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Multiple Sclerosis and Related Disorders (P Villoslada, Section Editor)

Therapeutic Approaches in CLIPPERS

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Abbreviations *CLIPPERS* Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids

Opinion statement

CLIPPERS for chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, is a steroid-sensitive and steroid-dependent brainstem inflammatory disease of unknown origin. Since its first description in 2010, about 60 cases have been reported throughout the world. The mean age at onset is 50 years and men seem to be more frequently affected. In patients without chronic corticosteroid therapy or immunosuppressive agents, the disease had a relapsing remitting course, and the mean annualized relapse rate was 0.5. During attacks, although clinical and radiological improvement after high doses of corticosteroids was systematically observed, patients could display subsequent disability and hindbrain atrophy. Since no progressive course was observed, clinical and radiological sequelae were correlated with previous severe attacks. Therefore, maintaining the disease in remission may prevent the accumulation of disability. In the literature, no relapse occurred when chronic corticosteroid therapy was maintained above 20 mg per day. However, steroids side effects led to propose corticosteroid-sparing therapies. Unfortunately, no controlled therapy studies for CLIPPERS have been performed yet, and no therapeutic recommendations exist. Using the PubMed database, all articles having the following keywords “chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids” and “CLIPPERS” have been analysed. Considering that the mean annual relapse rate was 0.5, and that no relapse occurred when corticosteroid therapy was maintained above 20 mg per day, the therapeutic efficiency of corticosteroid-sparing agents was considered as “probable” when patients had a relapse-free period ≥24 months, in the absence of concomitant

corticosteroid therapy. Corticosteroid-sparing agents whose efficiency is "probable" are methotrexate in two cases, cyclophosphamide in one case and hydroxychloroquine in one case. Considering the risk benefit ratio of corticosteroid-sparing agents, methotrexate seems to be the most suitable. Nevertheless, randomized controlled trials testing the different corticosteroid-sparing agents in CLIPPERS are necessary.

Introduction

CLIPPERS for chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids, is a brainstem inflammatory disorder of unknown origin [1••]. The core features of CLIPPERS are defined by (1) subacute brainstem signs and symptoms; (2) punctate and curvilinear enhancing lesions mainly involving the pons, which may extend to adjacent structures; (3) prompt clinical and radiological steroid sensitivity; and (4) the absence of alternative diagnosis. All these four criteria are mandatory to make the diagnosis of CLIPPERS. Considering that pathological examination is recommended in the presence of atypical findings concerning the first four criteria, the fifth criterion characterized by a (5) perivascular lympho-histiocytic infiltrates on brain biopsy is considered as a supportive criterion. Since its first description in 2010 by Pittock and colleague, about 60 cases have been reported throughout the world [2•, 3••, 4••, 5–16]. The mean age at onset is 50 years (range 13 to 86 years), and most studies showed a male predominance with a gender ration of 3:1. In our previous reported case series, 12 patients fulfilling the first 4 criteria were enrolled [4••]. The natural history of this newly described disorder has been analysed. In patients without chronic corticosteroid therapy or immunosuppressive agents, the disease had a relapsing remitting course, and the mean annualized relapse rate (ARR) was 0.5 (range, 0.25–2.8). During attacks, although clinical and radiological improvement after high doses of corticosteroids was systematically observed, patients could display disability including cognitive impairment together with hindbrain, spinal cord and even cortical atrophy. Since no progressive course was observed, clinical and radiological sequelae were correlated with previous untreated and/or severe attacks. Therefore, maintaining the disease in remission may prevent the accumulation of disability. Interestingly, in our case series and in the literature, no relapse occurred when chronic corticosteroid therapy was maintained above 20 mg per day [1••, 2•, 3••, 4••, 5–16].

In this review, we addressed successively the treatment of attacks, the usefulness of chronic corticosteroid therapy and the place of sparing corticosteroid agents. Finally, before discussing future therapies, we proposed a practical approach concerning the therapeutic management and the clinical and radiological monitoring.

Methods

Using the PubMed database, all articles having the following keywords "chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids" and "CLIPPERS" have been analysed. Only those written in the English language have been reviewed. Patients described in the largest case series were systematically included [1••, 2•, 3••, 4••]. Patients reported as a single case report were included when their clinical outcome and their therapeutic regimen were fairly informative. Patients presenting with clinical, radiological or histological atypical findings for CLIPPERS and obviously a steroid-resistance were excluded. For more reliability, each case included in this review was assigned into four categories according to the number of attacks (one or more) and the

performance of a brain biopsy (presence or not). Patients presented with one attack fulfilling the first four or the first five criteria were assigned into "PPERS" (pontine perivascular enhancement responsive to steroids) or "LIPPERS" (lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) respectively. While patients presented with two or more attacks fulfilling the first four or the first five criteria were assigned into "CPPERS" (chronic pontine perivascular enhancement responsive to steroids) or "CLIPPERS" (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids) respectively.

Considering that the mean ARR was 0.5 (range, 0.25–2.8), and that no relapse occurred when corticosteroid therapy was maintained above 20 mg per day, the therapeutic efficiency of corticosteroid-sparing agents was considered as "probable" when the patient had a relapse-free period ≥24 months, in the absence of concomitant corticosteroid therapy; "possible" when the patient had a relapse-free period ≥4 months, with the absence of or low dose of corticosteroids <20 mg/day; and "undetermined or probably ineffective" when the relapse-free period was less than 4 months and/or if the patient had a concomitant corticosteroid therapy above 20 mg per day.

Treatment of attack

Before treating attack related to CLIPPERS, alternative diagnosis, also called CLIPPERS mimics, should be excluded. The second criterion of CLIPPERS, defined by brainstem punctate and curvilinear enhancements, may conceal several diseases such as sentinel lesions of primary central nervous system lymphoma, initial stage of lymphomatoid granulomatosis (grade I), primary angiitis of the central nervous system, multiple sclerosis, myelin oligodendrocyte glycoprotein antibody-associated diseases and low-grade glioma [17–26]. Except for low-grade glioma, all of these diseases could respond to high doses of steroids. Furthermore, in patients presenting with prestages of primary central nervous system lymphoma and lymphomatoid granulomatosis, pathological examination could even fulfil the fifth criterion. However, unlike CLIPPERS, extensive investigations are usually suggestive of alternative diagnosis and/or atypical findings occur early in the course of the disease. Besides clinical and radiological "red flags" mainly represented by cortical neurological signs and large pontine lesions with necrosis, no response to high-dose of corticosteroids at the first attack or during a relapse is considered as a strong indicator of CLIPPERS mimics.

After exclusion of alternative diagnosis and contraindications of corticosteroid therapy, a short course of high-dose intravenous methylprednisolone (i.e. 500 mg or 1 g over 3 or 5 days) should be started as early as possible. Sometimes, sustained intravenous methylprednisolone up to 10 days is necessary before reaching a clinical improvement. Although spontaneous clinical and radiological improvement has been described, clinical worsening is usually observed until the initiation of corticosteroid therapy [4••, 10]. From the first attack to the last relapse, steroid

sensitivity is the rule in CLIPPERS patients. Clinical improvement is usually observed within 2 weeks following the start of corticosteroid therapy and seems to have a similar course with intravenous methylprednisolone or intravenous dexamethasone. By contrast with high-dose of intravenous corticosteroid therapy, 1 mg/kg/day of prednisone in one patient, six cycles of cyclophosphamide followed by azathioprine in a second patient and intravenous immunoglobulin in a third patient did not improve clinical signs during a CLIPPERS attack (Tables 1 and 2) [1••, 3••, 5]. Brain biopsies performed during the attacks showed the presence of perivascular lympho-histiocytic infiltrates (mainly composed of CD4 cells) together with axonal injuries (i.e. axonal spheroids and torpedoes) [3••, 4••]. Axonal injuries may explain the subsequent disability and atrophy. Therefore, as severe relapses seem to make the disability, early treatment with high dose of corticosteroids could further prevent clinical and radiological sequelae. Currently, high-dose corticosteroid treatment followed by oral prednisone with gradual tapering is commonly used. In addition to decrease the risk of early relapse, this therapeutic regimen could also further improve the clinical signs related to the recent attack.

Treatment in "relapse-free period"

Chronic corticosteroid therapy

No guidelines exist as to the length of corticosteroid therapy for CLIPPERS. Before starting corticosteroid therapy, contraindications such as infection and/or previous episode of steroid psychosis should be excluded. As described above, high-dose corticosteroid treatment followed by oral prednisone with gradual tapering is commonly used. Oral prednisone is usually started at 1 mg/kg/day for about 4–8 weeks, and then the dose is reduced slowly (e.g. 10 mg every 2 weeks to 20 mg/day, then 2.5 mg every 4 weeks to 10 mg, then 1 mg every 4 weeks until 5 mg/day). To prevent steroid-induced osteoporosis, prophylactic treatment including bisphosphonate, calcium and vitamin D is recommended. Once corticosteroid therapy has been tapered to below 5 mg/day of prednisone, in order to prevent the risk of adrenal insufficiency, blood cortisol levels should be analysed before stopping definitively corticosteroid therapy. Response to treatment should be monitored by periodic clinical examination and serial brain MRI (e.g. every 3 months), with a particular attention when corticosteroid therapy is below 20 mg per day. As radiological progression can precede clinical manifestations, brain MRI should be performed even in the absence of clinical signs or symptoms [1••]. Since gadolinium-enhancing lesions decrease in number as the distance from the pons increases, spinal cord MRI seems to be useful especially in case of new lesions in medulla on brain MRI and in the presence of signs or symptoms of spinal cord [1••, 2•, 3••, 4••, 5–16]. Long-term corticosteroid therapy can have consequences such as diabetes mellitus, high blood pressure, hyperlipidaemia, weight gain, infections, avascular necrosis, osteoporosis, steroid myopathy, amenorrhea, hirsutism, acne, cataracts, glaucoma and mood disorders. When steroid side effects become evident and/or relapse occurs, introduction of corticosteroid-sparing agents should be discussed.

Table 1. Chronic therapies and clinical outcome in CLIPPERS patients (patients 1–20)

Patient number (ref)	Age at onset (years), sex	Number of attack, follow-up (months)	Category	Enhancing lesions localization	Relapse under treatment (attack number, An°), therapy (dosage and duration)	Relapse-free period (months), treatment (dosage)	mRS at the last visit
1 [1••]	78, F	1, 20 months	LIPPERS	Brain, hindbrain	No	8 months, CT (nd)	nd
2 [1••]	37, M	6, 144 months	CLIPPERS	Hindbrain, spinal cord	Attack 6, HDC (400 mg/day, 6 months)	94 months, MTX (20 mg/week, 18 months, then 10 mg/week, 76 months)	nd
3 [1••]	47, M	1, 7 months	PPERS	Hindbrain	No	2 months, CT (nd)	nd
4 [1••]	86, F	1, 25 months	PPERS	Hindbrain	No	16 months, IVMP (1 g every 10–14 days)	6 pulmonary embolism
5 [1••]	70, M	1, 22 months	LIPPERS	Hindbrain	No	1 month, CT (60 mg/day)	nd
6 [1••]	41, F	2, 14 months	CLIPPERS	Hindbrain	Attack 2, mitoxantrone (nd)	No	nd
7 [1••]	16, F	>1, 43 months	CPPERS	Hindbrain, spinal cord	Attack 2, AZT (nd)	No	nd
8 [1••]	44, F	2, 7 months	CPPERS	Hindbrain, spinal cord	No	4 months, CT (nd)	nd
9 [2•]	58, M	3, 17 months	CLIPPERS	Brain, hindbrain	No	9 months, pulse of CYC (1200 mg/m)	2
10 [2•]	56, M	2, 15 months	CLIPPERS	Hindbrain, spinal cord	No	10 months, without treatment	2
11 [2•]	57, M	1, 9 months	LIPPERS	Brain, hindbrain	No	2 months, DXM (1 mg/day) + MTX (15 mg/week)	1
12 [3••]	65, F	1, 12 months	LIPPERS	Hindbrain	No	5 months, CT (nd)	3
13 [3••]	51, M	2, 36 months	CLIPPERS	Brain, hindbrain	No	18 months, CYC (4 cycles) then CT (nd) + AZT (nd)	1
14 [3••]	20, M	2, 64 months	CLIPPERS	Hindbrain, spinal cord	No, but attack 2, 18 months after CYC (6 cycles) and stop CT	40 months, CT (nd) + CYC (6 cycles) then CT (nd) + MMF (nd)	1
15 [3••]	54, M	3, 72 months	CLIPPERS	Brain, hindbrain			3

Table 1. (Continued)

Patient number (ref)	Age at onset (years), sex	Number of attack, follow-up (months)	Category	Enhancing lesions localization	Relapse under treatment (attack number, An°), therapy (dosage and duration)	Relapse-free period (months), treatment (dosage)	mRS at the last visit
					Increasing disability during attack 3 despite CYC (6 cycles) and AZT (nd)	14 months, CT (nd) + AZT, then CT (nd) + MMF (nd)	
16 [3••]	27, M	4, 100 months	CLIPPERS	Brain, hindbrain	No, but attack 4, 42 months after CYC (14 cycles) and stop CT	6 months, CT (nd)	4
17 [4••]	39, M	6, 24 months	CPPERS	Brain, hindbrain	No	1 months without treatment	1
18 [4••]	32; M	2, 16 months	CPPERS	Brain, hindbrain, spinal cord	Attack 2, CT 10 mg/day	No	1
19 [4••]	46, M	2, 16 months	CPPERS	Hindbrain, spinal cord	No	3 months, CT 25 mg/day	1
20 [4••]	62, M	3, 27 months	CPPERS	Brain, hindbrain	Attack 2, CT 19 mg/d, attack 3, CT 5 mg/day	1 months, CT 80 mg/day	1

AZT azathioprine, *CT* oral prednisone, *CYC* cyclophosphamide, *DXM* dexamethasone, *F* female, *HDC* hydroxychloroquine, *IVMP* intravenous methylprednisolone, *M* male, *MMF* mycophenolate mofetil, *MTX* methotrexate

Table 2. Chronic therapies and clinical outcome in CLIPPERS patients (patients 21–39)

Patient number (ref)	Age at onset (years), sex	Number of attack, follow-up (months)	Category	Enhancing lesions localization	Relapse under treatment (attack number, An°), therapy (dosage and duration)	Relapse free period (months), treatment (dosage)	mRS at the last visit
21 [4••]	53, F	3, 53 months	CPPERS	Brain, hindbrain	Attack 2, CT 7.5 mg/day	15 months, CYC (6 cycles) + CT 10 mg/day	3
22 [4••]	52, M	2, 16 months	CLIPPERS	Hindbrain	No	No	4
23 [4••]	46, M	4, 182 months	CLIPPERS	Brain, hindbrain, spinal cord	Attack 3, 20 months after CYC (6 cycles)	No	4
24 [4••]	13, M	12, 408 months	CLIPPERS	Brain, hindbrain, spinal cord	No	9 months, RB (375 mg/m^2 weekly for 4 weeks)	4
25 [4••]	48, F	2, 6 months	CLIPPERS	Hindbrain	Attack 2, CT 10 mg/day	No	1
26 [4••]	46, F	2, 8 months	CLIPPERS	Hindbrain	No	5 months, CT 20 mg/day	3
27 [4••]	64, M	3, 21 months	CLIPPERS	Brain, hindbrain	No	No	6 fatal pneumonia
28 [5]	28, F	4, 27 months	CPPERS	Brain, hindbrain, spinal cord	Attack 2, 3, 4 CT < 12.5 mg/day, no improvement after IVIG (2 g/kg)	9 months, CT 5 mg/day + AZT 150 mg/day	0
29 [6]	69, M	1, 18 months	PPERS	Hindbrain, spinal cord	No	6 months, MTX 10 mg/week	1
30 [7]	63, M	1, 19 months	PPERS	Hindbrain	No, but stop MTX and AZT due to side effects	18 months, CT 20 mg/day + MMF 1 g/day	0
31 [8]	49, F	2, 8 months	CLIPPERS	Brain, hindbrain	No	4 months, CYC (1 g), then MMF (1 g/day)	nd
32 [9]	64, M	2, 43 months	CPPERS	Brain, hindbrain, spinal cord	No	18 months, rifampicin (10 mg/kg/day)	0
33 [10]	76, F	2, 27 months	CLIPPERS	Brain, hindbrain	No (spontaneous healing of attack 1)	24 months, CT 20 mg/day	6 pneumonia
34 [11]	54, M	1, 60 months	PPERS	Hindbrain	No	48 months, HDC 400 mg/day	0
35 [12]	31, M	2, 31 months	CLIPPERS	Brain, hindbrain, spinal cord	Attack 2, CT 10 mg/day	8 months, CT (nd)	nd
36 [13]	50, F	1, 25 months	LIPPERS	Hindbrain	No	24 months, MTX 10 mg/w	2
37 [14]	49, F	1, 18 months	PPERS	Brain, hindbrain, spinal cord	No	14 months, CT 10 mg/day	nd
38 [15]	34, M	1, 7 months	PPERS	Hindbrain	No	6 months, CT 30 mg/day + entecavir 0.5 mg/day for chronic hepatitis B	0
39 [16]	31, M	10, 242 months	CPPERS	Hindbrain	Attacks 7, 8, 9, 10, in 192 months, combination of INFBeta-1a (22 µg sc 3 times/w) + CT 12.5 mg/day	No, ARR = 1 without therapy, but ARR = 0.25 under INFBeta-1a + CT 12.5 mg/day	nd

ARR annual relapse rate, *AZT* azathioprine, *CT* oral prednisone, *CYC* cyclophosphamide, *F* female, *HDC* hydroxychloroquine, *IVIG* intravenous immunoglobulins, *M* male, *MMF* mycophenolate mofetil, *MTX* methotrexate, *RB* rituximab, *INF* interferon, *Sc* subcutaneous

Corticosteroid-sparing agents

In the absence of randomized controlled trials or prospective studies about corticosteroid-sparing agents in CLIPPERS patients, no recommendations exist. The main issues concerning immunosuppressive therapies are (1) how to select the optimal corticosteroid-sparing therapy, (2) how long and what dosage and (3) when to start treatment?

1. Selection of the optimal corticosteroid-sparing therapy (Tables 1 and 2)

As described in methods, efficiency of immunosuppressive agents has been considered as "probable" (i.e. relapse-free period ≥24 months without corticosteroids), "possible" (i.e. relapse free period ≥4 months with no concomitant or low dose of corticosteroids <20 mg/day) and "undetermined or probably ineffective" (i.e. relapse free period <4 months and/or corticosteroids ≥20 mg/day). Corticosteroid-sparing agents whose efficiency is "probable" are methotrexate (10 mg/week) in two cases, cyclophosphamide (14 cycles) in one case and hydroxychloroquine (400 mg/day) in one case [1••, 3••, 11, 13]. In the patient receiving cyclophosphamide, a relapse occurred 28 months after cessation of treatment, suggesting that cyclophosphamide only suspends the symptoms. Concerning immunosuppressive agents whose efficiency is "possible", in addition to the three corticosteroid-sparing agents having a "probable" efficiency (i.e. methotrexate, cyclophosphamide and hydroxychloroquine), there are also azathioprine (150 mg/day), mycophenolate mofetil (1 g/day), rifampicin (10 mg/kg/day) and interferon beta-1a [1••, 2•, 3••, 4••, 5, 6, 8, 9, 16]. Therefore, considering the risk benefit ratio of corticosteroid-sparing agents, methotrexate seems to be the most suitable in absence of contra-indications. The other immunosuppressive agents (e.g. cyclophosphamide, hydroxychloroquine and azathioprine), possibly more toxic or less effective than methotrexate, could be considered as second-line treatments.

2. Dose, route of administration and duration of treatment

Initial dosing, route of administration and duration of methotrexate in the setting of CLIPPERS is undetermined. To our knowledge, no relapses occurred among patients taking methotrexate when the dosage was ≥10 mg/week [1••, 13]. Route of administration was usually oral in CLIPPERS patients, and duration of treatment was extremely variable (up to 94 months in one patient). To our knowledge, intentional discontinuation of successful therapy with methotrexate has not been tried in CLIPPERS patients.

3. Early or late start of corticosteroid-sparing therapies

Considering that disease re-emergence was expected during or after steroids tapering, corticosteroid-sparing therapies could be started after the first attack, especially when the daily dose of corticosteroid is close to 20 mg [4••]. In addition, this treatment regimen could also decrease the risk of long-term steroid side effects in case of relapse.

Conversely, some patients were free of relapse without chronic treatment [2•]. Furthermore, patients presenting with CLIPPERS mimics could have a first attack fitting with the first five criteria, and atypical

findings occurred during the second attack [17–20]. For these two reasons, introduction of corticosteroid-sparing therapy after the second attack is also conceivable.

CLIPPERS: a practical approach to treatment, author's point of view

No controlled therapy studies for CLIPPERS have been performed yet. Based on small case series, case reports and our experience, we propose a practical approach in five points.

1. Treatment of attack fitting with the first four or the first five CLIPPERS criteria

   - In the absence of contraindications, intravenous methylprednisolone 1 g/day over 5 days (up to 10 days if necessary) followed by oral prednisone 1 mg/kg/day over 1 month.
   - Two or four weeks from starting treatment: clinical improvement and vanishing of enhancing lesions should be observed.

2. Treatment during the "relapse free period"

   - Tapering oral prednisone: 10 mg every 2 weeks to 20 mg/day, then 2.5 mg every 4 weeks to 10 mg, then 1 mg every 4 weeks + prophylactic treatment of osteoporosis.
   - In the absence of contraindications, oral methotrexate 10–15 mg/week (+ vitamin B_9) should be started 4–6 weeks before to decrease prednisone below 20 mg/day, and continue methotrexate during at least 2 years.
   - Clinical examination + brain MRI every 3 months.

3. Methotrexate intolerance or contraindication

   - In the absence of contraindications azathioprine 150 mg/day combined with prednisone above 20 mg/day over 3 to 6 months before prednisone tapering, and continue azathioprine during at least 2 years.
   - Or cyclophosphamide (1 g/month) combined with prednisone above 20 mg/day over 1 month before prednisone tapering, and continue cyclophosphamide during at least 6 months.
   - Or hydroxychloroquine (400 mg/day) combined with prednisone above 20 mg/day over 1 month before prednisone tapering, and continue hydroxychloroquine during at least 2 years.
   - Clinical examination + brain MRI every 3 months.

4. Relapse under methotrexate with prednisone ≥20 mg/day

   - Questioned strongly the diagnosis of CLIPPERS,
   - If no alternative diagnosis, treatment should be restarted as described in point 1 and 2 except for methotrexate. The choice of immunosuppressive therapies could be either methotrexate with a higher dosage: up to 20–

25 mg/week (split into 2 doses ≥8 h apart in order to improve gastrointestinal absorption), or another cortico-sparing agents as proposed in point 3.

5. Relapse under methotrexate with prednisone <20 mg/day or without prednisone

- Questioned the diagnosis of CLIPPERS,
- If no alternative diagnosis, treatment should be restarted as described in point 1 and 2 except for methotrexate. The choice of immunosuppressive therapies could be either methotrexate with a higher dosage: up to 20–25 mg/week (split into two doses ≥8 h apart in order to improve gastrointestinal absorption), or another cortico-sparing agents as proposed in point 3.
- In the absence of steroid side effects, minimal dose of corticosteroid combined with corticosteroid-sparing agent could also be proposed.

A multidisciplinary consultation meeting should validate each therapeutic decision. The diagnosis of CLIPPERS must be questioned at each attack, especially in the first 2 years. Atypical clinical and/or radiological findings, relapse despite steroid therapy above 20 mg/day, and signs of steroid resistance strongly argue for a CLIPPERS mimics such as lymphoma or primary angiitis of the central nervous system.

Future perspectives

Seven years after its first description, pathogenesis of CLIPPERS remains largely unknown. CLIPPERS is a steroid-sensitive and steroid-dependent brainstem inflammatory disease that mainly involves the perivascular spaces of small vessels. Although venules seem to be predominantly involved on MRI, arterioles and capillaries are also concerned at a microscopic level. Histological findings show perivascular infiltrates with a predominance of CD4 cells and histiocytes [3••, 4••, 27]. However, CD4 cell subsets (i.e. Th1, Th2, Th17 and Foxp3 regulatory T cells) in CLIPPERS have not been determined. We have described in a CLIPPERS patient a clinical and radiological improvement after the beginning of rifampicin [9]. This therapy was given because CLIPPERS was initially misdiagnosed as a neurotuberculosis. Inhibiting the Th17 pathway, rifampicin is known to be beneficial in Th17-related autoimmune diseases such as psoriasis, Crohn disease and rheumatoid arthritis. Therefore, this case suggests that CLIPPERS could be a Th17-mediated central nervous system disease. Besides CD4 cells, inflammatory infiltrate in CLIPPERS includes several histiocytes. Then, targeting the Th17 pathway and/or histiocytes could be the future therapeutic approaches for CLIPPERS.

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Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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