

A Case of Multiple System Atrophy with Preexisting Alzheimer's Disease and Predating The Hot Cross Bun Sign

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Abstract-

Purpose: Synucleinopathy, tauopathy and amyloidopathy were classified as distinct clinical and pathological entities in traditional classification systems, and their interactions have been studied on neuropathology and molecular genetics recently.

Case Report: In this report, we present a 69-year-old male patient who had been diagnosed with probable Alzheimer's disease (AD) dementia due to progressive forgetfulness in February 2013. His Mini-Mental State Examination score was 21/30, and his Cognitive Abilities Screening Instrument score was 78/100, resulted from profound deficits in recent memory and abstract thinking domains. Initial brain magnetic resonance imaging (MRI) showed bilateral medial temporal lobe atrophy but was otherwise unremarkable. He presented with new-onset progressive gait disturbance 18 months after the diagnosis of AD, and mild ataxic gait and linear hyperintensity within the midline of the pons on axial T2-weighted MRI were documented. Neither extrapyramidal nor autonomic signs were observed. Ten months later, profound cerebellar signs, urinary incontinence, and mild axial rigidity consistent with the hot cross bun (HCB) sign were noted. Probable multiple system atrophy-cerebellar (MSA-C) type was finally diagnosed by the clinical and neuroimaging features. Of note, his diagnoses of AD and HCB sign predated the diagnosis of MSA-C by 28 and 10 months, respectively.

Conclusion: Given that the HCB sign rarely predates overt symptoms or a diagnosis of MSA, we hypothesized that the preexisting amyloidopathy and tauopathy exerted additional neurotoxicity on the synucleinopathy.

Key Words: Multiple system atrophy, hot cross bun sign, Alzheimer's disease

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INTRODUCTION

Multiple system atrophy (MSA) is a sporadic, progressive neurodegenerative disorder characterized

by varying degrees of extrapyramidal, cerebellar and autonomic features⁽¹⁾. Its subtypes, formerly called striatonigral degeneration, olivopontocerebellar atrophy, and Shy-Drager syndrome, are now termed MSA-

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parkinsonism (MSA-P), MSA-cerebellar system (MSA-C), and MSA-autonomic system (MSA-A) according to the predominance of the impaired system. Although there is a growing body of evidence describing the clinical presentations and neuroradiological features of MSA, several aspects have yet to be elucidated. Clinically, dementia was proposed to be one of the features not supporting a diagnosis of MSA in the 2008 consensus diagnostic criteria⁽¹⁾. However, an increasing number of pathologically-confirmed patients with MSA have been reported to have cognitive deficits and/or dementia⁽²⁾. Moreover, the synucleinopathy neurodegenerative diseases other than MSA have also been reported to progress or coexist with dementia⁽³⁾. In neuroradiological studies, several specific imaging features have been described, including putaminal slit, hot cross bun (HCB) sign, and associated atrophy of relevant regions⁽⁴⁾. While most patients with MSA share an identical pathognomonic pathology according to the hierarchy of region-specific susceptibility⁽⁵⁾, the pattern and development of imaging features vary according to clinical phenotypes. Moreover, the appearance of these imaging features is generally delayed, and they develop later than the clinical diagnosis and changes in pathology^(5,6). This suggests that additional pathology may participate in or coexist with the initially identified pathogenesis. In this report, we present a rare case of MSA with preexisting Alzheimer's disease (AD)⁽⁷⁾ predating the HCB sign, and discuss the possible pathogenesis.

CASE REPORT

This 69-year-old right-handed man with a past

history of diabetes mellitus was brought to our hospital in February 2013 by his family for a neuropsychiatric evaluation due to progressive cognitive complaints for 2-3 years. He had been the chief executive officer of a prestigious company with an education level of more than 12 years. He stated that he started having problems with managing his personal finances, followed by several episodes of getting lost after going for a walk around his neighborhood, causing distress to his wife and family. During the interview, heightened anxiety, especially when recalling his memory problems, was observed. While his thought contents were normal, the flow of thoughts was slow. His mood was not depressed, and his appetite and sleep remained unchanged. His Mini-Mental State Examination (MMSE) score was 21/30, and his Cognitive Abilities Screening Instrument (CASI) score was 78/100, which fell 1.5 standard deviations below the normative data⁽⁸⁾. Deficits were detected in recent memory and abstract thinking domains (Table 1).

Except for the cognitive impairments, his gait and motor performance were generally normal. Brain magnetic resonance imaging (MRI) showed bilateral hippocampal atrophy, but was otherwise unremarkable (Fig. 1). He was then diagnosed with probable AD dementia⁽⁷⁾ in the context of amnesic presentations supported by profound cognitive deficits and relevant medial temporal lobe atrophy. Treatment with rivastigmine, a cholinesterase inhibitor, with an optimized dose was initiated. The response to this treatment was good, as improvements in both MMSE (21/30 to 25/30) and CASI (78/100 to 80/100) scores we noted 1 year later (Table 1).

The patient remained neurologically stable until August 2014 (Table 2), when a mild but gradually

Table 1. The initial and follow-up cognitive assessment under treatment of cholinesterase inhibitor.

		Feb. 2013	Feb. 2014
Mini-Mental State Examination	(30)	21	25
Cognitive Abilities Screening Instrument Total score	(100)	78	80
Remote memory	(10)	10	10
Recent memory	(12)	6	4
Attention	(8)	8	8
Mental manipulation	(10)	9	10
Orientation	(18)	16	15
Abstract thinking	(12)	6	11
Language	(10)	7	10
Drawing	(10)	10	9
Verbal fluency	(10)	6	3

Number within parenthesis represents full score of each cognitive test.

Table 2. Clinical course of current case.

	Feb. 2013	Aug. 2014	Jun. 2015
Possible MSA			
Parkinsonism			V
Cerebellar syndrome		V	V
At least 1 feature of autonomic system disorder			V
At least 1 additional feature			V
Probable MSA			
Urinary incontinence or orthostatic hypotension			V
Poorly levodopa-responsive parkinsonism			V
Cerebellar syndrome			V

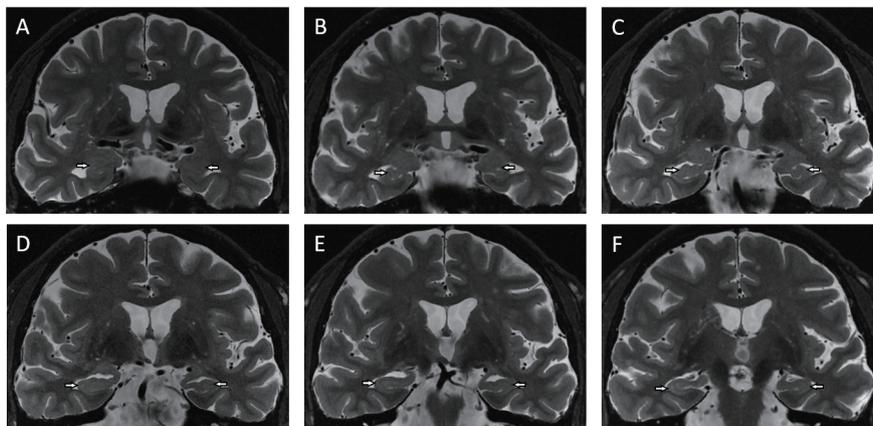


Figure 1. Initial coronal T2-weighted magnetic resonance images showing bilateral hippocampus atrophy (arrows) (A-F: rostral to caudal sections; thickness: 3 mm; Feb. 2013). The pathological changes are confined to the temporal regions. (Repetition time = 4000; echo time = 90).

progressive gait disturbance was noted, including difficulties in moving his feet, negotiating obstacles and maintaining balance. Months later, clumsiness involving his hands was noted, which was especially pronounced when using chopsticks or other utensils. A neurological examination revealed astasia, appendicular ataxia and generalized hyperreflexia. No extrapyramidal or autonomic signs were observed, however linear hyperintensity within the midline of the pons was noted in brain T2-weighted MRI. No horizontal lines in the pons or any pathological signs within the putamen in brain T2 fluid-attenuated inversion recovery image were noted at that time (Fig. 2B, E). Cervical spine MRI was also performed, and the results excluded the possibility of compressive cervical myelopathy. He was then advised to undergo rehabilitation

therapy to assist with balance and postural stability.

Unfortunately, his gait continued to deteriorate, and at a follow-up visit in June 2015 frequent falls were reported even with the assistance of a walker (Table 2). Additional findings including bradykinesia and axial rigidity were noted, which were consistent with symmetrically-impaired radio-uptake within bilateral basal ganglia as seen in a TRODAT scan (Fig. 3). He started experiencing voiding problems which finally resulted in implantation of a Foley tube due to a poor response to pharmacological treatment. A urodynamic study identified hypocontractility of the detrusor with mild outlet obstruction. Brain T2-weighted MRI at this time showed remarkable evolution compared with the previous two studies (Fig. 2C, F). The middle cerebellar peduncles appeared to be

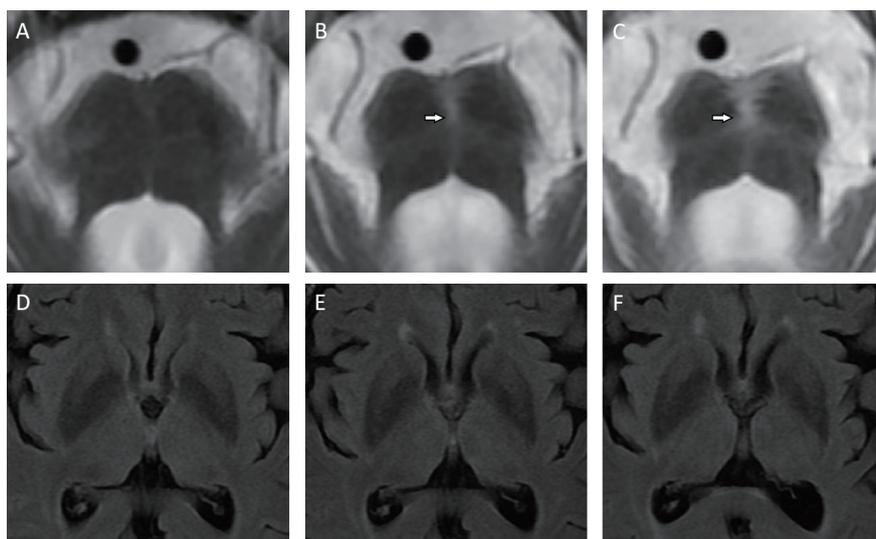


Figure 2. Axial magnetic resonance images showing sequential changes of pons and putamens (A & D: Feb. 2013; B & E: Aug. 2014; C & F: Jun. 2015) (A-C: T2-weighted images; D-F: T2 fluid-attenuated inversion recovery images). (A) normal appearance in pons (B) midline hyperintensity (arrow) (C) completion of hot cross bun sign (arrow) (D-F) no interval changes of putamens across serial studies (A-C: Repetition time = 5200; echo time = 100; D-F: Repetition time = 12000; echo time = 111).

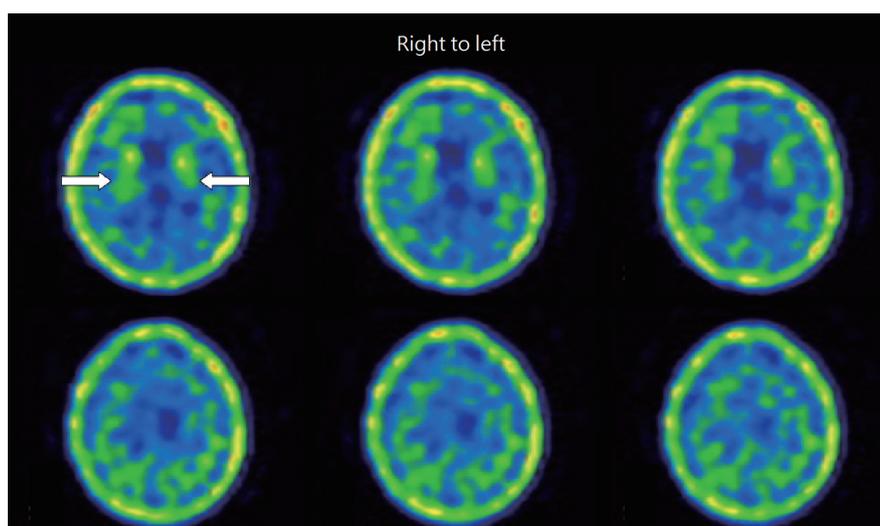


Figure 3. Tc-99m TRODAT-1 (Jun. 2015) showing impaired uptake in the bilateral basal ganglia (arrows) in line with additional parkinsonian features.

symmetrically atrophic and hyperintense (Fig. 4), with the new development of horizontal hyperintense lines within the pons forming a complete HCB sign with changes in the preexisting midline signal. In contrast to the findings in the infratentorial area, the putamen remained normal

(Fig. 2D-F). A diagnosis of MSA-C was finally made. Unfortunately, he became wheelchair-bound and required nasogastric feeding 8 months later, and finally succumbed to aspiration pneumonia 9 months after being diagnosed with MSA-C.

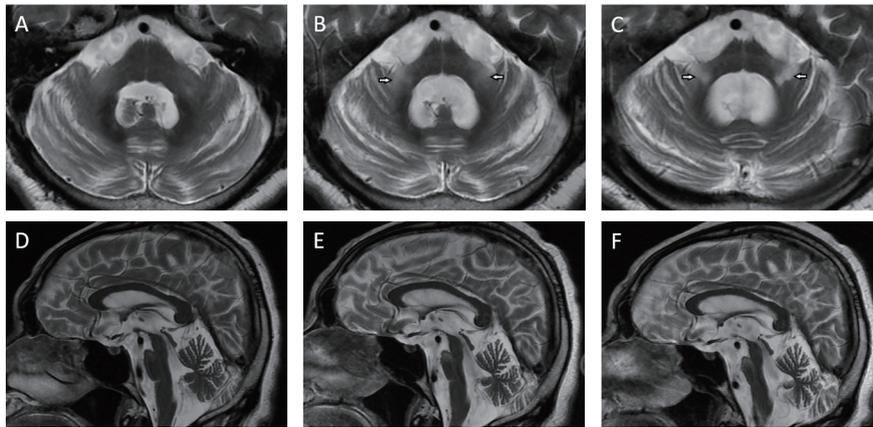


Figure 4. T2-weighted magnetic resonance images showing pathological changes of pons and cerebellums (A & D: Feb. 2013; B & E: Aug. 2014; C & F: Jun. 2015) (A-C: axial view; D-F: sagittal view). (A) normal appearance in pons (B) hyperintensity of bilateral middle cerebellar peduncles (arrows) (C) progression of hyperintensity and atrophy within bilateral middle cerebellar peduncles (arrows) (D-F) sequential volume reduction of pons and cerebellums, as evident by the distance between basilar artery to pons and prominence of folia of cerebellum (Repetition time = 5753; echo time = 111).

DISCUSSION

This case report describes the rare neurological consequences and evolution of neuroimaging findings in the context of coexisting AD and MSA. The rapid decline in motor performance and predating HCB sign provide an interesting insight into the interaction between two neurodegenerative diseases of distinct pathological properties. Delineating the time-based changes in the HCB sign with the neurological presentations also provides further insight into the fundamental pathogenesis of MSA.

Although the HCB sign is commonly seen in patients with MSA, its pathognomonic properties have yet to be determined, as its appearance has been reported in other neurodegenerative diseases. Differential diagnoses include spinocerebellar ataxia type II, III, VII, VIII⁽⁹⁾, variant Creutzfeldt-Jakob disease⁽¹⁰⁾, and parkinsonism secondary to vasculitis⁽¹¹⁾. A lack of family history and absence of signs related to ophthalmoplegia and myoclonus primarily excluded the possibility of spinocerebellar ataxia. The age at onset in the current case also favored MSA, as symptoms related to spinocerebellar ataxia generally appear between 30 to 50 years of age⁽¹²⁾. While variant Creutzfeldt-Jakob disease can present with a similar course, our patient had no relevant travel history and remained free from profound psychiatric symptoms during

the whole course. Furthermore, serial imaging evaluations did not reveal any signs typical of variant Creutzfeldt-Jakob disease. The clinical findings excluded vasculitis, as constitutional symptoms such as seizures, myoclonus, and fever were not present. Fragile X-associated tremor/ataxia syndrome may have been possible as part of the differential diagnosis with regards to cerebellar syndrome with additional extrapyramidal features. However, we regarded this to be unlikely, as he presented with a stable cognitive performance with acetylcholinesterase inhibitor treatment, normal appearing white matter, and no family history. Taken together, we are convinced that the diagnosis of MSA-C was properly made.

The pathogenesis of HCB in MSA is considered to involve glial cytoplasmic inclusions immunoreactivity for α -synuclein, accompanied by other pathological features such as neuronal cytoplasm inclusions positive for α -synuclein, neuritis, neuronal loss, myelin damage, and gliosis^(4,5). In one clinicoradiological study, the appearance of the HCB sign, which is far more commonly identified in MSA-C than in MSA-P or MSA-A, was mostly delayed until after the formal clinical diagnosis⁽⁶⁾. This delay between the appearance of MSA symptoms and completion of the HCB sign can be as long as 5 years or even longer in patients with MSA-C⁽⁶⁾. Intriguingly, a small proportion of patients with MSA have been

reported to be free of the HCB sign even in the presence of profound debility^(6,13). This suggests that the formation of the HCB sign may be an important (but not the sole) structural change resulting in the neurological consequences of MSA. With the advent of diffusion tensor imaging, microstructural changes within transverse and longitudinal fibers have been shown to predate the formation of the HCB sign and to be correlated with the clinical presentations in a more sensitive manner⁽¹⁴⁾. In addition, the detection of iron deposition adjacent to the HCB sign in T2-weighted imaging has also shown that ferritin-bound iron deposition within the basis pontis is an additional pathological change in patients with MSA⁽¹³⁾. Taken together, the structural changes related to MSA are: (i) gliosis, neuron loss, and myelin fiber damage along the transverse and longitudinal fibers; and (ii) ferritin-bound iron deposition within the basis pontis.

In a retrospective study, patients with MSA generally remained ambulant for 6 years from the onset of gait difficulties⁽¹²⁾. Although an older age at onset was mildly associated with accelerated disease progression and the risk of death⁽¹²⁾, our case had a relatively rapid deterioration in motor performance and a shorter life expectancy than average. We therefore suggest that the coexistence of synucleinopathy and tauopathy/amyloidopathy rather than the age at onset was responsible for our patient's dismal prognosis. The deposition of tau protein and amyloid plaque has frequently been reported to be the main pathogenesis of AD^(15,16), whilst synucleinopathy has been reported to be the main pathological findings for MSA^(17,18). Although synucleinopathy, tauopathy and amyloidopathy constitute distinct clinical and pathological entities in traditional classification systems, their interaction has been highlighted in studies on neuropathology and molecular genetics. Synuclein and tau protein have been proposed to act synergistically in neurodegeneration. From a clinical viewpoint, an overlapping spectrum of neurodegenerative diseases has frequently been reported (e.g., coexisting Parkinson's disease, synucleinopathy with AD, and tauopathy)⁽¹⁸⁾. Pathologically, neurons labeled with both α -synuclein and tau protein have also been associated with Lewy bodies in the brains of patients with Parkinson's disease or dementia with Lewy bodies⁽¹⁹⁾. At the molecular level, in vitro experimental evidence has demonstrated that α -synuclein not only binds to tau but also stimulates its

phosphorylation and aggregation⁽¹⁸⁾. Another in vivo study demonstrated that the tau protein itself can promote the accumulation of α -synuclein and vice versa in a bigenic mice model⁽²⁰⁾.

Interactions between α -synuclein and amyloidosis, although not conclusive, have been reported in recent neuroscience research. Several neuropathological studies have also reported that the deposition of amyloid plaque appears to be mitigated by the coexistence of Lewy bodies, as the amount of amyloid plaque has been reported to be lower in the hippocampus, frontal and temporal cortices in patients with AD with Lewy bodies compared to those without^(21,22). These results seem to be in contrast to clinical observations, as patients with Lewy body dementia often present with faster cognitive decline than those with pure AD⁽²³⁾. Another study reported that A β plaque and α -synuclein interact in vivo to promote the aggregation and accumulation of each other and accelerate cognitive dysfunction⁽²⁴⁾. Advanced molecular modeling has also shown that interactions between α -synuclein and A β dimers on the membrane results in additional α -synuclein molecules, leading to the formation of more stable pentamers and hexamers that adopt a ring-like structure which has been associated with increased intracellular calcium levels and eventually cell death⁽²⁵⁾. An animal study by Bachhuber et al.⁽²⁶⁾ appeared to bridge clinical observations and biochemical research findings. In their study, the authors compared two transgenic models, APPPS1 and double transgenic mice (APPPS1 mice crossed with A30P- α -synuclein mice). While there were no differences in the levels of soluble A β and APP mRNA in the younger mice without plaque deposition, the double transgenic mice had fewer hippocampal plaques but higher levels of cerebrospinal fluid A β at the age of 4 months. These findings suggest that α -synuclein interferes with the deposition but not production of A β . However, such α -synuclein-mediated inhibition of A β aggregation and deposition had a detrimental effect on synaptic structures, as dendritic spine density and synaptophysin levels in the hippocampus of the double transgenic mice were far lower compared to their single- or non-transgenic littermates, even before the onset of A β deposition.

In conclusion, we presented a 69-year-old man whose AD diagnosis and HCB sign predated the diagnosis of MSA-C by 28 and 10 months, respectively. Although the

spatial evolution of his HCB sign was consistent with previous studies, the earlier appearance of the HCB sign along with his motor decline supported the hypothesis that the preexisting amyloidopathy and tauopathy exert additional neurotoxicity on the current synucleinopathy.

REFERENCES

- Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Dürr A, Fowler CJ, Kaufmann H, Klockgether T, Lees A, Poewe W, Quinn N, Revesz T, Robertson D, Sandroni P, Seppi K, Vidailhet M. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology* 2008;71:670-676.
- Asi YT, Ling H, Ahmed Z, Lees AJ, Revesz T, Holton JL. Holton. Neuropathological features of multiple system atrophy with cognitive impairment. *Mov Disord* 2014;29:884-888.
- Irwin DJ, Lee VM, Trojanowski JQ. Trojanowski. Parkinson's disease dementia: convergence of alpha-synuclein, tau and amyloid-beta pathologies. *Nat Rev Neurosci* 2013;14:626-636.
- Fanciulli A, Wenning GK. Multiple-system atrophy. *N Engl J Med* 2015;372:249-263.
- Cykowski MD, Coon EA, Powell SZ, Jenkins SM, Benarroch EE, Low PA, Schmeichel AM, Parisi JE. Expanding the spectrum of neuronal pathology in multiple system atrophy. *Brain* 2015;138:2293-2309.
- Horimoto Y, Aiba I, Yasuda T, Ohkawa Y, Katayama T, Yokokawa Y, Goto A, Ito Y. Longitudinal MRI study of multiple system atrophy - when do the findings appear, and what is the course? *J Neurol* 2002;249:847-854.
- McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011;7:263-269.
- Lin KN, Wang PN, Liu HC, Teng EL. [Cognitive Abilities Screening Instrument, Chinese Version 2.0 (CASI C-2.0): administration and clinical application]. *Acta Neurol Taiwan* 2012;21:180-189.
- Lee YC, Liu CS, Wu HM, Wang PS, Chang MH, Soong BW. The 'hot cross bun' sign in the patients with spinocerebellar ataxia. *Eur J Neurol* 2009;16:513-516.
- Soares-Fernandes JP, Ribeiro M, Machado A. "Hot cross bun" sign in variant Creutzfeldt-Jakob disease. *AJNR Am J Neuroradiol* 2009;30:E37.
- Muqit MM, Mort D, Miskiel KA, Shakir RA. "Hot cross bun" sign in a patient with parkinsonism secondary to presumed vasculitis. *J Neurol Neurosurg Psychiatry* 2001;71:565-566.
- Klockgether T, Lüdtke R, Kramer B, Abele M, Bürk K, Schöls L, Riess O, Laccone F, Boesch S, Lopes-Cendes I, Brice A, Inzelberg R, Zilber N, Dichgans J. The natural history of degenerative ataxia: a retrospective study in 466 patients. *Brain* 1998;121 (Pt 4):589-600.
- Deguchi K, Ikeda K, Kume K, Takata T, Kokudo Y, Kamada M, Touge T, Honjo N, Masaki T. Significance of the hot-cross bun sign on T2*-weighted MRI for the diagnosis of multiple system atrophy. *J Neurol* 2015;262:1433-1439.
- Yang H, Wang X, Liao W, Zhou G, Li L, Ouyang L. Ouyang. Application of diffusion tensor imaging in multiple system atrophy: the involvement of pontine transverse and longitudinal fibers. *Int J Neurosci* 2015;125:18-24.
- Grundke-Iqbal I, Iqbal K, Quinlan M, Tung YC, Zaidi MS, Wisniewski HM. Microtubule-associated protein tau. A component of Alzheimer paired helical filaments. *J Biol Chem* 1986;261:6084-6089.
- Masters CL, Simms G, Weinman NA, Multhaup G, McDonald BL, Beyreuther K. Beyreuther. Amyloid plaque core protein in Alzheimer disease and Down syndrome. *Proc Natl Acad Sci U S A* 1985;82:4245-4249.
- Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). *J Neurol Sci* 1989;94:79-100.
- Galpern WR, Lang AE. Interface between tauopathies and synucleinopathies: a tale of two proteins. *Ann Neurol* 2006;59:449-458.
- Ishizawa T, Mattila P, Davies P, Wang D, Dickson DW. Colocalization of tau and alpha-synuclein epitopes in

- Lewy bodies. *J Neuropathol Exp Neurol* 2003;62:389-397.
20. Giasson BI, Forman MS, Higuchi M, Golbe LI, Graves CL, Kotzbauer PT, Trojanowski JQ, Lee VM. Initiation and synergistic fibrillization of tau and alpha-synuclein. *Science* 2003;300:636-640.
 21. Bergeron C, Pollanen M. Lewy bodies in Alzheimer disease--one or two diseases? *Alzheimer Dis Assoc Disord* 1989;3:197-204.
 22. Gibb WR, Mountjoy CQ, Mann DM, Lees AJ. A pathological study of the association between Lewy body disease and Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1989;52:701-708.
 23. Olichney JM, Galasko D, Salmon DP, Hofstetter CR, Hansen LA, Katzman R, Thal LJ. Cognitive decline is faster in Lewy body variant than in Alzheimer's disease. *Neurology* 1998;51:351-357.
 24. Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM. Synergistic Interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. *J Neurosci* 2010;30:7281-7289.
 25. Tsigelny IF, Crews L, Desplats P, Shaked GM, Sharikov Y, Mizuno H, Spencer B, Rockenstein E, Trejo M, Platoshyn O, Yuan JX, Masliah E. Mechanisms of hybrid oligomer formation in the pathogenesis of combined Alzheimer's and Parkinson's diseases. *PLoS One* 2008;3:e3135.
 26. Bachhuber T, Katzmarski N, McCarter JF, Loreth D, Tahirovic S, Kamp F, Abou-Ajram C, Nuscher B, Serrano-Pozo A, Müller A, Prinz M, Steiner H, Hyman BT, Haass C, Meyer-Luehmann M. Inhibition of amyloid-beta plaque formation by alpha-synuclein. *Nat Med* 2015;21:802-807.