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Phenotypic diversity of hereditary sensory and autonomic neuropathy type IE: a case series and review of the literature

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Abstract

Objective: DNA methyltransferase 1 (DNMT1) is crucial to maintaining methylation during DNA replication and DNA repair. DNMT1 mutations have been identified in two neurological syndromes, including hereditary sensory and autonomic neuropathy type IE (HSAN IE) with dementia and hearing loss and autosomal dominant cerebellar ataxia, deafness and narcolepsy. It is likely that DNMT1 mutations lead to various symptoms of the central and peripheral nervous system. The aim of this study was to examine the clinical characteristics, especially the initial symptoms, in the cases of DNMT1 mutations. *Methods:* We investigated the clinical manifestation and examination findings of four cases of HSAN IE from one family with the DNMT1 mutation c.1531Y>C (p.Try511His). *Results:* All four cases exhibited sensory neuropathy, cerebellar ataxia, and hearing loss, all of which were demonstrated by the audiograms. The initial symptoms of the four cases included hearing loss (n=1), gait disturbance (n=1), and depressive mood (n=2). Depressive symptoms are reported in some cases with HSAN IE, however, there are currently no published reports that describe them as primary symptoms. The CSF orexin level was measured in three cases, revealing normal values in two cases and intermediate values in one case, in which the patient exhibited rapid eye movement (REM) sleep behavior disorder.
Conclusion: Our findings suggest that in cases with HSAN IE or the DNMT1 mutation, psychiatric symptoms should be taken into account as one of the initial manifestations of the disease.

Keywords: DNMT1; hereditary sensory and autonomic neuropathy; HSAN IE; phenotypic diversity; psychiatric symptom; orexin

INTRODUCTION

DNA methyltransferase 1 (DNMT1) is a critical enzyme required to maintain methylation during DNA replication and DNA repair.[1] Heterozygous mutations of DNMT1 were identified as causal for two distinct diseases: hereditary sensory and autonomic neuropathy with dementia and hearing loss (HSAN IE) and autosomal dominant cerebellar ataxia, deafness and narcolepsy (ADCA-DN).[2,3] There are more overlapping clinical features between the two phenotypes than their acronyms describe.

We herein report on the clinical manifestations and examination findings of four members from one family with the DNMT1 mutation, as previously reported in cases with HSAN IE.

METHODS

We investigated the clinical manifestation and examination findings of four cases of HSAN IE from one family with the DNMT1 mutation c.1531Y>C (p.Try511His). Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and the Frontal Assessment Battery (FAB) were used to assess cognitive impairment.

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Ethical approval was obtained from local ethics committee and we acted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

RESULTS

The pedigree of the family is shown in Figure 1A. In this case series of four affected patients, the Miseq sequencing system (Illumina) allowed us to identify the heterozygous point mutation c.1531Y>C (p.Try511His) in exon 20 of the DNMT1 gene (RefSeq NM_001130823.1) (Figure 1B). The results of nerve conduction studies are shown in Figure 2.

The clinical history of each of the four cases is reported below.

Case 1: III-4

A 52-year-old male presented with hearing loss at age 40, when a hearing test demonstrated mild symmetric sensorineural hearing loss limited to high-frequency sound. Additionally, he had complained of gait disturbance and dysarthria since his late forties. On neurological examination, he exhibited behavioral disinhibition, bilateral hearing loss, explosive speech, distal dominant paresthesias of the lower limbs with reduced sensation, absent deep tendon reflexes in the lower limbs, and limb and truncal ataxia. A brain MRI demonstrated moderate diffuse cerebral and cerebellar atrophy. Nerve conduction studies revealed pure sensory axonal neuropathy (Figure 2). The results of neuropsychological testing showed mild cognitive impairment with predominant involvement of frontal lobe dysfunction (MMSE 25; MoCA 19; FAB 11). A hearing test demonstrated moderate bilateral sensorineural hearing loss. The cerebrospinal fluid (CSF) orexin level was within the normal range (259 pg/mL).

Case 2: III-5

A 48-year-old male presented with depressed mood and hypobulia which had begun at age 41, and was later diagnosed with bipolar II disorder. He had begun developing slowly progressive cognitive impairment and gait disturbance since age 47. Physical examination revealed foot ulcers, which was refractory despite making regular visits to a dermatologist. On neurological examination, he exhibited cerebellar ataxia and distal dominant reduced sensation with absent deep tendon reflexes in the lower limbs. A brain MRI demonstrated

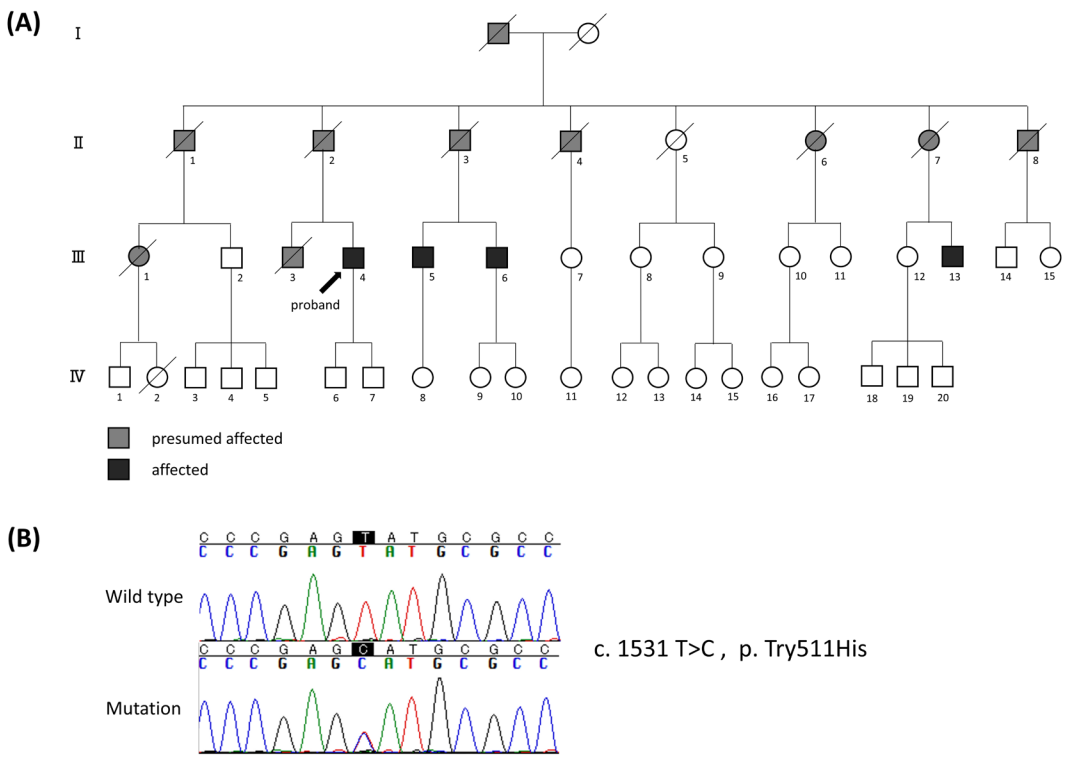

Figure 1. (a). Pedigree of the family. The black symbol indicates affected individuals, and the grey symbol indicates those presumed to be affected. (b). The Try511His mutation was found in the pedigree

	Case 1 *Right*	*Left*	Case 2 *Left*	Case 3 *Right*	Case 4 *Right*
Motor NCS					
Median N [APB]					
NCV (m/s)	58.4	58.8	54.2	64.5	55.2
CMAP (mV)	8.0	7.3	13.3	7.4	10.2
Ulnar N [ADM]					
NCV (m/s)	58.4	59.0	69.0	54.7	59.6
CMAP (mV)	9.3	9.8	7.2	7.4	15.1
Tibial N [AHM]					
NCV (m/s)	48.1	48.0	44.0	34.8	37.4
CMAP (mV)	21.5	15.8	17.7	5.7	21.2
Sensory NCS					
Median N [digit 2]					
NCV (m/s)	44.3	46.7	58.3	NE	44.3
SNAP (μV)	5.9	14.1	9.8	NE	4.0
Ulnar N [digit 5]					
NCV (m/s)	30.6	NE	52.6	NE	39.2
SNAP (μV)	4.8	NE	1.4	NE	4.4
Sural N [ankle]					
SNAP (μV)	NE	NE	NE	NE	NE

APB, abductor pollicis brevis; ADM, abductor digiti minimi; AHM, Abductor hallucis muscle; NE, not evoked.

Figure 2. Nerve conduction studies demonstrate axonal sensory neuropathy in all four cases

mild diffuse cerebral and cerebellar atrophy. 123I-metaiodobenzyl guanidine (123I-MIBG) myocardial scintigraphy showed normal cardiac uptake (heart-to-mediastinum (H/M) ratio: early 2.47, delayed 2.95). The NCS revealed pure sensory axonal neuropathy (Figure 2). A hearing test demonstrated mild bilateral sensorineural hearing loss. The results of the neuropsychological tests showed slight cognitive impairment (MMSE 28; MoCA 24; FAB 15). The CSF orexin level was within the normal range (323 pg/mL).

Case 3: III-6

A 44-year-old male presented with depressed mood that began at age 41, similarly to his brother (Case 2), and he was subsequently diagnosed with depression. He complained of difficulty with calculations and of a gait disturbance which began at age 43. Physical examination was remarkable for foot ulcers. On neurological examination, he showed distal dominant reduced sensation with absent deep tendon reflexes in the lower limbs and cerebellar ataxia without muscle weakness. A brain MRI demonstrated moderate diffuse cerebral and cerebellar atrophy. 123I-MIBG myocardial scintigraphy showed normal cardiac uptake (H/M ratio: early 2.98, delayed 3.35). The NCS revealed sensory axonal neuropathy and mild attenuated lower limb motor responses (Figure 2). A hearing test demonstrated moderate bilateral sensorineural hearing loss, especially with high-frequency sound. The results of neuropsychological testing demonstrated mild cognitive impairment (MMSE 23; MoCA 23; FAB 12). The CSF orexin level was within the normal range (437 pg/mL).

Case 4: III-13

A 48-year-old male presented with gait disturbance which had persisted since age 30; he reported that he often fell when walking on paths. He began relying on handrails to go up and down stairs since age 40. He reported episodes of shouting and moving his extremities when sleeping at night, which began at age 47; these were considered to be symptoms of rapid eye movement (REM) sleep behavior disorder (RBD). On neurological examination, he showed bilateral hearing loss, distal dominant reduced sensation with absent deep tendon reflexes in lower limbs, and cerebellar ataxia. A brain MRI demonstrated mild diffuse

cerebral and cerebellar atrophy. 123I-MIBG myocardial scintigraphy showed normal cardiac uptake (H/M ratio: early 2.78, delayed 2.94). The NCS revealed pure sensory axonal neuropathy (Figure 2). A hearing test demonstrated moderate bilateral sensorineural hearing loss. The results of neuropsychological testing revealed mild cognitive impairment (MMSE 23; MoCA 22; FAB 12). The CSF orexin level was in the intermediate range (182 pg/mL).Polysomnography (PSG) findings demonstrated REM sleep without atonia. Administration of clonazepam decreased his RBD symptoms.

DISCUSSION

In this study, we report on the clinical features of a series of four cases with the DNMT1 mutation, which are summarized in Table 1. The heterozygous mutation p.Tyr511His (RefSeq NM_001130823.1; c.1531 T>C), corresponding to p.Tyr495His (RefSeq NM_001379; c.1483 T>C), was previously reported in three families.[6-8] Moreover, amino acid Try495 (Try511) in DNMT was reported as a hot spot for mutation among patients with HSAN IE.[6]

To date, eight studies have described the clinical features of patients with HSAN IE[2,4-10], the data of which, is summarized in Table 2. With regard to the 83 affected patients from 21 families, we recognized that almost all of the patients exhibited hearing loss (97.5%) and sensory neuropathy (97.3%); dementia was also present in the majority of patients (86.3%). Although cerebellar ataxia was a relatively less common feature in the previous report (38.5%), all four cases in this study showed cerebellar ataxia and atrophy. In fact, this family had been diagnosed with autosomal dominant spinocerebellar ataxia. In addition, some HSAN IE patients presented with infections and resultant amputations of their feet, which was attributable to the loss of sensation in their lower extremities. Two patients in this study presented with ulcers on their feet, of which Case 2 was especially refractory.

In cases with the Try511His (Try495His) mutation, personality change was reported more frequently than other mutations, including the case of a patient who exhibited odd behaviors as the primary symptom and was initially diagnosed with frontotemporal lobar degeneration (FTLD).[6]

Table 1: Clinical features of four affected patients

	Case 1	Case 2	Case 3	Case 4
Age (years)/sex	52 / M	48 / M	44 / M	48 / M
Age of onset (years)	40	41	41	30
Primary symptom	Deafness	Depressed mood	Depressed mood	Gait disturbance
Psychiatric symptom	Behavioral disinhibition	Bipolar II disorder	Depression	N
Hearing loss	moderate	mild	moderate	moderate
Sensory neuropathy	Y	Y	Y	Y
Dementia	Y	Y	Y	Y
Cerebellar ataxia	Y	Y	Y	Y
Foot ulcer	N	Y	Y	N
Sleep disturbance	N	N	N	RBD
Cognitive impairment				
MMSE	25	28	23	23
MoCA	19	24	23	22
FAB	11	15	12	12
Cerebral atrophy	moderate	mild	moderate	mild
Cerebellar atrophy	moderate	mild	moderate	mild
^{123}I-MIBG myocardial scintigrahy	NE	Normal	Normal	Normal
CSF orexin (pg/mL)	259	323	437	182

M, male; F, female; Y, present; N, not present; NE, not eamined

Table 2: Summary of clinical features of patients with HSAN IE based on previous reports

The DNMT1 mutations marked with an asterisk refer to RefSeq NM_001130823.1, and the others without the mark refer to RefSeq NM_001379. (where Tyr495 corresponds to Try511, Asp490 to Asp506, and Pro491 to Pro507)

	Klein *et al.* 2011[2]		Klein *et al.* 2013[6]		Yuan *et al.* 2013[4]	Moghadam *et al.* 2014[5]		Beats *et al.* 2015[7]						Fox *et al.* 2016[9]	Kinariwala *et al.* 2016[10]	Watanabe *et al.* 2016[8]	Summary
DNMT1 mutation	**Try495Cys**	**Asp490Glu-Pro491Try**	**Tyr495His**	**Try495Cys**	**His569Arg***	**Pro507Asn***	**Lys521del***	**Thr481Pro**	**Pro491Leu**	**Try524Asp**	**Ile531Asn**	**Try495Cys**	**Cys353Phe**	**Try495His**	**Asn545del***	**Try511Cys***	**Tyr495His**	
Exon	20	20	20	20	21	20	20	20	20	21	21	20	20	20	20	20	20	
Patients (Kindred)	15 (3)	3 (1)	3 (1)	4 (1)	1 (1)	2 (1)	1 (1)	1 (1)	1 (1)	2 (1)	2 (1)	22 (3)	7 (1)	10 (1)	1 (1)	1 (1)	7 (1)	83 (21)
Age at onset (years)	~30	20s	40s	40s	Late teens	29	33	19	18	26	29	30s-40s	45	40	8	40s	44	30s-40s
Primary symptom																		
Deafness	13	3	2	2		1	1	1	1		1	8	3	3		1	1	41
Dementia			1	2								1		2				6
Sensory neuropathy	7		1	1	1	1				1	2	6		7	1	1	4	33
Gait disturbance			2	2								1	1					3
Personality change								1				1					2	4
Common presenting symptom	Deafness	Deafness	Deafness	Deafness	Sensory neuropathy	Deafness	Sensory neuropathy	Deafness	Deafness	Sensory neuropathy	Sensory neuropathy	Deafness	Deafness	Sensory neuropathy	Sensory neuropathy	Deafness	Sensory neuropathy	Deafness
Hearing loss	15/15	3/3	3/3	4/4	1/1	2/2	1/1	1/1	1/1	2/2	2/2	22/22	6/7	8/8	1/1	1/1	6/7	79/81
Sensory neuropathy	15/15	3/3	2/2	2/2	1/1	2/2	1/1	1/1	1/1	2/2	2/2	19/19	4/6	8/8	1/1	1/1	7/7	72/74
Sleep disturbance	NA	NA	NA	NA	NA	EDS 2	EDS 1 RBD 1 Cataplexy 1	EDS 1 RBD 1	EDS 1	0/1	EDS 2	Narcolepsy 3/13 RBD 1/13	EDS 1	RLS 2	Cataplexy 1	NA	NA	15/25 Narcolepsy 5 EDS 8 RBD 3
Dementia	15/15	3/3	3/3 (FTLD 1)	4/4	Mental retardation	0/2	1/1	1/1	1/1	0/1	2/2	21/22 (FTLD 1)	1/4	6/6 (FTLD 3)	0/1	NA	5/7	63/73 (FTLD 5)
Cerebellar ataxia	2/15	2/3	NA	NA	0/1	1/2	1/1	NA	NA	NA	2/2	1/1	NA	NA	NA	NA	1/1	10/26
Psychiatric symptom	NA	NA	Personality change 1	Obsessive-compulsive disorder 1	NA	0/2	0/1	Personality change 1 Hallucination 1	Personality change 1 Hallucination 1	NA	NA	Personality change 2 Hallucination 1	Personality change 1 Hallucination 1	Personality change 1	Depression 1	NA	Personality change 4 Depression 1	16/59 Personality change 12 Hallucination 4 Depression 2
Foot ulcer	6/15	3/3	NA	1/1	1/1	0/2	1/1	1/1	1/1	2/2	0/1	14/21	4/6	4/5	1/1	NA	5/7	44/68
Other symptoms	Muscle weakness 2	NA	Muscle weakness 1 Epilepsy 1	NA	NA	NA	Orthostatic hypotension 1	Myoclonus 1	Myoclonus 1	NA	Myoclonus 1	NA	NA	NA	Orthostatic hypotension 1	NA	NA	
Age at death	~50	46	~60	53	Alive (41)	41	59	Alive (34)	48	43	45	50s	68	55	Alive (24)	Alive (40s)	~60	~50

EDS, excessive daytime sleepiness; RBD, REM sleep behavior disorder; FTLD, frontotemporal lobar degeneration; NA, not applicable

In this study, one case (Case 1) showed behavioral disinhibition, which was present since the initial visit to our hospital. Additionally, personality changes could be considered as the characteristic symptom related to the Try511His (Try495His) mutation.

A remarkable finding of this study is that two out of the four patientspresented with depressed mood as the primary symptom. They initially visited a psychiatrist and were diagnosed with bipolar II disorder and depression, respectively. Previous reports that describe cases of HSAN IE recognized hearing loss or symptoms related to sensory neuropathy as the initial symptom (Table 2). Although depressive symptoms were reported in some cases of HSAN IE, there is currently no report that describes them as a primary symptom of this disease. Based on our findings, we propose that psychiatric symptoms, such as depressive symptoms, could be one of the initial clinical manifestations of disease in cases with HSAN IE.

Although clinical symptoms related with autonomic failure were observed in the cases, ^{123}I-metaiodobenzyl guanidine (^{123}I-MIBG) myocardial scintigraphy was performed in three cases. The results of ^{123}I-MIBGmyocardial scintigraphy in this study showed preserved ^{123}I-MIBG uptake as with the previous case. ^{6123}I-MIBGmyocardial scintigraphy can assess presynaptic postganglionic endings of the cardiac sympathetic nerve; therefore, our results imply that the postganglionic sympathetic nerve fibers might hardly be involved in cases with HSAN IE.

In our study, the patients without sleep disturbances demonstrated a normal CSF orexin level; however, the case with RBD symptoms (Case 4) had a level of CSF orexin in the intermediate range. Sleep disorders, including narcolepsy, excessive daytime sleepiness, and RBD, have been observed in cases not only with ADCA-DN but also with HSAN IE. However, previous reports showed that only the patients with ADCA-DN presented with low/intermediate CSF orexin levels.[3,5,11] These findings imply that orexin physiology could be altered even in cases with HSAN IE.

In conclusion, half of the patients in our study initially presented with depressive mood symptoms. Our findings suggest that psychiatric symptoms should be considered as one of the initial clinical manifestations of disease in cases with HSAN IE or the DNMT1 mutation.

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DISCLOSURE

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Conflicts of interest: None

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