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Subthreshold micropulse laser treatment – a procedure to resolve subretinal fluid in chronic central serous chorioretinopathy

Podprogowa laseroterapia mikropulsowa – zabieg powodujący resorpcję płynu podsiatkówkowego w przebiegu przewlekłej surowiczej chorioretinopatii

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Abstract:

Introduction: Chronic central serous chorioretinopathy is a serious therapeutic problem, as it may lead to significant visual impairment. To date, various invasive and non-invasive treatment methods have been tried with only moderate success.

Aim: To evaluate the efficacy of subthreshold micropulse laser treatment in different morphological types of chronic central serous chorioretinopathy.

Material and methods: A total of 29 patients with chronic central serous chorioretinopathy lasting for more than 6 months, underwent up to two sessions of subthreshold micropulse laser treatment, following which change in functional and morphological retinal parameters were measured (visual acuity, retinal thickness, maximum subretinal fluid height or maximum retinal pigment epithelial detachment). Results were analyzed separately for the two morphological types of chronic central serous chorioretinopathy: predominant subretinal fluid and pure retinal pigment epithelial detachment.

Results: In the group with predominant subretinal fluid, total resorption of the fluid was noted in 16 cases (75%). In the group with pure pigment epithelial detachment total flattening of the detachment was noted in 2 cases only (22%). Despite good morphological results, only a minor improvement in visual acuity in subretinal fluid group was noted. There was no visual acuity improvement in the pigment epithelial detachment group.

Conclusion: Subthreshold micropulse laser may be considered an option in the treatment of chronic central serous chorioretinopathy in patients with predominant subretinal fluid. To achieve better functional results, the procedure should be used early in the course of the disease. Long-standing chronic serous central chorioretinopathy may result in permanent loss of visual acuity.

Key words: subthreshold micropulse laser, central serous chorioretinopathy, subretinal fluid, pigment epithelial detachment, spectral optical coherence tomography.

Abstrakt:

Wprowadzenie: przewlekła postać centralnej surowiczej chorioretinopatii stanowi poważny problem terapeutyczny i może prowadzić do trwałego upośledzenia widzenia. Do dnia dzisiejszego stosowano rożne inwazyjne i nieinwazyjne metody leczenia, ale wyniki nie zawsze były satysfakcjonujące.

Cel: ocena efektów leczenia różnych morfologicznych form centralnej surowiczej chorioretinopatii za pomocą podprogowej laseroterapii mikropulsowej.

Materiał i metody: badaniem objęto 29 pacjentów z centralną surowiczą chorioretinopatią trwającą dłużej niż 6 miesięcy. U wszystkich wykonywano maksymalnie 2 sesje podprogowej laseroterapii mikropulsowej, oceniając następnie zmianę w parametrach morfologicznych i czynnościowych siatkówki (ostrość wzroku, grubość siatkówki centralnej, wysokość płynu podsiatkówkowego lub wysokość odwarstwienia nabłonka barwnikowego siatkówki). Wyniki analizowano oddzielnie dla 2 grup morfologicznych: postaci z dominującym płynem podsiatkówkowym oraz postaci z odwarstwieniem nabłonka barwnikowego.

Wyniki: w grupie z dominującym płynem podsiatkówkowym całkowitą resorpcję płynu osiągnięto w 16 oczach (75%). W grupie z odwarstwieniem nabłonka barwnikowego siatkówki zupełne spłaszczenie odwarstwienia odnotowano tylko w 2 oczach (22%). Pomimo dobrych wyników morfologicznych w grupie z płynem podsiatkówkowym poprawa ostrości wzroku była niewielka. W grupie z odwarstwieniem nabłonka barwnikowego nie odnotowano poprawy czynnościowej.

Wnioski: podprogowa laseroterapia mikropulsowa może być rozważana w przypadku postaci przewlekłej surowiczej chorioretinopatii z dominującym płynem podsiatkówkowym. Aby uzyskać lepsze efekty czynnościowe, decyzję o wdrożeniu terapii należy podejmować na wczesnym etapie choroby. Długotrwała surowicza chorioretinopatia może doprowadzić do trwałego pogorszenia widzenia.

Słowa kluczowe: podprogowa laseroterapia mikropulsowa, centralna surowicza chorioretinopatia, płyn podsiatkówkowy, odwarstwienie nabłonka barwnikowego siatkówki, spektralna optyczna koherentna tomografia.

The authors declare no conflict of interest/ Autorzy zgłaszają brak konfliktu interesów w związku z publikowaną pracą

Introduction

Central serous chorioretinopathy (CSCR) is a well-known ocular condition; however, its pathogenesis still remains unclear. CSCR occurs mostly as an idiopathic event, mainly affecting males, with a male to female ratio of 6: 1 or even as high as 10:1, and those aged 20 to 50, with the mean patient age of 40 to 50 years (1). It can also be diagnosed following steroid treatment (either systemic or topical), in the third trimester of pregnancy or concomitant to other diseases such as Cushing syndrome, *retinitis pigmentosa* or chorioretinal folds. Risk factors most often listed include stress, type A personality and systemic vascular diseases, such as hypertension or high heart rate. At present, most authors agree that the pathology is located within the choroid rather than the retinal pigment epithelium (RPE) (2). Indocyanine green angiograms revealed late hyperfluorescence corresponding to an increased permeability of choroidal vessels (3, 4). Alterations of the RPE are thought to be secondary to choroidal defects or dysfunctions (5, 6). Hypotheses abound as to why vasomotor control of the choroid is impaired in CSCR, with the concept of mineralocorticoid pathway attracting the attention of researchers in recent years (7). According to this hypothesis, activation of mineralocorticoid receptors, which are present in the kidneys, brain, heart, vessels, and also the choroid, results in the retention of fluid and its accumulation under the sensory retina. Mineralocorticoid receptors are activated by mineralocorticoids and glucocorticoids, which explains why CSCR sometimes occurs after steroid therapy, in Cushing syndrome or in the thirst trimester of pregnancy, when endogenous levels of cortisol are elevated. Corticoid involvement also explains the presence of vascular diseases and personality changes in CSCR patients. CSCR occurs in two basic forms, acute and chronic. The acute form predominantly presents morphologically as serous fluid accumulation under the neurosensory retina. The chronic form, on the other hand, may present in a few different ways, as subretinal fluid (SRF) – as in the acute form, as a retinal pigment epithelial detachment (PED) or as a mixture of both. The acute CSCR usually recedes spontaneously within a period of one to three months without any significant visual impairment. The chronic type (chronic central serous chorioretinopathy – CCSCR) lasts longer, even for a few years. Chronic accumulation of SRF, if central, leads to retinal thinning and photoreceptor loss. Patients usually end up with some visual impairment, which may be significant in some cases, which is why CCSCR is considered a serious therapeutic problem and why a number of different treatments methods have been tested over the years. The aim of this study was to analyze the utility of subthreshold micropulse laser treatment (SMPLT) in patients with CSCR.

Material and methods

In this retrospective study, twenty-nine patients with unilateral CCSCR were treated with SMPLT. CSCR was considered chronic if the duration of symptoms exceeded 6 months. The patients were divided into 2 groups according to the morphology of the CSCR: a group with predominant SRF (20 eyes) and a group with sole PED without SRF (9 eyes). All patients underwent full ophthalmic examination prior to treatment. The diagnosis of CSCR was determined by spectral optical coherence tomography (SOCT) (Zeiss Cirrus 4000) and fluorescein angiography (FA). Choroidal neovascularization (CNV) was excluded using FA. Best corrected visual acuity (BCVA) was measured using Snellen chart. Central retinal thickness (CRT), cube volume (CV), central retinal thickness average (CRTA), maximum SRF height in the SRF group and maximum PED height in the PED group were measured. The area of SRF or PED always covered the central part of the fovea, however, in some cases, the maximum height of SRF or PED did not exactly match the foveola, which is why we decided to determine other parameters, along with standard SOCT measurements, in order to assess the maximum change in retinal morphology after SMPLT.

BCVA and SOCT parameters were measured before treatment and 2 months after each SMPLT. In cases where absolute resorption of SRF was not achieved 2 months after the first SMPLT, a further SMPLT session was scheduled a month later (allowing a 3-month interval between the SMPLT sessions). BCVA and SOCT measurements were then repeated 2 months after the second SMPLT. During the SMPLT procedure, the whole area of SRF or PED, excluding the foveola, was covered with confluent foci of micropulse yellow laser (Supra Scan 577 from Quantel Medical) based on the SOCT retinal maps. The focus diameter was 160.0 μm, power was set at fixed level of 250 mW, time of exposure at 0.2 sec. and duty cycle at 5%. For the SRF group, the average number of laser expositions was 320 and for the PED group 220. The success criteria included a complete resorption of SRF or flattening of the PED. The autofluorescence imaging of the fundus (FAF) was also done during each scheduled appointment in order to exclude potential retinal damage. A correctly performed SMPLT procedure should result in no visible laser spots on FAF examination.

The Statistica 10.0 (StatSoft Inc., 2011) bundle was used for statistical analyses. The descriptive statistics were expressed by means of arithmetic mean (M), median (Me), standard deviation (SD), first and third quartiles (Q1 and Q3) and the minimum (Min) and maximum (Max) values. The assumption of normality of distribution was tested using the Shapiro-Wilk test. The statistical hypotheses were verified using the following nonparametric methods: Fisher's exact test, Mann-Whitney U test and Wilcoxon test. The results were considered statistically significant in cases where the calculated probability satisfied the inequality test, $p < .05$.

Results

The results were analyzed separately for the SRF and PED groups. In the SRF group, the age of the patients ranged from 41 to 80 years, with the mean age of 56 years. The group was predominantly made up of males, at a ratio of 15:5. The duration of CSCR symptoms ranged from 6 to 72 months, with the mean duration of 18 months. The final results following SMPLT are presented in Table I. A significant reduction was noted in all retinal thickness parameters: foveal CRT, CV and CRTA. A distinct retinal thinning in the central part was noted in 4 cases in the SRF group (CRT below 200.0 μm). The biggest change, from the mean value of 155 to 35.8 μm, was noted in the SRF height. The absolute resorption of SRF after one session of SMPLT was achieved in 12 out of 20 cases (60%). 4 patients

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with unsatisfactory results underwent another MPLT session, with 2 of them experiencing absolute resorption of SRF within 3 months after the second SMPLT. In one patient, the SRF resolved spontaneously after additional 3 months, without a second SMPLT treatment (Fig. 1). This results in an overall success rate of 75% (15 out of 20 patients).

Autofluorescence images of the fundus taken on scheduled follow-up visits showed no visible damage to the retina.

Good morphological results were, however, not reflected in satisfactory visual acuity improvement. BCVA improved slightly in the entire group – from 0.5 to 0.57. In patients with absolute resorption of SRF, BCVA improved from 0.54 to 0.6.

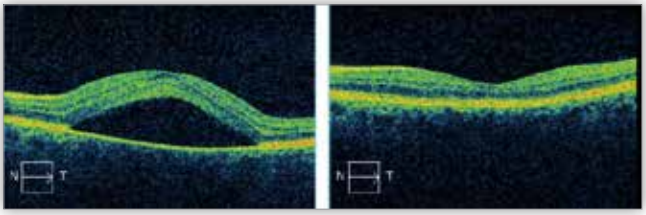

Fig. 1. SOCT of the retina before and after SMPLT in SRF case.
Ryc. 1. SOCT siatkówki przed SMPLT i po SMPLT u pacjenta z CSCR i SRF.

In the PED group, consisting of 2 women and 7 men, the age of the patients ranged from 42 to 69 years, with the mean age of 52. The duration of symptoms ranged from 6 to 72 months, with the mean duration of 21 months. The final results of SMPLT are presented in Table II (mean values). There was no significant change in foveal CRT and CV. CRTA was slightly reduced ($p<.05$), however, the most significant change was noted in the PED height. The total flattening of PED was achieved in 2 cases only (20%). 2 patients underwent further treatment during a second SMPLT session. However, it did not result in any further reduction of PED height.

Discussion

The first issue to be addressed in both therapeutic and diagnostic management of CCSCR is its retinal architecture, as baseline lesion morphology determines treatment outcomes. Retinal architecture in CCSCR differs significantly from its acute form. In the acute type, SRF is often present as a stand-alone symptom. PED may coexist with SRF in acute CSCR, however, this mixed type is seen less often. The chronic or recurrent type presents as a wide range of different retinal abnormalities, involving SRF, PED and RPE alterations, which present at different stages of the disease rather than coexist at the same time. As a result, CCSCR can be easily mistaken for age related macular degeneration and a distinction needs to be made between these two conditions.

Parameter/ Parametr	Before SMPLT/ Przed SMPLT	After SMPLT/ Po SMPLT	Change/ Zmiana	Statistical significance p< .05/ Istotność statystyczna p< ,05
CRT fovea μm	320.9	252.9	-98.0	yes/ tak
CV	10.67	10.19	-0.48	yes/ tak
Mean CRT μm	297.0	282.5	-14.5	yes/ tak
SRF maximum height μm	155.0	35.8	-102.45	yes/ tak
BCVA	0.5	0.57	+0.7	yes/ tak

CRT – central retinal thickness/ grubość siatkówki centralnej, CV – cube volume/ objętość siatkówki centralnej, BCVA – best corrected visual acuity/ najlepsza skorygowana ostrość wzroku

Tab. I. Results for SRF group after SMPLT (arithmetic mean values).
Tab. I. Wyniki SMPLT w grupie pacjentów z płynem podsiatkówkowym (wartości średnie).

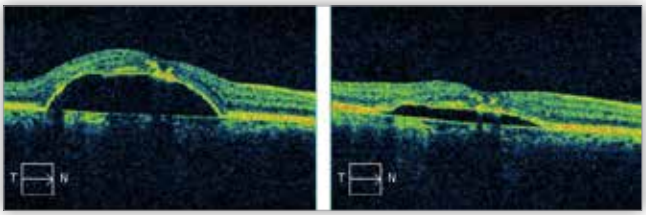

Fig. 2. SOCT of the retina before and after SMLT in PED case. The resolution of PED is not complete.
Ryc. 2. SOCT siatkówki przed SMPLT i po SMPLT u pacjenta z CSCR i PED. Resorpcja PED nie jest całkowita.

Chronic or recurrent CSCR presents as a serious therapeutic problem. Different approaches have been proposed, nevertheless, so far there seems to be no clear treatment algorithm.

Parameter/ Parametr	Before SMPLT/ Przed SMPLT	After SMPLT/ Po SMPLT	Change/ Zmiana	Statistical significance p< .05/ Istotność statystyczna p< ,05
CRT fovea μm	243.7	259.2	+15.55	no/ nie
CV	10.69	10.59	-0.1	no/ nie
Mean CRT μm	297.2	294.1	-3.11	yes/ tak
PED maximum height μm	360.8	228.8	-132.0	yes/ tak
BCVA	0.65	0.65	0	no/ nie

CRT – central retinal thickness/ grubość siatkówki centralnej, CV – cube volume/ objętość siatkówki centralnej, BCVA – best corrected visual acuity/ najlepsza skorygowana ostrość wzroku

Tab. II. Results for PED group after SMPLT (arithmetic mean values).
Tab. II. Wyniki SMPLT w grupie pacjentów z PED.

The available treatment strategies can be divided into systemic and topical approaches. Systemic medications used for the treatment of CCSCR include low doses of aspirin, acetazolamide, antibiotics (rifampicin, amoxicillin, or metronidazole), antifungals (ketoconazole), antimetabolites or beta-blockers. Some of these treatment strategies have been used with good results, however, further research is required in order to determine their efficacy (8–11). Topical treatment is generally not effective. There have been a few studies to evaluate non-steroid anti-inflammatory drops for CCSR, however, its role has not yet been confirmed by randomized studies (12).

Laser photocoagulation was shown to be an effective treatment in selected cases (13, 14). Usually green 532 nm or yellow 577 nm lasers are used for the procedure. Gass (15) proposed a list of indications for laser photocoagulation in CSRS. It should be used in cases where symptoms have persisted for more than 4 months or in recurrent CSCR. Fluorescein angiography is required for treatment planning. It is permissible to safely treat the foci of leakage located at least 300.0 to 500.0 μm from the foveola. Laser photocoagulation is, however, not suitable for treating all cases of CCSCR. There is a substantial number of cases where the leakage point is located within the center of the fovea or is itself difficult to define. Furthermore, laser photocoagulation close to the fovea results in a permanent scotoma, which may cause the patient a degree of discomfort.

Photodynamic therapy (PDT) with a half dose of verteporfin or low fluence laser emission has also been used with limited success (16–20). Despite an obvious benefit of leaving the retina intact, the access to PDT is limited due to its near withdrawal from the treatment of the exudative age-related macular degeneration (AMD). The significant cost of the procedure may also further impede its uptake. Intravitreal injections of Anti Vascular Endothelial Growth Factor (anti-VEGF) medications have also been used in the treatment of CCSCR, for the most part in interventional rather than randomized studies (21–24). Patients were normally required to receive a few injections, which, once again, is associated with considerable costs. Furthermore, an intravitreal injection, as an invasive procedure, carries a certain amount of risk for the patient. In most published papers, the anti-VEGF therapy did not prove to be superior to other treatments, including PDT and SMPLT (25–27).

Only recently, quite intensive research has been conducted on the efficacy of mineralocorticoid receptor inhibitors in the treatment of CCSCR (28–31). The use of medications from that group, predominantly eplerenone, is grounded in the theory that CCSCR is indirectly caused by mineralocorticoid receptor overactivation, which leads to fluid retention within the choroid, manifesting as serous chorioretinopathy. Some studies confirm the efficacy of mineralocorticoid receptor inhibitors in selected groups of patients (29–31), whereas others do not (28). Furthermore, such treatment needs to consider systemic side effects of eplerenone, such as electrolyte imabalance.

In the light of the current knowledge of CCSCR and available treatment options, subthreshold diode micropulse procedure appears to be an effective and relatively inexpensive therapeutic solution. Micropulse is, in fact, an additional feature of commercially available lasers of different wavelengths: 532 nm, 577 nm or 810 nm. Performed correctly, SMPLT does not affect sensory retina (32). Its impact is purely metabolic. It improves RPE function as a pump (33), thus achieving faster absorption of the subretinal fluid. It has also been suggested that SMPLT makes it possible to reset the faulty metabolic pathway of RPE cells and improve their function by triggering the production of different intracellular substances, known as heat shock proteins, by the RPE (34). The laser produces multiple short, low-power impulses separated by intervals, which enable the retinal tissue to cool and so that no thermal tissue damage is caused. The time for which the laser is effectively operational is called its duty cycle and in retinal diseases it is empirically set to 5% with each impact lasting for 0.2 s (35, 36). The issue of power level during SMPLT has raised some controversy. Two therapeutic approaches have been proposed: laser power titration and setting the power to fixed low values (ex. 200––300 mW for the Yellow laser). In our view, the titration method is associated with the risk of overtreatment. Primarily, it is difficult to determine which retinal tissue – edematous or healthy – is suitable for titration. Secondly, there is a question as to how much the laser power should be reduced by upon reaching the threshold power value, the standard recommendation being 50%. Our practice has seen a few cases of overtreatment despite very careful titration, and therefore, we opted for fixed low power parameters of 250 mW, as used by other authors for the SMPLT in diabetic macular edema (37, 38). Due to the possibility of overtreatment, we decided not to expose the foveola to SMPLT. The same strategy has been chosen by other authors who used yellow laser in CSCR (37, 38). A full transfoveolar procedure is, however, advocated by Luttrull, who uses 810 nm infrared laser (39).

The results of this study demonstrate the efficacy of the SMPLT procedure in cases of CCSCR with SRF and are, therefore, consistent with the results published recently by other authors (39–43). Luttrull successfully achieved SRF resolution after SMPLT in 11 cases of relatively short-lasting (up to 7 months) CCSR (39). Abd Elhamid reported significant improvement in CRT and contrast sensitivity in 15 eyes with CSCR, with symptoms lasting for an average of 4.6 months (40). Scholz et al. achieved a success rate of 74% in chronic CSCR, including patients unresponsive to PDT (41). Others reported short term efficacy of SMPLT in reducing the CRT in relatively small groups of patients with CSCR (42–44). In contrast to the majority of these studies, this study is based on assuredly chronic cases – the mean duration of symptoms being approximately one and a half years. Furthermore, to the best of our knowledge ours is the only study to date to have conducted separate analyses for SRF and PED groups. It was for the purpose of determining the eligibility of CCSCR patients for SMPLT that we decided upon this division in our methodology, following the observation of very poor response to SMPLT in patients with PED. Whereas pure serous PED is not uncommon in chronic CSCR, it is difficult to say whether sole PED is an active form of CSCR, resolved CSCR or rather an RPE dystrophy. Patients with this form of the disease usually present with decreased BCVA and hence our opinion that it is reasonable to attempt to treat them, especially considering that longstanding PED, if central, may result in further loss of vision in some cases. Nevertheless, we believe that it is equally important to be

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Study/ Badanie	No of eyes/ Liczba oczu	Type of CSCR/ Typ CSCR
Luttrull JK, Retina 2016	11	acute/ chronic/ ostry/ przewlekły
Abd Elhamid, Clin Ophthalmol. 2015	15	acute/ chronic/ ostry/ przewlekły
Scholz P, Ophthalmologica 2015	38	chronic, including resistant to PDT/ przewlekły, w tym niereagujący na PDT
Kim JY, Graefes Arch Clin Exp Ophthalmol. 2015	10	chronic and recurrent/ przewlekły i nawrotowy
Yadav NK, Eye 2015	15	chronic/ przewlekły
Malik KJ, Retina 2015	11	acute/ chronic/ ostry/ przewlekły

Tab. III. Number of eyes and average duration of CSCR symptoms in recent studies.
Tab. III. Liczba oczu i czas trwania CSCR wg doniesień z nowszych publikacji.

able to remove such patients from the sample where necessary, due to a potentially poor prognosis following SMPLT. In such cases, trying other forms of treatment than SMPLT, especially low fluence PDT, is advisable. In some stable cases, simple watchful waiting approach can also prove to be a good solution, as the case may be an RPE dystrophy rather than active inflammatory or endocrine processes.

Clearly, the analysis of the SRF group should define appropriate success criteria. Whilst assessing the effect of SMPLT on retinal morphology, the majority of authors focus on the CRT reduction (39, 40, 44, 45). However, cases where the maximum amount of retinal edema is located exactly in the center of the posterior pole are quite uncommon. The same applies to the location of the leakage point and maximum concentration of SRF (SRF height). It is, therefore, our view that the reduction of the maximum SRF height reflects the response to SMPLT treatment. Furthermore, considering the dynamics and the recurrent nature of CCSCR, the real treatment success is to achieve a complete SRF resolution, rather than its reduction. As a rule, the studies conducted to date have been carried out in a relatively small number of cases and have omitted the criterion of chronicity, often failing to analyze chronic and acute cases in a unison.

The very good morphological effect of SMPLT in the SRF group demonstrated in the current study was not reflected in the BCVA measurements. This is likely a result of the CSCR duration of almost 2 years in the study sample. In some cases, a significant retinal thinning was observed along with photoreceptor loss due to the longstanding accumulation of SRF. It is, therefore, plausible for CSCR patients to be eligible for SMPLT earlier. Ordinarily, in acute CSCR, symptoms resolve within 4 months following the onset. However, for some professionally active patients, this might seem too long to wait. Therefore, commencing treatment as early as upon the onset of symptoms should be considered as an option especially in patients with recurrent CSCR or in very active individuals, who find it hard to cope with even moderate visual impairment. There is no evidence to date to suggest that promptly undertaken CSCR treatment offers any advantage over waiting for a few months for a spontaneous resolution. Some researchers have, however, attempted to use SMPLT in treating acute CSCR, reporting good results (39, 40). Further research on the subject is definitely needed.

Conclusion

Patients with chronic CSCR, especially the phenotype with predominating subretinal fluid, may respond to subthreshold micropulse laser. According to the available data, the efficacy of SMPLT in pure serous PED seems to be poor, however, a larger population-based study is needed for firm conclusions. The duration of CCSCR has a negative impact on visual treatment outcomes. Significant improvement in BCVA is not to be expected in longstanding cases.

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