An Uncommon Cause of Transient Neurological Dysfunction

**Muhammad U. Farooq, MD, FACP, FAHA¹,
Archit Bhatt, MD, MPH, FACP, FAHA²,
and Howard T. Chang, MD, PhD³**

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Abstract

Transient neurological dysfunction may be associated with uncommon disorders and should prompt consideration of a broad differential diagnosis when assessing patients with episodic symptoms. The most common causes of transient neurological dysfunction include transient ischemic attack (TIA), seizure disorder, and migraine and its variants. However, underlying unusual pathophysiological processes such as brain tumors can also cause transient neurological dysfunction. Here we present a case of a 68-year-old male with oligodendroglial gliomatosis cerebri (OGC) who presented with TIA-like symptoms. Brain magnetic resonance imaging revealed multiple diffuse T2 hyperintensities within the white and gray matter. Magnetic resonance spectroscopy was suggestive of gliomatosis cerebri and was particularly helpful in this case. The diagnosis of OGC was confirmed by histopathology and molecular genetic studies on brain biopsy tissue. In this report, we discuss the clinical and radiological characteristics of OGC and highlight the unusual presentation of this case.

Keywords

gliomatosis cerebri, oligodendroglioma, magnetic resonance spectroscopy

Introduction

The differential diagnosis of transient neurological symptoms is broad, including transient ischemic attack (TIA), seizure disorder, migraine and its variants, demyelinating disorders, hypertensive encephalopathy, brain tumors, glucose and electrolyte abnormalities, and psychiatric disorders including panic and conversion disorders. We describe a case of a patient with oligodendroglial gliomatosis cerebri (OGC) who presented with symptoms consistent with TIA and simple partial seizures. This case emphasizes how important it is to keep the differential broad while assessing these patients in routine daily practice. Further discussion in this report is about OGC and its diagnosis.

Gliomatosis cerebri (GC) is a malignant infiltrative glioma that typically does not form discrete mass lesions and, by definition, involves more than 2 cerebral lobes.¹ It was first described at postmortem in 1938 and the first clinically diagnosed case was reported in 1987.^{2,3} There are different histological variants of GC consisting of astrocytic, oligodendrocytic, and mixed variants.^{1,3,4} However, GC consisting of oligodendrocytic cells is relatively uncommon compared to the astrocytic variant. In a series of 296 individual cases of GC, 108 cases were astrocytic, 54 oligodendroglial, and 17 mixed (oligoastrocytomas).¹ However, the true incidence of mixed GC may be

underestimated because biopsy of these lesions often includes only small fragments of tumor and may miss sections that could contain additional astrocytic or oligodendroglial elements. In contrast to the diffuse infiltrative nature of GC, typical oligodendrogliomas usually appear as a relatively well-circumscribed but nonenhancing mass involving the cortex or subcortical white matter, most commonly in the frontal lobes.^{5,6}

Case Report

A 68-year-old man with multiple cerebrovascular risk factors including hypertension and coronary artery disease was admitted with 2- to 5-minute episodes of transient right- or left-sided numbness, tingling, and weakness of upper and lower

¹ Hauenstein Neuroscience Center, Grand Rapids, MI, USA

² Providence Neurological Specialties, Mother Joseph Plaza, Portland, OR, USA

³ Department of Neurology & Ophthalmology, Michigan State University, East Lansing, MI, USA

Corresponding Author:

Muhammad U. Farooq, Hauenstein Neuroscience Center, 220 Cherry Street SE, Grand Rapids, MI 49503, USA.
Email: farooqmu@mercyhealth.com

Figure 1. A, T2-FLAIR hyperintense regions involving the temporal and occipital lobes. B, T2-FLAIR hyperintense regions within the white and gray matters involving the temporal, occipital lobes, and basal ganglia. C, Diffusion-weighted image of corresponding area in (A) appeared normal. D, Diffusion-weighted image of corresponding area in (B) appeared normal. E, T1 postcontrast imaging of corresponding area in (A) showed no evidence of enhancement. F, T1 postcontrast imaging of corresponding area in (B) showed no evidence of enhancement. FLAIR indicates fluid-attenuated inversion recovery.

Figure 2. A, MRS (short TE) from the frontal lobe showing normal choline, creatine, N-acetylacetate (NAA), and myoinositol peaks. B, MRS (short TE) from the temporal lobe showing normal choline, creatine, NAA, and abnormal myoinositol peaks. MRS indicates magnetic resonance spectroscopy; TE, echo time.

extremities associated with dysarthria. Although an isolated episode could involve the right or the left, his symptoms remained unilateral during each spell. The frequency of these episodes varied from 1 to 2 times per week and sometimes occurred 4 to 5 times per day. These episodes began 2 months prior to admission. His general physical and neurological examination was normal. A stroke workup including non-contrast brain computed tomography, carotid Doppler, and 2-dimensional echocardiography was unremarkable. Brain magnetic resonance imaging (MRI) revealed multiple T2 hyperintense regions within the white and gray matters in the bilateral temporal lobes, insular cortices, thalami, and centrum semiovale as well as the right cingulate subcortical white matter (Figure 1A and B). Additionally, there were scattered punctate foci of increased T2 signal in the subcortical and deep periventricular white matter. The absence of hyperintensity on diffusion-weighted images (Figure 1C and D) suggested that these changes were not related to acute ischemia. The absence of enhancement (Figure 1E and F) also made an underlying

acute inflammatory process unlikely. Further workup including electroencephalogram (EEG) and lumbar puncture was performed. The cerebrospinal fluid analyses including protein, glucose, cell count, viral and bacterial antigen, Gram and acid fast staining, culture, myelin basic protein, oligoclonal bands, immunoglobulin G index, and cytology were normal. The EEG did not show any epileptiform activity in spite of capturing multiple typical spells during the prolonged EEG monitoring. Cerebral angiography did not show any stenosis of extra- or intracranial vasculature.

At this juncture, he was discharged on aspirin and simvastatin, with a plan to repeat a brain MRI in 3 months and follow-up as an outpatient. Although the brain MRI was abnormal, the clinical significance was unclear. The presumed diagnosis was recurrent TIAs versus simple partial seizure disorder, and he was started on levetiracetam.

He was readmitted 2 weeks later with similar symptoms. Repeat brain MRI did not demonstrate any interval changes. Magnetic resonance spectroscopy (MRS) was then ordered

Figure 3. A, Portion of the biopsy shows very sparse infiltration of neoplastic cells in the gray matter (hematoxylin and eosin). B, Immunocytochemistry for Ki67 in an adjacent section to (A) shows focal labeling of nuclei in the neoplastic cells. C, A different area of the biopsy is marked by a hypercellular lesion with many neoplastic cells infiltrating the gray matter. Boxed area is shown at higher magnification in (E). D, Immunocytochemistry for Ki67 in a section adjacent to (C) shows labeling of many nuclei in neoplastic cells. E, Higher magnification of boxed area in (B), showing minigemistocytes (arrows) and cells with perinuclear halo (block arrows). Mitosis is noted (arrowhead). F, Immunocytochemistry shows that many minigemistocytes are positive for GFAP, while cells with perinuclear halo are negative for GFAP. (A to D) and (F) are at the same magnification.

to further characterize the multiple T2 hyperintensities and rule out any underlying neoplastic component. Characteristic MRS are shown in Figure 2. There were normal choline, creatine, and N-acetylacetate (NAA) peaks. The ratios between choline, creatine, and NAA appeared normal. However, there was a prominent peak at 3.5 to 3.7 ppm in the left temporal lobe, which was felt to likely represent glycine because of suppression at long echo time (TE) and elevation at short TE (Figure 2). These spectra findings helped narrow the differential

diagnosis in favor of a neoplastic lesion like GC. For diagnostic confirmation, a left temporal biopsy was performed.

The hematoxylin and eosin–stained sections revealed some regions of gray matter with very sparse infiltrating neoplastic cells (Figure 3A), while other areas were densely infiltrated with glioma cells that have round to oval nuclei with either eccentric pink cytoplasm (minigemistocytes) or perinuclear “halo” clear cytoplasm (Figure 3C and E). A stain for Ki67, a cellular proliferation marker, showed positive labeling in

up to 10% of tumor cells focally (Figure 3B and D). Fluorescence in situ hybridization study on paraffin-embedded tissue for the chromosomes 1p and 19q deletion status showed deletion of 19q. Given the widespread involvements of multiple brain regions, the overall features were consistent with OGC. The patient was treated with radiation and chemotherapy without any good response and died 18 months after the initial diagnosis.

Discussion

This report describes the unusual clinical as well as radiological presentation of OGC in an elderly man with multiple episodes of right- or left-sided sensory and motor symptoms and dysarthria. The initial diagnostic considerations included TIA, seizure disorder, atypical migraine, neoplasm, and multiple sclerosis. His symptoms, in retrospect, were likely due to simple partial seizures, which is a common presentation of GC.⁷ Despite his multiple vascular risk factors, TIA was considered unlikely given the ongoing bilateral symptoms over 2 months with multiple daily episodes at times. Since there was no history of associated headaches or prior history of migraines, atypical migraine was also considered unlikely. The duration of these episodes was atypical for transient focal symptoms related to a demyelinating disorder.

The MRIs showing abnormalities involving multiple lobes of brain were consistent with multicentric infiltrative glioma. However, MRS showed relatively normal peaks and ratios of choline, creatine, and NAA, in contrast to the moderate to marked elevation in choline, depressed creatine, and NAA values one would expect in anaplastic glioma or glioblastoma multiforme. On the other hand, the dramatic myoinositol/glycine peak demonstrated at the 3.5 to 3.7 ppm region on the MRS was suggestive of OGC.⁸

Magnetic Resonance Spectroscopy measures biochemical changes in the brain and can detect changes in brain metabolites, including choline, creatine, and NAA. It can be used to complement MRI in the characterization of tissue, especially the presence of tumors and their differentiation from infarct. When MRS is combined with conventional MRI, it improves diagnosis and treatment of brain tumors. However, MRS is prone to artifacts, and it is very important to carefully select a volume of interest on the imaging studies, where the spectrum will be acquired. As noted earlier, glycine and myoinositol occupy the same spectral location between 3.5 and 3.7 ppm. An elevated peak in the short TE PRESS 35 sequence was interpreted as more representative of glycine rather than myoinositol. A significant elevation in glycine on MRS might be indicative of the cell lineage from which the tumor arose.^{8,9}

In vitro-purified normal rodent oligodendrocytes and their precursors are found to have glycine peak 5 times higher than other central nervous cell types.⁹ Thus, elevated glycine/myoinositol levels are suggestive of oligodendrogliomas,⁸ as also demonstrated in our present case.

In summary, one needs to keep the differential broad when assessing patients with transient neurological deficits. In selected patients when the diagnosis is not clear, imaging modalities such as MRS can be very helpful to reach the correct diagnosis in the daily practice of neurohospitalists.

Declaration of Conflicting Interests

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