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Case Report

Enigmatic Clinical Presentation of Neuroinflammatory CLIPPERS Syndrome; Excavation of Pathophysiology, and Clinical Course

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Abstract

Introduction: Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) is an autoimmune mediated inflammatory syndrome that primarily effects pons, cerebellum and brain stem. Prompt diagnosis and treatment is deemed necessary for favorable clinical outcomes and best possible prognosis. We report on a well-documented patient who presented with clinical, radiological, and pathological characteristics of CLIPPERS, and who responded with steroids. In this case report, we would like to present a clinical case along with short review of pathophysiological basis, clinical spectrum, radiological signs and current management strategies of CLIPPERS syndrome.

Clinical case: We present a clinical case where a 71-year-old female patient presented with vertigo, gait ataxia, and lower limb weakness over a period of few months. Extensive clinical work up including imaging studies revealed gadolinium enhancement of pons and peri-pontine region. As CLIPPERS syndrome is suspected due to type and site of lesions, a clinical trial of steroids is promptly administered, after which she exhibited a drastic clinical response with resolution of clinical and radiological signs, thus confirming the clinical diagnosis of CLIPPERS syndrome.

Conclusion: CLIPPERS syndrome is form of autoimmune and reversible form of CNS encephalitis. It presents with insidious onset of neurological symptoms and radiological signs including gadolinium enhancement of pons, peri-pontine region, thalamus and unilateral cerebral hemisphere. Our case had demonstrated additional sites of CNS involvement in addition to those already reported in the current literature, thus making our case unique. By reporting this clinical case, we would to the highlight this widened imaging spectrum seen in CLIPPERS syndrome that should be looked in each case of CLIPPERS syndrome. Given its autoimmune basis for is occurrence, steroid therapy is very effective in abatement of clinical symptoms and near total fading of radiological signs. Without treatment, the disease process follows a relapsing-remitting course, thus making them increasingly vulnerable to late complications like cerebral atrophy and cognitive dysfunction. Resultantly, long-term steroid therapy is strongly advocated. Some patients become so much dependent on steroids that any lowering of doses is followed by resurgence of clinical symptoms and radiological signs. Steroid sparing drugs are recommended to maintain remission and limit steroid induced side effects. Long-term MRI follow up is always almost necessary to uncover future onset of clinical relapses as well as primary CNS lymphoma.

Keywords: Chronic lymphocytic inflammation with pontine perivascular inflammation responsive to steroids (Clippers); Autoimmunity; Lymphocytes; Hind brain; Pons; Cerebellum; Steroids; Lymphoma; Neuroinflammation

Introduction

(CLIPPERS) syndrome is a clinical disease presenting with encephalitis like clinical picture with the pathology mainly predilected to pons and cerebellum [1]. More than 100 cases have been reported in the literature since its discovery by Pittock SJ, et al [2,3]. It takes shape due to autoimmune mediated inflammatory assault on the perivascular territory of pons, with associated excess lymphocyte amassment [4]. Patients with history of autoimmune diseases, allergy, elevated IgE levels, hypersensitivity, and viral infections particularly seem to be vulnerable [5-8]. The resulting symptoms that spring up are imputable to inflammation of brain stem and cerebellum. Accordingly, patients experience gait imbalance, dysarthria and diplopia that linger for weeks to months before they seek medical help [3]. Its presenting symptoms are obscure, thence it should be separated from vasculitis, tumors, infectious encephalitis and connective tissue diseases [3]. Curvilinear and speckled appearance of the pons and cerebellum is commonly encountered on MRI imaging without evidence of vasculitis, vasogenic edema and mass effect [9]. Given the autoimmune basis of this disorder, this encephalitis syndrome is amenable and very responsive to steroid therapy [9]. Without effective therapy, disease process is liable to undergo relapsing and remitting course, thus increasing the risk of complications including cerebral atrophy and cognitive dysfunction in the long term. Patients who have complete resolution of clinical symptoms and radiological signs should undergo serial follow up with MRI scans as these patients are increasingly prone to develop relapses, thus increasing the morbidity and mortality in patient population [3].

We present this clinical case of Clipper syndrome to increase the clinical awareness to this autoimmune encephalitis syndrome.

Apart from the lesions in the usual pontine and peri-pontine regions, the brain MRI had showcased involvement of thalamus and cerebral hemisphere in our case. These uncommon sites of involvement are unique and expands imaging spectrum that can be found in the CLIPPERS syndrome. Incrimination of these additional sites might insert new symptoms to the varied clinical profile of the CLIPPERS syndrome. By presenting this clinical case, we would like to bring attention to this neuroinflammatory syndrome which should

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be included in the differential diagnosis in a patient with hybrid neurological symptoms that reflect brain stem involvement.

Heightened awareness, detailed clinical history, prompt imaging workup and administration of steroids will prevent mortality and morbidity. On an important note, this fully reversible clinical syndrome should be carefully demarcated from other neuroinflammatory and autoimmune conditions so that it can be effectively managed.

The aim of the manuscript is to present this rare case of CLIPPERS syndrome. We would like to take this opportunity to provide a mini review highlighting its risk factors, pathophysiology, clinical symptomatology, diagnostic signs and treatment. Particularly, this review is more focused on treatment aspects of CLIPPERS syndrome which principally comprises of steroids and immunosuppressive therapeutics. A peculiar feature of CLIPPERS syndrome is complete recovery of brain stem lesions with therapy and resurgence upon withdrawal, thus making it one of the few reversible brain encephalitis syndromes.

Case Presentation

71-year-old female presented to the clinic due to insidious progressive neurological process starting June 2016. Her symptoms have been a combination of lightheadedness, fatigue, decreased sensation in the right hand/peri-oral regions, ataxia, dizziness, tingling, paresthesia's of fingers/lips and diplopia. Symptoms have been stable from past 3 months, but have suddenly started to become worse since last few weeks. Over the last few weeks, she feels her dizziness, balance issues and diplopia have become dramatically worse. She had fallen multiple times. She also had 20lb weight loss over the last month. She had a mild cough. No night sweats or fever. On examination, pupils are equal, round and reactive to light. Extraocular motion intact, but she does complain of horizontal diplopia when looking to the right. There is multidirectional nystagmus. CN V1-V3 intact. No facial asymmetry. Hearing clinically intact bilaterally. Tongue protrusion intact and no uvular deviation. Muscle strength is decreased in lower limbs. Sensory examination revealed decreased pain and touch in upper limbs. Gait instability has been documented. Tandem gait and Romberg test is abnormal. CBC is within normal limits. CSF analysis [WBC: 1, RBC:2, protein 49, glucose: 67, cytology: no malignant cells, Flow cytometry no evidence of lymphoma, fungal culture: negative]. CT scan brain is within normal limits. MRI brain patchy areas of enhancement and T2 hyperintensity involving pons, cerebellum, left thalamus, lateral right temporal lobe, posterior limbs of both internal capsules (Figure 1). Based on the clinical findings and radiological signs, the diagnosis of CLIPPERS syndrome is suspected. Her work up for other causes has been extensive and we have not found a reasonable cause to explain her symptoms. She was given a trial of steroids and her radiological signs completely resolved (Figure 2). She will need steroids long-term to maintain remission. Rituximab was also administered to reduce the risk of steroid induced side were advised to monitor Clippers syndrome induced radiological signs.

Discussion

71-year-female presented with ataxia, diplopia, dizziness and gait ataxia from the past few weeks, but increased in intensity over last week. CT scan is within normal limits, but MRI brain revealed patchy enhancement of the pons, and cerebellum. After careful exclusion of other relevant diagnosis, CLIPPERS syndrome is suspected. A trial of steroids was prescribed and patient had complete resolution of the clinical and radiological signs. Long-term steroid therapy is recommended to keep completely suppress the autoimmune inflammation and abort its resurgence, so as to avert further relapses. Outpatient follow up with serial MRI scan was advised to detect further relapses and malignancies.

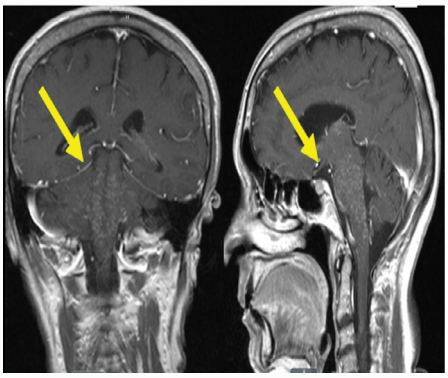

Figure 1: MRI brain patchy areas of enhancement and T2 hyperintensity, revealing curvilinear and punctate appearance of pons, cerebellum, left thalamus, lateral right temporal lobe, posterior limbs of both internal capsules. The classic salt and pepper appearance of the pons and peri-pontine areas are tell-tale signs of CLIPPERS syndrome. This syndrome represents autoimmune attack paving the way for lymphocytic infiltration and inflammation of the brain stem.

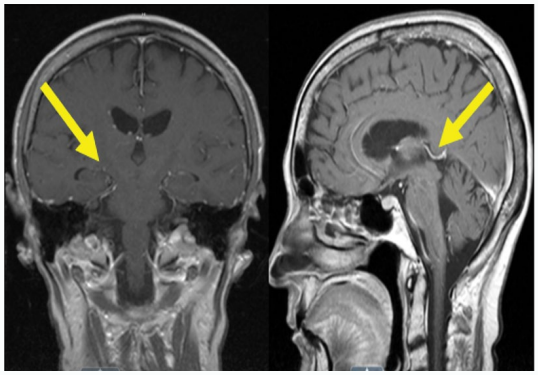

Figure 2: Abnormal areas of enhancement completely resolved after treatment with steroids. Given steroid dependency and steroids induced side effects, rituximab has been administered and patient exhibited a drastic clinical response without experiencing resurgence of clinical symptoms and MRI brain findings. Serial MRI brain follow up is recommended to detect relapses so that they can be promptly treated for reducing mortality/morbidity, improving clinical outcomes.

This pontine predominant encephalomyelitis is first discovered by Pittock CJ, et al. [10] 22 patients were serially followed from 1999-2009 in the Mayo Clinic, USA and Ghent University, Belgium. Patients presented with facial paresthesia and diplopia were serially followed for a period of 22 months [10]. These patients demonstrated symmetric curvilinear gadolinium enhancement of medulla, pons, cerebellum and midbrain, which showed predominant T-lymphocyte infiltration without vasculitis or granuloma or mass effect [10]. Peculiarly, these lesions completely resolved with steroid and immunosuppressive therapy, thus underscoring autoimmune basis for its evolvement [10]. So far, around 140 cases of Clipper syndrome have been reported and approximately 15.7% of these were associated with hematological malignancy such as lymphoma [11]. The mean age of presentation is 46-58 years and there is predilection towards males as compared to females [9,11].

Although some researchers speculated the disease inception as a disguised form of pre-lymphoma state, cluster of clinical cases reported thus far favor the preposition towards an autoimmune like phenomenon for its origination [4,9,12]. Most of the patients report a past history of flu infection, COVID-19 infection, influenza vaccination, herpes zoster virus infection, EBV, allergies and hypersensitivity pneumonitis [6,7,13,14]. Other possible triggers for provoking the inflammatory process in CLIPPERS syndrome can be vaccination, atopic disease, atopic myelitis, elevated and immunoglobulin levels E levels [6,7,15,16].

The dawning of the Clippers Syndrome can be postulated due to autoimmune mediated damage of pons, cerebellum and brain stem secondary to molecular mimicry, epitope spreading, bystander activation and anergic resurgence of B-cells [17].

Most likely, a flu or COVID-19 infection precedes this undertaking. In the viral-hit hypothesis, the convergence of factors including genetic susceptibility, environmental factors, and unbridled immune responses will set in motion pathological inflammatory pathways that ultimately crystallizes in an autoimmune mediated attack that will predominantly transpires in the central nervous system [17]. In the setting of pathological state, re-energizing of autoreactive B-cells will bring forth a scenario where auto-antibodies will be generated against native dsDNA [double stranded DNA] and ssDNA [Single stranded DNA] [18,19]. Viral particles that circulate in the blood and dislodge in host tissue are bound to share similar amino-acid sequences as neural proteins, thus providing an avenue for evocation of cross-reactive immune response [20]. Studies have documented that auto-antibodies were triggered against IL-6 [Interleukin-6], IL-7 [Interleukin-7], IL-12 [Interleukin-12] and IL-22 [Interleukin-22] in flu and COVID-19 patients [17]. As viral infections are contained by the migration, activation and secretion of pro-inflammatory cytokines by inflammatory cells, a collateral damage foments in the form of bystander activation of CD8 and CD4 cells [21]. Activation of these T-cells can be detrimental as they can initiate and propagate endothelial injury and tissue damage in the nervous tissues [22].

The immune targets in this clinical disorder are inclined to be the antigenic epitopes in the perivascular region of the pons and peri-pontine region [23]. Keeping in mind the anatomical location of the inter-axial veins in the brain stem, some researchers speculated that CLIPPERS syndrome as a predominant venous inflammatory disorder [23].

CLIPPERS syndrome is reported to be in a patient with Epstein Barr Virus (EBV) infection. It is speculated that EBV associated auto-immunity might serve as a harbinger for setting in motion regulatory T-lymphocyte abnormalities which provides the driving force for triggering CLIPPERS syndrome [24-26]. Furthermore, TH17 [T-helper] lymphocytes and amassment of autoimmune antigens in the perivascular regions are implicated for lymphocyte accumulation and subsequent inflammation in the CLIPPERS syndrome [10,12].

The hallmark histopathological findings are pertained to infiltration of the CD4 [Cluster of differenciation 4], CD3 [Cluster of differenciation 3] & CD2 [Cluster of differenciation 2] lymphocytes, plasma cells, eosinophils and neutrophils along the microvasculature of the white and grey matter without evidence of vasculitis [4,9]. Specifically, these atypical T-cells that migrate are known to have T-cell rearrangement [27]. Clinical researchers have predominantly identified CD4 T-lymphocytes in the brain biopsy and CSF samples of the CLIPPERS syndrome [28,29]. These findings give credence to the hypothesis that CD4 T-lymphocytes might be the primary galvanizing force for initiating and propelling the inflammatory process through MHC [Major Histocompatibility Complex] Class-II complex induced processing of exogenous antigens [30]. These processed antigens can be primary impelling force for production of autoantibodies, inflammation and subsequent tissue injury.

Some clinical researchers speculate that the underlying triggering factors for emigration of this T-lymphocytes is because of the inherent anatomical situation of intra-axial venous vasculature in the pontine and peri-pontine regions [31].

As a golden rule, symptoms get under way, flourish and unfold gradually over a period of days to weeks. The constellation of symptoms that comes to light can range from diplopia, dysarthria, dysphagia, dysgeusia, dizziness, facial tingling, facial nerve palsy, gait ataxia, nystagmus, tinnitus, tremors, headache, vertigo, hearing impairment, hoarse voice, hiccup, tinnitus, tremor, sensory loss, spasticity, pseudobulbar effect, psychomotor slowing to cognitive dysfunction [1,30,32]. Some clinical signs noted can range from paraparesis, spasticity, sensory loss, decreased vibration sense to neurogenic bladder [30]. The presence of symptoms such as fever, weight loss, night sweats lymphadenopathy, arthritis, uveitis, oral /genital ulcers, meningitis, polyuria, polydipsia and loss of consciousness should alert us to revise the diagnosis of CLIPPERS syndrome [30].

Non-specific findings that be seen include increased autoimmune antibodies, raised ACE [Angiotensin converting enzyme), hypercalcemia, elevated vitamin D, raising IgE [Immunoglobulin E] levels and pan-lymphopenia [5,10,28,33,34]. Other findings that are unveiled on CSF analysis can include elevated protein levels [1g/L], pleocytosis [50/ul], increased CD4:CD8 [Cluster of differentiation 8] ratio and mild spiking of oligoclonal bands [2,5,23,29, 35].

In our patient, immunophenotyping of the CSF did not reveal any antibodies to CD14 [Cluster of differenciation 14], CD19 [Cluster of differenciation 19], CD45 [Cluster of differenciation 45] & CD56 [Cluster of differenciation 56], thus ruling out Hodgkin lymphoma, or T-cell lymphomas. Mayo autoimmune/ paraneoplastic/ encephalopathy panel was negative in our patient, thus eliminating paraneoplastic syndrome as a probable cause. Moreover, meningitis/ encephalitis PCR [Polymerase Chain reaction] panel was negative, thereby ruling out infections as causative factor. Furthermore, there was absence of antibodies to AQP4 [Aquaporin 4) and MOG [myelin oligodendrocyte antibody] in the CSF, thereby ruling out Neuromyelitis Optica Spectrum Disorders [NMOSD]. CSF oligonal bands panel was also negative.

The tell-tale signs of CLIPPERS syndrome are homogenous, enhancing, curvilinear and punctate lesions on pons, middle cerebellar peduncles, pons, cerebellar hemispheres and spinal cord without adjacent soft tissue or edema effect [9,13,36]. The fingerprint lesions in CLIPPERS syndrome are typically described as speckled, patchy-spot like gadolinium those having salt and pepper appearance [5].

Over and above that, medulla oblongata, cervicothoracic spinal cord, mid brain, thalamus, internal capsule, cerebellum basal ganglia, corpus callosum, cerebral white matter and deep cerebral nuclei are occasionally seemed to be inflicted [1,5 6,37,38]. It is important to emphasize the fact that the number and severity of lesions decrement as we recede away from pons and cerebellum [30]. Homogenous

perivascular gadolinium enhancing nodules less than 3 mm in diameter are demarcating lesions that will help to draw a distinction from non-clipper syndrome [9]. On top of these, a homogenous and faint T2 signal enhancement is always present that does overpower T1 signal [9].

Some cases of CLIPPERS Syndrome who have a routine MRI follow up are known to develop cerebral atrophy even in those with complete resolution of inflammatory lesions, thus raising the possibility of underlying vasculitis and neuro-axonal injury in the pathophysiology in few patients [28,31]. Magnetic Resonance Angiography (MRA) of the intracranial and neck vessels will not reveal any relevant abnormalities [35,39,40].

The clinical and radiological signs of Clippers syndrome can mirror other clinical conditions like vasculitis, neurosarcoidosis, paraneoplastic syndrome, infections, behcet syndrome, glioma, primary CNS lymphoma, Bickerstaff brainstem encephalitis, acute disseminated encephalitis, infectious rhombhoencephalitis, and demyelinating diseases [1,41]. Moreover, absence of brain stem lesions on MRI and presence of necrotic pontine lesions might symbolize primary CNS lymphoma or tumors [42]. As a matter of fact, cerebral lymphoma might indeed regress in size following steroid administration, thus mirroring CLIPPERS syndrome on contrast weighted MRI [42]. Malignant diseases that can simulate CLIPPERS syndrome include lymphomatoid granulotoisis, primary CNS lymphoma, glioma, EBV lymphoma, systemic T-cell lymphoma, Hodgkin lymphoma, Cutaneous T-cell lymphoma. Primary lymphatoid granulomatosis and Limbic encephalitis [42]. Immune mediated diseases that can mimic Clippers syndrome include angiitis, lymphohistocytosis, cutaneous scleroderma, Erdheim Chester histiocytosis, multiple sclerosis, and HLA-B27 uveitis [42].

Brain biopsy is indicated when unilateral and patchy gadolinium lesions, lesions greater 3 mm to 9 mm and T2 hyperintensities larger than contrast enhanced lesions are documented in CLIPPERS syndrome [9,42,43]. Despite these findings, brain biopsy might be not feasible in all clinical scenarios on the grounds that sites of involvement are located on the delicate regions of the brain stem, thence amplifying the risk.

The most common sites chosen for tissue biopsy in CLIPPERS syndrome include pons and cerebellum [30]. Although these sites in the brain stem are regarded to be delicate structures which controls vital bodily functions, tissue biopsies are generally considered to be relatively safe with minimal complications reported thus far [44, 45].

Tissue biopsy and histopathological examination might document parenchymal involvement with perivascular infiltration of CD3 T-lymphocytes, CD4 T-lymphocytes, histiocytes, macrophages, neutrophils, plasma cells and eosinophils in the perivascular area as well as parenchymal infiltrates in the meninges, white matter and grey matter in unison with changeable tissue loss, myelin loss, neuronophagia and astrogliosis [2,9,31,46,47]. If there is presence of atypical lymphocytes, necrotizing vasculitis, giant cells, or vasculitis, then the diagnosis of Clippers syndrome should be revisited [23]. Microvasculature including small veins and arterioles had shown transmural lymphocytic infiltrate, occlusion due to massive infiltrative lymphocytes and split walls without evidence of vasculitis [28,48].

Although specific to CLIPPERS syndrome, analogous conglomeration of inflammatory cells was also documented in some CNS malignancies [49]. Immunophenotyping of these infiltrated lymphocytes might uncover CD20 B-lymphocytes, a finding that can be considered as premonition for transpiration of lymphoma [50]. Proton-weighted MR spectroscopy is considered to be very sensitive for differentiating between CLIPPERS syndrome and lymphoma [51].

As the diagnosis of Clippers syndrome is suspected based on the clinical presentation and radiological findings, it would be prudent to start high-dose IV methyl prednisolone (500mg-1g for 4-10 days) followed by oral glucocorticoids (1mg/kg/day or 80 mg/day) with gradual tapering, which is considered to be most effective treatment in this clinical scenario [1,43,52]. Studies indicate that after acute phase undergoes remission, chronic steroid therapy with prednisolone 10-20 mg will be required to maintain clinical remission [23,29,35,37]. Clinical studies suggest that curvilinear and punctate lesions in the brain stem seem to retrocede with steroid treatment, as autoimmune mediated inflammatory lesions completely vanishes and structural integrity of the brain stem is restored [53].

If dose of steroids is lower than aforementioned doses, then it culminates in resurgence of the inflammatory lesions, recurrence of clinical symptoms and reappearance of MRI signs [46,54-57]. Patients cannot be placed on the long-term steroid therapy to maintain clinical remission as they are vulnerable to steroid induced side effects; namely short-term [hypertension, hyperglycemia, pancreatitic, immunologic and neuropsychologic] and long term [osteoporosis, aseptic joint necrosis, adrenal insufficiency, gastrointestinal, hepatic, and ophthalmologic effects, hyperlipidemia, growth suppression [58]. On the grounds of these side-effects, patients receiving long term steroids should be carefully monitored for infection, osteoporosis prevention, weight gain and diabetes [9]. Keeping in the mind the prompt response of CLIPPERS syndrome, sub-optimal or delayed response to steroid challenge should make us to cross-examine and reevaluate the diagnosis.

With CLIPPERS syndrome being autoimmune based assault on the microvasculature of the white and grey matter with no permanent cure, clinical end-goal would be sustaining long-term remission. Multiple clinical studies reported that patients require continuous steroid maintenance without which there will be relapses with clinical worsening and resurgence of MRI radiological signs. Taking this into account, some authors recommend starting alternate immunosuppressive drugs at higher doses hoping that patients can be eventually be weaned from steroids [9]. As the patients are gradually weaned off steroids, there is slight risk of resurgence of brain lesions, thus making MRI imaging surveillance unavoidable and indispensable [59]. The optimal duration of steroid therapy is set in stone as it varies from patient to patient.

In our clinical case, usage of rituximab has been successfully used in maintaining clinical remission. In a clinical report by Cipraine, et al, [46] patient initially exhibited a complete clinical response to 5 months of steroids, but immediately after steroid tapering the patient developed gait ataxia and MRI worsening. Eventually, she was placed on Rituximab 1000 mg IV every 6 months for 1 year, which resulted in clinical remission [46]. Despite Rituximab treatment, she developed breakthrough relapses, thus making them to alter the therapy to Rituximab 1000 mg every 4 months for 4 years [46]. Following this long-term Rituximab treatment, she developed complete clinical and radiological remission [46]. In a retrospective case series by Castro, L.T. et al. [60] rituximab has been associated with clinical stability and remission in one patient although 50% treatment failure has been observed with azathioprine, methotrexate, cyclophosphamide and

interferon-alpha [60].

Since CLIPPERS syndrome is an autoimmune phenomenon, efficacy of Rituximab stems from its primary mechanism of action where its binds to CD20+ B-lymphocytes, thence making them vulnerable to complement-mediated cytotoxicity, antibody dependent cytotoxicity, and apoptosis [54]. Multiple reports suggest most of the inflammatory infiltrate heaping up in the brain tissues of CLIPPERS syndrome is primarily consists of CD4 T-lymphocytes. Nevertheless, the efficacy of rituximab in CLIPPERS syndrome materializes due to the numbers of reasons. First, it is a common perception that B-lymphocytes are primary checkpoints for T-lymphocyte proliferation, antigen presentation and co-stimulation [46]. As a consequence, destruction of B-lymphocytes will be instrumental in removing the T-lymphocytes and their emanating secretions including pro-inflammatory and cytotoxic cytokines as well as chemokines [61]. Second, it has been reported that at least 5% of the T-lymphocytes are to habour CD20 receptor [62]. As, riruximab has strong affinity of CD20 bearing lymphocytes, usage of this immunosuppressive drug will virtually eliminate CD20 antigen expressed B-lymphocytes as well autoreactive T-lymphocytes [source of autoantibodies], thus buttressing the presumption for its clinical efficacy in CLIPPERS syndrome [54]. Studies have shown that rituximab has been as a monotherapy, adjuvant therapy as well as in combined regimens with modestly successful clinical outcomes in CLIPPERS syndrome [55-57,63].

Taking into account this high risk of relapse, some clinicians had recommended a longer duration of steroid maintenance therapy to perpetuate the disease process quiescence [2,5]. Thenceforwards, if the state of affairs commands longer duration of steroid therapy to maintain remission, it would be judicious to replace steroids with steroid sparing immunosuppressants such as and rituximab, which has shown efficacy in the clinical trials for maintaining remission, preventing relapses and curbing the steroid induced side effects [23,29,33,39].

Apart from rituximab, steroid-sparing immunosuppressives such as tocilizumab, hydroxychloroquine, azathioprine, methotrexate, and cyclophosphamide has also yield moderate success in few reports [3,64]. In cases where CLIPPERs syndrome is misdiagnosed or where there is a delay in diagnosis, due to which steroid therapy was not administered at appropriate time, the clinical course runs through relapsing or remitting course, thus setting the stage for irreversible and severe cerebral injury and clinical sequelae [30]. The peculiarity of these lesions lies in the fact that they completely vanish from sight upon steroid therapy, which turn the spotlight towards autoimmune process as high-powered driving force instigating the disease pathology in this clinical scenario [9].

A few times, these lesions are so dependent on steroids that withdrawal of steroids is followed by swift resurgence of lesions, thus requiring steroids or steroid sparing immunosuppressive drugs for maintaining remission in few subsets of patients. There are few specific guidelines on the average duration of steroid therapy required for keeping the disease in abeyance. But, taking into account the incrimination of vasculitis in the pathophysiology, some clinical researchers proposed the minimum duration to be around 4 months [65]. Nevertheless, all these patients that experience complete resolution of lesions will need regular MRI follow up for uncovering CNS neoplasms in the next few years. Relevantly, the lack of steroid response or presence of unilateral lesions along with edema/mass effect or pial enhancement should bestow the green light to contemplate alternate diagnosis in this clinical scenario [9,29,32,46 66].

CLIPPERS syndrome can kick-start chronic T-cell lymphocytic dysfunction, thence commencing altered relationship between T and B lymphocytes as well as discordant regulation of tumor suppressor genes and oncogenes. These aforementioned changes can put in motion unregulated proliferation of EBV-infected lymphoma cells and thereby enkindle the origination of lymphomatoid granulomatosis [51,67-69]. In addition, multiple sclerosis, hemophagocytic lymph histiocytosis, CMV and hepatitis B infection were seemed to associated with CLIPPERS syndrome as per few clinical reports [3,70]. In few case reports, remission of CLIPPERS syndrome was followed by development of Erdheim–Chester disease (ECD) which is delineated by infiltration of systemic tissues including brain by foamy CD68(+) CD1a (-) histiocytes [32,71,72]. Involvement of brain tissues in ECD is risk factor for worse prognosis and reduced life expectancy [72]. In the contrary, CLIPPERS syndrome was also reported to commence following the treatment and remission of Hodgkin's lymphoma or peripheral T-cell lymphoma [24,73,74]. Sporadically, in multiple sclerosis patients treated with natalizumab, CLIPPERS Syndrome has transpired after short period of time following stoppage of therapeutics by the way of immune reconstitution inflammatory syndrome (IRIS) [75]. Even following complete resolution of neurological lesions, in serial MRI follow up of these patients, few have sustained brainstem, cerebellar, spinal cord and cortical atrophy [28,29]. The mortality rate in simple & straightforward cases, relapsed and malignancy prone cases are 10%, 12% and 30% respectively [11]. Furthermore, the mean duration of steroid therapy in non-relapsed and relapsed cases is 10 days and 6 days respectively [11].

Conclusion

1. Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS) is autoimmune mediated inflammatory disorder primarily effecting brain stem, cerebellum and spinal cord.
2. The most risk factors speculated for this clinical disorder is flu, EBV, hypersensitivity and allergy.
3. Autoimmune attack transpires against antigenic epitopes lurking in the perivascular region of pons and cerebellum.
4. The tell-tale signs of pathology entails heaping up of CD4&CD3 lymphocytes in the perivascular and parenchymal regions of the pons and peri-pontine region, thus raising the possibility of venous inflammatory disorder.
5. The clinical symptoms are insidious in onset over the period of few weeks, with diplopia, ataxia, tremors, dizziness and nystagmus and cognitive dysfunction.
6. Radiological signs include bilateral curvilinear, punctate, speckled lesions [<3mm] of pons and cerebellum, perivascular lymphocytic infiltration with parenchymal extension. The lesions decrease in intensity and number as we move away from pons.
7. Homogenous T2 abnormality should be lesser than the size of lesions depicted on the post-gadolinium enhancement.
8. There should be absence of peripheral nervous system involvement.

9. Neurosarcoidosis, Sjogren syndrome, Neuro-Behcet disease, multiple sclerosis, autoimmune encephalitis, CNS vasculitis, lymphoma, glioma and paraneoplastic syndrome should be carefully excluded for confirmation of diagnosis.
10. Without treatment, patients experience relapsing remitting course, thus making them liable to cerebral atrophy and cognitive dysfunction.
11. The patient exhibits a rapid clinical and radiological improvement to steroid therapy (IV methylprednisolone followed by oral steroids).
12. Suboptimal steroid dosage or withdrawal of steroids is followed by return of inflammation, resurgence of radiological signs and recurrence of clinical symptoms.
13. Clinical researchers suggest long term steroid therapy to keep the disease process in quiescence. In some instances, usage of steroid sparing immunosuppressives might be necessary to limit steroid induced side effects.
14. Regular MRI follow up is required to uncover relapses and to detect onset of primary CNS lymphoma.

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