American College of Radiology
ACR Appropriateness Criteria®

Movement Disorders and Neurodegenerative Diseases

Variant: 1 Rapidly progressive dementia; suspected Creutzfeldt-Jakob disease. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without and with IV contrast	Usually Appropriate	O
MRI head without IV contrast	Usually Appropriate	O
CT head without IV contrast	May Be Appropriate	☢☢☢
FDG-PET/CT brain	May Be Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢

Variant: 2 Chorea; suspected Huntington disease. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	May Be Appropriate	O
CT head without IV contrast	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢

Variant: 3 Parkinsonian syndromes. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	May Be Appropriate	O
CT head without IV contrast	May Be Appropriate	☢☢☢
FDG-PET/CT brain	May Be Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
Amyloid PET/CT brain	Usually Not Appropriate	☢☢☢
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢

Variant: 4 Suspected neurodegeneration with brain iron accumulation. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	May Be Appropriate	O
CT head without IV contrast	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢

Variant: 5 Suspected motor neuron disease. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
MRI head without and with IV contrast	May Be Appropriate	O
MRI spine without and with IV contrast	May Be Appropriate	O
MRI spine without IV contrast	May Be Appropriate (Disagreement)	O
CT head without IV contrast	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT spine with IV contrast	Usually Not Appropriate	☢☢☢
CT spine without IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢
CT spine without and with IV contrast	Usually Not Appropriate	☢☢☢☢

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Summary of Literature Review

Introduction/Background

Movement disorders and neurodegenerative diseases are a variety of conditions that involve progressive neuronal degeneration, injury, or death and may involve the cortex, deep gray nuclei, subcortical white matter, brainstem, cerebellum, and spinal cord, along with connections to associated motor pathways in the cortex or extrapyramidal system. Movement disorders can

present as either hypokinetic disorders, which include the Parkinsonian syndromes (idiopathic and atypical), or hyperkinetic disorders, which include Huntington disease (HD), prion disease, and neurodegeneration with brain iron accumulation (NBIA). Motor neuron diseases are a related group of syndromes that involve degeneration of upper or lower motor neurons. Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease and is characterized by degeneration of both the upper and lower motor neurons.

Establishing the correct diagnosis of a movement disorder or neurodegenerative process can be difficult because of the variable and complex features of these conditions, the unusual clinical presentations of some of these patients, and the overlapping symptoms and characteristics. A combination of imaging techniques is often needed for complete evaluation of the patient and to help establish the most likely diagnosis. Initial assessment using structural imaging, with MRI preferred over CT, is helpful not only to look for patterns of atrophy, parenchymal abnormality, or abnormal substance deposition but also to exclude other potential etiologies, including underlying structural or vascular lesions, autoimmune or infectious processes, drug or medication toxicity, or hydrocephalus. More advanced MRI techniques, including diffusion tensor imaging, magnetization transfer ratio imaging, and postprocessing techniques such as quantitative volumetric analysis, may be useful in the evaluation of the microstructural makeup of the brain parenchyma, including the integrity of gray matter, white matter, and their connecting neural pathways. Nuclear medicine studies can be used to evaluate for abnormal patterns of glucose metabolism, buildup of abnormal particles or proteins within neurons, dysfunction or loss of specific categories of neurons, or individual neurochemical deficits.

Discussion of Procedures by Variant

Variant 1: Rapidly progressive dementia; suspected Creutzfeldt-Jakob disease. Initial imaging.

Rapidly progressive dementias (RPDs) are a group of conditions that result in onset of dementia over weeks or months. Although prion diseases, such as Creutzfeldt-Jakob disease (CJD), are the prototypical example of RPD, the differential diagnosis of RPD is robust, including both reversible and irreversible causes. For instance, a study out of the Memory and Aging Center at the University of California, San Francisco, showed that the diagnostic breakdown of RPDs in their patient population was 62% prion disease (all forms), 15% other neurodegenerative diseases, 8% autoimmune, 4% infectious, 2% psychiatric, 2% cancer, 2% toxic-metabolic, 2% vascular, and 4% of undetermined etiology, often representing leukoencephalopathies [1]. Importantly, 17% of their patients had potentially treatable etiologies (50% autoimmune, 13% infectious, 13% psychiatric, 13% cancer, and 10% toxic-metabolic).

Human prion diseases, also known as transmissible spongiform encephalopathies, represent the most common cause of RPD and are a group of uniformly fatal neurodegenerative disorders associated with accumulation of a misfolded form of the normal prion protein. CJD is the most common human transmissible spongiform encephalopathy and can be either infectious or neurogenetic in nature. Four distinct types are currently recognized: sporadic, familial/genetic (mutations of the prion protein gene), iatrogenic, and variant. Sporadic is the most common type, comprising approximately 85% of the cases, with an annual incidence of 1 to 2 cases/million and peak age of onset from 55 to 75 years [2]. The most common clinical course of sporadic CJD is rapidly worsening dementia, which may be followed by myoclonic jerks and akinetic mutism.

Sporadic CJD has a median survival of approximately 5 months [2]. The diagnosis of CJD is multifactorial and includes clinical history, physical examination, electroencephalography, diagnostic imaging, cerebrospinal fluid analysis for real-time quaking-induced conversion (CSF RT-QuIC), 14-3-3, and tau proteins, and PRNP gene sequencing [3].

Variant 1: Rapidly progressive dementia; suspected Creutzfeldt-Jakob disease. Initial imaging.
A. CT Head

CT is not the preferred imaging modality for CJD because of its limited soft-tissue characterization when compared with MRI. However, CT may be useful for excluding other etiologies as a cause of the patient's RPD, as described above, such as an underlying neoplastic lesion or other acute process. Contrast is typically not indicated when CT of the head is being utilized in the initial evaluation of RPD. CT imaging is often normal early in the course of CJD, with progressive volume loss and generalized atrophy only becoming apparent on follow-up scans.

Variant 1: Rapidly progressive dementia; suspected Creutzfeldt-Jakob disease. Initial imaging.
B. FDG-PET/CT Brain

PET using the tracer fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) may be helpful in the evaluation of a patient with suspected CJD. FDG-PET/CT demonstrates widespread cerebral hypometabolism, even early on in the disease process, which has been noted to correspond with histopathological astrocytosis, neuronal death, and spongiform changes [4,5]. However, the lack of specificity of the findings limit its utility as the initial imaging study.

Variant 1: Rapidly progressive dementia; suspected Creutzfeldt-Jakob disease. Initial imaging.
C. MR Spectroscopy Head

Although not indicated as the initial imaging study, MR spectroscopy of the brain may be helpful in providing additional information for more atypical cases of CJD. MR spectroscopy has shown decreased absolute levels of N-acetyl aspartate and ratios of N-acetyl aspartate to other metabolites in a pattern similar to the signal abnormalities seen on T2-weighted and diffusion-weighted imaging, particularly later in the disease course [6,7].

Variant 1: Rapidly progressive dementia; suspected Creutzfeldt-Jakob disease. Initial imaging.
D. MRI Functional (fMRI) Head

There is no relevant literature for functional MRI (fMRI) of the brain in the initial imaging evaluation of a patient with RPD or suspected CJD.

Variant 1: Rapidly progressive dementia; suspected Creutzfeldt-Jakob disease. Initial imaging.
E. MRI Head

In patients with RPD or suspected prion disease, MRI of the brain is the optimal imaging modality, with the most sensitive sequences being diffusion weighted and T2-fluid-attenuated inversion recovery (FLAIR) [8,9]. Although intravenous (IV) contrast is not specifically needed for the diagnosis of CJD, use of IV contrast can provide important diagnostic information for identifying other known causes of RPD, most notably including autoimmune and inflammatory etiologies.

The most common focal MRI abnormality in CJD is T2 hyperintensity and diffusion restriction in

gray matter structures. This includes the cortex (particularly throughout the frontal, temporal, and parietal lobes—though often asymmetric—with occipital and cerebellar involvement in less common variants of sporadic CJD, the Heidenhain, and Brownell-Oppenheimer variants, respectively), the basal ganglia (60%, predominantly the anterior caudate and putamen), and the thalami (13%; including the posterior thalamus [pulvinar sign] or the posteromedial thalamus [hockey stick sign]) [6-8,10-15]. A hallmark of the disease is the prominence of gray matter involvement with relative sparing of the underlying white matter on conventional MRI [16]. T1-weighted imaging is typically normal initially, with volume loss noted later in the disease course [17].

Variant 1: Rapidly progressive dementia; suspected Creutzfeldt-Jakob disease. Initial imaging.

F. HMPAO SPECT or SPECT/CT Brain

Tc-99m hexamethyl-propylamine-oxime (HMPAO) single-photon emission computed tomography (SPECT)/CT of the brain may be helpful in the evaluation of a patient with suspected CJD. Tc-99m HMPAO SPECT/CT demonstrates changes in regional cerebral blood flow that can be seen even before signal changes are apparent on MRI [18,19]. Despite the increased sensitivity for early changes, the lack of specificity of the SPECT findings limits its utility as the initial imaging study.

Variant 2: Chorea; suspected Huntington disease. Initial imaging.

Chorea is characterized by involuntary, flowing, nonstereotyped movements that often possess a writhing quality. HD is the prototypical choreiform disorder and the most common cause of chorea in adults. However, the differential diagnosis of chorea includes a number of additional genetic and neurodegenerative disorders in addition to myriad acquired conditions, such as cerebrovascular, infectious, autoimmune, metabolic, neurodegenerative, and drug-induced syndromes. As such, the diagnostic workup, although often focused on HD, must nonetheless consider these other potential etiologies.

HD is a hereditary, autosomal dominant fatal neurodegenerative disorder with complete penetrance characterized by progressive behavioral symptoms, choreoathetosis and/or rigidity, and cognitive dysfunction. The genetic basis of the disease is an abnormally increased number of CAG repeats in the huntingtin gene on the short arm of chromosome 4 (more than 38 repeats used to confirm the diagnosis), often with progressive increase in the length of the repeating sequences in successive generations, resulting in symptoms earlier in life (anticipation). The incidence is ~10/100,000, with average age of onset between 35 to 45 years and symptom progression until death within 15 to 20 years of onset [20]. Abnormal aggregates of the huntingtin protein accumulate in the brain and impair the function of a variety of transcription factors, ultimately leading to the loss of GABAergic medium spiny neurons, particularly in the striatum and cortex [20]. Genetic testing to determine the CAG repeat number for each allele is commercially available and the diagnostic test of choice. Patients with suspected HD should undergo genetic counseling and testing to exclude or confirm HD in concert with initial imaging, given that imaging may be normal early on in the disease course.

Variant 2: Chorea; suspected Huntington disease. Initial imaging.

A. CT Head

CT is not the preferred imaging modality for suspected HD because of its limited soft-tissue characterization when compared with MRI. However, CT may be useful for excluding other etiologies of chorea, such as cerebrovascular disease or acute infectious or inflammatory

processes. Contrast is typically not indicated when CT of the head is being utilized in the initial evaluation of chorea. As with MRI, CT imaging may be normal early in HD, with the progressive and disproportionate volume loss of the neostriatum only becoming apparent on later imaging studies.

Variant 2: Chorea; suspected Huntington disease. Initial imaging.
B. FDG-PET/CT Brain

There is insufficient evidence to support the use of FDG-PET/CT of the brain in the initial evaluation of a patient with chorea or suspected HD. Among known HD gene carriers, FDG-PET may help demonstrate early neostriatal dysfunction (manifested as hypometabolism), which can precede neuronal loss detectable on structural imaging [21]. Note that FDG hypometabolism has also been noted to involve the frontal and temporal lobe cortices in both HD patients and asymptomatic carriers [21].

Variant 2: Chorea; suspected Huntington disease. Initial imaging.
C. MR Spectroscopy Head

There is no relevant literature to support the use of MR spectroscopy of the brain in the initial imaging evaluation of a patient with chorea or suspected HD.

Variant 2: Chorea; suspected Huntington disease. Initial imaging.
D. MRI Functional (fMRI) Head

There is no relevant literature to support the use of fMRI of the brain in the initial imaging evaluation of a patient with chorea or suspected HD.

Variant 2: Chorea; suspected Huntington disease. Initial imaging.
E. MRI Head

MRI of the brain without IV contrast is the optimal imaging modality in patients with chorea or suspected HD, although it is often normal early on in the disease course of HD. Although often unnecessary, IV contrast may offer limited utility in certain circumstances when infectious or inflammatory conditions are among the differential diagnoses being considered.

MRI findings of HD include progressive marked degeneration and atrophy of the neostriatum, particularly the head of the caudate nuclei (with enlargement of the frontal horns of the lateral ventricles), with associated abnormal signal (either T2 hyperintensity or hypointensity) [22-26]. Additionally, abnormal T2 hyperintensity may be seen in the putamen and can help to highlight more subtle changes of atrophy [22-25]. Although disproportionate volume loss of the neostriatum is the hallmark of HD, voxel-based morphometry has shown that patients with symptomatic and asymptomatic HD have significant reduction in volume in almost all brain structures when compared with normal age-matched controls [27,28].

Variant 2: Chorea; suspected Huntington disease. Initial imaging.
F. HMPAO SPECT or SPECT/CT Brain

There is insufficient evidence to support the use of Tc-99m HMPAO SPECT/CT of the brain in the initial evaluation of a patient with chorea or suspected HD.

Variant 3: Parkinsonian syndromes. Initial imaging.

Parkinsonian syndromes are a group of movement disorders characterized by motor symptoms of tremor, rigidity, postural instability, and bradykinesia. Parkinson disease (PD) is the most common cause of Parkinsonism, with other common causes, including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and vascular Parkinsonism, with a

number of rarer conditions also within the differential.

PD is a neurodegenerative disease and movement disorder characterized by progressive degeneration of the dopaminergic neurons in the substantia nigra/striatum. It is the most common Parkinsonism syndrome, with an annual incidence estimated at 10 to 18/100,000 in the total population and peak age of onset between 60 to 70 years [29]. PD, also known as idiopathic Parkinsonism, is a synucleinopathy with neuronal deposits of Lewy bodies (predominantly composed of alpha-synuclein and ubiquitin). Initially, Lewy body deposition is seen involving the medulla oblongata, pontine tegmentum, and olfactory system, with later involvement of the substantia nigra and other deep gray nuclei (corresponding to the onset of clinical symptoms), and finally with deposition of Lewy bodies in the cortex.

The clinical presentation of PD is characterized by resting tremor, bradykinesia, and rigidity and is related to progressive degeneration of the dopaminergic neurons in the substantia nigra projecting to the striatum. The estimated interval between initial loss of dopaminergic neurons and the appearance of symptoms is approximately 5 years (after approximately 40% to 50% of the dopaminergic neurons in the substantia nigra have been lost) [29]. Other features include autonomic dysfunction, behavioral changes, and dementia.

MSA, PSP, and CBD are a group of adult-onset, sporadic neurodegenerative disorders. These conditions are considered the more common of the degenerative "Parkinson-plus" syndromes or atypical Parkinsonisms and demonstrate the classic findings of PD, including bradykinesia and rigidity, with additional clinical features [30]. CBD and PSP are considered tauopathies, in which tau proteins abnormally accumulate in different regions of the brain and differ from MSA (as well as PD), a synucleinopathy in which abnormal cytoplasmic inclusions of ubiquitin and alpha-synuclein in oligodendroglia are seen on histopathology.

MSA can be subdivided into three distinct clinical subtypes: MSA-P (striatonigral degeneration), in which extrapyramidal/parkinsonian features predominate, MSA-C (olivopontocerebellar atrophy), in which ataxia and cerebellar symptoms predominate, and less commonly, MSA-A (Shy-Drager syndrome), in which autonomic dysfunction predominates. The majority of cases of MSA exhibit Parkinsonian symptoms at some stage of the disease, with cerebellar ataxia, pyramidal signs, and dysautonomia (including urinary incontinence) frequently reported. The typical onset is 55 to 65 years of age with a mean disease duration of almost 6 years [30].

Corticobasal degeneration initially presents with asymmetric limb clumsiness in patients between 50 to 70 years of age and progresses to include unilateral limb rigidity and dystonia (including the "alien limb phenomenon"), postural imbalance, and cortical features (including apraxia, cortical dementia, cortical sensory deficits, and impaired language production) [30].

PSP, also known as Steele-Richardson-Olszewski syndrome, is the most common atypical Parkinsonism with a prevalence of around 5/100,000 [30]. Patients classically present in the sixth or seventh decade (mean age of onset at 63) with a lurching gait and axial dystonia, manifested as unexplained falls [30]. Ocular symptoms, including blurred vision and slow saccades, can be seen early in the disease; however, the classic finding of vertical supranuclear gaze palsy is usually only seen later in the course of the disease.

Correctly diagnosing a Parkinsonian syndrome on clinical features alone can be quite challenging, and imaging remains an essential diagnostic tool in the evaluation of a patient presenting with Parkinsonian symptoms.

Variant 3: Parkinsonian syndromes. Initial imaging.
A. CT Head

CT is not the preferred imaging modality for the workup of Parkinsonian syndromes because of its limited soft-tissue characterization when compared with MRI. Nonetheless, CT imaging can effectively demonstrate the patterns of regional volume loss characteristic of MSA, CBD, or PSP, as described in the MRI section. CT findings are nonspecific for PD but can help to exclude focal or regional atrophy, underlying structural lesions, or vascular disease that might signal an alternative diagnosis. Contrast is typically not indicated.

Variant 3: Parkinsonian syndromes. Initial imaging.
B. Amyloid PET/CT Brain

There is no relevant literature to support the use of amyloid PET/CT in the initial imaging evaluation of a patient with Parkinsonian syndrome.

Variant 3: Parkinsonian syndromes. Initial imaging.
C. FDG-PET/CT Brain

Despite widespread use of FDG-PET/CT in clinical practice and extensive research, there is still very limited good-quality evidence for the use of FDG-PET/CT in Parkinsonian syndromes. FDG-PET is useful for discriminating PSP from idiopathic PD on the presence of a typical metabolic pattern for PSP, which is not present in PD. PSP is characterized by hypometabolism in the medial frontal and anterior cingulated cortices, striatum, and midbrain. FDG-PET may therefore be useful in early stages of the disease when the clinical diagnosis is less certain. In PD-related cognitive decline, FDG-PET have a typical pattern of hypometabolism mainly affecting the posterior cortical areas [31].

Variant 3: Parkinsonian syndromes. Initial imaging.
D. Ioflupane SPECT/CT Brain

I-123 ioflupane SPECT/CT is a valuable test used to differentiate Parkinsonian syndromes (PD, MSA, PSP, CBD) from essential tremor and drug-induced tremor, demonstrating abnormality early in the disease course compared with anatomic imaging such as standard CT or MRI [32]. A normal I-123 ioflupane SPECT/CT essentially excludes Parkinsonian syndromes. I-123 ioflupane binds to the dopamine transporters and can be used to demonstrate the loss of presynaptic dopaminergic neurons in PD. It can demonstrate decreased radiotracer uptake in the striatum, usually in a posterior to anterior direction from the putamen to the caudate nuclei. I-123 ioflupane SPECT would demonstrate abnormal patterns of dopaminergic depletion for patients with PD, MSA, PSP, and CBD [33-39].

Note is made of a steady emergence of new nuclear medicine tracers, which are yet to be approved by the US FDA for clinical use, designed to target the postsynaptic dopamine receptors (D1 and D2), including 11C-raclopride-PET and I-123-iodobenzamide SPECT scans. These radiotracers compete with endogenous dopamine to bind to the postsynaptic D2 receptors and show increased uptake within the putamen and, to a lesser extent, the caudate in patients with PD when compared with normal controls. The role of these tracers in the evaluation of patients with suspected PD may grow in the future.

Variant 3: Parkinsonian syndromes. Initial imaging.
E. MR Spectroscopy Head

There is no relevant literature to support the use of MR spectroscopy of the brain in the initial imaging evaluation of a patient with Parkinsonian syndrome.

Variant 3: Parkinsonian syndromes. Initial imaging.
F. MRI Functional (fMRI) Head

There is no relevant literature to support the use of fMRI of the brain in the initial imaging evaluation of a patient with Parkinsonian syndrome.

Variant 3: Parkinsonian syndromes. Initial imaging.
G. MRI Head

In patients with Parkinsonian syndrome, MRI of the brain without IV contrast is the optimal imaging modality because of its soft-tissue characterization and sensitivity to iron deposition [40-44]. Although IV contrast is not typically needed for the evaluation of Parkinsonian syndromes, it may be helpful for excluding additional differential considerations.

Conventional MRI findings are often nonspecific for PD but can be helpful in demonstrating the parenchymal atrophy and signal abnormality that characterize MSA, PSP, and CBD [41,42]. Recent literature, however, has suggested clinical utility of susceptibility-weighted imaging for diagnosing PD by demonstrating signal changes in the dorsolateral substantia nigra, known as the "swallow tail" sign, although the sensitivity and specificity of this finding remain unclear [45,46].

In patients with MSA, two specific patterns of atrophy and signal abnormality are most commonly seen on MRI imaging. T1-weighted imaging demonstrates atrophy of the brainstem and cerebellum in MSA-C and atrophy of the putamen in MSA-P [43,47-50]. In MSA-C, abnormal T2 hyperintense signal in the pons, middle cerebellar peduncles, and cerebellar white matter with sparing of the corticospinal tracts can be seen (more common later in the disease course) and results in the characteristic cruciform "hot cross bun sign" in the pons [43,47-52]. In MSA-P, there is abnormal T1/T2 hypointensity within the atrophic putamen and caudate nuclei, reflecting iron deposition, with a thin hyperintense rim noted laterally, known as the "hyperintense putaminal rim" [43,47-51,53-56]. Although classically described, the sensitivity and specificity of these findings remain unclear.

In patients with CBD, MRI shows asymmetric atrophy of the frontal and parietal lobes, typically contralateral to the more affected side, as well as the striatum [42,57-60]. Faint T2/FLAIR hyperintensity can also be seen in the subcortical white matter in the atrophic regions, likely related to neuronal loss and gliosis [42,57,59,60].

In patients with PSP, MRI generally shows midbrain atrophy [42,61-65]. This atrophy may result in classic patterns, including a concave upper profile of the rostral midbrain tegmentum, known as the "penguin" or "hummingbird sign" (best appreciated on sagittal imaging), or a concave appearance of the lateral margin of the tegmentum with widening of the interpeduncular cistern, known as the "morning glory sign" (best appreciated on axial imaging), although the exact sensitivity and specificity of these signs remain unclear [42,61-65]. Abnormal T2 hypointensity in the putamen and hyperintensity in the tegmentum has also been described [64,65].

In contrast to conventional MRI, advanced MRI may offer more meaningful and earlier diagnostic

opportunities for patients with suspected PD and other Parkinsonian syndromes. For instance, 7-T MRI has shown promise in accurately differentiating healthy subjects from PD patients because it can demonstrate increased susceptibility in the substantia nigra and thinning of the pars compacta with blurring of the borders between the substantia nigra and red nucleus [66]. Additionally, recent studies in patients with PD have shown decreased magnetization transfer ratio and functional anisotropy within the substantia nigra (particularly caudally) when compared with normal controls [67].

Variant 3: Parkinsonian syndromes. Initial imaging.
H. HMPAO SPECT or SPECT/CT Brain

There is no relevant literature to support the use of Tc-99m HMPAO SPECT/CT of the brain in the initial imaging evaluation of a patient with Parkinsonian syndrome.

Variant 4: Suspected neurodegeneration with brain iron accumulation. Initial imaging.

Although some iron accumulation within the basal ganglia and dentate nuclei can normally be seen as we age, NBIA is a distinct group of conditions characterized by excess iron deposition in the basal ganglia with progressive neuronal degeneration. Four subtypes have been defined, the most common of which is NBIA type 1, also known as pantothenate kinase-associated neurodegeneration and formerly known as Hallervorden-Spatz disease. NBIA type 1 is a rare autosomal recessive disease (annual incidence of 1/1,000,000), which classically presents in the first decade with slowly progressive gait disturbances, dystonia, dysarthria, spasticity, and pyramidal tract signs [68].

Variant 4: Suspected neurodegeneration with brain iron accumulation. Initial imaging.
A. CT Head

CT is not the preferred imaging modality for suspected NBIA because of its limited sensitivity to basal ganglia iron accumulation compared with MRI. Contrast is not needed. The utility of CT in this situation is largely limited to excluding other etiologies as a cause of the patient's symptoms, such as an underlying lesion or other abnormality. However, CT may be helpful to distinguish between calcium and iron deposition in the brain, which can appear similar on MRI.

Variant 4: Suspected neurodegeneration with brain iron accumulation. Initial imaging.
B. FDG-PET/CT Brain

There is no relevant literature to support the use of FDG-PET/CT of the brain in the initial imaging evaluation of a patient with suspected NBIA.

Variant 4: Suspected neurodegeneration with brain iron accumulation. Initial imaging.
C. MR Spectroscopy Head

There is no relevant literature to support the use of MR spectroscopy of the brain in the initial imaging evaluation of a patient with suspected NBIA.

Variant 4: Suspected neurodegeneration with brain iron accumulation. Initial imaging.
D. MRI Functional (fMRI) Head

There is no relevant literature to support the use of fMRI of the brain in the initial imaging evaluation of a patient with suspected NBIA.

Variant 4: Suspected neurodegeneration with brain iron accumulation. Initial imaging.
E. MRI Head

MRI of the brain without IV contrast, including susceptibility-weighted sequences, is the optimal

imaging modality for patients with suspected NBIA because of its soft-tissue characterization and sensitivity to iron deposition [69-72]. MRI commonly demonstrates diffuse T2 hypointense signal with blooming on susceptibility-weighted sequences within the globus pallidus and, later in the disease process, the substantia nigra and dentate nuclei, reflecting abnormal iron deposition [69,72,73]. The hallmark imaging finding on MRI is the "eye-of-the-tiger sign," a focus of T2 hyperintensity within the anteromedial aspect of the otherwise T2 hypointense globus pallidus, consistent with focal tissue gliosis and vacuolization in a background of iron deposition [69,72,73]. However, this finding may not be seen in all cases and has been noted to change or disappear with time [69,73]. There is no associated enhancement or restricted diffusion in these areas of iron deposition, although diffusion tensor imaging has shown increased fractional anisotropy in both the globus pallidus and substantia nigra in patients with NBIA [74]. The white matter and cortex are spared in NBIA type 1. MRI may also be helpful in distinguishing the other less common subtypes of NBIA [69,71,72]. IV contrast may be useful in the initial evaluation of suspected NBIA, considering the presence of limited inflammatory etiologies among the differential diagnoses.

Variant 4: Suspected neurodegeneration with brain iron accumulation. Initial imaging.
F. HMPAO SPECT or SPECT/CT Brain

There is no relevant literature to support the use of Tc-99m HMPAO SPECT/CT of the brain in the initial imaging evaluation of a patient with suspected NBIA.

Variant 5: Suspected motor neuron disease. Initial imaging.

ALS is a progressive neurodegenerative disorder characterized by degeneration of the upper and lower motor neurons in the brain and spinal cord along the corticospinal tracts and is the most common motor neuron disease, representing ~85% of all cases [75]. The majority of cases are sporadic (85% to 90%) with an overall annual incidence of 1 to 2/100,000 and a median survival of 3 to 4 years after symptom onset [75]. Typically, patients present with hypertonicity and hyperreflexia (upper motor neuron degeneration) and muscle fasciculations, weakness, and atrophy (lower motor neuron degeneration). Electromyography and nerve conduction velocity are key tests in diagnosing ALS, with imaging relied upon mainly to exclude other conditions with similar clinical presentations rather than confirm or facilitate the diagnosis of ALS.

Variant 5: Suspected motor neuron disease. Initial imaging.
A. CT Head

CT is not the preferred imaging modality for suspected ALS because of its limited soft-tissue characterization when compared with MRI. Contrast is not needed. The utility of CT in this situation is limited to excluding other etiologies as a cause of the patient's symptoms, such as an underlying lesion or other abnormality.

Variant 5: Suspected motor neuron disease. Initial imaging.
B. CT Spine

CT of the spine (either with, without, or without and with IV contrast) is not useful in making the diagnosis of ALS because of its limited soft-tissue characterization.

Variant 5: Suspected motor neuron disease. Initial imaging.
C. FDG-PET/CT Brain

There is no relevant literature to support the use of FDG-PET/CT of the brain in the initial imaging evaluation of a patient with suspected motor neuron disease.

Variant 5: Suspected motor neuron disease. Initial imaging.
D. MR Spectroscopy Head

There is no relevant literature to support the use of MR spectroscopy of the brain in the initial imaging evaluation of a patient with suspected motor neuron disease.

Variant 5: Suspected motor neuron disease. Initial imaging.
E. MRI Functional (fMRI) Head

There is no relevant literature to support the use of fMRI of the brain in the initial imaging evaluation of a patient with suspected motor neuron disease.

Variant 5: Suspected motor neuron disease. Initial imaging.
F. MRI Head

In patients with suspected motor neuron disease involving upper motor neurons, MRI of the brain without IV contrast is the optimal imaging modality [76]. Contrast is typically not needed for the evaluation of suspected motor neuron disease, but it may be helpful in excluding other infectious, inflammatory, or neoplastic differential considerations.

The most common MRI finding in the brain in ALS is abnormal signal on T2/FLAIR or proton density–weighted images, which can be seen anywhere within the corticospinal tracts from the subcortical white matter to the pons (though it is most frequently seen in the posterior limb of the internal capsule and the cerebral peduncles), which likely corresponds to the underlying demyelination, axonal degeneration, and gliosis seen on histopathology [77-81]. T2*-weighted imaging or susceptibility-weighted imaging is also important in the evaluation of suspected ALS because abnormal hypointensity in the precentral gyrus and gray matter has been noted to be highly sensitive and specific for ALS [82-85]. Macroscopic atrophy on MRI is uncommon in patients with ALS, although voxel-based morphometry studies have shown volume changes and atrophy in classic motor areas, including the precentral gyrus, and in white matter areas, particularly along the corticospinal tracts.

Variant 5: Suspected motor neuron disease. Initial imaging.
G. MRI Spine

MRI of the spine without IV contrast is often normal early in the disease course of ALS, but may be useful in certain clinical circumstances to exclude structural, infectious, or neoplastic etiologies of the spine that can mimic motor neuron disease [86-88]. To this end, the addition of IV contrast may add utility in patients who are at increased risk for infection or neoplastic mimics.

The most common MRI finding in the spine in ALS is abnormal T2/short tau inversion recovery signal in the anterior horns (“snake eyes” appearance), which corresponds to the lateral corticospinal tracts and reflects lower motor neuron disease, although this finding is not specific for ALS and may only be present later in the disease course [89]. MRI may also demonstrate corresponding atrophy of the spinal cord secondary to motor neuron loss, although this may be difficult to appreciate without volumetric analysis [90,91].

Variant 5: Suspected motor neuron disease. Initial imaging.
H. HMPAO SPECT or SPECT/CT Brain

There is no relevant literature to support the use of Tc-99m HMPAO SPECT/CT of the brain in the initial imaging evaluation of a patient with suspected motor neuron disease.

Summary of Recommendations

- **Variant 1**: MRI head without and with IV contrast or MRI head without IV contrast is usually appropriate for the initial imaging of patients with rapidly progressive dementia and suspected CJD. These procedures are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care).
- **Variant 2**: MRI head without IV contrast is usually appropriate for the initial imaging of patients with Chorea and suspected HD.
- **Variant 3**: MRI head without IV contrast is usually appropriate for the initial imaging of patients with Parkinsonian syndromes.
- **Variant 4**: MRI head without IV contrast is usually appropriate for the initial imaging of patients with suspected NBIA.
- **Variant 5**: MRI head without IV contrast is usually appropriate for the initial imaging of patients with suspected motor neuron disease. MRI spine without IV contrast may be appropriate for certain patients with suspected motor neuron disease.

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents, please go to the ACR website at https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria.

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document.

Relative Radiation Level Designations

Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv

*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (e.g., region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as “Varies.”

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Disclaimer

The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

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