LARYNGEAL AND PHRENIC NERVE INVOLVEMENT IN A PATIENT WITH HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES (HNPP)

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Introduction

Hereditary neuropathy with liability to pressure palsies (HNPP) is an autosomal dominant inherited disorder of peripheral nerve due to *PMP22* deletion, or more rarely, *PMP22* intragenic mutations, which presents with painless, recurrent, focal motor and/or sensory neuropathies usually preceded by compression or stretching of the affected nerve. Peroneal and ulnar are the most vulnerable nerves, followed by the brachial plexus, radial nerve and median nerve. Cranial nerves are rarely affected and involvement of lower cranial nerves and phrenic nerve in HNPP is anecdotal (1-3).

Case report

The patient suffered after the age of 30 from episodes of reversible left hand and left foot drop and transitory distal limb paraesthesias. His general medical history was uneventful apart from chronic obstructive pulmonary disease (COPD) since his forties and chronic tobacco smoking for 20 years. At the age of 44, following severe weight loss from 65 to 55 kg (15% of body weight), he developed progressively over one month dysphonia and hoarseness.

Neurological examination showed diffuse muscular atrophy, which was more prominent at lower limbs and shoulder girdle. He had a hoarse voice. There was mild weakness of left hand extensors and finger extensors, left foot dorsiflexors and left toe extensor. Tendon reflexes were present throughout except right biceps reflex and bilateral Achilles reflexes, reduced on the right and absent on the left. Light touch and pinprick sensations were reduced at dorsal foot bilaterally and at left hand. Vibration sense was reduced at ankle, bilaterally. His position sensation was normal. Cough and respiratory movements were normal as was the remainder of the neurological examination.

Nerve conduction studies revealed mild slowing in motor and sensory conduction velocities (MCV and SCV) of median and ulnar nerves with low-amplitude motor unit action potentials (MUAPs), as well as mild slowing of peroneal nerves MCV with low-amplitude MUAPs and mild slowing of sural nerve SCV with low-amplitude sensory action potentials. Partial motor conduction block and more prominent slowing along common sites of entrapment and compression were also recorded.

Laryngeal fibroscopy showed bilateral vocal cord palsy.

EMG of cricoarytenoid and thyroarytenoid muscles bilaterally showed the presence of polyphasic motor unit potentials of long duration and active denervation potentials..

Routine screening for acquired neuropathy was normal.

PMP22 gene testing by multiplex ligation-dependent probe amplification demonstrated the presence of the common deletion confirming the diagnosis of HNPP.

His speech disturbance recovered gradually. Two years later, dysphonia had subsided but the patient reported a rapid worsening of dyspnoea, mainly under exertion and in the supine position, occasional nocturnal awakenings with the perception of suffocation and a substantial diurnal sleepiness.

Diaphragm ultrasonography was performed and diaphragm movements were recorded in M-mode, according to the procedure previously described (4). A reduced right hemi-diaphragm excursion during quiet breathing (QB), deep breathing (DB) and voluntary sniffing (VS) was demonstrated (respectively 0.92 cm, 3.04 cm and 1.7 cm) [limit values in men: QB 1.8 ± 0.3 cm, DB 7 ± 1.1 cm, VS 2.9 ± 0.6 cm (0)] **(Fig. 1**).

Polysomnography recording confirmed the marked reduction in right phasic electric diaphragm activity and showed obstructive events associated with phasic and tonic oxygen desaturations.

Pulmonary function tests revealed a very severe, non-reversible obstructive deficiency with marked signs of hyperdistension and a very severe reduction in diffusing capacity for carbon monoxide.

ENG showed increased distal latency of right phrenic nerve (right 10.2 ms, left 7.9 ms [normal<8]) (**Fig. 2/A,B**) while EMG of cricoarytenoid and thyroarytenoid muscles had normalized.

The patient was started on nocturnal automatic continuous positive airway pressure ventilation, with optimal compliance and adequate correction of the events. Both inhaled long-acting β2-adrenergic and anticholinergic drugs were prescribed with better control of cough and dyspnoea. A four-week in-hospital rehabilitation exercise training program was also performed.

Six months later, at the last follow-up, respiratory function and blood gas analysis had significantly improved and both phrenic nerve conduction **(Fig.2/C)** and right diaphragm excursion had completely restored.

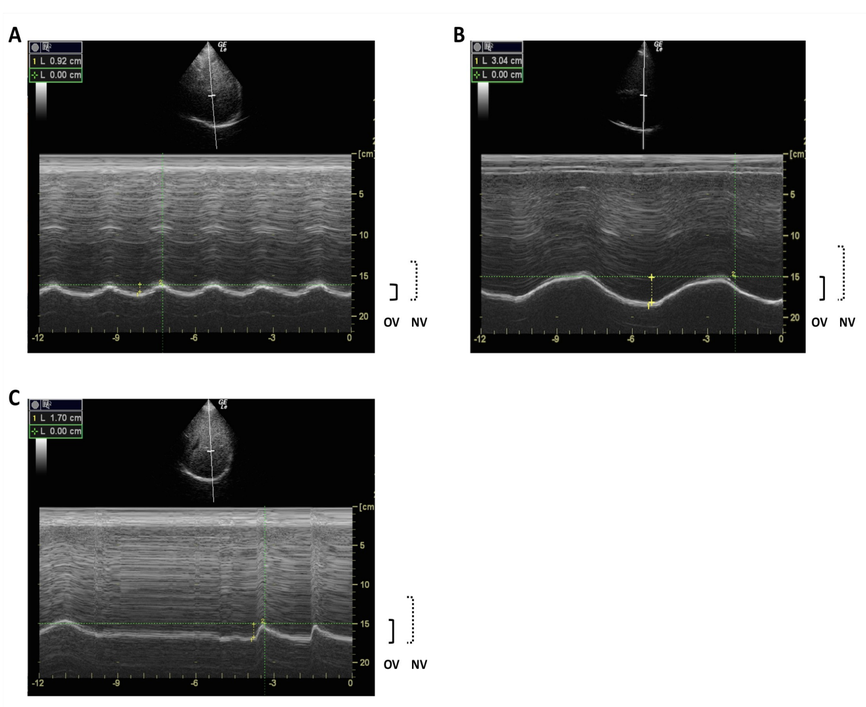

Figure 1. Diaphragm ultrasonography. Measurements of the right hemi-diaphragm excursions during quiet breathing (A), deep breathing (B) and voluntary sniffing (C) in the acute phase of right phrenic nerve paralysis. Continuous lines on the right represents observed values (OV), dotted lines represents normal values (NV).

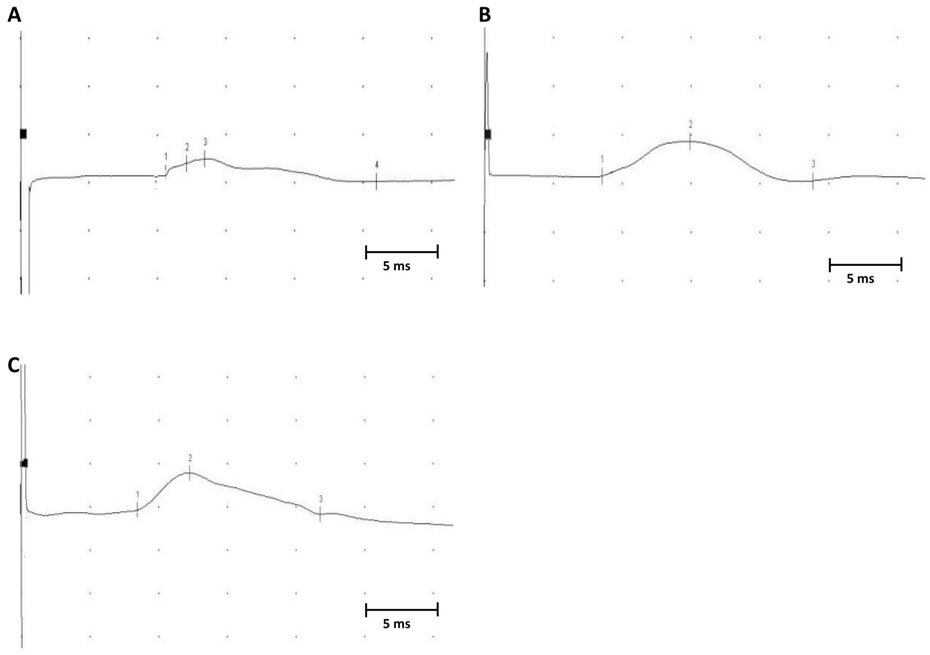

Figure 2. Electroneurography of right phrenic nerve during paralysis (A), non affected left phrenic nerve (B) and of right phrenic nerve after recovery (C)

Conclusions:

Low-cranial nerve involvement is exceptional in the context of HNPP. Self-limiting acute unilateral vocal cord paralysis causing aphonia and hoarseness was reported in one patient following sleeping in prone position (1). Respiratory insufficiency due to phrenic nerve involvement was observed in another patient with HNPP and proximal weakness (2). Patients developing both conditions have never been reported.

In our patient weight loss, by making nerves more vulnerable to minor traumatisms, seems the more likely triggering mechanism for bilateral vocal cord palsy, as already reported for limb nerves in HNPP (3). Regarding phrenic nerve involvement, we hypothesize that chronic cough in the context of CODP could have caused repetitive traumatism of the nerve. Moreover, nerve stretching associated with hyperinflation-induced diaphragmatic descent can be a further suggested mechanism for phrenic nerve lesion (5). In both cases, the reversibility of the process, plead for an involvement of such nerves in the context of HNPP.

Our report highlights the possibility of lower cranial nerves and of phrenic nerve involvement in HNPP and would encourage paying particular attention to optimal management of comorbitities such as CODP as well as thigh control of weight in patients with HNPP in order to avoid potentially harmful complications.

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