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Cortical Basal Ganglionic Degeneration

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Abstract

In this case study, we describe the symptoms, neuropsychological testing, and brain pathology of a retired mason's assistant with cortical basal ganglionic degeneration (CBGD). CBGD is an extremely rare neurodegenerative disease that is categorized under both Parkinsonian syndromes and frontal lobe dementias. It affects men and women nearly equally, and the age of onset is usually in the sixth decade of life. CBGD is characterized by Parkinson's-like motor symptoms and by deficits of movement and cognition, indicating focal brain pathology. Neuronal cell loss is ultimately responsible for the neurological symptoms.

Introduction

At the age of 64, a retired mason's assistant began to experience problems with accuracy while driving. He also had trouble putting his shoes on correctly, often confusing left and right. At age 65, his limbs stiffened and his movements slowed (bradykinesia). He also began to ignore his right arm; even though it was not weak, it hung at his side as if he no longer knew how to use it. In addition, the right hand grabbed onto anything that happened to be in front of him. Although he had been a superb carpenter, these symptoms prevented him from performing wood crafting. He also lost the ability to handle his finances. Over the course of several months, he became unable to make lunch, brew coffee, or dress himself. Personality changes occurred as well: Apathy grew, as did obsessive-compulsive and rigid behavior. For example, he asked for things repeatedly and demanded that they be done immediately (such as requesting that candlesticks be moved back and forth).

The patient's medical history was unremarkable except for hypertension; he had been taking aspirin and antihypertensive medications. Neither the patient nor any of his blood relatives had a history of neurological or psychiatric disease.

Neurological examination

A neurological exam that took place about 2 years after the onset of symptoms revealed deficits that were more pronounced on one side of the body than the other (asymmetric deficits). He showed no elicitable optokinetic nystagmus to the left. (An optokinetic nystagmus is an eye movement with a fast and a slow component. It is evident when the patient watches a striped piece of tape moving in front of his eyes, as if he were looking out of the window of a moving train. Absence of either or both components of these movements indicates ipsilateral frontal or parietal brain dysfunction.) The patient also had severe right

arm apraxia; he could not perform actions such as saluting, combing his hair, or brushing his teeth, and cognitive or motor abnormalities could not account for these disturbances (video clip 1, video clip 2, video clip 3).

He also had some evidence of right hemi-neglect; he would use his left arm almost exclusively for spontaneous actions even when he was instructed to perform the actions with the right arm (video clip 1, video clip 2, video clip 3).

However, he tended to grab with his right hand whatever was placed in front of him (an exaggerated grasp reflex). He also lost the ability to recognize by feel alone both the shape and identity of an object, such as a key or a coin placed on his palm (stereognosis) and numbers or letters written on his palms (graphesthesia).

When walking, the muscles in the patient's right arm frequently flexed briefly at the elbow, wrist, and fingers, and his right big toe extended intermittently and remained briefly in the extended position (right arm and right big toe dystonia)(video clip 2, video clip 3). The patient also displayed asymmetric signs reminiscent of Parkinson's disease (see Andersen), which included mild rigidity or tensing in the right arm and leg and a decrease in the swing of his right arm when walking (video clip 4). His right hand trembled slightly when he simply stretched it out (postural tremor) and when he reached for something or attempted to pour liquid into a cup (action tremor). His eye movements were normal.

Mental status testing

Mental status testing revealed evidence of dementia (deficits in multiple cognitive domains). He was perseverative; that is, when asked to recall three words he had heard several minutes earlier, he would repeat one of the words, as if he were unable to disengage from it. Similarly, when he was switched from one cognitive test to another, he behaved as if he were still performing the previous test.

He also manifested deficits in attention and working memory. For example, he could not repeat more than five digits forward and was unable to repeat digits in reverse order. Similarly, he had problems with anterograde memory (registering and recalling new information) and retrograde memory (recalling information registered in the past); he could remember only one out of three words after five minutes had passed and he could list only two of the last five U.S. presidents. In addition, the patient could not perform simple calculations (for example, "how much is 93 minus 7?") or spell the word "world" backwards. He also displayed deficits in orientation to time and place.

Language testing was notable for the patient's normal ability to comprehend and follow commands, to name objects, and to repeat phrases. However, he was unable to write a sentence. Finally, his visual-spatial abilities were severely impaired, as evidenced by his tremendous difficulty copying pictures. Such a task entails showing the patient a picture of a cube or intersecting pentagons and asking him to draw the diagram exactly as it appears.

Neuropsychological testing

Formal neuropsychological testing confirmed the deficits in orientation, attention, memory, and visual-spatial skills. In addition, the patient was unable to comprehend the essence of a simple story or answer simple questions (for example, "is one pound of flour heavier than two pounds?"). He displayed problems with fine motor coordination and dexterity, as well as with verbal and nonverbal learning (for example, the ability to recall a list of words or shapes within seconds to minutes after presentation). Other deficits included verbal and nonverbal abstract reasoning: The patient was unable to identify similarities and differences and, therefore, to conceptualize an abstract link between mental concepts or shapes. He also

had trouble listing words starting with a particular letter (phonological fluency) and displayed limited ability to name several nouns that belong to a particular category, such as animals (categorical fluency).

Other tests

A full laboratory work-up was unrevealing. Brain magnetic resonance imaging (MRI) was also unrevealing. Single photon emission computerized tomography (SPECT) of the brain revealed focal or localized low blood flow (hypoperfusion) in the following brain areas: posterior left frontal lobe, left inferior and medial temporal lobe, left basal ganglia, and right cerebellum.

The patient's motor and mental symptoms progressed over the next few years; eventually he faced great difficulty performing simple household chores and basic activities of daily living, such as feeding himself, dressing, and bathing. He eventually deteriorated to a rigid, immobile state. Finally, at the age of 70, six years after the onset of his symptoms, he died from aspiration pneumonia.

Pathology

Basal ganglia anatomy. The basal ganglia are three large subcortical gray masses that are intimately associated with the cerebral cortex, thalamus, and substantia nigra. The structures of the basal ganglia are referred to as the caudate nucleus, lentiform nuclei, amygdala, and claustrum. The basal ganglia control circuit functions to facilitate or inhibit motor activities. For clinical purposes, the basal ganglia are considered to consist of the corpus striatum, subthalamic nucleus, and substantia nigra. The corpus striatum comprises the caudate nucleus, putamen, and globus pallidus.

Pathological examination. An autopsy limited only to the brain was performed on this patient. The fresh brain weight was 1200 grams, which is low for an adult man; normal brain weight typically varies from 1300 to 1400 grams. Examination of the macroscopic features of the surface of the brain showed that the cerebral hemispheres were symmetrical. Consistent with the observed reduction in brain weight, the frontal lobes in both hemispheres of the brain showed moderate amounts of shrinkage or loss of tissue. This atrophy indicates a loss of cells and is common in neurodegenerative conditions. The temporal, parietal, and occipital lobes of the brain appeared normal. The brainstem and cerebellum were also externally unremarkable. Neither showed areas of discoloration, softening as detected by palpitation, or herniation. Herniation is the abnormal protrusion or displacement of tissue into the adjacent space. Herniations are caused by lesions such as tumors, hemorrhage, and cerebral edema, and may be immediately life-threatening. An example of a life-threatening herniation is tonsillar herniation, where the displaced cerebellar tissue compresses the underlying medulla, which contains vital centers for cardiopulmonary function. The leptomeningeal membrane, a thin, soft layer of tissue that envelops the brain and spinal cord, was thin and translucent, as in a normal brain. The blood vessels at the base of the brain were in the normal adult configuration referred to as the circle of Willis and did not show any evidence of atherosclerosis.

The cerebral hemispheres were sectioned sequentially along a cross-sectional plane and inspected visually with the naked eye. The volume of the lateral ventricles, cavities in the brain that hold cerebrospinal fluid, was abnormally large in both hemispheres. This is a compensatory change, in this case to make up for the loss of tissue, and is consistent with the observed atrophy. The gray matter of the cerebral cortex was of normal thickness, and the underlying white matter was also grossly unremarkable. The globus pallidus, a structure of the basal ganglia involved in motor control, appeared to be brownish instead of its

normally pale tan color. This discoloration suggests possible gliosis, a reactive response of the central nervous system equivalent to scarring. The remaining basal ganglia and the thalamus appeared normal. Sequential sections of the midbrain, pons, and medulla revealed that the substantia nigra, a structure in the midbrain that contains dopamine-producing nerve cells, and the locus coeruleus, a region of the brainstem with many norepinephrine-containing neurons, had lost their typical black color. This indicates significant loss of the normally pigmented neurons in these regions of the brain. Function of the substantia nigra is impaired in patients with Parkinson's disease. Sections of the cerebellar hemispheres did not reveal abnormalities upon gross examination.

The right half of the brain was frozen and placed in the brain tissue bank for special research studies, and the left half was fixed in formalin and subsequently sampled for histopathological examination. A standard set of neuroanatomical sites were sampled, including the inferior parietal lobe, calcarine cortex, hippocampus, amygdala, basal forebrain, basal ganglia, thalamus, midbrain, pons, medulla, cerebellum, upper spinal cord, and various gyri (middle frontal gyrus, superior temporal gyrus, precentral gyrus, and cingulate gyrus), which are convoluted ridges between anatomical grooves in the brain. The resulting paraffin sections were examined with hematoxylin-eosin, thioflavine S, modified Bielschowsky silver, and Gallyas silver stains. The hematoxylin-eosin stain is a routine histological stain used universally to evaluate general microanatomic changes, such as infarctions, infections, inflammation, neoplasia, and degenerative cell loss. Thioflavine S is a fluorescent dye that is helpful for identifying the amyloid protein, such as that found in senile plaques or deposits, and neurofibrillary tangles, the twisted protein structures observed in the brains of patients with Alzheimer's disease (also see "Detangling Alzheimer's Disease"). The modified Bielschowsky and Gallyas silver stains are specialized stains used chiefly by neuropathologists to identify various neuropathological features including senile plaques, neurofibrillary tangles, inclusions in glial cells (the nonneuronal cells of the nervous system), and neuropil threads, abnormal tissue between cell bodies that usually is found in the vicinity of neurofibrillary tangles.

Examination of a sample of the atrophic frontal lobe revealed a loss of neurons associated with astrogliosis of the gray matter. Astrogliosis refers to scarred regions of brain tissue composed of astrocytic glial cells (star-shaped, highly branched neuroglial cells). The frontal lobe also contained optically clear spaces in the neuropil, and this abnormality was most prominent in layer II of the cerebral cortex (Fig. 1). These frontal lobe pathologies are observed in a host of neurodegenerative diseases and indicate the loss of brain tissue. The underlying white matter showed changes secondary to the loss of neuronal cells in the gray matter, including astrogliosis and a decrease in tissue density.

In various cortical regions, including the middle frontal gyrus, precentral gyrus, inferior parietal lobe, cingulate gyrus, and entorhinal cortex, we observed numerous achromatic and enlarged neurons (Fig. 2). Achromatic neurons were detected in layers IV and V of the neocortex and in the amygdala. The relative frequency of these abnormal neurons particularly in the neocortex is highly suggestive of CBGD, which is also referred to as corticobasal ganglionic degeneration with neuronal achromasia. We used Gallyas silver stain to characterize further the microscopic pathology of this case.

The Gallyas silver stain revealed the presence of numerous argyrophilic threads, a microscopic pathology defined by silver-stained, linear, threadlike processes that are either neuronal or glial in nature. In CBGD, much of the argyrophilic thread pathology derives from oligodendroglial cell processes; oligodendroglia cells form the insulating myelin sheaths of axons in the central nervous system. Some of the argyrophilic thread pathology, however, is the result of occasional astrocytic plaques. Considered by some

neuropathologists to be specific to CBGD, astrocytic plaques arise from astrocytic glial cells and are so named because of their superficial resemblance to the senile plaques of Alzheimer's disease. Astrocytic plaques exhibit Gallyas silver-positive staining of their distal cytoplasmic processes. The abnormal filamentous inclusions in these distal processes consist largely of tau protein tangles present within the upper cortical layers (Fig. 3). When viewed at high magnification, the silver-stained processes of the astrocytic plaques showed the characteristic short side-branching, or lamp-brush morphology (Fig. 4).

The basal ganglia showed marked astrogliosis, particularly within the globus pallidus and the dorsal putamen. The Gallyas silver stain revealed the presence of numerous argyrophilic threads and so-called "coiled bodies" within the globus pallidus and white matter fiber tracts, bundles of axons that serve as the brain's information highway (Fig. 5). These argyrophilic threads and coiled bodies form a glial tangle pathology, which is a hallmark feature of a number of neurodegenerative disorders. The classic example of tangle pathology is seen in Alzheimer's disease, where the tangle pathology is neuronal and is referred to as neurofibrillary tangles. In recent years, tangle pathology has been identified in glial cell populations as well, and this observation suggests that glial cells play a yet to be defined role in neurodegenerative diseases. In this patient, occasional neurofibrillary tangles were identified within neurons of the basal ganglia and the nucleus basalis of Meynert in the forebrain. The hippocampus also contained a moderate number of argyrophilic threads.

Sections of the midbrain showed a remarkable loss of pigmented neurons within the substantia nigra (Fig. 6). Neuromelanin granules from substantia nigra neurons appeared to have spilled out into the surrounding neuropil. The midbrain also showed astrogliosis and numerous abnormally distended axonal processes known as spheroids (Fig. 7). The hematoxylin-eosin stain revealed the presence of rounded collections of neurofibrillary tangles within some of the remaining pigmented substantia nigral neurons (Fig. 8). The Gallyas silver stain clearly highlights these neuronal tangles and, in addition, reveals the presence of thread pathology in the surrounding neuropil (Fig. 9 and Fig. 10). Similar pathology was discerned in the locus coeruleus in the pons.

We arrived at the neuropathological diagnosis of CBGD because of (i) the distinctive neuroanatomic distribution of degenerative changes, (ii) the presence of distinctive histopathological features such as neurofibrillary tangles, astrocytic plaques, argyrophilic threads, and ballooned and achromatic neurons, and (iii) the absence of features characteristic of other related disorders such as Alzheimer's disease and progressive supranuclear palsy. Neuronal cell loss is ultimately responsible for the neurological symptoms of the patient.

Discussion

CBGD is a neurodegenerative disease categorized under both Parkinsonian syndromes and frontal lobe dementias. It affects men and women nearly equally, and the age of onset is usually in the sixth decade of life. This rare disorder is seen mainly by specialists and is studied by a small number of neuroscientists.

CBGD is characterized by Parkinson's-like motor symptoms and by deficits of movement and cognition, indicating focal (rather than diffuse) brain pathology. The Parkinsonism is usually asymmetric and manifests as rigidity, slowness of movements (bradykinesia) or an almost complete lack of movements (akinesia), and gait difficulties with postural instability and falls. There is a characteristic absence of resting tremor (our patient suffered postural and action tremor, but no tremor at rest). Other manifestations include asymmetric limb

dystonia, action tremor, and brief, involuntary, jerky movements of a muscle or group of muscles (myoclonus).

Asymmetric loss of cortical sensation (graphesthesia and stereognosis) and asymmetric involvement of the corticospinal tracts (which causes weakness, spasticity, and hyperreflexia) can also occur. Focal limb apraxia is very common and extremely disabling, because it interferes with even the simplest self-care tasks (video clip 1, video clip 2, video clip 3). Apraxia involving the eyelids results in the inability to open or close the eyes on command; apraxia involving the oculomotor system results in an inability to gaze upon command, while spontaneous eye movements are performed without problem.

Perhaps the most striking characteristic deficit in CBGD is the “alien limb phenomenon,” in which one of the patient's limbs behaves in a semipurposeful, autonomous way. For example, the patient's arm may rise even though the patient does not intend that movement. Indeed, the patient may not even notice the elevation of his or her arm, which to some degree is a form of neglect--the loss of attention, on behalf of the patient, to either half their body or half of the space surrounding them (video clip 1, video clip 2, video clip 3). It is usually the left half of the body or space that is neglected, and the underlying pathology is commonly in the right parietal lobe. Neglect may result in decreased movement of the left limbs, a preferential or persistent gaze to the right, and failure to recognize one's disease (nosoagnosia) or ownership of one's limbs (somatoagnosia). Affected limbs also demonstrate a compulsive tendency to explore and manipulate objects placed in front of the patient (utilization behavior), as well as exaggerated frontal lobe reflexes such as the grasp reflex.

Other higher cognitive problems include language and visual spatial deficits. The more prominent language deficits are in naming (the patient is asked to name displayed drawings) and phonological and categorical fluency. Visual spatial deficits, psychomotor slowing, and apraxia result in a remarkably low performance IQ. Attention and abstract reasoning are also impaired.

In contrast to Alzheimer's disease (the most common dementia), where memory deficit is the earliest and most prominent effect, CBGD spares the memory, but only in its early stages. As the disease progresses, memory deficits emerge.

As is the case with the patient described here, routine serum and cerebrospinal fluid laboratory tests are typically unrevealing in CBGD. The electroencephalogram appears normal early in the course of the disease but may show an asymmetric, nonspecific slowing as the disease progresses. Imaging studies such as a head Computerized Tomography (CT) scan or MRI may be normal or may reveal an asymmetric loss of brain tissue, usually from the frontal lobe or parietal lobe of the brain. Similarly, SPECT and Positron Emission Tomography (PET) scans may show blood flow or metabolic asymmetries in the frontal lobe, parietal lobe, and temporal lobe of the brain, implying that the nerve cells in these regions function abnormally. Deep structures such as the basal ganglia may also exhibit blood flow or metabolic asymmetries, which indicate abnormalities in the dopaminergic system. Regions of the brain that participate in this system include an area of the brainstem called the substantia nigra (composed mainly of cell bodies of neurons that produce dopamine) and basal ganglia (projections of dopaminergic substantia nigra neurons secrete dopamine to the basal ganglia, which express dopaminergic receptors). This dopamine deficiency likely causes the slow Parkinson-like movements observed in patients with CBGD. Early in the CBGD disease process, all of the morphological and metabolic abnormalities of the brain described above localize in one hemisphere of the brain; however, in the late stages of the disease, these abnormalities spread to involve both hemispheres. Our

patient's brain MRI was normal, but his brain SPECT was strikingly asymmetric, revealing low blood flow in the left frontal lobe and temporal lobe and in the basal ganglia.

To diagnose a patient with CBGD, a physician must first rule out other possible illnesses. These include other Parkinsonian syndromes and dementias. The most conspicuous feature of CBGD is the alien limb phenomenon and its prominent asymmetry. The absence of resting tremor, lack of response to dopaminergic agents, and rapid progressive course distinguish CBGD from Parkinson's disease. The absence of vertical supranuclear gaze palsies (that is, the inability to look up or down on command) until late in the disease differentiates CBGD from Progressive Supranuclear Palsy. The autonomic dysfunction (for example, dizziness or fainting from drops in blood pressure and urinary, gastrointestinal, or sexual dysfunction) and cerebellar abnormalities (such as an uncoordinated gait or movement) frequently observed in patients with Multiple System Atrophy are not seen in CBGD patients.

CBGD can be difficult to differentiate from Alzheimer's disease or frontotemporal dementias. One difference between CBGD and Alzheimer's disease is that Parkinsonism is generally observed late in the progression of Alzheimer's disease but manifests very early in CBGD. Indeed, Parkinson-like symptoms are often the first deficits noticed in CBGD. However, diagnosis is complicated by the fact that CBGD patients can also present with cognitive deficits. In general, the relative sparing of memory early on, the pronounced asymmetry, and prominent Parkinsonism suggest CBGD. However, the diagnosis of CBGD can be complicated, particularly if the patient has deficits suggestive of primary progressive aphasia or semantic dementia. Both are frontotemporal dementias, where problems with speech expression or comprehension manifest early in the progression of the disease, but memory is spared.

Unlike Parkinson's disease, CBGD does not respond to treatment with dopaminergic agents. Our patient deteriorated to a rigid immobile state and subsequently to death within 6 years from the onset of symptoms. This is a fairly typical pattern for CBGD patients, who usually suffer neurodegeneration for 5 to 8 years before a medical complication overtakes them.

Glossary

Arytrophilic Threads	A microscopic pathology defined by silver-stained, linear, threadlike processes that are either neuronal or glial in nature
Astrocytic Plaques	An accumulation of neuroglial cells (astrocytes) in cortical gray matter, usually occurring close to a degenerative lesion. These plaques are characteristic of corticobasal ganglionic degeneration (CBGD)
Akinesia	An absence or diminution of voluntary movement, ranging from moderate inactivity to almost complete immobility. Lesions of the cingulate gyrus can generate extreme akinesia
Autonomic	Not under conscious control; related to the actions of the autonomic nervous system. The autonomic nervous system regulates vital functions, including activity of cardiac muscle, smooth muscle (in the vascular, respiratory and digestive systems), and glands
Amygdala	Almond-shaped mass of subcortical gray matter within the tip of the temporal lobe, with olfactory, limbic, thalamic, and hypothalamic connections. The amygdala receives highly

	preprocessed sensory impressions, is responsible for initiation and integration of somatic and autonomic responses, and is associated with affective behavior function. The amygdala also is referred to as the amygdaloid body
Aphasia	The inability to produce or comprehend spoken or written language due to brain lesions and not a result of faulty innervation of speech muscles, disorders of articulation, or mental retardation. Head trauma, stroke, Alzheimer's disease, and infection can damage language areas of the brain--specifically, the left temporal lobe or nearby frontal lobe--and produce disturbances in language function
Apraxia	Loss of the ability to sequence, coordinate and execute purposeful, previously learned motor acts in the absence of sensory impairment, motor weakness, or paralysis. Stroke, brain tumors, head injury, infection, or other conditions that damage regions of the cerebral cortex in the frontal or parietal lobe can result in apraxia. The specific site of the lesion may be localized by a Computerized Tomography (CT) scan of the head or a radionuclide brain scan
Basal Ganglia	Several large clusters of neurons located within the cerebral hemisphere and upper brainstem, made up of the putamen, caudate nucleus, and globus pallidus. The cells of this region are crucial to initiating and coordinating movement. Disorders associated with diseases of the basal ganglia include chorea, athetosis, hemiballism, and Parkinson's disease
Bradykinesia	A slowness of voluntary motor activity and a reduction of autonomic movement. Bradykinesia can be a symptomatic of neurological disorders of the basal ganglia, such as Parkinson's disease, or can be a side effect of medication
Brainstem	The portion of the brain immediately superior to the spinal cord, consisting of the pons, medulla, and midbrain. Collected here are neuronal circuits that control respiration, cardiovascular function, eye movement, equilibrium, and many stereotyped movements of the body. Many of the cranial nerves arise in the brainstem, and all of the nerve fibers running between the spinal cord and higher brain centers pass through this region
Calcarine	Spur-shaped eminence situated on the medial wall of the posterior horn of the lateral ventricle and overlying the calcarine fissure. The calcarine also is referred to as the calcar avis
Cerebellum	Portion of the brain that lies just below the posterior part of the cerebrum and behind the brainstem. Integrating information from the cerebrum and peripheral parts of the body, the cerebellum plays an essential role in coordinating voluntary movement, controlling muscle tone, and maintaining balance. Symptoms of cerebellar lesions include

	motor incoordination, tremors, disturbances of gait and balance, slurred speech, and nystagmus
Cerebral Cortex	Thin mantle of gray matter that covers the cerebral hemispheres, folded into ridges and furrows (gyri and sulci). The cortex is involved in cognition, memory, consciousness, behavioral reactions, and speech. Deficits associated with lesions of the cerebral cortex depend on the specific area affected
Cingulate Gyrus	An important component of the limbic system, the cingulate gyrus is a convolution located on the medial surface of the cerebral hemisphere with connections to the hypothalamus, striatum, and association cortex. This region plays a role in behavioral modes for food intake, drive, and motivation. Tumors in this area can cause pronounced sedation, loss of initiative, and apathy
Computerized Tomography	Computerized tomography (CT) is a noninvasive method that creates a two-dimensional image of a brain or body structure from a series of plane cross-sectional x-rays made along an axis. CT can show acute hemorrhage, differentiate between gray and white matter, and reveal ventricular enlargement and other changes in the brain
Dementia	The loss of cognitive and intellectual capacities characterized by deficits in memory, attention, orientation, language, and judgment, motor and spatial skills, and altered emotional behavior and personality. Dementia is most commonly caused by conditions that impair vascular and neurological structures of the brain
Dopamine	A catecholamine neurotransmitter and hormone synthesized by the cells of the substantia nigra and essential to normal movement and balance. Parkinson's disease is linked to neurodegeneration in the substantia nigra and an associated decrease in dopamine
Dystonia	Alteration in muscle tone causing sustained abnormal postures and disruption of voluntary movement, existing as a separate disease entity or as one of a complex of symptoms in a broader condition (for example, Parkinson's disease). Changes in activity in several brain areas--the basal ganglia, thalamus, and cerebral cortex--appear to be present in dystonia
Electroencephalogram	An electroencephalogram (EEG) is a recording of electrical impulses arising from the activity of neurons within the brain and is performed by attaching electrodes to the scalp. Electroencephalography can be used in the diagnosis of epilepsy, herpes simplex encephalitis, toxic and metabolic encephalopathies, and dementia
Entorhinal Cortex	Anterior portion of the parahippocampal gyrus, located on the medial surface of the temporal lobe and involved in odor processing and memory. This area serves as a relay station between the association cortex and the hippocampus, and is

	frequently the first region of the brain to exhibit pathology in Alzheimer's disease
Forebrain	The forwardmost part of the brain, composed of the telencephalon and diencephalon. The forebrain is divided into six anatomical areas: neocortex, basal ganglia, limbic system, thalamus, olfactory bulb and tract, and lateral ventricles
Frontal Lobe	A region of the anterior cerebral hemisphere where the motor cortex, speech centers, and some association cortices are located. Damage to the frontal lobe may be marked by deficits in motor function, language use, memory, abstract and creative thinking, problem solving, concentration, judgment, and impulse control and changes in behavior and personality
Glial Cells	The nonneuronal cells of the nervous system
Gliosis	A proliferation of glial cells in response to injury or disease in the central nervous system, which leaves a glial scar composed primarily of astrocytes. Gliosis coupled with neuronal loss in certain brain regions is associated with various neurodegenerative diseases
Globus Pallidus	One of the basal ganglia, with connections to the striatum, thalamus, and mesencephalon. The globus pallidus acts as an antagonist of the striatum and facilitates motor information. Dysfunction in this area results in hypokinesia, poor timing of movements, and motor clumsiness
Graphesthesia	The ability to identify tactually letters or numbers written on the skin. A disturbance of this function (graphanesthesia) can arise from damage to the dominant parietal lobe
Grasp Reflex	An involuntary flexion of the fingers elicited by tactile or tendon stimulation of the palm or fingers of the hand. The grasp reflex persists despite requests not to grasp. This abnormal response can be a symptom of focal frontal lobe damage or, more commonly, diffuse neurological disease
Gray Matter	The portion of the brain and spinal cord that appears gray in unstained specimens. It is composed of nerve cell bodies, dendrites, unmyelinated portions of axons, and glial cells and it forms the cortex of the cerebrum and the cerebellum
Gyrus	A convolution or ridge on the surface of the cerebrum, separated from other gyri by grooves or furrows known as sulci
Hippocampus	Part of the limbic system located in the medial temporal lobe and important in memory formation. Hippocampal lesions lead to an inability to transfer contents of short-term memory suggesting upper motor tract disease
Hypoperfusion	Abnormally low blood flow through a tissue
Inferior Parietal Lobe	A subdivision of the parietal lobe on the lateral surface of the cerebral hemisphere, containing the secondary sensory cortex and involved in analysis, recognition, and assessment of tactile

	information. Although tactile perception is not undermined, lesions in this area affect recognition, judgment, and association processes
Ipsilateral	Situated on, pertaining to, or affecting the same side; usually used in reference to a cerebral lesion and its clinical manifestation
Lateral Ventricles	Cavities situated deep within the cerebral hemispheres, containing the cerebral spinal fluid. Ventricle size may increase in various neurodegenerative disorders to offset a decrease in volume due to cell loss
Leptomeningeal Membrane	The membranous covering of the brain and spinal cord, consisting of the arachnoid and the pia mater. The pia mater rests on the brain tissue and the arachnoid lies on the dura mater, the outermost membrane. Between the two layers of the leptomeningeal membrane is the subarachnoid space, which contains the cerebrospinal fluid
Locus Coeruleus	A collection of norepinephrine-rich neurons located in the lateral isthmus of the pons, with projections to the hypothalamus, cerebral cortex, amygdala, hippocampus, and thalamus. The locus coeruleus plays a role in alertness, observational skills, regulation of respiration, micturition, control of central nervous system blood vessels, and REM sleep. There is a marked decline of neurons here in Alzheimer's disease
Magnetic Resonance Imaging	An MRI is a diagnostic technique in which the body to be imaged is inserted into a magnetic field, causing the magnetic spin of the hydrogen nuclei to align with the magnet. Radio signals are used to transiently perturb this alignment. As the nuclei snap back to alignment, weak electromagnetic signals are produced. Multiple signals are integrated by computer to construct an image of the tissue. MRI provides excellent resolution for detecting and localizing brain pathologies. MRI also is referred to as Nuclear Magnetic Resonance Imaging
Medulla	The medulla, or medulla oblongata, is the lowermost part of the brainstem, lying between the spinal cord and pons. Ascending and descending nerve tracts pass through this area, and nerve centers controlling vital functions are housed in the medulla. Injury or disease affecting this region (blows to the base of the skull, bulbar poliomyelitis) can be fatal if impulse conduction is interrupted in the centers controlling cardiovascular and respiratory functions
Midbrain	Region of the brainstem lying between the pons and the cerebral hemispheres. This area is involved in eye movement and skeletal muscle control and contains auditory and visual relay nuclei. Lesions in the midbrain can cause spastic paralysis, involuntary movement, rigidity, and abnormal eye movement patterns

Multiple System Atrophy

A classification of neurodegenerative disease syndromes characterized by symptoms of parkinsonism (rigidity, bradykinesia, balance problems, mumbling speech), ataxia (lack of coordination, postural imbalance, unsteady gait, slurred speech), and autonomic dysfunction (postural hypotension, incontinence, impotence) with underlying pathologies in the basal ganglia, cerebellum, spinal cord, and peripheral sympathetic ganglia. Striatonigral degeneration, olivopontocerebellar atrophy, and Shy-Drager syndrome are classed as multiple system atrophy disorders

Myoclonus

A movement disorder characterized by brief, involuntary twitching or jerking contractions of a muscle or muscle group. Although myoclonus can occur as an isolated symptom, it often appears along with other neurologic abnormalities in nervous system disorders such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, Creutzfeld-Jakob disease, and epilepsy

Neglect

A failure to attend to or respond to stimuli on one side of the body; a disregard of or failure to perform a task on one side of the body. A parietal lobe lesion appears as neglect on the opposite side of the body

Neocortex

Six-layered portion of the cerebral cortex that formed most recently during evolution and consists of the cortex excluding the olfactory, hippocampal, and piriform regions. The wrinkled surface of the neocortex has distinct territories concerned with sensory, motor, and association functions

Neurofibrillary Tangles

Abnormal structures located in various parts of the brain composed of dense arrays of paired helical filaments. These filaments likely incorporate intermediate filaments, microtubule-associated proteins tau and MAP-2, actin, and ubiquitin. One of the hallmarks of Alzheimer's disease, the number of these tangles as seen post-mortem correlates with the degree of dementia during life

Neuropil

A dense area in the gray matter of the central nervous system, made up of interwoven dendrites and axons--the cytoplasmic processes of nerve cells--and neuroglial cells

Nosoagnosia

An inability to recognize or unawareness of one's condition or disease. This loss of bodily perception is commonly associated with parietal lobe lesions. Referred to by some neurobiologists as anosognosia

Nucleus Basalis

A small region of the basal forebrain that has wide projections to the neocortex and is rich in acetylcholine and choline acetyltransferase. In Alzheimer's disease, there is marked cellular degeneration in the region with concomitant disorientation, motor unrest, and impairment of memory and speech

Occipital Lobe	Posterior region of the cerebral hemisphere where the primary visual cortex and other visual processing and association areas are located. Damage to the occipital lobe can result in loss of object vision and light perception, impaired visual memory and pattern recognition, spatial disorientation, and visual word blindness
Parietal Lobe	Upper central area of the cerebral hemisphere, containing the sensory cortex and some association areas. The parietal lobe is involved in integration of sensory stimuli, understanding of visual-spatial relationships, awareness of body position and orientation in space, mathematical function, language recognition, and word memory. Aphasia, apraxia, difficulty calculating, astereognosis, right-left disorientation, and global confusion are identified with lesions in this region
Parkinson's Disease	A degenerative disorder of the central nervous system distinguished by bradykinesia, rigidity, postural instability and resting tremor. Additional symptoms include changes in gait, stooped posture, "mask-like" facial expression and vocal weakness. A progressive loss of neurons in the substantia nigra and the resultant depletion of dopamine underlie this condition
Pons	Brainstem region lying superior to the medulla. The pons serves as a relay station between the cerebral hemispheres and the cerebellum and is involved in regulating blood pressure, respiration, and aspects of eye movement. Alterations in eye movement are symptomatic of lesions in this region, usually due to stroke
Positron Emission Tomography	Also called a PET scan, this diagnostic technique uses positron-emitting radioactive tracers injected into the body. When the positron combines with an electron, two high-energy photons are emitted in opposite directions. When two photons are detected on opposite sides of the body simultaneously, this information is combined with other such events to create a three-dimensional image that depicts blood flow patterns, metabolic activity, neuroreceptor density, and other functional aspects of tissues and organs
Precentral Gyrus	The primary motor area of the cerebral cortex, lying between the precentral sulcus and the central sulcus. All voluntary movement is orchestrated by this area, and damage to this region alone results in flaccid paralysis on the opposite side. If premotor areas are also affected, spastic paralysis can ensue
Putamen	One of the basal ganglia, with an inhibitory role in motor movement programs and diverse connections with the globus pallidus, substantia nigra, and motor cortex. Lesions of the putamen result in athetosis--involuntary, slow, writhing movements
Progressive Supranuclear Palsy	A neurological disease characterized by bradykinesia, rigidity, balance problems, loss of voluntary eye movement, and throat

	muscle weakness. This condition is associated with neurodegenerative changes in the basal ganglia and brainstem and is unresponsive to treatment with L-DOPA, unlike Parkinson's disease
Rigidity	Stiffness or inflexibility due to an increase in muscle tone at rest and characterized by increased resistance to passive movement of a limb. In Parkinson's disease, cell degeneration in the substantia nigra results in rigidity
Single Photon Emission Computerized Tomography	A SPECT is a functional imaging method using the radioisotope of Tc-99m injected into the body. Tc-99m emits a single gamma ray photon that is detected externally. Multiple detections are used to depict the level of blood flow through various regions. Although SPECT has lower resolution than PET, it is widely used as a relatively inexpensive and straightforward first assessment of cerebral blood flow and brain function
Somatoagnosia	A denial of one's own body part and a lack of awareness of one's body functioning in space. Referred to by some neurobiologists as asomatognosia
Spasticity	An abnormal increase in muscle tone associated with hyperactive tendon reflexes that generally accompanies upper motor neuron impairment, particularly lesions in the precentral gyrus. Spasticity is a frequent complication of cerebral palsy, brain injury, multiple sclerosis, and stroke
Stereognosis	The faculty of perceiving and understanding the form and nature of objects by the sense of touch. The loss of the ability of tactile recognition (astereognosis) follows lesions of the parietal lobe, especially the posterior regions
Striatum	Also called the corpus striatum, this brain structure is a subcortical mass of gray and white matter located frontolateral to the thalamus in the cerebral hemisphere. This part of the basal ganglia, divided into the caudate nucleus and putamen, plays an important inhibitory role in processing cortical motor signals. Damage to the striatum results in symptoms of chorea and athetosis
Substantia Nigra	Deeply pigmented subcortical nucleus of the basal ganglia where cells synthesize the neurotransmitter dopamine. This region is critical to movement control, and cellular degeneration in the substantia nigra, as seen in Parkinson's disease, can result in symptoms of rigor, tremor, and akinesia
Tau Protein Tangles	An aggregation of tau (a microtubule-associated protein) into twisted threads inside neural cells. Such masses of tau-containing filaments are a feature of Alzheimer's disease, corticobasal ganglionic degeneration, and some other neurodegenerative diseases
Temporal Lobe	Lower lateral portion of the cerebral hemisphere involved in visual recognition, auditory perception, emotion, and the

processing and retrieval of memory. Right temporal lobe damage may result in loss of acuity for nonverbal auditory stimuli (e.g., music), while severe interference with recognition, memory, and language formation can signal lesions in the left temporal lobe

Thalamus

Ovoid mass of gray matter that forms part of the lateral wall of the third ventricle. It is the principle relay site for sensory signals traveling to the cerebral cortex and is involved in emotional associations of sensations and in arousal and alerting mechanisms. Thalamic lesions can cause decreased or increased sensitivity to sensory stimuli

Utilization Behavior

The propensity to grasp and use an object when presented, regardless of whether its application is relevant to the present task. Utilization behavior is associated with bilateral frontal lobe damage, especially inferior frontal lesions

White Matter

The portion of the brain and spinal cord that appears white in unstained specimens and occurs in the more central (nonsurface) regions of the central nervous system. It is composed of myelinated nerve fibers and myelin-producing oligodendrocytes

Further Reading

1. Lang, AE.; Riley, DE.; Bergeron, C. Neurodegenerative Diseases. Calne, DB., editor. Saunders; Philadelphia, PA: 1994. p. 877-894.
2. Watts, RL.; Mirra, SS.; Richardson, EP. Movement Disorders III. Marsden, CD.; Fahn, S., editors. Butterworth-Heinemann; Boston: 1994. p. 282-299.
3. Sagar, HJ. The Dementias. Growdon, JH.; Rossor, MN., editors. Butterworth-Heinemann; Boston: 1998. p. 98-101.
4. Kumar, R.; Bergeron, C.; Pollanen, MS.; Lang, AE. Parkinson's Disease and Movement Disorders. Jancovic, J.; Tolosa, E., editors. Lippincott Williams and Wilkins; Philadelphia, PA: 1998. p. 297-316.
5. For related information generated by a computer algorithm, click on **Related Info** in the left navigation bar.
6. To view related information on SAGE KE selected by the editors, click on **Editors' Choice** in the left navigation bar or scroll to the bottom of the page.

Fig. 1. Hematoxylin-eosin-stained section of middle frontal gyrus. This medium magnification view of the frontal cortex shows optically clear spaces (“spongy changes”) within the neuropil of the upper layers. This observation is consistent with the grossly observed frontal lobe atrophy. A x20 objective lens was used.

Fig. 2. Hematoxylin-eosin-stained section of cingulate gyrus. A cluster of so-called ballooned, achromatic neurons is evident in this high-magnification view taken from the cingulate gyrus. The large central neuron is abnormally swollen, and its cytoplasm is pale. The optically clear halos present around many of the neurons and blood vessels are artifacts due to tissue processing. A x40 objective lens was used.

Fig. 3.

Gallyas silver-stained section of middle frontal gyrus. Three astrocytic plaques are evident in this silver-stained section of the frontal cortex. The plaques consist of a collection of darkly stained processes confined to a zone that corresponds roughly to the territory occupied by an astrocyte. A 40x objective lens was used.

Fig. 4.

Gallyas silver-stained section of insular cortex. When viewed at very high magnification, the silver-stained processes of an astrocytic plaque show characteristic short side branches. This is a useful diagnostic feature, because it distinguishes the astrocytic plaque from morphologically similar tufted astrocytes (seen in progressive supranuclear palsy) and neuritic senile plaques (seen in Alzheimer's disease). A 60x objective lens was used.

Fig. 5.

Gallyas silver-stained section of the putamen. The black, wavy processes seen in this high-magnification micrograph are located within a white matter tract (in this case, a pencil fiber of Wilson) and represent argyrophilic threads. The thicker processes seen partially wrapped around cell nuclei are referred to as “coiled bodies.” A 60x objective lens was used.

Fig. 6. Hematoxylin-eosin-stained section of the substantia nigra. This medium magnification view of the substantia nigra shows a severe loss of pigmented neurons, which normally would fill this field. Only two surviving pigmented neurons are seen at the top and bottom of this figure. Aggregates of brown neuromelanin granules are present. The field shows a gliotic background, as evidenced by the increased number of small glial cells. Pink-stained spheroids are present at the right and left periphery of the field. A 20x objective lens was used.

Fig. 7. Hematoxylin-eosin-stained section of the substantia nigra. This is a high magnification view of a field similar to that seen in Fig. 6. Reactive astrocytes with irregularly shaped nuclei and thin pink cytoplasmic processes are evident. Clusters of neuromelanin granules that originated in pigmented nigral neurons have been consumed by phagocytic cells. A 60x objective lens was used.

Fig. 8. Hematoxylin-eosin-stained section of the substantia nigra. A rounded or "globose" neurofibrillary tangle is evident within a pigmented nigral neuron. A 60x objective lens was used.

Fig. 9.

Gallyas silver-stained section of substantia nigra. Neurofibrillary tangles are present within nigral neurons and are darkly stained with silver. The tangle is distinctly spherical and is referred to as globose in shape. A few argyrophilic threads are evident in the background. A 60x objective lens was used.

Fig. 10.

Gallyas silver-stained section of substantia nigra. Neurofibrillary tangles are present within nigral neurons and are darkly stained with silver. The tangles are more irregular in shape than those seen in Fig. 9. A few argyrophilic threads are evident in the background. A 60x objective lens was used.