Central Serous Chorioretinopathy: A Review of the Literature

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Abstract: Central serous chorioretinopathy (CSCR) is an incompletely understood multifactorial disease of those who are middle aged characterized by the collection of fluid between the retinal pigment epithelium and the neurosensory retina. The exact etiology of CSCR and the reason of its predominance in middle-aged males are still unknown. Many pharmacologic modalities are suggested for CSCR with no proven efficacy. So this article was written to give a review of the relevant and recent literature on CSCR and to summarize the etiology, clinical features, and diagnostic modalities for CSCR with special emphasis on the treatment options available and those that are still under trial and can be of help in the future to fasten the recovery and reduce the recurrences.

Key Words: central serous chorioretinopathy, serum cortisol, autofluorescence, retinal pigment epithelium, micro pulse laser

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In 1866, von Graefe first described a disease of the macula with recurrent serous detachment and named it recurrent central retinitis. In 1955, Bennet named it central serous retinopathy. At the same time, Maumenee observed, using fluorescein angioscopy, that macular detachment resulted from a leak at the level of retinal pigment epithelium (RPE). In 1967, Gass provided the classic description of the pathogenesis and clinical features of this condition and termed it idiopathic central serous choriodiopathy.

Because the disease involves both the choroid and the retina, the currently accepted name is central serous chorioretinopathy (CSCR). Central serous chorioretinopathy is characterized by collection of fluid between the RPE and the neurosensory retina. It is incompletely understood with systemic associations, a multifactorial etiology, and a complex pathogenesis. From 1866, when Graefe first described CSCR, to the present, much study and effort continue to be directed toward the understanding and treatment for patients with CSCR. We need large, prospective, or even retrospective long-term follow-up studies to decide on 1 or more safe and effective forms of treatment, which will be generally accepted by clinicians. Until then, it seems reasonable to suggest laser or reduced dose/fluence/irradiation time verteporfin photodynamic therapy (PDT) in recurrent chronic CSCR or in single CSCR episodes, not resolving for a period of at least 3 months, accompanied by signs of chronic CSCR. Ongoing efforts include study regarding methods of evaluation, understanding of pathogenesis, and strategies for the treatment and prevention of this disease, which can cause significant short-term and long-term vision loss in affected individuals.

TYPES OF CENTRAL SEROUS CHORIORETINOPATHY

Acute/Typical/Classic CSCR

This is the commonest, seen in younger patients, characterized by acute localized detachment of retina, mild to moderate loss of visual acuity, 1 or few focal leaks seen in fluorescein angiography, and benign self-limiting course.

Chronic CSCR

This is also known as diffuse retinal pigment epitheliotropism or decompensated RPE.9 There is chronic presence of shallow subretinal fluid with widespread alteration of pigmentation of the RPE. This subtype is associated with older age, chronic (>6 months) detachment of the posterior pole, poorly defined RPE leakage or “ooze,” multiple pigment epithelial detachments (PEDs), and poor visual prognosis owing to cystoid macular edema, foveolar atrophy, subretinal fibrosis, and less commonly, choroidal neovascularization (CNV).10–12

There is third less common form that causes bullous retinal detachments usually inferiorly. It is usually associated with shifting fluid and more often seen in patients of organ transplantation.13,14 Patients using corticosteroids,15,16 and patients of Asian descent.17

PATHOGENESIS OF CENTRAL SEROUS CHORIORETINOPATHY

Retinal Pigment Epithelium Dysfunction

In fluorescein angiography, focal leakage sites are seen, which caused detachment of RPE or neurosensory detachment. This suggests that fluid emanates through the choroid and escapes into subretinal space through defect in tight junctions between cells of the RPE.18 According to experimental studies, injury to RPE speeds the resorption of subretinal fluid.19,20 These studies pointed out that a simple defect in the RPE integrity alone could not explain the findings of CSCR.21

One theory suggests that CSCR results from dysfunction of the RPE. This occurs after an undefined insult. Affected RPE cells (may be even a single cell) lose their normal polarity and pump fluid from the choroid toward the retina, causing a neurosensory detachment.22

All these theories failed to explain why the cells pumped in the wrong direction, how the pigment epithelium detachments formed, and how the single isolated disturbance of few RPE cells may overwhelm the physiologic RPE pump of neighboring normal RPE. Another factor for limitation of many theories of the etiology of CSCR is the lack of a suitable animal model to test hypotheses.
Choroid Dysfunction

Gass\(^3\) suggested that a focal increase in the permeability of the choriocapillaris was the primary cause of damage to the overlying RPE in patients with idiopathic central serous chorioretinopathy. Guyer et al\(^2\) suggested a potential model for the pathogenesis of CSCR based on indocyanine green (ICG)—videoangiography (ICG-V). They noted diffuse hyperpermeability around active leakage sites seen with ICG-V but not with fluorescein angiography. Therefore, they concluded that hyperpermeability was at the level of the choroid rather than the RPE. Excessive tissue hydrostatic pressure within the choroid from the vascular hyperpermeability may lead to mechanical disruption of the RPE barrier, damage of RPE cells, and abnormal egress of fluid under the retina.

Alterations in choroidal circulation may also cause choroidal ischemia. This was first noted by Hayashi et al.,\(^24\) who used similar diagnostic equipment and found areas of choroidal ischemia as well as leakage of ICG dye from the choriocapillaris. Fluorescein angiography and ICG angiography (ICG-A) with a scanning laser ophthalmoscope and a digital imaging system were performed to evaluate choroidal circulation changes in CSCR by Prunte and Flammer.\(^25\) In their study, segments with late choroidal hyperpermeability showed delay in filling, which has been attributed to decreased arterial perfusion or decreased venous outflow. This may create pressure overload and thus cause choroidal hyperpermeability. These observations are suggestive of a localized lobular inflammatory or ischemic choroiditis. However, the cause of the choroidal abnormality is still unknown. The answer may lie in changes of the autoregulation in the choroidal blood flow.\(^26\) Tittl et al\(^27\) suggested that a persistent abnormal regulatory response was involved in the pathogenesis of chronic CSCR. They found that subfoveal choroidal blood flow regulation in patients with chronic CSCR was impaired. This dysregulation occurred after substantial functional restoration at least 6 months after the last episode. Measurements of ocular fundus pulsation in patients with newly diagnosed active CSCR have previously provided evidence that choroidal perfusion in the macular region might be abnormal.\(^28\)

Combined RPE and Choroid Dysfunction

It has been shown that leaks at the levels of the RPE seen on the fluorescein angiography were contiguous with the areas of vascular hyperpermeability in ICG-A.\(^23\) However, all the areas of choroidal hyperpermeability are not associated with actual fluorescein leaks. These areas may be clinically silent and could affect the ability of overlying RPE to pump fluid from retina to the choroid.\(^26\)

ETIOLOGY OF CENTRAL SEROUS CHORIORETINOPATHY

Central serous chorioretinopathy is a disease that usually affects men between the age of 20 and 50 years. However, the youngest patient with CSCR ever described is a 7-year-old girl.\(^29\) Men are affected approximately 8 or 9 times more often than women.\(^30\) When CSCR occurs in women, it is more likely to occur between age 30 and 40 years. Idiopathic CSCR has been associated with type A\(^31\) personality and elevated endogenous cortisol.\(^32\) Cortisol is a hormone secreted by the adrenal cortex, which assists the body to deal with various forms of stress. It reduces inflammation and immune system function and triggers the breakdown of protein into sugars. The association of objective and subjective stress with CSCR also points to cortisol because stress raises cortisol levels. In addition, a high level of corticotrophin-releasing factor, the hypothalamic hormone that drives cortisol levels, causes a subjective experience of stressfulness. Patients with CSCR have high levels of cortisol made by their own adrenal gland (50%–80% higher than the average and outside the reference range).\(^32\)

This condition, predominantly, affects young males and its incidence declines with advancing age. Because plasma testosterone levels also decline with age,\(^33\) there might be some relation of CSCR with testosterone levels. Central serous chorioretinopathy has been associated with the use of corticosteroids\(^34\) and also with vasoconstrictive agents. There have been several cases where CSCR has recurred during each of several courses of treatment with cortisone drugs and gone away each time the treatment was stopped. It can be produced in animals by injection of intravenous epinephrine.\(^35\)

Haimovic et al\(^35\) evaluated systemic risk factors for CSCR. Systemic steroid use and pregnancy were most strongly associated with CSCR according to their study. Other risk factors included antibiotic use, alcohol use, untreated hypertension, and allergic respiratory disorders.

There is study that showed an association between Helicobacter pylori infection and CSCR. The prevalence of H. pylori infection was 78% in patients with CSCR compared with a prevalence of 43.5% in the control group in that study. The authors proposed that H. pylori infection may represent a risk factor in CSCR, although no further studies have substantiated this claim.\(^36\)

There are also studies that suggest that CSCR may be caused or modulated to some degree by psychological factors. Personality tests administered to patients with CSCR and a matched controlled group showed higher values on the hyperchondriac and hysteria scale in the group with CSCR.\(^37\) The association with migraine headache in some cases and the association with corticosteroids and epinephrine also imply a possible connection with stress. Central serous chorioretinopathy is also associated with pregnancy, but the underlying mechanism of CSCR in pregnancy remains unclear. It is believed that raised levels of endogenous steroid cortisol could set off a chain of events that alter the blood retinal barrier, choriocapillaris, and RPE, resulting in focal areas of increased permeability and thus leading to CSCR.\(^38\)

SYMPTOMS OF CENTRAL SEROUS CHORIORETINOPATHY

Mild blurring of vision with visual acuity ranging from 6/6 to 6/60, usually correctable with hyperopic correction,\(^39,40\) with varying degrees of central scotoma (due to detached retina), metamorphopsia (owing to irregular retinal plane), micropsia\(^41\) (due to increased distance between photoreceptors in the detached retina), dyschromatopsia (due to anatomic derangements),

FIGURE 1. Fundus photograph of the left eye of a patient having CSCR showing transparent detachment of neurosensory retina.
hypermetropization (due to anterior displacement of retinal plane), and migraine-like headaches.6

**SIGNS OF CENTRAL SEROUS CHORIORETINOPATHY**

Biomicroscopic examination reveals transparent detachment of neurosensory retina with a halo delimiting the elevated area (Fig. 1). There is absence of foveal light reflex. Sometimes there is yellowish discoloration of fovea due to increased visibility of retinal xanthophylls. Sometimes yellowish white deposits are seen covering the posterior surface of detached retina. Multiple yellowish white dotlike deposits covering the posterior surface of the detached retina can be seen.43,44

Usually, PED is present in patients with CSCR, and it has a round or oval shape with a pink halo owing to shallow separation of retina at the edge of the PED. Subretinal fluid is usually clear, thus details of RPE and choroid are visible but may be grayish or cloudy.43,44 Histopathologic studies show fibrin in subretinal fluid, which may polymerize and cause opacification.18

Peripheral dependent bullous neurosensory detachments have been described in patients with CSCR.45

**IMAGING TECHNIQUES**

**Fundus Fluorescein Angiography**

A typical finding is one or more hyperfluorescent leaks at the level of RPE.46 In most (approximately 90%) cases, inkblot pattern is seen (Fig. 2), and the dye spreads symmetrically to all sides and slowly and evenly stains the subretinal detachment. In approximately 10% of the cases, smokestack pattern is seen (Fig. 3), that is, the dye rises within the detachment and then expands laterally in a mushroom-or umbrella-like fashion along the upper limits of the detachment. This occurs because of the convection currents and a protein gradient with increased protein within the subretinal fluid.47 Focal leaks are more common nasally and superiorly than temporally and inferiory.46,48 Most leaking points are in a ring 1 mm wide starting 0.5 mm from the center of the fovea maybe because of the absence of rod cells in the foveal area resulting in weaker adhesions between RPE and neurosensory retina.46 In some cases, the leakage point is not seen either because the leak has healed or because of other mimicking conditions such as exudative age-related macular degeneration or unilateral acute idiopathic maculopathy.

Fundus autofluorescence (FAF) imaging is recently used as diagnostic modality because it is noninvasive, unlike FFA. In FAF, images of normal fundus, retinal vessels, and optic disc are dark because of lack of autofluorescence. In cases of CSCR, there are patches of autofluorescence in macular area because of intraretinal and subretinal precipitates. Spaide and Klaunck.49

**FIGURE 2.** Inkblot appearance on FFA of a patient having CSCR.

微型血管炎的典型特征是一致型荧光透射性漏点在视网膜外层的水平位置。46 在大多数（约90%）病例中，荧光素血管造影（FFA）模式可见（图2），染料以对称方式扩散到所有区域并缓慢均匀地染色。约10%的病例中，可见“烟斗”样模式（图3），其特点是光起源于视网膜色素上皮（RPE）内的漏点，然后在上部扩散形成蘑菇或伞状模式。46,47 在某些情况下，泄漏点不明确，可能是由于漏点已愈合或存在其他假性病变，如年龄相关性黄斑变性或中心性视网膜炎。

**Indocyanine Green**

This demonstrates multifocal areas of choroidal vascular hyperpermeability (unifying feature of all CSCRs irrespective of demography or etiology)50 representing occult PEDs.25,51,52 These areas are best seen in the mid phases of angiogram; in the later phases, choroidal hyperfluorescence becomes less prominent with silhouetting or negative staining of the larger choroidal vessels. Sometimes in quiescent phase of CSCR, there is no fluorescein leakage, but still there are areas of choroidal vascular hyperpermeability in ICG, which serves as a marker of the disease.

**Optical Coherence Tomography**

This is an effective and noninvasive method for quantifying serous detachments of retina and RPE (Fig. 4). Patterns seen are optically empty vaulted area representing neurosensory detachment, small bulges from RPE related to leaking spots, or semicircular space under the RPE with overlying thinned retina related to PEDs.53,54 (Fig. 4, white arrow). Longitudinal measurements help to track the resolution of subretinal fluid and provide an objective measure of the clinical course, thus reducing need for angiograms in each follow-up visit.55

**TREATMENT OF CENTRAL SEROUS CHORIORETINOPATHY**

Most of the CSCR cases resolve spontaneously within few months with final visual acuity of 6/9 or better.2,56,57 Only 5% of all CSCR cases experience severe permanent visual loss.5 Although CSCR has been described as a benign and self-limiting disease, it has a tendency to recur in about half of the cases, with decreased visual function. The need for early treatment emerges from clinical evidence that stresses that if the resolution of the neuroepithelial detachment occurs within 4 months after onset of symptoms, it is possible to reduce the incidence of retinal atrophy and the consequent decrease in visual acuity.58 In the largest case series of CSCR with exudative bullous retinal detachments, no significant difference was noted in the resolution of subretinal exudation, detachment, or final visual acuity in lasered versus nonlasered CSCR with exudative bullous retinal detachment patients.59 However, because their sample size was small and cases were not randomized for laser or nonlaser treatment, a prospective randomized study in future with a large
number of patients could possibly establish the efficacy of laser or some other alternative treatment.

**Pharmacologic Treatment**

Earlier psychotherapy was suggested as a therapy but was abandoned when the pathogenesis became clear. Several years ago, corticosteroids were presented as only pharmacologic treatment of CSCR, but its use was stopped once steroids were established as causative agents in CSCR. All the proposed pharmacologic therapies are based on pathologic mechanisms. Efficacy of barbiturates or tranquilizers in reducing the psychogenic component of this disorder is unknown. Because CSCR may be related to the abnormal circulating levels of epinephrine, the use of β-blockers has been suggested. Adrenocorticotropic hormone, anti-inflammatory drugs, retroluberal toxol injections, subconjunctival injections of milk, albumin and salt solutions, antisyphilitic and antitubercular drugs, insulin-free pancreatic extract, and thyroid extract have all also been suggested in the past. The use of the aforementioned agents was not proven to be effective by any clinical trials. The use of acetazolamide has been suggested with short-term encouraging results but no evidence of long-term benefit.

The use of low-dose aspirin results in more rapid visual rehabilitation and less recurrences in patients with CSCR according to a large case series. Its beneficial effect supports the hypothesis of impaired fibrinolysis and platelet aggregation in choriocapillaris in CSCR. Intravitreal bevacizumab (Avastin, F. Hoffmann-La Roche Ltd, Switzerland) has been used to successfully treat the rare complication of CNV after CSCR by reducing the choroidal hyperpermeability and choroidal ischemia. However, all of the related reports are small, uncontrolled case series with a short duration of follow-up. Larger, controlled trials are still needed to evaluate the efficacy and safety of anti-vascular endothelial growth factor agents for this indication.

Discontinuation of corticosteroids in atypical CSCR could lead to obliteration of RPE leaks and retinal reattachment without laser treatment.

**Argon Laser Treatment**

It is the most commonly used treatment modality. It reduces the leakage through the RPE and thus resolution of subretinal fluid. When applied at the site of leakage seen during FFA, it shortens the duration of macular detachment but does not affect the final visual acuity. According to some studies, laser reduces the rate of recurrence and according to others, it does not. Robertson and Ilstrup suggested a reduction in CSCR recurrences and shortening of the duration of detachment with direct laser photocoagulation compared with sham or indirect (away from the site of leakage) photocoagulation within a follow-up period of 18 months. Dellaporta concluded that untreated eyes were 3.3 times more likely to develop a recurrence than treated eyes.

The worst complication of laser treatment is photocoagulation of fovea, which leads to persistent scotoma, others being secondary choroidal neovascular membrane especially when excessive laser intensity is used, but this may also occur in untreated eyes.

Because CSCR is a self-limiting disease and also the literature on argon laser suggests that there is only a speedy resolution with no effect on final visual acuity and there are possible complications of laser especially when applied very close to fovea, thus there are only specific indications for photocoagulation: it is a general recommendation to observe a new-onset acute serous macular detachment for the first 3 months unless there are special occupational needs that require rapid resolution or in cases of unilocular patients. If macular detachment has not resolved in 3 months and leakage is remote from fovea, it is reasonable to do a laser treatment in a symptomatic patient. If the leakage is within 500 μm of fovea, it is recommended to observe for 6 months. Other indications for laser are history of CSCR in fellow eye with unfavorable outcome and recurrent macular detachment in the eye of a patient who has experienced permanent visual loss from initial episode. It is also indicated in severe forms of CSCR with poor prognosis if left untreated such as multiple serous detachments of RPE, bullous sensory retinal detachments, dependent neurosensory detachment, epithelial tracts, diffuse RPE decompensation, subretinal deposits of fibrin and lipids, and CSCRs associated with CNV. With a recent angiogram as a guide, more peripheral leaks are treated first, only up to the point of dull gray coagulation to avoid risk of secondary CNV.

After laser application at leakage point, resolution of macular detachment generally takes 2 weeks in uncomplicated cases or may be up to 6 weeks in long-standing cases with turbid subretinal fluid. Complete visual recovery requires twice that time. The patient should be monitored carefully for CNV in follow-up visits with repeat FFA if hemorrhage, increased turbidity of subretinal fluid, or thickening at the level of RPE in, at, or adjacent to the area of laser application is noted.

**Transpupillary Thermoderapy**

According to a study, it leads to resolution of CSCR with subfoveal angiographic leaks and significant improvement in visual outcome, in comparison with the natural history of persistent CSCR. Long-term results are unknown.

**Photodynamic Therapy**

Photodynamic therapy with verteporfin is a treatment modality with a rationale of reducing the blood flow in hyperpermeable choriocapillaris. Indocyanine green–guided PDT has shown promising results especially in cases of diffuse decompensation of RPE, which was earlier a challenge to treat because of multiple indistinct leaks. It causes the reduction of subretinal fluid; recurrences do occur but are responsive to retreatment.

Both fluorescein-guided (as it tightens the blood retinal barrier at the level of RPE) and ICG-A–guided (as it decreases choroidal hyperpermeability) PDT have been recommended for treatment of idiopathic CSCR. Fluorescein angiography–guided PDT can be used for typical acute leaks, but because of high cost, its use is limited to focal leaks near the center of the fovea where laser photocoagulation may cause excessive harm. In chronic CSCR, location of laser spot is based on regions of choroidal hyperpermeability seen on ICG.
Choroidal hypoperfusion, which is the main mechanism of action of PDT in CSCR, can also lead to complications, especially if conventional PDT is performed, according to the treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study guidelines. Lee et al described 3 cases of abrupt visual loss due to severe choroidal ischemia after using standard PDT in patients with CSCR. Retinal pigment epithelium atrophy, juxtafoveal CNV, and transient reduction in macular function demonstrated by multifocal electro-retinogram led investigators to reconsider PDT parameters for the treatment of CSCR. Zhao et al reduced the dosage of verteporfin and shortened the interval between infusion and laser application to induce choroidal vascular remodeling and minimize any collateral damage to adjacent retinal structures. The safe and beneficial effect of “safety enhanced” (half-dose verteporfin) PDT was demonstrated in both acute and chronic CSCR by the same investigators. Zhao suggested that 30% of verteporfin full dose was the effective lowest dose in the treatment of their patients with acute CSCR. Reibaldi et al described 2 cases of long-standing CSCR treated with ICG-A-guided low-fluence PDT. The anatomical and functional outcomes were encouraging. They concluded that ICG-A-guided low-fluence PDT seemed effective and safe for treating long-standing chronic CSCR. The same investigators studied the efficacy of ICG-guided low-fluence PDT compared with standard PDT in a prospective nonrandomized clinical trial; both standard-fluence PDT and low-fluence PDT resulted in complete subretinal fluid reabsorption with visual acuity improvement. They postulated that choroidal hypoperfusion related to PDT could be reduced by low-fluence PDT. Recently, Inoue et al shortened the irradiation time and reduced the total energy using the same light intensity and the same verteporfin dosage as the standard protocol. They reported that the success rate of PDT for CSCR depends on the degree of hyperfluorescence seen on ICG-A. Photodynamic therapy is not effective or the recurrence rate is predicted to be high in eyes without intense hyperfluorescence.

Long-term efficacy from this form of treatment is unknown. In addition, the number of patients in most of the relevant studies is limited, and often there is no dramatic improvement in terms of the functional outcome of the treatment despite impressive anatomical outcomes observed with OCT. In addition, using conventional PDT, visual improvement may be limited in patients with prolonged symptom duration and in those who have baseline confluent RPE atrophy and disintegrity of the junction between foveal outer and inner photoreceptor layer or progression of RPE atrophy after PDT. The risk of PDT-induced foveal injury in these patients should also be considered. As far as direct comparison of laser photoacogulation with PDT treatment is concerned, we now have some results coming from the study by Maruko et al., in which authors showed that the choroidal thickness and hyperpermeability seen during ICG-A was reduced after PDT. They suggested that PDT reduces the choroidal vascular hyperpermeability seen in CSCR and it may act by a different mechanism than laser photoacoulation. Most published studies suggest that PDT with verteporfin is a safe and efficacious treatment even in chronic CSCR and that complications are rare. This is especially true when PDT parameters are changed to minimize potential damage. However, conventional laser is still the choice because of its low cost and good efficacy as compared with PDT.

**Micropulse Laser Photoacogulation**

IQ 577 laser have been successfully used in few patients of chronic CSCR. The 577 nm yellow wavelength is ideal for CSCR and other retinal applications because it is highly selective for the RPE. Oxyhemoglobin in the RPE absorbs yellow light better than any other wavelength, whereas xanthophylls have negligible uptake of yellow light, localizing the effects to the RPE and further protecting the fovea. Yellow micropulse laser appears to be effective for chronic CSCR. In every case treated in 1 series, the improvement after treatment was significant. No retinal damage was seen in any of the eyes, except for minimal hyperfluorescence in 1 immunocompromised patient with RPE changes in both eyes before treatment. Although most patients in the series responded well within 30 days of treatment, some may need more than 1 laser treatment. Long-term, prospective studies are needed to confirm the safety and efficacy of this approach.

**CONCLUSIONS**

Central serous chorioretinopathy is an incompletely understood multifactorial disease of those in middle age characterized by the collection of fluid between RPE and neurosensory retina owing to RPE dysfunction and choroidal hyperpermeability. There is a proven association of CSCR with endogenous hypercortisolism and stress. It causes variable visual loss. Diagnosis can be aided with OCT, FFA, and ICG. Recently, there has been an increase in FAF imaging for CSCR owing to its noninvasive nature. There is no proven medical treatment for CSCR to date although trials are going on to test the efficacy of drugs antagonistic to the suggested causative factors. Conventional laser is still considered the choice because of its low cost and good efficacy compared with PDT. Trials are going on to establish the safety and efficacy of micropulse laser because it is selective to RPE and thus will protect the fovea, unlike laser, which can cause foveal scarring.

**REFERENCES**

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