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CASE REPORT

Isolated Demyelination of Corpus Callosum Following Hypoxia

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Corpus callosum includes a large amount of axons with various degrees of myelination, interconnecting cerebral hemispheres. Tumors, demyelinating diseases, infections, trauma and metabolic diseases as well as vascular lesions may affect corpus callosum, often extending to other white matter areas of the brain. We describe the case of a 76 years old male patient with history of arterial hypertension, diabetes mellitus and normal pressure hydrocephalus, developing dysphagia during hospitalization. Ab-ingestis pneumonia caused brain hypoxia and coma; brain magnetic resonance disclosed isolated demyelination of corpus callosum that was not present before hypoxia. Compared to neurons and astrocytes, oligodendrocytes are reported as particularly sensitive to hypoxia. Respiratory involvement without blood flow impairment could have lead to a prevalent oligodendrocytes damage, resulting in a selective demyelination of corpus callosum. Our patient indeed evolved into persistent vegetative state and died five months after hypoxic episode. This case report could give some insight about in vivo brain susceptibility to hypoxic damage.

Keywords: brain; hypoxia; anoxia; ischemia; vegetative state; oligodendrocytes

Introduction

Corpus callosum (CC) is the most important cerebral inter-hemispheric connecting structure, characterized by densely packed myelinated and unmyelinated white matter tracts originating by cortical neurons. Acquired lesions of CC can derive from many causes such as ischemic damage, tumors, demyelinating diseases, infections, trauma and metabolic diseases (Renard et al., 2014). Clinical pictures resulting from CC lesions are variable and may depend on which part is mainly involved. Anterior lesions may cause alien limb syndrome, left agraphia and right constructional apraxia, lesions of the body may cause left tactile anomia and left hemialexia when the splenium is involved (Berlucchi, 2012). Extensive lesions of CC are frequently associated with impairment of consciousness and correlate with poor prognosis (Kampfl et al., 1998; Kuchta et al., 2009). Vascular ischemic lesions of CC are usually associated with ischemia occurring also in other brain regions (Li et al., 2015). We describe a patient developing isolated CC lesions following hypoxic damage, with consequent coma, vegetative state and death.

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Case presentation

A 76-years-old man with hypertension and diabetes mellitus developed a normal pressure hydrocephalus that was treated with ventriculo-peritoneal shunt. Three months later, appearance of stupor and confusional state was investigated with a brain computerized tomography. Since cerebral venticuli enlargement was unaltered, the patient underwent repeated shunt revision, finally replaced with a ventriculoatrial shunt. Clinical conditions improved, however mild dysphagia was detected during a phoniatric examination. Despite a creamy diet was suggested, the patient underwent an ab-ingestis pneumonia. Admitted to the intensive care unit, the patient was stuporous but able to execute simple commands. A percutaneous endoscopic gastrostomy allowed enteral feeding, following a laryngoscopic evaluation consistent with severe dysphagia. He performed the first brain magnetic resonance imaging (MRI) scan (**Figure 1A** and **1C**) then, one week later, he presented a severe respiratory failure and developed coma. The EEG was poorly responsive showing bilateral slowing (6–7 Hz) with diffuse delta waves (1–3 Hz, 60–200 μV), more evident bilaterally in fronto-temporal regions. Blood examination showed moderate increase of leukocytes (10500/μl, nv 4500–9800), C-reactive protein (15.8 mg/l, nv < 5) and blood glucose (180 mg/dl, nv 65–110), while creatinine, transaminase, creatine phosphokinase, sodium, potassium and calcium plasma levels were normal. Coma evolved in a vegetative state without evidence of temporary clinical recovery. Three weeks later a second brain MRI scan (**Figure 1B** and **1D**) showed isolated demyelinating lesions of CC, mostly involving the

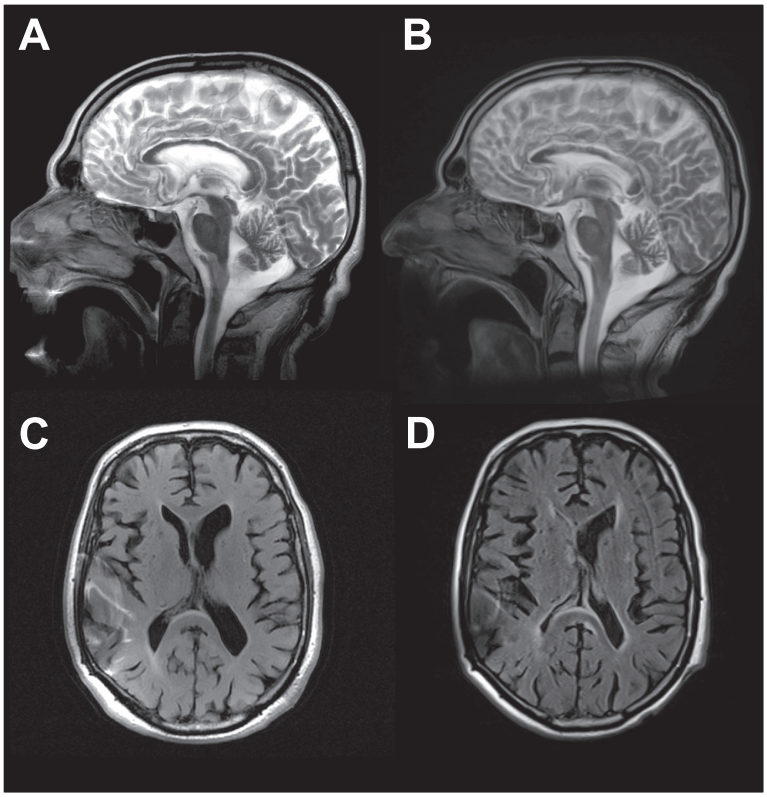

Figure 1: Baseline MRI (**A, C**: 1.5T-GE_Medical-System-Signa-Excite) and 3-weeks after anoxia (**B, D**: 1.5T-Siemens-Magnetom-Avanto). Baseline lacks alterations in the corpus callosum (A: T2-sagittal) and white matter (C: FLAIR/T2-axial). Anoxia produced T2 hyperintense lesions of corpus callosum appearing thickened, while rostrum and splenium are partly spared (B) as well as bihemispherical white matter (D).

truncus. The patient persisted in a vegetative state until death, occurred 5 months after anoxic injury.

Discussion

We describe a patient developing isolated demyelination of CC following brain hypoxia due to ab-ingestis pneumonia. Brain arterial occlusion often determine a typical ischemic stroke limited to brain tissue supplied by the involved vessel. Instead, cardiac or respiratory involvement may reduce oxygenated arterial blood supply to the entire brain tissue. Experimental conditions in manuscripts concerning damage following reduced oxygen supply differentiate "ischemia" from "anoxia/hypoxia". The term "ischemia" refers to reduction of blood flow resulting in both lack of oxygen and other nutrients (such as glucose); this usually occurs because of arterial occlusion or cardiac pump deficit, such as cardiac arrest. Conversely, it may occur that oxygen cannot reach blood in absence of arterial flow alterations, sometimes because of respiratory dysfunction, such as in pneumonia: this is referred as anoxia or hypoxia.

The extent of permanent lesions depends on the duration of perfusional deficit as well as on the susceptibility of the involved tissue. Reduced arterial supply may affect differently cerebral grey and white matter; metabolic requirements of neurons, astrocytes and oligodendrocytes may differ. Experimental in-vitro evidences indicate that neurons are more resistant to ischemia than astrocytes, even if astrocytes are particularly resistant to hypoglycemia (Alves et al., 2000), while oligodendrocytes appear the most vulnerable cells during either hypoxia or hypoglycemia (Lyons and Kettenmann, 1998). Neurophysiological evidences on animal model of experimental hypoxia show that within CC, larger myelinated axons are more susceptible to hypoxic damage compared to smaller and less myelinated axons, suggesting that myelin may be the structural element underlying the vulnerability to anoxia (Baltan, 2006).

In our patient, brain hypoxia was consequent to ab-ingestis pneumonia, determining reduced arterial blood oxygenation, without occurrence of cardiac arrest. Three weeks after hypoxia, brain MRI demonstrated a selective involvement of CC, with partial sparing of rostrum and splenium. Given data available on in-vitro and animal study, we can hypothesize that hypoxia affected mainly oligodendrocytes devoted to myelinate axons passing through CC. Respiratory involvement without blood flow impairment could have favoured the hypothetical prevalent damage to these glial cells, even if we cannot find a clear explanation about the involvement of CC and not of other white matter regions. Conversely, in those patients where brain hypoxia follows cardiac arrest, neurons are mostly affected, particularly in brain regions considered more susceptible to anoxia, such as hippocampus. Indeed, some cardiac arrest survivors suffer persistent memory and executive dysfunction due to hyppocampal involvement, whose volume appears reduced at MRI examination performed during follow-up (Stamenova et al., 2018).

In a rare condition, described as "delayed posthypoxic leukoencephalopathy", patients undergo a neurological relapse following 1–4 weeks of clinical stability or improvement following brain hypoxia. Brain MRI shows diffuse and confluent white matter changes, but a specific early involvement of CC has not been reported (Katyal et al., 2018; Zamora et al., 2015). Although our patient did not perform further brain MRI to exclude a late involvement of hemispheric white matter, the isolated involvement of CC 3 weeks after injury and the absence of any temporary clinical recovery, make such diagnosis unlikely.

Our patient had diabetes and was treated with insulin during most of the hospitalization period, however glycemia was daily monitored and no significant fluctuations were reported. Cerebral lesions caused by hypoglycemia may determine persistent vegetative state, but usually involve gray matter such as cerebral cortex, hippocampus and basal ganglia (Guler et al., 2015).

Brain hypoxia may determine diffuse and irreversible damage possibly leading to vegetative state and death. Since post-hypoxic lesions are often extensive, a correlation between spatial distribution of lesions and prognosis is difficult (Topcuoglu et al., 2009). It is however reported that involvement of CC predicted a poor outcome in patients with post-traumatic vegetative state (Kampfl et al., 1998).

To our knowledge this is the first case where isolated CC anoxic damage can be demonstrated in an adult patient. This case report could give some insight about in vivo brain susceptibility to hypoxic damage.

Competing Interests

The authors have no competing interests to declare.

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