopsy specimen should be placed in 10 % formaldehyde solution (*Formalin*) for appropriate processing. Biopsy of skin by excision is rarely required for diagnosis in children. More recommended is the *punch biopsy*, which is a relatively painless procedure and usually provides adequate tissue for examination.

Treatment protocol

Group A was treated with low level laser, using two GaAlAs diode lasers (670 nm and 830 nm, maximum output power 50 mW, respectively 300 mW). The density of energy was 4 - 10 J/cm². Irradiation (2.4 Hz frequency) at both wavelengths combined with the same dosages - was applied one session daily, using scanning technique on cutaneous purpuric areas (21 sessions). These patients had an unrestricted regime of life concerning the sleep and resting period.

Group B was administrated a complex medication: the classical therapy (antihistamines, capillaro-trophics, steroidal anti-inflammatory drugs) and all patients had an obligatory period of rest. Both groups were prescribed a non-allergic diet. Corticosteroid therapy was initiated in group B whenever it was necessary to relieve severe gastrointestinal or joint manifestations; in group A only two patients were administrated this kind of therapy. But this did not alter skin manifestations (or renal involvement). *Diclofenac* was administrated in cases of manifested arthritis, only in group B.

Sedatives represented a benefit for patients with gastrointestinal pain. If culture for group A and B β -hemolytic streptococci was positive or if the ASLO titer was elevated, penicillin had been given in full therapeutic doses for 10 days, in both groups. Patients have been monitored also after the end of treatment protocol for 2 years, and some are still under observation.

Data Analysis

The evolution of the total acuity score of allergic purpura manifestations was the main objective of the present study. A step by step approach was used for the statistical evaluation. Initially, score data were transformed by square rooting. On this transformed data, a paired two-way t test was performed within each group, evaluating the clinical symptoms and parameters, from the beginning of the treatment until the end. Any difference was considered to be significant for p values less than 0.05. Data were analyzed using appropriate software.

RESULTS

Even if the distribution of patients was randomly designed, both groups resembled each other concerning the initial clinical manifestations and laboratory findings (two relatively homogeneous groups of patients) (see Tables 1 and 2).

The onset of the disease was abrupt with simultaneous appearance of several manifestations in 71% of patients, and gradual with sequential appearance of different manifestations for the rest. The dominant clinical feature of allergic purpura, cutaneous purpura was present in 100% of the children, with a symmetrical anatomic distribution (mostly on the buttocks and lower extremities) and the same patterns of skin involvement. The rash was associated with maculopapular lesions and variable elements of urticaria and erythema.

Most patients had arthritis, which frequently affected the knees and ankles (100% - group A and 75% - group B), abdominal pain (80% - group A and 68.7% - group B), angioedema (53.3% -group A and 37.5% - group B), and none of the patients manifested nephritis at onset.

Laboratory findings revealed anemia in both groups (60% - Group A and 62.5% - Group B), an increased number of leukocytes (73.3% - Group A and 73.3% - Group B) and platelets (26.7% - Group A and 31.3% - Group B), while platelet function tests, and bleeding time were normal. One can also notice the elevation of serum C-reactive protein and increased serum immunoglobuline A (IgA) concentrations, IgA-containing circulating immune complexes (see Table 1).

The associations of group A beta-hemolytic streptococcal infections and allergic purpura was identified in both groups A and B (26.7% and 18.8%, respectively). A potential eliciting factor mostly infectious could be respiratory infections (20% - group A and 25% - group B) (see Table 2).

Biopsy data from the patients who underwent skin biopsies revealed vasculitis and inflammatory perivascular infiltrate with mononuclears in derma, useful for the differential allergic purpura diagnosis (Photos 1 and 2).

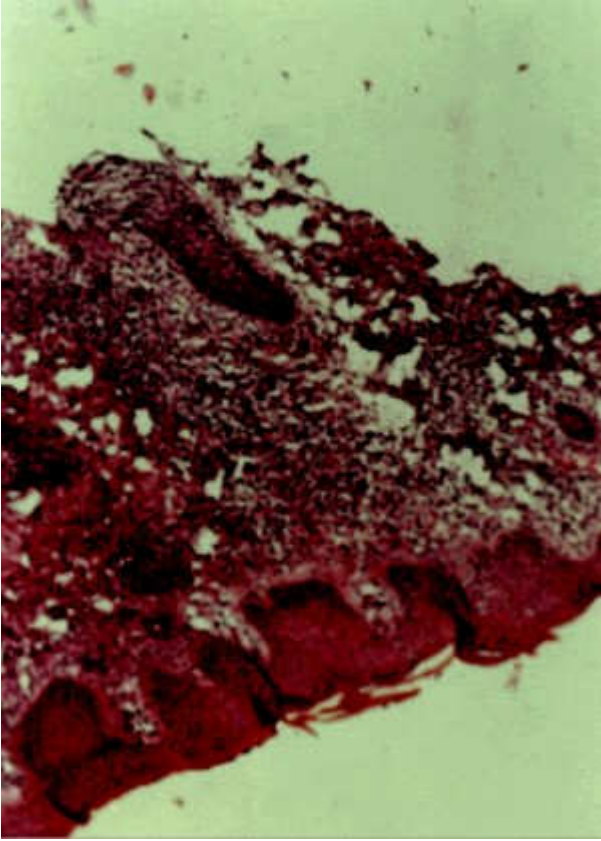
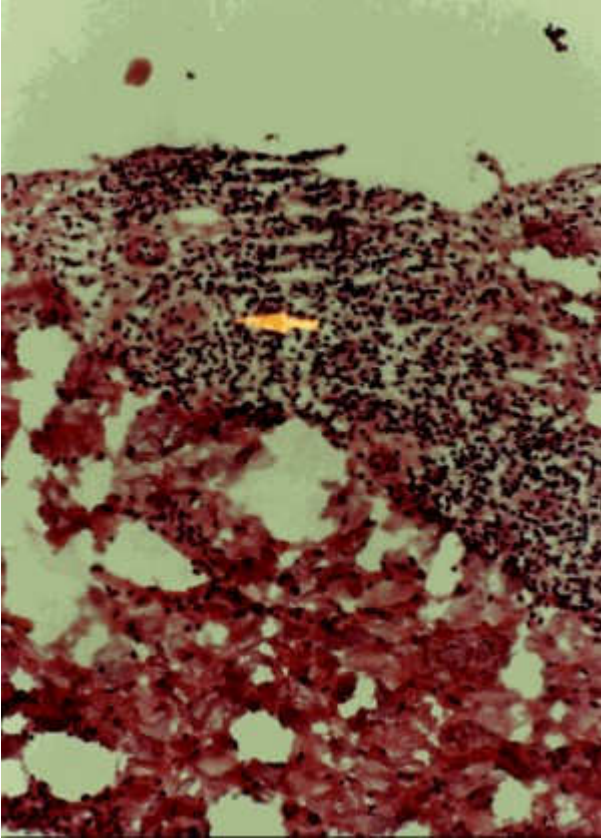


Photo 1: Perivascular mononuclear infiltrate (<- detail). Photo 2: Skin biopsy for allergic purpura.

All patients completed the protocol of treatment. The outcome comparison using the up-mentioned acuity scoring system with respect to allergic purpura evolution - between LLLT-group and the group B - is represented in Figures 1 and 2. This portion of the analysis was based solely on clinical information and did not use biopsy data.

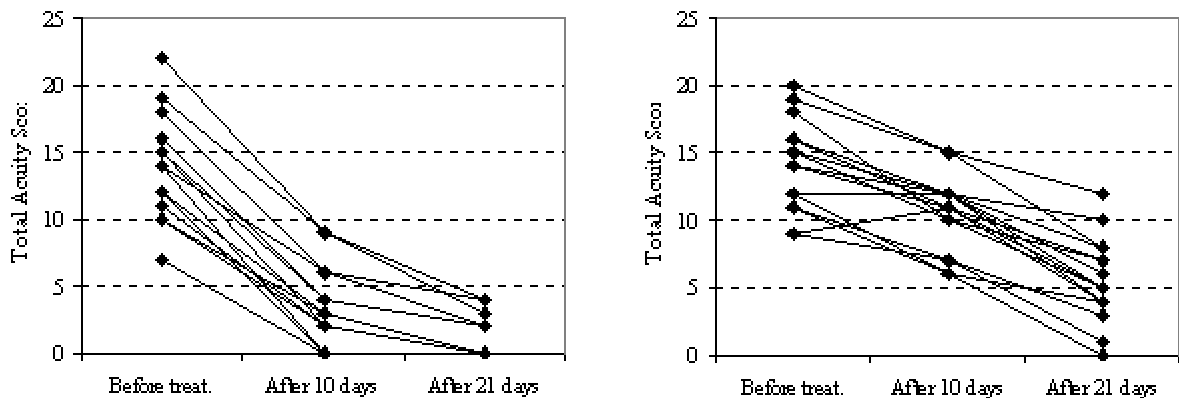


Figure 1: Evolution of the total score for group A. Figure 2: Evolution of the total score for group B.

Both in the LLLT-group and in the second group, the total acuity score for the clinical manifestations of allergic purpura was decreasing for each patient, but in different manners. It is observed the fact that the decrease rate was spectacularly in the first 10 days for the LLLT-group, with a great impact on the patient's next evolution.

The results demonstrate the efficiency of LLLT in triggering the healing process, which is much greater, then in the group treated conventionally. The laboratory data had in both groups a good evolution close to normality, accordingly with clinical symptoms. However, in the group B, 18.75% of children had renal involvement revealed by hematuria (see Figure 3).

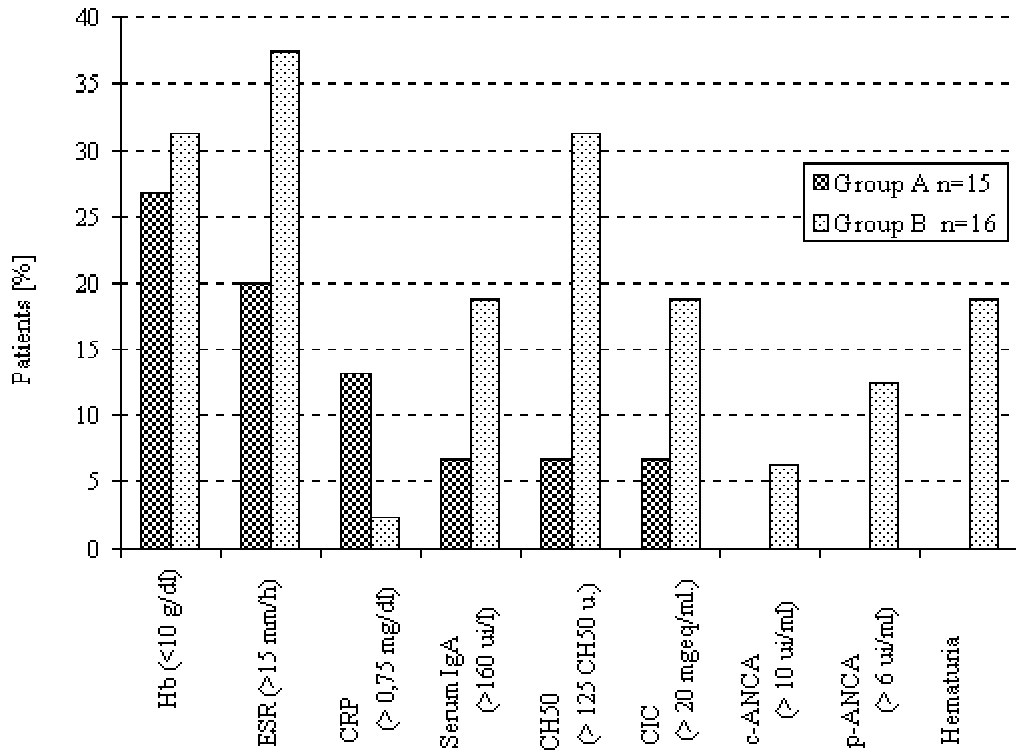


Figure 3: Laboratory findings after 21 days of treatment.

The recurrences of symptoms, the renal involvement and the remission of disease in the end of the treatment are represented for the LLLT group and the control group (Figures 4 and 5).

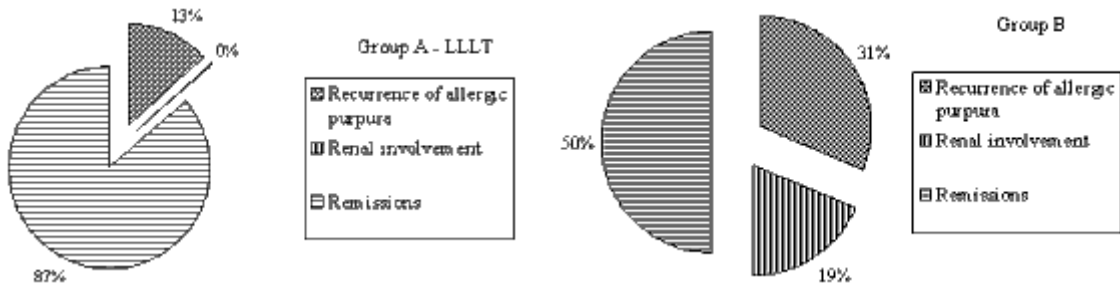


Figure 4: The results of LLLT in the end of treatment. Figure 5: The results of treatment in the control group.

The results for both therapeutic modalities were reevaluated after 6 and 12 months of treatment, concerning the mean number of recurrences and the remission of symptoms (Figures 6 and 7).

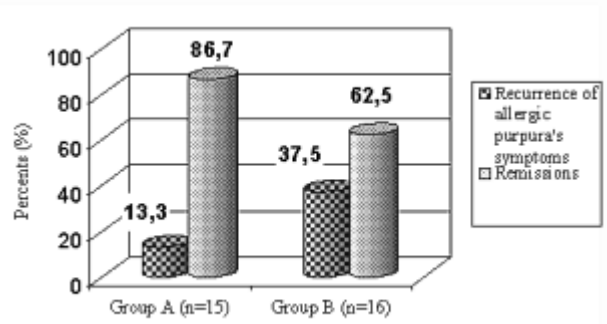
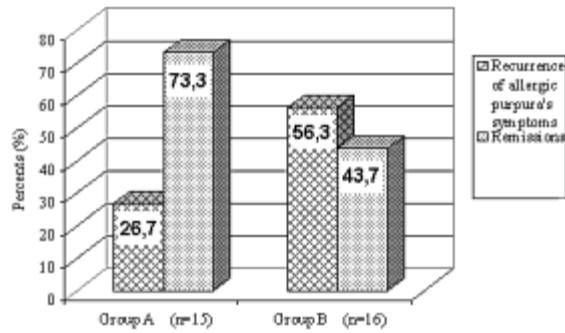


Figure 6: Distribution of the recurrences and Figure 7: Distribution of the recurrences and the remissions of allergic purpura after 6 the remissions of allergic purpura after 12 months.

One patient from the control group, who was more likely to have an unfavorable outcome, underwent a biopsy after six months from the initial therapy. The biopsy specimen showed abnormalities in the glomeruli, tubulointerstitium and vasculature, features that helped to identify the chronic nephritis in allergic purpura (Photo 3).

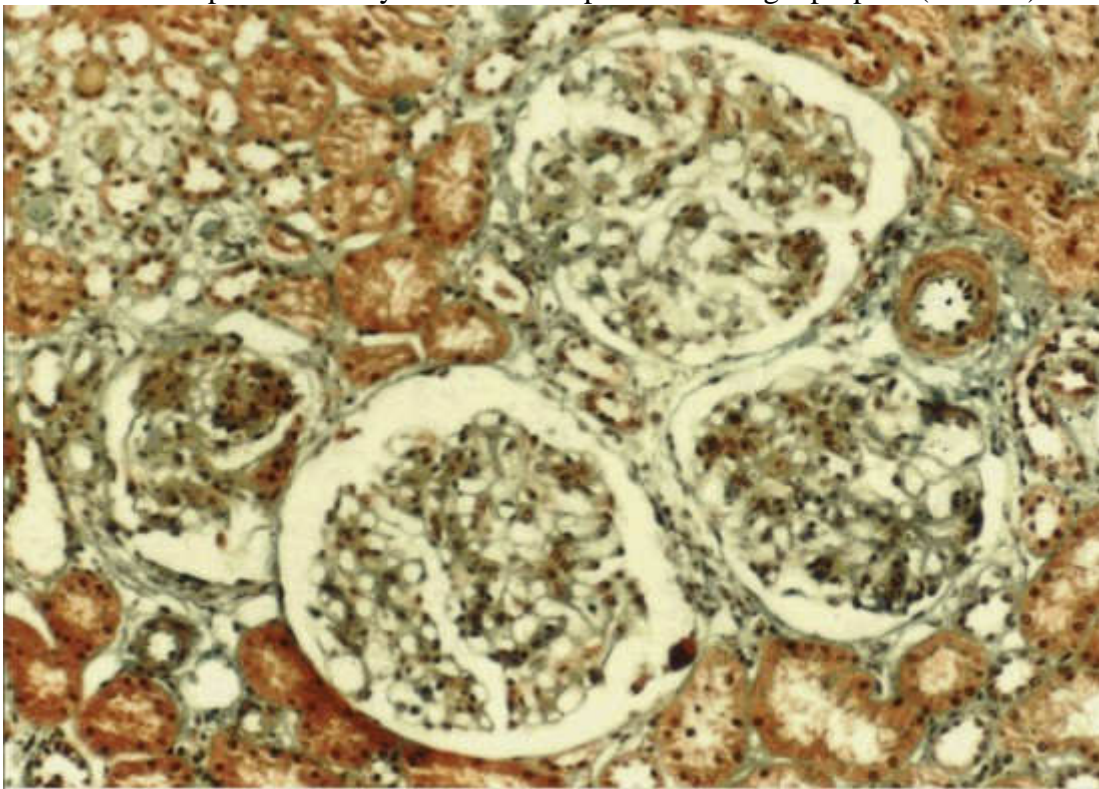


Photo 3: Histopathologic aspects of chronic glomerulonephritis with focal segmental sclerosis.

The results of LLLT and the favorable daily outcome for a patient from group A are presented in photos 4 and 5.



Photo 4: Allergic purpura - Day 1.



Photo 5: Allergic purpura - Day 5.

DISCUSSIONS and CONCLUSION

Allergic purpura is a systemic vasculitis of unknown cause that primarily affects children. Microvascular injury occurring during acute inflammation often results in increased vascular permeability and microvascular hemorrhage. Damage to vascular endothelial cells, basement membrane, and matrix components results from both neutrophil-dependent and neutrophil-independent mechanisms. Neutrophil-mediated injury of endothelial cells involves a complex cascade in which products from both cell types affect the cytotoxic outcome. It is also clear that the acute inflammatory response is carefully regulated by the endogenous gene expression of both pro-inflammatory and anti-inflammatory mediators.^{8,9}

We think that laser radiation of a certain frequency and wavelength could influence and control some mechanisms of endothelial cell injury. These interactions could be explained by synergetics, correlating the accelerated regulation of vascular damage in allergic purpura due to LLLT with the up-to-date concepts of low-level laser interaction with living cells and its systemic effects through circulating blood.

Previously applying LLLT we have succeeded in relieving the symptoms of asthma and rhinitis by inducing self-organizing phenomena at cellular level, with local and general effects of irradiation, making this a quick and effective form of treatment in children.^{10,11}

We conclude that early use of LLLT can cure allergic purpura in children and it is a better modality of treatment comparatively with the classical therapy. The very good results obtained in children are a challenge for future trends in applying lasers in medicine. The results prove that LLLT is acting as a triggering factor, which induces systemic effects through the circulation, followed by a response of the children's entire immune system.

That is why LLLT is a very promising modality of treatment for the allergic diseases in children.

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