

Concomitant fragile X-associated tremor ataxia syndrome and Parkinson's disease: a clinicopathological report of two cases

INTRODUCTION

Parkinsonism is common in fragile X-associated tremor/ataxia syndrome (FXTAS) but its underlying pathophysiology remains unknown. Our group reported a patient with FXTAS and parkinsonism, and in vivo evidence of presynaptic and postsynaptic nigrostriatal dysfunction.¹ We report the histological findings of this case (case 1) and another case with dual pathologies of FXTAS and Lewy body Parkinson's disease (PD).

METHODS

Genetic testing for FXTAS was requested in seven cases from the Queen Square Brain Bank for Neurological Disorders (QSBB) based on the characteristic radiological 'middle cerebellar peduncle' (MCP) sign (case 1, diagnosis confirmed in life) and histological findings of round, eosinophilic

p62-positive neuronal intranuclear inclusions in the hippocampus or unexplained cerebellar degeneration (6 postmortem cases were tested). Two cases were positive for *FMR1* premutation and both showed histological features of FXTAS and PD. The QSBB brain donor programme was approved by a Research Ethics Committee and written consent for research was obtained from all cases.

CASE REPORTS

Case 1

A 68-year-old man presented with a 10-year history of slowly progressive right-hand tremor. There was no family history of neurological disorders or mental retardation. Examination showed hypomimia, asymmetric rest and kinetic tremor, rigidity, mild bradykinesia and inability to tandem walk. The patient was diagnosed with tremor-predominant PD but did not respond to L-dopa (600 mg/day). Over the next few years he developed mild cognitive impairment, gait ataxia and intention tremor. Brain MRI demonstrated the MCP sign and diffuse atrophy. Genetic analysis confirmed *FMR1* premutation with 87 CGG expansion. ¹²³I-FP-CIT SPECT revealed asymmetric reduced tracer uptake with the right side more affected. D₂ receptor (123I) IBZM-SPECT (IBZM) scan showed slightly reduced tracer uptake bilaterally. There was clinical and neurophysiological evidence of large fibre axonal peripheral neuropathy. The patient's University of Pennsylvania Smell Identification Test (UPSIT) score was 25/40 (severe hyposmia: 19–25). His condition gradually deteriorated and he died of pneumonia at age 72.

Case 2

A 21-year-old man was diagnosed with schizophrenia and his symptoms responded well to long-term fluphenazine. At the age of 35, he developed a right-hand tremor initially attributed to the neuroleptic treatment. The tremor persisted despite switching fluphenazine to olanzapine 5 mg/day and administering anticholinergics (orphenadrine and procyclidine). His tremor remained stable and only began to deteriorate at age 51 along with the onset of slurred speech and dragging of right leg. Examination showed mild hypomimia, hypophonia, restricted downgaze, slow vertical saccades, jaw and tongue tremor, intermittent right-sided predominant hand tremor, bradykinesia and cogwheel rigidity. Olanzapine was replaced by quetiapine 200 mg/day and L-dopa (300 mg/day) was administered without any improvement.

Brain MRI showed global atrophy without the MCP sign. At age 58, his symptoms rapidly deteriorated with severe hand tremor and frequent falls requiring a wheelchair. ¹²³I-FP-CIT SPECT demonstrated asymmetrical reduction of tracer uptake in putamen and left caudate. A clinical diagnosis of progressive supranuclear palsy (PSP) was made due to the rapid motor deterioration, postural instability, restriction of downgaze and absence of L-dopa response. He died of pulmonary embolism at age 59. Neuropathological findings prompted genetic testing and the identification of *FMR1* gene premutation with 100 CGG expansions.

NEUROPATHOLOGICAL EXAMINATION

In both cases, histological examination demonstrated widespread p62-positive and ubiquitin-positive and 1C2-negative neuronal and glial intranuclear inclusions with mild Purkinje cell depletion consistent with FXTAS. There was loss of pigmented neurons in the substantia nigra with α -synuclein-positive Lewy bodies, in keeping with PD. Lewy body pathology conformed to Braak stage 5 in case 1 and stage 3 in case 2. Age-related neurofibrillary tangle pathology was also noted in both cases (Braak and Braak stage II in case 1 and stage I in case 2). An acute left

middle cerebral artery territory infarction was observed in case 2.

DISCUSSION

In the literature, only 13 of 29 (45%) cases with *FMR1* premutation and parkinsonism had abnormal dopamine transporter scans (see online supplementary table) and it is likely that these 13 cases may have had concomitant PD pathology akin to the two cases in this series. On the other hand, IBZM scans were only available in four cases with *FMR1* premutation including our case and all had abnormal findings (see online supplementary table). We propose that postsynaptic dopaminergic striatal pathway dysfunction is responsible for parkinsonism in individuals with FXTAS. *FMR1* premutation carriers with an abnormal dopamine transporter scan probably signifies the presence of concomitant PD pathology and may have a rapidly progressive disease course due to the dual pathologies. These patients may benefit from L-dopa therapy.

Of the 22 FXTAS cases with postmortem data (table 1), concomitant pathologies were identified in nine cases (41%): four had Alzheimer's disease pathology,² one had multiple sclerosis (MS)² and four had PD pathology including the two cases presented here.^{2,3}

Table 1 Features of 22 reported postmortem FXTAS cases

	Duration from onset (years)		CCG repeats	MCP sign	Additional neuropathological findings
	Wheelchair	Death			
Greco <i>et al</i> ³ ; 11 males ⁶	6	10	113	–	–
	–	13	80	–	–
	NA	5	80	Y	–
	13	14	71	–	PD
	12	19	105	–	–
	7	13	77	Y	–
	5	6	88	Y	–
	NA	3	92	–	–
	13	16	88	Y	–
	4	6	93	Y	–
	NA	1	65	–	–
	NA	NA	70	–	–
	–	10	80	N	AD (B&B V-VI)
Tassone <i>et al</i> ² ; 8 females	–	6	87	–	–
	–	14	75	Y	MS
	–	7	65	–	AD (B&B V-VI)
	4	7	–	N	AD (B&B V-VI)
	4	6	59	N	PD
	–	8	78	–	AD (B&B V-VI)
	7	9	90	–	–
Louis <i>et al</i> ; 1 male ⁷	7	9	90	–	–
Present series: De Pablo-Fernandez	13	14	72	Y	PD (Braak 5)
<i>et al</i> ; 2 males	7	8	100	N	PD (Braak 3)
Total: 8 females; 14 males	8	9		Y	

AD, Alzheimer disease; B&B, Braak and Braak stage for Alzheimer; Braak, Braak stage for Parkinson's disease; FXTAS, fragile X-associated tremor/ataxia syndrome; MCP, middle cerebellar peduncle; MS, multiple sclerosis; N, no; NA, not applicable; PD, Parkinson's disease; Y, yes.

It is difficult to ascertain the exact contribution of each pathology to the clinical course of parkinsonism in our cases. In case 2, the long-term use of neuroleptics complicated the clinical picture, thus the long-standing hand tremor could have been caused by a combination of FTXAS and neuroleptics. However, at age 51, the deterioration of hand tremor, relentless progression of parkinsonism and the onset of typical features of PD including jaw and tongue tremor collectively marked the onset of an additional underlying neurodegenerative process of PD. Both cases had a relatively benign course in the first decade of symptom onset followed by rapidly progressive parkinsonism and motor disability leading to death. This rapid deterioration is atypical for either FXTAS or PD. Indeed, the clinical diagnosis for case 2 was revised to PSP. Among the four patients with dual FXTAS and PD pathology in the literature,^{2,3} the time from onset to use of walking aid (median: 7.5 years) and life expectancy (median: 11 years) are much shorter than in other patients with isolated FXTAS, in whom the median time to walking aid is 15 years and median survival is 21 years.⁴ These data suggest that the synergistic effect of more than one neurodegenerative condition might have contributed to an accelerated disease course. Carriers of *FMR1* premutation with concomitant Alzheimer's disease,² heterozygous *Parkin* mutation⁵ or *MS2* have been reported and these secondary pathological processes have been postulated to modulate the effect of *FMR1* premutation.

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Competing interests None.

Patient consent Obtained.

Ethics approval The brain donor programme of the QSBB was approved by a London Multi-Centre Research Ethics Committee and tissue is stored under a license from the Human Tissue Authority. Consent for use of tissue for research was obtained from donors and/or their next of kin.

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Supplemental Table: Clinical, genetic and imaging findings of 30 FXTAS cases with functional neuroimaging reported in the literature.

	Clinical findings		CGG repeats	MCP sign	SPECT	
	Symptoms	L-Dopa response			DaTSCAN	IBZM
Zuhlke et al; 1 female (J Neurol 2004)	T, A, N, P	-	84	N	Abnormal	Abnormal
Ceravolo et al; 4 males (Neurology 2005)	T, A, P	-	105	Y	Normal	-
	T, P	-	73	N	Normal	-
	A, C, AutD, P	N	85	N	Normal	-
	T, P	N	97	-	Normal	-
Kamm et al; 1 male (Brain 2005)	T, P, A, AutD	N	61	N	-	Abnormal
Scaglione et al; 5 Males (J Neurol 2008)	T, P, G, A	-	103	Y	Normal	-
	T, P, G, A	-	80	Y	-	-
	T, P, A	N	91	Y	Abnormal	Abnormal
	T, P, G, A	N	97	Y	Abnormal	-
	T, P, A	-	95	Y	Abnormal	-

Apartis et al; 4 females, 18 males* (Neurology 2012)	A (91%) T (86%) P (64%) C (55%)	N (3/3)	102	64% (14/22)	47% (7/15) abnormal	-
Hall et al; 2 females, 1 male (Parkinsonism Relat Disord 2010)	T, P T, P, C T, P	Y Y Y**	41 51 60	N N N	Normal Normal Normal	- - -
Healy et al (case 1) (Mov Disord 2009)	T, P, N, A	N	72	Y	Abnormal	Abnormal
& De Pablo-Fernandez et al (case 2) 2 males	T, P, A, G	N	100	N	Abnormal	-
Total:		Y 23% (3/13)		Y 57% (21/37)	Abnormal 45% (13/29)	Abnormal 100% (4/4)

* Only 15 patients with functional neuroimaging available

** responded to pramipexole

Abbreviations: A, ataxia; AutD, autonomic dysfunction; C, cognitive decline; DaTSCAN, striatal dopamine transporter SPECT; G, vertical gaze palsy; IBZM, striatal postsynaptic D2 receptor SPECT; MCP, middle cerebellar peduncle; N, no; P, parkinsonism; T, tremor; Y, yes.