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Case Report
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Bilateral Facial Palsy and Rapid Cognitive Decline Indicating *Lymphomatosis cerebri*: A Case Report

Waltener M[1], Hanseeuw B[2,3,4], Benjamin L[5], Hugues J[5] and Sibille FX[6,7]*

[1]Department of Neurology, CHU UCL Namur, Belgium

[2]Department of Neurology, Saint-Luc University Clinics, Belgium

[3]Department of Neuroscience, University in Ottignies-Louvain-la-Neuve, Belgium

[4]Department of Radiology, Massachusetts General Hospital, USA

[5]Department of Clinical Biology, CHU UCL Namur, Belgium

[6]Department of Geriatric Medicine, CHU UCL Namur, Belgium

[7]Institute Health and Society, UCLouvain, Belgium

Abstract

Background: *Lymphomatosis cerebri* (LC) is a rare variant of Primary Central Nervous System Lymphoma (PCNSL). This unusual presentation differs from systemic lymphoma or intravascular CNS lymphoma. It is often misdiagnosed, leading to delayed diagnosis and treatment. As the literature contains only case reports and small case series, it has not been adequately characterized.

Case Report: We present the history of an 85-year-old man with a recent history of bilateral facial palsy. He was admitted with a rapidly progressive cognitive impairment not consistent with delirium. Diagnosis of LC was based on magnetic resonance imaging and cerebrospinal fluid analysis. Due to the patient's poor health status, biopsy was not performed. He passed away two weeks later.

Conclusion: To avoid misdiagnosis and delayed treatment of LC, multiple CSF analysis should be performed.

Keywords: ***Lymphomatosis cerebri*; Cognitive decline; Facial palsy**

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Correspondence:
François-Xavier Sibille, Department of Geriatric Medicine, CHU UCL Namur, Avenue Dr Gaston Therasse, 15530 Yvoir, Belgium,
E-mail: francois-xavier.sibille@uclouvain.be

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Abbreviations

AD: Alzheimer's Disease; CSF: Cerebrospinal Fluid; EEG: Electroencephalogram; ENMG: Electroneuromyography; LC: *Lymphomatosis cerebri*; MRI: Magnetic Resonance Imaging; OD: Once a Day; PET-CT: Positron Emission Tomography-Computerized Tomography; PCNSL: Primary Central Nervous System Lymphoma

Background

Primary Central Nervous System Lymphomas (PCNSL) includes hematopoietic tumors restricted to the central nervous system. LC is one of its many variants.

The clinical manifestations of LC have usually been described as cognitive and behavioral changes; gait disturbances rather than focal deficits; headache; and more frequent seizures than in PCNSL [1]. Its radiological manifestation also differs: Whereas PCNSL are characterized by single or multiple well-defined lesions, intense homogeneous contrast enhancement, and markedly restricted diffusion, LC has rather diffuse, bilateral, poorly circumscribed lesions in deep and lobar white and gray matter. Contrast enhancement is patchy or absent, and restriction diffusion is variable [1-3].

LC treatments include high doses of corticoids and/or methotrexate-based chemotherapy. If empirical treatment with corticosteroids has not yielded clinical improvement, brain biopsy is recommended [4].

Diagnosis of LC also confers a poor prognosis, with a median survival of 3 months.

The systematic review published most recently suggested that a favorable outcome may be independently associated with a Karnofsky performance status score >70, treatment with methotrexate, and histological findings of B-cell rather than T-cell Lymphoma [1].

Below we present our study of an 85-year old man with a recent history of bilateral facial palsy and rapidly progressive cognitive impairment. Diagnosis of LC was based on cytomorphological analysis and flux cytometry on the CSF.

Case Presentation

Two months before presenting at our Geriatric Department, our patient developed predominantly left peripheral bilateral facial palsy (House Brackmann III left and II right) without any cognitive impairment. He had then undergone initial neurologic assessment at another hospital. CSF analysis highlighted lymphocytic meningitis performed then. Infection workup with PCR HSV, VZV and Lyme antibodies in the CSF was negative. Miller-Fisher and Guillain-Barre Syndromes were excluded on the basis of a lower-limb EMG and the absence of anti-GQ1b antibodies. No facial Electroneuromyography (ENMG) was performed. Magnetic Resonance Imaging (MRI) showed FLAIR hyperintensity in the right head of the caudate nucleus and the right anterior arm of the internal capsule; this was consistent with ischemic lesions.

The patient's facial bilateral palsy improved after oral corticosteroid therapy (methylprednisolone 64 mg OD for 10 days). After discharge, however, he developed lower-limb pain (which was poorly controlled by several analgesics, including opioids); as well as repeated falls, and deterioration of higher brain functions.

He was then admitted to our Geriatric Department, where he developed faintness, stiffness in the four limbs, hallucinations and fever. Investigations after an infectious outbreak (blood and urine cultures, and chest radiography) came back negative. An Electroencephalogram (EEG) showed a highly diffused slow component of the trace that was consistent with encephalopathy. A new ENMG showed severe motor and sensory axonal and demyelinating polyneuropathy of the lower limbs.

The patient's cognitive functions continued to decline. Due to the great variation in symptoms and the interaction with constipation and medications such as opioids –which caused us to suspect added delirium – we carried out no formal cognitive testing. Three months earlier, the patient had been fully independent, with no previous cognitive difficulties. Language and executive function were the first to be affected. Attention and memory were initially preserved. Within a few weeks, however, he had become restless, disorientated, and dependent on others for basic activities of daily living. We therefore carried out cerebral scintigraphy, which showed a discrete bilateral parietal and posterior cingular hypofixation compatible with early Alzheimer's disease (AD) and a second lumbar puncture.

The second CSF analysis showed pleocytosis with 34 cells/mm^3. Cytomorphological examination of the CSF showed abnormal lymphocytes highly suggestive of lymphoid malignancy (Figure 1). Subsequent flow-cytometry analysis showed the presence of monoclonal B cells, with light chain restriction (kappa) on a sub-population of B lymphocytes, whose high CD20 expression and low CD10 expression represented 4 cells/µl (Figure 2).

PET-CT total body showed no hypermetabolic neoplastic, infectious or inflammatory focus.

A new brain MRI showed diffuse multifocal white-matter and basal ganglia lesions (Figure 3) without contrast enhancement and without hyperintensity in diffusion-weighted imaging. This was consistent with *Lymphomatosis cerebri* (LC).

In view of his severe functional and cognitive decline, multidisciplinary discussions that included the patient's relatives decided on best supportive care. Oral corticosteroid treatment was initiated, and the patient was discharged to a nursing home with palliative care. He passed away two weeks after discharge.

Discussion and Conclusion

Although the cerebral scintigraphy findings may have been related to non-diagnosed Alzheimer's disease (AD), they could also

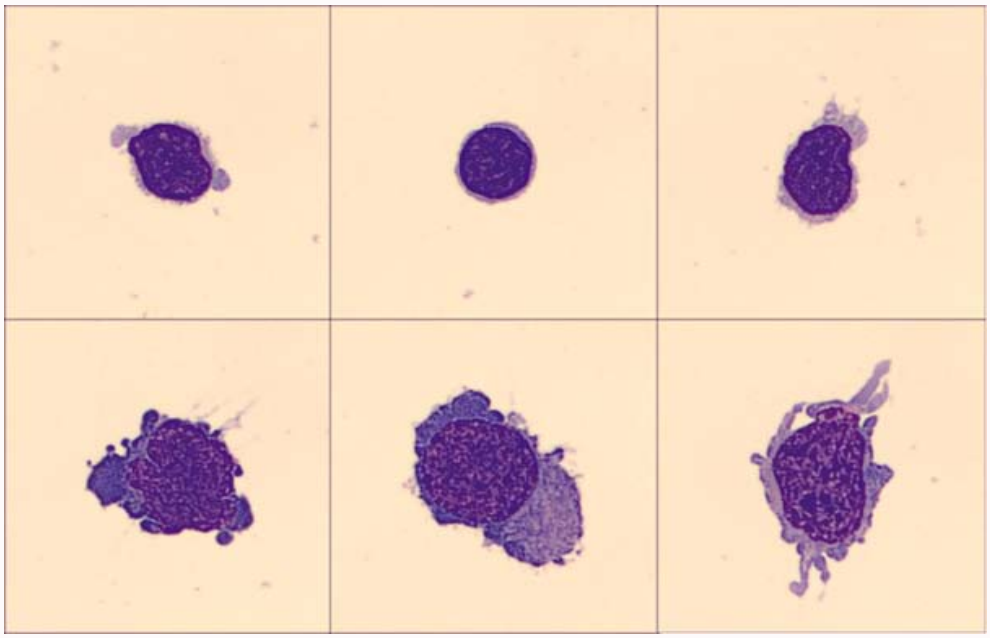

Figure 1: Cytomorphological analysis on CSF was assessed after a cytospin and May-Grunwald-Giemsa staining method that highlighted large to medium-sized lymphoid cells with basophilic cytoplasm containing an irregular-shaped, finely condensed nucleus (bottom section). The top section shows residual normal lymphocytes.

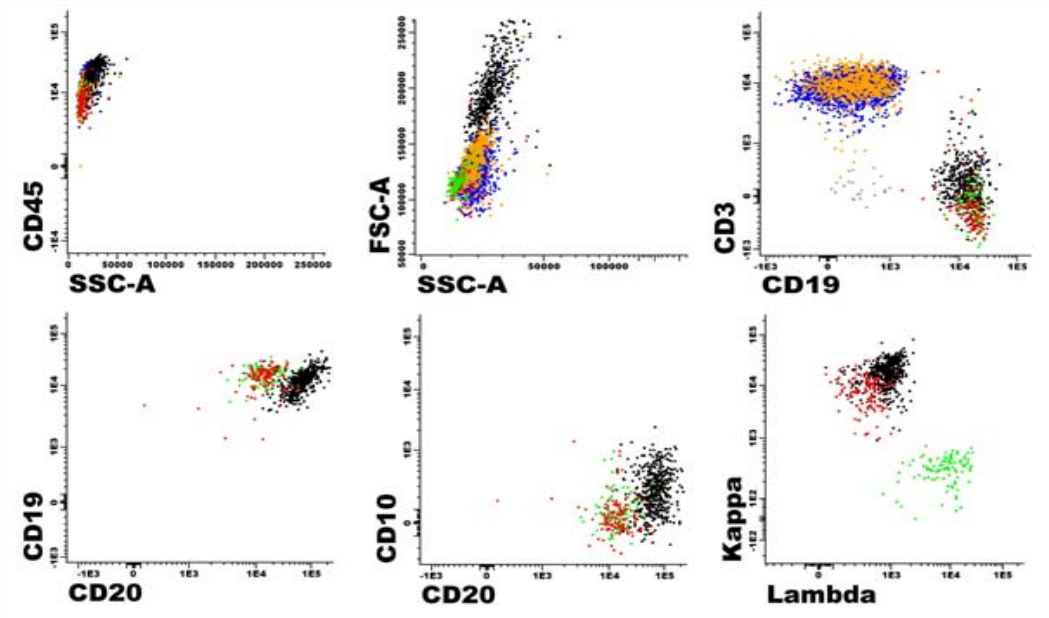

Figure 2: Flow-cytometry analysis was performed using a FACS Lyric-1 + flow cytometer (BD Biosciences, Erembodegem, Belgium) with a panel comprising markers for lymphocyte subset quantification and B-cell-clonality assessment. The malignant B-cell population (black) shows higher expression of CD20 and CD10 than in residual normal B lymphocytes (red: Kappa; green: Lambda); and shows a higher FSC/SSC pattern, indicating larger and more complex cells. These represent 12% of the total lymphocyte cell population. Normal T-cells (CD4+ (blue) & CD8+ (orange)) represent 82%; B cells (red) represent 5%; and NK cells (gray) represent 1%.

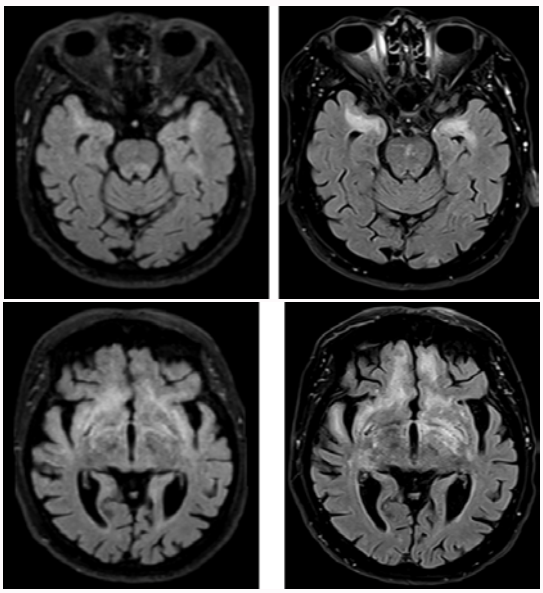

Figure 3: Axial T2-weighted FLAIR images show increased hyperintense lesions in bilateral frontal and temporal white matter and in left basal ganglia (left: May 2020; right: August 2020).

have indicated LC. As AD biomarkers were not measured in the CSF, it was impossible to exclude or confirm that the patient had presented with preclinical AD prior to the LC, a condition that could have hastened his cognitive decline. In any case, as this decline was accompanied by facial palsy, it was most likely caused by LC [5].

Due to the clear diagnosis of lymphoma, which was based on the flow cytometry and the absence of residual CSF, we did not perform other analyses, including exploring paraneoplastic meningoencephalitis.

Although it is known that bilateral facial palsy can be related to PCNSL, we have found no data in the literature that describe a possible link between bilateral facial palsy and LC. To the best of our knowledge, this case report is the only one to describe such a link. Although we hypothesize that the nucleus of the VII nerve was affected, no facially dedicated MRI sequences were performed in the first hospital. While the polyneuropathy may have been an incidental finding that was independent of LC, which is a pathology affecting the central nervous system, LC may have been responsible for the lower back pain.

Formal diagnosis of LC requires biopsy findings [6,7]. Although we considered brain biopsy, we did not perform it due the patient's poor performance status.

In this case, cytomorphological analysis combined with flow cytometry appeared to be the key to effective diagnosis.

LC is a rare variant of PCNSL that has a different radiological and clinical presentation than other variants. As it is often misdiagnosed, treatment is often delayed. In the event of rapid cognitive decline and the presence of bilateral, poorly circumscribed lesions without enhancement in MRI, multiple lumbar punctures and cerebral biopsies should be considered.

Declarations

Ethics approval and consent to participate

This study received the approval of the ethical committee at CHU UCL Namur (OM039).

Consent for publication

Formal consent has been obtained for this study. Written informed consent of the patient's clinical details and/or clinical images was obtained from his relatives. A copy of the consent form is available for review by the Editor of this journal.

Authors' contributions

Original draft preparation, reviewing and editing: MW and FXS. Analysis of biological data: LB and JH. Reviewing and editing: BH. All authors read and approved the definitive manuscript.

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