

Facial Diplegia as the Presenting Manifestation of Acute Lymphoblastic Leukemia

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Abstract

A 36-year-old man with recent onset of unilateral peripheral 7th nerve paresis presented ten days later with involvement of the other side of his face. Physical examination was otherwise normal, and since blood tests and imaging were also normal, he was considered to have bilateral Bell's palsy. However, unexpected headaches and worsening of the paresis led to a gallium-67 scan which revealed uptake in the mediastinum. A repeat lumbar puncture revealed cells which were identified as lymphoblasts. T-cell acute lymphoblastic leukemia (T-ALL) was diagnosed, although the peripheral blood smear was normal. The differential diagnosis of bilateral 7th nerve palsy and of mononuclear cerebrospinal fluid pleocytosis is discussed, as well as this rare central nervous system presentation of acute leukemia.

Key Words: Acute lymphoblastic leukemia, Bell's palsy, cerebrospinal fluid, cranial seventh nerve, facial diplegia.

Introduction

PERIPHERAL CRANIAL NERVE AFFLICTIONS usually have a benign cause. Thus, trigeminal neuralgia is most commonly a primary disorder; only rarely is it a secondary disorder due to a systemic disease. The same is true of peripheral 7th nerve palsy, which almost always occurs in the setting of "idiopathic" Bell's palsy. However, the following report highlights that this illness can be far more ominous despite a misleadingly normal examination and laboratory test results. In particular, bilateral facial palsy is an uncommon occurrence and may have diverse etiologies (1). Occasionally it can be the presenting symptom of an occult systemic disease and present a considerable diagnostic challenge.

Case Report

A healthy 36-year-old farmer woke up with right hemifacial pain and asymmetry, diagnosed as Bell's palsy. However, he continued to suffer

from intermittent pain over the right side of his face and around the eye, which radiated to the right occipital area and the posterior aspect of the neck. Ten days later the left side of the face was affected, and the patient was admitted with bilateral complete facial paralysis, complaining that he could neither smile nor smoke. Physical examination revealed only bilateral peripheral 7th nerve palsies. He had no stiff neck or other notable neurological findings on repeated examinations. The ophthalmologic exam was also normal. The ESR was 6 mm/hr, hemoglobin 14 g/dL, white blood count (WBC) $6.7 \times 10^3/\mu\text{L}$ (normal differential), and platelets $144 \times 10^3/\mu\text{L}$. Urinalysis and blood chemistry tests were normal, as were the ECG, chest X-ray, abdominal ultrasound and a head CT and MRI scans. Lumbar puncture (LP) revealed a normal pressure. The glucose value in cerebrospinal fluid (CSF) was normal, the protein was 62 mg/dL, and the WBC $0.4 \times 10^3/\mu\text{L}$, of which 80% were considered to be normal mononuclear cells. Stains and cultures for microorganisms were negative as were tests for viruses. PPD was 4 mm. Serum protein immunoelectrophoresis and serum angiotensin-converting enzyme were normal. Autoantibody screen and extensive serological testing for varied infectious diseases were all negative. During evaluation, improvement in the facial palsy occurred and a tentative diagnosis of bilateral Bell's palsy was made.

The patient continued to complain of poorly localized headache and nuchal pain. His facial

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diplegia worsened. Although no other pathology was found on repeated thorough physical examination, and laboratory evaluation remained normal and unchanged, a gallium-67 scan was ordered and a repeat LP was performed. The scan revealed an area of marked uptake in the anterior mediastinum, where a longitudinal midline mass was confirmed by a chest CT scan. The mass was not easily accessible to biopsy but a bone marrow aspiration and biopsy yielded a massive infiltrate of blast cells with lobulated nuclei. The cells, analyzed using monoclonal antibodies and a laser flow cytometry system, were identified as LCA positive, CD2+, CD7+, CD5+, CD4+, CD8+, CD1+ and CD3 negative, consistent with T-cell acute lymphoblastic leukemia (T-ALL). The LP yielded $0.62 \times 10^3/\mu\text{L}$ cells characterized as lymphoblasts (Fig.). A subsequent review of the patient's cranial CT scan and MRI scan with gadolinium contrast enhancement, was still considered normal by expert radiologists. However, a review of the cytology slides of the CSF fluid obtained at the initial LP, revealed that some of the cells previously identified as normal mononuclear cells were re-interpreted as lymphoblasts. These malignant cells now seen in the initial LP sample were similar in all respects to those seen in the fluid obtained on the second LP. The malignant cells were more numerous in the second LP sample.

Ten days following the patient's admission, systemic and intrathecal chemotherapy were started according to ALL-BFM 95 protocol MR1 (intermediate risk) with some modifications (high-dose cytosine arabinoside instead of methotrexate). Triple intrathecal injections of

methotrexate, cytosine arabinoside and hydrocortisone were administered twice weekly until the CSF became normal; they were then continued once every two weeks, together with cranial irradiation (1800 rad). Complete remission was achieved after four weeks. Twelve months later, the patient shows no evidence of recurrence.

Discussion

In *Alice in Wonderland* the Cheshire cat gradually vanished, leaving only his smile behind. Here, our patient's smile disappeared first but it soon became apparent that unless quickly treated, the patient himself might follow suit. Bell's palsy has an average annual incidence of 25 per 100,000 population (1), but simultaneous bilateral facial palsy, or facial diplegia, is decidedly uncommon, encountered in only 3 of 1000 consecutive patients with facial paralysis (2). Thus, there are very few small series of patients with bilateral 7th nerve palsy. These few patients reveal diverse causes for facial diplegia, most being benign, including bilateral Bell's palsy, atypical Guillain-Barré syndrome, and granulomatous diseases and infections such as Lyme disease, syphilis, TB meningitis, sarcoidosis, mycoplasma, herpes virus infections and HIV (1). Tumors, in particular hematological malignancies involving the meninges or tumors of the pontine area, are also important etiologies to consider, accounting for about 20% of the cases.

The sparing of other cranial nerves and long tracts in our patient, his negative initial evaluation including the normal MRI (3) and the partial spontaneous improvement which occurred at first, were all considered favorable signs in a patient who was considered to have bilateral Bell's palsy. The mononuclear cells in the first CSF were thought to be consistent with the finding of mononuclear pleocytosis seen in some cases of Bell's palsy (2, 4). This finding has many varied causes, as listed in the Table (5–11). In one study of 164 patients with Bell's palsy, examination of the CSF disclosed that 33% of the patients had an elevated protein level and 10% had pleocytosis (4). In another large study of 1048 patients, 10% had headache and 62% had facial pain when presenting with Bell's palsy (2). However, in our case the number of cells in the CSF was greater than expected, and facial and nuchal pain, and continued headache are distinctly unusual in patients with Bell's palsy (12). When the bilateral facial palsy worsened (it should have improved in the

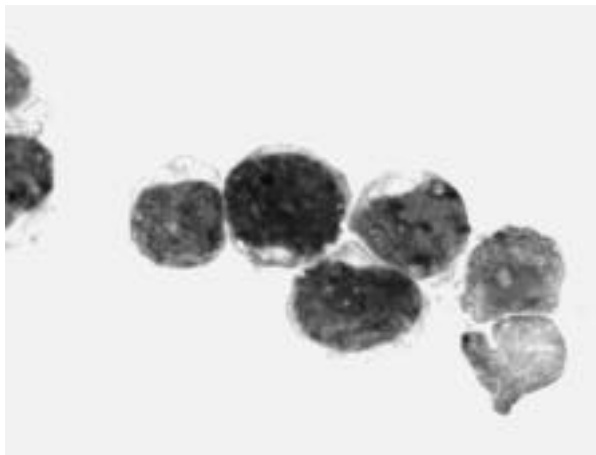


Figure. Cytocentrifuge of patient's second CSF examination showing lymphoblasts (May-Grunwald Giemsa staining, x 800).

TABLE

Main Causes of Predominantly Mononuclear Cells in the CSF (5–7).

Infectious	
Viral infections [†]	‘Viral aseptic meningitis’ often caused by non-polio enteroviruses, or as part of distinct diseases such as mumps, herpesvirus* infections or HIV* [reported also postvaccination against viral diseases].
Infections caused by “unusual” organisms	<i>Mycobacterium tuberculosis</i> (“TB meningitis”*), <i>Treponema pallidum</i> (syphilis*), <i>Borrelia burgdorferi</i> (Lyme disease*), brucella, leptospira, <i>Mycoplasma pneumoniae</i> *, rickettsiae, toxoplasma and fungi — especially <i>Cryptococcus neoformans</i> *.
Parameningeal focus of infection such as brain abscess or sinusitis.	
Non-infectious	
Neurosarcoidosis*	Aseptic meningitis may be the sole manifestation of neurosarcoidosis (9) in about 17% of patients.
Neoplastic* meningeal or CNS involvement	Reported in both benign and malignant tumors, both primary and secondary — including hematological malignancies‡.
Multiple sclerosis or other demyelinating disorder.	CSF is normal in 66% of patients; in the remainder 5–20 lymphocytes/mm ³ can be found
Behçet’s disease	Also uncommonly reported in varied autoimmune disorders including lupus*, primary Sjögren’s syndrome*, polyarteritis* and in granulomatous arteritis.
Idiopathic chronic (benign) lymphocytic meningitis (11)	
Guillain-Barré syndrome*	Possibly 10–100 mononuclear cells, usually none.
Bell’s palsy*	Possibly 10–100 mononuclear cells, usually none.

*Some of these disorders may cause cranial 7th nerve palsy.

†Some patients with acute bacterial meningitis who have a low CSF WBC count (< 1000/mm³) may have >50% mononuclear cells early in the course of their illness, but associated findings will establish the correct diagnosis. In particular, listeria monocytogenes meningitis may be confused with viral lymphocytic meningitis (8).

‡Malignant meningeal involvement is the only entity cited, where careful and expert examination of CSF cytology may itself be diagnostic (10).

case of Bell’s palsy) (12), the gallium-67 scan and LP were repeated. The gallium scan was ordered in an attempt to identify a site from which pathological tissue might be biopsied (13). We had in mind the high avidity of gallium-67 for lymphomas (14), after other more benign causes of facial diplegia (such as infections) had been ruled out and brain imaging was

not diagnostic. Following the abnormal results of both the gallium scintigraphy and CSF analysis, a bone marrow biopsy was done. The diagnosis of T-ALL with central nervous system presentation soon followed. In retrospect, a careful examination of the initial CSF by an expert cytologist would have yielded the correct diagnosis. The MRI, with gadolinium enhancement (which is often very useful in establishing the diagnosis of bilateral facial paralysis [3, 15]), was misleadingly normal in our patient. This demonstrates again that the most simple tests are often highly rewarding in difficult cases, provided they are meticulously performed and interpreted. However, in patients with leukemia and CNS involvement, the CSF may not reveal pathological cells in all cases. In leptomeningeal carcinomatosis, for example, the sensitivity of CSF cytology has been consistently found to range from 75–90% (15, 16).

Initial CNS involvement can be found in fewer than 1% of adult patients diagnosed with acute leukemia and is rarely documented as the presenting feature. Although the central nervous system is an important site of relapse, meningeal involvement is an uncommon pattern of presentation of leukemia. Moreover, the presence of normal peripheral blood cell and even normal bone marrow cytology may cause diagnostic delay (17). Acute leukemia, lymphoma and amyloidosis are the main hematological malignancies which may present initially as facial diplegia (1). Such presentation has been reported in the English language (18, 19) in only ten cases.

Nevertheless, this patient’s presentation of isolated 7th nerve involvement and head and neck pain, is consistent with the anatomy of the facial nerve. The 7th nerve nucleus is located in the base of the pons. Central lesions are rarely so discrete as to affect only one cranial nerve nucleus. Signs implicating the brainstem as the site of the lesion would be expected if sensory, cerebellar or corticospinal pathways, or adjacent nuclei or nerves (5th, 6th) were involved. When the 7th nerve is solely affected, the lesion is most likely outside of the brainstem (20). Upon its exit from the brainstem, the 7th nerve must cross the subarachnoid space before entering the internal auditory meatus. This is the most likely site of nerve involvement in the presence of meningeal leukemia and pathological cells in the CSF, and may also explain the patient’s headache and nuchal pain (21). Importantly, neuropsychiatric symptoms may also indicate malignant meningitis in patients

with hematological malignancies, even when no neurologic findings are present (22).

In conclusion, our case demonstrates that unusually persistent bilateral 7th nerve palsies may indicate the presence of a serious underlying disease, such as leukemia. In these uncommon cases, a high index of suspicion and careful examination of the CSF by an experienced cytologist may lead to the correct diagnosis and rapid initiation of appropriate chemotherapy and irradiation.

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