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CASE REPORT

Two rare complications of glioblastoma multiforme: persistent hiccup and acquired haemophilia A

C.M.P.G. van Durme[1], R.N. Idema[2], C. van Guldener[1*]

Department of [1]Internal Medicine and [2]Laboratory of Haematology and Clinical Chemistry, Amphia Hospital, Breda, the Netherlands, [*]corresponding author: e-mail: cvguldener@amphia.nl

ABSTRACT

A 69-year-old man was admitted to the hospital with persistent hiccups. Computed tomography and magnetic resonance imaging of the brain were performed and revealed a glioblastoma multiforme localised in the right temporal lobe. After resection, the hiccups disappeared, suggesting that temporal areas are involved in control mechanisms of hiccups. A month later, the patient was readmitted because of skin, mucosal and soft tissue bleedings. Laboratory findings showed a prolonged aPTT, a low factor VIII activity and a factor VIII inhibitor, leading to the diagnosis of acquired haemophilia A. Acquired haemophilia A is a potentially life-threatening haemorrhagic disorder resulting from the presence of antibodies against factor VIII. We believe that this disorder developed due to exposure of factor VIII(-like) tumour antigens to the immune system. This case illustrates two yet unknown complications of a glioblastoma multiforme: persistent hiccups and acquired haemophilia A.

KEYWORDS

Glioblastoma, haemophilia, hiccups

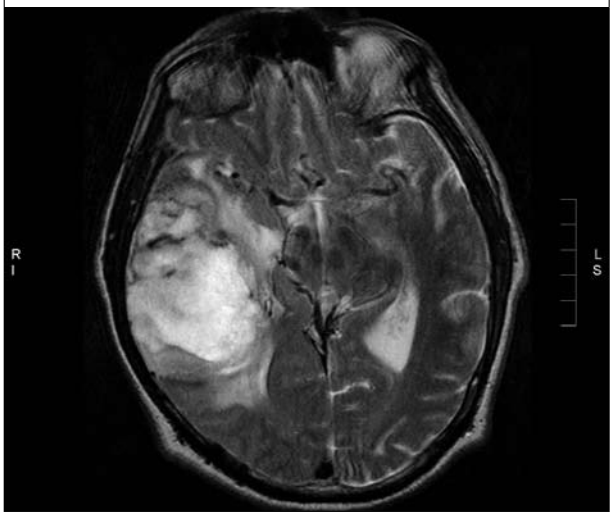
INTRODUCTION

Hiccups are a common, benign and usually transient phenomenon that affects nearly everyone. Hiccups that continue for more than 48 hours are called persistent, and those lasting for more than two months are called intractable. Persistent or intractable hiccups may herald serious underlying disease. We report the case of a persistent hiccup, which was the first sign of a brain tumour. At follow-up, a second rare phenomenon of this tumour presented in the form of acquired haemophilia with a severe haemorrhagic diathesis.

CASE REPORT

A previously healthy 69-year-old man was admitted with persistent hiccups for seven days, which had not responded to metoclopramide, diazepam and piracetam. At physical examination, there were no abnormalities. Laboratory tests were unremarkable and the chest radiograph was also without abnormalities. Baclofen was prescribed. During the first night, the patient developed a generalised seizure. Magnetic resonance imaging (MRI) of the brain showed a solitary tumour in the right temporal lobe, most likely a glioblastoma multiforme (*figure 1*). The tumour

Figure 1. *MRI scan of the cerebrum showing a large tumour in the right temporoparietal lobe*



was resected and histology confirmed the diagnosis of a glioblastoma multiforme. Postoperatively, the hiccups disappeared.

Four weeks after neurosurgery, the patient was re-admitted because of gross haematuria, melena, skin bleedings and a large retroperitoneal haematoma. Laboratory examination showed a haemoglobin of 3.8 mmol/l (normal >8.0 mmol/l), an elevated thrombocyte count (513 x 10^9/l), a normal PT (12 s) and a prolonged APTT of 124 s (normal <32 s). The APTT of a 1+1 mixture of patient's plasma with pooled normal plasma (APTT 29 s) was prolonged (45 s) and increased markedly to 57 s after one hour of incubation at 37°C. Lupus anticoagulant was excluded by means of a dilute Russel Viper Venom Time (41.8 s, normal <42.9 s). Further evaluation showed a decreased factor VIII activity of 1.9% of normal. Dilution of the patient's plasma showed a linear decrease in factor VIII activity. Other coagulation factors were not measured. An unmodified Bethesda assay demonstrated a factor VIII inhibitor of 4 BU/ml, leading to the diagnosis of acquired haemophilia A.[1]

Treatment was started with transfusion of packed cells, tranexaminic acid (500 mg three times/day) and DDAVP (24 µg twice daily). Postoperative dexamethasone therapy (2 mg twice daily) was switched to prednisone 75 mg/day. Because transfusion with three to four units of packed cells per day remained necessary to maintain the haemoglobin concentration above 5.0 mmol/l, 6000 units of porcine factor VIII concentrate were administered. This neither corrected the coagulation abnormalities (plasma factor VIII activity: 3.7%, APTT: 73 s and factor VIII inhibitor concentration: 1.8 BU/ml) nor terminated the ongoing blood loss. Then, recombinant factor VIIa was administrated (bolus 90 µg/kg followed by 1.2 mg/hour) for one day. This resulted in cessation of the bleeding and discontinuation of the transfusions. Coagulation tests, however, remained abnormal. One week after the administration of recombinant factor VIIa, the APTT was 132 s, factor VIII activity 0.7% and factor VIII inhibitor concentration 5.0 BU/ml. Because of the persistence of the inhibitor, cyclophosphamide was started at 100 mg/day orally and the patient was discharged. At follow-up, there were no recurrent bleedings. Seven weeks after discharge, factor VIII activity remained low at 3.2%, but APTT had decreased to 49 s and factor VIII inhibitor to 1.6 BU/ml. Cyclophosphamide was discontinued and prednisone was tapered. Three weeks later, APTT was 38 s and factor VIII activity 22%. Ten weeks later, i.e. five months after discharge, APTT (29 s) and factor VIII (87%) had normalised. One year after surgery, the tumour reappeared. There were no accompanying bleeding complications and APTT (26 s) and factor VIII activity (118%) were normal at that moment.

DISCUSSION

In this case, two yet unreported phenomena were observed in a patient with a glioblastoma multiforme: persistent hiccups and acquired haemophilia A.

Hiccups are caused by contractions of the diaphragm, the scalenic and intercostals muscles, followed by abrupt closure of the glottis, which causes the typical sound. Hiccup is considered to be a primitive respiratory reflex with the phrenic or vagal nerves or the sympathetic ganglia as afferent pathways, and the phrenic, cervical, intercostal and the recurrent laryngeal nerves as efferent pathways. The central connection is unknown, but it is thought to involve the brainstem, the respiratory centre in the medulla, the reticular formation, the phrenic nerve nuclei and the hypothalamus. In addition, supratentorial areas may be involved in normal inhibition of the hiccup reflex. Stimulation or irritation of the afferent pathways controlling the diaphragm (usually hiatus hernia with reflux oesophagitis) are responsible for most cases of chronic hiccups.[2,3]

Most cases of chronic hiccups due to disorders of the central nervous system are caused by brainstem lesions such as trauma, ischaemic stroke or compression by infection or tumour. The rare supratentorial lesions that have been associated with chronic hiccups, were all, as in our case, located in one of the temporal lobes.[4,5] Our case therefore strengthens the suggestion that temporal areas are involved in control mechanisms of hiccups.

With an incidence of only 1.5 per 1 million persons per year,[6] acquired haemophilia A is an uncommon but potentially life-threatening haemorrhagic disorder with an associated mortality between 8 and 22%.[7-9] It results from the presence of IgG autoantibodies directed against clotting factor VIII. These antibodies are usually of low affinity (type II) and may permit measurable levels of factor VIII, as was the case in our patient. The titre of these antibodies does not linearly correlate with the inactivation of factor VIII and the clinical manifestations. High affinity (type I) antibodies more frequently develop in response to infusions of factor VIII in patients with congenital haemophilia A. For unknown reasons, patients with acquired haemophilia A are more likely to have a severe bleeding diathesis than patients with congenital haemophilia A with the same inhibitor level.[10]

In the majority of patients with acquired haemophilia A, there is no underlying disease.[6-8] Autoimmune diseases (systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome) or malignancies (both solid and haematological) are found in 20 to 30% of cases. About 10% of the cases develop postpartum. In malignancy-associated acquired haemophilia A, there is no clear relationship between the type or extent of the tumour and the occurrence or severity of acquired haemophilia A.[11,12]

Glioblastoma multiforme has not yet been reported in malignancy-associated haemophilia A. The pathogenesis of the factor VIII inhibitors in malignancy remains elusive. Tumours may contain factor VIII-like antigens, which are able to elicit an immune response. In our patient, the inhibitor occurred four weeks after neurosurgery and it can be speculated that the tumour indeed contained factor VIII-(like) antigens which activated the immune system after the blood-brain barrier was severed.

The treatment of acquired haemophilia A requires a two-pronged approach: treatment of bleeding and elimination of the inhibitor. Treatment options for the bleeding episodes in patients with a low titre of inhibitor (i.e. <5 BU/ml) are DDAVP or factor VIII concentrate. In patients with severe bleeding and an inhibitor titre of >5 BU/ml, treatment with factor VIII-bypassing agents such as activated prothrombin complex concentrate or recombinant factor VIIa is preferred. Recombinant factor VIIa seems to be very effective,[13] as it was in our case. The fact that factor VIII was bypassed by this treatment explains that the bleeding stopped while APTT and factor VIII activity were still abnormal. Eradication of the inhibitor should immediately be attempted in every patient. Prednisolone at 1 mg/kg/day results in inhibitor elimination in approximately 30% of patients. Other agents that can be used include cyclophosphamide, azathioprine, ciclosporin A, rituximab and high-dose immunoglobulins.[14] In our patient, two weeks of high-dose prednisone was not successful in removing the inhibitor, after which cyclophosphamide was added. Seven weeks later, the inhibitor started disappearing from the plasma.

CONCLUSION

This case report illustrates two uncommon complications of glioblastoma multiforme: persistent hiccups and acquired haemophilia A. The location of the tumour in the temporal lobe and the disappearance of hiccups after removal of the tumour support earlier suggestions that the hiccup reflex is supratentorially controlled from this area. In addition, glioblastoma multiforme had not yet been described as the underlying disease of acquired haemophilia A. Interruption of the blood-brain barrier and exposition of tumour antigens to the immune system may explain its occurrence in the present case.

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