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Case Report

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Retrograde Amnesia and Disorientation after Intraocular Injection of Anti-VEGF Agents

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Abstract

We present a case of a 77-year-old male patient who was treated in our outpatient clinic for memory disorders because of episodic confusion and retrograde amnesia. The patient reported having symptoms repeatedly following intraocular treatment with Anti-Vascular Endothelial Growth Factor Agents (Ranibizumab and Bevacizumab) as a treatment for wet macular degeneration. EEG showed a localized deceleration that intensified under prolonged voluntary hyperventilation. Symptoms resolved after the intraocular Anti-Vascular Endothelial Growth Factor treatment was stopped and anticonvulsive treatment with lamotrigine was begun. This case is important in that it describes a potential association between intraocular treatments with Anti-Vascular Endothelial Growth Factor Agents and seizures. Symptoms occurred in temporal correlation with intraocular treatment. Clinicians should be aware of this potential side effect on intraocular treatment with Anti-Vascular Endothelial Growth Factor Agents in patients with high risk for seizures.

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Introduction

Although late-onset idiopathic generalized epilepsy is very rare among elderly patients, epilepsy is a significant health care issue of the elderly population [1–3]. Important known risk factors for seizures in the elderly are cerebrovascular diseases, neurodegenerative disorders, tumors, traumatic head injuries, metabolic pathologies and toxins [4]. Progressive cognitive decline including Alzheimer disease as well as microangiopathy are also associated with a higher risk for seizures [5,6].

Ranibizumab and Bevacizumab are Anti-Vascular Endothelial Growth Factor Agents used in macular degeneration treatment [7]. Studies have found increased serum levels of Bevacizumab after intravitreal application for as long as 2 weeks after injection, and have therefore assumed that it could cause systemic side-effects [8]. Systemic side-effects are nevertheless considered to be rare [9]. Generalized seizures have been reported as a side effect after intravenous administration of Bevacizumab in patients with metastatic colorectal cancer [10]. A case of an 81-year-old female with tonic-clonic seizures following intravitreal application of Bevacizumab was reported in 2010 [11].

Intravitreal administration of Ranibizumab has not been associated with significant serum concentrations [12]. This is in line with a greater decrease of systemic Vascular Endothelial Growth Factor – A level after intravitreous treatment with Bevacizumab compared to Ranibizumab [13]. Vitreous half-life of 1.25 mg Bevacizumab (4.32 days) was found to be longer than of 0.5 mg Ranibizumab (2.88 days) in an animal model [14,15]. For both substances intraocular half-life in human beings is reported to be longer than in the study mentioned before: Intraocular half-life of Ranibizumab was reported at 7.19 days, and half-life of Bevacizumab was reported at 9.82 days – while systemic half-life of Ranibizumab is much shorter (2 hours) than systemic half-life of Bevacizumab (20 days) [16].

In this case we report EEG abnormalities, episodic confusion and retrograde amnesia after intravitreal treatment with Ranibizumab and Bevacizumab in an elderly patient with microangiopathy.

Clinical Details

The 77-year-old male patient first presented to our outpatient clinic for patients with memory disorders in March 2014. The patient was concerned about a subjective mild memory dysfunction with no significant impairment in daily life functions. Family history revealed a case of dementia (aunt from the mother's side) and the patient reported to be a carrier of a haemochromatosis-gene mutation. Past medical history included arterial hypertension, hyperlipidemia, wet macular degeneration and presbycusis. The patient had been a nonsmoker since 1998 and consumed limited amounts of alcohol on occasion. Psychiatric exploration did not reveal any significant psychopathological findings.

Blood sample showed a mild decrease of glomerular filtration rate and a mild increase of urea (52 mg/dl; norm: <45 mg/dl). Serum tests for borrelia and treponema were negative. A cranial MRI revealed moderate, generalized brain atrophy and microangiopathy primarily located in the medullary layer and the supratentorial region.

A detailed neuropsychological test battery in July 2014 revealed that score for delayed retentivity was below-average. Verbal fluency was well above-average. All other domains tested were normal. MMSE screening revealed a score of 29 out of 30.

Dementia as a cause of the symptoms was considered unlikely at this point.

A repeat neuropsychological testing showed improved results in 2015 with all test results being within the normal range, which supports our clinical impression that the patient did not suffer from a neurodegenerative disease and therefore treatment with antidementia drugs was not initiated.

In 2016 intraocular application of Ranibizumab as a treatment for wet macular degeneration was begun. The patient reported an unspecific weakness that began suddenly 20 days after the second administration. The first episode of confusion occurred after the third intraocular injection. A cranial MRI performed 10 days later did not reveal any new findings.

On May 18th the patient received the 4th dose. On June 3rd the patient developed confusion again and suffered from partial retrograde amnesia with sudden onset. The patient was suspected of having a transient ischemic attack and was admitted to a stroke unit. There

were no significant findings. The patient was discharged with aspirin.

In August the patient was treated with intraocular Bevacizumab for the first time. The patient developed recurrent episodes of nausea, retrograde amnesia und local disorientation after awakening one month after the second treatment with Bevacizumab was administered. He was admitted to a stroke unit the same day. Once again, no significant results were found.

The patient presented for a follow-up examination in our outpatient clinic in November 2016. An EEG was conducted because of temporal disorientation and nausea. Theta activity was found temporal right in rest. The localized deceleration converted to delta activity under hyperventilation with remission in one to two minutes after hyperventilation was stopped. Steep potentials underpinned an increased electrical excitability.

An anticonvulsive therapy with lamotrigine 25 mg/d was started and after 3 weeks increased to 50 mg/d. The intraocular treatments were stopped. An EEG control in October 2017 showed the known localized deceleration pronounced. MRI follow-up in 2018 did not show any significant changes. The patient reported that he had not experienced any additional episodes of confusion since the antiepileptic medication had been started.

Discussion

We report a case that shows a temporal association between episodic confusion and intraocular treatment with Ranibizumab and Bevacizumab. The medical record was free from epilepsy and seizures prior to treatment with intraocular Anti-Vascular Endothelial Growth Factor Agents for macular degeneration. Dementia was excluded by repeated neuropsychological testing. The patient was at increased risk for seizures as cerebral MRI scans had revealed pronounced microangiopathy. The occurrence of episodic confusion and disorientation began in direct temporal correlation with administration of intravitreal injections. The first EEG study was conducted on a day the patient reported the episodic confusion and revealed a localized deceleration. The patient did not report any additional episodes of confusion after intraocular treatments was stopped and anticonvulsive therapy was started.

The idea of Bevacizumab causing systemic side effects is in line with research showing systemic occurrence after intravitreal application, and seizures after treatment with Bevacizumab have been reported in literature [8–10]. The association between intravitreous Ranibizumab and systemic side effects remains doubtful, but a side effect is possible in this case. As a limitation no data for drug concentrations in patient serum is available.

In our opinion the temporal coherence of intraocular treatment with anti-VEGF agents and reported episodic confusion in connection with the EEG findings could be linked. Anti-VEGF treatment could have lowered the seizure threshold in this individual with higher risk for seizures. A case of a witnessed tonic-clonic seizure lasting 2-3 minutes after Bevacizumab injection was reported [11]. To our knowledge this is the first case linking intraocular anti-VEGF treatment and episodes of confusion with retrograde amnesia temporal. Clinicians should consider macular degeneration and potential anti-VEGF treatment when anamnesis data are collected for elderly – especially for those with higher risk for seizures. Before starting an anti-VEGF treatment documented anamnesis should include known epilepsy and risk factors for epilepsy such as neurodegenerative disease, traumatic head injuries, stroke, and metabolic disease. Under anti-VEGF treatment clinicians should ask patients and family members for possible clinical manifestations of epilepsy such as absence seizures, drop attacks, as well as tonic and myoclonic seizures.

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