A case of multiple system atrophy-parkinsonian type with stuttering- and palilalia-like dysfluencies and putaminal atrophy

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出版情報：Journal of Fluency Disorders. 57, pp.51-58, 2018-09-01. Elsevier
バージョン：
権利関係：

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Financial Disclosures: This work was supported by the Japan Agency for Medical Research and Development (to Y. K.) and Grant-in-Aid for Young Scientists (B) (17K16922) (to Y. K.).

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Abstract

Both developmental and acquired stuttering are related to the function of the basal ganglia-thalamocortical loop, which includes the putamen. Here, we present a case of stuttering- and palilalia-like dysfluencies that manifested as an early symptom of multiple system atrophy-parkinsonian type (MSA-P) and bilateral atrophy of the putamen. The patient

was a 72-year-old man with no history of developmental stuttering who presented with a stutter for consultation with our otorhinolaryngology department. The patient was diagnosed with MSA-P based on parkinsonism, autonomic dysfunction, and bilateral putaminal atrophy revealed by T2-weighted magnetic resonance imaging. Treatment with levodopa improved both the motor functional deficits related to MSA-P and stuttering-like dysfluencies while reading; however, the palilalia-like dysfluencies were much less responsive to levodopa therapy. The patient died of aspiration pneumonia two years after his first consultation at our hospital. In conclusion, adult-onset stuttering- and palilalia-like dysfluencies warrant careful examination of the basal ganglia-thalamocortical loop, and especially the putamen, using neuroimaging techniques. Acquired stuttering may be related to deficits in dopaminergic function.

Keywords: neurogenic stuttering, L-dopa, parkinsonism, putamen, basal ganglia

Abbreviations: BGTC loop, basal ganglia-thalamocortical loop; CVA, cerebrovascular accident; MRI, magnetic resonance imaging; MSA-P, multiple system atrophy, Parkinsonian type; PD, Parkinson’s disease; SLD, stuttering-like dysfluency; T2WI, T2-weighted imaging; TBI, traumatic brain injury; UPDRS, Unified Parkinson's Disease Rating Scale.

1. Introduction

Neurogenic stuttering is an acquired speech disorder that typically affects adults with neurological disease; such stuttering is most often associated with cerebrovascular accident (CVA) (Theys et al., 2011, 2013; Tani and Sakai 2010, 2011; Jokel, De Nil, and Sharpe, 2007; Grant et al., 1999; Ardila and Lopez 1986; Helm-Estabrooks, 1986; Helm et al., 1978; Rosenfield, 1972), traumatic brain injury (TBI) (Strasberg et al., 2016; Jokel et al., 2007; Helm-Estabrooks and Hotz, 1998; Ludlow et al., 1987), and neurodegenerative disease (Koller, 1983; Leder, 1996). TBI and CVA are easily diagnosed as causes of neurogenic stuttering; TBI is normally reported after a traumatic event, and CVAs such as brain infarction can be diagnosed in early stages using diffusion-weighted imaging (Minematsu et al., 1992), while brain hemorrhages can be diagnosed with computed tomography (Tohgi et al., 1981). In contrast, stuttering accompanying neurodegenerative disease is frequently overlooked or misdiagnosed, especially in early stages of the disease.

To some degree, the phenomenology of stuttering resembles that of a gait disorder in Parkinson's disease (PD). PD is a disorder that involves the basal ganglia, and gait in patients with PD is typically characterized by small steps (i.e., reduced stride length) and lower cadence associated with reduced gait speed, together with festination and freezing (i.e., difficulty in gait initiation or stopping when turning or approaching an obstacle) (Giladi et al., 1992). Visual (e.g., floor markers) or auditory (e.g., metronome) cueing can improve gait performance in

patients with PD (Suteerawattananon et al., 2004; Lim et al., 2005). Similarly, stuttering is also improved by use of a metronome or other external auditory cueing (Brady, 1969; Toyomura et al., 2011). Recently, the cortico-basal ganglia-cortical network was implicated as a neural substrate of both acquired stuttering (Theys et al., 2013) and developmental stuttering (Sitek et al., 2016; Yang et al., 2016; Toyomura et al., 2015; Chang et al., 2016, 2013; Craig-McQuaide et al., 2014; Ingham et al., 2013). In developmental stuttering, putaminal neuropathology appears to underlie the disorder (Ingham et al., 2013; Beal et al., 2013; Jiang et al., 2012; Toyomura et al., 2011, 2015; Chang et al., 2009; Lu et al., 2010; Alm, 2004). Putaminal atrophy has been reported in Parkinson-plus syndromes such as multiple system atrophy-parkinsonian type (MSA-P) (Schrag et al., 1998; Feng et al., 2015). MSA-P is characterized by parkinsonism (bradykinesia, rigidity, irregular jerky tremor, and postural instability), as well as autonomic failure in the form of bladder dysfunction (including early urinary incontinence) and/or orthostatic hypotension (Gilman et al., 2008). Here, we describe a case of adult-onset stuttering associated with MSA-P and bilateral putaminal atrophy diagnosed using magnetic resonance imaging (MRI).

2. Case presentation

The patient was a 72-year-old right-handed man with no history of stuttering. At the age of 70 years, the patient's wife reported that he was repeating his speech and that this was

the time at which he first noticed his stuttering. He went to a hospital complaining of only the stutter and underwent diagnostic MRI, but no abnormalities were detected. However, at the age of 71 years, he noticed a tremor of the hands and abnormal gait (short steps and difficulty changing direction). Thereafter, he went to another hospital to receive a second opinion, but, once again, there were no abnormal findings on MRI. At the age of 72 years, the patient read a newspaper advertisement about consultation for stuttering and visited our department. His speech was characterized by repetitions and blocks. He also presented with hand and tongue tremors, and it was suggested that he undergo MRI for suspected basal ganglia abnormalities.

MRI revealed bilateral atrophy of the putamen and hyperintensity of the putaminal rims on T2-weighted imaging (T2WI; Figure 1). Our patient showed an average putamen: caudate volume ratio of 1.24 (right 1.43, left 1.07); based on the ratio values reported by Shin et al. (2007), MSA-P was suspected. The patient was then referred to the Department of Neurology for consultation and was admitted. Upon examination by a neurologist, the patient exhibited parkinsonian symptoms (rigidity of the extremities and body trunk, bradykinesia, irregular jerky tremor of the hands and tongue, postural instability, micrographia, hypophonia, retropulsion, difficulty changing direction, and abnormal gait [stooped posture, wide-based and small steps, and reduced arm swing]) and other findings (dysdiadochokinesia, hyperactive perioral and jaw jerk reflex, hyperactive deep tendon reflexes). The patient also exhibited autonomic symptoms (i.e., orthostatic hypotonia [positive Schellong test results], urinary

dysfunction, and impaired sweating [abnormal quantitative sudomotor axon reflex test results]). The patient also presented with impaired smooth pursuit eye movements, limited upgaze but normal downgaze, dysmetria and intention tremor on finger-nose and heel-knee-shin tests, and mild cognitive impairment (Frontal Assessment Battery score of 7 and Mini-Mental State Examination score of 25). Myocardial scintigraphy with I-123 metaiodobenzylguanidine revealed no abnormal scores in early- and delayed-phase imaging.

The patient's treatment course is summarized in Figure 2. After his consultation at the Department of Neurology, the patient was treated for MSA-P with L-DOPA/carbidopa (L-DOPA 100 mg/day); the dose of L-DOPA was increased about 6 weeks later (L-DOPA 300 mg/day) and again 1 week after that (L-DOPA 600 mg/day). L-DOPA at a dose of 600 mg/day caused the patient to have trouble sleeping; hence, the dose was decreased to 450 mg/day.

Motor function was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) part-III (Fahn, Elton, & Members of the UPDRS Development Committee, 1987). The UPDRS is used to rate the severity of various common areas of impairment in PD; part-III is a motor examination containing 27 items that are each scored from 0 (normal) to 4 (severe disability), with a range of total possible scores from 0 (normal) to 108 (severely impaired). Our patient's UPDRS part-III score was 46 with L-DOPA/carbidopa (L-DOPA 100 mg/day), and decreased to 29 when the dose of L-DOPA was increased to 450 mg/day. No UPDRS part-III score data were obtained prior to medication.

The patient's "stuttering" was not completely typical; hence, stuttering-like dysfluencies (SLDs) of this patient were evident through repetitions of sounds, syllables, monosyllabic words and prolongations or blocks (dysfluencies typical of stuttering), as well as repetition of whole words or phrases (palilalia-like dysfluency), while reading sentences from Jack and the Beanstalk. The frequency of SLDs was calculated as a percentage by dividing the number of stuttering occurrences by the number of segments (Moriyama et al., 1981). The proportion of presented SLDs was 13.1% (2.4% for syllable repetitions, 8.3% for whole word repetitions, and 2.4% for blocks) before medication, 10.7% (1.2% for syllable repetitions and 9.5% for whole-word repetitions) with L-DOPA/carbidopa 300 mg/day, 4.8% (4.8% for whole-word repetitions) with L-DOPA/carbidopa 600 mg/day, and 9.5% (1.2% for syllable repetitions and 8.3% for whole-word repetitions) with L-DOPA/carbidopa 450 mg/day (Table 1). The dysfluencies typical of stuttering were improved with L-DOPA/carbidopa doses of 300, 450, and 600 mg/day, but those typical of palilalia only improved with a L-DOPA/carbidopa dose of 600 mg/day. We encountered a reading adaptation effect and no improvement in SLDs during singing. The patient read the same sentences aloud 5 times from Jack and the Beanstalk. SLDs decreased with each reading (first reading, 13.1%; second, 11.9%; third, 6.0%; fourth, 7.1%; fifth, 8.3%); they occurred for both functors and content words, and the patient felt no anxiety about dysfluencies. Most dysfluencies did not include the initial syllables of words or phrases. There were no secondary symptoms such as facial grimacing, fist clenching, or eye

blinking. Stuttering persisted throughout the treatment course. The patient died from aspiration pneumonia 2 years after his first visit to the Department of Otorhinolaryngology.

3. Discussion

This is the first report to describe adult-onset stuttering as an early symptom of MSA-P. A detailed evaluation of the basal ganglia on MRI was diagnostically useful in this case.

3.1 Neurogenic stuttering as an early symptom of MSA-P

The presence of extrapyramidal symptoms indicated that the possible diagnoses were MSA-P, PD, or progressive supranuclear palsy (PSP). Because the patient also had autonomic symptoms, and MRI revealed bilateral putaminal atrophy, the most probable diagnosis was MSA-P. Cardiac sympathetic denervation on myocardial scintigraphy with I-123 metaiodobenzylguanidine would have provided supportive criteria for distinguishing PD from MSA-P (Postuma et al., 2015; Marini et al., 2010); however, our patient did not present with any abnormal scores. Affected downgaze with parkinsonian symptoms would have indicated PSP (Litvan et al., 1996; Chen et al., 2010), but the patient's downgaze was normal. Many healthy elderly subjects have a limited range of upgaze (so-called "Blickerschwernis") but not downgaze (Clark and Isenberg, 2001; Oguro et al., 2004); thus, the patient's eye movements did not indicate PSP.

MSA is a sporadic neurodegenerative disorder that encompasses olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome, all of which were originally described as independent clinicopathological entities (Dejerine and Thomas, 1900; van der Eecken et al., 1960; Shy and Drager, 1960). Pappe et al. (1989) and Nakazato et al. (1990) described glial cytoplasmic inclusions in oligodendroglia as a hallmark of MSA, regardless of clinicopathological phenotype. Watanabe et al. (2002) investigated MSA disease progression and survival and found that the median time from initial symptom onset to combined motor and autonomic dysfunction was 2 years (range, 1–10 years). Median intervals from onset to requiring assistance for walking, confinement to a wheelchair, a bedridden state, and death were 3, 5, 8, and 9 years, respectively. In the case presented here, MSA-P was diagnosed 2 years after the onset of stuttering. Accordingly, we suggest that it may be difficult to diagnose MSA in its early stage. Thus, adult-onset speech dysfluencies such as stuttering should be considered as possible early symptoms of basal ganglia disorders.

3.2 MRI for the diagnosis of neurodegenerative disease

Neurodegenerative diseases involving neurogenic stuttering can be difficult to diagnose. The diagnosis of PD largely relies on clinician experience, and an accurate diagnosis often requires 3–5 years of follow-up (Wang et al., 2016). The diagnosis of MSA-P has been made easier by advances in MRI. Findings suggestive of MSA-P on T2WI include

hyperintensity of the putaminal rim, putaminal hypointensity, and putaminal atrophy (Schrag et al., 1998); however, the two former signs are not specific to MSA-P (Kraft et al., 1999; Lee et al., 2005). In contrast, putaminal atrophy is highly specific to MSA-P, and has been shown to distinguish MSA-P from PD and healthy control subjects with 92.3% specificity and 44.4% sensitivity (Feng et al., 2015). To identify possible putaminal atrophy, we measured the putamen: caudate volume ratio, and found our patient had an average ratio of 1.24 (right 1.43, left 1.07). Shin et al. (2007) had measured the putamen: caudate volume ratio, and found that the ratio in MSA (1.29 ± 0.28) was significantly lower than that in PD (1.91 ± 0.29, $p < 0.0001$). Setting an arbitrary cutoff ratio of 1.6 resulted in about 90% of patients with MSA falling into the group with the lower ratio, whereas more than 80% of patients with PD belonged to the other group. In the present case, bilateral putaminal atrophy and hyperintensity of the putaminal rim facilitated a diagnosis of MSA-P.

3.3 Neurogenic stuttering and the basal ganglia-thalamocortical loop

The six features of neurogenic stuttering include: 1) dysfluencies occur for grammatical words at a similar rate of occurrence to that of substantive words; 2) repetitions, prolongations, and blocks occur in all word positions; 3) there is a consistency in stuttering behavior in all word positions; 4) the speaker does not appear overly anxious about the stuttering behavior; 5) secondary symptoms such as facial grimacing, fist clenching, and eye

blinking are rarely observed; and 6) an adaptation is not observed (Lundgren, Helm-Estabrooks, & Klein, 2010; Jokel et al., 2007; Rosenfield, 1972).

Our patient presented with five of the six features of neurogenic stuttering, but an adaptation effect was observed. Jokel et al. (2007) considered the adaptation effect to occur if dysfluencies over the three readings decreased by minimum of 30%. Our patient showed a 54.5% decrease in the third reading compared to that in the first reading at the first visit (with no medication). Thus, according to Jokel et al.'s (2007) criteria, our patient showed the reading adaptation effect. Those with neurogenic stuttering sometimes show the reading adaptation effect, and the absence of the adaptation effect does not seem to be a reliable differential criterion (Theys, van Wieringen, & De Nil, 2008).

Neurogenic stuttering has been associated with dysfunction of the basal ganglia-thalamocortical (BGTC) loop, including the putamen and supplementary motor area (SMA) (Alm, 2004). Neurogenic stuttering associated with lesion of the left putamen was reported in one case by Kono et al. (1998), in 1 of 3 cases reported by Heuer et al. (1996), in 2 of 3 cases reported by Ciabarra et al. (2000), and in 5 cases reported by Tani et al. (2011). Neurogenic stuttering was also associated with lesions of the left thalamus has been reported by Van Borsel et al. (2003) and Heuer et al. (1996). Furthermore, stuttering after SMA lesions has been described by Van Borsel (1998). Concurrent with these findings, Alm (2004) proposed that the BGTC loop plays a key role in stuttering via the putamen. The case presented here provides

further evidence for a relationship between stuttering and the BGTC loop via the putamen.

3.4 The effectiveness of L-DOPA in MSA-P

The UPDRS part-III is a reliable scale for rating the severity of parkinsonism in MSA-P (Tison et al., 2002). In the case here, increasing the dose of L-DOPA led to temporary improvements in the UPDRS part-III score. Relative changes in dopamine levels can be inferred from changes in UPDRS motor performance, as reported in a study by Kempster et al. (1989). Although a poor response to L-DOPA is one of the consensus criteria for the diagnosis of MSA (Gilman et al., 2008), positive L-DOPA motor responsiveness has been reported in 33–75% of patients with MSA (Colosimo et al., 1995; Wenning et al., 1994, 1995, 2005; Hughes et al. 1992; Fearnley and Lees, 1990; Rajput et al. 1990). This beneficial effect has been found to persist for several years in only 13% of all patients (Wenning et al., 1994). Because our patient died two years after being diagnosed, the ability to evaluate any such effect was limited.

Positive L-DOPA/carbidopa effects on SLDs despite bilateral putamen atrophy could be due to two reasons. One reason is that dopaminergic treatment probably increases cortical connectivity between prefrontal and premotor areas (Michely et al., 2015; Herz et al., 2014). Thus, improvement of SLDs could be due to dopamine enhancement of these cortical regions and/or the putamen, all of which have been associated with SLDs. The other reason is that the improvement of SLDs was probably related to noradrenaline levels. L-DOPA/carbidopa

increases the blood levels of both dopamine and noradrenaline (Delmas, Rothmann, & Flesch, 2008). Freezing of gait with difficulty initiating step movements in the late phase of PD could be attributed to the loss of noradrenergic neurons in the locus coeruleus and their projections to the frontal lobe (Espay, Lewitt & Kaufmann, 2014; Ono et al., 2016). The frequency of SLDs in our case also appeared to change according to the L-DOPA/carbidopa dose. Thus, the case presented here suggests a possible relationship between dopamine or norepinephrine function, Parkinsonian symptoms, and stuttering in MSA-P.

It is notable that this finding is partly inconsistent with those of previous studies regarding neurogenic stuttering and L-DOPA. L-DOPA treatment has been reported to improve (Koller, 1983; Leder et al., 1996), worsen (Louis et al., 2001; Anderson et al., 1999), or have no effect (Goberman and Blomgen, 2003) on the frequency of SLDs in parkinsonism. Goberman and Blomgen (2003) suggested that speech dysfluency might be related to any changes (increase or decrease) in brain dopamine levels.

Since repetitive speech phenomena have been classified in two categories in past studies (Sterling, 1924; Benke et al., 2000; Benke and Butterworth, 2001; Goberman, Blomgren & Metzger, 2010; Brabo, Minett & Ortiz, 2015), we divided the SLDs into dysfluencies typical of stuttering and those typical of palilalia. Notably, there were significant discrepancies between types in terms of their improvement in response to L-dopa/carbidopa treatment. Dysfluencies typical of stuttering responded well to L-DOPA/carbidopa, whereas

palilalia-like dysfluencies decreased in response to only the highest L-DOPA/carbidopa dose. Benke et al. (2000) noted that the origin of palilalia seemed to be a disruption of fronto-subcortical circuits at the level of the basal ganglia. It is well known that repetitive speech phenomena appear in patients with dementia (Benke and Butterworth, 2001), and in our case, mild dementia with frontal lobe dysfunction was noted, as revealed by his low Frontal Assessment Battery score. Therefore, we consider the neuroanatomical (i.e., frontal lobe inclusion) differences between stuttering- and palilalia-like dysfluencies to be the substrate underlying the different responses to L-DOPA/carbidopa. Future studies are required to determine the exact role of dopamine and/or norepinephrine and the BGTC loop in neurogenic stuttering.

Acknowledgments

We would like to thank Dr. Dai Matsuse and Dr. Reiko Sakoda at the Department of Neurology in Kyushu University Hospital, who diagnosed and treated this patient. We would also like to thank Editage (www.editage.jp) for English language editing.

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Table 1. The proportion of stuttering-like dysfluencies corresponding to the dose of L-DOPA/carbidopa.

		Before medication	L-DOPA/carbidopa (L-DOPA, 300 mg/day)	L-DOPA/carbidopa (L-DOPA, 600 mg/day)	L-DOPA/carbidopa (L-DOPA, 450 mg/day)
Dysfluency typical of stuttering	Syllable repetitions	2.4%	1.2%	0%	1.2%
	Blocks	2.4%	0%	0%	0%
Palilalia-like dysfluency	Whole word repetitions	8.3%	9.5%	4.8%	8.3%
Total		13.1%	10.7%	4.8%	9.5%

Figures

Figure 1. Bilateral putaminal atrophy and rim hyperintensity on T2WI

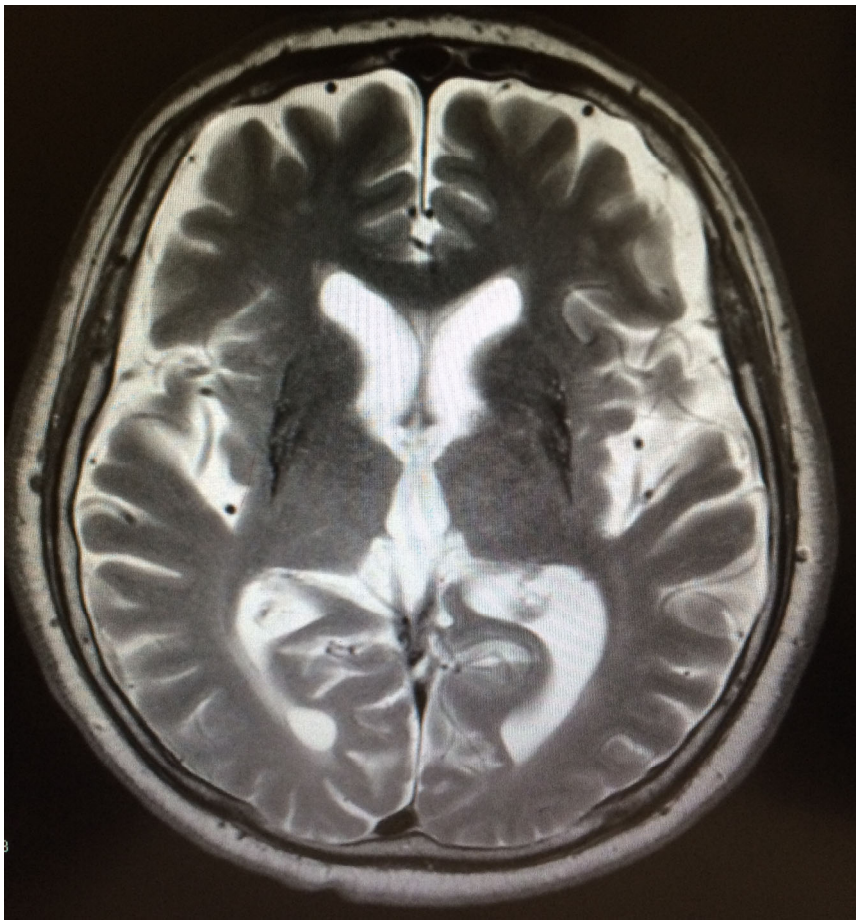

Figure 2. The patient's treatment course; UPDRS, Unified Parkinson's Disease Rating Scale; SLD, stuttering-like dysfluency.