Torres et al., *Cogent Medicine* (2018), 5: 1564530
https://doi.org/10.1080/2331205X.2018.1564530

cogent medicine

NEUROLOGY | CASE REPORT

A "hot crossed buns" sign, orthostatic syncope & gait ataxia point to probable multiple systems atrophy with dysarthria and slowed fluency suspicious for associated cognitive impairment

Anthony C. Torres[1]*, Garet J. Zaugg[1], Nasir Tufail[2] and Paul H. Janda[1]

Received: 21 June 2018
Accepted: 26 December 2018
First Published: 31 December 2018

*Corresponding author: Anthony C. Torres, Valley Hospital Medical Center, 620 Shadow Lane, Las Vegas, NV 89106, USA
E-mail: anthonyto@pcom.edu

Reviewing editor:
Anne Spurkland, University of Oslo, Norway

Additional information is available at the end of the article

Abstract: Multiple systems atrophy (MSA) describes a group of rare neurodegenerative disorders classified as Parkinsonism predominant (MSA-P) or cerebellar ataxia (MSA-C) subtypes. Parkinsonism or cerebellar ataxia is frequently the initial motor symptom; it is often accompanied by autonomic dysregulation presenting as orthostatic hypotension. MSA is a clinical diagnosis. Three levels of diagnostic certainty are recognized. A diagnosis of "definite MSA" requires autopsy confirmation. A "probable" diagnosis has a sporadic and progressive adult-onset with prominent dysautonomia and either motor symptoms which are poorly responsive to levodopa, or cerebellar ataxia. A diagnosis of "possible" MSA requires at least one feature suggesting autonomic dysfunction plus another feature, which is either determined on clinical grounds or via neuroimaging. The case described here is a case of adult onset recurrent syncope, unambiguous orthostatic hypotension, progressively worsening gait ataxia, slowed fluency, and dysarthria with cognition remaining grossly intact. Axial T2-weighted imaging depicted hyper-intense

ABOUT THE AUTHORS

Anthony C. Torres DO studied Osteopathic Medicine at the renowned Philadelphia College of Osteopathic Medicine. Following undergraduate studies in Psychology and Biology at the York College of Pennsylvania, he was surrounded by influence from The Center for Chronic Diseases of Aging while studying at The Philadelphia College of Osteopathic Medicine where he developed interest in the field of Neurology. Research interests include aspects of infections brain disease and behavior as well as cognition and components of language. This case report presented here highlights a particular case of the relation between brain and motor function coupled the fluency component of language and the suspected relation to cognition.

Garet J. Zaugg DO completed his undergrad studies in Psychology at Brigham Young University before obtaining his degree in Osteopathic Medicine at Touro University, Nevada. He currently practices as a resident physician specializing in Neurology at Valley Hospital Medical Center in Las Vegas, Nevada, and is anticipated to graduate in 2020.

PUBLIC INTEREST STATEMENT

Multiple system atrophy (MSA) is a rare Neurological disorder with similarities to Parkinson's disease. MSA typically presents in middle age and will often cause difficulty walking, dizziness and passing out due to trouble maintaining blood pressure when changing positions. Unfortunately it is a degenerative disease without an effective treatment. More and more evidence is suggestive of MSA having an association with cognitive impairment. This article describes a case of probable MSA in which some signs of speech production may point to an association with impaired thought processes. Unique MRI images known as "hot-cross-bun" sign are shown and the significance of these images are discussed.While this is a rare disorder there is potentially promising and beneficial new genetic research on the rise.

enhancement forming a cross, indicative of degeneration of pontocerebellar tracts ("hot cross bun sign").

Subjects: Health and Social Care; Allied Health; Medicine, Dentistry, Nursing & Allied Health; Medicine

Keywords: hot crossed bun sign; multiple systems atrophy; dysarthria; slowed fluency; cognitive impairment; orthostatic hypotension

1. Introduction

Multiple system atrophy (MSA) is a rare group of neurodegenerative disorders that has included Shy-Drager syndrome, striatonigral degeneration, and olivopontocerebellar atrophy. Shy-Drager syndrome is no longer considered a distinct entity. MSA is currently divided into the Parkinsonism predominant subtype MSA-P (formerly striatonigral degeneration) and cerebellar ataxia subtype MSA-C (formerly sporadic olivopontocerebellar atrophy).

MSA is mainly a clinical diagnosis because definitive diagnosis necessitates neuropathologic demonstration of glial cytoplasmic inclusions consisting of alpha-synuclein within the olivopontocerebellar or striatonigral structures (Gilman, Wenning, & Low et al., 2008; Trojanowski & Revesz, 2007). Clinical features include any combination of Parkinsonism and cerebellar ataxia with autonomic dysfunction. Dysautonomia most often manifests as orthostatic hypotension, urinary dysfunction, and sexual dysfunction. Other clinical indicators include poor levodopa responsiveness (particularly with Parkinsonism predominant MSA-P), REM sleep disturbances, preserved cognition, cold peripheral limbs, and dysarthria (particularly with MSA-C) (Iodice, Lipp, & Ahlskog et al., 2012).

Imaging may support the diagnosis. FDG-PET may demonstrate decreased metabolism of the putamen, brainstem, or cerebellum. Magnetic resonance imaging (MRI) may show atrophy of the putamen, middle cerebellar peduncle, pons, or cerebellum (Brooks & Seppi, 2009; Gilman et al., 2008). Hyper-intensities may be seen in the above implicated areas, commonly referred to as the "hot cross bun sign" when visualized in the pons.

2. Case report

A 56yo Thai male admitted after non-contrasted computed tomography (CT) brain imaging revealed a small left frontal subarachnoid hemorrhage following a syncopal episode. The patient remained oriented to self, place, time, and situation. The reported history described episodes of "passing out" preceded by lightheadedness occurring multiple times during the preceding months. A progressive four year history of bilateral lower extremity fatigue and ataxia was reported. Disabled at the time of examination, the patient said that the fatigue in his legs had eventually spread to his hands, prohibiting him from reliably fulfilling his occupational physical requirement. He also reported a 6 month history of worsening dysarthria and severely slowed fluency refractory to speech therapy. There was no reported fever or recent illness; no significant weight change; and no bladder incontinence or symptoms of urinary retention. The family medical history revealed no similar physical findings or autonomic dysregulation. A trial of carbidopa-levodopa yielded no significant improvement in symptoms.

On physical exam, an unsteady, ataxic gait was seen. The patient's speech demonstrated dysarthria, and slowed fluency. There was no appreciable deficit in extremity motor strength, though encouragement was required to elicit full effort. There was no tremor, rigidity, fasciculation or myoclonus. Sensation was intact to light touch. The patient remained afebrile. Supine hypertension was noted; orthostatic vital signs were significant for severe orthostatic hypotension on repeated assessment. The typical sitting blood pressure was 120s/70s mmHg; the standing blood pressure was 80s/50s mmHg. Although the patient was often hypertensive in the supine position,

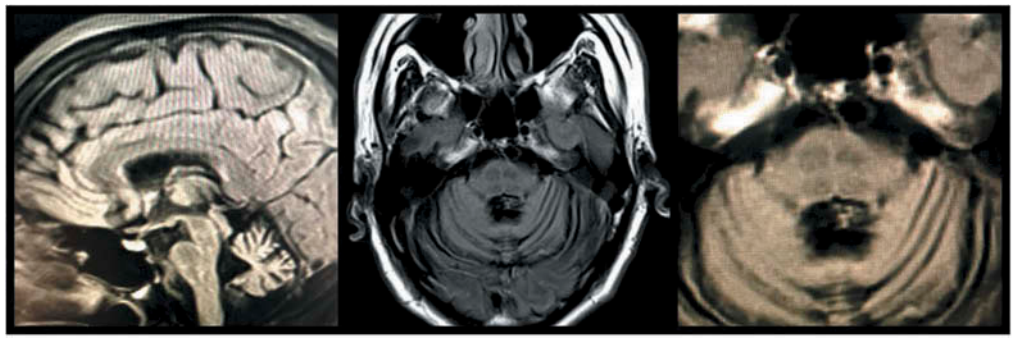

Figure 1. A 56yo Thai male presented with a new subarachnoid hemorrhage following syncope. Further history and physical exam revealed recurrent syncope, orthostatic hypotension, progressive extremity weakness and gait ataxia with persistent dysarthria and slowed fluency. Patient subsequently underwent MRI brain as depicted above.

Left: Sagittal T-2 FLAIR imaging depicts cerebellar and pontine atrophy.
Middle: T-1 axial image depicts degeneration of pontocerebellar tracts leading to the appearance of a cross referred to as hot-cross-buns sign.
Right: Magnified axial T-2 Fluid attenuated inversion recovery (FLAIR) image. Note the pons with the appearance of a formed cross secondary to degeneration of pontocerebellar tracts (hot-cross-buns sign).

orthostatic vital signs repeatedly elicited evidence of orthostasis, with declines in systolic blood pressure consistently greater than 40 mmHg.

Laboratory testing revealed elevated triglycerides and the HgbA1c was diagnostic for diabetes mellitus. The vasculatides panel was negative. Cerebral spinal fluid (CSF) studies yielded normal cell counts with mild elevation of glucose and protein (95mg/DL and 63mg/DL, respectively). CSF studies for cytology yielded no malignant cells; inflammatory cells were observed and consistent with the diagnosed traumatic subarachnoid hemorrhage. A paraneoplastic panel revealed no evidence of a paraneoplastic neurologic disorder. The rapid plasma regain test was nonreactive and serologic tests for HIV and hepatitis serology were negative. On electroencephalography, a normal appearing, posterior dominant alpha rhythm was appreciated. Non-contrasted brain CT scan demonstrated a stable small, left frontal subarachnoid hemorrhage, consistent with a traumatic etiology. On MRI of the brain, disproportionate cerebellar and pontine atrophy was appreciated and axial fluid-attenuated inversion recovery (FLAIR) sequences demonstrated a hyperintense crossed appearance of the pons as known as the hot-crossed-buns sign (Figure 1). For the MRI, Gadolinium contrast was used; there was no evidence of abnormal enhancement.

3. Discussion

3.1. Diagnosis

Currently, as defined by the second consensus statement on MSA in 2008, a *definite* diagnosis of MSA requires micropathological evaluation for the presence of alpha-synuclein–positive glial cytoplasmic inclusions obtained via autopsy. A *probable* MSA diagnosis requires sporadic, progressive adult-onset disease with rigorously defined autonomic failure and Parkinsonism poorly responsive to levodopa, or cerebellar ataxia; and a *possible* MSA requires the above criteria with at least one feature suggesting autonomic dysfunction plus one other clinical feature or by neuroimaging (Gilman et al., 2008).

The described patient met probable MSA-C diagnostic criteria, which were supported by the neuroimaging findings. Although the hot cross bun sign has occasionally been associated with progressive multifocal leukoencephalopathy, (Padmanabhan, Cherian, & Iype et al., 2013) in this case, physical presentation, including an ataxic gait and confirmation of autonomic dysregulation, coupled with unremarkable serology studies and cerebrospinal fluid analysis yielded little expectation for an infectious etiology. Given the sporadic onset of autonomic insufficiency, as elucidated by positive orthostatic vital signs, accompanied by severe supine hypertension in the setting of cerebellar ataxia, the most likely diagnosis is MSA-C. Neuroimaging supported the suspicion, as demonstrated by cerebellar and pontine atrophy and hot-cross-bun sign. Although imaging modalities are continuing to improve, imaging to assess for the hot cross bun sign continues to prove invaluable (Deguchi, Ikeda, & Kume et al., 2015). Further imaging techniques, for example, diffusion tensor tractography imaging

(DTI) as described by Fukui and colleagues have shown promising results for distinguishing MSA from cortical cerebellar atrophy (Fukui, Hishikawa, & Sato et al., 2016).

Although commonly associated with MSA-C, the hot cross bun sign has been found in spinocerebellar atrophy (SCA) types 2, 3, 6, 7, and 8 at an overall prevalence of 8.7%, according to one study (Lee, Liu, & Wu et al., 2009). Even though there was no familial history of similar symptoms or autonomic dysregulation, it is reasonable to evaluate for SCA because genetic testing will help confer the diagnosis (Gilman et al., 2008). Genetic testing may help to rule out the specific possibility of SCA (Gilman et al., 2008; Trojanowski & Revesz, 2007); further research on genetic testing in some populations has shown that it may help in the diagnosis of MSA, as well as recognize patterns in prevalence of MSA in Japanese, European, North American populations (Fukui et al., 2016; Sun, Ohta, & Yamashita et al., 2016). Unfortunately the described patient did not undergo genetic testing. He was unable to be followed on an outpatient basis.

Currently, a definite diagnosis cannot be made in a living person. Further genetic research may allow future testing so that features of MSA can be diagnosed in living patients (Stemberger, Scholz, Singleton, & Wenning, 2011; The Multiple-System Atrophy Research Collaboration, 2013). Another option has shown promise is the recognition of a potential biomarker for alpha-synuclein in the skin (Doppler, Weis, & Karl et al., 2015). Like serum genetic testing, it may bolster diagnostic capabilities in living patients. In this study, the known alpha-synuclein found in the brains of those with MSA was confirmed in nearly two thirds of skin biopsies performed using unmyelinated somatosensory nerve fibers.

With the impact of increased occurrence of cognitive impairment in MSA patients, it has been suggested that exclusion criteria no longer be the basis for a diagnosis (Brown et al., 2010). Cognitive impairment usually becomes apparent approximately 7 years following the initial diagnosis, but it may present earlier in the disease progression (Koga, Parks, & Dickson et al., 2017). Slowed fluency, which was overtly appreciated in the patient case outlined here, may be an early indicator of cognitive impairment (Stankovic, Krismer, & Jesic et al., 2014). It has been suggested that patients may demonstrate evidence of cognitive impairment more frequently when undergoing more detailed neuropsychiatric testing versus less in depth cognitive screening assessments (Koga et al., 2017). Therefore it is reasonable to obtain more detailed neuropsychiatric testing in patients of this population or cohort.

3.2. Treatment

Unfortunately, there is not a cure currently available for MSA. Treatment is based upon supporting the blood pressure and managing the symptoms of Parkinsonism. Physical therapy, implanted pacemakers and efforts made to manage speech, swallowing and breathing dysfunction are often paramount. Preserving quality of life also remains essential; this includes bladder care and impotence medications because both incontinence and erectile dysfunction are common features. Palliative care considerations are increasingly used in cases of MSA, given the poor prognosis and typical progressive decline in functional ability (Wiblin, Lee, & Burn, 2017).

4. Conclusion

In conclusion, it is within reason to obtain genetic testing to rule out the possibility of SCA in patients meeting MSA criteria. Possible confirmation of the diagnosis of MSA via other genetic testing methods may be an option as more specific tests become available. Although advanced imaging techniques may not be widely available, it appears neuroimaging will continue to be an integral diagnostic tool to accurately assess for cerebellar atrophy and the hot-cross-bun sign. Obtaining a thorough history including the time of onset and progression of symptoms, as well as physical examination findings consistent with Parkinsonism in the setting of poor responsiveness to carbidopa-levodopa remain absolutely paramount to the diagnosis. It has been nearly a decade since the second consensus statement. As more and more diagnostic data and treatment options become available, subsequent consensus statements may yield further adjustments to diagnostic

criteria and thus help further guide the treatment and management of symptoms. Whether the inclusion of cognitive impairment becomes integral to achieving the diagnosis has yet to be determined. It should be considered beneficial to ask patients to undergo in-depth neuropsychiatric testing early. This step will help to assess for cognitive impairment, so that cognition can be addressed and preserved, if possible, in an effort to maintain the quality of life.

Funding
The authors received no direct funding for this research.

Competing Interests
There are no conflicts of interest.

Author details
Anthony C. Torres[1]
E-mail: anthonyto@pcom.edu
Garet J. Zaugg[1]
E-mail: zaugg.neurology@gmail.com
Nasir Tufail[2]
E-mail: mntams23@yahoo.com
Paul H. Janda[1]
E-mail: pauljanda@gmail.com
[1] Department of Neurology, Valley Hospital Medical Center, Las Vegas, NV, USA.
[2] Nevada Hospitalist Group, Las Vegas, NV, USA.

Citation information
Cite this article as: A "hot crossed buns" sign, orthostatic syncope & gait ataxia point to probable multiple systems atrophy with dysarthria and slowed fluency suspicious for associated cognitive impairment, Anthony C. Torres, Garet J. Zaugg, Nasir Tufail & Paul H. Janda, *Cogent Medicine* (2018), 5: 1564530.

References

Brooks, D. J., & Seppi, K. (2009). Neuroimaging working group on MSA. Proposed neuroimaging criteria for the diagnosis of multiple system atrophy. *Movement Disorders Journal*, *24*(7), 949–964.

Brown, R. G., Lacomblez, L., Landwehrmeyer, B. G., Bak, T., Uttner, I., Dubois, B., … Leigh, N.P. (2010). Cognitive impairment in patients with multiple system atrophy and progressive supranuclear palsy. *Brain*, *133*(Pt 8), 2382–2393. doi:10.1093/brain/awq158

Deguchi, K., Ikeda, K., Kume, K., Takata, T., Kokudo, Y., Kamada, M., … Masaki, T. (2015). Significance of the hot cross bun sign on T2-weighted MRI for the diagnosis of multiple systems atrophy. *Journal of Neurology*, *262*(6), 1433–1439. doi:10.1007/s00415-015-7728-1

Doppler, K., Weis, J., Karl, K., Ebert, S., Ebentheuer, J., Trenkwalder, C., … Sommer, C. (2015). Distinctive distribution of phospho-alpha-synuclein in dermal nerves in multiple system atrophy. *Movement Disorders Journal*, *30*(12), 1688–1692. doi:10.1002/mds.26293

Fukui, Y., Hishikawa, N., Sato, K., Nakano, Y., Morihara, R., Ohta, Y., … Abe, K. (2016). Characteristic diffusion tensor tractography in multiple systems atrophy with predominant cerebellar ataxia and cortical cerebellar atrophy. *Journal of Neurology*, *263*(1), 61–67. doi:10.1007/s00415-015-7934-x

Gilman, S., Wenning, G. K., Low, P. A., Brooks, D. J., Mathias, C. J., Trojanowski, J. Q., … Kaufmann, H. (2008). Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*, *71*(9), 670–676. doi:10.1212/01.wnl.0000324625.00404.15

Iodice, V., Lipp, A., Ahlskog, J. E., Sandroni, P., Fealey, R. D., Parisi, J. E., … Gehrking, T. L. (2012). Autopsy confirmed multiple system atrophy cases: Mayo experience and role of autonomic function tests. *Journal of Neurology, Neurosurgery, and Psychiatry*, *83*(4), 453–459. doi:10.1136/jnnp-2011-301068

Koga, S., Parks, A., Uitti, R. J., van Gerpen, J. A., Cheshire, W. P., Wszolek, Z. K., & Dickson, D. W. (2017). Profile of cognitive impairment and underlying pathology in multiple system atrophy. *Movement Disorders Journal*, *32*(3), 405–413. doi:10.1002/mds.26874

Lee, Y. C., Liu, C. S., Wu, H. M., Wang, P. S., Chang, M. H., & Soong, B. W. (2009). The "hot cross bun" sign in the patients with spinocerebellar ataxia. *European Journal of Neurology: The Official Journal of the European Federation of Neurological Societies*, *16*(4), 513–516. doi:10.1111/j.1468-1331.2008.02524.x

Padmanabhan, S, Cherian, A, Iype, T, Mathew, M, & Smitha, S. (2013). Hot cross bun sign in hiv-related progressive multifocal leukoencephalopathy. *Annals of Indian Academy of Neurology*, *16*(4), 672–3.

Stankovic, I., Krismer, F., Jesic, A., Antonini, A., Benke, T., Brown, R. G., … Ling, H. (2014). Cognitive impairment in multiple system atrophy: A position statement by the neuropsychology task force of the MDS Multiple System Atrophy (MODIMSA) study group. *Movement Disorders Journal*, *29*(7), 857–867. doi:10.1002/mds.25880

Stemberger, S., Scholz, S. W., Singleton, A. B., & Wenning, G. K. (2011). Genetic players in multiple systems atrophy: Unfolding the nature of the beast. *Neurobiology of Aging*, *32*(10), 1924.e5–1924.e14. doi:10.1016/j.neurobiolaging.2011.04.001

Sun, Z., Ohta, Y., Yamashita, T., Sato, K., Takemoto, M., Hishikawa, N., & Abe, K. (2016). New susceptible variant of COQ2 gene in Japanese patients with sporadic multiple system atrophy. *Neurology Genetics*, *2*((2)), e54. doi:10.1212/NXG.0000000000000054

The Multiple-System Atrophy Research Collaboration. (2013). Mutations in COQ2 in familial and sporadic multiple-system atrophy. *The New England Journal of Medicine*, *369*(3), 233–244. doi:10.1056/NEJMoa1212115

Trojanowski, J. Q., & Revesz, T. (2007). Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy. *Neuropathology and Applied Neurobiology*, *33*(6), 615–620. doi:10.1111/j.1365-2990.2007.00907.x

Wiblin, W., Lee, M., & Burn, D. (2017). Palliative care and its emerging role in multiple system atrophy and progressive supranuclear palsy. *Parkinsonism & Related Disorders*, *34*, 7–14. doi:10.1016/j.parkreldis.2016.10.013

Cogent Medicine **(ISSN: 2331-205X) is published by Cogent OA, part of Taylor & Francis Group.**