

Multiple system atrophy in a patient with primary ciliary dyskinesia

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Abstract

We present the case of a patient with primary ciliary dyskinesia who later developed clinically probable multiple system atrophy. Multiple system atrophy is a sporadic neurodegenerative disorder clinically characterised by various combinations of parkinsonism, cerebellar ataxia, autonomic failure, and pyramidal sign. Primary ciliary dyskinesia is a genetically heterogeneous disorder of motile cilia and results in chronic bronchitis, bronchiectasis, chronic rhinosinusitis, chronic otitis media, situs inversus, and male infertility. Most of the causative genes for primary ciliary dyskinesia encode proteins that are part of the heavy or intermediate chain of axonemal dynein in ciliary outer dynein arms. We hypothesised that axonemal dynein dysfunction in primary ciliary dyskinesia results in reduced autophagy, accompanied by impaired cytoplasmic dynein function, which in turn accelerates α -synucleinopathy in multiple system atrophy. Furthermore, we contemplated a potential association between primary cilia and neuronal function. Although it is not yet clear if a causal link between multiple system atrophy and primary ciliary dyskinesia exists, further investigation into the relationship between axonemal dynein dysfunction in primary ciliary dyskinesia and α -synucleinopathy should be conducted.

INTRODUCTION

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder clinically characterised by any combination of parkinsonism and autonomic, cerebellar, and pyramidal signs. Pathologically, this disorder is defined by cell loss, gliosis, and glial cytoplasmic inclusions in several central nervous system structures.¹ Primary ciliary dyskinesia (PCD) is a genetically heterogeneous disease of motile cilia that is clinically characterised by recurrent respiratory tract infections, male infertility, and randomisation of left–right body asymmetry. Patients with PCD show mutations in the heavy/intermediate chain of axonemal dynein.² Here, we present a case study of a patient with PCD who later developed clinically probable MSA. We also discuss the possible association of axonemal dynein with MSA pathology.

CASE REPORT

A 47-year-old Japanese man of consanguineous parentage had experienced recurrent episodes of respiratory tract infections since his birth and was diagnosed with bronchiectasis. In his childhood, he had had otitis media. At the age

of 16, he underwent an operation for bilateral sinusitis. An electron microscopic examination performed after he was married indicated that he had sperm dysfunction (90% deformity rate and 0% function rate) and oligospermia. Since the age of 40, he has been treated with antidepressants for depression.

In June 2008, when he was 46 years old, he became aware of his walking imbalance, urinary frequency, incomplete bladder emptying, and constipation. In January 2009, he developed erectile and ejaculation dysfunction. He gradually experienced difficulty in walking and was unable to walk straight without falling. He was then referred to our institution.

On admission, neurologic examination revealed wide-based gait, horizontal saccadic eye movement, and incoordination characterised by dysmetria and dyssynergia, as observed in the nose–finger–nose test. Repeated examinations revealed orthostatic hypotension (defined as a >20 mmHg systolic blood pressure drop on standing for 2 min), persistent constipation, and incomplete bladder emptying. Deep tendon reflexes were normal. There was no sign of parkinsonism.

Biochemical screening tests and tests for autoantibodies and infection markers yielded

normal findings. Levels of carcinoembryonic antigen (CEA) was normal (4.1 ng/mL [normal <5.0 ng/mL]), but those of carbohydrate antigen 19-9 (CA19-9) and cancer antigen 125 (CA125) were significantly elevated to 61.5 U/mL (normal <37.0 U/mL) and 189.6 U/mL (normal <35.0 U/mL), respectively. Cerebrospinal fluid (CSF) examination revealed 5 lymphocytes/ μ L, protein content of 35.7 mg/dL, and normal levels of immunoglobulins (IgG: 3.1 mg/dL; IgA: 0.43 mg/dL; IgM: 0.0 mg/dL). CSF cytology showed no malignant cells.

Brain magnetic resonance imaging revealed mild atrophy in the cerebellum, pons, and middle cerebellar peduncles. T2-weighted images revealed cruciform hyperintensity in the atrophied pons (hot cross bun sign) (Fig. 1). High-resolution computed tomography (CT) of the chest revealed hypertrophy and dilatation of the bronchial wall and bronchiectasis in both the lungs, especially in the inferior lobes. Given that CA19-9 and CA125 levels were elevated, contrast-enhanced CT and ultrasonography of the abdomen, fiberoptic of the gastrointestinal and colon, and gallium scintigraphy were performed, all of which tested negative for malignancy.

In the summer of 2012, he experienced frequent falling and symptomatic orthostatic hypotension with syncope and became wheelchair-dependent. During the follow-up period, no malignancy was detected.

DISCUSSION

We diagnosed the patient with probable cerebellar MSA (MSA-C), on the basis of the consensus statement on the diagnosis of MSA described by Gilman *et al.*³ The typical clinical course of PCD was observed, such as chronic bronchitis, bronchiectasis, chronic rhinosinusitis, chronic otitis media, situs inversus, and male infertility.⁴ These observations, along with electron microscopy examination of his sperm⁵, strongly suggested the co-existence of PCD. However, the patient declined to undergo genetic testing to confirm PCD. Despite the high concentration of neoplastic markers, intensive investigations during the follow-up period revealed no malignancy.

Recent advances in research on the molecular pathogenesis of MSA have revealed α -synuclein to be the major components of both oligodendroglial and neuronal inclusions, firmly establishing MSA as an α -synucleinopathy.¹ Decreased function of cytoplasmic dynein has been demonstrated to impair autophagic clearance of aggregate-prone proteins, suggesting that cytoplasmic dynein plays an important role in the clearance of misfolded proteins.⁶ In autophagic pathway, a minus end-directed delivery along microtubules is required for mature autophagosomes to reach and engage with perinuclear lysosomes, thus dynein dysfunction decreases the clearance of aggregate-prone proteins by reducing autophagosome-lysosome

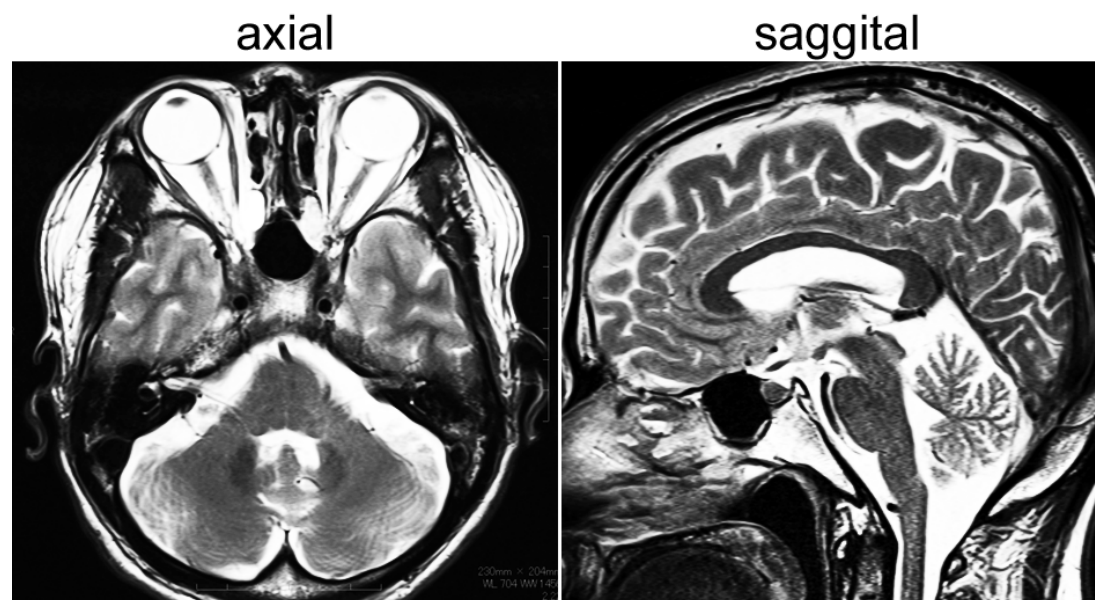


Figure 1. T2-weighted magnetic resonance images in axial (left) and sagittal (right) views revealed cruciform hyperintensity in the pons (hot cross bun sign), with atrophy in the cerebellum, pons, and middle cerebellar peduncles.

fusion.⁷ It has been emphasised that cytoplasmic dynein motor protein is involved in axonal transport of α -synuclein to autophagosomes in neurons.^{8,9} Thus, aggregation of α -synuclein may be attributable to dysfunction of cytoplasmic dynein.

Most of the genes causative of PCD encode proteins that are a part of the heavy or intermediate chain of axonemal dynein in ciliary outer dynein arms (ODA)², highlighting the importance of dynein motors in ciliary motility. Genes encoding dynein heavy chain of cytoplasmic and outer arm axonemal dyneins are reported to have similar sequences in their central and 3'-end regions.¹⁰ Moreover, the axonemal dynein, Dnali1, has also been shown to interact with a fragment of cytoplasmic dynein heavy chain 1.¹¹ Tctex1 and Tctex2, ODA light chains, are present in both flagellar and cytoplasmic dyneins, thus their impairment may lead to the dysfunction of both axonemal and cytoplasmic dynein.

In this case study, we hypothesised that axonemal dynein dysfunction in PCD results in reduced autophagy, accompanied by impaired cytoplasmic dynein, which in turn accelerates α -synucleinopathy in MSA. It is possible that the co-occurrence of MSA and PCD in our patient was coincidental. However, coincidental co-occurrences should be extremely rare given the low incidence of each disorder: 0.6/100,000 for MSA and 1/16,000 for PCD. We previously reported the case of a patient with clinically definite amyotrophic lateral sclerosis, who was previously diagnosed with Kartagener syndrome.¹² Although a causal link between neurodegenerative disorders and PCD has not been clearly established, the relationship between axonemal dynein dysfunction in PCD and α -synucleinopathy should be further investigated.

DISCLOSURE

Conflicts of Interest: None

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