A CASE OF ISOLATED BRAINSTEM DEMYELINATING LESION WITH SUPPOSED HERPETIC ETIOLOGY

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ABSTRACT
This report describes the clinical and radiological findings of a 48-years-old man suffering from acute impairment of trigeminal sensibility in the left side of his face. This neurological focal symptom started within few weeks after an herpetic oral infection. Brain magnetic resonance imaging showed a single abnormal and ill-defined signal intensity in the left side of pons and middle cerebellar peduncle. Enhancement was noted with involvement of left trigeminal root. The lesion, with atypical demyelinating and inflammatory features, was interpreted as localized herpetic infection in the brainstem on clinical and radiological bases.

Key words: Rhomb-encephalitis, herpes virus, trigeminal nerve, demyelinating lesion.

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Introduction

Demyelinating diseases are defined as disorders of the central and peripheral nervous system with destruction of the myelin and concomitant axonal loss to varying degrees as well, resulting in long-term disability\(^1\). Viral infections cause a variety of demyelinating diseases; the mechanisms of the demyelisation range from direct infection and lysis of oligodendrocytes to immune destruction of myelin by cell-mediated immune responses, antibody, and cytokines\(^2\). This explains the continued interest in viruses as triggers for Multiple Sclerosis (MS) and other demyelinating diseases of the brain\(^3\). Herpes viruses are of particular interest because of their neurotropic, ubiquitous nature and their tendency to produce latent, recurrent infections.

Moreover, today is recognized that viruses are associated with typical demyelinating syndromes, such as the “progressive multi-focal leukoencephalopathy” (PML), the “sub-acute sclerosing pan-encephalitis” (SSPE), and the “post-infectious encephalitis”. Acute Disseminated Encephalomyelitis (ADEM) is an acute perivenular demyelinating disease of the brain and spinal cord that usually follows viral infections. The focal presentation of ADEM is heterogeneous and dependent upon the location and degree of the inflammatory-demyelinating process within the central nervous system (CNS). Multi-focal neurological deficits consisting of combinations of pyramidal and cerebellar signs are very common, as are cranial neuropathies, including bilateral optic neuritis, encountered more frequently in ADEM than MS\(^4\).

Isolated transverse myelitis is usually considered a separate, although related, entity to ADEM, and is part of an ADEM presentation in about a quarter of cases. However, transverse myelitis, optic neuritis, cerebellitis, and brainstem encephalitis, can be single expression of site-restricted forms of monophasic acute inflammatory demyelinating disorders that occur after a viral illness or vaccination.

Generally, viral infections of the brain may result in a clearly diagnosed encephalitis, sometimes resulting in lethal consequences. However, a growing understanding of the biology of the viruses that infect the brain and the resultant host responses have raised the possibility of viral causation of a number of more subtle neurological conditions\(^5\).

We report a case with an isolated lesion which could be referred to a damage of the CNS occurring after a viral illness. This case in our opinion is
instructive because it is characterized by a neurological condition with focal clinical expression linked to a previous herpetic reactivation, and associated with isolated anatomical changes in the brainstem with inflammatory and demyelinating features on the magnetic resonance imaging (MRI).

**Case report**

A 48-old-year man presented with reduction of sensibility, numbness and tingling in the left trigeminal territory of one week’s duration. His medical history was significant for recent onset of hypertension, which had diagnosed few months previously and treated with calcium antagonist and angiotensin-converting-enzyme inhibitor. Two weeks before his neurological complaint, patient presented a recurrence of labial herpetic infection with vesicular lesions spreading to left margin of tongue and palate. Findings at physical examination, thoracic radiography, EKC and laboratory routine tests were normal.

On the neurological examination sensory section of the V cranial nerve was compromised, with anaesthesia in touch-pain-temperature in the ophthalmic, maxillary and mandibular divisions of left side, and corneal reflex absent. The motor division supplying the muscles of mastication was intact with normal jaw jerk reflex. Sensibility was normal in the right face and the entire body (vibratory and postural sensation included). Both pupils were alert to light and with the same diameter. Either peripheral or central motor deficit of facial nerve was not bilaterally noted, and both elevation of soft palate and tongue movements were normal. Lateral gaze nystagmus was absent, but a mild dysmetria in the left finger-to-nose test was observed. There was not unsteadiness and patient walking normally. Deep tendon reflexes were well elicited and no pathological reflex was observed. Neck stiffness or other meningeal signs were absent.

Patient was submitted to MRI study, which showed a circumscribed area of abnormal signal intensity within the left dorsal portion of the pons and the contiguous middle cerebellar peduncle (fig. 1, B). In the T1 weighted sequence post-gadolinium, within the lesional hypo-intensity appeared a well-demarcated area of enhancement involving the left trigeminal nerve root as compared with the contralateral normal-appearing (fig. 1, A).

An analysis of his cerebrospinal fluid (CSF) was conducted in order to confirm a central nervous system infection: CSF showed a normal opening pressure, a slight increase in white blood cells, and normal protein and glucose levels. Varicella-zoster virus (VZV) antigen, entero-virus, and adenovirus resulted all negative. Human herpes simplex-1 (HSV-1) was positive, although DNA herpetic detection by polymerase chain reaction (PCR) resulted negative. The CSF IgG index was normal and oligoclonal bands did not were detect.

Based on these laboratory results and MRI findings, we made diagnosis of “rhomb-encephalitis”. Although the underlying cause remained at first doubtful, a possible herpetic infectious etiology was supposed on clinical bases.

After intravenous therapy of acyclovir at full dosage (10 mg/Kg three times/die) and corticosteroids, in reality, the patient reported some improvement in the sensitive trigeminal function. He left the hospital on the tenth day after admission; follow-up MRI examinations showed appreciably a reduction of the lesion.

**Discussion**

What can be considered unusual in our patient is certainly the modality of presentation. After an herpetic eruption in the inferior left facial region, he
experienced suddenly a condition of complete suppression of trigeminal sensibility in the same side of face, without fever or signs of nervous system infection. Neurologically there was not vertigo, horizontal nystagmus, facial paralysis, hearing loss, and crossed sensory disturbance: all usually associated with a central trigeminal lesion. There was no weakness of the limbs, but only a mild hemi-ataxia in the left arm consisting in a finger-nose test mildly uncoordinated and dysmetric.

This unusual clinical condition was later explained by the magnetic resonance study, which revealed the anatomical characteristic and presumptive nature of the lesion. First, in sagittal view was evident the involvement of the pontine trigeminal nucleus and annexed spinal tract, which represent the main sensory nucleus for the face sensibility (fig. 2).

MRI findings showed normal signal at the ventral edge of the pons, explaining why the patient had an undamaged motor function, any focal involvement of motor cranial nerve, and hypo-aesthesia only in the left face without contra-lateral trunk and limbs involvement, due to integrity of lateral spino-thalamic and cortico-spinal tracts (fig. 3). Involvement of the left middle cerebellar peduncle resulted in associated ipsilateral mild deficit in motor coordination of the left arm.

Another puzzling aspect of this case is in relation to nature of the lesion. A first possibility is an infarction involving the brainstem territory supplied by anterior inferior cerebellar artery (AICA), which often manifests as lateral inferior pontine syndrome. Typically, therefore, thrombosis of the AICA produces a clinical picture more rich of symptoms than those observed in our patient. The AICA usually arises from the proximal two-third of the basilar artery. It then supplies the pons, the floculus, and the anterior portion of cerebellar hemisphere. So the occlusion of stem portion of the AICA can cause ischemic lesions in pons and cerebellum. A few studies disclosed that middle cerebellar peduncle is the core of the territory involved\(^5\), and frequently extended to cerebellum\(^6\).

Nevertheless, besides ataxia the classical pattern of inferior lateral pontine infarct includes the characteristic crossed sensory disturbance in the ipsilateral face and contra-lateral trunk and limbs. In our patient we observed only a sensory defect in the left facial region, justified by the radiological involvement of the descending spinal trigeminal tract and its nucleus (fig. 2). Further, angiographic RM imaging showed a normal intracranial blood circulation without occlusive pathology within the vertebro-basilar system. Except for hypertension, patient did not present vascular risk factors, and basal diagnostic cardiovascular work-up was normal.

Although atypical for a diagnosis of brainstem infarct, MRI findings raise the possibility for an inflammatory lesion of the pons. We have supposed as possible diagnosis a rhomb-encephalitis, in spite of the difficulty to confirm it on clinical and radiological basis. Most Authors actually use the term “rhomb-encephalitis” (RE) and “brainstem encephalitis” (BE) interchangeably\(^8\), even though anatomically and clinically they are different.

A case of isolated brainstem demyelinating lesion with supposed herpetic etiology

**Fig 2**: Sagittal RM imaging T1-weighted: the lesion involves the tegmentum of the pons (white arrow) including the principal sensory nucleus and the spinal tract (descending fibers) of V cranial nerve, with sparing of the motor nucleus located in medial position (see anatomical drawing in the left side, modified from Gray’s Anatomy, 35th ed.: Churchill Livingston, 1973).

**Fig 3**: In this anatomical diagram the area of the dorso-lateral pontine lesion of our patient is outlined in relation to RMI findings (trapezium with dotted line in the left side). It is evident the preservation of the lateral spino-thalamic tract, medial leminiscus, cortico-spinal tract and main motor nuclei (V, VI, VII). Trigeminal root and spinal nucleus (main sensory nucleus) of the V cranial nerve are included.
BE was first described in 1951 by Bickerstaff and Cloake\(^9\), and revised in 1978\(^10\). Since then, such a condition has been called Bickerstaff’s syndrome, and this diagnosis should be made for patients who have acute onset of disturbance of consciousness, brisk tendon reflexes or long tract sensory impairment in addition to ophthalmoplegia and ataxia\(^11\). Abnormal findings on MRI have been reported mainly involving midbrain, cerebellum and thalamus, and may move or regress with the clinical course\(^12\). As reported in the original description by Bickerstaff, these lesions pathologically consist in oedematous changes, with astrocytic proliferation and lymphocytic cuffing around some blood vessels, considered secondary to viral infection or to hypersensitivity\(^13\).

Although the similarity, RE is referred to inflammatory conditions affecting distinctively the hindbrain (pons and cerebellum)\(^14\). The causes of RE include three main categories: paraneoplastic syndromes, autoimmune diseases, infections\(^15\).

In our patient we did not performed survey of anti-neuronal antibody, but chest x-ray and tumour-markers were negatives. Among autoimmune aetiologies of RE the most common is the Behçet’s disease, but in our patient diagnostic criteria for this diagnosis are not fulfilled (skin manifestations, recurrent oral and genital sores, specific ocular pathology such as anterior or posterior uveitis, and retinal vasculitis, were all absents). ADEM, MS, and sarcoidosis are further inflammatory conditions that can be excluded in our case.

Meningo-encephalitis provoked by Listeria is considered the most common cause of infectious RE\(^16\). Listeria Monocytogenes is a gram-positive organism transmitted by consumption of contaminated food. Our patient did not present fever, signs of meningitis, and increased count of leucocytes in the liquor. Further, the lack of history of exposure to contaminated food with nausea and diarrhoea ruled out this diagnosis.

On the other hand, MRI findings and clinical features led us to consider the pontine lesion of the patient a possible atypical herpetic “encephalitis”, localized in the brainstem, preceded by mouth eruption. Cases with atypical localization in brainstem related to herpetic infection are reported in literature\(^16\). Pathogenetic mechanism could be the reactivation of the virus within the trigeminal ganglion. The lesion at the junction of the trigeminal nerve with the pons and middle cerebellar peduncle might be explained by trans-axonal spread of the virus from the Gasser’s ganglion to the brainstem. Axonal diffusion is considered a characteristic behaviour of the herpetic viruses. For example in a patient with AIDS who developed encephalitis, pathological and biological evidence of VZV was found in the eye, optic chiasm, lateral geniculate bodies, and occipital cortex, indicating spread of the virus throughout the visual pathways\(^17\). Pathology of herpetic lesions in the nervous tissue ranges from demyelination to necrosis produced by the viral replication. Radiological evidences of the lesion in our patient suggest this possibility.

A last controversial aspect of this case is represented by the biological findings in the CSF. We have detect anti-herpes antibody in the liquor without presence of viral DNA. Although a positive PCR for herpes virus DNA in CSF is helpful, a negative PCR does not exclude the diagnosis; only negative results in both herpes virus PCR and anti-herpes IgG antibody tests in the CSF can reliably rule out the diagnosis\(^18\).

The detection of antibody without viral DNA might depend on the protracted clinical course of the herpetic reactivation in our patient, or because the spinal tap was performed about three week after the onset of the disease. It is reported that in the acute encephalitis caused by HSV-1, the CSF is positive for HSV-1 DNA by PCR and negative for antibody to HSV-1 during the first week of disease, whereas viral DNA begins to disappear from the CSF as anti-HSV-1 antibody becomes detectable during the second week\(^19\).

In conclusion, this report highlight the possibility of a not progressive and narrow localization of the herpes virus in the nervous system. In this case the lesion revealed mild destructive and demyelinating features, with focal neurological manifestations, demonstrating that herpetic infection can present in unusual ways and reinforce the need of high grade of suspicion in cases without the dramatic, diffuse and devastating symptoms of encephalitis.

References


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