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Imaging of the Aging Brain

Part I. Normal Findings[1]

A thorough knowledge of the normal changes that occur in the brain with age is critical before abnormal findings are analyzed. Magnetic resonance (MR) imaging improves the ability to distinguish normal and abnormal findings in the brain. The major changes that may occur in elderly individuals without neurologic deficits include enlargement of the ventricles, cortical sulci, and vermian subarachnoid spaces; multifocal areas of hyperintensity in the white matter and basal ganglia; a progressive prominence of hypointensity on T2-weighted images of the putamen, almost equal to that of the globus pallidus; an increase in the oxygen extraction ratio with normal or mildly decreased neuron metabolism; arteriosclerosis in large and small arteries and amyloid angiopathy in leptomeningeal cortical vessels; and decreased dopamine receptor binding in the corpus striatum. Since approximately half of the elderly population exhibits only negligible brain alterations, MR imaging may facilitate the distinction between usual (no neurologic dysfunction) and successful (no brain or vascular changes) aging.

Index terms: Aging • Arteriosclerosis, 17.721 • Brain, atrophy, 10.83 • Brain, MR studies, 10.1214 • Iron • State-of-Art reviews

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ADVANCES in sophisticated and sensitive imaging techniques and the expanding population of the elderly necessitate an understanding of normal and pathologic neurologic findings in the elderly. At this time, approximately 21% of the population in the United States is over 55 years old. By 2020, it is estimated that this segment of the population will exceed 30% (1). Elderly people harbor a far greater percentage of neurologic disease per capita than young people. The diagnosis of disease in elderly patients is often complicated because alterations in brain structure and function may occur normally. There is a surprising lack of clinical, radiologic, and pathologic information regarding the normal aging process in humans. Magnetic resonance (MR) imaging should result in a dramatic expansion of our understanding of aging due to its in vivo neuropathologic imaging capabilities and the ability to perform repeat studies over time.

There are various pitfalls that must be recognized when analyzing elderly people who are healthy or diseased (2). Studies may accentuate results from very healthy individuals because those with underlying illnesses will have died (survivor effect). Population heterogeneity is also greater in the elderly, due partially to an increased incidence of other nonneurologic disease. Socioeconomic status, environment, education, nutrition, and exercise may affect the manner in which an individual ages. Rowe and Kahn (3) suggest that normal human aging may be subdivided into *usual aging* (no overt neurologic symptoms) and *successful aging* (minimal physiologic loss even when compared with younger individuals). In usual aging, individuals may exhibit abnormalities on glucose tolerance tests (abnormal carbohydrate metabolism), arteriosclerosis (after 50 years of age, only 50% of brains are free of atherosclerotic arterial changes), systolic hypertension, declining renal and immune function, decreased sensory input (visual and hearing loss), declining crystallized (verbal) and fluid (inductive reasoning and spatial orientation) intelligence, and progressive slowness in movement (4). These underlying alterations may increase the occurrence of various central nervous system (CNS) disorders (e.g., cerebral infarction) in the elderly. It is an enticing theory that successful aging may be enhanced by modification of diet, exercise, and social and intellectual stimulation—all of which may prevent or delay the onset of arteriosclerosis, hypertension, carbohydrate intolerance, or cognitive dysfunction (3).

NORMAL AGING

The analysis of MR images of normal brain requires a thorough understanding of the normal and pathologic alterations that occur in the elderly. Most studies of normal aging describe findings from pathologic or imaging studies from individuals who do not have overt neurologic dysfunction. They generally do not include a comprehensive analysis of vascular risk factors (e.g., hypertension, diabetes mellitus, myocardial infarction, arrhythmias), neuropsychologic tests, and extrapyramidal function. The possibility thus exists—and requires further testing—that pathologic differences may be manifest in those individuals with usual aging as compared with those with successful aging.

Gray Matter and CSF Spaces

A mild-to-moderate progressive enlargement of the ventricles, cortical sulci, and pericerebellar subarachnoid spaces may occur with aging (2, 5–9). In an autopsy study of 28 previ-

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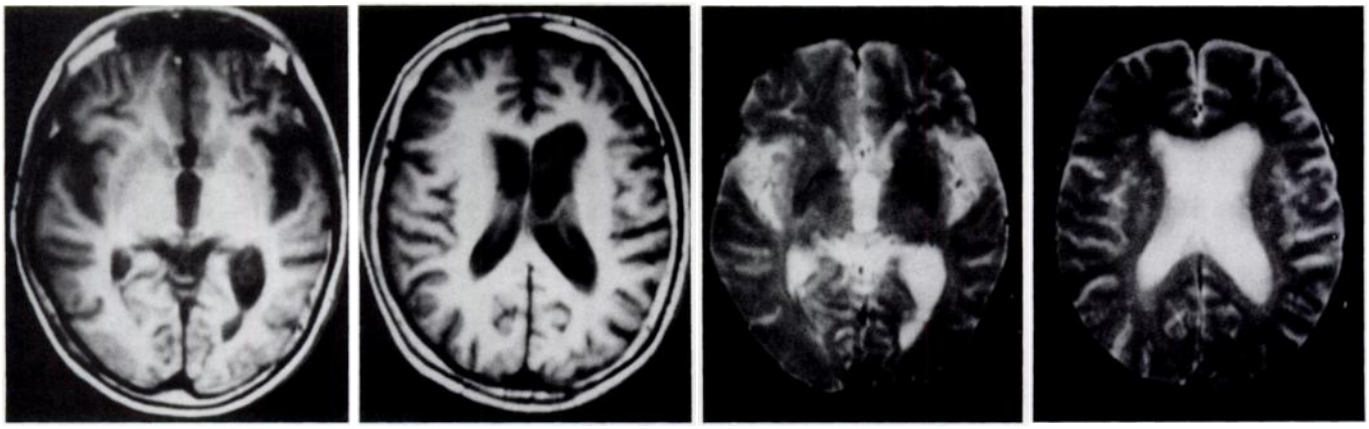
See also the article by Drayer (pp. 797–806) in this issue.



a. b. c. d.

Figure 1. MR images of the brain of an asymptomatic, 86-year-old person. **(a, b)** T1-weighted MR images (repetition time [TR] 500 msec, echo time [TE] 20 msec, spin echo [SE 500/20]). Effects of age include widening of the third ventricle, left lateral ventricle (vs. right), left circular sulcus (vs. right), vermian subarachnoid spaces, and anterior interhemispheric fissure. **(c, d)** T2-weighted MR images (SE 2,000/100). In addition to the above findings, subtle white matter hyperintensities are noted, suggesting arteriolar/hypoperfusion changes due to age.

ously hospitalized patients (age range, 65–92 years; mean, 75 years) without neurologic symptoms, Tomlinson et al. (10) found that 13 patients did not have cortical atrophy and 17 had normal or only mild ventricular enlargement. Cortical atrophy was most prominent in the frontal and parietal parasagittal regions in the study, and moderate ventricular enlargement was associated with infarction of the basal ganglia in six of 11 patients. The brain weights in these 28 patients varied from 1,170 g to 1,430 g (mean, 1,320 g) in men and from 1,080 g to 1,390 g (mean, 1,213 g) in women. Senile neuritic plaques (dense amyloid core surrounded by neurites, astrocytic processes, amyloid, adipose tissue, and microglia containing iron), neurofibrillary degeneration (tangles of twisted tubules and helically wound fibrils), and granulovacuolar degeneration (vacuoles in cytoplasm of hippocampal pyramidal cells) were found in significant numbers (though far less than that in Alzheimer disease) in five patients.

Various authors have reported a selective loss of neurons with age (10–18). These changes were most prominent in the superior frontal and temporal gyri, precentral gyrus, corpus striatum, hippocampus, thalamus, amygdaloid body, inferior olive, and Purkinje cells and dentate nucleus of the cerebellum. There is a progressive intraneuronal accumulation of lipofuscin, melanin, and ceroid with age—similar findings were noted in healthy individuals and those with dementia (2, 13, 19–21). Lipofuscin is most prominent in the cranial and spinal motor nuclei, red nucleus, thalamus, globus pallidus, inferior olive, and dentate nucleus of the cerebellum. A decrease in dendritic branching and possible loss of neuronal synapses in the temporal, frontal, and limbic regions of the cerebrum also characterize normal aging (22). Widening of the cortical sulci may be related to cortical and subcortical gray matter versus white matter loss. Miller et al. (23) reported that the ratio of gray matter to white matter was 1.28 at age 20, 1.13 at age 50, and 1.55 at age 100, which suggests that white matter atrophy exceeds that of gray matter with age.

Numerous and extensive studies have been performed with computed tomography (CT) to analyze the limits of normalcy in healthy, elderly individuals (8, 24–34). The methods that were used included visual ratings by experienced observers, measurements of a variety of ventricle-to-brain indices (e.g., Evans, frontal horn, bicaudate, cella media, third ventricle-Sylvian fissure), and volumetric pixel counting. Most CT studies indicate that a progressive enlargement of the ventricles and cortical sulci ("physiologic atrophy") is characteristic of the normal aging brain (Fig. 1). An analysis of 500 healthy patients by Nagata et al. (32), who used pixel counting and linear ventricle-to-brain measurements, confirms that the CSF-to-brain ratio (CSF volume/cranial volume) remains constant from 10 to 50 years of age, followed by a highly variable, progressive dilation of the CSF spaces with increasing age. This study corroborates the findings of Yamaura et al. (35) (228 healthy adults) and Schwartz et al. (36) (30 healthy men) who suggest physiologic atrophy (CSF-space enlargement) begins in the 5th decade. Other large CT studies that describe the CSF spaces in healthy adults conclude that dilatation may not become apparent until the 6th or 7th decade. Jacoby et al. (31), who studied 50 healthy subjects (ten men, 40 women) aged 62–88 years (mean, 73 years), found no significant alterations in neuropsychologic tests for memory and orientation or in Evans ratio (maximum width of frontal horns of lateral ventricles to the maximum diameter of the internal skull) but defined definite progressive alterations in the CSF spaces as determined with a visual rating scale and planimetry.

The CT studies correlate closely with pathologic reviews of CSF-space expansion with normal aging. Hubbard and Anderson (37) described individuals with ventricular enlargement after 60 years of age. Morel and Wildi (38) studied brains that were formalin fixed and found a progressive increase in ventricular size from 55 to 99 years of age. Tomlinson et al. (10) found enlargement of the cortical sulci or ventricles in approximately half of the autopsy studies of nondemented people over 65 years old. Both CT and postmortem studies highlight the heterogeneity of CSF-space size in the elderly population, with approximately 30%–50% within the range of normal for young adults (8). Although most authors have focused on the cortical sulci, the pericerebellar subarachnoid (especially superior vermian) spaces also dilate in the elderly (7, 26, 39).

Even though enlargement of the CSF spaces during aging is generally diffuse, there are specific locations in which dilatation and asymmetries are

best delineated (8, 40) (Fig. 1, Table 1). There is regression of the median nuclei of the thalamus after 50 years of age (14), which explains the early demonstration of third ventricular enlargement (8, 25, 41). There is generally only mild enlargement of the temporal horns of the lateral ventricles with aging (10, 42). The left lateral ventricle is normally larger than the right (8). Widening of the superficial cortical sulci is often seen first in the frontal and parietal parasagittal regions (8, 10, 43). The anterior interhemispheric fissure and the cerebellar vermis also progressively widen with age (8, 18, 24, 26, 33). Enlargement of the cortical sulci in the central, precentral, postcentral, and superior frontal gyri occurs later and may be related to loss of white matter (8, 23, 44, 45). Because of involutionary changes in the temporal lobes with aging, the anterior end of the circular sulcus (Sylvian fissure) may become prominent in the 5th decade (8). At all times of life, the left circular sulcus is larger than the right; this finding should not be mistaken for adjacent ischemic changes (40).

Table 1 Summary of MR Imaging: Normal and Pathologic Aging

Disorders	MR Findings												
	Atrophy in CSF Spaces		Subcortical T2 Hyperintensities			Basal Ganglia Hypointensity*		Arterial Narrowing		Amyloid Angiopathy	Brain Metabolism		
	Ventricles	Sulci	White Matter	Basal Ganglia	Pons/ Thalamus	GP/RN/SN/DN	Putamen	Atheroma Infarction	Occlusion		↓rCBF ↓$CMRO_2$ ↓CMRGlu		↓Dopamine
Normal													
Adults ≤50 yr	0	0	1	0	0	3	1	0	0	0	0		0
Successful aging	1	1	1	1	0	3	1	1	0	1	0		1
Usual aging	2	2	2	2	1	3	2	2	1	2	1		2
Dementia													
Alzheimer	2	4	3	2	1	3	2†	1	1	4	2		2
Pick‡	3	4	3	2	1	3	2	1	1	NK	2		2
Binswanger	4	3	4	4	3	3	2-3	3	3	NK	2		2
NPH§	4	2	2	1	1	3	2	1	1	NK	2		2
Wernicke	3	3	2	2	3	3	2	1	1	NK	2		2
Bradykinesia/ rigidity													
Parkinson	2	4	3	2	1	4	3	1	1	3	2		3
Multiple system abnormalities	2	4	3	2	1	4	4+	1	1	NK	2		4+
Progressive supranuclear palsy	2	4	3	2	2	4	3	1	1	NK	2		4+
Hypothyroidism	2	3	1	1	0	4+	4+	1	1	NK	2		2
Focal deficit													
Infarction	2	3	3	3	3	3	2-3	4	4+	2	4		2
Hematoma‖	2	2	4	4	4	3	2	2	2	4#	3		2

Note.—0 = not present, 1 = equivocal, 2 = mildly prominent, 3 = moderately prominent, 4 = extensive; NK = not known, rCBF = regional cerebral blood flow, $CMRO_2$ = cerebral metabolic rate of oxygen, CMRGlu = cerebral metabolic rate of glucose.

* GP = globus pallidus, RN = red nucleus, SN = substantia nigra, DN = dentate nucleus.

† Abnormal gyral hypointensity in half, particularly in parietal cortex.

‡ Predominantly frontotemporal atrophic changes.

§ NPH = normal pressure hydrocephalus.

‖ Hyperintensity in subacute hematoma (hypointensity if acute or chronic).

Lobar hematoma.

Cerebral White Matter

A variety of neuropathologic, CT, and MR imaging studies suggest that 30%–80% of elderly individuals without neurologic deficits have focal abnormalities in the cerebral white matter (10, 46–55). These alterations are usually demonstrated by MR imaging as small, focal (sometimes confluent) areas of increased signal intensity (SI) on T2-weighted images that are often found scattered throughout the deep cerebral white matter (especially in the frontal and parietooccipital areas), basal ganglia (notably globus pallidus and putamen), and capping the lateral ventricular margins. These signal hyperintensities, particularly when small and patchy, have been facetiously called "unidentified bright objects" or white matter/basal ganglia, that is, "subcortical hyperintensities" (Fig. 2). Because of the high prevalence of this MR finding in the elderly (47, 56–59) and an ongoing discussion on the nature of vascular dementia (52, 56, 60, 61), a certain amount of confusion exists concerning the pathologic substrate of subcortical hyperintensities. The issue of white matter and basal ganglia changes in normal aging is further confounded by limitations of normal postmortem studies,

such as inclusion of patients with chronic systemic, cardiac, psychiatric, and neurologic diseases; incomplete premorbid information on cognitive function and vascular risk factors; and absence of comprehensive analyses of incidental alterations in the deep white matter or basal ganglia.

Subcortical hyperintensities are distributed in long, noncollateralizing, perforating vessels, such as medullary and lenticulostriate arteries. The common denominator of all such lesions is the loss of a focal area of brain parenchyma with increased tissue water, resulting in an increased SI on the MR image. After studying 240 consecutive MR imaging studies and concluding that patchy, subcortical foci of increased SI correlated best with ischemic cerebrovascular disease, hypertension, and aging, Awad et al. (57, 58) compared MR images with neuropathologic studies on eight postmortem brains. They found that the hyperintensities on MR images involved the periventricular white matter, optic radiations, basal ganglia, and centrum semiovale in a decreasing order of frequency and were associated with a spectrum of histologic changes. The most common histologic change was arteriolar ectasia with enlargement of surrounding perivascular spaces that reflected atrophy of the brain tissue around blood vessels. This change resulted in an "extensive network of tunnels filled with extracellular water." This condition was named *état criblé* (sievelike) by Durand-Fardel (62) in 1843; its association with hypertension and aging and confusion with, at times, coexisting multiple subcortical infarctions (état lacunaire) are of greatest importance (63–65). Additional associated findings that were less commonly found by Awad et al. (57, 58) and had the same hyperintense appearance were myelin pallor and lacunar infarction with associated arteriosclerosis of perforating arterioles. Degeneration of myelinated axons and gliosis was limited to subependymal (immediate periventricular) areas and surrounding areas of a small infarction.

Kirkpatrick and Hayman (59) performed a postmortem neuropathologic analysis of brains from 15 healthy (52–72 years old) subjects who had a high frequency (ten of 15) of systemic cancer. The researchers found small white matter lesions in 12 of the 15 autopsy examinations. The most common findings (eight subjects) were atrophy of axons and myelin with associated gliosis; tortuous, sclerotic, and thickened vessels; and increased extracellular water (i.e., atrophic perivascular demyelination). They found vascular malformations in four subjects (three telangiectasia, one capillary angioma). Awad et al. (57) also found, at autopsy, a small telangiectasia in two of eight brains and a diverticulum of the lateral ventricle that extended into the adjacent white matter in three brains. These researchers (57–59) postulate that hypertension may predispose to the atrophic perivascular demyelination—suggesting that arteriolar thickening and sclerosis result in a loss of the normal nutritive function of the arteriole (66); chronic, low-grade vascular insufficiency; and atrophic perivascular demyelination or myelin pallor rather than frank infarction.

It is difficult to analyze the significance of subcortical hyperintensities without an understanding of the theories concerning white matter abnormalities and their proposed relationships to multiinfarct and Binswanger dementia (Fig. 3). A review of this literature makes one increasingly aware that limitations in analysis of unidentified bright objects on MR images are a direct correlate of neuropathologic uncertainties (10, 52, 55, 67, 68). Vascular dementia secondary to multiple subcortical infarctions and diffuse myelin pallor, sparing of the subcortical arcuate fibers, and clinical hypertension was initially reported by Binswanger in 1894 (69). Multiple articles have provided refinements, theoretical considerations, and alterations in nomenclature (70–73) (e.g., subcortical arteriosclerotic encephalopathy). Hachinski et al. (74) popularized the term "multiinfarct dementia" for patients with large areas of cortical and subcortical infarction, decreased cerebral blood flow, and a clinical picture that differed from that of Alzheimer disease (75).

One theory suggests that the brain substance in the distribution of the most distal branches of the brain arteries—the cerebral white matter and basal ganglia—is most susceptible to a reduction in blood flow; that is, the deep centrum ovale is a watershed zone (71, 76). Studies in baboons and dogs have shown that a progressive reduction in blood pressure can result in absent blood flow in the centrum ovale (with infarction) while the cerebral cortex is still being perfused (77, 78). The subcortical arcuate fibers are spared because the blood supply for this region is from the cortical (or from the cortical Duvernoy type-5 and medullary arterioles) rather than exclusively from the deep medullary supply (79–82). Hypoperfusion in humans—whether due to carotid artery occlusion, hypoxia, or hypotension—often results in cerebral infarction that involves the deep white matter in a distribution similar to Binswanger dementia with sparing of the cortical surface due to a leptomeningeal collateral arterial supply. Ginsburg et al. (83, 85) further correlated the extent of the white matter abnormality with the degree of systolic hypotension and metabolic acidosis rather than with the amount of hypoxia.

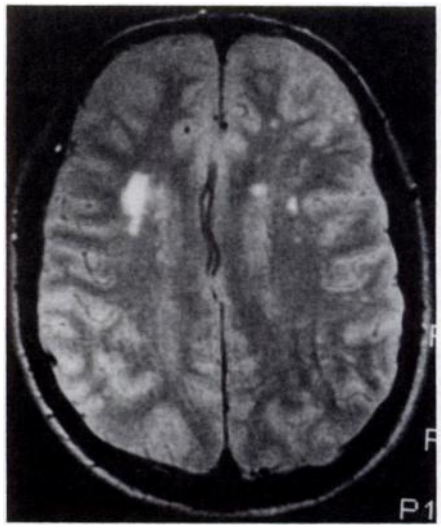


Figure 2. MR image shows subcortical hyperintensities. Intermediate-weighted MR images (SE 2,500/40) are often optimal for delineating white matter hyperintensities, particularly when they are periventricular as seen in this MR image of the brain of an asymptomatic 71-year-old patient with hypertension. These lesions may represent état criblé, atrophic perivascular demyelination, gliosis, myelin pallor, demyelination, or infarction.

Another theory suggests that the long, perforating medullary arteries that supply the centrum semiovale are particularly sensitive to the effects of hypertension (76). Arteriolar narrowing, loss of vasoregulation, and chronic ischemia may result in atrophic perivascular demyelination, myelin pallor, gliosis, and/or infarction (56, 71, 76). Feigin et al. (85, 86) postulated that cerebral edema played a key role in white matter disease leading to secondary myelin pallor and thick-walled, hyalinized arterioles. Congestion and stasis within the deep venous system secondary to obstruction or right-sided heart failure may also cause damage to the deep white matter. Van den Bergh and vander Eecken (87) found that

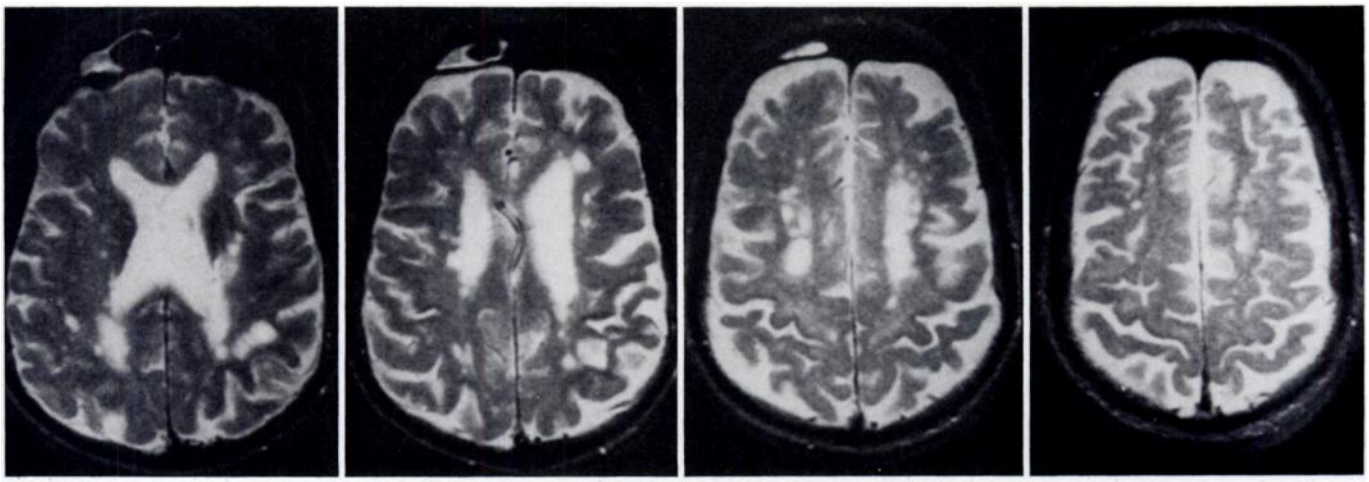
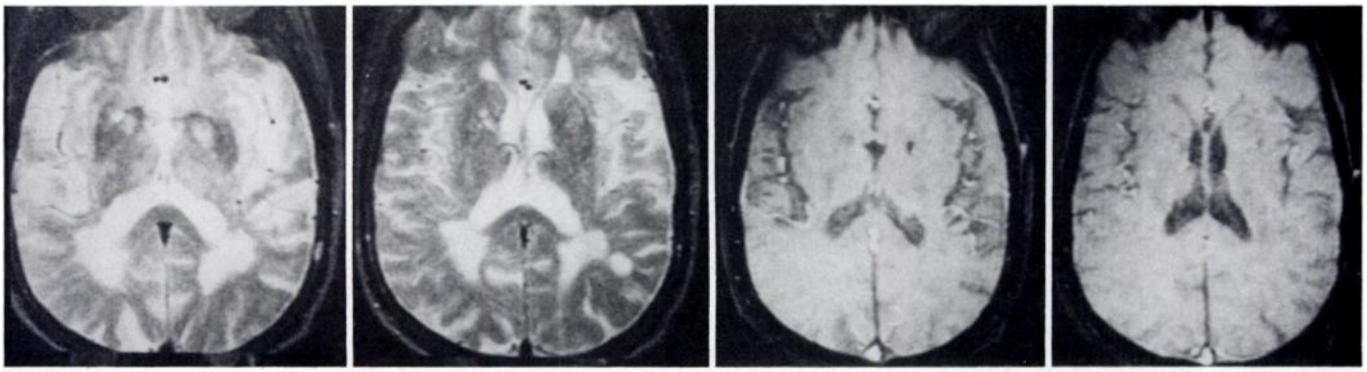


Figure 3. MR images show microangiopathic leukoencephalopathy. T2-weighted MR images (SE 2,500/80) demonstrate multiple, at times confluent, areas of increased SI throughout the deep white matter with sparing of the arcuate fibers in the brain of a 73-year-old patient with dementia. Although the marked prominence of the cortical sulci may be related to white matter destruction, the dementia and atrophy in this case could also be due to a primary degenerative dementia (Alzheimer disease) with arteriolar/hypoperfusion abnormalities that was suspected clinically. This case highlights the complex problems of determining a precise cause for a signal hyperintensity (i.e., infarction vs. myelin pallor vs. gliosis vs. atrophic perivascular demyelination) and distinguishing a vascular versus a degenerative cause for dementia.



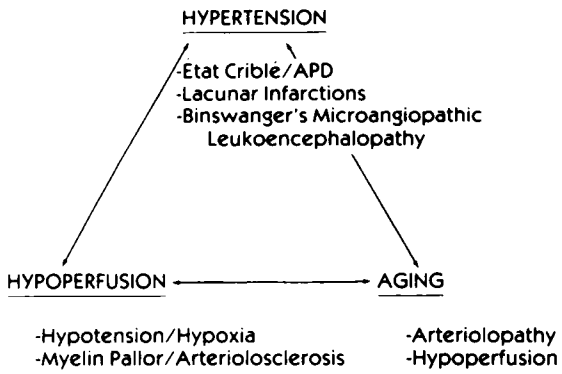
a. b. c. d.

Figure 4. Microangiopathic leukoencephalopathy with dementia and hemorrhage. **(a, b)** T2-weighted MR images (SE 2,500/80). Extensive, confluent hyperintensities in the cerebral white matter (particularly adjacent to the occipital horns), internal capsules, basal ganglia, and thalamus likely represent infarction secondary to hypertensive arteriolar disease; however, myelin pallor, atrophic perivascular demyelination, and/or état criblé may also be present. **(c, d)** Gradient-echo T1-weighted MR images (SE 300/12, flip angle 60°). Small hypointensity in the left genu of the internal capsule-globus pallidus region is consistent with a slit hemorrhage residual of hypertensive hematoma, confirming hypertensive vascular (arteriolar) disease.

the cerebral cortex and underlying arcuate fibers drained via the superficial venous system, while the cerebral white matter was drained by the deep venous system.

Although many of the reported MR and neuropathologic studies (46, 47, 52, 57, 59) suggest that hypertension is an important accompanying feature with subcortical hyperintensities (Fig. 4), many healthy individuals with white matter alterations do not have hypertension. In a recent study, Fazekas et al. (48) found subcortical hyperintensities in the majority of patients who were either healthy (control subjects) or suffering from Alzheimer disease but found no relationship of this finding to hypertension or other vascular risk factors. They did, however, describe a correlation between multiinfarct dementia with prominent hyperintensities in the white matter and basal ganglia and a history of hypertension. Autopsy studies of 97 patients (20 with Alzheimer disease, 28 with senile dementia Alzheimer-type, 23 with multiinfarct dementia, 16 nondemented, normotensive patients 70–100 years old, and ten nondemented, normotensive patients 49–69 years old) by Brun and Englund (56) found definite white matter abnormalities in 11 of 20 (four moderate or severe) patients with presenile Alzheimer disease, 19 of 28 (six moderate or severe) with senile dementia of the Alzheimer-type, 23 of 23 with multiinfarct dementia, zero of ten nondemented, normotensive patients aged 49–69 years, and two of 16 nondemented, normotensive patients aged 70–100 years. Although 32 of 48 patients with Alzheimer dementia or disease had a history of cardiovascular disease and/or hypotension, only one of 48 was hypertensive and none had nephrosclerosis. This suggests that brain hypoperfusion and hypotension were more important than hypertension as precursors to white matter damage and that white matter alterations were common in Alzheimer disease at all ages (56).

The white matter changes described by Brun and Englund (56) consisted of myelin pallor (rather than frank infarction); fibrohyaline arteriosclerosis with no staining with Congo red; partial loss of axons, myelin sheaths, and oligodendroglia; and mild reactive astrocytosis—these



5.

	↑T2 Focal	↑T2 Confluent	↓T2 Focal	↑T1 Focal	LOCALIZATION WM	BG	TH/Pons	CSF Spaces
Hypertension								
Etat Criblé/APD	+	–	–	–	+	+	–	–
Lacune	+ + +	–	±	+	+ +	+ +	+ +	+
BML	+ +	+ + +	±	+	+ + +	+ +	+ +	+ + +
Hypoperfusion (Hypotension/ Hypoxia)	+ +	+ +	–	±	+ +	+	–	+ +
Usual Aging	+	–	–	±	+	+	–	+

APD = Atrophic Perivascular Demyelination
BML = Binswanger's Microangiopathic Leukoencephalopathy
WM = White Matter; BG = Basal Ganglia; TH = Thalamus

6.

Figures 5, 6. **(5)** Diagram shows hypoperfusion/arteriolopathy spectrum. **(6)** Diagram shows the MR imaging characteristics of arteriolar disease.

changes are similar to those seen with Binswanger disease, except that the myelin loss and asymmetric scattered infarctions in the white matter and basal ganglia were less common. The cerebral white matter changes were predominantly symmetric, extended from the periventricular region outward, spared the subcortical arcuate fibers, and were most prominent in the frontal and parietal lobes. In a series of 40 patients with Alzheimer disease who underwent MR imaging, 21 had subcortical hyperintensities of variable extent; these 21 had a far higher frequency of hypertension—extensive information concerning hypotensive episodes was not obtained (personal observations).

It is increasingly apparent that various theories regarding the origin of white matter and basal ganglia hyperintensities may all be at least partially true. An attempt has been made to synthesize these MR imaging and pathologic observations into a single, unifying hypothesis (Figs. 5, 6). A common denominator of subcortical hyperintensities, particularly in the asymptomatic elderly population, is brain hypoperfusion and arteriolar disease. The hypoperfusion occurs in the distribution of the long, noncollateralizing, perforating vessels that supply the periventricular and deep cerebral white matter (sparing the arcuate fibers) and basal ganglia. The most common causes of hypoperfusion are episodes of hypotension, hypoxia secondary to cardiac or carotid artery disease, hypertension, and/or aging. The entire centrum semiovale is a watershed zone supplied by the most distal intraparenchymal penetrating arterioles. Finally, other chronic processes that involve the white matter (including multiple sclerosis, acute disseminated encephalomyelitis, traumatic injury) and diseases such as systemic lupus erythematosis may mimic the leukoencephalopathic alterations seen with the hypoperfusion arteriolar diseases. The absence of white matter changes in an elderly individual may be an important hallmark of successful aging.

Basal Ganglia

Nonheme brain iron is normally found within oligodendroglia and astrocytes with smaller amounts in neurons and myelinated axons. Approximately half the cellular iron is in the mitochondria and microsomes, 10%–15% in the nuclei, and 40% in a soluble fraction presumably representing ferritin (88). Histochemical, histopathologic, and MR imaging studies have determined that maximum iron concentration in normal adults is found in the globus pallidus, red nucleus, pars reticulata of the substantia nigra, and dentate nucleus of the cerebellum (88–94) (Figs. 7, 8). Intracellular brain iron is probably stored in two metabolically active compartments—ferritin and free iron (95–98). Iron plays an important role in oxidative phosphorylation, dopamine synthesis (99, 100) and turnover (cofactor in monoamine oxidase reaction), and hydroxyl free radical formation (101). Iron is present in all animal systems with the localization quite similar in rats, baboons, and humans (102, 103). The mechanism and site of transport across the blood-brain barrier (BBB) is poorly understood because the greatest transferrin receptor density correlates poorly with the highest iron distribution (104). The concentration of brain iron is independent of body stores, even in hemochromatosis. Iron is best seen on T2-weighted and gradient-echo MR images as a hypointensity due to field heterogeneity and magnetic susceptibility (T2) effects (90, 105, 106) (Fig. 9).

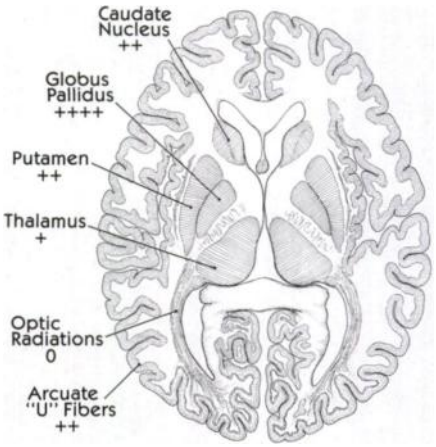


Figure 7. Diagram shows the localization of iron in normal brain. ++++ = >20 mg Fe/100 g, +++ = 15–20 mg Fe/100 g, ++ = 10–15 mg Fe/100 g, + = 5–10 mg Fe/100 g, 0 = 0–5 mg Fe/100 g.

There is a preferential progressive increase of iron in the corpus striatum (caudate and putamen) with aging so that the iron concentration normally may be equal to that in the globus pallidus by the 8th decade (88, 90). This increased accumulation of iron with aging may be related to a combination of factors including decreased oxidative phosphorylation, declining oligodendroglial function, decreased dopamine production and turnover, abnormal BBB permeability, or accelerated hydroxyl free radical formation with lipid membrane peroxidation. Aging is not only associated with increased iron in the brain tissue but also with an increased concentration of iron in the walls of blood vessels (vascular ferrugination). In addition to the normal increases of iron in the corpus striatum of the elderly, there is smudging and an increased indistinctness of the iron in the dentate nucleus (90), and a mild increase of iron in the oc-

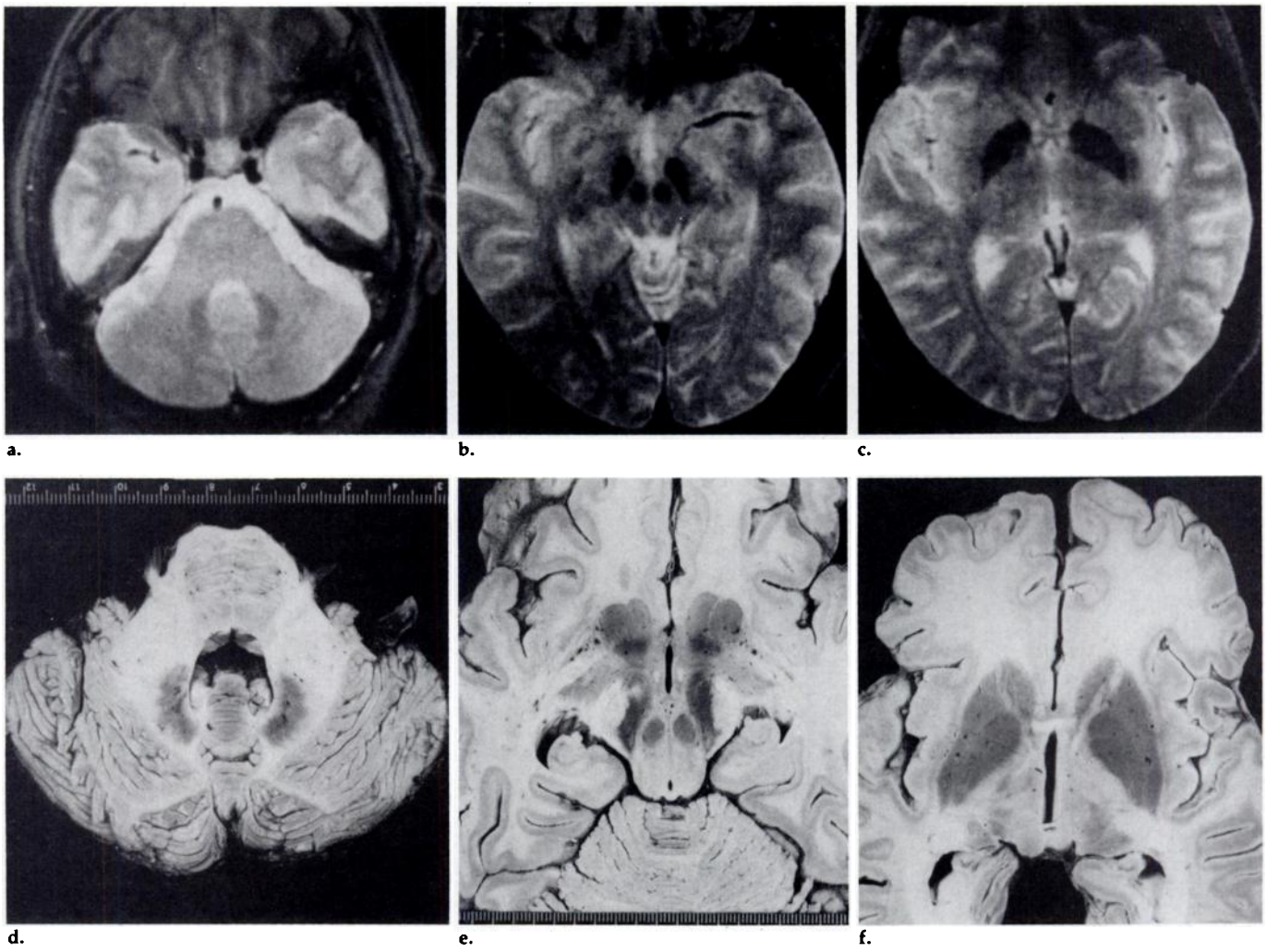


Figure 8. Normal brain iron in asymptomatic, middle-aged adults. **(a-c)** T2-weighted MR images (SE 2,500/80). There is normally a decreased SI in the dentate nucleus **(a)**, red nucleus and pars reticulata of substantia nigra **(b)**, and globus pallidus **(c)**, correlating with sites of maximum iron distribution. **(d-f)** Anatomic sections stained for hemosiderin with Perls reaction confirm the iron localization in the dentate nucleus **(d)**, red nucleus and pars reticulata of substantia nigra **(e)**, and globus pallidus **(f)**. A higher iron concentration than that in the thalamus or white matter is apparent in the caudate nucleus and putamen.

cipital and motor cortices that roughly parallels lipofuscin in neurons and neuroglia (107). MR studies that show decreased signal intensity on T2-weighted images and Perls reaction, which shows increased blueness, for demonstration of ferric iron in postmortem brains of elderly patients (90) correlate fully with prior histochemical and histopathologic findings of a progressive increase of iron concentration in the corpus striatum with aging in individuals who do not have neurologic deficits (88) (Fig. 10). An abnormal accumulation of iron has been described in parkinsonism (91, 108–110) and Alzheimer disease (107, 111, 112).

The formation of hydroxyl free radicals requires iron ions and oxygen free radicals and results in membrane lipid peroxidation, aldehyde production, and accumulation of lipofuscin in brain neurons (21, 101, 113). Neurons in the thalamus, lateral geniculate body, and dentate nucleus of the cerebellum are particularly rich in lipofuscin. Oxidative mechanisms are important in the formation of lipofuscin, which accumulates in postmitotic cells, such as brain neurons. The aging brain is quite susceptible to oxidative damage (114–117) because it contains a high concentration of unsaturated lipids, it uses over 20% of the body oxygen, and it has low concentrations of antioxidant enzymes (e.g., superoxide dismutase catalase, glutathione peroxidase) and vitamin E. Iron in the brain helps regulate the dopamine receptor, dopamine synthesis, and monoamine oxidase activity (90, 99, 100); nigrostriatal dopaminergic function is the only neurotransmitter system that declines with normal aging (118–120). Floyd et al. (117) described a direct correlation of total iron content in the brain (ferritin plus mobile iron) and brain peroxidation. To initiate membrane lipid peroxidation, iron must be moved from ferritin into a mobile form (e.g., iron nucleotide complex). The correlation of iron concentration and peroxidation may not hold true for the corpus striatum, presumably because iron dominantly ligates with dopamine and prevents the participation of mobile iron in hydroxyl free radical formation and membrane peroxidation (117). The high concentration of iron in the basal ganglia makes these structures quite susceptible to oxidative injury when the dopamine activity decreases and may help explain the decline in mobility (bradykinesia, tremor) that occurs with normal and accelerated (Parkinson disease) aging. There is also a loss of neurons in the putamen of elderly patients (121).

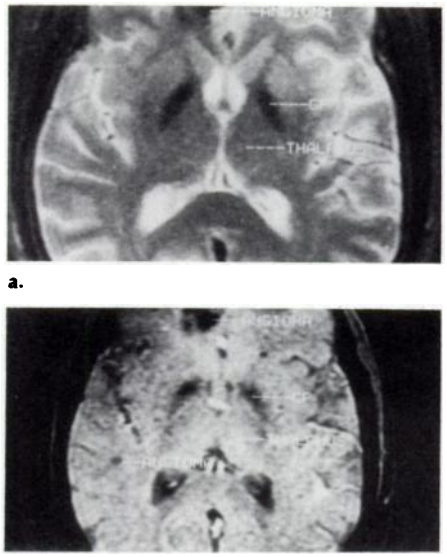
Vascular

Evidence of arteriosclerosis is seen in the brain vasculature in 50% of patients over 50 years of age (122). In a

series of 994 consecutive autopsy examinations, Jorgensen and Torvik (123) found that 320 patients had ischemic cerebrovascular disease. Of these 320 patients, symptoms of infarction were absent in 124 cases. Fisher (61, 64) found neither a history of stroke nor evidence of neurologic deficits in 88 of 114 cases of a single lacunar infarction, even though a history of hypertension was common. Cerebrovascular disease is seven times more common in patients with hypertension, and approxmately 25% of elderly patients who have had cerebrovascular accidents had hypertension (124, 125). Cardiac disease ranked first (even before hypertension) as the major risk factor for cerebrovascular disease in the elderly (124, 125). Although atrial fibrillation and other cardiac arrhythmias with resultant bradycardia are the most important risk factors for cerebrovascular accidents (126, 167), congestive heart failure and coronary heart disease may also play a significant role.

Cerebral amyloid angiopathy is a common finding in elderly individuals both with and without neurologic abnormalities. Esiri and Wilcock (128) described amyloid changes in the leptomeningeal, intracortical, and other small arteries in 37 (11 extensive) of 45 autopsy cases of Alzheimer disease, 14 (three extensive) of 41 cases with other degenerative or cerebrovascular dementias, ten (three extensive) of 32 cases with cerebrovascular disease and no dementia, and 34% (none extensive) of nondemented individuals either with or without associated, nonvascular disease. In the non-Alzheimer group as a whole, amyloid angiopathy was found in 33% of patients and did not increase with age from 60 to 102 years. In mild cases, only the tunica media of small vessels is involved while the full vessel wall may be involved in the more severe cases. Esiri and Wilcock (128) also reported more extensive leptomeningeal vessel involvement at the depths of sulci, sparing of subcortical and deep white matter as well as lenticulostriate vessels, equal involvement of each cerebral lobe, and only minimal amyloid changes in the hippocampus. Vinters and Gilbert (129) reported similar findings in 84 consecutive autopsy examinations: a patchy asymmetric amyloid angiopathy that affected 46% of the brains of patients over 70 years old, involvement of small- and medium-sized cortical and leptomeningeal vessels with sparing of the hippocampus and cerebral white matter, and no correlation with amyloid outside the CNS. This high frequency of cerebral amyloid angiopathy in all aging brains and the greater extent and higher frequency of Alzheimer disease has been confirmed by many investigators (130–133).

There is a close relationship between amyloid angiopathy and intracerebral hematoma (134–137) (Fig. 11). These hematomas generally occur in elderly, often demented (with histologic abnormalities that resemble Alzheimer disease) individuals. They are characterized by cortical or immediate subcortical localization, direct extension into the adjacent subarachnoid space, multiplicity of sites, and amyloid replacement of the tunica media in small- and medium-sized arteries. There is a close similarity in the immunologic staining of the core of vascular and senile plaque amyloid, which share a common antigen with neurofibrillary tangles. Vascular amyloid may reflect an abnormality in the nerve terminals that innervate the leptomeningeal and cortical blood vessels. In a familial form of cerebral amyloid angiopathy found in younger individuals, a gamma trace-protein deposition has been reported (137).



a.

b.

Figure 9. MR images show ferritin and hemosiderin T2 hypointensity. The signal hypointensity in the globus pallidus (*GP*) due to ferritin is prominent on **(a)** T2-weighted (SE 2,500/80) and **(b)** T1-weighted gradient-echo (SE 300/12, flip angle 60°) MR images confirming that visualization is due to magnetic susceptibility. A cavernous hemangioma is also hypointense due to hemosiderin-laden macrophages.

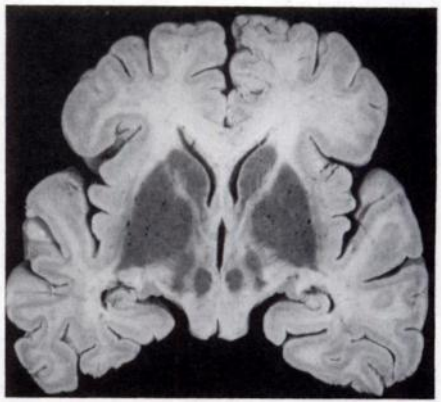


Figure 10. Anatomic section represents normal aging. A Perls reaction for hemosiderin in the brain of a 74-year-old man (no premortem neurologic abnormalities) shows excess staining in the putamen and caudate (almost equal to the globus pallidus), which may occur normally with aging.

Brain Metabolism

Controversy exists concerning whether regional cerebral blood flow, the cerebral metabolic rate for oxygen, or the cerebral metabolic rate for glucose declines with age in healthy individuals (2, 138–144). These discrepancies may occur due to a variety of problems that plague metabolic imaging studies, particularly in the aged: Auditory and visual stimuli will affect regional cerebral blood flow, and vision and hearing are often physiologically impaired in the elderly (138, 145–149); precise anatomic localization is difficult with positron emission tomography (PET) techniques that result in partial volume averaging of gray (approximately 80 mL/100g/min) and white (approximately 20 mL/100g/min) matter flow (148, 150–156); arteriosclerotic cerebrovascular disease is present, even if minimal, in approximately 50% of individuals over 50 years old, possibly resulting in decreased regional cerebral blood flow (2, 4, 122, 138, 144, 157); and cerebral atrophy and ventricular enlargement associated with aging result in less tissue per unit volume and thus may cause the false impression of decreased regional cerebral blood flow and cerebral metabolic rates for oxygen and glucose, when actually the intrinsic resting cellular metabolism of the tissue per unit weight is normal (2, 138, 151, 156).

To account for some of these factors, some researchers have suggested that cerebral blood flow and metabolic rate for oxygen do not vary with age (138, 139, 148, 157). Frackowiak and Gibbs (154) report that regional cerebral blood flow and

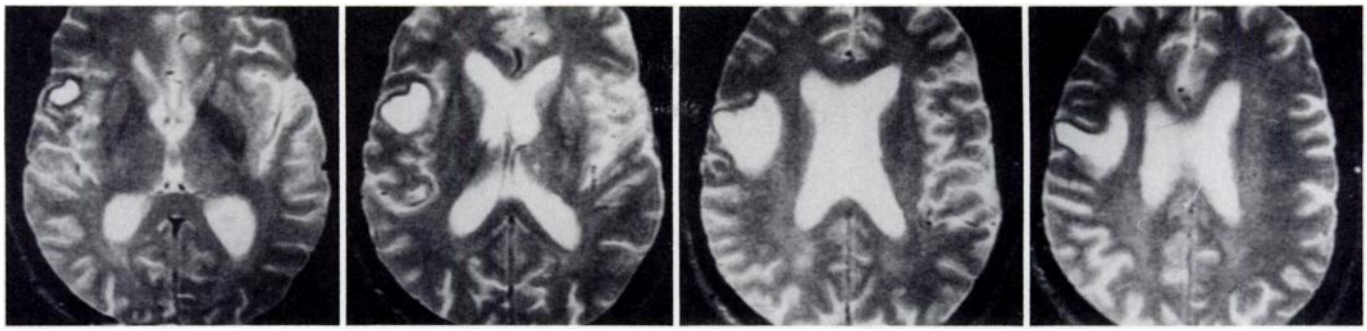


Figure 11. Lobar intracerebral hematoma: amyloid angiopathy. T2-weighted MR images (SE 2,500/80). A prominent mass of hyperintensity (extracellular deoxyhemoglobin) surrounded by a rim of hypointensity (macrophages laden with hemosiderin) in the brain of a 75-year-old patient with mild dementia and acute onset of a focal neurologic deficit is indicative of subacute lobar hematoma.

oxygen extraction decrease with age, while the cerebral metabolic rate for oxygen is normal. Smith (138) concludes that vascular disease is an important contribution to senescence, may accelerate the aging process, and may account for reported declines in cerebral blood flow and metabolism.

Kuhl et al. (158), using F-18 deoxyglucose and PET imaging, suggested that healthy, elderly individuals may have a decrease in the cerebral metabolic rate for glucose. Declines have also been noted in the dominant electroencephalogram rhythm (50% have slowing, particularly over the left anterior temporal region [159–161]), reaction times in psychomotor tests (2), and fluid (reasoning and spatial orientation) intelligence (148). A reduction in the cerebral metabolic rate for glucose was found in the auditory system, visual system, globus pallidus, and corpus striatum in middle-aged and elderly Sprague-Dawley rats (162). The decline of glucose utilization in the visual and auditory cortex, however, may reflect degenerative alterations in the retina and cochlea (138, 145–148). Slowed movements (parkinsonian features) and deterioration of the dopamine system may be either the cause or the result of decreased glucose utilization in the corpus striatum and globus pallidus. Duara et al. (148) found that age did not affect the cerebral metabolic rate of glucose when patients 21–83 years old were studied during sensory (visual and auditory) deprivation; this suggests that declines in brain metabolism with aging may reflect decreased sensory input (138, 163).

Age-related alterations have been pronounced in only the nigrostriatal dopaminergic system (119, 120, 164). Wong et al. (118) studied 44 healthy volunteers with PET and carbon-11-labeled 3-N-methylspiperone, which preferentially binds to the D2 dopamine receptor. They found a progressive decline in specific binding to the D2 dopamine receptor in the corpus striatum with increasing age; this decrease was less prominent in women. Explanations for decreased receptor binding include a decline in the number of D2 dopamine receptors, a decrease in the number and size of cell bodies in the substantia nigra (pars compacta) and putamen, and/or a decline in the concentration of the synthetic enzyme tyrosine hydroxylase in the corpus striatum and nucleus accumbens. Although the muscarinic cholinergic system is thought to play an important role in memory functions (165), there is no consensus on whether choline acetyltransferase or the density of cholinergic receptors decrease with age (120, 165–167). ■

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