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Case Report
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Psychological Symptoms in Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS): A Case Report

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Abstract

Introduction: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is a inflammatory central nervous system (CNS) disorder, prominently involving the brainstem and in particular the pons, characterized by perivascular pathologic reaction lymphocyte infiltration, leading to dysarthria, ataxia, diplopia, altered sensation and paraesthesias of the face, dizziness, nystagmus, spastic paraparesis as well different psychological symptoms. The radiological distribution is focused in the pons and adjacent rhombencephalic structures such as the cerebellar peduncles, cerebellum, medulla and the midbrain [1]. Diagnosis of CLIPPERS is challenging, and requires careful exclusion of alternative diagnoses. Pathogenesis of CLIPPERS remains poorly understood, and the nosological position of CLIPPERS has still to be established.

Case presentation: A 44-year-old Croatian man presented in our emergency room with aggressive behavior, disorganization, emotional liablity and psychotic delusions. He had been having neurological symptoms like dysarthria, ataxia, poor balance, sensory loss in the extremities, a tingling sensation in the affected limbs/hemiparesis, dizziness and instability. He had been diagnosed with state after inflammation of the brain and peripheral nerves and ataxia and was recieving neurological treatment for approximately one year. On MRI, which was done one year ago, there was evidence of hyperintensity in the central part of the pons, spreading into the middle peduncules, with reduced volume of pons, cerebellum, cerebellar peduncules and left olive. According to psychological symptoms, he was treated with antipsychotic agents, but on very low doses, such as haloperidol 2mg, klozapin 25mg as a result he developed Neuroleptic Malignant Syndrome (NMS). He was hospitalized in psychiatric and neurological departments three times in several months, before he was diagnosed with CLIPPERS syndrome, after excluding infections, malignant and autoimmune paraneoplastic processes.

Conclusion: CLIPPERS syndrome affecting the brain, in general, presents with neurological symptoms, but also psychological symptoms, which can not be excluded or isolated. Without neurological diagnosis, psycholocigal symptoms can misslead the provider which can lead to a misdiagnosis. In our case, psychological symptoms that were presented in CLIPPERS syndrome manifested as disorganization, aggression, emotional lability and delusions. The symptoms were very well managed with low doses of olanzapine, carbamazepine and aripiprazol.

Keywords: CLIPPERS, Autoimmunity, Psychoorganic, Psychotic

Introduction

CLIPPERS is described as pontine-centric inflammatory disorder with distinct clinical and radiological features. The disorder was first described in 2010 by Pittock et al. [1] as a distinct form of brainstem encephalitis centred on the pons, which is characterized by a predominant T cell pathology, and responsive to immunosuppression with glucocortico- steroids (GCS). The cardinal feature of the condition is a punctate and/or curvilinear gadolinium enhancement, 'peppering' the pons and adjacent hindbrain structures on MRI. Characteristic imaging patterns of punctate enhancement involving white and grey matter and neuropathology with prevailing perivascular inflammatory infiltrates favour an inflammatory disorder with a vascular or perivascular tropism [2]. These immunological targets may be microstructures localized preferentially in the pons and peripontine region. Considering the anatomical arrangement of small intra-axial veins of the CNS, the predominant involvement of brainstem structures might also be related to a primary venous inflammatory CNS disorder. Effectors

of the inflammation process seem to be T lymphocytes, with a predominance of CD4 cells. The pathogenesis of CLIPPERS is still unknown, and its nosological position is still to be established. Potential predispositions or triggering events of the postulated immune mediated/inflammatory process are unclear and a specific biomarker of the disorder is lacking [3].

Case Report

A 44-year old Croatian man came to our emergency room with police escort after inappropriate behavior at home. He suddenly became agressive, disorganized, and emotionally labile. He was disinhibited and had a psychotic episode, including delusions. He was already recieving neruological treatment for one year. His initial symptoms included: ataxia, hemiparesis l.dex., dysarthria, dizziness, poor balance, and sensorimotor neuropathy. After MRI, which had shown hyperintensity in the central part of the pons, spreading in middle peduncules, with reduced volume of pons, cerebellum, cerebellar peduncules and left olive, he was diagnosed with state after inflammation of the brain and peripheral nerves and ataxia. He was not taking any neurological medications. The patient's first neurological symptoms presented when he was 22 years old, after trip to Brasil. He recalled that suddenly, he had no strength in his right arm, he was sweating profusely, and felt disorganized. He refused to go to the hospital in Sao Paulo. When he came back to Croatia, he was evaluated and noted that infections were excluded, stating that his neurological symptoms were remissed. A few months thereafter, he became depressed and began to have some troubles at work and in his marriage. He began looking for help for his difficulities and was diagnosed with depression. At the same time, his neurological symptoms started to get worse, presenting with ataxia, loss of muscle strength and dizziness. The first MRI showed hyperintensity in the central part of the pons, spreading in middle peduncules, with reduced volume of pons, cerebellum, cerebellar peduncules and left olive. Few days after, he was hospitalization in our psychiatric hospital. According to his clinic presentation he started to be treated with low doses of haloperidol, risperidon, then klozapine, but very quicky he developed NMS (Malignant Neuroleptic Syndrome). His leukocytes rose to 14.38, CRP 55.3. He was transfered to neurology. Diagnostic methods that check the function of optic and leg nerve /latin n. tibialis/, showed the block of conduction of electric impulse in those nerves. EMNG showed chronic radiculopathy at L5 billateral with sensoric acsonal polineuropathy. EEG was diffuse dissrythmic slow, HV and post HV elements BIPLEDs in the left frontotemporal area. Negative results were for autoimmune, paraneoplastic process or infections /negative anti- HV, Yo, Ri, Anti VGKC, NMDA, Anti Tr, negative on B. Burgdorferi, CMV, EBV, syphilis, VZV, HIV, HBV, Fabry disease, Lupus anticoag., Freidraich. ataksia. Antibodies anti-SS/LA, RF, ANA, aCI-IgG, aCI-IgM, beta2-GPI, as-GMI1. GM2, GD1a were negative or in the normal range, except for CD1b, which was possitive. CDFI of carotides and VB was normal. Neurocognitive tests showed mild cognitive impairment for verbal memory and attention. Control MRI: with no changes in T2/FLAIR hyperintensity lesions in the central part of the pons and in the middle cerebellar peduncules; loss of volume in the pons, cerebellar peduncules and cerebellum . When he was discharged from neurology, his psychological state worsened, he again started to became disorganized, aggressive, disphoric and had psychotic episodes. His medication therapy included karbamazepine, aripiprazol and kvetiapin in low doses, which he reacted very well to. In the meantime, antiganliozid antibodyes were done and GQ1b was negative but Anti MAG was positive. Control MRI was done with no change in comparison to the pevious MRI. As a result of the findings, he was diagnosed with CLIPPERS syndrome. With antipsychotic agents and treatment, with ivIG 0.4g/kg at first and then with glucocorticosteroids, his mental state improved and fell into remission.

Discussion

CLIPPERS is an inflammatory disorder of the brainstem, which is very responsive to steroids offering excellent prognosis [1]. CLIPPERS is an inflammatory central nervous system (CNS) disorder, prominently involving the brainstem and in particular the pons, characterized by perivascular pathologic reaction lymphocyte infiltration, leading to dysarthria, ataxia, diplopia, altered sensation and paraesthesias of the face. In addition, dizziness, nystagmus, spastic paraparesis and different psychological symptoms as also part of the presentation but are not well documented. The radiological distribution is focused in the pons and adjacent rhombencephalic structures such as the cerebellar peduncles, cerebellum, medulla and the midbrain. Our patient had some clinical neurological and typical radiologic findings that met the diagnostic criteria for CLIPPERS, but also had some psychological symptoms that are not well described yet. Our patient also had anti MAG positive antibodies. Anti-MOG antibodies are also described in some cases of CLIPPERS [4]. We cannot exclude the possibility that our patient developed antibodies subsequent to his initial pontine inflammation, as anti-MAG antibodies were not checked at original presentation. Assessing only the psychological symptoms, without radiological and neurological tests, can lead to missdiagnosis and improper treatment. Pathogenesis of CLIPPERS remains poorly understood, and the nosological position of CLIPPERS has still to be established. It has yet to be determined if CLIPPERS is a disease entity or just an immunological response to a disease [5]. In previous case reports the clinical and radiological features of CLIPPERS are very distinct and therefore an extensive immunological workup should be done in order to exclude paraneoplastic syndromes, neoplasma, vasculitis or infection processes. Some reviews suggest that immunosuppressive therapy should be continued for at least 2 to 5 years [6]. The question still remains for how long a dual use of antipsychotic agents with glucocorticosteroids must be taken, and if tretament of CLIPPERS starts immediately, will psychological symptoms present themselves at all.

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Conclusion

CLIPPERS is an immune- mediated inflammatory disorder of the brainstem, which is presented by different neurological, but also psychological, symptoms. It is well managed by immunosuppression treatment but it still remains a question for how long antipsychotic agents must be taken, parallell with immunosuppressants. In addition, if CLIPPERS started to be treated immediately, will psychological symptoms present at all. Further studies are needed to confirm that prolonged corticosteroid therapy prevents further relapses and develoment of psychological /psychorganic symptoms, and if antipsychotic agents are needed, or if immunosuppressants are enough.

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