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CASE REPORT

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When the Circus is in Town The Hoof Beats You Hear Can Be Zebras

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INTRODUCTION

The medical aphorism stating that “when you hear hoof beats, think of horses not zebras” may not be true if a circus is in town. When confronted with a clinical differential diagnosis, we first think of the most frequent clinical conditions; but the unique scenario shown here reminds us that the less obvious conditions can be a realistic consideration.

METHODS

Patients

The five patients used to illustrate the point of this paper were seen at the Texas Tech Neurology Clinic and University Medical Center in El Paso. Three of them were German Luftwaffe active duty or dependent family personnel assigned to the German Air Force Flying Training Center at Holloman Air Force base in Alamogordo, NM. (This German center has approximately 500 active duty personnel of the German Luftwaffe in training; many are on an accompanied tour with their family¹). The other 2 cases were third generation Hispanic-American individuals living in El Paso.

Case One

A 19 year-old woman, a dependent daughter of an active duty German Air Force airman, was hospitalized at the UMC of El Paso with headache, transient recurrent left hemiparesis, and left central facial weakness. When she was examined, she was asymptomatic, but her mother reported that the patient had problems with immediate recall and concentration.

She denied blackout spells, seizures, insomnia, depression, orthostasis, dizziness, neck pain, chest pain, shortness of breath, palpitation, vomiting, diarrhea, blood in stool or urine, problems urinating, edema of the legs, numbness, tingling, paralysis, weakness, imbalance, or gait difficulty. No history of optic neuritis, hypertension, heart disease, diabetes mellitus, or dyslipidemia was present. She had no history of use of cocaine or other stimulant drugs.

Blood pressure was 110/75, pulse 72 per minute, and weight 134 lbs. She was alert, oriented to time, person, place, and purpose; cooperative and in no acute distress. Information and calculation were normal. She had normal immediate recall but poor short term memory. Remote memory also was slightly impaired. Judgment and abstraction were normal, as were thought content and progression of thought. There was no aphasia, agnosia or apraxia. Verbal fluency was normal. Cranial nerves were intact. There was no atrophy, fasciculations, or abnormal movements. There was

no alteration of muscle tone. There was no motor deficit of upper or lower extremities. Gait, station and coordination were normal. Muscle stretch reflexes were present and symmetrical. There were no pathologic reflexes. Perception of pinprick and light touch was normal. Motion and position sense of the fingers and toes were normal.

MRI of the brain showed no abnormalities on T1-weighted images, but on spin echo T2-weighted images there were subcortical high intensity signals and subcortical lacunar strokes some of them with hemosiderin pigmentation consistent with previous small hemorrhages.

An extensive workup was performed to exclude metastatic disease, a cardiac source of emboli, or coagulation abnormalities. Carotid ultrasound and echocardiogram, were normal. Coagulation profile and antiphospholipid antibody detection were negative.

DNA test for hereditary cerebral angiomas was negative. However, she had a positive DNA test for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

Case Two

The mother of the patient described in case one, a 49 year-old German lady, brought to us her MRI done in Germany three years previously. She had a history of migraine headaches for about twenty years. She had been taking sumatriptan for control of the acute pain. She had no history of hypertension diabetes, hypercholesterolemia or heart disease. There is also no history of imbalance, optic neuritis, weakness, or history of use of drugs of abuse. She did demonstrate decreased verbal fluency, impaired short term memory and reduced executive functions. Examination was otherwise normal. Her MRI showed multiple high intensity signals on T2-weighted images. Carotid ultrasound and echocardiogram were normal. Coagulation profile and antiphospholipid antibody detection were negative. She had a positive DNA test for CADASIL-associated mutation.

Case Three

A 42-year-old man, a Colonel in the German Air Force, was referred by the military hospital in El Paso to Texas Tech for a second opinion because of chronic headaches and abnormal MRI. He gave a history of migraine-like headaches with aura occurring for more than 15 years. He had no history of seizures,

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transient ischemic attacks, optic neuritis, weakness, imbalance, hypertension, diabetes, hypercholesterolemia or hearing problems. There was no history of use of drugs of abuse. Upon questioning he had impaired working memory and reduced executive functions interfering with his work as a logistic officer.

His blood pressure was 120/70, pulse 80 per minute, and weight 190 lbs. He was alert, oriented for time, person, place, and purpose; cooperative and in no acute distress. There was no neck bruit. Cardiac rhythm was regular. The liver was not palpable. Peripheral pulses were present. Information, memory, and calculation were normal on direct testing. Judgment and abstraction were normal. The thought content and progression of thoughts were normal. There was no aphasia, agnosia or apraxia. Cranial nerves were intact. There was no atrophy, fasciculations, or abnormal movements. There was no alteration of muscle tone. There was no motor deficit in either his upper or lower extremities. Gait, station and coordination were normal. Muscle stretch reflexes were present and symmetrical. Abdominal reflexes were present and equal. There were no pathologic reflexes. Perception of pinprick and light touch were normal. Motion and position sense of the fingers and toes are normal.

MRI of the brain showed multiple high intensity signals in the periventricular region, basal ganglia, corona radiata, and centrum semiovale on T2-weighted images.

Carotid ultrasound and echocardiogram were normal. Coagulation profile and antiphospholipid antibody detection were negative.

DNA test for CADASIL was positive.

Case Four

In this case, a 41-year-old woman had recurrent headaches for 10 years. The headaches were generalized, throbbing, almost daily and sometimes preceded by visual disturbances consisting of blind spots in front of the eyes.

The headaches were not relieved with triptans, hydrocodone, ergotamine tartrate, or Demerol. She was attending college classes, and she reported problems with learning new material. She attributed this to the inability to concentrate because of the headaches.

There was no history of hypertension, diabetes mellitus, heart disease or hyperlipidemia. Three years prior to her presentation to the clinic, she had syncope of unknown etiology.

There was no history of depression, orthostasis, neck pain, chest pain, shortness of breath, palpitation, vomiting, diarrhea, blood in stool or urine, problems urinating, edema of the legs, numbness, tingling, paralysis, weakness, imbalance, or gait difficulty. She has gained weight due to inactivity as the result of knee surgery. There was no history of optic neuritis. There was no history of use of drugs of abuse.

Her father and sister had migraine headaches, and her father also had mild cognitive problem, a stiff right leg and he had the diagnosis of multiple sclerosis. Her blood pressure was 110/70, pulse was 86 and weight was 149. She was alert and oriented. Her immediate recall, short term memory and past memory were slightly impaired. She had poor fund of information about recent events, and she

could not subtract well. Judgment, abstraction and language were normal. She had astigmatism corrected with glasses. Examination of her eye fundi was normal. No visual field defect was noted. Extraocular muscles were intact. Palate and tongue moved in the midline. No motor deficit of upper or lower extremities was demonstrated. Gait and coordination were normal. Muscle stretch reflexes were normal. There were no pathologic reflexes. Sensory examination was normal. MRI of the brain showed many areas of high intensity distributed in temporal and frontal white matter, basal ganglia, brain stem and cerebellum on T2-weighted images. Cervical MRI was negative. Cerebrospinal fluid was normal without oligoclonal banding. Brain stem auditory evoked potentials and visual evoked potentials were normal. A DNA test for CADASIL was positive.

Case Five

Patient was a 65-year-old man and the father of patient 4. He was not evaluated but his medical history, neuroimaging, and laboratory reports were reviewed. He had recurrent episodes of right hemiparesis with cumulative residual weakness of the right side of the body. He had no history of optic neuritis. He had a residual weakness of the right side of the body and the family had not noticed any impairment of speech. There was no history of use of drug of abuse. He was using a cane. He had no history of arterial hypertension, diabetes, heart disease, or hypercholesterolemia. MRI of the brain showed focal lacunar infarcts in the basal ganglia, external capsule, insular region, and many hyperintensities in the white matter were seen on T2-weighted images. Cerebrospinal fluid examination was negative for oligoclonal banding, and visual evoked responses were normal. A DNA test for CADASIL was positive.

DISCUSSION

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a small cerebral blood vessel arteriopathy, most frequent in people from Western Europe. CADASIL patients may present with recurrent transient attacks or strokes or with migraine with aura. About 39 per cent of patients have a history of migraine, particularly migraine with aura at presentation.² Seizures occur in about 10 per cent of patients. CADASIL is also the cause of early dementia, cognitive impairment and functional decline. Cognitive impairment is noted at presentation in 48 per cent of patients.² In the case series of Dichgans et al fewer than half of patients older than 60 walked without assistance.²

CADASIL is found worldwide. The genetic cause of CADASIL is a mutation in the NOTCH3 gene which maps to chromosome 19p13.1.^{3,4,5}

The disease is markedly underdiagnosed. Most of the families carrying the NOTCH3 mutation are of Western European extraction (Finland, Germany, France, Italy, Spain, and the United Kingdom).^{5,6}

T2-weighted magnetic resonance imaging shows high intensity signals in subcortical white matter and lacunar lesions in the area of basal ganglia, periventricular region, and brain stem. Typical white matter changes in CADASIL involve the anterior temporal poles and the external capsules of the brain. These findings make the radiographic features of this disease unique. Brain MRI can detect white matter abnormalities in CADASIL long before symptomatic stroke occurs.

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Pathologic examination of the brain shows angiopathy affecting leptomeningeal and long perforating arteries of the brain with thickened arterioles, degeneration of the smooth muscle layer;⁷ and on electron microscopy there are osmiophilic granules within the media of the small and medium sized vessels.⁸ These osmiophilic granules are also found in skin, muscle and peripheral nerves.⁹ The pathogenesis of CADASIL is unknown. It has been hypothesized that there is an endothelial dysfunction in CADASIL. Cells from bone marrow, such as endothelial progenitor cells and circulating progenitor cells, which participate in endothelial structure and repair, are reduced in CADASIL.¹⁰

The clinical picture displayed by patients with CADASIL requires an evaluation to exclude most common disorders of recurrent neurologic deficit including artery-to-artery and heart emboli, thrombotic and hemorrhagic cerebral infarcts, slowly evolving vasculopathies of the brain,¹¹ coagulation disorders, antiphospholipid antibody syndrome, arterial dissection, arteriovenous malformations, and multiple sclerosis.

The presence of a permanent home at Fort Bliss, Texas of a Germany's Air Force Command, and of a German Air Force Flying Training Center in the vicinity of El Paso, Texas, and the prevalent large Hispanic population of El Paso require the clinician to think about CADASIL, especially when confronted with transient ischemic attacks in a relatively young population in the absence of heart disease, hypertension, diabetes, and hypercholesterolemia. This is particularly important if there is a family history of migraine and high intensity signals on T2-weighted MRI imaging.

CADASIL has no proven treatment. Aspirin is often used in the hope of preventing thrombotic occlusion, but aspirin should be used cautiously. Hemorrhagic lesions⁶ and microbleeds (as seen in Case One) can occur in CADASIL. This suggests that anticoagulant treatment should be used cautiously.¹²

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