Diffuse glioma manifesting as normal pressure hydrocephalus: A potential pitfall in diagnosis-a case report

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1. Introduction

Diffuse glioma is the most common malignant brain tumor in adults, associated with high mortality despite treatment with chemotherapy, radiotherapy and surgical removal [1]. According to the 2016 WHO classification, diffuse glioma includes WHO grade II and grade III astrocytic tumors, oligodendrogliomas and the grade IV glioblastomas [2]. Stem-like cells within the CNS are considered to be the originating cells of many primary brain tumors, including gliomas [3]. In adults, lesions are described within the thalamus, spinal cord, corpus callosum, hypothalamus, pineal region, basal ganglia and third ventricle [4]. Symptoms related to diffuse glioma depend on the tumor's anatomic location and include gait disturbances, nausea, vomiting, headaches, blurred vision or diplopia, confusion, lethargy and seizures. More rarely, hydrocephalus is reported in these patients.

Hydrocephalus is the most common neurosurgical disorder defined as an hydrodynamic imbalance between the absorption and production of cerebrospinal fluid (CSF), characterized by enlargement of the brain ventricles [5]. Hydrocephalus can be classified based on CSF flow obstruction to communicating and non-communicating or obstructive hydrocephalus [6]. Intraventricular obstruction occurs more frequently in the foramen of Monroe, third ventricle, aqueduct of Sylvius, and fourth ventricle. An acute obstructive hydrocephalus could lead to a sudden increase of intraventricular pressure and even cause coma or death. In contrast, when obstruction is incomplete or chronic, patients may be asymptomatic and report only ventriculomegaly in brain MRI. Two main therapeutic approaches are available for treating hydrocephalus: ventriculoperitoneal shunting of CSF or endoscopic third ventriculostomy (ETV) [5].

Normal pressure hydrocephalus (NPH) is a form of communicating hydrocephalus [7] that may present with a classic triad of cognitive impairment, gait disturbances, and urinary incontinence [5]. Symptoms vary depending on site and nature of the obstruction and whether the obstruction occurs acutely or chronically. The various causes of NPH include infections, hemorrhage, trauma and neoplasms. However, in many cases etiology of NPH is not found and diagnosis of NPH remains controversial up to now. Brain and spine magnetic resonance imaging (MRI) are the imaging modality of choice essential to the diagnosis and management of hydrocephalus [7]. Radiological features of NPH include ventricle dilation and confluent periventricular hypoattenuation from transependymal (interstitial) flow (hyperintense on T2-weighted MRI (hypodense on CT) areas in the periventricular white matter) [7]. The radiological finding usually appearing first is rounding of the frontal horns of the lateral ventricles and dilatation of the temporal horns [8]. Other imaging features include reduced mamillopontine distance, upward bowing and thinning of the corpus callosum particularly if non-communicating hydrocephalus is chronic [8]. Ventriculoperitoneal shunt has been shown to improve symptoms in a subset of patients.

Herein, we report a patient with a low-grade glioma presenting a complex phenotype characterized by cognitive deterioration with fluctuations, initially masquerading as NPH of unknown etiology.

2. Case report

A 53-year-old woman presented with a one-year history of progressive cognitive decline, confusion, irritability, visual disturbances and focal seizures. Extended laboratory investigations and neuroimaging at onset of disease revealed findings typical of hydrocephalus (Fig. 1A). At that time, as the lateral and third, but not the fourth ventricle, were dilated, she received a diagnosis of obstructive hydrocephalus of unknown etiology and underwent ventriculoperitoneal shunting, with improvement and partial resolution of her symptoms that lasted about 4 months. Neurological examination at presentation, showed a gait disturbance with a shuffling gait, bradykinesia, pyramidal signs bilaterally (brisk tendon reflexes, Babinski sign), and upgaze limitation. A detailed neu-
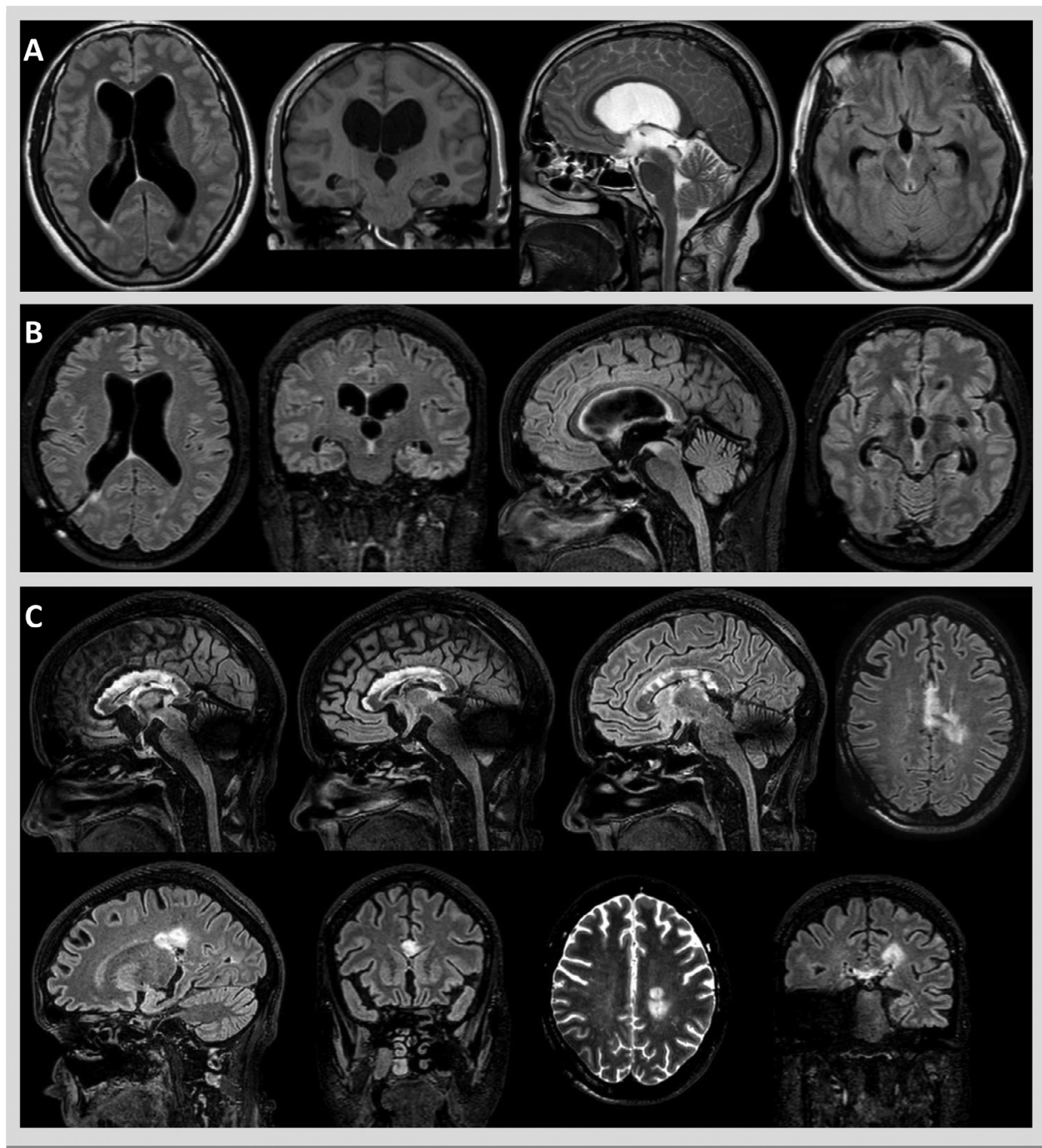

Fig. 1. Brain MRI of this case. A: Axial, coronal and sagittal fluid attenuated inversion recovery (FLAIR) sequences, T1W and T2W sequences prior to ventriculoperitoneal shunt placement showing ventricular dilation and periventricular and frontal hyperintensity; B: Axial, coronal and sagittal fluid attenuated inversion recovery (FLAIR) sequences, and T1W sequences after ventriculoperitoneal shunt placement. Dilated ventricles, hyperintensities on the left side of the optic chiasm and tract, in the area of the midbrain in the level of the interpeduncular cistern, mammillary bodies, and splenium are revealed; C: Follow-up at deterioration. Axial, coronal and sagittal fluid attenuated inversion recovery (FLAIR) sequences, T2W and T1W sequences showing extension of lesions particularly in corpus callosum.

ropsychological assessment was ordered to assess cognitive status. Mini Mental State Examination (MMSE) was 28/30, Frontal Assessment Battery (FAB) 16/18, clock drawing test CLOX1 10/15, and CLOX2 13/15. The patient presented fluctuations in cognitive function with periods of marked catatonic-like state and somnolence. Brain MRI at this time revealed findings consistent with normal pressure hydrocephalus (dilated ventricles, periventricular and frontal hyperintensities, bulging of the floor of third ventricle, reduced mamillopontine distance, upward bowing and thinning of the corpus callosum). In addition, hyperinten-

sities were noted on the left side of the optic chiasm and tract, in the area of the midbrain in the level of the interpeduncular cistern, mammillary bodies, splenium with no restriction of molecular diffusion or contrast enhancement (Fig. 1B). An extensive laboratory examination was ordered again (including autoimmune encephalopathy panels, tumor markers, cerebrospinal fluid (CSF) analysis immunophenotyping, immunology markers and infectious agents). Apart from CSF protein that was considerably elevated, no other abnormal findings were reported. Further investigations included spinal MRI that was normal and

EEG examination in which non-specific slow waves were reported. Additionally, screening for a paraneoplastic syndrome was also negative (whole-body CT scan, full body PET scan and paraneoplastic antibodies screening). A CSF tap test was performed with removal of 30 ml and a significant improvement in cognitive status was noted that lasted, however, only 2 days. During this period, the patient was consistently communicative and alert, and upgaze was performed normally. Corticosteroids were administered intravenously with no clinical benefit. Re-evaluation of the shunt was requested from neurosurgeons to exclude shunt failure. The ventriculoperitoneal shunt was replaced. However, the patient further deteriorated and she was intubated due to refractory status epilepticus. Brain MRI was ordered again and revealed extension of the lesions; hyperintensities in T2/FLAIR sequences were detected across the corpus calosum without diffusion restriction or contrast enhancement (Fig. 1C). A brain biopsy was carried out from a lesion near the corpus callosum. Histologic examination of the tumor specimen led to a diagnosis of a low-grade glioma (LGG, WHO grade II). Molecular classification of glioma was not available. A diagnosis was reached and the disease progressed more rapidly over the following year.

3. Discussion

Although rare, diffuse glioma should be considered in differential diagnosis of hydrocephalus, especially if no etiology for hydrocephalus is apparent after extensive investigation. This case illustrates the complex phenotype resulting from a low grade glioma, slowly and insidiously growing, manifesting as an hydrocephalus of unknown etiology. Neuroimaging findings at onset of this case were typical of NPH with no lesions providing hints of an underlying neoplasm. NPH is a controversial entity with often ambiguous imaging findings. Brain MRI (T2/FLAIR sequences) usually shows transependymal exudate as periventricular hyperintensity and ventriculomegaly as in the case described here [9]. In chronic hydrocephalus, temporal horns may not be so prominent and thinning of corpus callosum is noted.

At presentation, despite the initial improvement following shunt placement, the patient had clinically deteriorated and a second MRI revealed dilated ventricles and hyperintensities on the left side of the optic chiasm and tract, in the area of the midbrain, mammillary bodies, and splenium. It is well reported that diffuse signal changes in corpus calosum can rarely occur even after successful shunting for hydrocephalus [10]. However, our patient also presented lesions in the optic chiasm and the midbrain area.

Low-grade gliomas often show extensive infiltration of brain, limiting thus surgical removal, leading to recurrence and progression of the disease. Normal Pressure Hydrocephalus (NPH) as an initial presentation of low grade glioma is rare [11]. NPH is a form of communicating hydrocephalus manifesting the same clinical features in both idiopathic normal pressure hydrocephalus (iNPH) and secondary normal pressure hydrocephalus (sNPH) [9]. However, symptoms vary depending on site and nature of the obstruction and whether the obstruction occurs acutely or slowly. In acute hydrocephalus, impaired consciousness, headache, vomiting, are common symptoms and may lead to coma [6]. Prolonged increased intracranial pressure may cause blindness. In chronic hydrocephalus, the classic Hakim triad of NPH including gait disturbances, cognitive decline and urinary incontinence is described. However, the triad is full only in about half of the cases and usually atypical symptoms such as dizziness and headache are reported [6].

Several theories have been proposed to explain the underlying pathomechanism of glioma-associated hydrocephalus. An increase in CSF protein is a common finding in these patients [11], as we report in our patient. CSF is also known as "the third circulation", with a constant interaction between cerebral arterial circulation, CSF circulation, and venous circulation. A decreased CSF absorption that leads to intracranial venous hypertension and to hydrocephalus remains critical to understanding the pathogenesis of NPH [9,12]. The glymphatic system is thought to clear brain fluid and metabolic wastes from CNS via glia-supported perivascular channels to the meningeal and cervical lymphatic vessels, driven by cardiac-induced arterial pulsation [13]. Such an increase in CSF protein could result in dysregulation of lymphatic drainage, via altering CSF viscosity. Furthermore, fibrinogen was found elevated in a few cases, that could also induce an inflammatory reaction or, when transformed to fibrin, alter CSF hydrodynamics [11,14].

Another explanation with a mechanical nature could be that the subarachnoid space is used as a reservoir to balance the normal variations of CSF pressure, in relation to arterial and venous pressure modifications, and body position [11]. Blockage in this area could prevent thus the compensation of CSF normal variations, causing in this way ventricular dilation. Moreover, leptomeningeal dissemination after shunting procedures, and subarachnoid adhesions should be considered. Of note, a high prevalence of developmental venous anomaly was recently identified in adult patients with diffuse glioma and it remains to be seen whether it is a potential underlying predisposition or an etiological factor [15].

4. Conclusions

The exact pathophysiological mechanism underlying hydrocephalus in the setting of diffuse glioma remains to be elucidated. A better understanding is needed both of the molecular landscape of adult low-grade gliomas but also of hydrocephalus causes. Caution is advised regarding hydrocephalus of unknown etiology, and reevaluation is necessary. Further studies are needed to better define low grade gliomas and their heterogenous clinical, molecular phenotypes and underlying mechanisms.

Declaration of Competing Interest

Funding

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