NEUROPATHOLOGICAL CONFERENCE

Editor: David A. Ramsay

A 67-year-old woman with Parkinsonism

Ging-Yuek R. Hsiung and Arthur W. Clark

Can. J. Neurol. Sci. 2001; 28: 150-155

CLINICAL PRESENTATION

A 67-year-old woman was seen in the Movement Disorders Clinic because of a one-year history of Parkinsonism.

Several years prior to her presentation, she had a mild postural tremor in her hand, which caused some difficulty holding a cup or soup spoon. One year prior to presentation, she developed a resting tremor in her right hand with some difficulty walking and shuffling of her gait, and several falls while working in her garden. She also had problems buttoning up her clothes. Her symptoms progressed rapidly. Six months after onset of symptoms, she required a cane. She had 10 more falls over the next six months, including one resulting in rib fractures. She typically fell backwards, precipitated by turning. At the time of evaluation, she was mostly wheelchair-dependent.

Prior to referral to our clinic, she had been placed on levodopa-carbidopa 100/25mg tid, and by history she had improvement in her tremor and overall mobility. However, the benefits were short-lasting and the dose was titrated up to 200/50 mg (controlled release formulation) five times per day in three months. Selegiline was added but later discontinued because of intolerable side effects. One month prior to presentation at our clinic, pramipexole was added, but she developed frightening hallucinations such as tarantulas on her bed. The pramipexole was discontinued, and the levodopa was reduced. She then developed frequent freezing episodes.

At the time of presentation, she was noted to have some fluctuations in her cognitive status, short-term memory difficulties, marked visual-spatial disorientation, and waxing-and-waning hallucinations.

Her past medical history included borderline diabetes mellitus, remote appendectomy and gout. Her medications on presentation included levodopa-carbidopa CR 200/50mg qid, olanzapine 5mg qd, paroxetine 10mg qd, allopurinol 300mg qd, and zopiclone 7.5mg nocte prn for sleep. She was an ex-smoker with a 40 pack/year history, having quit 10 years earlier. She drank alcohol rarely. Her family history was significant only for postural hand tremor in her mother, two siblings, and in one of her five children.

On examination at presentation, she was pleasant and co-operative. She had had a dose of levodopa one hour prior to examination. Her blood pressure was 120/80 with no significant postural changes. Her general physical examination was unremarkable. Her Mini-Mental Status Examination was 22/30. She was disoriented to place and had 0/3 word recall after five minutes. No apraxia was noted. Cranial nerve examination revealed normal pupillary reflexes and visual fields. Extraocular movements showed smooth pursuit with normal optokinetic nystagmus in vertical and horizontal directions. Tongue and palate movements were normal. There was a fairly constant rest tremor in her chin and periorbital region on the left side. Her strength was normal throughout and her sensory examination was normal to all primary modalities. Graphesthesia, stereognosis and two-point discrimination were normal. Reflexes were 2+ bilaterally in upper and lower extremities and plantar responses were flexors bilaterally. She had tremendous difficulty rising from a chair by herself and needed assistance from two people to stand. Gait examination revealed small steps with festination, severe start hesitation, postural instability and retropulsion. Axial tone was normal but there was mild to moderate cogwheel rigidity in both upper and lower limbs bilaterally with no clear asymmetry. Fine finger movements and rapid alternating movements revealed mild bradykinesia bilaterally. There was a moderate intermittent resting tremor in both upper extremities, which persisted and worsened with posture. Finger-to-nose movements were slow but accurate, and there was no evidence of dysdiadochokinesis, dysmetria, or past pointing.

Chest X-ray was clear and CT scan of the head was normal. The clinical diagnosis of diffuse Lewy body disease (DLB) was made.

After the initial visit, her levodopa-carbidopa CR was changed to regular formulation and the dose was reduced to 100/25mg qid. Over the next two months, her hallucinations decreased but her dementia worsened. She became completely wheelchair-dependent. An MRI of the brain was performed

The discussion was transcribed from a Clinical Neurosciences round presentation at University of Calgary on September 19, 1999.
From the Department of Clinical Neurosciences (G-YRH) and Department of Pathology and Laboratory Medicine (AWC), University of Calgary, Calgary, Alberta, Canada
RECEIVED MAY 26, 2000. ACCEPTED IN FINAL FORM JANUARY 4, 2001.
Reprint requests to: Arthur Clark, Department of Pathology and Laboratory Medicine, University of Calgary, 3330 Hospital Drive NW, Calgary, Alberta, Canada. T2N 4N1

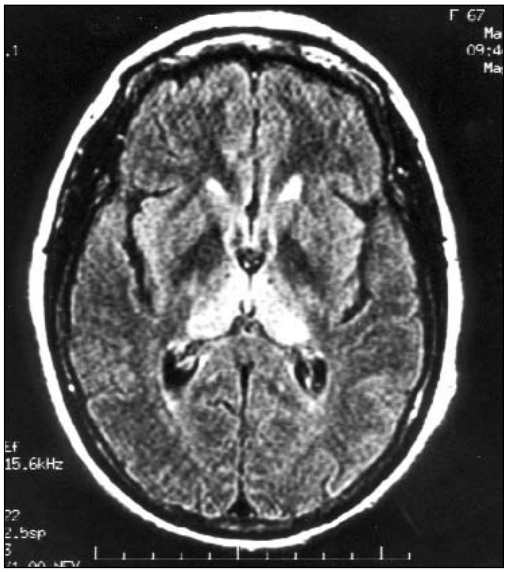


Figure 1: *MRI head axial FLAIR image shows symmetric signal hyperintensity in the thalami bilaterally, most marked posteriorly. There is also subtle signal hyperintensity in the corpus striatum.*

(Figure 1). An EEG showed occasional epileptiform activity over the left mid-temporal region, and possibly in the right mid-temporal region as well. A repeat EEG one month later showed diffuse slow background of 4-7 Hz activities with frequent episodes of generalized 1-3 Hz activity lasting for prolonged intervals. No epileptiform discharges were observed this time.

The patient had a progressive deteriorating course and died four months after initial presentation. A pathological examination was performed.

Clinical Diagnosis

Diffuse Lewy body disease

Differential Diagnosis

Dr. Robin Hsiung: This is a very interesting case because of its unusual presentation and it also illustrates how difficult it is to make a diagnosis on the first presentation. Only with time and follow-up did the diagnosis become clear in this case.

Let's consider the differential diagnoses as the clinical history evolves.

In the beginning, the patient had a postural tremor that worsened when holding objects. There was a family history of tremor with an autosomal dominant pattern. This was most likely familial essential tremor and was unrelated to her current symptoms. She then developed symptoms of parkinsonism, including resting tremor, gait shuffling, and difficulty with fine motor control. However, her symptoms were atypical of idiopathic Parkinson's disease (IPD) because of the rapidity of progression – requiring a cane within six months of onset and becoming wheelchair-dependent within one year. She also had a number of falls, with severe retropulsion. This brought up the differential diagnoses of progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) with striatonigral degeneration (SND). Both of these diseases tend to have frequent falls, retropulsion, and gait instability early in the course of the disease, whereas in IPD falls are usually late complications. However, resting tremor is uncommon in either PSP or MSA. Other features that may help to differentiate these syndromes are the asymmetry of onset and the distribution of rigidity. In IPD, there is usually asymmetric onset of the tremor and the bradykinesia, whereas in PSP the bradykinesia is usually symmetric. The rigidity in IPD is usually more pronounced in the distal extremities such as the wrist, while the rigidity in PSP and MSA is often axial and proximal such as in the neck and shoulders.[1,2]

The patient had a good response initially to levodopa, but the benefit was temporary, and she developed complications with hallucinations early on. Again, this would argue against IPD, which typically shows sustained benefits to parkinsonian treatments in the early phase, but could be consistent with MSA or PSP. However, this also brings up the differential diagnosis of DLB. In patients with DLB, hallucinations are common early in the course of the disease and are often precipitated by dopaminergic medications. These patients are highly sensitive to neuroleptics, especially with the older generation neuroleptics such as haloperidol or chlorpromazine, which may lead to catatonic spells and severe rigidity. They also exhibit marked fluctuations in alertness and cognitive abilities.[3] This patient's loss of short-term memory, visual spatial disorientation, sensitivity to parkinsonian medications, as well as waxing and waning hallucinations were all very suggestive of DLB. In PSP, dementia is also reported in up to 60-80%, and is usually characterized as "subcortical" with slowing of thought process, forgetfulness, personality change, and inability to manipulate acquired knowledge in the relative absence of aphasia, agnosia, or apraxia.[4]

Her past medical history was mostly unremarkable. However, the use of zopiclone as a sleeping aid caused me to wonder whether the sleep disturbance was early or late in the course of the disease, and what the nature of the sleep disturbance was. In MSA and DLB, and less commonly PSP, patients may develop Rapid Eye Movement behavioural disturbances which is felt to be due to the lack of atonia during REM sleep, leading to acting out the motions of dreams that can lead to injury of bed partners.[5] On the other hand, insomnia occurring early in the disease process with dementia may suggest prion diseases such as Creutzfeldt-Jakob disease (CJD). The history of smoking also raised the question of a paraneoplastic syndrome. Although this is not typical of paraneoplastic brain stem encephalitis or cerebellar degeneration, it would be reasonable to obtain a chest X-ray to screen for possible neoplastic processes in the lung.

In the initial physical examination, significant dementia was documented. Her cranial nerve functions were normal and had a fairly normal axial tone. She had an intermittent resting tremor with increasing intensity during postural exacerbation. This presentation would argue against PSP because the pathological hallmarks of supranuclear ophthalmoplegia and neck dystonia are absent, although sometimes the ophthalmoplegia does not appear until the very end stage of the disease. She had severe difficulties with rising from a chair and trying to walk. These motor problems would be consistent with MSA-SND, but in the

https://doi.org/10.1017/S0317167100052859 Published online by Cambridge University Press

series reported by Wenning,[2] frank dementia in MSA is actually rare, accounting for only 0.5 % of cases in 200 patients. Therefore, the diagnosis is most consistent with DLB at this point. The absence of apraxia was particularly mentioned which argues against corticobasal degeneration (CBD). The other main features of CBD, such as asymmetric onset, alien hand phenomenon, dystonia, action myoclonus, and corticospinal tract signs are all absent in this patient.

A CT scan was done at this point and was reported to be normal. This ruled out normal pressure hydrocephalus and frontal lobe tumours as a possible cause of the patient's symptoms.

With the MRI findings and the rapid worsening of her dementia, my differential diagnoses are narrowed down considerably. May we review the MRI at this point?

Dr. Robert Sevick: There is bilateral symmetric signal hyperintensity in the thalami. There is also subtle increased signal in the caudate and putamen bilaterally on the FSE T2-weighted image. The signal changes are not accompanied by any mass effect. There is no evidence of hydrocephalus, mass lesion, or extra-axial fluid collection.

Dr. Robin Hsiung: Very few of the neurodegenerative diseases actually show definitive abnormalities in MRI studies. Alzheimer's disease, IPD and DLB typically do not show any focal abnormalities except for diffuse volume loss. In PSP, there are a few reports showing atrophy of the midbrain area with increase signal intensity in proton density images in the periaquaductal gray matter, but it is not very sensitive.[6] CBD may be associated with asymmetric cortical atrophy. In MSA, the abnormalities seen are usually hypointense signals in the putamen region.[6,7] In sporadic CJD, however, there are several reports demonstrating abnormal signals in the basal ganglia with MRI.[8,9] Diffusion-weighted imaging shows these basal ganglia signal abnormalities with greater sensitivity than conventional T2-weighted images, and cortical signal abnormalities may also be seen.[10-12] Two other diseases that may present with parkinsonism and dementia with hyperintense basal ganglia signals in MRI are Wilson's disease and Hallervorden Spatz disease (HSD). Wilson's disease is an inborn error of metabolism of copper, while HSD is related to abnormal metabolism of iron in the central nervous system. In Wilson's disease, T2-hyperintense signal in the caudate and putamen can be detected.[13] In HSD, the abnormality is often described as "eye of the tiger" which refers to the hyperintensity around a dark hypointense core in the pallidum. However, these metabolic diseases usually present at an earlier age, and have never been reported with onset after age of 50.

Although the two EEGs were felt to be nondiagnostic, there was a noticeable deterioration with diffuse background slowing and the appearance of generalized 1-3 Hz activity. One certainly does not require the classical appearance of periodic sharp wave complexes for the diagnosis of CJD.[14] Together with the rapidly progressive course and the MRI abnormality, I believe the most likely diagnosis is sporadic CJD. Although CJD presenting with primarily parkinsonian symptoms are unusual, it has been reported in the literature.[15] If the patient's MRI was normal and the rate of progression was slower, I would have agreed that DLB was the most likely diagnosis.

Dr. Robin Hsiung's Diagnosis

Sporadic Creutzfeldt-Jakob disease with an unusual parkinsonian presentation

Pathological Discussion

Dr. Arthur Clark: The post-mortem examination, largely restricted to the brain, revealed a brain weight of 1164 g and no noteworthy abnormalities on external inspection. Sectioning revealed a ventricular system of normal size and substantia nigra slightly paler than usual (Figure 2). Microscopic examination revealed conspicuous spongiform change in the caudate nucleus (Figure 3), putamen, and thalamus as well as some cortical areas such as cingulate and occipital. Immunostains for glial fibrillary acidic protein confirmed gliosis in these areas.

The spongiform change and gliosis were characteristic of CJD. There were other features unusual in that disorder. The substantia nigra had undergone marked cell loss (Figure 4). Moderate cell loss was apparent in the nuclei basis pontis. The inferior olivary nucleus showed patchy, bilateral cell loss, more intense in the ventral folia, with focally total loss of neurons and gliosis (Figure 5). Synaptophysin stains confirmed focal attenuation of synaptophysin staining (Figure 6), suggesting loss of afferents to the inferior olive. Prion protein immunostains were positive not only in caudate nucleus and cortex, but also in the inferior olive (Figure 7), substantia nigra, and other areas. The cerebellar cortex showed only subtle, if any, changes referable to CJD. There were no Lewy bodies in the substantia nigra, locus coeruleus, or cingulate cortex.

Creutzfeldt-Jakob disease presenting with parkinsonism is well-documented though quite unusual.[15] The neuronal loss and gliosis in the inferior olive of our case is characteristic of fatal familial insomnia, another prion disorder, but not of CJD. Coexistence of CJD and IPD has been reported,[16] but was excluded in the present case, based on the absence of Lewy bodies.

Pathological Diagnosis

Creutzfeldt-Jakob disease.

Key point Summary

1. Diagnostic Category	Parkinsonism
2. Key Differential	Idiopathic Parkinson's disease, multiple systems atrophy, progressive supranuclear palsy, corticobasal degeneration, Lewy body dementia, Creutzfeldt-Jakob disease
3. Resolving investigation(s):	MRI (abnormal high signal intensity in basal ganglia)
4. Definitive pathological findings:	Spongiform changes, prion protein immunostain positivity

Acknowledgements

The authors thank Dr. Cathy Bergeron for performing the prion protein immunostaining, and Dr. Oksana Suchowersky for suggestions on the manuscript.

https://doi.org/10.1017/S0317167100052859 Published online by Cambridge University Press

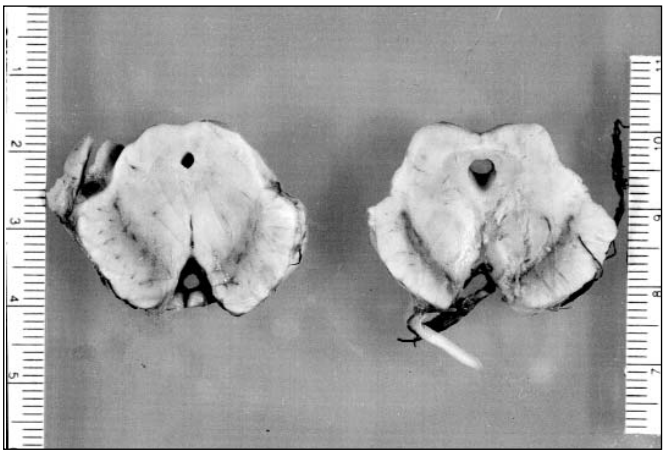


Figure 2: *Midbrain of the patient (left) shows pallor of the substantia nigra compared with a control subject (right).*

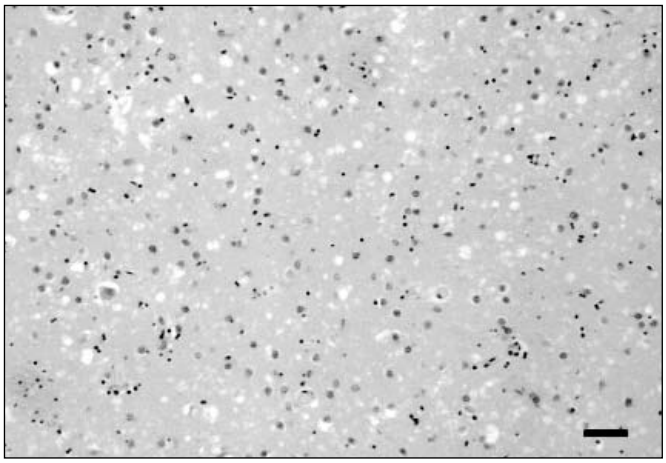
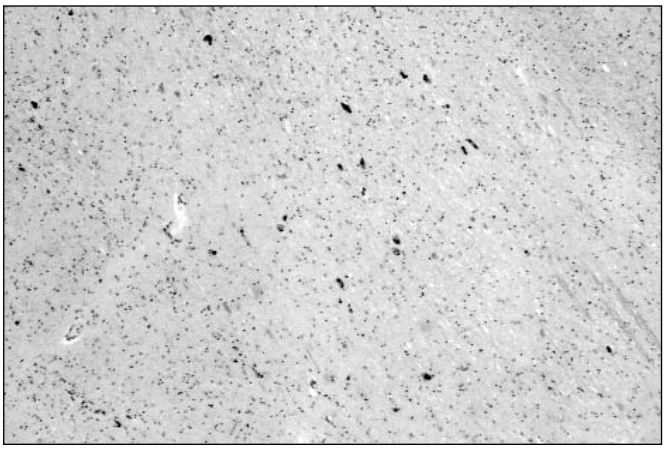


Figure 3: *Marked spongiform change in the caudate nucleus, characteristic of CJD. Hematoxylin eosin. Bar = 60 micra*



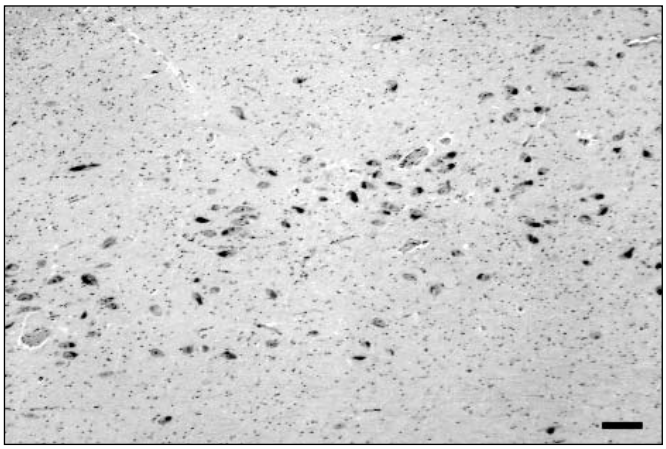
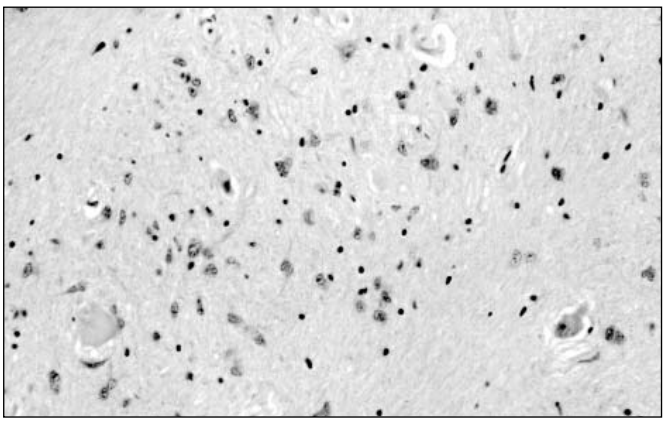


Figure 4: *Marked cell loss in substantia nigra of the patient (left panel) compared to a control (right panel). Hematoxylin eosin. Bar = 150 micra*



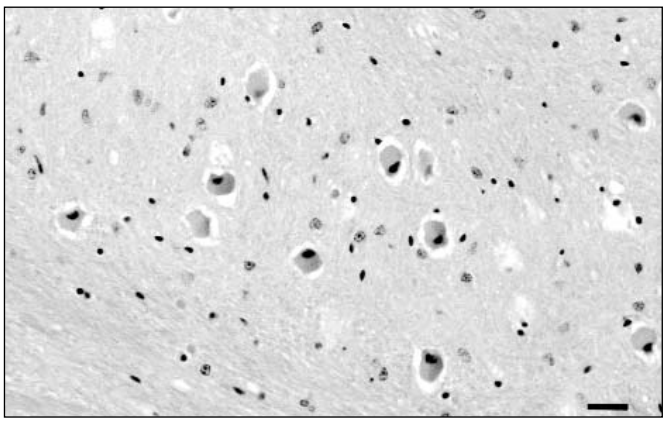


Figure 5: *Focally severe cell loss in the ventral folium of the inferior olive (left panel) with less severe cell loss in the dorsal folium (right panel). Hematoxylin eosin. Bar = 30 micra*

https://doi.org/10.1017/S0317167100052859 Published online by Cambridge University Press

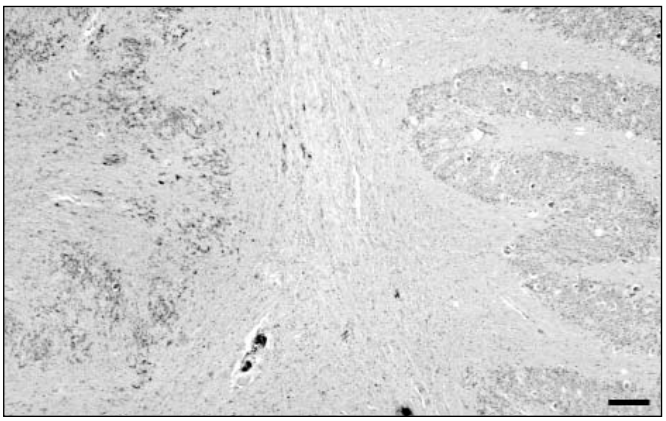


Figure 6: *Focal loss of synaptophysin in the ventral folium (left side of figure) of the inferior olive compared with the dorsal folium (right side of figure). Immunostain for synaptophysin. Bar = 150 micra*

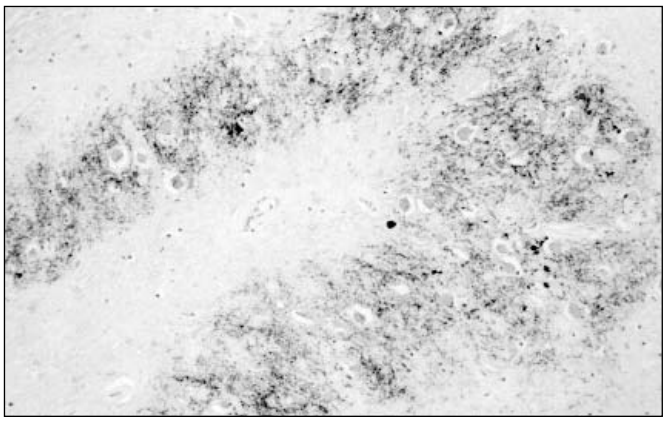


Figure 7: *Dorsal folium of the inferior olive shows intense prion protein immunopositivity. Immunostain for prion protein. Magnification identical to Figure 3.*

References

1. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for progressive supranuclear palsy: report of the NINDS-SPSP international workshop. Neurology 1996;47:1-9.
2. Wenning GK, Tison F, Ben-Shlomo Y, et al. Multiple system atrophy: a review of 203 pathologically proven cases. Mov Disord 1997;12:133-147.
3. Gibb WR, Luthert PJ, Janota I, et al. Cortical Lewy body dementia: clinical features and classification. J Neurol Neurosurg Psychiatry 1989;52:185-192.
4. Pillon B, Dubois B, Ploska A, Agid Y. Severity and specificity of cognitive impairment in Alzheimer's disease, Huntington's and Parkinson's diseases, and progressive supranuclear palsy. Neurology 1991;41:634-643.
5. Wright BA, Rosen JR, Buysse DJ, et al. Shy-Drager syndrome presenting as a REM behaviour disorder. J Geriatr Psychiatry Neurol 1990;3:110-113.
6. Saboiardo M, Girotti F, Strada L, Ciceri E. MRI in progressive supranuclear palsy and other parkinsonian disorders. J Neural Transm 1994;Suppl 42:93-110.
7. Konagaya M, Konagaya Y, Iida M. Clinical and MRI study of extrapyramidal symptoms in multiple system atrophy. J Neurol Neurosurg Psychiatry 1994;57:1528-1531.
8. Milton WJ, Atlas SW, Lavi E, et al. Magnetic Resonance Imaging of Creutzfeldt-Jacob disease. Ann Neurol 1991;29:438-440.
9. Finkenstaedt M, Szudra A, Zerr I, et al. MR imaging of Creutzfeldt-Jakob disease. Radiology 1996; 199:793-798.
10. Demaerel P, Heiner L, Robberecht W, et al. Diffusion-weighted MRI in sporadic Creutzfeldt-Jakob disease. Neurology 1999;52:205-208.
11. Bahn MM, Parchi P. Abnormal diffusion-weighted MRI in Creutzfeldt-Jakob disease. Arch Neurol 1999;56:577-583.
12. Duk LN, Chung KS, Seong HY, et al. Diffusion-weighted MRI in probable Creutzfeldt-Jakob disease. Arch Neurol 1999;56:951-957.
13. Magalhaes ACA, Caramelli P, Menezes JR, et al. Wilson's disease: MRI with clinical correlation. Neuroradiology 1994;36:97-100.
14. Zochodne DW, Young GB, McLachlan RS, et al. Creutzfeldt-Jakob disease without periodic sharp wave complexes: a clinical, electroencephalographic, and pathologic study. Neurology 1988; 38:1056-1060.
15. Vingerhoets FJG, Hegyi I, Aguzzi A, et al. An unusual case of Creutzfeldt-Jakob disease. Neurology 1998;51:617-619.
16. Ezrin-Waters C, Resch L, Lang AE. Coexistence of idiopathic Parkinson's disease and Creutzfeldt-Jakob disease. Can J Neurol Sci 1985;3:272-273.