Surgical Neurology International

SNI: Stereotactic, a supplement to Surgical Neurology International

OPEN ACCESS

For entire Editorial Board visit : http://www.surgicalneurologyint.com

Editor
Antonio A. F. DeSalles, MD
University of California, Los Angeles, CA, USA

Holmes tremor in a patient with progressive multifocal leukoencephalopathy

Vimal Raj Nitish Gunness, Georges Dooms[1], Bernd Wauschkuhn[2], Wolfgang Feiden[3], Frank Hertel

Departments of Neurosurgery, [1]Neuroradiology, Center Hospital Luxembourg, Luxembourg City, Luxembourg, [2]Neurology, Hospital of Ettelbruck, Luxembourg, [3]Trier Histopatological Center, Germany

E-mail: *Vimal Raj Nitish Gunness - nitish57@hotmail.com; Georges Dooms - Georges.Dooms@chl.lu; Bernd Wauschkuhn - drwausch@pt.lu; Wolfgang Feiden - feiden@hotmail.de; Frank Hertel - Frank.Hertel@chl.lu
*Corresponding author

Received: 18 December 13 Accepted: 23 May 14 Published: 05 September 14

This article may be cited as: Gunness VR, Dooms G, Wauschkuhn B, Feiden W, Hertel F. Holmes tremor in a patient with progressive multifocal leukoencephalopathy. Surg Neurol Int 2014;5:S413-5.
Available FREE in open access from: http://www.surgicalneurologyint.com/text.asp?2014/5/9/413/140205

Abstract

Background: Progressive multifocal leukencephalopathy (PML) is a rare, sometimes fatal viral disease in patients with primary or secondary immunosuppression.

Case Description: A 57-year-old immunocompetent female with intractable Holmes tremor and elongated unique brainstem lesion reported to our hospital. The cerebrospinal fluid (CSF) screening for John Cunningham virus was negative and the diagnosis was established by brain biopsy. The course was rapidly fatal.

Conclusion: This atypical presentation of PML in an immunocompetent patient illustrates that diagnosis can be missed without brain biopsy.

Key Words: Brainstem, Holmes tremor, immunocompetence, JC virus, progressive multifocal leukencephalopathy

Access this article online
Website: www.surgicalneurologyint.com
DOI: 10.4103/2152-7806.140205
Quick Response Code:

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is caused by the JC virus, a polymavirus discovered in 1971 and named using the initials of a patient with PML.[8] Patients with PML are usually seen when there is already significant impairment of cognition or motor function. Polymerase chain reaction (PCR) of cerebrospinal fluid (CSF) is highly specific (92-99%), but less sensitive (74-93%) for the detection of JC virus (JCV) in patients with PML.[2] However, brain biopsy with demonstration of presence of JCV DNA within brain tissue is both the most specific and sensitive test.[7]

We report about a female patient with PML, but without any known immunodeficiency. The fulminate clinical course was dominated by intractable Holmes tremor and fatal outcome.

CASE REPORT

A 57-year-old female had been evaluated in two other departments 4 months before admission to our hospital. She initially complained of weakness of the right hand and weakness in both legs. At the initial examination, she presented a palsy of the left abducens nerve as well as dysarthria and right-sided hemiparesis with dysmetria, ataxia, and loss of epicritic sensibility. She demonstrated intermittent tremor of unknown etiology of the right thumb and index. There was mild and reproducible lymphopenia of 0.860 G/L (normal values: 1.500-4.000 G/L), but the hematological work-up was normal. Human immunodeficiency virus (HIV) serology was negative. PCR screening in the CSF for Herpes simplex virus, tropherymawhippelii, and PML was negative. The initial MRI (Flair and T2-weighted sequences) showed a

hyperintense lesion extending from the postero-lateral left portion of mesencephalon. Most characteristic sequences are shown in Figure 1.

The patient received a 3-day-trial of high dosage steroids, without any benefit. Brain biopsy was considered too risky to be performed. This decision was reversed 4 months later, as there was further rapid deterioration. Therefore, the patient was admitted to our neurosurgical department. She had noted further progressive weakness and, in particular, constant "shaking" of the right hand. She complained of intractable pain in the right leg and constant diplopia. The neurological examination demonstrated divergent strabismus due to possible left-sided paresis of 3rd and 6th cranial nerve. At the paretic right arm, there was constant, spontaneous, rapid, mostly arrhythmic tremor both at rest and when the patient tried to move the extremity. Tremor abatement was only observed during sleep.

Mild lymphocytopenia was confirmed. Electroencephalography did not reveal focal epileptic discharges. MRI of the brain revealed further local brainstem extension; as for the initial MRI there was no detectable cortical lesion. After informed consent stereotactic brain biopsy of the left brainstem was performed. The tremor syndrome remained refractory to various therapeutic approaches. The patient died 6 months after the onset of the disease. The results of the histological examination (see below) were not yet known at the time of death. The biopsy specimen [Figure 2] showed brain tissue with reactive astrocytosis, a few lipid-filled macrophages, a venule with some perivascular lymphocytes, and dark nuclei of glial cells. Within these dark nuclei JCV antigen was detected by immunohistochemistry (test performed in the laboratory of the Center for Neuropathology and Prion Research, University of Munich, Director: Prof. Dr. med H. Kretzschmar, MD).

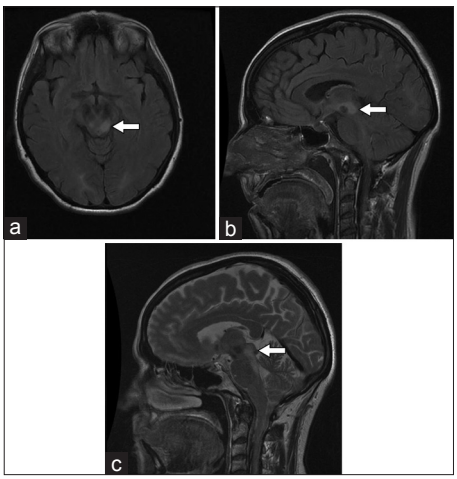

Figure 1: MRI on admission (5 months before death). MRI on admission (a and b) transversal and sagittal Flair sequence; (c) Sagittal T2-weighted sequence. Demonstration of a hyperintense lesion extending on both side of the pons (arrow), predominantly on the left side beneath the red nuclei up to the right sided mesencephalon along the third ventricle

DISCUSSION

The present case with PML involving the brainstem and fatal outcome within 6 months is remarkable for several reasons. The patient had no overt signs of immunodeficiency. Only a few cases have been reported in immunocompetent patients.[3] However, it has to be argued that the fluctuating lymphocytopenia, although mild, may have been the only sign of a so far undetectable, underlying disease of the hematopoietic system. Furthermore, despite the negative hematological work-up, we cannot exclude covert immunosuppression in relation to the heavy smoker status or an unrecognized cancer. Finally, idiopathic lymphocytopenia (ILP) has to be discussed as well.

Screening for the JC antigen by PCR technique in the CSF had been negative 9 weeks before the positive brain biopsy. Due to the brainstem extension, no further CSF analysis was performed. Remarkably only a few PML cases have been reported where JCV was undetectable in the CSF, but detected by brain biopsy.[9] As visualized by sequential neuroimaging, PML had been exclusively localized within the brainstem in this patient, with striking elongated extension from lower medulla oblongata to the confinement of the midbrain. Such a localization is remarkable.[6]

The complex tremor best fits descriptively with Holmes tremor, and it was refractory to any treatment. This tremor was high-amplitude, but low frequency while extending to the arm. It was also present at rest and with intention, evoking this phenomenological classification.[4,5] The athethoid-twisting, grasping-like movements of the hand during rest were remarkable as well. Involvement of cerebello-thalamo-cortical or rubro-olivary pathways has been proposed and is compatible with the lesion extension seen in this patient. The particular phenomenology, the accompanying other neurological signs, as well as the neuroimaging definitely

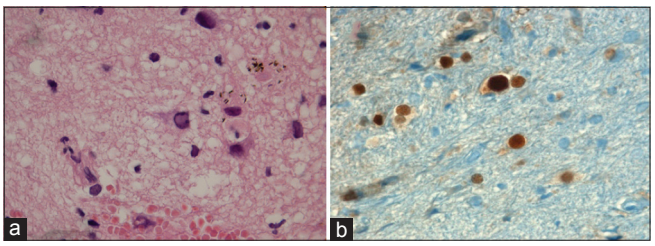

Figure 2: Microscopical findings within the biopsy specimen. (a) hematoxylin and eosin staining: Enlarged dark nuclei of oligodendroglial cells. (b) immunhistochemical staining with immunoperoxidase: Detection of JC virus antigen within these nuclei (visualized as dark brown nuclei)

exclude a cortical etiology. The syndrome has been described in brainstem infections including abscesses.[4] However, to the best of our knowledge, it has not yet been described in PML.

The fulminant course with rapidly fatal outcome is not unusual. We cannot exclude that steroids given twice may have hastened the course first, by initiating the immune reconstitution inflammatory syndrome (IRIS), second by slowing IRIS at an inappropriate time.[1] Controversy on the adequate strategy persists even in cases with established PML diagnosis and etiology: Given at the appropriate moment of IRIS, steroids can indeed also be beneficial.[1]

CONCLUSION

This case report highlights several points. Immunocompetent persons may develop PML; diagnosis may be missed by CSF screening for JCV; localization can be exclusively in the brainstem, Holmes tremor can be the predominant clinical syndrome.

ACKNOWLEDGMENT

The authors thank the husband of the deceased patient for permission of publication and Prof. Dr. med H. Kretzschmar, MD, Center for Neuropathology and Prion Research, University of Munich (Germany) for permission to publish the JC immunostaining results.The authors are grateful for helpful phenomenological discussion at the Department of Neurological Sciences, Section Movement Disorders, Rush University, Chicago (Director: Christopher G Goetz, MD, FAAN).I would like to thank my colleagues Dr. Hana, Dr. Berthold and Paul Fougenne for their contribution.

REFERENCES

1. Antoniol C, Jilek S, Schluep M, Mercier N, Canales M, Le Goff G, *et al.* Impairment of JCV-specific T-cell response by corticotherapy: Effect on PML-IRIS management? Neurology 2012;79:2258-64.
2. Bossolasco S, Calori G, Moretti F, Boschini A, Bertelli D, Mena M, *et al.* Prognostic significance of JC virus DNA levels in cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy. Clin Infect Dis 2005;40:738-44.
3. Dobson R, Mcmillan A, Kung K, Thom M, Davis A, Simister R, *et al.* Think outside the box, collapse the box and take a sharp knife to it! J Neurol Neurosurg Psychiatry 2013;84:e2.
4. Johnson T, Nath A. Immune reconstitution inflammatory syndrome and the central nervous system. Curr Opin Neurol 2011;24:284-90.
5. Lekoubou A, Njouoguep R, Kuate C, Kengne AP. Cerebral toxoplasmosis in Acquired Immunodeficiency Syndrome (AIDS) patients also provides unifying pathophysiologic hypotheses for Holmestremor. BMC Neurol 2010;10:37.
6. Metha SH, Sethi KD. Holmes tremor. In: Kompoliti K, Verhagen L, editors. Encyclopedia of Movement Disorders. Vol. 3. Amsterdam: Elsevier; 2010. p. 283-4.
7. Naess H, Glad S, Storstein A, Rinaldo CH, Mork SJ, Myhr KM, *et al.* Progressive multifocal leucoencephalopathy in an immunocompetent patient with favourable outcome. A case report. BMC Neurol 2010;10:32.
8. Padgett BL, Walker DL, ZuRhein GM, Eckroade RJ, Dessel BH. Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. Lancet 1971;1:1257-60.
9. Tallantyre EC, Paine SM, Sharp CP, Lowe JS, Gran B. Atypical progressive multifocal leukoencephalopathy associated with an unusual JC polyomavirus mutation. Arch Neurol 2009;66:1021-4.