

PAPER

Central nervous system lupus: a clinical approach to therapy

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Management of central nervous system (CNS) involvement still remains one of the most challenging problems in systemic lupus erythematosus (SLE). The best available evidence for the treatment of CNS lupus is largely based on retrospective series, case reports and expert opinion. Current therapy is empirical and tailored to the individual patient. Symptomatic, immunosuppressive and anticoagulant therapies are the main strategies for the management of CNS lupus. The choice depends on the most probable underlying pathogenic mechanism and the severity of the presenting neuropsychiatric symptoms. Thrombotic and nonthrombotic CNS disease needs to be differentiated and requires different management strategies. However, this is often challenging since many, if not most CNS manifestations, may be due to a combination of different pathogenic mechanisms and multiple CNS events may occur in the individual patient. Patients with mild manifestations may need symptomatic treatment only, whereas more severe acute nonthrombotic CNS manifestations may require pulse intravenous cyclophosphamide. Plasmapheresis may also be added in patients with more severe illness refractory to conventional treatment. Recently, the use of intrathecal methotrexate and dexamethasone has been reported in a small series of patients, with a good outcome in patients with severe CNS manifestations. Anticoagulation is warranted in patients with thrombotic disease, particularly in those with the antiphospholipid syndrome (APS). This article reviews the clinical approach to therapy in patients with CNS lupus. *Lupus* (2003) 12, 935–942.

Key words: aPL; CNS; immunosuppression; ischemia; SLE

Introduction

The involvement of the central nervous system (CNS) is one of the major causes of morbidity and mortality in systemic lupus erythematosus (SLE) patients and is the least understood aspect of the disease. Its recognition and treatment continue to represent a major diagnostic and therapeutic challenge for the clinician in daily practice.

Nervous system manifestations are present in up to 70% of patients with SLE.¹ The spectrum of CNS manifestations varies widely, from those with severe, life-threatening presentation, such as transverse myelitis or stroke, to those with more subtle and subclinical abnormalities in neurocognitive function, such as memory, intellect and learning.²

The different pathogenic mechanisms involved are poorly understood and the available therapy is often disappointing.³ The clinical diversity of the disorder,

the difficulty in defining outcome measures and the lack of diagnostic criteria have been considered the biggest obstacles to study treatment options and compare different therapeutic regimens.³ Only recently the American College of Rheumatology (ACR) has formulated specific criteria for neuropsychiatric lupus (NPSLE). This new nomenclature includes case definitions, reporting standards and diagnostic testing recommendations for 19 different neuropsychiatric syndromes.⁴

These definitions should provide reliable classification instruments to recruit homogeneous groups of patients in the design of randomized controlled trials. To date, the management of CNS lupus has been entirely empirical, largely based on uncontrolled series, anecdotal evidence and expert opinion.

With the exception of a study from Denburg *et al.*,⁵ there is no data from prospective controlled trials for the treatment of CNS lupus, and only a few recent studies have applied the new ACR criteria for NPSLE.^{6–10} In this review we discuss the current practice and pharmacological regimens available for the treatment of CNS lupus.

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CNS lupus: a clinical approach to therapy

Before starting specific therapy for CNS lupus it is important to make an accurate diagnosis and establish whether the neuropsychiatric event is likely to be primary to SLE or secondary to other concomitant conditions, which frequently occur in SLE patients. A careful and comprehensive differential diagnosis is imperative and exclusion of other possible aetiologies is mandatory. Thus the identification and treatment of infection, hypertension, hyperlipidemia, metabolic derangement and toxic effects of therapy is of paramount importance in these patients. Moreover, immunosuppressive therapy may also be associated with several opportunistic infections of the brain and differentiation between primary CNS involvement and CNS infection may be extremely difficult.¹¹ Cerebrospinal fluid (CSF) analysis, brain imaging and serological studies, including the C-reactive protein level, are particularly useful when considering infection or haemorrhage, especially when fever is present. Specific therapy for CNS lupus should only be started when CNS infection has been ruled out and the treatment of contributing/concomitant causes addressed. Therapy for CNS lupus should be adjusted according to the needs of the individual patient.¹² Symptomatic, immunosuppressive and anticoagulant therapies are the main treatment strategies available in the management of CNS lupus. Therapy will therefore depend on the severity of the presenting neuropsychiatric symptoms and the probable underlying pathogenic mechanism.¹²

It is important to differentiate between mild and severe manifestations and between thrombotic and nonthrom-

botic CNS disease, although making such a clear-cut differentiation may be challenging. To complicate this intricate issue, many of these CNS manifestations may be due to a combination of different pathogenic mechanisms and multiple CNS events may occur concomitantly in the individual patient. This is particularly true for some types of diffuse CNS manifestations, such as cognitive disorders, which may be related with the presence of antiphospholipid antibodies (aPL),^{13,14} and in cases of focal CNS disease, such as transverse myelitis, where the distinction between various pathogenic mechanisms, such as vasculitis, antibody mediated injury, thrombosis, or a combination of these is extremely difficult. The current therapeutic approach to CNS lupus is summarized in Table 1.

Mild CNS disease

Patients with mild neuropsychiatric disease may be treated conservatively – even, in some cases, not treated at all – since it seems that many of these cases are spontaneously reversible. Avoiding steroids in these particular cases has also helped in the reduction of complications such as secondary infection and steroid-induced osteoporosis and aseptic necrosis.¹⁵

Patients with mild diffuse manifestations such as anxiety and depression may need symptomatic treatment only. It is often difficult to decide whether anxiety/depression are due to SLE or simply related to having a chronic debilitating disease. Analgesics are largely used in patients with headache and migraine. Episodes of psychosis may be managed with psychotropic agents alone.¹⁶

Table 1 Therapeutic approach in CNS lupus

<i>Mild CNS disease</i>	<i>Severe CNS disease</i>	
<i>Symptomatic therapy</i>	<i>Diffuse/nonthrombotic disease</i>	<i>Focal/thrombotic disease – aPL associated</i>
<ul style="list-style-type: none"> • Analgesics/NSAIDs/calcium antagonists • Ergotamine • Anxiolytics • Antidepressants <ul style="list-style-type: none"> – Tricyclics-amitriptyline – Fluoxetine • Anticonvulsants <ul style="list-style-type: none"> – Carbamazepine – Phenytoin – Phenobarbitone – Valproate – Lamotrigine • Antipsychotics <ul style="list-style-type: none"> – Haloperidol – Chlorpromazine – Risperidone • Low dose corticosteroids 	<ul style="list-style-type: none"> • Acute treatment <ul style="list-style-type: none"> – High-dose corticosteroids – IV pulse methylprednisolone – IV pulse cyclophosphamide – Plasmapheresis – IV immunoglobulins – Methotrexate (? intrathecal) – Azathioprine – Mycophenolate mofetil • Chronic treatment <ul style="list-style-type: none"> – Taper corticosteroids – IV pulse cyclophosphamide – Methotrexate – Azathioprine – Mycophenolate mofetil 	<ul style="list-style-type: none"> • Prophylaxis <ul style="list-style-type: none"> – Low-dose aspirin • Thrombosis <ul style="list-style-type: none"> – Long-term warfarin <ul style="list-style-type: none"> – Arterial: INR=≥3.0 – Venous: INR=2.5–3.0 • Recurrent thrombosis <ul style="list-style-type: none"> – Warfarin INR ≥ 3.0 + low-dose aspirin • Difficult (resistant) cases with recurrent thrombosis <ul style="list-style-type: none"> – Warfarin INR ≥ 3.0 <li style="text-align: center;">+ – Corticosteroids – Immunosuppressants – IV immunoglobulins – Plasmapheresis

Patients with seizures are generally responsive to standard anticonvulsant therapy. The duration of the anticonvulsant treatment varies according to the clinical evolution of symptoms and is always patient tailored.¹⁷ Treatment does not differ from the treatment of epilepsy in the non-SLE population. Focal/partial seizures are generally treated with carbamazepine or phenytoin. Sodium valproate, lamotrigine and phenobarbitone are effective alternatives for some patients with partial seizures, with or without secondary generalization. Patients with generalized seizures respond to sodium valproate or lamotrigine. Suitable alternatives are carbamazepine and phenytoin, followed by phenobarbitone and diphenylhydantoin.^{18,19} There is no evidence to suggest that established SLE is aggravated by the use of anticonvulsant medication, even though these agents may occasionally cause drug-induced lupus. However, patients need to be close monitored for possible haematologic side effects, bone marrow suppression, drug-induced rashes and hepatotoxicity.¹⁷

Long-term antiepileptic treatment is indicated in the presence of concomitant cerebrovascular disease and/or persistent EEG abnormalities. In the absence of both, therapy may be discontinued after one year. Where seizures recur in spite of antiepileptic treatment, corticosteroids and/or immunosuppressants are generally used, especially when seizures occur with other nonthrombotic CNS disorders.¹⁷ Anticoagulation may be considered in a selected group of patients with seizures and persistent aPL positivity, as we will discuss later.

Severe CNS disease

Severe CNS disease may present as a focal manifestation, usually thrombotic in nature, or as a diffuse manifestation, consequent to various pathogenic mechanisms, such as vasculitis, antibody mediated injury, multifocal thrombosis or a combination of these. However, precise attribution responsibility to one particular mechanism is not always easy and in some cases, focal and diffuse manifestations may coincide in the same patient.

Focal/thrombotic disease

The most common manifestations of focal CNS disease in SLE patients are transient ischemic attacks (TIAs) and ischemic stroke. One of the most important advances in the treatment of CNS lupus has come from the recognition of the antiphospholipid syndrome (APS),²⁰ a prothrombotic disease, and the importance of thrombotic mechanisms in the development of a number of CNS manifestations in SLE patients.^{10,21} The presence of aPL is strongly associated with

thrombotic CNS events, including TIAs, ischemic stroke, amaurosis fugax, and cerebral venous thrombosis. aPL have been also associated with chorea, dementia, headache, transverse myelitis and seizures.²²

Many SLE patients with focal neurological manifestations and aPL, who would have previously received a high dose of corticosteroids and/or immunosuppression, are today being successfully treated with anticoagulation.²³ Corticosteroids do not seem to be helpful for the treatment of focal/thrombotic CNS disease.

The titres and persistence of aPL and the findings on brain MRI scanning are of major importance when deciding anticoagulant or antiaggregant treatment.¹⁶ Minimum treatment requires antiaggregant therapy as a prophylactic measure, but long-term anticoagulation with warfarin is mandatory where previous thrombotic events have occurred, mainly due to the high risk of recurrence seen in these patients.²⁴ Intensive warfarin therapy with an international normalized ratio (INR) ≥ 3 seems to be the most effective antithrombotic treatment in APS.²³

A frequent therapeutic dilemma is whether SLE patients with small high-density lesions on the brain MRI (suggestive of cerebral vasculopathy or thought to be due to multiple small infarcts) need to be treated at all, and if so, how they should be treated, mostly in the absence of overt neuropsychiatric manifestations.²⁵ In our experience, subclinical cognitive disorders, usually undetected in the absence of a formal neuropsychometric assessment, are frequent in these patients. Neuropsychometric testing often reveals a lower performance on tasks of attention, memory, language and psychomotor speed. In a recent study, we showed that the presence of small high-density lesions on MRI was associated with the presence of aPL,¹⁰ suggesting that SLE patients – especially when young (< 40-years old) – would benefit from antiaggregant/anticoagulant treatment. Due to the lack of prospective data, we generally consider antiaggregant therapy (aspirin 75–100mg/daily) as a first option. In our daily practice, patients who fail to respond to antiaggregant therapy, show progression on the brain MRI lesions or develop cognitive dysfunction, are then offered oral anticoagulation with warfarin.

Transverse myelitis has also been associated with aPL and, in some 'atypical' presentations, differential diagnosis with multiple sclerosis (MS) should be considered.^{26,27} Although improvement with anticoagulation has been reported in some selected cases,²⁷ aggressive immunosuppression has also been shown to be useful.²⁸

Chorea is a rare manifestation of SLE, occurring in 1–3% of patients,¹⁰ which may respond to a variety of

medications, including steroids, haloperidol, antiaggregant, anticoagulation or a combination of therapy.²⁹

Anticoagulant therapy is indicated in patients with seizures and aPL associated ischemic events. In a previous study from our group, seizures were found to be associated with moderate-to-high titres of aPL, suggesting a role for these antibodies in the aetiopathogenesis of epilepsy in SLE.³⁰ Our more recent experience confirmed a strong association between the presence of aPL and cerebrovascular disease, headache, cognitive dysfunction and seizures in a large series of SLE patients¹⁰ supporting the theory that an occlusive vasculopathy may be a major mechanism for neuropsychiatric lupus. These findings are of both theoretical and practical interest, especially from the therapeutic point of view and may warrant the consideration of anticoagulant treatment in those patients with more severe manifestations and an unsatisfactory response to conventional antiepileptic drugs.

Early studies showed that headaches might respond to corticosteroid treatment.³¹ In some cases, corticosteroids even proved to be more effective than conventional antimigraine therapy in controlling headache in SLE patients.³² Other types of headache such as chronic headache and tensional headache normally require symptomatic treatment only.

Recent anecdotal reports described a dramatic clinical improvement in patients with APS and chronic severe headache after commencing anticoagulation to prevent recurrences of thrombosis.^{33,34} However, a double blind crossover trial comparing low-molecular-weight heparin with placebo in patients with aPL and chronic incapacitating headache, not responsive to conventional treatment, did not show any beneficial effect.³⁵

Diffuse/nonthrombotic disease

Corticosteroids

Acute inflammatory CNS disease requires immunosuppression and for many years corticosteroids have been the mainstay of treatment for diffuse neuropsychiatric lupus. However, variable success rates and a high incidence of side effects associated with long-term use have been reported. Although the approach to corticosteroid therapy for CNS lupus remains largely empirical, corticosteroids continue to represent the first line of treatment for SLE with suspected diffuse CNS involvement.

High dose oral prednisolone (1–2 mg/kg/daily) or intravenous methylprednisolone infusions (500 mg–1 g daily for three days), with oral prednisolone to follow, are indicated for acute severe CNS manifestations.³⁶

The prompt use of high dose corticosteroids is also associated with a better prognosis in patients with transverse myelitis. The use of high dose corticosteroids is recommended during the early phases of myelitis. Harisdangkul *et al.*²⁸ showed that high dose intravenous pulse corticosteroids resulted in a good outcome when administered within one week of the onset of symptoms. Patients whose diagnosis and treatment were delayed resulted in a poor outcome.

Quintero del Rio *et al.*³⁷ reported good response to high dose intravenous methylprednisolone in 18/25 children with severe CNS disease. Those who did not respond required either cyclophosphamide ($n = 6$) or plasmapheresis ($n = 1$) with a good outcome.

Corticosteroids are useful in cases of aseptic meningitis that usually respond well to these drugs and the management of episodes of psychosis not responsive to antipsychotic treatment.³² It should be remembered though that aseptic meningitis may occasionally result from the use of drugs such as Ibuprofen. One should always keep in mind that corticosteroid treatment may itself induce psychosis and negative effects on cognition and mood, particularly in patients with long-term treatment and/or treated with high doses corticosteroids. Nevertheless, these effects have also been seen in healthy volunteers.³⁸

In patients with SLE the differentiation between cognitive difficulties secondary to the underlying illness, which might warrant more aggressive corticosteroid treatment, versus those secondary to corticosteroid treatment itself, which might warrant dosage reduction, may be problematic.³⁹ A prompt response to treatment with increased doses of steroids may help in differentiating SLE-related psychosis from steroid-induced psychosis.¹⁶

Denburg *et al.*⁵ assessed the efficacy of corticosteroids in patients with mild neuropsychiatric symptoms and inactive SLE, showing that improvement in cognition and mood can be observed following brief exposure (six months) to relatively low doses of corticosteroids (0.5 mg/kg of prednisone daily), effects that persist over repeated drug exposure.

Funauchi *et al.*⁴⁰ recently reported a good response to intrathecal corticosteroids, without serious adverse reactions, in two SLE patients with diffuse CNS involvement after systematic corticosteroid administration proved ineffective.

Cyclophosphamide

The use of intravenous cyclophosphamide is the recommended current practice in cases of acute severe CNS disease,^{36,37,41–43} in those refractory to

corticosteroids or when a steroid-sparing effect is desired.^{3,44}

Although the ideal therapeutic regimen is still poorly characterized, studies in animal models support this practice. Several studies have recently shown that immunosuppression with cyclophosphamide in autoimmune MRL/lpr mice prevents neuronal atrophy,⁴⁵ reduces levels of autoantibodies and attenuates leukocytes infiltration in the brain⁴⁶ while improving behavioural abnormalities.⁴⁷

However, in the absence of randomized controlled trials comparing the effectiveness and safety of cyclophosphamide to methylprednisolone in the treatment of severe CNS disease,⁴⁸ the use of cyclophosphamide in severe CNS lupus continues to be based on expert opinion and clinical experience.

Some data from small series show some beneficial effect with the use of this combination of drugs. Boumpas *et al.*⁴² showed that cyclophosphamide pulses were well tolerated and were shown to be an effective adjunctive therapy for the management of CNS lupus. Barile *et al.*⁴⁹ reported successful outcomes in seven SLE patients with transverse myelitis using pulse methylprednisolone for the acute episode followed by pulse cyclophosphamide for six months.

In our experience intravenous cyclophosphamide is effective and provides benefit in patients with steroid-refractory CNS lupus, mainly when immunologically mediated nonthrombotic mechanism is likely to be present. In selected patients, when it is not possible to clearly differentiate between thrombotic and nonthrombotic disease, especially in patients with aPL, the simultaneous but closely monitored use of corticosteroids, cyclophosphamide and anticoagulant treatment may be required.

Neuwelt *et al.*³ reported a substantial improvement in 61% of patients with severe and refractory NPSLE who received intravenous cyclophosphamide after failing therapy with corticosteroids, azathioprine and/or other cytotoxic drugs. Partial improvement was seen in 29% and progressive deterioration was reported in 10% of the patients. In this series, intravenous cyclophosphamide proved to be beneficial for severe NPSLE and transverse myelitis.

Overall, the immunosuppressive regimen that has shown to be most effective in severe NPSLE is monthly cyclophosphamide (0.75–1.0 g/m² body surface area) administered intravenously every month, as described by the investigators of the NIH.⁴²

However, in the St Thomas' Hospital regimen, the use of lower doses of intravenous pulse cyclophosphamide (500 mg fortnightly for at least three pulses, followed by monthly 500 mg pulses for six months) in aPL-negative SLE patients with CNS involvement, proved effective with clinical improvement often

recorded within days, and a lower incidence of side effects (especially herpes zoster and permanent ovarian failure) when compared with the NIH regimen.^{50,51}

Stojanovich *et al.*⁵² recently reported their experience with low doses of intravenous cyclophosphamide (200–400 mg month), even lower than the St Thomas' Hospital regimen. In this pilot study, low dose cyclophosphamide proved beneficial, especially in patients who received treatment in the early stages of NPSLE. Both clinical and electrophysiological abnormalities improved after six months of treatment. However, in most of the cases the symptoms relapsed during the first few months after completion of therapy.

Plasmapheresis

Plasmapheresis is useful to remove free antibodies, complement components and circulating immune complexes. It seems that patients who respond better to plasmapheresis are those with more severe illness, refractory to corticosteroids and cyclophosphamide therapy, and with the highest levels of circulating immune complexes. The efficacy of plasmapheresis is anecdotal and there are no controlled studies to confirm its efficacy. Combination therapy with synchronized plasmapheresis and subsequent cyclophosphamide in severe SLE has been proposed by some authors.⁵³ Treatment-free clinical remission for a mean observation period of almost six years was reported in 12/14 patients who received this regime.⁵⁴

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has proved useful in the treatment of autoimmune and inflammatory neurological diseases such as peripheral neuropathy, myasthenia gravis, MS⁵⁵ and Guillain-Barré syndrome,⁵⁶ but there are few reports of the use of IVIg in CNS lupus. Uncontrolled studies have shown temporary beneficial effects of IVIg in mild to moderately active SLE,⁵⁷ in the course of lupus nephritis⁵⁸ and in various SLE manifestations including arthritis, fever, thrombocytopenia and neuropsychiatric symptoms.⁵⁹ Successful treatment with high-dose IVIg has been reported in a patient with SLE and acute severe diffuse CNS disease,⁶⁰ including psychosis.⁶¹

Intrathecal methotrexate

Intrathecal administration of methotrexate has been reported as a possible treatment for SLE CNS involvement. Valesini *et al.*⁶² described three patients in whom improvement following intrathecal combination therapy with methotrexate and dexamethasone was observed.

These observations have recently been confirmed by a study from Dong *et al.*,⁶³ where 22/24 patients not responsive to conventional steroid therapy improved considerably after receiving intrathecal injection with methotrexate 10–20mg and dexamethasone. Side effects including itching sensation of lower limbs, headache and incontinence were mild and transient, suggesting that this therapeutic approach may represent a promising method for treating severe CNS lupus in selected cases and deserves further investigation.

Other agents

Azathioprine is used for the treatment of a wide spectrum of SLE manifestations and its use as a steroid-sparing agent is widely accepted. Anecdotal successful use of azathioprine in CNS lupus has been reported by some authors.^{64,65} Patients with severe manifestations (i.e., encephalopathy, chorea) who were unable to tolerate cyclophosphamide and plasmapheresis have been shown to respond to this drug,⁶⁶ though these effects have not been confirmed by others.⁶⁷

Mycophenolate mofetil has also been used in the treatment of NPSLE. Grisanti *et al.*⁶⁸ recently published their preliminary experience in 10 patients with NPSLE. Clinical improvement of neuropsychiatric symptoms and improvement in brain SPECT hypoperfusion patterns were reported in more than two thirds of the patients when 1 g/day mycophenolate was given for 12 months.

The efficacy of iloprost in a patient with SLE, severe cognitive dysfunction and cerebral blood flow abnormalities detected by SPECT has also been described.⁶⁹ Dramatic improvement was seen over four weeks after iloprost infusion for severe Raynaud's, along with concomitant normalization of perfusion abnormalities as shown by serial brain SPECT scans.⁶⁹

Hyperbaric oxygen may act as an immune modulator and might inhibit the actions of certain cytokines that may play a role in the pathogenesis of NPSLE symptoms. There is one anecdotal case reported where cognitive dysfunction improved in a patient after hyperbaric oxygen therapy.⁷⁰

Conclusion

Due to the lack of controlled randomized trials there is a desperate need to assess the efficacy of various therapeutic interventions in CNS lupus, where the treatment is still empirical and based on clinical experience.

Before deciding to treat and how to treat, the major points that need to be considered are: i) accurate diagnosis; ii) identification and treatment of contributing causes of CNS disease; iii) assessment of

the severity; and iv) identification of the probable underlying pathogenic mechanism(s).

In this context, a better approach to management of CNS lupus may be achieved by: i) the recognition of the APS (a common thrombotic disease) and its treatment with anticoagulants; ii) a more conservative use of steroids, especially in patients with mild manifestations; and iii) the use of pulse cyclophosphamide in diffuse/nonthrombotic CNS lupus.

Patients with mild manifestations (e.g., headache or depression) may need symptomatic treatment only, with analgesics, antidepressants and psychological support. In more severe CNS manifestations it is vitally important to distinguish between thrombotic and non-thrombotic mechanisms.

Focal CNS manifestations, generally due to an underlying thrombotic mechanism, are more often associated with the presence of aPL, and long-term anticoagulation is the therapeutic choice in these cases. Heparin is indicated during the acute phase, followed by long-term warfarin in order to prevent recurrences. Other focal CNS manifestations, such as demyelinating syndrome, transverse myelitis, chorea, migraine and seizures, when associated with aPL, may also benefit from anticoagulation.^{27,33}

Severe diffuse CNS manifestations, such as acute confusional states, generalized seizures, anxiety, mood disorders and psychosis generally require corticosteroids in the first instance. High dose of corticosteroids may only be used in severe cases and, preferably for short periods. Pulse intravenous cyclophosphamide therapy may help when more severe manifestations are refractory to corticosteroids and other immunosuppressive agents, generally when response is not seen in three to five days. Plasmapheresis, intrathecal methotrexate and dexamethasone, iloprost, azathioprine and mycophenolate mofetil deserve further studies to confirm their usefulness in the treatment of NPSLE. It is imperative to enrol homogeneous groups of patients in the design of multicentre randomized controlled trials with good sample sizes and accurate power calculations, to give an answer to the many questions currently remaining in the treatment of NPSLE, ultimately yielding to more effective treatments for this serious and potentially life-threatening manifestation of SLE.

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