Familial amyloidotic polyneuropathy (Portuguese type variant I) and female pelvic floor dysfunction: a tribute to Magellan

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Received: 21 February 2011 / Accepted: 18 May 2011 / Published online: 28 May 2011
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Familial amyloidotic polyneuropathy, Portuguese type variant I (FAP-1) is an inherited autosomal dominant disorder caused by disturbance in protein metabolism that was first described by Corino de Andrade in 1939 [1]. The disease originated in Northern Portugal but is found all over the world as a result of the Portuguese navigating expeditions of the fifteenth century, pioneered by Magellan. Most patient clusters are now observed in Portugal, Sweden, and Japan [2]. In Portugal, according to population data from 2008, 3,525 patients with FAP-1 were enrolled in the Portuguese Amyloidosis Centre of Studies. In Sweden, there are 7,500 carriers of the genetic mutation, whereas in Japan, over 350 patients with FAP-1 have been identified. Majorca, Spain, is the area with the highest prevalence in the Mediterranean region and the fourth in the world after Portugal, Sweden, and Japan with 44 patients described. There are also isolated case reports from France, Netherlands,

Greece, Italy, USA, and Australia. The exact prevalence of FAP-1 in Brazil which is considered the hub of historical Portuguese colonies, however, remains unknown (Fig. 1). The principal pathology is a mutation on chromosome number 18 of the transthyretin protein where the amino acid methionine replaced valine at position 30 (ATTR V30M) leading to the production of an abnormal amyloid protein by the liver [3]. Systemic deposition of this amyloid in various tissues particularly the axons of peripheral neurons leads to progressive peripheral neuropathy of the sensory, motor, and autonomic nerves.

Neurogenic digestive disturbances (44.2%) and neurological symptoms of the lower extremities (43.7%) are the most common primary clinical manifestations of FAP-1 [2, 3]. The early clinical features of FAP-1 are summarized in Table 1. FAP type 1 manifests itself during adulthood. The Portuguese variant of the disease has an early age of onset, an average of 33.5 ± 9 years. Late age of onset (above 50 years of age) tends to occur in non-Portuguese disease clusters. When patients show these suspicious clinical features, FAP-1 is diagnosed by confirming the presence of amyloid deposits in tissue biopsies obtained from the subcutaneous tissues of the abdominal wall, skin, gastric or rectal mucosa, peri-tendinous fat, or sural nerve and further gene sequencing studies to identify the mutation ATTR V30M [2]. The only curative treatment option available for patients with FAP-1 is liver transplantation in order to eliminate abnormal hepatic synthesis of the ATTR V30M amyloid protein [3]. A brief urogynecologic review of FAP-1 is important because of the potential for causing pelvic floor dysfunction associated with variable non-urogynecologic clinical presentations in mutation women carriers, the multi-disciplinary approach needed for management of this unusual condition and the wide geographical distribution of the disease. Our data are supported by

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Fig. 1 World distribution of FAP-1. The *polygon* corresponds to the number of patients in each location (adapted from Ando et al. [10])

clinical observations over the period of 15 years and our cohort included more than 500 FAP-1 patients. Over the last 5 years, a systematic investigation of 150 more FAP-1 carriers was also performed. More than 60% of this patient population is women.

Table 1 Symptoms of FAP-1

Neuropathic	Superficial sensory disturbances
	Muscle atrophy
	Sporadic pain in the lower limbs
	Changes of the pupil
	Skin changes
	Hypoesthesia in the trunk
	Cold extremities
	Hoarseness of voice
	Urological disorders
	Diarrhea/constipation
Autonomic	Orthostatic hypotension
	Sexual dysfunction/anejaculation
	Dyshidrosis
	Nausea
	Anemia
General	Weight loss
	Cardiac arrhythmias
	Skin edema
	Burns

The effects of FAP-1 on the genito-urinary system in both sexes are common and may be early and progressive—like previously described [4]. The natural history is typically a progressive deterioration in the function of the urinary bladder and urethra similar to other peripheral neuropathy disorders such as that associated with diabetes mellitus. The degree of FAP gene mutation and penetrance determines the type of lower urinary tract symptoms in carriers with storage problems occurring at a higher rate (56.5%) than voiding dysfunctions (52.2%). The first abnormality is thus diminished bladder sensation followed by reduced detrusor contractility (myogenic, vasculogenic, or neurogenic patterns) leading to incomplete voiding, urinary retention, and subsequent back-pressure complications on the upper urinary tract and chronic renal failure [4]. One study in progress has shown that the incidence of reduced bladder sensation and reduced detrusor contractility among female carriers of FAP-1 was 33% and 25%, respectively, with the former abnormality appearing earlier (unpublished observation). In women, the changes in urinary bladder storage and voiding functions are associated with symptoms of recurrent urinary tract infections and both overflow and urge urinary incontinence.

The pathogenesis of cystopathy induced by FAP-1 is not clearly understood but could result from the combination of intrinsic and neurological injuries to the urinary bladder [5]. Initially, the selective loss of small myelinated fibers and axonal degeneration responsible for autonomic regulation and conduction of peripheral thermal sensitivity from the

bladder leads to diminished sensitivity. Recent evidence has shown that the bladder urothelium, previously considered to be a passive lining of the urinary bladder, has important sensory functions. In fact, this layer responds to distension stimuli, expresses sensory receptors, and releases neurotransmitters that influence the nervous and cellular activity of the urinary bladder. Amyloid deposition at the sub-urothelial level of the urinary bladder in patients with FAP-1 creates a mechanical barrier that further interferes with the transmission of neuro-hormonal signals across the urothelium to the interstitial cells of Cajal found in the lamina propria and the detrusor myofibers. The development of detrusor hypo-contraction represents the final stage of FAP-1 and indicates the spread of the disease to the cholinergic motor efferent neurons of the urinary bladder.

Treatment of women with lower urinary tract symptoms associated with FAP-1 depends on the specific stage of the disease. Patients with storage dysfunction will benefit from regular and timed voiding in the earlier stages. In some cases, the supra-pubic vibration device may improve bladder emptying provided that there is a positive response to the therapeutic probe [6]. In more advanced cases with detrusor underactivity complicated by a high post-void residual urine volume, vesico-ureteral reflux, and recurrent urinary tract infections, more aggressive therapeutic measures should be used such as a clean intermittent self-catheterization or supra-pubic cystostomy. Urological screening of close female family members of women with FAP-1 is also recommended to detect asymptomatic lower urinary tract complications [7].

The association between female sexual dysfunction (FSD) and lower urinary tract symptoms particularly urinary incontinence in women with FAP-1 leads to further deterioration in their quality of life. Similar to diabetic peripheral neuropathy, a significant proportion of women with FAP-1 have FSD (21.7%) as a result of sensory and motor disturbances in the function of the pelvic nerves (unpublished observation). Histological studies have shown amyloid deposition in the afferent myelin fibers that conduct sensitivity to touch, light pressure, and vibration from the genital tract through the dorsal horns of the spinal cord to the central nervous system in women with FAP-1 [8]. Diminished blood flow to the genital organs as a result of amyloid vasculopathy may also be responsible. It is also likely that changes in sex hormone levels particularly diminished ovarian testosterone production as a result of pelvic ischemia may be related to the etiology of FSD in women with FAP-1.

During the later course of FAP-1, the neuro-degeneration process spreads to the somatic nervous system with the involvement of the pudendal nerve. This lesion combined with the indirect vascular and myogenic effects of FAP-1 leads to neuromuscular transmission abnormalities in the pelvic floor striated muscles. A high incidence of pelvic floor muscle dysfunction has thus been reported in women with FAP-1

(73.9%) characterized by a reduction in the tone and strength of pelvic floor muscles (unpublished observation). This is clinically manifested as pelvic organ prolapse and/or stress urinary incontinence at a younger age and/or in nulliparous women [7]. Biofeedback training can promote the myo-aponeurotic functions of the pelvic floor muscle in these women, namely by improving coordination, tone, and recruitment of new functional motor units [9]. This may delay the development of pelvic organ prolapse and stress urinary incontinence in women with FAP-1 and help to improve their overall sexual function, particularly the orgasmic stage. The surgical treatment of stress urinary incontinence and pelvic organ prolapse in women with FAP-1 is similar to that in other women. However, the surgical approach to stress urinary incontinence should be meticulously planned with particular attention given to identify detrusor hypo-contraction because postoperative urinary retention is more frequent in women with FAP-1 than in the average female patient population with stress urinary incontinence. Likewise, when deciding the surgical strategy for the treatment of pelvic organ prolapse in women with FAP-1, it is important to exclude occult stress urinary incontinence. We also recommend peri-operative systematic antibiotic prophylaxis with anti-incontinence and reconstructive pelvic surgery in women with FAP-1 who tend to be more prone to postoperative urinary tract infections because of poor general condition and neurogenic bladder dysfunction.

In conclusion, Portugal is the source of an autosomal mutation—ATTR V30M—that was transmitted to remote countries during the maritime Portuguese discoveries at the beginning of the modern age. The genetic disorder is called familial amyloidotic polyneuropathy, Portuguese type variant I, which is characterized by generalized and progressive peripheral neuropathy with multi-system involvement. The disease is associated with severe lower urinary tract, pelvic floor, and sexual dysfunctions in female carriers when the pelvic nerves are affected. Increased urogynecologic awareness of this condition allows early detection and appropriate management of urogenital manifestations before the occurrence of irreversible structural damage to the kidneys. Therefore, a close liaison between the urogynecologist, neurologist, and clinical geneticist is needed for providing holistic care to women with FAP-1.

References

1. Andrade C (1951) A peculiar form of peripheral neuropathy. *Acta Psych et Neurol Scand* 53:251–257
2. Saraiva MJ, Birken S, Costa PP, Godman DS (1983) Amyloid fibril protein in familial amyloidotic polyneuropathy, Portuguese type. Definition of molecular abnormality in transthyretin (pre-albumin). *J Clin Invest* 74:104–190

3. Monteiro E, Freire A, Barroso E (2004) Familial amyloid polyneuropathy and liver transplant. *J Hepatology* 41:188–194
4. Andrade MJ (2009) Lower urinary tract dysfunction in familial amyloidotic polyneuropathy, Portuguese type. *Neurourol Urodynam* 28:26–32
5. Wada Y, Ando Y, Kai N et al (2006) Lower urinary tract dysfunction in type 1 familial amyloidotic polyneuropathy in Kumamoto, Japan. *Int Urogynecol J* 13:1475–1478
6. Dasgupta P, Haslam C, Godwin R, Fowler CJ (1997) ‘Queen Square bladder stimulator’: a device for assisting emptying of neurogenic bladder. *Br J Urol* 80:234–237
7. Gomes MJ (2006) Kidneys and lower urinary tract diseases. In: Instituto da Segurança Social (eds) *Pericial Evaluation Criteria on Social Security*, in Portugal. Portugal, pp N1–N1.15
8. Romanzi LJ, Groutz A, Feroz F, Blaivas JG (2001) Evaluation of female external genitalia sensitivity to pressure touch: a preliminary prospective study using Semmes-Weinstein monofilaments. *Urology* 57:1145–1150
9. Tibaek S, Gard G, Jensen R (2005) Pelvic floor muscle training is effective in women with urinary incontinence after stroke: a randomized, controlled and blinded study. *Neurourol Urodynam* 24:348–357
10. Ando Y, Nakamura M, Araki S (2005) Transthyretin-related familial amyloidotic polyneuropathy. *Arch Neurol* 62:1057–1062