Clinical Autonomic Research (2019) 29:245–251
https://doi.org/10.1007/s10286-018-0514-2

REVIEW

Autonomic involvement in hereditary transthyretin amyloidosis (hATTR amyloidosis)

Alejandra Gonzalez-Duarte[1]

Received: 31 October 2017 / Accepted: 21 February 2018 / Published online: 6 March 2018

Abstract

Purpose Hereditary transthyretin amyloidosis (hATTR amyloidosis) is a progressive disease primarily characterized by adult-onset sensory, motor, and autonomic neuropathy. In this article, we discuss the pathophysiology and principal findings of autonomic neuropathy in hATTR amyloidosis, the most common methods of assessment and progression, and its relation as a predictive risk factor or a measure of progression in the natural history of the disease.

Methods A literature search was performed using the terms "autonomic neuropathy," "dysautonomia," and "autonomic symptoms" in patients with hereditary transthyretin amyloidosis and familial amyloid polyneuropathy.

Results Various scales to measure autonomic function have been employed, particularly within the major clinical trials, to assess novel therapies for the disease. Most of the evaluations were taken from diabetic clinical trials. Questionnaires include the COMPASS-31 and Norfolk QOL autonomic nerve function domain, whereas clinical evaluations comprise HRDB and the orthostatic tolerance test. Several treatment options are being employed although only diflunisal and tafamidis have reported improvement in the autonomic abnormalities.

Conclusions Autonomic nerves are often affected before motor nerve impairment, and dysautonomia may support the diagnosis of hATTR amyloidosis when differentiating from other adult-onset progressive neuropathies and from other types of amyloidosis. Most of the progression of autonomic dysfunction is seen in early stages of the disease, commonly before motor impairment or affection of the overall quality of life. Unfortunately, there is no current single standardized approach to evaluate dysautonomia in hATTR amyloidosis.

Keywords TTR amyloidosis · Hereditary amyloidosis · Autonomic dysfunction in amyloidosis

Abreviations

AL	Light chain amyloidosis
COMPASS-31	Composite Autonomic Symptom Score-31 items
FAP	Familial amyloid polyneuropathy
hATTR	Hereditary transthyretin amyloidosis
HP5	Heat as pain sensation
HRdb	Heart rate deep breathing
IENFD	Intraepidermal nerve fiber densities
mNIS	Modified neuropathy impairment score
PMNFD	Pilomotor nerve fiber
PND	Polyneuropathy disability score
QOL-DN	Quality of life-diabetic neuropathy
NCV	Nerve conduction velocities
NIS	Neuropathy impairment score
SGNFD	Sweat gland densities
SSA	Serum protein A
TTR	Transthyretin

Introduction

Hereditary transthyretin amyloidosis (hATTR amyloidosis) is a progressive disease primarily characterized by adult-onset sensory, motor, and autonomic neuropathy associated with cardiac, gastrointestinal, ocular, and renal symptoms. The diagnosis of hATTR amyloidosis is often delayed with a median time of 2.8–4.3 years after the first symptom [1, 2]. The disease is fatal within 2–15 years from onset [1]. There are more than 50,000 patients worldwide [2, 3]. hATTR amyloidosis is caused by mutations in the TTR gene (chromosome 18q11.2–12.1) that destabilize variant TTR

✉ Alejandra Gonzalez-Duarte
gonzalezduarte@aol.com

[1] Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, México

proteins, thereby facilitating its misfolding and deposition as amyloid fibers in body tissues [1–3].

One major finding that differentiates hATTR amyloidosis neuropathy from other adult-onset progressive neuropathies is that autonomic neuropathy typically accompanies sensory deficits early in the course of the disease [4–6]. Autonomic neuropathy is also present more often in hATTR amyloidosis than in other types of amyloidosis, such as AL amyloidosis, which is the result of the accumulation of fibrils from the immunoglobulin light chains (AL), or AA amyloidosis, which results from the accumulation of the serum protein A (SAA) in patients with chronic inflammatory states [7]. Autonomic neuropathy is reported in around 10% [6] to 14% [8] of patients with AL amyloidosis, whereas peripheral and autonomic neuropathy is exceedingly rare in AA amyloidosis [5, 7]. Moreover, while the clinical decline in AL amyloidosis is usually determined by the extent of cardiac or renal involvement, autonomic disturbances typically affect the severity of the disease and survival in hATTR amyloidosis [5–10].

Very novel anti-amyloid drugs are emerging: tafamidis, a TTR stabilizer, showed its ability to slow stage I progression in a phase III controlled study [11]; diflunisal, a NSAID, has been included in clinical trials as a TTR kinetic stabilizer [12]; patisiran, a small interfering RNA agent, and inotersen, an antisense oligonucleotide, have recently revealed their effectiveness in delaying disease progression [12, 13]. Other strategies such as the combination of doxycycline-tauroursodeoxycholic acid or monoclonal antibody antiserum amyloid P component are being developed [3].

As with other types of amyloidosis, it is preferable to identify the disease by the chemical identity of the amyloid fibril-forming protein [14]; thus, hATTR amyloidosis is preferred instead of familial amyloid polyneuropathy (FAP) and will encompass its various systemic symptoms in addition to neuropathy. However, the progression of the disease is commonly defined by the evolution of the peripheral neuropathy from sensory symptoms to overt motor dysfunction, disregarding other systemic abnormalities, including autonomic alterations. Two-stage classifications are used: the Coutinho FAP Disease Stage, introduced in 1980 in Portugal, and the PND Score, introduced in Sweden in 1994 [3].

Since autonomic disturbances affect patient survival, an understanding and recognition of these disturbances are important. Given the advent of clinical trials for novel therapies aimed at modifying the course of the disease, evaluating autonomic disturbances has become crucial. Therefore, various scales to measure the autonomic function have been employed. In this article, we discuss the most common methods of assessment and progression of the autonomic features in patients diagnosed with hATTR amyloidosis and its relation as a predictive risk factor or a measure of progression in the natural history of the disease.

Pathophysiology

The peripheral autonomic nerves are often affected before motor nerve impairment has been noted [5]. This can be attributed to the morphologic characteristics of the nerves as unmyelinated, small myelinated and large fibers, becoming impaired in that order [6]. More amyloid deposits have been found in the spinal ganglion and posterior root of the spine than in the anterior root of the motor nerves, and peripheral catecholamine depletion has also been described [5].

Autonomic nervous system involvement consists of orthostatic hypotension, sexual impotence, disturbances of gastrointestinal motility (most commonly diarrhea alternating with constipation, but also constipation, diarrhea, nausea, or vomiting), dyshidrosis, erectile dysfunction, and neurogenic bladder [5–7, 15].

The most dangerous autonomic manifestation is cardiovascular autonomic neuropathy, as it may induce life-threatening arrhythmias and sudden death. It is due to the impairment of autonomic control of the cardiovascular system. Warning signs include reduced heart rate variability (HRV) and decreased baroreflex sensibility with abnormal blood pressure regulation and orthostatic hypotension [16]. Sudden death has been reported in patients with complex ventricular arrhythmias and with orthostatic hypotension without cardiac conduction abnormalities, attributed to low sympathetic and parasympathetic responses [17]. Cardiovascular impairment of the autonomic function has been found to be unrelated to the severity of the peripheral polyneuropathy, particularly the presence of vagal hyperactivity or parasympathetic receptor hypersensitivity and sympathetic denervation of the heart [16–18].

Gastrointestinal symptoms are the result of a loss in the inhibitory and increase in the excitatory enteric neurons, which may result in gastroparesis, dysmotility, constipation, or diarrhea [15]. Amyloid deposition occurs in the muscularis mucosae, in proximity to the vasculature, nerves, and nerve plexuses. This deposition increases the frailty of blood vessels, hinders intrinsic peristalsis, and decreases the compliance of the gut wall [19]. Amyloid infiltration and destruction of the celiac ganglion, vagus nerve, and sympathetic chain ganglia and nerves have been found in the small intestine and esophagus of patients with hATTR amyloidosis [5].

Earlier damage of the sacral parasympathetic fibers contributes to genitourinary dysfunction, starting from impaired bladder sensation with an increase in urine retention to dysuria, nicturia, incomplete bladder emptying, and urgency up to overflow incontinence due to the progressive involvement of motor sympathetic and somatic nerves. Urinary retention and urinary tract infections contribute

to severe morbidity to the point that urosepsis may be the cause of death in some patients [20]. Erectile dysfunction is one of the earliest findings in the course of the disease in males, and most patients develop bladder dysfunction during the course of the disease.

Pupillomotor and sudomotor functions are also impaired. The sympathetic predominance in pupil control decreases its diameter at rest. Scalloped pupils, defined as bilateral, irregular pupillary margins and fringed edges, are a unique sign of patients with hATTR [21] (Fig. 1a, b).

Patients have inappropriately cold hands and feet with discoloration, suggesting that the vasoregulation of the peripheral vessels is impaired. Several Doppler ultrasound studies have supported blood flow alterations [5, 22, 23]. These vasomotor changes, in addition to pain insensitivity, result in chronic ulceration and mutilation of the acral extremities that habitually complicate the disease (Fig. 1c–e).

Assessments of autonomic function in hATTR

Several methods of assessment of the autonomic function have been used for describing the natural history and outcomes of hATTR. The most common ones are described below.

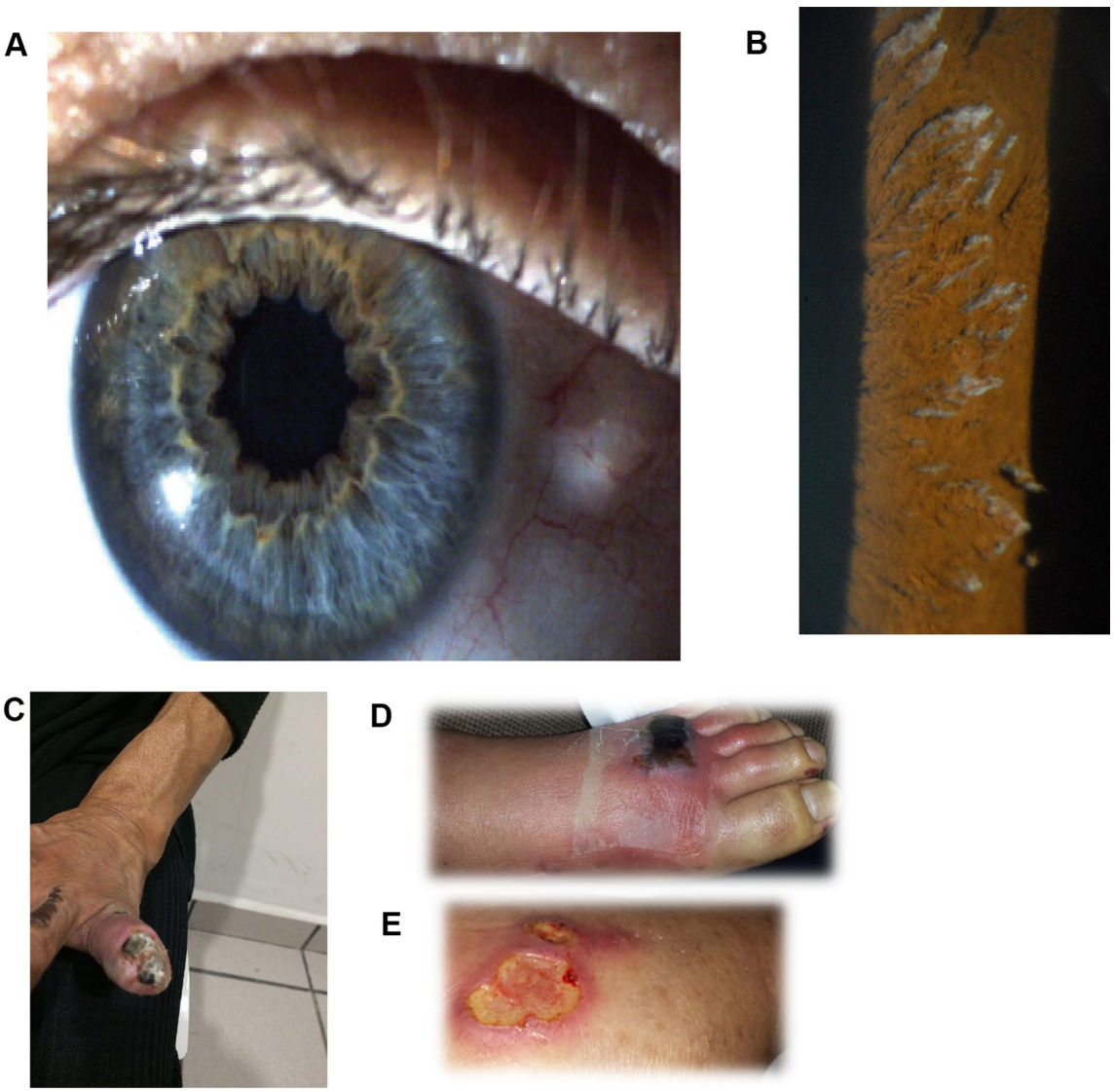

Fig. 1 **a** Scalloped pupil in a patient with hATTR amylodiosis. **b** Amyloid deposits in trabeculae of the iris. **c** Trophic changes due to insensibity to pain and temperature; **d**, **e** ulcerations due vascular and neuropathic abnormalities

Autonomic cardiopathy assessments

Abnormally low heart rate variability (HRV) is a good marker of autonomic dysfunction as significantly less heart rate variation has been shown in patients than controls and is proportional to the severity of the neurologic disability [17] (Fig. 2a, b). HRV can be assessed at rest in a quiet environment for 10 min in a resting position, or with deep breathing (HRDB), following a respiratory cycling pattern of eight respirations with 5 s for inspiration and 5 s for expiration. HRV and HDDB may be precluded in patients with pacemakers. Orthostatic hypotension (OH) is a very early manifestation of dysautonomia, but patients with hATTR amyloidosis may not be aware of its presence because it develops slowly, allowing for some habituation. Also, OH masks some of the signs of congestive cardiac failure. OH can be assessed by asking the patient to lie down for 5 min and then to stand up while recoding the brachial systolic and diastolic blood pressure and heart rate, or with a tilt test assessing beat-to-beat blood pressure (Fig. 2c). MIBG uptake is a sensitive method for the detection of sympathetic denervation of the heart, and no uptake has been observed in hATTR amyloidosis patients [16].

Modified Neuropathy Impairment Score Plus 7 (mNIS+7)

The mNIS+7 is an adaptation of the Neuropathic Impairment Score (NIS) and NIS-LL (lower limb) designed to evaluate peripheral diabetic neuropathy [24, 25]. NIS+7 is a composite score of polyneuropathy signs and neurophysiologic tests [26, 27]. In addition to the neuropathy impairment examination, which evaluates motor function, reflex abnormalities, and sensory loss, mNIS+7 compounds smaller fiber function, nerve conduction velocities (NCV), and autonomic testing (HRDB or OH measurements) [26, 27]. While NIS+7 evaluates the vibration detection threshold of the toe, mNIS+7 uses a complicated standardized QST approach to estimate the touch-pressure (TP) and heat as pain (HP5) sensation loss over the surface of the body. Exponentially increasing monofilaments are used to measure TP and thermoelectric heat pulses to measure HP5. Testing

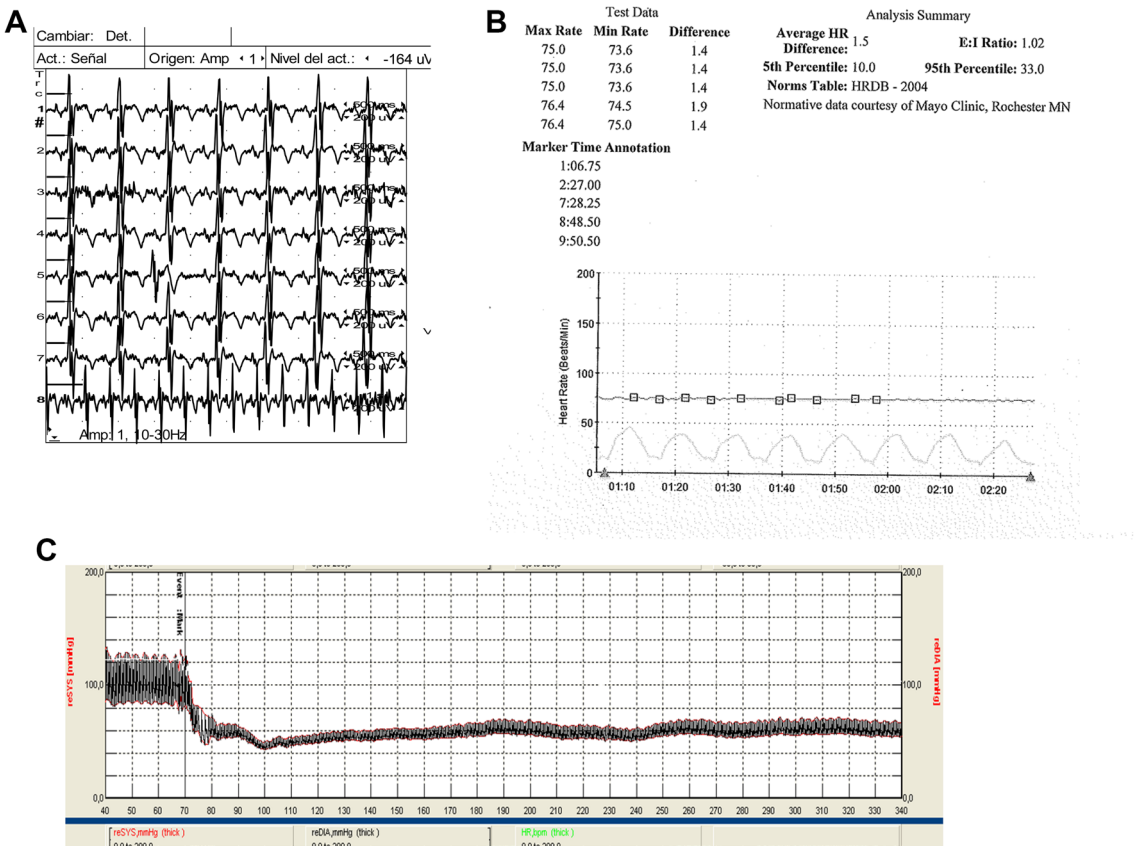

Fig. 2 **a** Impaired heart variability at rest (HRV). HRV is the physiological phenomenon of variation in the time interval between heartbeats. **b** Heart rate responses to deep breathing. In normal conditions, HR (upper line) increases following inspiration and decreases following expiration (respiration is indicated by the lower line). **c** Decreased blood pressure (BP) after head-up tilt. BP is continuously monitored by plesthysmograpy. Baseline measurement was obtained after 5 min of recumbence, and then the table was tilted up rapidly at 70° eliciting an acute drop in BP for as long as the tilt was maintained

is computed through algorithms, and thresholds are found according to reference values. The scoring is based on percentile reference value at each time [26]. Scoring of the postural hypotension is based on grading of function: normal (< 95th percentile) = 0 points; mildly reduced (≥ 95th to < 99th percentile) = 1 point; very reduced (≥ 99th percentile) = 2 points. Scoring of HRdb is expressed as normal deviates (0–3.72) based on healthy-subject parameters. An increase indicates worsening impairment. The notable differences between mNIS+7 scores is that one trial used postural blood pressure instead of HRdb with the rationale that HRdb has limitations for patients with pacemakers or cardiac arrhythmias [26–28]. All evaluations throughout the tests are ranked with a grade that goes from 0 (normal) to 3.7 points (very abnormal). At the end, all the evaluations are added to provide a total score of 0–244 in the NIS+7, 0–304 in the mNIS+7 with postural hypotension, and 0–346 points in the mNIS+7 with HRdb. The mNIS+7 score system was used for the patisiran, inotersen, and tafamidis trials and showed excellent correlation with the FAP stage and PND score [27].

Norfolk QOL-DN

The Norfolk is a 35-item patient reported questionnaire with five question domains grouped according to small-fiber, large-fiber, and autonomic nerve function and symptoms and activities of daily living. It captures patient-reported perceptions of neuropathy in individuals with symptoms of both peripheral and autonomic neuropathy. Its maximum impairment is 138 points. Autonomic function is captured according to the patient's prompt response and classified from always to never on a 5-point scale [30].

A recent publication assessed the relationship between the NIS-LL and Norfolk QOL-DN in 61 patients with hATTR amyloidosis stages 1–3 and 16 healthy controls [31]. The small-fiber and autonomic neuropathy domains differed between stages 1 and 2, but not stages 2 and 3, showing that the initial stages were significant for autonomic functioning scores before impairment of the activities of daily living. In contrast, stage two showed an increase in all domains except the small-fiber and autonomic domains, which had reached a maximum, underscoring the initial progression of these symptoms. The Norfolk QOL was used for the trials of inotersen, patisiran, and tafamidis, but the analysis of the separate components, including the automatic domain, is pending.

COMPASS-31

The Composite Autonomic Symptom Score (COMPASS-31) is a recently developed questionnaire for assessing symptoms of dysautonomia [32]. It was originally designed as an 85-item instrument and further refined to an easily scored 31-item questionnaire. It has 6 different autonomic domains: 3 questions for orthostatic intolerance, 3 for vasomotor symptoms, 4 for secretomotor function, 12 for the gastrointestinal domain, 3 for bladder functioning, and 5 for pupillomotor function. Each question has a weighting factor that results in a maximum impairment score for each domain. The total maximum impairment is 100 points. COMPASS-31 was used for the patisiran trial [18]. Results are expected in November 2017.

Sweat gland nerve fiber density

Amyloid in skin biopsies can be detected early in the course of the disease, and it may serve as a biomarker for the disease severity and progression as it has been found in the epidermis, sweat glands, and arrector pili [33]. A few studies have been performed to assess sweat gland and pilomotor nerve fiber densities and their correlation with autonomic function [33].

Ebenezer et al. studied 3-mm skin biopsies of symptomatic and asymptomatic patients with ATTR mutations and compared them against biopsies of patients with diabetic neuropathy and with healthy controls [33]. Amyloid deposits were observed in myoepithelial cells of the basement membrane of sweat gland complexes or ducts in the biopsies of hATTR patients. Also, intraepidermal (IENFD), sweat gland (SGNFD), and pilomotor nerve fiber densities (PMNFD) were reduced in these patients. Denervation correlated inversely with the cutaneous amyloid deposits and with the punctuation in the Neuropathy Impairment Score (NIS-LL), consistent with a deleterious effect on cutaneous nerve fibers secondary to the amyloid deposition. However, denervation did not correlate with HRDB, a test used to measure parasympathetic activity.

Chao et al. [34] also studied autonomic innervation of skin biopsies of 28 patients with TTR mutations and their correlation to autonomic function. SGNFD was significantly lower in patients with orthostatic hypotension compared to those without it. SGNFD was also lower in patients with absent sympathetic skin response (SSR) at the palm than in those with present SSR and inversely correlated with the disability score at the time of the biopsy. Because orthostatic hypotension and SSR are measurements of the sympathetic function, the possibility exists that skin denervation has a greater impact on sympathetic than parasympathetic function.

Increases in sweat gland nerve fiber innervation in the distal thigh and leg after 24 months were observed in the phase 2 open-label extension study of patisiran [28, 29]. Therefore, sensory and autonomic innervations in the skin-punch biopsies of participants in the double-blind clinical trial with patisiran

(APOLLO) are being evaluated to determine whether patisiran can increase nerve fiber density.

Improvement of autonomic function after treatment

Reports of improvement of separate components of the autonomic function have been published. In one study using diflunisal as a TTR stabilizer in five patients for 3–5 years, autonomic symptoms improved (orthostatic hypotension and gastrointestinal symptoms) after treatment in two of four patients. Also, a delayed heart-to-mediastinum ratio on 123 I-MIBG imaging, a marker of cardiac postganglionic sympathetic nerve function, increased during a 3-year treatment, while the Kumamoto FAP scores for motor and sensory symptoms gradually deteriorated [35]. Two patients were reported with improvement of autonomic symptoms, including postural hypotension, nausea, and diarrhea after undergoing parenteral nutrition [36].

In a longitudinal multicenter study of 61 patients in a non-endemic area after 3 years of using tafamidis in Italy, autonomic function remained stable in 33%, worsened in 56%, and improved in 10% of patients with tafamidis [37]. Improvement was seen in urinary retention, orthostatic hypotension, and eye and mouth dryness. Two of the 15 patients without autonomic dysfunction at baseline developed dysautonomia (orthostatic hypotension in four cases and diarrhea in two cases) with dry mouth and urinary incontinence.

Conclusions

Patients with hATTR amyloidosis exhibit a wide variety of autonomic dysfunction. Autonomic nerves are often affected before motor nerve impairment, and dysautonomia may support the diagnosis of hATTR when differentiating from other adult-onset progressive neuropathies and in other types of amyloidosis. Most of the progression of autonomic dysfunction is seen in early stages of the disease, commonly before motor impairment or affection in the overall quality of life. Unfortunately, there is not one standardized current approach to evaluate dysautonomia in hATTR amyloidosis. Therefore, many different methods of assessment have arisen to document the natural history and arrest of autonomic signs and symptoms in the ongoing clinical trials. Understanding its significance may aid in the evaluation treatment options available and could support the onset of the disease in carriers of TTR mutations.

References

1. Adams D, Coelho T, Obici L (2015) Rapid progression of familial amyloidotic polyneuropathy: a multinational natural history study. Neurology 85:675–682 **(9. (Progression FAP Scales))**
2. Ando Y, Coelho T, Berk J et al (2013) Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis 8:31
3. Hawkins PN, Ando Y, Disperzeri A et al (2015) Evolving landscape in the management of transthyretin amyloidosis. Ann Med 47:625–638 **(3)**
4. Hund E (2012) Familial amyloidotic polyneuropathy: current and emerging treatment options for transthyretin-mediated. Appl Clin Genet 5:37–41
5. Ando Y, Suhr O (1998) Autonomic dysfunction in familial amyloidotic polyneuropathy. Amyloid Int J Exp Clin Invest 5:288–300
6. Loavenbruck AJ, Singer W, Mauermann ML et al (2016) Transthyretin amyloid neuropathy has earlier neural involvement but better prognosis than primary amyloid counterpart: an answer to the paradox? Ann Neurol 80(3):401–411
7. Hazenberg BP (2013) Amyloidosis: a clinical overview. Rheum Dis Clin N Am 39(2):323–345
8. Picken M, Herrera G, Dogan A (2015) Amyloid and related disorders. 2nd edn. Humana Press, Switzerland, pp 11–29
9. Dingli D, Tan TS, Kumar SK et al (2010) Stem cell transplantation in patients with autonomic neuropathy due to primary (AL) amyloidosis. Neurology 74(11):913–918
10. Gertz MA, Kyle RA, Thibodeau SN (1992) Familial amyloidosis: a study of 52 North American-born patients examined during a 30-year period. Mayo Clin Proc 67(5):428–440
11. Waddington-Cruz M (2015) Benson MD a review of tafamidis for the treatment of transthyretin-related amyloidosis. Neurol Ther 4(2):61–79
12. Sekijima Y, Tojo K, Morita H et al (2015) Safety and efficacy of long-term diflunisal administration in hereditary transthyretin (ATTR) amyloidosis. Amyloid 22(2):79–83
13. Adams D, Cauquil C, Labeyrie C et al (2016) TTR kinetic stabilizers and TTR gene silencing: a new era in therapy for familial amyloidotic polyneuropathy. Expert Opin Pharmacother 16(6):791–802
14. Sipe JD, Benson MD, Buxbaum JN et al (2014) Nomenclature 2014: amyloid fibril proteins and clinical classification of amyloidosis. Amyloid 21(4):221–224
15. Verotti A, Prezioso G, Scattoni R et al (2014) Autonomic neuropathy in diabetes mellitus. Front Endocrinol (lausanne) 5:205
16. Ando Y, Obayashi K, Tanaka Y, Tsuji T, Uchino M, Takahashi M, Ando M (1994) Radiolabelled meta-iodobenzylguanidine in assessment of autonomic dysfunction. Lancet 343(8903):984–985
17. Delahaye N, Le Guludec D, Dinanian S, Delforge J, Slama MS, Sarda L, Dollé F, Mzabi H, Samuel D, Adams D, Syrota A, Merlet P (2001) Myocardial muscarinic receptor upregulation and normal response to isoproterenol in denervated hearts by familial amyloid polyneuropathy. Circulation 104:2911–2916
18. iklasson U, Olofsson BO, Bjerle P (1989) Autonomic neuropathy in familial amyloidotic polyneuropathy. a clinical study based on heart rate variability. Acta Neurol Scand 79:182–187
19. Kyle Rowe, Pankow J, Nehme J et al (2017) Gastrointestinal amyloidosis: review of the literature. Cureus 9(5):e1228
20. Conceicao I, Gonzalez-Duarte A, Obici L et al (2016) Red flag symptom custers in transthyretin familial polyneuropathy. J Peripher Nerv Syst 21(1):5–9
21. Rubinow A, Cohen A (1986) Scalloped pupils in familial amyloid polyneuropathy. Arthritis Rheum 29(3):445–447
22. Obayashi K, Ando Y, Nakamura M, Yamashita T, Ueda M, Haraoka K, Terazaki H, Uchino M (2004) Near-infrared

spectrophotoscopy of finger venules in assessment of autonomic dysfunction. Neurology 63:164–166 **(antes 18)**
23. Obayashi K, Ando Y, Nakamura M et al (2000) Endothelium-dependent vasodilatation in patients with familial amyloidotic polyneuropathy. Muscle Nerve 23:1084–1088 **(antes 19)**
24. Adams D, Lozeron P, Lacroix C (2012) Amyloid neuropathies. Curr Opin Neurol 25(5):564–572
25. Peripheral Nerve Society (1995) Diabetic polyneuropathy in controlled clinical trials. report of the peripheral nerve society. Ann Neurol 38:478–482
26. Dyck PJ, Kincaid JC, Dyck PJB et al (2017) Assessing mNIS+7_{ionis} and international neurologists' porficiency in a familial amyloidotic polyneuropathy trial. Muscle Nerver 56(5):901–9011
27. Adams D, Surh OB, Dyck PJ et al (2017) Trial design and rationale for APOLLO, a phase 3, placebo controlled study of patisiran in patients with hereditary ATTR amyloidosis with polyneuropathy. BMC Neurol 17:181
28. Adams D, Coelho T, Conceicao I, et al (2017) Phase 2 open-label extension (OLE) study of patisiran, an investigational RNA interference (RNAi) therapeutic for the treatment of hereditary ATTR amyloidosis with polyneuropathy (S27.004). Neurology 88(16 Supp)
29. Suhr O, Adams D, Coelho T, Waddington Cruz M, Schmidt H, Buades J, Campistol J, Pouget J, Berk J, Polydefkis M, et al (2016) Phase 2 open-label extension study of patisiran, an investigational RNAi therapeutic for the tereatment of hereditary ATTR amyloidosis with polyneuropathy. In: The XVth International Symposium on Amyloidosis (International Society of Amyloidosis) Uppsala: Abstract PA80
30. Vinik EJ, Vinik AI, Paulson JF et al (2014) Norfolk QOL-DN: validation of a patient reported oucome measure in transthyretin familial amyloid polyneuropathy. J Peripheral Nerv Syst 19:104–114 **(2)**
31. Coehlo T, Vinik A, Vinik EJ et al (2017) Clinical measures in transthyretin familial amyloid polyneuropathy. Muscle Nerve 55:323–332
32. Trester R, O'Neil K, Downs HM et al (2015) Validation of the composite autonomic symptom scale 31 (COMPASS-31) in patients with and without small fiber polyneuropathy. Eur J Neurol 22(7):1124–1130
33. Ebenezer GJ, Judge DP, Cunningham K et al (2017) Cutaneous nerve biomarkers in transthyretin familial amyloid polyneuropathy. Ann Neurol 82(1):44–56
34. Chao CC, Huang CM, Chiang HH, Luo KR, Kan HW, Yang NC, Chiang H, Lin WM, Lai SM, Lee MJ et al (2015) Sudomotor innervation in transthyretin amyloid neuropathy: pathology and functional correlates. Ann Neurol 78(2):272–283
35. Takahashi R, Ono K, Nakumura K et al (2014) Efficacy of diflunisal on autonomic dysfunction of late-onset familial amyloid polyneuropathy (TTR Val30Met) in a Japanese endemic area. J Neurol Sci 345(1.2):231–235
36. Russo M, Vita GL, Stancanelli C et al (2016) Parenteral nutrition improves nutritional status, autonomic symptoms and quality of life in transthyretin amyloid polyneuropathy. Neuromuscul Disord 26(6):374–377
37. Cortese A, Vita G, Luigetti M et al (2016) Monitoring effectiveness and safety of Tafamidis in a transthyretin amyloidosis in Italy: a longitudinal multicenter study in a non-endemic area. J Neurol 263(5):916–924