탈수초신경병으로 최초 진단 후 유전성 Transthyretin 아밀로이드증으로 최종 진단된 증례 모음

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Hereditary Transthyretin Amyloidosis Misdiagnosed as Demyelinating Neuropathy: A Report of Three Cases

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Transthyretin amyloidosis (aTTR) is a life-threatening type of systemic amyloidosis that has been associated with autosomal dominant mutations in the transthyretin gene. In this case series, we reviewed 3 patients initially treated for acquired demyelinating neuropathy that was later confirmed by pathologic testing and genetic analysis as aTTR. These patients had systemic symptoms and family records of sudden deaths that could not be explained by acquired demyelinating neuropathy. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a treatable neuropathy; however, 20% to 33% of CIDP patients remain refractory to conventional immunotherapy, and incorrect diagnoses might be the cause of this therapeutic failure. This case series revealed that the electrophysiological findings of aTTR could resemble the findings of demyelinating neuropathy.

Keywords: Amyloidosis; Polyneuropathies; Polyradiculoneuropathy, chronic inflammatory demyelinating

Received: September 22, 2021

Revised: October 31, 2021

Accepted: November 13, 2021

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Introduction

Transthyretin amyloidosis (aTTR) is a rare life-threatening systemic amyloidosis resulting from autosomal dominant mutations in the transthyretin (TTR) gene. Amyloid deposition in the peripheral nerves causes a form of polyneuropathy known as familial amyloidotic polyneuropathy [1].

Identification of demyelination features in the diagnosis of polyneuropathy is clinically important because of their treatable

characteristics. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a typical example of treatable acquired polyneuropathies. Patients with CIDP usually receive immunotherapy including intravenous immunoglobulin, plasmapheresis, or corticosteroids. However, 20% to 33% of CIDP patients remain refractory [2]. The refractory CIDP is not completely understood; however, incorrect diagnosis is considered to be among the causes of this therapeutic failure [3,4]. The most commonly used electrophysiological criteria for CIDP showed 80% of accu-

racy and this limitation can sometimes lead to misdiagnoses resulting to prescription of ineffective treatment [5,6].

We performed a retrospective review of 3 patients initially treated as acquired demyelinating polyneuropathy such as CIDP but finally confirmed as aTTR. This report was approved by the Institutional Review Board (IRB) and the Pharmacy and Therapeutic Committees at Konkuk University Medical Center, Seoul, South Korea (No. KUH1170167). In consideration of the characteristics of medical record analysis, informed consent was waived by the IRB.

Case Reports

The clinical characteristics and the *TTR* gene mutations of the 3 aTTR patients are summarized in Table 1.

Case 1

This male patient initially exhibited paresthesia of both lower limbs at the age of 38. After 3 years of progression of the sensory symptoms, he developed weakness of his distal limbs in a length-dependent pattern. His mother had died of heart disease but there was no information on whether she had any form of neuropathy. On the initial nerve conduction study (NCS), a severe sensorimotor polyneuropathy was noted. Conduction block and increased duration of compound muscle action potential (CMAP) were presented on 3 nerves in both upper limbs (Table 2, Fig. 1). The laboratory tests excluded all other potential causes of demyelinating polyneuropathy. The patient was treated with oral prednisolone (1 mg/kg for a month) and intravenous immunoglobulin (over a course of 2 g/kg, divided within 5 days) without improvement. He further developed new symptoms, including orthostatic hypotension and diarrhea. Dilated cardiomyopathy was confirmed by echocardiography. After the presentation of autonomic symptoms, he was diagnosed with amyloidosis by colon tissue biopsy and was genetically confirmed to have a Lys35Asn

mutation in the *TTR* gene.

Case 2

This female patient initially presented urinary incontinence at the age of 45, 2 years before the onset of the neuropathic symptoms. The patient had already been aware of her high arched foot in her 40s. She referred to the neurology department with progressive generalized weakness and anorexia. Her father had died in his 60s of an unknown cause. On neurological examination, amyotrophy of her feet and distal dominant weakness with sensory loss were noted. Upon electrophysiological examination, severe sensorimotor polyneuropathy was identified (Table 2). Late responses and motor nerve conduction of the lower limbs were not evoked, whereas significantly delayed terminal latencies, slow nerve conduction velocities and extended duration of CMAP were indicative of demyelinating neuropathy. Despite of the administration of steroids, her symptoms kept worsening and she complained of decreased visual acuity. Considering that cataract caused by steroids, she was subjected to ophthalmological examination. Nevertheless, the vitreous opacity was associated to amyloid deposit. Holter monitoring confirmed arrhythmia with right bundle branch block of suggesting systemic dispersion of amyloidosis. Genetic analysis demonstrated that the patient was heterozygous for the Lys35Asn mutation in the *TTR* gene.

Case 3

The third patient was a 46-year-old man who complained of weakness of distal lower limbs and paresthesia of all 4 limbs. He had lost 11 kg in 1 year, due to chronic diarrhea. On neurological examination, sensory loss and distal dominant weakness with a length-dependent pattern were noted. Upon electrophysiological examination, severe sensorimotor polyneuropathy was confirmed. On motor NCS, conduction block and increased duration of CMAP were presented on 2 nerves of both upper limbs (Table 2). Despite steroid treatment, he exhibited no clinical im-

Table 1. Summary of Patients' Clinical Features

Patient	Sex	Age at onset (y)	Age at diagnosis (y, genetic analysis)	Main neurologic signs of neuropathy	Combined systemic symptoms	Mutation
1	Male	38	42	Distal dominant weakness and paresthesia of all limbs Generalized areflexia	Diarrhea Arrhythmia Orthostatic hypotension	Lys35Asn
2	Female	45	47	Distal dominant weakness of lower limbs Generalized areflexia Carpal tunnel syndrome	Urinary incontinence Arrhythmia Cataracts	Lys35Asn
3	Male	45	46	Distal dominant weakness of lower limbs Generalized areflexia	Diarrhea Orthostatic hypotension	Ala36Pro

Table 2. Patients' Initial Nerve Conduction Studies

Nerve/site	Latency (ms)*			Amplitude			NCV (m/s)			Peak duration (ms)		
	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3
Motor NCS												
Right median nerve												
Wrist	4.45	9.05	5.15	7.7	0.7	5.2				7.0	7.20	7.05
Elbow				3.1	0.5	2.4	45.7	22.3	38.4	8.65	7.05	4.75
Axilla				2.8	0.5	2.1	53.3	25.5	57.1	8.65	6.50	4.85
F-wave	27.6	65.6	36.0									
Left median nerve												
Wrist	4.95	9.85	4.10	6.5	2.6	5.4				5.5	8.60	6.60
Elbow				3.5	2.2	4.4	51.9	20.8	43.5	5.4	10.0	6.90
Axilla				2.7	2.0	4.4	60.0	27.7	57.1	10.0	10.0	6.90
F-wave	27.20	66.5	28.4									
Right ulnar nerve												
Wrist	3.60	7.05	6.40	6.8	2.7	0.9				6.50	7.55	5.95
Below the elbow				3.0	1.5	0.7	54.1	15.7	20.2	5.85	8.05	8.80
Above the elbow				3.0	1.5	0.6	62.1	19.4	34	9.10	9.60	9.40
Axilla				2.9	1.4	0.6	66.7	18.6	60	9.60	10.6	8.65
F-wave	25.9	NP	30.0									
Left ulnar nerve												
Wrist	4.60	6.6	3.80	7.1	3.0	5.6				6.50	8.25	7.60
Below the elbow				3.7	1.6	2.6	41.2	15.8	45.5	8.70	11.0	7.75
Above the elbow				3.4	1.6	2.6	48.6	16.6	48.6	11.0	11.5	7.20
Axilla				2.9	1.6	2.6	52.6	26.2	60	10.2	11.5	7.05
F-wave	29.7	NP	32.7									
Right common peroneal nerve												
Wrist				NP	NP	NP						
Left common peroneal nerve												
Wrist				NP	NP	NP						
Right tibial nerve												
Wrist				NP	NP	NP						
Right H-wave												
Wrist				NP	NP	NP						
Left tibial nerve												
Wrist				NP	NP	NP						
Left H-wave												
Wrist				NP	NP	NP						
Sensory NCS												
Right median nerve												
Finger-wrist	2.95			2.3	NP	NP	37.3					
Palm-wrist	2.55			3.6	NP	NP	39.2					
Wrist-elbow	4.50		4.85	7.8	NP	10.0	46.7		41.2			
Elbow-axilla	2.35	2.05	2.20	33.5	5.7	22.2	51.1	53.7	54.5			
Left median nerve												
Finger-wrist			3.15	NP	NP	4			41.3			
Palm-wrist			2.75	NP	NP	4.1			43.6			
Wrist-elbow	4.70		4.70	9.6	NP	11.2	44.7		44.7			
Elbow-axilla	2.40	2.75	2.15	39.8	9.6	54.3	50.0	43.6	55.8			
Right ulnar nerve												
Finger-wrist				NP	NP	NP						
Palm-wrist				NP	NP	NP						
Wrist-elbow	4.40		5.20	7.4	NP	5.4	45.5		36.5			
Elbow-axilla	2.45	2.85	2.45	26.2	2.7	7.4	49.0	42.1	49.0			
Left ulnar nerve												
Finger-wrist			3.15	NP	NP	1.1			38.1			
Palm-wrist			2.50	NP	NP	2.7			44.0			
Wrist-elbow			5.00	NP	NP	6.2			44.0			
Elbow-axilla	2.72	2.40	2.35	33.5	4.6	11.3	43.6	45.8	51.1			

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Table 2. Continued

Nerve/site	Latency (ms)*			Amplitude			NCV (m/s)			Peak duration (ms)		
	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3	Patient 1	Patient 2	Patient 3
Right sural nerve				NP	NP	NP						
Left sural nerve				NP	NP	NP						
Right superficial peroneal nerve				NP	NP	NP						
Left superficial peroneal nerve				NP	NP	NP						

Amplitudes are measured in millivolt (mV, motor NCS) and microvolt (μ V, sensory NCS).

NCV, nerve conduction velocity; NCS, nerve conduction study; NP, no potential.

*Motor NCS: terminal latency, sensory NCS: latency.

Fig. 1. Motor nerve conduction studies of case 1. A demyelinating pattern with conduction block and temporal dispersion was observed in the left median nerve (A) and the right ulnar nerve (B).

provement. In addition to weakness progression, orthostatic hypotension occurred, and diarrhea got aggravated. However, he had no family members with similar symptoms. The possibility that the patient had amyloidosis was considered after the autonomic abnormalities significantly worsened. Gastrointestinal amyloidosis was confirmed by following colon tissue biopsy and the heterozygous mutation as Ala36Pro was detected in *TTR* gene.

Discussion

NCS has been considered the gold standard for detecting segmental demyelination of peripheral nerves. Although electrophysiologic confirmation is key factor in diagnosis of acquired demyelinating polyneuropathies, they do not always accurately reflect the pathology of the disease [3]. A recent study showed 15% of demyelinating aTTR patients in French cohort (13 of 84

patients) and demonstrated misleading features of aTTR fulfilling electrodiagnostic criteria of CIDP are not uncommon in clinical practice [7]. In previous studies, the most notable features of NCS in aTTR fulfilling electrodiagnostic criteria of CIDP were prolonged distal latency of the median nerve and the other is co-existence of severe motor axonal loss not only demyelinating features [7,8]. These features are also shown in all patients in this report (Table 2).

These 3 patients had significant clinical symptoms that could have also been considered as clues for correct diagnosis, such as gastrointestinal, urinary, or cardiac dysfunction. Moreover, the unevaluated causes for the sudden death of the patients' parents were clue for the existence of a hereditary disease. All 3 patients initially received immunomodulatory treatment considering CIDP, but it might be also noticeable that all 3 patients presented distal dominant weakness. Although distal acquired demyelinat-

ing symmetric polyneuropathy and others (e.g., Lewis-Sumner syndrome, pure motor or pure sensory) are classified as subtypes of CIDP, they are still considered atypical and uncommon.

CIDP still has no typical biomarker diagnosed by the identification of characteristic electrophysiological findings. Because of their treatable characteristic, many clinicians might tend to try an early application of therapy considering the CIDP in the case of an incomplete diagnosis. In addition, the diagnostic criteria for refractory CIDP also have not yet been established. Steroids or immunoglobulins are usually applied as the first-line treatment, and if there is no effect, additional immunomodulatory treatment is performed. If there is no effect leading to remission in this series of treatments, it is considered refractory [9]. Yet, recent studies on CIDP reported that almost half of the patients referred for second opinion due to insufficient outcome of immunotherapy and were finally diagnosed with alternative diseases, with aTTR being the case for 5% of them [3,4]. Other diseases to consider when the final alternative diagnosis was made in patients with presumed refractory CIDP were diverse including diabetic polyneuropathy, amyotrophic lateral sclerosis, multifocal motor neuropathy, idiopathic small fiber neuropathy, fibromyalgia and etc. Therefore, in the case of clinically refractory CIDP, the differential diagnosis may need to be re-examined [3,4].

Since current medical or surgical intervention can halt the progression of aTTR, early and correct diagnosis becomes an important issue. In conclusion, clinicians should be aware that the electrophysiological outcome of aTTR patients can sometimes mimic the findings of patients with a demyelinating disease.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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