To the Editor

ATTR Amyloidosis Complicated by Phrenic Nerve Palsy

Amyloidoses are groups of protein misfolding and deposition diseases, and many proteins are known to form amyloid fibrils. Mutated transthyretin (TTR) can cause familial amyloid polyneuropathy (FAP), which is associated with systemic disorders including neuropathy and cardiac diseases. Here we report a rare case of ATTR amyloidosis presenting with fatal hypoventilation accompanied by bilateral phrenic nerve palsy.

A woman began to suffer from numbness in her hands and soles when she was 69-years-old. Her past history was unremarkable. She was born in Yokosuka city, away from the endemic foci of FAP in Japan, and had no family history of any neurological diseases. She was diagnosed as carpal tunnel syndrome, but surgery did not improve her symptoms. She came to our clinic one year later. Neurologic examination revealed muscle weakness, atrophy, and sensory loss, predominantly in the distal limbs. Deep tendon reflexes were all absent. Conventional nerve conduction studies (NCSs) in limbs showed severely decreased amplitudes of the compound muscle action potentials (CMAPs) and the sensory nerve action potentials (SNAPs). Conduction velocities were almost normal. A left sural nerve biopsy showed axonal loss, but Congo-red staining did not disclose amyloid deposits at that time. Her symptoms further progressed and she became bedridden at the age of 72. At the same time, she was also suffering from syncope and alternating diarrhea and constipation, suggesting complication of autonomic dysfunction. At the age of 74 she began to suffer from dyspnea. Physical examination revealed pitting edema in her legs. Blood tests were unremarkable, but plasma brain natriuretic peptide was elevated to 264 pg/mL (normal: <20 pg/mL). An arterial blood gas under inhalation of 2 L/min oxygen showed chronic hypoventilation (pH: 7.34; $PaCO_2$: 66.0 Torr; PaO_2: 85.9 Torr; HCO_3^-: 34.5 mM). Spirometry revealed reduced vital capacity (53% of predicted) and forced expiratory volume in 1 s (56%). Chest X-ray and high-resolution computed tomography of the lung indicated cardiomegaly and mild pleural effusion without any pulmonary lesions. Electrocardiogram was normal, though coefficient of variation of R-R intervals was markedly low (0.37%). Ejection fraction was preserved (66.7%), but concentric hypertrophy, diastolic dysfunction and granular sparkling pattern in the ventricular walls were demonstrated by cardiac ultrasonography (left ventricular end-diastolic dimension: 36 mm; inter-ventricular septum thickness: 12 mm; E/A ratio: 0.78). Even after oral diuretics decreased the pleural effusion and edema, her dyspnea scarcely improved. Phrenic NCSs performed using Bolton's method[1] showed low negative-peak-amplitudes of CMAPs (left: 0.051 mV, right: 0.079 mV; normal: >0.3 mV) and prolonged latencies (left: 12.4 ms, right: 11.5 ms; normal: <8 ms) (Figure 1). The patient rejected tracheostomy and she was treated with non-invasive positive pressure ventilation (NIPPV). However, she could hardly adapt to NIPPV and finally died from respiratory failure. Her DNA could not be analyzed, but Congo-red staining of her right sural nerve necropsy specimen revealed amyloid deposits that were positively immunostained with an anti-TTR antibody (Figure 2), which was prepared against the peptide "SYSTTAVVTN" corresponding to the TTR#115-TTR#124.

Our patient presented with chronic progressive polyneuropathy, cardiomyopathy, and finally died of respiratory failure resistant to diuretics. Postmortem pathology revealed ATTR amyloidosis. Although no gene study was performed, she suffered from typical complications of sporadic familial amyloid polyneuropathy, a group of systemic disorders that includes symptoms of polyneuropathy and cardiomyopathy. Mutations in the transthyretin gene can be proven even in sporadic cases.

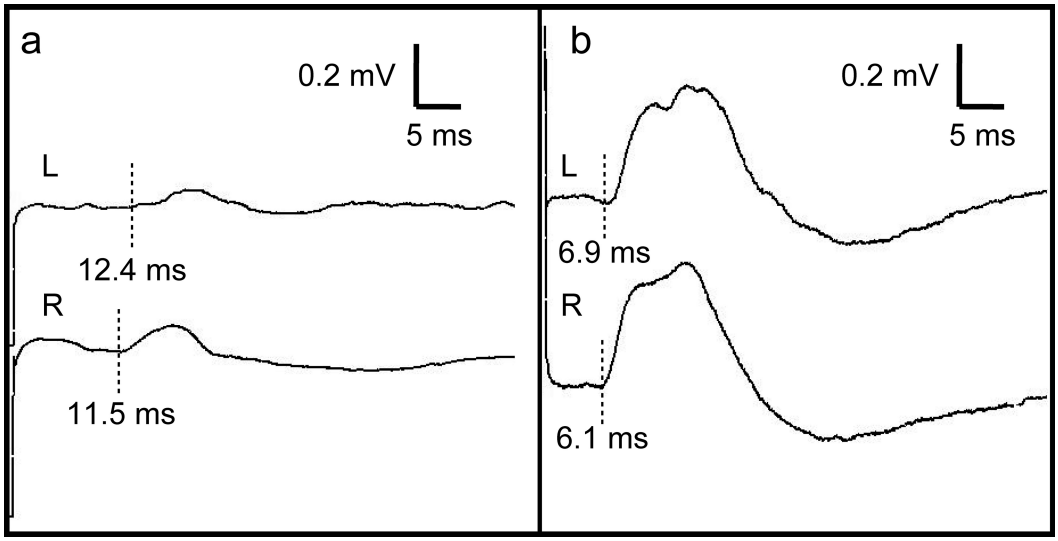

Figure 1: *Compound muscle action potentials recorded on the diaphragm of our patient (A) and an age-matched control (B) after phrenic nerve stimulation at the posterior border of the sternocleidomastoideus muscle at the level of the carotid cartilage. L: left; R: right.*

https://doi.org/10.1017/S0317167100017431 Published online by Cambridge University Press

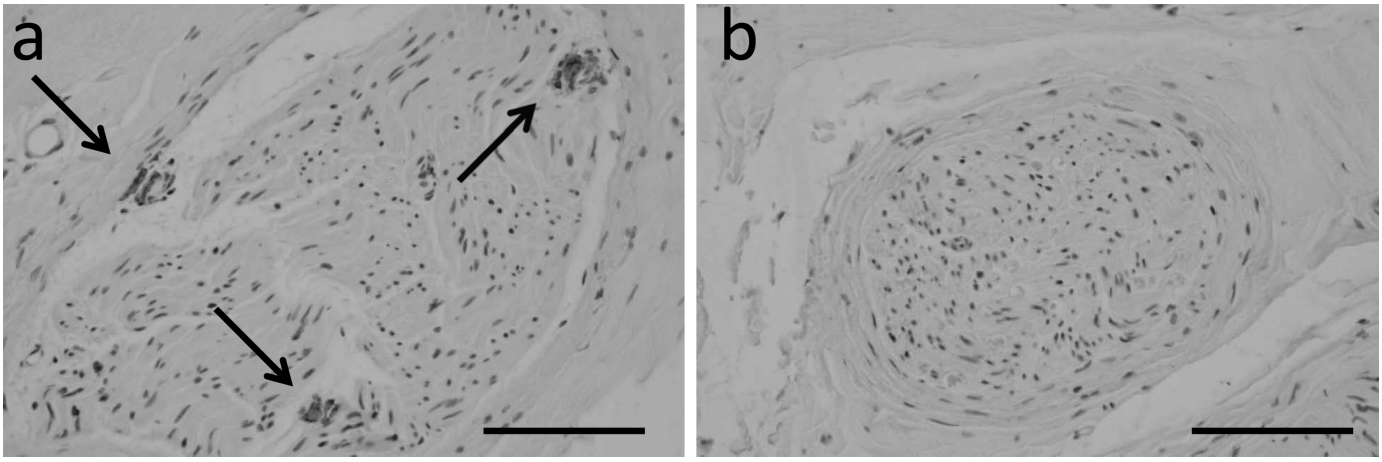

Figure 2: *(A) The right sural nerve necropsy specimen from our patient stained positively with an antibody against TTR(115-124) in the area around nerve bundles as indicated by arrows. (B) A sural nerve biopsy specimen stained with the same antibody showed no deposits in a patient with AL amyloidosis. Bar: 100 μm.*

Differentiating causes of respiratory failure in amyloidosis patients is often difficult because of concomitant heart failure. Some types of amyloidoses other than ATTR amyloidosis have been pathologically shown to cause hypoventilation by pulmonary mechanisms,[2] amyloid myopathies in the diaphragm,[3] or phrenic neuropathies.[4] However, ATTR amyloidosis has never been reported to involve phrenic nerves with the exception that low maximum inspiratory and expiratory pressures were shown by respiratory function tests in Swedish FAP patients,[5] indirectly suggesting the involvement of respiratory neuromusculature. Because no pathological studies of lungs or diaphragms were performed, we cannot exclude the coexistence of amyloid depositions in her respiratory system or diaphragm. However, the decreased CMAP amplitudes with prolonged latencies in the phrenic NCS cannot be explained by lung amyloidosis, diaphragm myopathy, or both. The latencies in the phrenic NCS may be prolonged even in axonopathies,[1] which were pathologically convinced in sural nerve necropsy of our patient.

In conclusion, this is the first case with ATTR amyloidosis showing phrenic nerve palsy, directly proven by NCS. In the advanced stage, ATTR amyloidosis can also involve phrenic nerves and cause fatal hypoventilation. As reported in cases with amyotrophic lateral sclerosis and critical illness polyneuropathy,[1] phrenic NCS should also be valuable for evaluating the function of the respiratory neuromusculature in cases with chronic progressive neuropathies such as amyloid neuropathies.

Teruhiko Sekiguchi, Hiroyuki Tomimitsu
Tokyo Medical and Dental University, Tokyo, Japan

Teruhiko Sekiguchi, Yoichiro Nishida,
Takashi Irioka, Akira Inaba
Yokosuka Kyosai Hospital, Yokosuka, Japan

Yoshinobu Hoshii,
Yamaguchi University Graduate School of Medicine,
Ube, Japan

References

1. Bolton CF. AAEM minimonograph #40: Clinical neurophysiology of the respiratory system. Muscle Nerve. 1993;16(8):809-18.
2. Utz JP, Swensen SJ, Gertz MA. Pulmonary amyloidosis. The Mayo Clinic experience from 1980 to 1993. Ann Intern Med. 1996;124(4):407-13.
3. Ashe J, Borel CO, Hart G, Humphrey RL, Derrick DA, Kuncl RW. Amyloid myopathy presenting with respiratory failure. J Neurol Neurosurg Psychiatry. 1992;55(2):162-5.
4. Berk JL, Wiesman JF, Skinner M, Sanchorawala V. Diaphragm paralysis in primary systemic amyloidosis. Amyloid. 2005;12(3):193-6.
5. Olofsson BO. Pulmonary function in familial amyloidosis with polyneuropathy. Acta Med Scand. 1981;209(5):379-84.

https://doi.org/10.1017/S0317167100017431 Published online by Cambridge University Press