

**CASE REPORT**

# 'Hummingbird' Sign in a Patient with Guam Parkinsonism–Dementia Complex

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**ABSTRACT**

We present a case of a 71-year-old male Chamorro patient from Guam who presented with progressive supranuclear palsy (PSP)-Richardson's syndrome. Considering his strong family history of parkinsonism and a PSP phenotype, he was clinically diagnosed with Guam parkinsonism-dementia complex (PDC). Magnetic resonance imaging (MRI) of the brain revealed prominent midbrain atrophy with preserved pontine volume, forming the 'hummingbird' sign, which has not been described before in Guam PDC. Molecular analysis of the chromosome 9 open reading frame 72 gene (*C9orf72*) showed only 6 GGGGCC repeats. We discuss the clinico-pathological similarities and differences between PSP and Guam PDC, and highlight the topography of neuropathological changes seen in Guam PDC to explain the appearance of the 'hummingbird' sign on MRI.

**Key Words** Guam parkinsonism dementia complex; progressive supranuclear palsy; MRI; hummingbird sign; mesial temporal sclerosis.

Guam amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS/PDC) is a unique and seemingly familial neurodegenerative condition affecting the Chamorro people of Guam.<sup>1</sup> ALS affects younger patients while PDC occurs in later life.<sup>1</sup> Guam PDC usually presents with akinetic-rigid parkinsonism, occasionally with supranuclear gaze palsy akin to progressive supranuclear palsy (PSP).<sup>1</sup> Few imaging studies have been conducted on Guam PDC patients,<sup>2,3</sup> and despite their clinical similarities, there have been no reports of PSP-like features on brain magnetic resonance imaging (MRI) in patients with Guam PDC. Herein, we report a patient with Guam PDC whose MRI of the brain showed prominent midbrain atrophy with the 'hummingbird' sign.

**CASE REPORT**

A 71-year-old Chamorro male presented with worsening postural instability, gait freezing and frequent falls. He developed parkinsonism 5 years prior, characterized by bradykinesia, mild

tremors and occasional falls. Along with motor deterioration, he also developed executive dysfunction with fluctuating short-term memory loss. His current medications included Sinemet (Carbidopa/Levodopa, 25 mg/250 mg) four times a day and Rivastigmine (1.5 mg twice a day).

Family history of the patient revealed parkinsonism in multiple family members (Figure 1). The patient was told that his paternal grandmother suffered from 'Lytico-Bodig', the Chamorro name for Guam ALS/PDC; however, he was not certain of the age of onset. His father developed parkinsonism in his late 40's while his paternal uncles developed parkinsonism in their 50's. The patient was not aware if his paternal cousins had parkinsonism. His sister has also developed parkinsonism characterized by limb slowness and gait difficulties.

Examination revealed a PSP-Richardson's syndrome (Supplementary Video 1 in the Online-only Data Supplement). There was frontalis overactivity with reduced blink rate producing a 'staring' appearance. Neuro-ophthalmological examination showed impairment of down gaze, slowing of vertical and hori-

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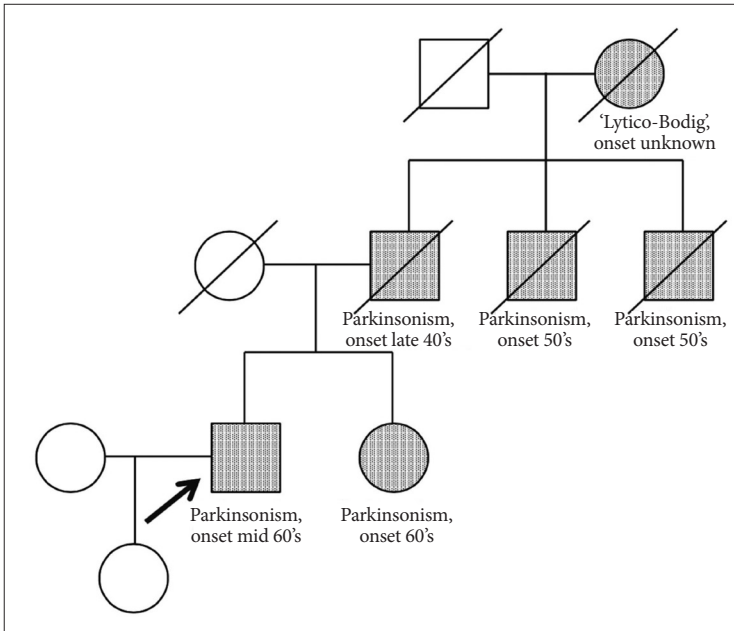
zontal saccades and frequent saccadic intrusions. Parkinsonian features included symmetrical limb bradykinesia and rigidity, axial rigidity, and marked postural instability with frequent gait freezing. The applause sign was not consistently present. There were no apraxia, dysmetria, postural hypotension or Babinski signs observed. Motor response to dopaminergic medications was minimal. The Montreal Cognitive Assessment score was 16/30 with

prominent deficits in visuospatial and executive functions as well as poor performance on delayed recall. In view of the strong family history of parkinsonism, together with clinical features mimicking PSP-Richardson's syndrome, our clinical diagnosis was Guam PDC.

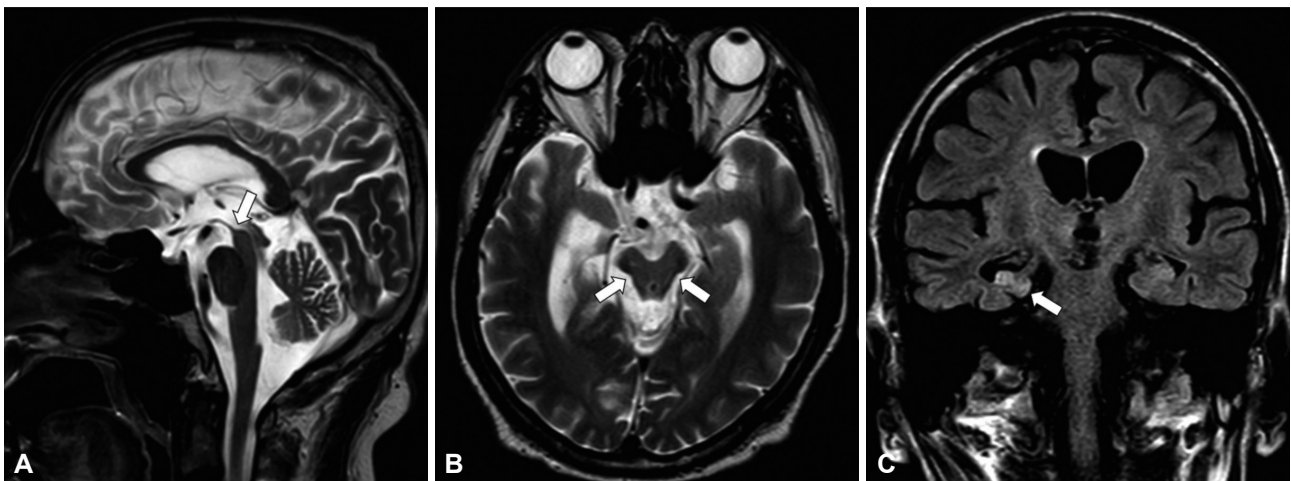
MRI of the brain showed prominent midbrain atrophy without pontine atrophy, producing the 'hummingbird' sign typically seen in PSP (Figure 2A and B).<sup>4</sup> Severe right hippocampal atrophy with fluid-attenuated inversion recovery (FLAIR) hyperintensity was also noted, suggestive of radiologically defined mesial temporal sclerosis (Figure 2C). Needle electromyography showed no ongoing denervation or chronic reinnervation to suggest ALS. To exclude other causes of familial ALS and parkinsonism, molecular analysis of the chromosome 9 open reading frame 72 gene (*C9orf72*) was done which showed only 6 GGGGCC repeats.

## DISCUSSION

Despite the many clinical and neuropathological similarities between PSP and Guam PDC, there have been no reports of the 'hummingbird' sign on MRIs of the brain in Guam PDC. We believe that the radiological features seen in our patient correlates with the pathological findings of severe neuronal loss and high neurofibrillary tangle load in the midbrain, especially within the substantia nigra and ventral tegmental area of Guam PDC patients.<sup>5</sup> It is also dem-



**Figure 1.** Genogram of patient's family. Bold black arrow indicates patient; squares indicate male; circles indicate female; slash indicates deceased; shaded indicates affected family member.



**Figure 2.** MRI of the brain of the patient. A: Mid sagittal T2-weighted imaging show prominent midbrain atrophy with preserved pontine volume, forming the silhouette of the head and body, respectively, of a hummingbird. Concavity of the superior midbrain profile is also present (arrow). B: Axial T2-weighted imaging show marked midbrain atrophy with concavity of the midbrain tegmentum (arrows). C: Coronal fluid-attenuated inversion recovery (FLAIR) imaging show marked right hippocampal atrophy with increased FLAIR signal (arrow), suggestive of mesial temporal sclerosis.

onstrated pathologically that only slight neuronal loss occurs within the pedunculopontine and pontine nuclei in Guam PDC, compatible with the preserved pontine volume seen in our patient.<sup>5</sup> A recent neuropathological study has shown that pathologically defined hippocampal sclerosis exists in Guam PDC patients, with some patients showing extensive scarring and severe neuronal loss with fibrillary gliosis in the cornu ammonis 1 area of the hippocampus.<sup>6</sup> We postulate that these pathological findings are likely to explain the right mesial temporal sclerosis observed on MRI in our patient. A brain volumetric study also showed preferential atrophy of the parahippocampal gyrus, hippocampus, temporal lobe, frontal lobe and basal ganglia-thalamic region in Guam PDC patients compared to asymptomatic Chamorros.<sup>2</sup>

The clinical and histological similarities of Guam PDC and PSP were already observed in the 1960's.<sup>1</sup> Both are considered tauopathies and show a similar topography of neurofibrillary degeneration in the subcortical and brainstem regions.<sup>1,5,7</sup> Some differences however, do exist between PSP and Guam PDC. PSP is a universal, sporadic disease and is almost never associated with ALS; Guam PDC is usually familial with frequent association with ALS, either within the same family or in the same individual.<sup>1</sup> The neurofibrillary tangles are also different; they are almost exclusively 4-repeat tau in PSP, while in Guam PDC, they are a mixture of 3-repeat and 4-repeat tau.<sup>7</sup> Finally, although Guam PDC is considered as a tauopathy, it has been demonstrated that the transactivation-responsive region DNA-binding protein (TDP)-43 is present in the brain and spinal cord of Guam ALS/PDC patients.<sup>6-8</sup>

While it has been reported that polymorphisms in the microtubule-associated protein tau gene (*MAPT*) region increase the risk for Guam ALS/PDC, no pathogenic mutations in *MAPT* or other genes have been identified.<sup>9,10</sup> Expansion of the GGGGCC hexanucleotide repeat sequence in an intron of *C9orf72* has been shown to cause autosomal dominant ALS and frontotemporal dementia, as well as in some cases of familial parkinsonism.<sup>9</sup> A study of familial ALS in the Kii Peninsula of Japan, a closely related condition having shared clinical and neuropathological features with Guam ALS/PDC, reported that 20% of these patients carry *C9orf72* expansions.<sup>9</sup> In contrast, it is reported that Chamorro

Guam ALS/PDC patients have normal copies ranging from 2 to 17, showing that *C9orf72* expansions do not explain Guam ALS/PDC.<sup>9</sup> No pathogenic mutations in the *LRRK2* gene were found in the same study. The 6 repeats of GGGGCC in *C9orf72* in our patient is consistent with this observation.

Etiological hypotheses concerning beta-N-methylamino-L-alanine neurotoxicity via ingestion of cycad seeds and flying foxes have proved inconclusive and genetic studies have not found any causative genetic mutations.<sup>7,10</sup> With the decline in disease incidence, particularly that of the ALS phenotype,<sup>1</sup> the cause of Guam ALS/PDC remains enigmatic.

### Supplementary Video Legends

Video 1. Segment 1: Neuro-ophthalmological examination. The patient had frequent saccadic intrusions, impaired down gaze and slowing of vertical and horizontal saccades. Segment 2: Parkinsonian features. The patient had fine postural hand tremors, symmetrical limb hypokinesia and bradykinesia, and marked postural instability with frequent gait freezing. The applause sign was not consistently present.

### Supplementary Materials

The online-only Data Supplement is available with this article at <https://doi.org/10.14802/jmd.17025>.

### Conflicts of Interest

The authors have no financial conflicts of interest.

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