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Case Report
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Primary Angiitis of the Central Nervous System Mimicking a Prion-Like Disease

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Abstract

We describe a patient with a 2 month course of dementia, Parkinsonism and myoclonus highly suggestive of a prion disease. We review the differential diagnosis and subsequent comprehensive assessment, including brain biopsy, to identify treatable causes in the setting of possible prion-related encephalopathy. Brain MRI showed a nodular parenchymal and linear leptomeningeal enhancement but no vessel abnormalities and cerebrospinal fluid sample had 324 leukocytes/µl (98% lymphocytes) and 150.35 mg/dl proteins leading to final differential diagnosis of CNS lymphoma, infection, chronic granulomatous disease or a primary central nervous system vasculitis. Brain biopsy confirmed a primary angiitis of the central nervous system.

The combination of rapidly progressive dementia with Parkinsonism and myoclonus is highly suggestive of a prion encephalopathy. However, determining potentially treatable causes is imperative, particularly atypical presentations of uncommon disorders such as primary angiitis of the central nervous system. Common presentations of primary angiitis of the central nervous system are headache or seizures, with a rapidly progressive dementia being less frequent. This case illustrates the need for a comprehensive assessment of rapidly progressive dementia, especially when a prion disorder appears to be the cause.

Keywords: Prion disease; Encephalopathy; Vasculitis

Background

Rapidly Progressive Dementia (RPD) is a clinical syndrome that is often challenging for the clinician [1], with a significant proportion of patients not having an identified cause. Broadly, the potential causes of a rapidly progressive dementia fall into these major categories: vascular, infectious, traumatic, metabolic, autoimmune, idiopathic/iatrogenic, neoplasm or inborn errors [2]. Identifying additional symptoms is an important step in narrowing the diagnostic consideration. When RPD is associated with Parkinsonism and myoclonus, Creutzfeldt - Jakob Disease (CJD) is a primary consideration. However, other entities should be considered, and some of them are treatable. Several complementary exams must be done [3], so it is important to prioritize the most sensitive and least invasive ones to reach the right diagnosis quickly. However, multiple different tests are often required.

Case Presentation

A previously healthy 78-years-old man presented to the emergency room with a subacute neurological disorder. Two months prior, he observed an irregular tremor affecting both arms and legs. He also developed gait difficulties and a freezing phenomenon. The physical examination also showed diffuse moderate bradykinesia and rigidity. He was diagnosed with Parkinson's disease and started on levodopa treatment, but without any improvement. A month later, his wife began to observe cognitive impairment including forgetting conversations, impaired speech fluency, and problems recognizing his family members. Shortly thereafter he developed worsening motor and gait symptoms and was unable to stand up unassisted. Moreover, he developed dysphonia and dysphagia for liquids resulting in a 10 kg weight loss over 2 months. Two days before consulting in our hospital, he was not able to carry on his basic activities of daily living.

On the physical examination, the patient was disoriented in time, but he was oriented to place. He obtained 16 at 30 points in the mini mental test. He was unable to execute complex orders and

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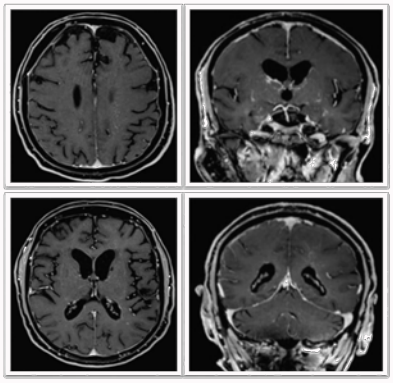

Figure 1: Coronal and transversal post-gadolinium brain MRI: *Prominence of vascular structures, which may correspond to deep veins, and pose the possibility of some type of vasculitis, including granulomatous angiitis or even angiocentric lymphoma.*
MRI finding: Post-gadolinium images showing nodular parenchymal and linear leptomeningeal enhancement.

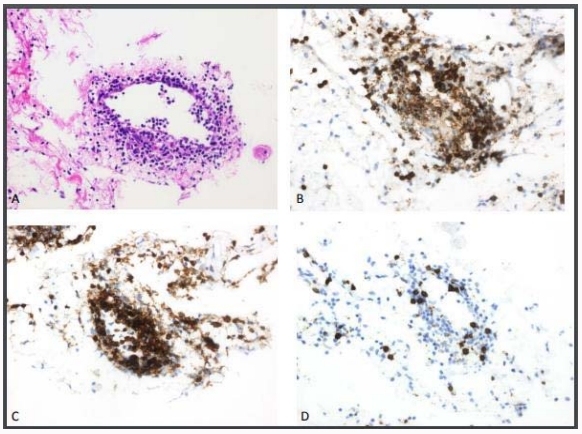

Figure 2: Brain biopsy.
A meningeal lymphocytic vasculitis composed by T lymphocytes with predominant CD4 cells was observed. A) H&E, x200. B) Immunohistochemistry against CD3, x200. C) Immunohistochemistry against CD4, x200. D) Immunohistochemistry against CD8, x200).

his short-term memory was severely impaired. Grasping and palm mental reflex were present bilaterally. His language was bradylalic and non- fluent and he had severe hypophonia and hypomimia. He had diffuse, spontaneous and inducible limb myoclonus, bradykinesia, and muscular rigidity. He was unable to walk unaided. The sensory exam, deep tendon reflexes and response to plantar reflexes were normal.

To rule out a systemic infectious disease, a metabolic/iatrogenic problem, an immune-mediated dementia complete blood test must be done [3] and in the absence of a clear diagnosis cerebrospinal fluid analysis is necessary. For this patient, cell blood count, inflammatory markers, liver and kidney function, thyroid hormones, B-group vitamins, and autoimmune profile were normal. Serum onconeuronal and anti neuronal antibodies were not detected. HIV and Lyme serologies were negative. Urine analyses were also normal.

An EEG can be helpfulin the diagnosis of CJD when it exhibits the characteristic changes depending on the stage of the disease, such as diffuse slowing and Frontal Rhythmic Delta Activity (FIRDA) or disease-typical periodic sharp wave complexes [4]. It would also help to differentiate a non-convulsive epileptic status or a metabolic encephalopathy. In this case the EEG showed slow waves and 3-8 seconds, occasionally, FIRDA waves, with triphasic morphology. A brain MRI with contrast should also be obtained to exclude vascular, inflammatory, or other focal lesions. Sometimes, typical MRI finding are observed in subjects with RPD and help to make the right diagnosis, for example in CJD or limbic encephalitis. A brain MRI was performed, including post-gadolinium infusion sequences, and a nodular parenchymal and linear leptomeningeal enhancement was noticed (Figure 1). Brain MRI did not show typical CJD findings, such as basal ganglia, thalamic or cortical hyper intensities on T2, FLAIR or DWI [5]. According to the MRI findings, our differential diagnosis included an intracranial vasculopathy; for example, an infection of the CNS (varicella zoster virus vasculitis, meningo vascular syphilis, angio invasive fungal infections or CNS-TBC), an immune disease, a paraneoplastic disease, granulomatous disease or a CNS lymphoma.

CSF analysis showed 324 leukocytes/µl (98% lymphocytes), 0 erythrocytes, protein 150.35 mg/dl, glucose 56 mg/dl. CSF serology was negative. A lymphocytic pleocytosis was informed at the CSF cytology, without atypia or duplicity. All the CSF cultures, Polymerase Chain Reaction (PCR) for virus and serologies were negative. 14.3.3 Protein result was also negative.

The lymphocytic pleocytosis supported the differential diagnosis of an autoimmune disease, a CNS lymphoma or a chronic infection of the CNS. At this point, an empirical treatment was not possible, because treating a vasculitis could be fatal for a CNS infectious disease and antibiotics would not heal a vasculitis or lymphoma and would carry side effects.

Brain biopsy is considered in patients where clinical or complementary findings show the possibility of a potentially treatable process [6,7]. In patients with no identifiable cause a brain biopsy may be required to obtain a definitive diagnosis. However, in the absence of clear abnormalities on imaging, the utility of brain biopsy is less. Although there are often concerns about the risk of brain biopsy, in experienced centres this risk is relatively low. A large series that examined the safety of over 7000 stereotactic brain biopsies concluded that the mortality rate was less than 1%, the morbidity rate was 3.5% and very few patients had permanent disability [6,7]. Subsequently, neurosurgery was consulted for a diagnostic meningo-cortical biopsy. It was run out without complications. The biopsy found: "The arachnoid presents a perivascular lymphocytic infiltrate affecting capillary and venous vessel. The lymphocytes are mature without atypia" (Figure 2). With the biopsy result, we excluded a potential CNS infectious disease or a CNS lymphoma. The perivascular lymphocytic infiltrate affecting capillary and venous vessel were highly supportive of a diagnosis of Primary Angiitis of the Central Nervous System (PACNS). PACNS is a heterogeneous disease. It is described as an angiocentric inflammatory infiltrate along with granulomatous, lymphocytic or necrotizing vasculitis.

The patient was given 1 gram of methyl prednisolone for five days with a remarkable improvement. The patient began to talk and to stand up after the second dose of corticoids. At the end of the treatment, a significant improvement in his cognition was also observed. He was able to eat by himself, walk, write and read normally. The patient was discharged with an oral descending corticosteroid treatment. He also received six doses of Cyclophosphamide 750 mg/m^2/month with a good tolerance and he is still under immunosuppressive treatment with Mycophenolate mofetil. With the current treatment resulting a

return to near normal function.

Discussion

RPD is a rare but serious syndrome that requires an expedited assessment to identify potentially treatable causes. There is no universally accepted rate of progression that defines RPD, but two years or less from cognitively normal to dementia is typical. However, it often progresses faster. Prion disease is a common consideration, but one with a fatal outcome. Yet, compared with typical neurodegenerative dementia, RPD is much more likely to result from reversible causes. This requires a systematic approach to increase the probability of an early and precise diagnosis and decrease mobidity and moratilty. The truth is that you cannot diagnose a disease that you ignore. A simple way to remember the possible etiologies of RPD is the word VITAMIN C (vascular, infectious, traumatic, autoimmune, metabolic, idiopathic/iatrogenic, neoplasm, congenital) [2] and the diagnosis effort must go to identify the possible causes. As this case highlights, when all the routine tests are done, additional diagnostic studies are commonly necessary, including brain biopsy.

Primary Angiitis of the Central Nervous System (PACNS) is a rare condition that can mimic all the neurological syndromes. The incidence is estimated in 2.4 cases per 1,000,000 person-years. It affects predominantly the small and medium sized vessels of the CNS [7]. Headache is the most common presentation and there are few cases of this entity reported as a RPD. There is no pathognomonic routine test to diagnose this entity. Brain MRI can help the diagnosis, but it is not specific. CSF shows pleocytosis and/or elevated protein. Brain biopsy is the gold standard test, it is highly specific for the PACNS diagnosis and it helps to identify other treatable diagnoses. Treatment protocols are not well standardized due to the rarity of the disease. Usually, it is treated with high doses of corticosteroids and chronic immunosuppressive treatment with Cyclophosphamide, Methotrexate, Azathioprine or Mycophenolate mofetil [7]. Initially, it is generally recommended a high dose of corticosteroids in combination with Cyclophosphamide and a close monitoring of the patient. Up to the 80% of the patients respond well to this treatment [7].

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