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Potential multisystem degeneration in Asidan patients

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ABSTRACT

Objective: To evaluate a potential multisystem involvement of neurodegeneration in Asidan, in addition to cerebellar ataxia and signs of motor neuron disease.
Methods: We compared the new Asidan patients and those identified in previous studies with Parkinson's disease (PD, n = 21), and progressive supranuclear palsy (PSP, n = 13) patients using ^{123}I-2β-Carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) dopamine transporter single photon emission computed tomography (DAT-SPECT) and ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy (Asidan, DAT: n = 10; MIBG: n = 15).
Results: Both the PD and PSP groups served as positive controls for DAT decline. The PD and PSP groups served as a positive and negative control, respectively, of MIBG decline in the early phase H/M ratio. Of the Asidan patients, 60.0% showed DAT decline without evident parkinsonian features and 6.7% showed impaired MIBG in only the delayed phase H/M ratio. Combined with a normal range of the early phase H/M ratio, this phenotype was newly named Declined DAT Without Evident Parkinsonism (DWEP).
Interpretation: The results of present study including DWEP suggest a wider spectrum of neurodegeneration for extrapyramidal and autonomic systems in Asidan patients than expected, involving cerebellar, motor system and cognitive functioning.

1. Introduction

Spinocerebellar ataxia (SCA) is a progressive neurodegenerative disorder with symptoms of truncal ataxia, dysarthria and limb ataxia. We previously reported the unique clinical characteristics of Asidan (SCA 36) with both cerebellar ataxia and a motor neuron disease phenotype, which is caused by a hexanucleotide GGCCTG repeat expansion in intron 1 of the NOP56 gene [1–4]. Common symptoms of Asidan patients are truncal ataxia, dysarthria and limb ataxia (a sign of cerebellar ataxia), hyperreflexia and tongue atrophy, fasciculation (a sign of motor neuron disease), and cognitive impairment. Recent reports showed sporadic and familial amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD) in the Caucasian population is caused by hexanucleotide GGGGCC repeat expansion in intron 1 of the C9orf72 gene [5,6], similar to the genetic mutation in Asidan patients. C9orf72 mutation induces neurodegeneration of Purkinje cells [7,8]. It is possible that a similar genetic pathology for cerebellar ataxia, motor neuron disease signs and cognitive impairment may be at play in both Asidan and ALS/FTD. Most of our Asidan patients did not show parkinsonian features or autonomic failures [1–4], consistent with other studies from Japan (other areas), Spain, France, China and Taiwan [9–15]. However, a potential multisystem involvement of neurodegeneration in Asidan has not yet been evaluated.

Dopamine transporter single photon emission computed tomography (DAT-SPECT) with ^{123}I-2β-Carbomethoxy-3β-(4-iodophenyl)-*N*-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) was recently developed to evaluate striatal dopamine transporter activity in patients with parkinsonism [16–18]. ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy evaluates the activity of cardiac sympathetic nerve terminals [17]. DAT is usually decreased both in Parkinson's disease (PD) and progressive supranuclear palsy (PSP) patients, and MIBG is decreased in PD but not in PSP [16–18]. Therefore, the combination of DAT-SPECT and MIBG myocardial scintigraphy is useful for the diagnosis of PD and differentiation from PSP. However, the techniques have not been used for the evaluation of neurodegeneration in SCAs.

In this study, we present the clinical characteristics of 11 Asidan patients from six independent families, and a case with mild parkinsonism and autonomic failure. None of these 11 patients have been previously studied. Using DAT-SPECT and MIBG myocardial scintigraphy, we compared our new and previous [1,2,4] Asidan patients with PD and PSP patients to investigate a potential multisystem involvement of neurodegeneration in Asidan.

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2. Patients and methods

In the present study, we recruited 11 patients with Asidan (SCA36), who were not studied in any of our previous reports [1,2,4], and compared their clinical characteristics with those of previous patients (n = 14). In addition to the new cohort, we recruited a part of our previous Asidan patient cohort (DAT: new Asidan, n = 2, previous Asidan, n = 8; MIBG: new Asidan n = 5, previous Asidan, n = 10) [1,2,4] for the comparison with patients with PD (n = 21) and PSP (n = 13), using DAT-SPECT and MIBG myocardial scintigraphy. Diagnosis of Asidan cases was confirmed by DNA analysis [2,3]. PD cases were diagnosed clinically by neurological specialists in our specialized PD

Table 1
Clinical characteristics of new Asidan patients.

	Summary of all new Asidan patients (n = 11)	Pedigree A III-2	Pedigree B III-1	Pedigree C III-4	Pedigree D III-3	Pedigree E	Pedigree F 1	Pedigree F 2	Pedigree F 3	Pedigree F 4	Pedigree F 5	Pedigree F 6
Age at onset, y	52.9 ± 5.7	63	47	51	45	46	52	62	55	52	52	57
Duration of illness, y	14.1 ± 9.3	11	5	8	12	30	26	21	21	1	18	2
Age at examination, y	67.1 ± 10.8	74	52	59	57	76	78	83	76	52	72	59
Cranial nerves												
Pupil	9.1% anisocoria	Isocoria	Isocoria	Isocoria	Isocoria	Isocoria	Anisocoria	Isocoria	Isocoria	Isocoria	Isocoria	Isocoria
EOM	63.6% saccadic	Saccadic	Smooth	Saccadic	Smooth	Saccadic	Saccadic	Saccadic	Saccadic	Smooth	Smooth	Saccadic
Nystagmus	0%	−	−	−	−	−	−	−	−	−	−	−
Cerebellar systems												
Ataxia	Truncal >dysarthria >limb	Truncal ≫ dysarthria >limb	Truncal > dysarthria ≫limb	Truncal > dysarthria >limb	Truncal ≫ dysarthria >limb	Truncal > dysarthria ≫limb	Truncal >dysarthria >limb	Truncal > dysarthria >limb	Truncal > dysarthria >limb	Truncal > dysarthria >limb	Truncal > dysarthria >limb	Truncal > dysarthria >limb
SARA scale	16.6 ± 8.0	21	13	15	16	27	19	33	15	5	14	5
Motor signs												
Dysphagia	45.5%	−	−	±	−	±	±	+	−	−	+	−
Tongue atrophy	72.7%	+	−	+	−	+	±	+	2+	±	+	−
Tongue fasciculation	72.7%	+	±	−	−	+	−	+	2+	±	±	±
Muscle atrophy	18.2%	−	−	−	−	+	−	+	−	−	−	−
Muscle weakness	27.3%	−	−	−	−	+	−	+	+	−	−	−
Fasciculation in U/E, L/E	9.1%	−	−	−	−	−	−	+	−	−	−	−
Reflexia in U/E, L/E	54.5% hyperreflexia	1+	3+	3+	2+	3+	4+	1+	3+	+	3+	2+
Babinski	18.2%	−	−	−	−	+	−	−	+	−	−	−
Parkisonian symptoms												
Muscle tonus	9.1% rigidity	Normal	Normal	Normal	Normal	Normal	Normal, Bil.ankle clonus+	Rigidity 0.5+ (Lt.U/E)	Normal	Normal	Normal	Normal
Bradykinesia	0%	−	−	−	−	−	−	−	−	−	−	−
Resting tremor	0%	−	−	−	−	−	−	−	−	−	−	−
Autonomic failure	9.1%	−	−	−	−	−	−	+	−	−	−	−
Sensory disturbance	0%	−	−	−	−	−	−	−	−	−	−	−
Others		−	−	−	−	−	Hypertension	−	Depression	−	Hearing loss	Hearing loss
Cognitive function												
MMSE	27.3 ± 2.9	27	27	28	28	29	28	19	26	30	28	30
HDS-R	26.7 ± 4.4	29	30	25	29	30	27	15	22	30	27	30
CDR	0.1 ± 0.2	0	0	0	0	0	0	ne	0.5	0	0	0
FAB	13.8 ± 4.2	ne	17	17	17	10	15	5	9	18	17	13
MoCA	22.3 ± 4.9	ne	25	25	24	20	24	11	17	30	24	23
GDS	6.4 ± 4.5	14	7	11	ne	6	0	4	13	4	2	3
Apathy	17.5 ± 8.4	20	17	23	ne	ne	3	ne	34	15	11	17
ABS	1.6 ± 2.9	5	8	ne	ne	ne	0	0	0	0	0	0
Atrophy on brain (MRI)		Cerebellar	Cerebellar	Cerebellar, cerebral	Cerebellar	Cerebellar, brainstem	ne	Cerebellar, brainstem	ne	ne	ne	ne
Hypoperfusion of brain (SPECT)		Cerebellar, brainstem	ne	Cerebellar	ne	Cerebellar	ne	ne	ne	ne	ne	ne

Data are expressed mean ± SD.