

Frontal Lobe Syndrome in a Patient With Bilateral Globus Pallidus Lesions

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● This article describes a patient who experienced the rapid onset of an irreversible behavioral change while vacationing in La Paz, Bolivia (altitude, 4070 m). The only lesions demonstrated on a magnetic resonance imaging scan were bilateral hemorrhages in the globus pallidus. The behavior change was characterized by apathy and lack of motivation, features commonly associated with bilateral frontal lobe disease. This case is a further demonstration of how subcortical lesions can produce behavioral syndromes that are clinically indistinguishable from classic cortical syndromes. It is cases such as this that show how a strict localizationist concept of behavioral function is too restrictive and how it is necessary to consider a wide network of neuronal interconnections when explaining the mechanism of a dissolution of complex higher functions.

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More than 100 years ago, a man named Phineas Gage developed an abrupt change in character and personality after sustaining a destructive lesion in the prefrontal portion of the frontal lobes of his brain. The syndrome of apathy, nonmotivation, indifference, irritability, and lack of social restraint has come to be known as the frontal lobe syndrome. With the examination of large numbers of patients with frontal damage it has become obvious that there is no unitary behavioral constellation of symptoms among these patients. Several clinical subtypes, possibly with separate anatomic localizations, have now been described.¹ In addition to this elaboration and separation of the clinical presentations of patients with damage restricted to the frontal lobes, patients

have been described with the clinical features of a classic frontal lobe syndrome, yet whose lesion or lesions lay elsewhere in the brain.

This article describes a man who developed a clinical irreversible frontal lobe syndrome secondary to bilateral hemorrhages in the globus pallidus. One unusual feature of this case was that the behavior change began abruptly after disembarking from a commercial airliner in La Paz, Bolivia, at an altitude of 4070 m.

REPORT OF A CASE

A healthy 60-year-old man from Louisiana (altitude, sea level) arrived in La Paz, Bolivia (altitude, 4070 m), after an uneventful flight from Santiago, Chile (altitude, 550 m). He disembarked, and as he was entering the terminal his wife noticed that he was acting as if he were drunk. He made inappropriate remarks to traveling companions, scattered coins to children at the airport, and began talking in an expansive fashion. He claimed that the altitude made him feel "high," and announced that "the trip was a drag and he needed to get out and walk." He was physically active that first day and did not have any physical complaints.

He vomited once that night, but in the morning did not complain of headache or respiratory distress. On the second day, he again felt drunk yet continued to be active. Throughout the course of that day he began to look somewhat dazed and show signs of lethargy. He slept much of that evening and the following day. On the evening of the third day, he was taken to a lower altitude. Over the subsequent few days he became more alert but was quiet and withdrawn. He had no memory of the 3 days spent in Bolivia.

Six days after leaving Bolivia he was examined at the Ochsner Clinic in New Orleans, La. His wife stated that since the trip the patient had undergone a complete personality change. Prior to his arrival in Bolivia the patient had been an outgoing, ambitious "dynamo," who owned and operated several small businesses. He had previously also been outgoing socially. After the trip he was socially withdrawn, had no motivation for business, showed no interest in his hobbies, and spent much of the day watch-

ing television. He had no specific physical or neurologic complaints other than the behavior change and the period of amnesia for the time spent in Bolivia.

On brief mental status evaluation he was quiet, laconic, and offered no spontaneous conversation. He was oriented, accurate about his recall of recent news events, and could name the last four presidents in proper order, albeit rather slowly. He was, however, able to store and retrieve only one of four specific verbal items after 5 minutes.

Neurologically, he showed some mild cogwheel rigidity in the left arm and a tendency to fall to the left on tandem walking. He had a slightly increased muscle stretch reflex in the left ankle, and there was a positive Hoffmann's sign on that side.

His medical history was unremarkable; he was normotensive, nondiabetic, with no history of cardiac or cerebral ischemia. He had been a heavy drinker in the past but had not had any alcohol in 2½ years. His wife believed that he had developed some mild recent memory problems in the preceding year, but this did not interfere with his work. He had intermittent hip pain for which he took carisoprodol; that was his only medication. He had taken one of these pills the day of his flight into La Paz.

Eight weeks after the onset of his frontal lobe syndrome he was only marginally improved. He tended to talk little and watch television for hours at a time. The family did not notice any significant memory problem other than his amnesia for the time spent in Bolivia. He was totally unable to run his business, not because of an inability to understand the details of the business, but because he was completely unmotivated and procrastinated on every detail. Before, he had spent many hours on the phone making business calls; now he sat long hours in the office and rarely made a single call. He napped after lunch and slept 8 to 9 hours every night, an unusual pattern for him. At that time an electroencephalogram and magnetic resonance imaging scan of the brain were performed. The electroencephalogram was normal, but the magnetic resonance imaging scan demonstrated bilateral hemorrhages involving the inner surface of the globus pallidus and the white matter tracts of the posterior limb of the internal capsule (Figs 1 and 2).

On that visit a full mental status examination was performed.² The patient was alert and attentive, but quiet and laconic.

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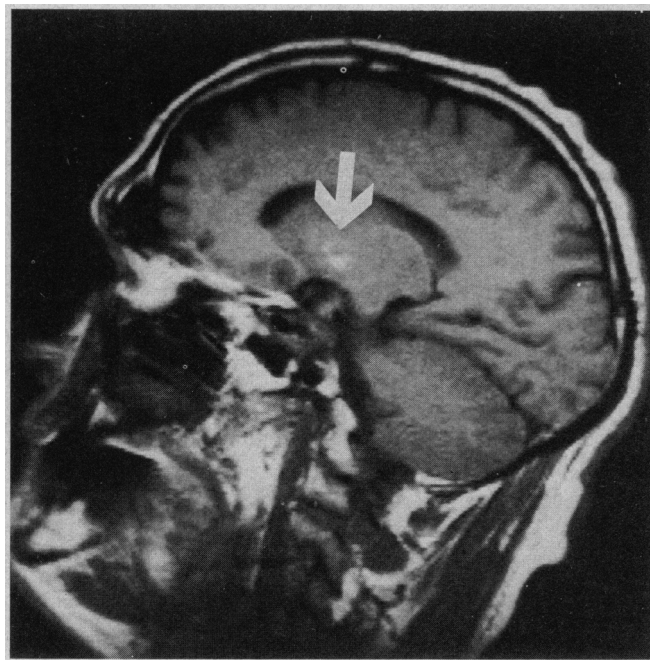
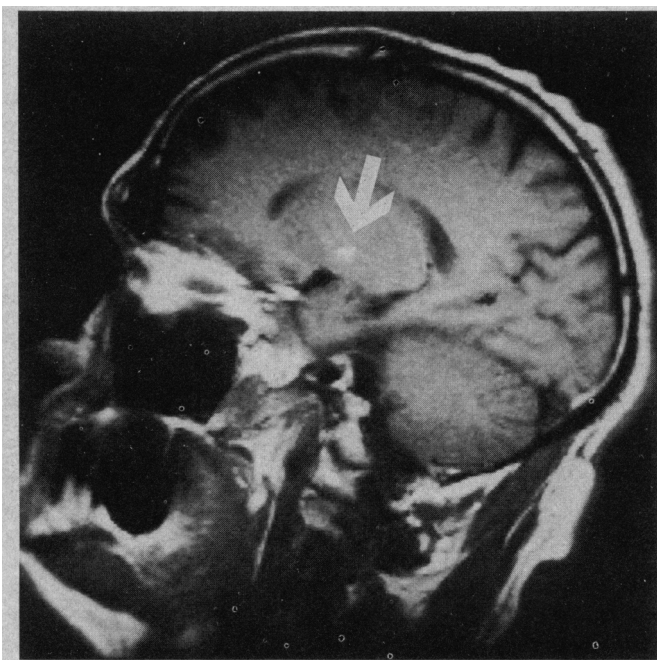


Fig 1.—Sagittal magnetic resonance imaging (T₁) demonstrating hemorrhage in the right globus pallidus (arrow). Six weeks after hemorrhage.

Fig 2.—Sagittal magnetic resonance imaging (T₁) demonstrating hemorrhage in the left globus pallidus (arrow). Six weeks after hemorrhage.

Language functions were normal. He was fully oriented and had good recall of recent presidents. Again he could retain only one of four unrelated words after 5 minutes and two of four at 10 minutes. Only 11 of 26 bits of information were recalled from a verbally presented short story and he could find (after 5 minutes) only three of five objects that he had seen the examiner hide in the room. Drawing ability was slightly impaired. Proverb interpretation was only fair; however, similarity testing was good. Alternating motor sequencing and repetitive drawings designed to elicit perseveration and poor set shifting were normal. On this examination the patient demonstrated behavioral features of the frontal lobe syndrome plus impairment of new learning ability (recent memory) and a mildly decreased verbal abstracting ability.

Five months after onset of frontal lobe syndrome a complete neuropsychologic test battery was administered. Full-scale (revised Wechsler Adult Intelligence Scale) IQ was 103 with a verbal IQ of 105 and a performance IQ of 101. The only significantly impaired intellectual functions were visual sequencing (digit symbol) and visual organization (object assembly). Memory testing showed marked impairment in the ability to hold verbally presented material over time. The Trailmaking Test (Parts A and B) was normal. The tests that showed the maximum impairment were the Wisconsin Card Sorting Test and the Stroop Color Word Test. These tests evaluate the ability to shift sets rapidly and are characteristically abnormal in patients with frontal lobe disease.³

Since the second month after onset of his behavioral syndrome the patient has remained clinically stable. He has shown no response to either methylphenidate (30 mg

daily) or bromocriptine (80 mg daily). A follow-up magnetic resonance imaging was obtained 12 weeks after onset of frontal lobe syndrome (Figs 3 and 4); this second scan again demonstrated the globus pallidus lesions. These lesions gave the signal characteristics of resolving hemorrhage. In the fifth month a single-photon emission computed tomographic scan was obtained, which showed a slight decrease in blood flow in the anterosuperior portion of the right frontal lobe and an equivocal decrease in blood flow in the posterior frontal lobe on the left side.

COMMENT

The patient's outstanding clinical signs and symptoms are those that typify the frontal lobe syndrome. He is apathetic, socially withdrawn, and nonmotivated. He has given up his hobbies and fails to make timely decisions in his work. He knows what actions are required in his business, yet he procrastinates and leaves details unattended. Depression is not present. He does not display or admit to any dysphoric mood; he is not sad and has not changed his eating habits; however, he tends to sleep more than he did in the past. Neuropsychologic testing demonstrated a significant impairment on the sensitive set shifting tasks (Stroop Color Word Test and the Wisconsin Card Sorting Test) that are usually associated with frontal lobe dysfunction.³

The frontal lobe syndrome is usually seen in patients with significant disease of the frontal cortex. In cases of

the apathetic variety of frontal syndrome, such as this patient displays, it has been proposed that it is the lateral portion of the frontal lobes that is usually involved (Brodmann's areas 9, 10, 11, 46, and 47).¹ This dorsolateral localization is by no means universal; bilateral anterior cerebral artery lesions that are sometimes seen after anterior communicating artery aneurysm rupture will produce an apathetic frontal lobe syndrome with mesial and orbital frontal infarction.

In this case there was no evidence on the magnetic resonance imaging scan of any damage to the frontal cortex, although the single-photon emission computed tomographic scan did show a minimal decrease in blood flow in the superior frontal lobe on the right side. It is proposed, therefore, that the subcortical lesions in the globus pallidus alone are responsible for this patient's clinical findings.

The behavior changes of the frontal lobe syndrome can occur, however, from noncortical as well as nonfrontal lesions. Deep white matter lesions in the frontal lobe that interrupt the reciprocal connections between the frontal cortex and limbic structures elsewhere in the brain can certainly produce the syndrome. The frontal leukotomies performed in the 1940s by Freeman and Watts⁴ purposely involved producing such lesions by the rather nonselect cutting of these fiber tracts in the inferior frontal lobe. Such procedures were performed to produce

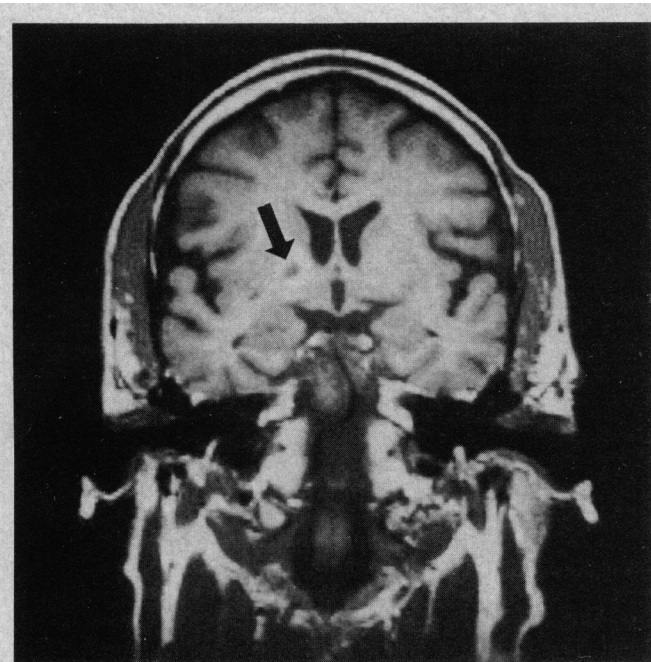


Fig 3.—Coronal magnetic resonance imaging (T₁) 10 weeks after onset of frontal lobe syndrome demonstrating area of residual damage in the right globus pallidus (arrow).



Fig 4.—Coronal magnetic resonance imaging (T₁) 10 weeks after onset of frontal lobe syndrome demonstrating bilateral residual lesions in the globus pallidus (arrows).

a state of relative apathy in psychotic patients.⁴ More recently, selective cingulotomies have been performed to help seriously obsessive-compulsive individuals to be less obsessive. In these cases, fiber tracts connecting the frontal lobe with the cingulate gyrus are interrupted.^{5,6}

Involvement or disconnection of the deep frontal white matter is also one of the possible mechanisms for the frontal lobe syndrome that is sometimes demonstrated in patients after rupture of anterior communicating artery aneurysms.^{7,8}

It is not difficult to imagine how damage to the major afferent and efferent systems of an extensive area of association cortex such as the frontal lobes could produce a clinical picture similar to that produced by damage to the cortex itself. But how more remote lesions, such as those seen in this patient, can explain the frontal lobe symptoms is more problematic. One explanation could be that the frontal lobe syndrome is not exclusively a frontal lobe phenomenon but rather is a general behavioral syndrome that can be seen in patients with destructive lesions in various areas of the brain. Many of the features of the syndrome, eg, apathy and nonmotivation, are common general behavioral symptoms that are seen in a wide variety of organic and functional behavioral syndromes (eg, akinetic mute states, dementia, confusional states, right parietal lesions, depression). A second ex-

planation is that the symptoms of the frontal syndrome are produced not only by damage to the frontal lobes and their major fiber pathways but also by damage to other brain structures that have strong interconnections with the frontal lobes. The frontal lobes have rich interconnections with many subcortical structures: caudate nuclei, thalamus (dorsomedial and anterior nuclei), temporal lobe limbic structures, and the periaqueductal gray and associated mesencephalic limbic structures.⁹ Because of this system of dense reciprocal interconnection it is not surprising that patients with subcortical lesions in some of these areas can have symptoms of frontal lobe dysfunction. Several recent clinical reports support this notion.

Richfield et al¹⁰ described a 25-year-old patient who developed a pattern of inappropriate, vulgar, impulsive, antisocial behavior after bilateral destruction of the head of the caudate nuclei; and Bogousslavsky et al¹¹ described a 72-year-old patient with an infarct in the right thalamus who demonstrated a behavioral state that fluctuated between manic delirium and apathy. In addition to these cases in which the frontal lobelike behavior change was the principal behavioral feature of the subcortical lesions, Katz et al¹² have described six patients with dementia secondary to multiple subcortical strokes in the mesencephalon and diencephalon in whom features of a frontal lobe syndrome (apathy, lack of mo-

tivation, and impulsiveness) accompanied the cognitive loss.

In the case described here, the exact anatomic extent of the lesions is not known; however, they appear to be largely confined to the globus pallidus and possibly some portion of the posterior limb of the internal capsule. It may be possible that some of the fibers from dorsomedial thalamus to frontal lobe may be affected by this lesion. Crosby et al¹³ also describe thalamofrontal fibers that make connections through the putamen and globus pallidus. It is not known whether these pathways are of sufficient influence that their damage could cause this degree of behavior change,¹³ but it is possible. Further speculation without pathologic examination is clearly unjustified.

The functions of personality, drive, and character that are attributed to the frontal lobes are enormously complex functions that undoubtedly require vast integrated cerebral neuronal networks for their elaboration.¹⁴ The frontal cortex is an important part of that network, but, as this and other reported cases show, it is not the exclusive center for such functions. Damage anywhere within the entire network is likely to produce, in some measure, symptoms akin to the classic frontal lobe syndrome.

This same network model can be used to explain the findings in cases of subcortical dementia,¹⁵ subcortical aphasia,¹⁶ subcortical neglect,¹⁷ and

any number of similar cases that do not fit the strict localizationist model of the 19th century.

Other than the anatomic mechanism in this case, there is a further unexplained issue in this particular patient; ie, the exact relationship among this patient's symptoms, his brain lesions, and the fact that they both occurred at an altitude of more than 4000 m above sea level. The patient's initial symptoms of light-headedness, intoxication, and poor judgment occurred within minutes of entering the rarefied air of La Paz. These symptoms are certainly consistent in many ways with the symptoms of acute anoxia that have been reported by military recruits exposed to low oxygen tension in experimental decompression chambers and by pilots who have experienced explosive decompression at high altitudes (8000 to 16000 m) when the canopy of their aircraft unexpectedly ejected.^{18,19} In such cases of anoxia, however, patients usually experience paresthesias in various parts of the body, which this patient did not; and they are usually not amnesic unless the anoxia is severe and their behavior much more disordered and confusional than that of this patient. Simple hypoxia is probably an insufficient explanation for his initial behavior change.

In commercial airplanes the pressure in the cabin is maintained at an equivalent of between 1830 and 2440 m above sea level. Ambient cabin pressure is supposed to be gradually decreased during descent into La Paz so as to avoid the explosive decompression (by definition, a drop in pressure of 1524 m in 1 minute or less) that would occur if the cabin door was opened in La Paz without the gradual change. Assuming that these precautions were taken, this patient should not have experienced a rapid change in pressure, but rather, a gradual one.

There are other clinical syndromes that can occur when individuals are exposed to a change in ambient barometric pressure. One is acute mountain sickness, a syndrome seen in mountaineers who climb at altitudes above 3350 m.^{20,22} This syndrome evolves over hours to days and is characterized by both pulmonary and cerebral edema. The patient presented here did not describe the headache, blurred vision, and respiratory problems associated with that condition, so it is doubtful that diffuse edema played a part in his symptoms. Acute mountain sickness can be fatal but autopsy reveals cerebral edema, petechial hemorrhages on the pial surface of the

brain and anoxic necrosis in basal ganglion and cortex but no parenchymal hemorrhage.^{23,24} Another mechanism of neurologic symptoms with rapid decompression is the release of nitrogen bubbles into the system. This is usually associated with decompression from underwater dives and is rarely, if ever, seen in high-altitude exposure.²⁵

The relationship between the globus pallidus hemorrhage and the altitude exposure remains, therefore, unclear. It is possible that the hemorrhages are coincidental and that the high altitude played no physiologic role in the production of the hemorrhage. Several factors, however, make it difficult to accept this supposition; basal ganglion hemorrhage is uncommon in normotensive individuals, basal ganglion hemorrhage is usually unilateral, and such hemorrhages are much more common in the striatum and thalamus than in the globus pallidus. It is possible that this patient had bilateral cryptic vascular malformations in each globus pallidus and that the combination of tissue hypoxia and compensatory vasodilatation produced the hemorrhage, but this seems unlikely. A final possibility is that the hypoxia, to which the globus pallidus is relatively sensitive, coupled with vasodilatation that occurs at high altitude caused the rupture of some small normal vessels in this area thus causing the restricted areas of hemorrhage. If this is what happened, this event most likely occurred in the first hour after disembarking. The patient's excitation the first day would therefore have represented the combined effects of the acute hemorrhage and general cerebral hypoxia. By the third day, the intoxication of the hypoxia receded and the apathy and lethargy caused by the focal lesions prevailed.

From review of the literature and the general knowledge that people fly in and out of high-altitude airports on a daily basis without developing the problems encountered by this patient, it is clear that this case is, if not unique, decidedly rare. There was nothing in the patient's medical history or his evaluation after the incident to suggest a medical condition that would render him unusually susceptible to the effects of high-altitude exposure. Since this is an isolated case, there seems little reason to suggest that people not engage in air travel to altitudes above 2000 m; however, this case does bring up many interesting issues about the rather sudden exposure to high altitude experienced during air travel.

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