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LETTER TO THE EDITOR

Secondary parkinsonism due to hereditary hemorrhagic telangiectasia: A case report

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Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder that causes abnormal blood vessel formation.[1] It is characterized by mucocutaneous telangiectasia and arteriovenous malformations (AVM). Large AVMs cause symptoms, and they occur in the lung, liver, or brain.[1] Migraine, intracranial hemorrhage, seizure, intracranial abscess, paradoxical embolism, hepatic encephalopathy, cerebral or spinal AVMs, and cerebral aneurysms may be observed in HHT, with neurological involvement at a rate of 8 to 10%.[2,3] The development of parkinsonism in these patients is very rare. Herein, we reported a patient presenting with parkinsonism symptoms who was diagnosed with HHT. Furthermore, this study aimed to describe parkinsonism as a possible neurological symptom in elderly patients with HHT and explore the mechanisms of parkinsonism.

A 70-year-old male patient, who was diagnosed with HHT due to recurrent nosebleeds and gastrointestinal bleeding 25 years ago, was admitted due to complaints of fatigue, slowness of movements and speech, and difficulty in walking. The patient was a farmer with no alcohol or smoking habit. The patient had a history of hepatic encephalopathy and multiple red blood cell transfusions due to iron deficiency anemia (IDA). The patient was being treated with bevacizumab. The physical examination was normal, except for multiple hemangiomas on the tongue, lip, face, fingertips, and outer ear. The patient's neurological examination was normal, except for extrapyramidal system findings. Symmetrical bradykinesia and significant rigidity were observed in bilateral upper and lower extremities in the patient with hypomimia and hypophonia. The gait was in the anteflexion posture with small steps. In laboratory studies, renal function tests, serum electrolytes, and glucose levels were normal. The parameters of the complete blood count and the serum iron profile were as follows: hemoglobin, 5.8 g/dL; hematocrit, 19.4%; MCV (mean corpuscular volume), 67 fL; ferritin, 5.4 ng/L; serum iron, 11 ug/L; TIBC (total iron binding capacity), 326 ug/dL. Iron deficiency anemia was identified. Serum gamma-glutamyl transferase and leucine aminopeptidase values were normal. The ammonia value was slightly elevated, with 162.11 ug/dL (normal range: 20-90 ug/dL). Serum zinc, aluminum, and ceruloplasmin levels were normal. An elevated manganese (Mn) level was detected, with 60.8 ug/L (normal value <15.0 ug/L). Increased portal vein flow and capacity were detected on portal vein Doppler ultrasonography. Cranial computed tomography showed no hemorrhage (Figure 1). Cranial magnetic resonance imaging (MRI) revealed a hyperintensity in the bilateral globus pallidus in T1-weighted sections (Figure 2). The contrast-enhanced cranial MRI did not reveal an aneurysm or AVM. Levodopa treatment was started. A minimal improvement in extrapyramidal findings was detected with levodopa at 600 mg. Secondary parkinsonism was considered due to the symmetrical complaints of the patient

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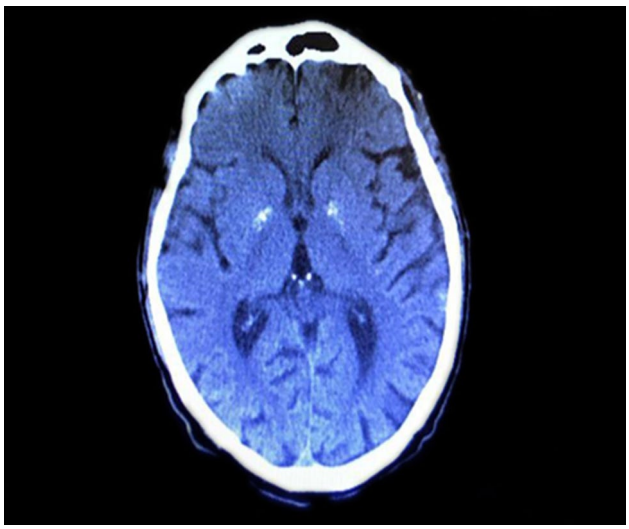

Figure 1. Unenhanced cranial computed tomography showed no hemorrhage.

related to the extrapyramidal system, absence of resting tremor, detection of hyperintensity in globus pallidus on T1-weighted cranial MRI and low response to levodopa. In our patient, hepatic failure with hyperammonemia, accompanying portal hypertension, hypermanganesemia, and T1-weighted cranial MRI revealed hyperintensity in the globus pallidus and secondary parkinsonism due to Mn accumulation caused by hepatic involvement of HHT.

Liver involvement in HHT is observed in 8 to 31% and is observed as angiodysplasias, fibrosis, cirrhosis, portal hypertension, and portosystemic shunts.[4] In studies performed on patients with portal hypertension and hepatic insufficiency in HHT, T1-weighted cranial MRI may show hyperintensity in the basal ganglia (BG), particularly in the globus pallidus, corresponds to Mn deposits facilitated by hyperammonemia or hypermanganesemia.[3] In healthy people, Mn is excreted by the biliary system, but in the case of liver failure and portosystemic shunts, the clearance of Mn from the biliary system is reduced, as in HHT.[3] Increased ammonia in these patients may lead to an increase in glutamine in astroglia and a decrease in glutamate, myoinositol, and choline.[3,5] Consequently, these changes lead to an increase in vascular permeability in the central nervous system, which facilitates Mn transmission.[3] Increased Mn in the brain is stored in the BG and creates a neurotoxic effect.[5] Serra at al.[3] detected the frequency of motor complications and hepatic vascular malformations is increased in HTT patients with hyperintensity in the BG on T1-weighted cranial MRI.

In severe cases, IDA is the most important and chronic complication due to gastrointestinal system bleeding and nosebleeds.[4] Manganese uses the same transport system as iron. In concomitant IDA, the transferrin-Mn complex is formed more than the iron-transferrin complex. This complex is retained in BG with high levels of transferrin receptors. Therefore, an increase in Mn absorption and accumulation may occur even in mild hepatic insufficiency in patients with HHT.[3] The presence of IDA and

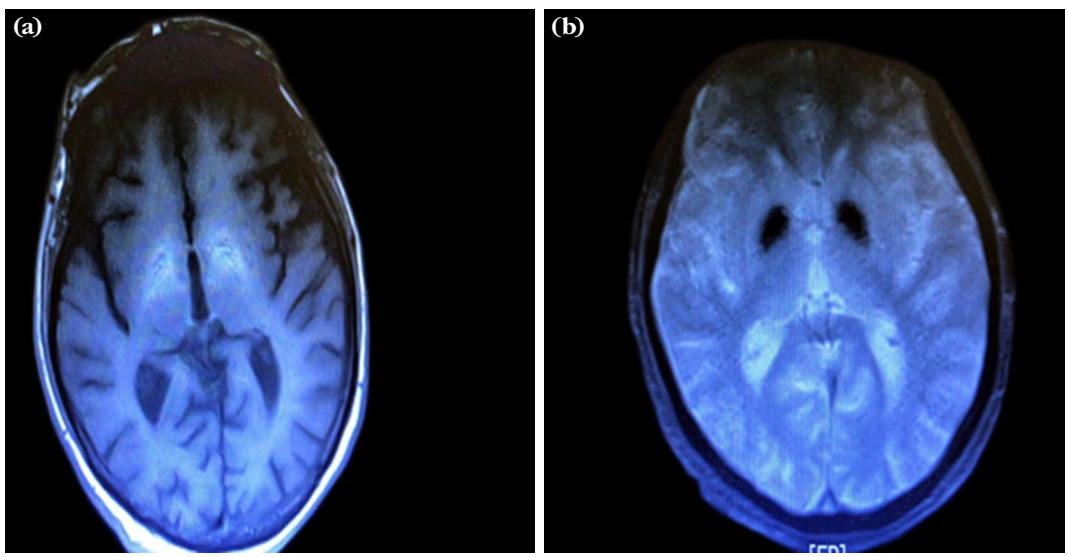

Figure 2. (a) Increased signal in bilateral globus pallidus was detected in T1-weighted sections. **(b)** Decreased signal on gradient echo sequence.

hepatic involvement facilitate the accumulation of Mn in the central nervous system.[3] In our patient, mildly increased ammonia levels, Mn elevation, and chronic IDA were determined even though severe liver failure was not detected. Therefore, secondary parkinsonism due to Mn deposits was considered in our patient.

Yoshikawa et al.[6] reported a 44-year-old female with HHT, who presented with parkinsonism, portosystemic shunts, elevated Mn levels, and BG lesions. The patient had IDA and normal ammonia levels. They hypothesized that the portosystemic shunting in the patient was compensated for by adequate liver function. Our patient was older and had elevated ammonia levels. Other study also demonstrated that an increase in ammonia leads to an increase in vascular permeability, facilitating the access and deposits of Mn in BG.[3,5] All these might explain why our patient's symptoms of parkinsonism were more pronounced.

In conclusion, this case report highlighted that parkinsonism may be a neurological symptom occurring as a result of Mn deposition in BG due to hepatic involvement and IDA in patients with HHT. The importance of early treatment in IDA is emphasized to prevent Mn accumulation. Cranial MRI is recommended to predict the presence of hepatic involvement in patients with HHT.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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