IFN beta 1a as Glucocorticoids-Sparing Therapy in a Patient with CLIPPERS

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Patient: Male, 31
Final Diagnosis: CLIPPERS
Symptoms: Ataxia • diplopia
Medication: IFNbeta 1a
Clinical Procedure: —
Specialty: Neurology

Objective: Rare disease
Background: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a recently described inflammatory disease of the central nervous system, distinguished by brainstem- and spinal cord-centered lesions with a characteristic contrast enhancement on MRI, a lymphocytic perivascular infiltrate on pathological exam, and a dramatic response to and dependence on steroids therapy. Since its initial description in 2010, different glucocorticoid-sparing agents, mostly immunosuppressant drugs, have been used to minimize the dosage, but these therapies also carry the risk of important secondary effects. We present the first reported case of CLIPPERS treated with interferon beta 1a as add-on therapy.

Case Report: A previously healthy 31-year-old man presented with gait ataxia and dysarthria. MRI showed pons-centered hyperintense patchy lesions on T2-weighted images. Additional tests ruled out other possible diagnoses and symptoms reversed with intravenous methylprednisolone. Over the years the patient presented with several episodes of deterioration each year, which were partly reversed with glucocorticoid therapy, but leaving him with growing sequelae. Four years after the initial event, treatment with interferon-beta-1a was initiated, achieving reduced frequency of the relapses to 1 every 4 years, which were no longer associated to increasing disability. This allowed reducing glucocorticoids to 30 mg of Deflazacort every other day.

Conclusions: Interferon beta-1a could be an alternative to corticosteroid-combined therapy in CLIPPERS and its more benign profile of secondary effects compared to immunosuppressants could make it an attractive choice.

MeSH Keywords: Demyelinating Autoimmune Diseases, CNS • Interferon-beta • Neuroimmunomodulation

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Background

In 2010, Pittock et al. described a new inflammatory disease that they named Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS). Hallmarks of this new syndrome were brainstem and spinal cord centered lesions, presenting as punctate patchy contrast enhancement on T1W-MRI images, lymphocytic perivascular infiltrate on pathological exam and, especially, a dramatic response and dependence on steroids therapy [1].

Long-term treatment with glucocorticoids seems to be mandatory in CLIPPERS but, as this is bound to lead to long-term adverse effects, different glucocorticoid-sparing agents have been tried in an attempt to reduce dosage to a minimum. So far, methotrexate and rituximab seem to be the most promising immunosuppressive add-on therapies [2–4]. However, cases are scarce and no controlled trial comparing the different alternatives has been performed yet.

Herein, we describe a patient with CLIPPERS who responded to subcutaneous interferon beta 1a (IFNβ-1a) therapy. This has not been reported before.

Case Report

In 1996, a 31-years-old previously healthy man presented with right hemiparesis, unsteadiness and dysarthria. After a more detailed physical examination horizontal nystagmus while looking to the right and both right arm and leg ataxia were patent. A demyelinating disease of the central nervous system was initially suspected.

Extensive laboratory tests were completed, all of them normal or negative. Erythrocyte sedimentation rate (ESR) was normal, as well as autoimmune screening including serum tests for antinuclear antibodies, antineutrophil cytoplasmic antibody, HLA-B27, HLA-DR2, anti-double stranded DNA antibodies, antithyroglobulin, and serum angiotensin-converting enzyme. Several infectious diseases were ruled out by serological and spinal cerebral fluid (CSF) tests, including Lyme disease, syphilis, HIV, herpes simplex virus, human herpes virus 6 and 8, varicella zoster virus, Epstein-Barr virus, cytomegalovirus, and Mycobacterium tuberculosis complex. On CSF analysis, the level of proteins, glucose, and cells were normal. Neither was there evidence of intrathecal immunoglobulin synthesis, as 8 identical oligoclonal bands (OCB) were found in blood and CSF.

Somatosensory-evoked potentials showed a prolongation of latencies in the right hemisphere and in brainstem auditory-evoked potentials, bilateral central conduction time prolongation was found. Visual-evoked potentials were normal.

A brain MRI showed hyperintense patchy lesions without mass effect in the brainstem, mostly affecting the pons and the cerebellar peduncles; these lesions were confluent and undefined, unlike the typical lesions described in multiple sclerosis (MS). No intravenous contrast was administered on this occasion. However, the inflammatory appearance of the lesions in the absence of proven infection or malignant cells on CSF testing prompted the decision to start treatment with intravenous methylprednisolone at high doses. After 5 of daily 1-gram doses, a significant improvement of the symptoms was observed, leaving only a minimal right arm paresis and mild gait ataxia. Due to the remaining neurological deficits, a tapering dose of 70 mg of oral prednisone after discharge was prescribed.

Unfortunately, only 2 months after stopping treatment with oral glucocorticoids, our patient presented again with symptoms similar to those in the first admission, in addition to diplopia. A second MRI with gadolinium contrast was requested then, which showed the same patchy lesions in the brainstem (Figure 1A) but with no gadolinium enhancement. However, this new imaging was obtained after initiating intravenous treatment with methylprednisolone 5 days prior, which probably altered the final results.

Over the next 4 years, despite long-term therapy with oral corticosteroids, our patient had several relapses, always involving the brainstem, with a frequency of at least 1 exacerbation per year. Each relapse was treated with intravenous glucocorticoids, but the improvement achieved was only partial and residual ataxia was more severe each time. It was clear that maintaining a low dose of oral corticosteroids was the only way to reduce the time between relapses.

On May 2000, a control MRI between relapses showed a patchy and curvilinear gadolinium enhancement on T1-weighted images, peppering the cerebellum (Figure 1B). By then, several data suggested that our patient did not have MS: he did not meet the dissemination-in-space criteria because lesions were always restricted to the cerebellum and the pons; their appearance on T2-weighted-MRI was atypical for MS; the presence of a mirror pattern on OCB testing did not fit the pattern; and the ultimate dependence on daily steroids to avoid worsening was inconsistent with the diagnosis. On the other hand, an autoimmune origin was suspected, as the infectious or tumor etiologies were safely ruled-out after 4 years of follow-up. A vasculitis of the central nervous system was considered, but the ESR and other analytical features were normal, CSF showed no pleocytosis, and there was no proof on MRI of vascular-related lesions such as microbleeds. However, after 4 years of treatment, the deleterious effects of chronic corticoid therapy caused concern and the need for a glucocorticoid-sparing therapy was evident.

After careful consideration, on July 2000, immunomodulatory treatment with subcutaneous IFNβ-1a (Rebif 22® 3 times
a week) was decided on. The choice was based on the uncertainty of the diagnosis and the search for a treatment with a more secure profile than classic immunosuppressants. From that moment on, relapses occurred further apart, with a frequency of 1 exacerbation every 4–5 years, and they were no longer associated to increasing disability. The patient had a good tolerance to the treatment; he reported no significant flu-like syndrome or injection-site reactions and consecutive laboratory studies showed no alteration in leucocytes, liver, or thyroid function. However, low doses of oral Deflazacort (30 mg every 2 days, equivalent to 25 mg of Prednisone every 2 days) were sustained, in fear of further exacerbations. Suspension of corticosteroids was achieved during 11 months in 2001, but after a new relapse, we chose not to insist on total withdrawal. When Pittock et al. published their research in 2010 and the diagnosis was evident, a modification of the treatment was considered, but, taking into account both the patient’s clinical stability and the excellent tolerance to immunomodulatory treatment, watchful waiting was decided on.

Discussion

The inflammatory disorders of the central nervous system include a wide variety of diseases whose immunopathogenesis is poorly understood in many cases. Since the initial description of CLIPPERS by Pittock et al. [1] in 2010, approximately 50 more cases have been reported [4] and in all of them, immunosuppressive therapy with glucocorticoids seems to be a common feature, to the extent of being considered one of the core features of the disease [5]. Doses over 20 mg of oral prednisone per day seem to keep relapses at bay [3], but the secondary effects associated to sustained GCS therapy necessitate the use of GCS-sparing therapies. Several immunosuppressive agents have been used for long-term therapy and, except for methotrexate [2] and possibly rituximab [3], no drug has been able to have sustained control of the disease without combined oral glucocorticoids, and those who have are only isolated cases.

Other immunosuppressive drugs that have been used as add-on therapy in patients with CLIPPERS are cyclophosphamide, azathioprine, and mycophenolate mofetil [4], but to date, no previous use of IFNβ-1a has been reported. In our patient, the IFNβ-1a substantially reduced the frequency of relapses, stopped the increasing neurological sequelae, and allowed changing to a lower dose (30 mg every 2 days) of oral Deflazacort.

IFNβ-1a belongs to a large family of secreted proteins, the interferons, which are involved in the defense against viral infections, the regulation of cell growth, and in the modulation of immune responses [6]. IFNβ-1a has for years been a first-line
CLIPPERS is suspected to have an autoimmune nature [1]. Pathological of brain biopsy samples have demonstrated the existence of T cell-predominant inflammatory cell infiltrates [5]. The preponderance of CD4 cells suggests the primary involvement of the MHC class II-restricted antigen presentation [4]. In addition, the predominant perivascular inflammatory infiltrates suggest a vascular access of the immune system arsenal through the blood-brain barrier, where IFNβ-1a is believed to act as well. These factors all could explain the effectiveness of IFNβ-1a in CLIPPERS disease.

Conclusions

IFNβ-1a could be an alternative to corticosteroid-combined therapy in CLIPPERS, and the more benign profile of secondary effects compared to some immunosuppressants could make it an attractive choice. Whether its efficacy is similar to or below that of immunosuppressive agents remains to be explored, preferably in controlled trials that include a many patients. However, this seems to be a difficult task given the low prevalence of the disease.

Statement

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