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Late-onset hereditary ATTR V30M amyloidosis with polyneuropathy: Characterization of Brazilian subjects from the THAOS registry☆

Marcus Vinicius Pinto[a,b,*], Luiz Felipe Pinto[a], Moises Dias[a], Renata Santa Rosa[a], Rajiv Mundayat[c], Roberto Coury Pedrosa[a], Marcia Waddington-Cruz[a,*]

[a] National Amyloidosis Referral Center, CEPARM, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[b] Department of Neurology, Mayo Clinic, Rochester, MN, USA
[c] Pfizer Inc, New York, NY, USA

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ABSTRACT

Background: Despite growing numbers of patients diagnosed with late-onset hereditary ATTR V30M amyloidosis with polyneuropathy (ATTRv-PN), this condition remains poorly characterized in Brazil.
Objective: Characterize late-onset V30M ATTRv-PN in Brazil.
Material and methods: Demographic and clinical data at the time of enrolment for Brazilian subjects with symptomatic V30M ATTRv-PN were extracted from the ongoing, multinational, longitudinal, observational Transthyretin Amyloidosis Outcomes Survey (THAOS; cut-off date: January 30, 2017). Subjects were divided into those with symptom onset at age < 50 years (EO-V30M), and at age ≥50 years (LO-V30M).
Results: A total of 96 Val30Met patients were symptomatic. LO-V30M (n = 25, 26.0%) had a longer time to diagnosis (mean 5.1 vs. 2.8 yrs.; p = 0.006) and less frequently positive family history (40% vs. 95.8%; p < 0.0001) than EO-V30M. Clinically, subjects with LO-V30M had more imbalance (92% vs. 54.9%; p = 0.006), deep sensory loss (100% vs. 80%; p = 0.0178), electrocardiogram abnormalities (88.9% vs. 59.4; p = 0.0241), and interventricular septum hypertrophy (69.2% vs. 0%; p < 0001) and less frequently sensory dissociation (12% vs. 74%; p < 0.0001). Also, LO-V30M tended to have more severe mean Neurologic Composite Score (101 vs. 70 pts.; p = 0.1136).
Conclusions: LO-V30M ATTRv-PN is not unusual in Brazil, tending to be more difficult to diagnose and present with a more severe phenotype, with more large nerve fibers and cardiac involvement than EO-V30M.
Trial Registration: ClinicalTrials.gov: NCT00628745

1. Introduction

Hereditary Transthyretin Amyloidosis with Polyneuropathy (ATTRv-PN) is a rare, progressive, life-threatening disorder with a varied clinical presentation. Val30Met (V30M) mutation is the most common mutation in the transthyretin gene worldwide, and the classical V30M ATTRv-PN phenotype is of a small-fiber predominant neuropathy with onset in third or fourth decade [1]. A late-onset form of V30M ATTRv-PN in which symptoms manifest in the sixth decade or later has been reported in several countries, and seems to be the most common form outside endemic regions [2–6]. Late-onset V30M ATTRv-PN affects both large and small sensory fibers and has few autonomic symptoms and more severe motor and cardiac involvement than early-onset disease [7,8]. Despite being well characterized in other parts of the world, late-onset V30M ATTRv-PN is still poorly characterized in Brazil.

In Brazil, the ATTRv-PN mean age at symptom onset (AO) is 32.5 years; 91.9% have V30M mutation; 90.6% have positive family history [9]; and there is an estimated penetrance of 83% at 60 years old [10]. These numbers are very similar to endemic regions in Japan and Portugal [3,11,12]. Brazil was colonized by Portugal and is estimated to have > 25 million Portuguese descendants. In a previous study, we

Abbreviations: ATTRv-PN, Hereditary Transthyretin Amyloidosis with Polyneuropathy; EO-V30M, Early-onset Val30Met Transthyretin Amyloidosis; IVS, interventricular septum; LVIDd, left ventricular internal dimension in diastole; LO-V30M, Late-onset Val30Met Transthyretin Amyloidosis; PW, posterior left ventricle wall; THAOS, Transthyretin Amyloidosis Outcomes Survey; TTR, transthyretin

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* Corresponding authors at: National Amyloidosis Referral Center, CEPARM, Federal University of Rio de Janeiro, Rodolpho Paulo Rocco street, 7° floor, 21941-913 Rio de Janeiro, Brazil.

E-mail addresses: pinto.marcus@mayo.edu (M.V. Pinto), mwaddingtoncruz@gmail.com (M. Waddington-Cruz).

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showed that 96.1% of our patients had Portuguese ascendance and only 9% had late-onset ATTRv- PN [13]. However, the number of late-onset cases diagnosed at our center increases every year.

In this study, we characterized demographic and clinical manifestations of late-onset Val30Met ATTRv-PN patients from the Brazilian National Amyloid Referral Center (CEPARM).

2. Material and methods

Demographic and clinical data at the time of enrollment were extracted from the ongoing, multinational, longitudinal, observational Transthyretin Amyloidosis Outcomes Survey (THAOS)[7], with a cut-off date of January 30, 2017. All symptomatic Val30Met ATTR-PN subjects in Brazil (our center is the only Brazilian site participating in THAOS) were included in the analysis and divided into two groups: Late-onset (LO-V30M), subjects with symptom onset at age ≥ 50 years, and Early-onset (EO-V30M), subjects with symptom onset at age < 50 years. Descriptive analyses of patients' demographic information, medical histories, and clinical assessments at enrollment were performed. Misdiagnosis was defined as the last diagnosis received before the diagnosis of ATTRv-PN. Symptoms were categorized in symptoms of motor neuropathy, sensory neuropathy, autonomic neuropathy, gastrointestinal disorders, and cardiac disorder (Supplementary Table S1). In addition, symptoms of muscle weakness, imbalance, and insensitivity to pain or temperature were included. Assessments included: Neuropathy Impairment Score in the Lower Limbs (NIS-LL), Neurologic composite score (NCS), Modified Polyneuropathy Disability Score (mPND), electrocardiogram (ECG), and echocardiogram (ECHO). The NIS-LL has been described extensively [14], but briefly it comprises scores of muscle weakness in the lower limbs, decrease of patellar and ankle reflexes, and abnormality of 4 different modalities of sensation on the big toe, and total score ranges from 0 to 88. The NCS is a neurological examination score specifically designed for the THAOS registry. It extracts motor, reflex, and sensory findings from the THAOS database, and ranges from zero to 294 points. The motor subscale ranges from zero to 160, and is composed of the MRC grading system score of 16 anatomical sites of the body bilaterally. The reflexes subscale ranges from zero to 10 and scores zero for normal and 1 for reduced/absent reflex at the ankle, knee, biceps, triceps, and brachioradialis bilaterally. The sensory score ranges from zero to 124, and assess bilateral body distribution and severity of pinprick, light touch, vibration, and position sense loss. mPND is a disability scale that ranges from I to IV, being I-sensory disturbances but no difficulty walking (no motor involvement); II-difficulty walking but no need for a gait aid; IIIa- one cane/crutch required for walking; IIIb- two crutches/walker required; IV-wheel-chair or bed bound [15]. Patient records were individually reviewed (M.V.P.) for the presence of superficial (thermal and/or pinprick) and deep (vibration and/or proprioception) sensory loss, distal and proximal limb weakness, and absent deep tendon reflexes on neurological exam. Sensory dissociation was defined as predominant small-fiber impairment with more superficial than deep sensory loss (pain and thermal sensation impaired more than vibration and joint position). Twelve lead electrocardiogram findings were reported as normal or abnormal and presence/absence of rhythm abnormalities, conduction abnormalities, first degree AV block, abnormalities in QRS morphology, low voltage and ST segment-T wave abnormalities. Transthoracic Echocardiogram (Echo) pictures were obtained and analyzed according to THAOS protocol [16]. Interventricular septum hypertrophy was defined as ≥ 12 mm.

2.1. Statistical analysis

Data are presented as mean ± standard deviation and percentages unless otherwise noted. Differences were assessed using a chi-square analysis for dichotomous variables and student's *t*-test for continuous variables. Tests were two-sided and $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SAS ver 9.4.

Table 1
Demographic findings.

	LO-V30M N = 25	EO-V30M N = 71	p-Value
Male, n (%)	15 (60.0)	45 (63.4)	0.8126
Age at symptom onset, years, mean (SD)	62.1 (5.5)	30.5 (8.5)	0.0135
Time from symptom onset to diagnosis, years, mean (SD)	5.1 (4.1)	2.8 (4.4)	0.0912
Misdiagnosis, n (%)	17 (68.0)	19 (26.8)	0.0006
Family history, n (%)	10 (40.0)	68 (95.8)	< 0.0001
Subjects with biopsy, n (%)	18 (72.0)	48 (67.6)	0.8041
Amyloid demonstrated, n (%)	15 (83.3)	42 (87.5)	1.0000

Values are % or mean ± SD. LO-V30M = Late-onset Val30Met Transthyretin Amyloidosis; EO-V30M = Early-onset Val30Met Transthyretin Amyloidosis.

3. Results

3.1. Study demographic

Of 162 Brazilian subjects enrolled in THAOS, 148 had the Val30Met mutation, of which 96 were symptomatic and were included in this analysis (Table 1). Of the 96 symptomatic patients 25 (26%) had late-onset V30M (LO-V30M) and 71 (74%) had early-onset V30M (EO-V30M) ATTRv-PN. 63.4% were males in the LO-V30M group compared to 60% in the EO-V30M group (p = 0.8126). The mean AO in the study population was 38.7 years, and the mean AO in LO-V30M was 62.1 compared to 30.5 years in EO-V30M (p = 0.0135). 68%(17/25) of LO-V30M patients were misdiagnosed compared to 26.8%(19/71) of EO-V30M (p = 0.006) and most common miasgnosis in the LO-V30M group was CIDP (41%-7/17), followed by idiopathic peripheral neuropathy (23.5%-4/17). LO-V30M had a tendency for longer mean time for diagnosis (5.1 vs. 2.8 years; p = 0.0912). LO-V30M cases had family history of ATTR-PN in only 40% of the cases compared to 95.8% in EO-V30M (p < 0.001). The number of patients that underwent biopsy and had amyloid tissue confirmation was similar between groups (Table 1).

3.2. Clinical features of Brazilian Late-onset Val30Met ATTRv-PN

3.2.1. Symptoms

100% of LO-V30M patients presented with symptoms of sensory neuropathy, 92% of motor neuropathy, 80% of autonomic neuropathy, 92% with imbalance, 80% with insensitivity to pain or temperature, 84% with gastrointestinal disorders, and 40% with cardiac disorders. We found significantly more imbalance and less autonomic neuropathy and a trend for more frequent muscle weakness in the LO-V30M group compared to EO-V30M (Fig. 1). mPND score was I or II in 53.3%, IIIa or IIIb in 26.7% and IV in 20% of the LO-V30M group, compared to 0 in 5.9%, I or II in 58.8%, IIIa or IIIb in 33.3% of the EO patients.

3.2.2. Neurological exam

In the LO-V30M group all patients had superficial and deep sensory loss and 88% had distal lower limbs weakness (Table 2). LO-V30M patients more frequently had deep sensory loss (100% vs. 80%; p = 0.0178), distal LL and UL weakness (88% vs. 66%; p = 0.0413; and 76% vs. 42%; p = 0.005, respectively), and diffuse loss of deep tendon reflexes (76% vs. 49%; p = 0.0338) compared to the EO-V30M group. Sensory dissociation was rarely found in the LO-V30M group (12% vs. 74%; p < 0.0001). There was a trend for more severe neurologic impairment in the LO-V30M group (Fig. 2).

3.2.3. Cardiac involvement

Abnormal ECG occurred more frequently in LO-V30M patients

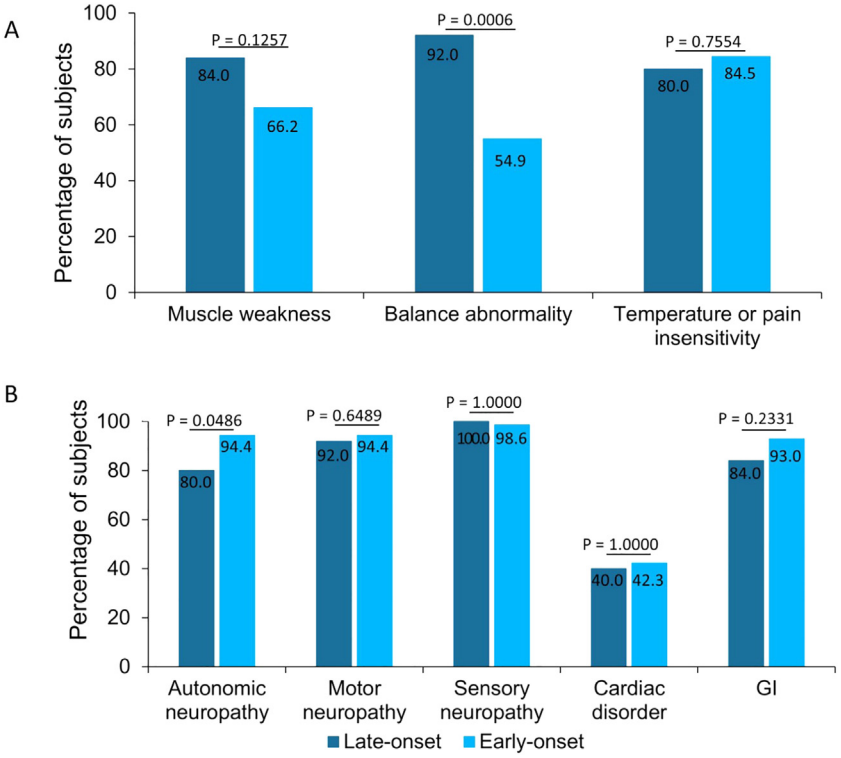

Fig. 1. Frequency of symptoms. GI: gastrointestinal.

Table 2
Neurological exam findings at enrollment.

	LO-V30M N = 25	EO-V30M N = 71	p-Value
Sensation loss			
Superficial	25 (100%)	69 (97%)	1.0
Deep	25 (100%)	57 (80%)	0.0178
Sensory dissociation	3 (12%)	51 (74%)	< 0.0001
Weakness			
Distal LL	22 (88%)	47 (66%)	0.0413
Proximal LL	10 (40%)	20 (28%)	0.3192
Distal UL	19 (76%)	30 (42%)	0.005
Proximal UL	5 (20%)	13 (18%)	1.0
Deep tendon reflexes			
Absent only at lower limbs	4 (16%)	18 (25%)	0.4162
Diffuse loss	19 (76%)	35 (49%)	0.0338

Sensory dissociation is defined as predominant small-fiber impairment with more superficial than deep sensory loss (pain and thermal sensation impaired more than vibration and joint position sensation). LO-V30M = Late-onset Val30Met Transthyretin Amyloidosis; EO-V30M = Early-onset Val30Met Transthyretin Amyloidosis.

(88.9% vs. 59.4%; p = 0.0241), and interventricular septum hypertrophy on ECHO was found only in LO-V30M patients (69.2% vs. 0%; p < 0.0001) (Fig. 3). Only 22% (2/9) LO-V30M patients with cardiomyopathy had symptomatic heart failure. Interventricular septum thickness, posterior wall thickness and left atrial size were higher in the LO-V30M group (p < 0.0001) but ejection fraction and left ventricular internal dimension in diastole were not different between groups (Table 3).

4. Discussion

For decades, ATTRv-PN was known as small fiber predominant neuropathy with severe autonomic involvement, strong positive family history, and onset at third or fourth decades [11,17,18]. However, late-onset cases have emerged as the most common phenotype outside endemic areas. The change in this paradigm is crucial, as probably the most common presentation of ATTRv-PN worldwide is of a length-dependent axonal peripheral neuropathy with pan-modality sensation loss [15]. As ATTRv-PN is a treatable disease [19], physicians should be aware of clues and red-flags for ATTR-PN in progressive undiagnosed peripheral neuropathies [19,20]. Differences in the clinical phenotype of early and late-onset Val30Met ATTR-PN have been described in Japan and Portugal, but little was known about these differences in Brazil before our study.

We found that 26% of V30M ATTRv-PN patients from our referral center registered in THAOS are late-onset cases. Brazilian LO-V30M patients have less autonomic and small sensory nerve fiber involvement than EO-V30M, and more large-sensory nerve fiber and motor involvement. Also, we found a trend for more severe neurological impairment compared to the early-onset group and the late-onset cases were more disabled at enrolment. The high rate of misdiagnosis and the huge delay in the diagnosis are worrisome and reflect the challenge in diagnosing late-onset ATTR-PN in Brazil. In the LO-V30M group, CIDP was the most common misdiagnosis, similarly to previous studies [21–23]. Our study showed that probably one important clue is the cardiac involvement in late-onset cases. We found interventricular septum hypertrophy in almost 70% and an abnormal ECG in almost 90% of LO-V30M patients. Interestingly, 78% of the LO-V30M patients with cardiomyopathy did not have symptoms of heart failure. Detection of subclinical cardiomyopathy in old adults and elderlies with progressive polyneuropathies of uncertain etiology should raise the possibility of ATTRv [22].

Similar neurologic differences between early and late-onset V30M ATTRv-PN patients were encountered in Japan and Portugal [2,3,24]. Interestingly, Brazil, Japan, and Portugal appear to share the same origin of the V30M mutation [25,26], which came from Portugal probably during the time of the "Age of Discoveries" in the 16th century [27]. The phenotype of our LO-V30M is also similar to LO-V30M patients reported in non-endemic regions in other parts of the world [15,28,29]. The reason why V30M is the most common mutation worldwide is not only because of "the travels of genes" in the 16th

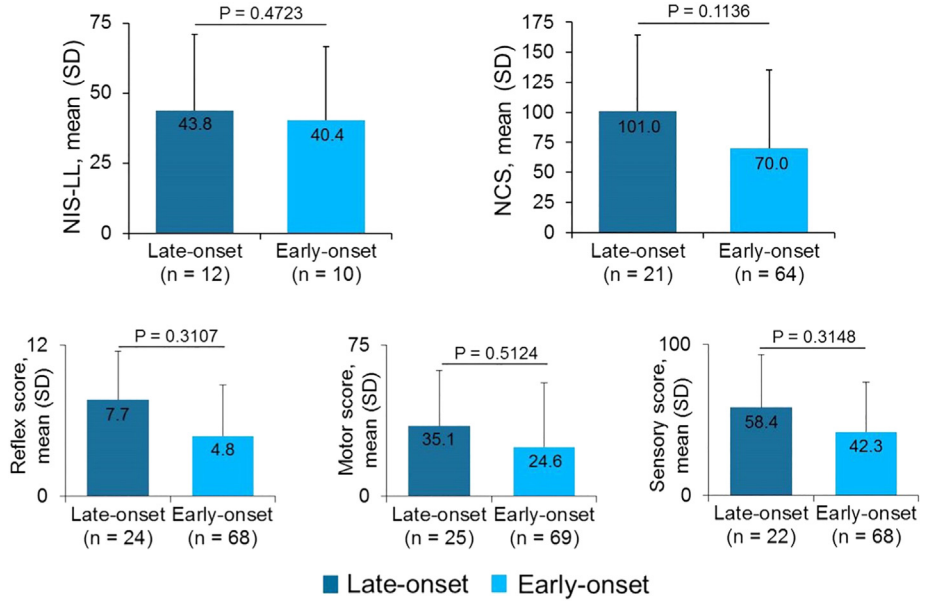

Fig. 2. Neurological exam findings. NIS-LL: neuropathy impairment score – lower limbs; NCS: neurological composite score.

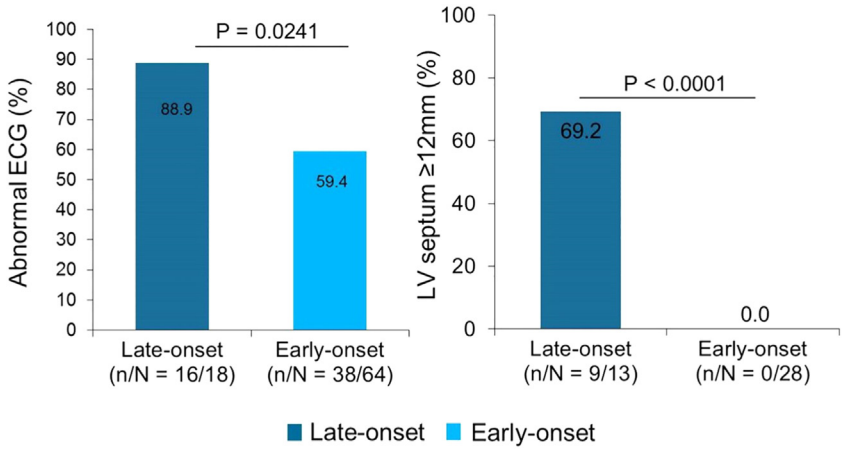

Fig. 3. Frequency of ECG abnormalities and LV septum hypertrophy on Echocardiogram. ECG: electrocardiogram; LV: left ventricle.

century but also probably due to de novo mutations, as there is an CpG dinucleotide sequence in the Val codon at position 30, which is a hot-spot for mutations in the human genome [27]. Although it is unknown why LO-V30M has more severe neurologic and cardiologic involvement than do EO-V30M, different patterns of amyloid deposition and sensory nerve fiber involvement have been reported in these two groups.

In V30M ATTRv patients amyloid fibril composition seems to be related to age of symptom onset [30,31]. In EO-V30M patients fibrils are essentially composed of full-length TTR, are strongly congophilic, and disposed in parallel. In contrast, amyloid fibrils in LO-V30M patients are usually fragmented, weakly congophilic, and disposed haphazardly, like wild-type ATTR amyloid fibrils [31–33]. Nerve biopsy studies have shown predominant loss of small sensory fibers in EO-V30M patients and more severe fiber loss in LO-V30M, with variable size distribution [34]. An electron microscopy study showed more blood-nerve-barrier impairment in LO-V30M patients and more prominent amyloid deposits and involvement of small sensory nerve fibers in EO-V30M [35]. These pathological differences may explain the worse response to liver transplant [36] or TTR stabilizers [37] in LO-V30M patients. Recently, an ultrastructural study done on a Brazilian V30M ATTRv-PN patient's nerve biopsy showed same very long TTR fibrils that have been shown in Japanese early-onset cases [38].

The reason why patients with Val30Met ATTR-PN have different ages of symptoms onset is still unclear. Initially, environmental factors were hypothesized but the most important factors are likely genetic [12]. Single-nucleotide haplotypes polymorphisms in the untranslated region of the *TTR* gene [39], variants in the *RBP4* and *AR* genes [40] and mitochondrial polymorphisms [41] have been found to modulate age at onset in V30M ATTR-PN. Recently, the Mitochondrial DNA copy number has been proposed as a potential mechanism for earlier disease onset and anticipation [42]. These mechanisms may also play a role in the different clinical phenotypes encountered in EO and LO-V30M patients.

Our study has some limitations. First, this is a retrospective analysis from our National Amyloid Referral Center, the only Brazilian center in the THAOS registry, which is located in a presumptively endemic region which may not reflect the same characteristics of the rest of the country. Second, we were not able to sort the patients by region of birth because the THAOS registry does not collect this information. However, a previous study showed that 77% of our patients are from Rio de Janeiro [13]. Third, there is no epidemiological study to define endemic and non-endemic regions in Brazil.

5. Conclusions

The late-onset V30M ATTRv-PN is not unusual in the Brazilian

Table 3
Electrocardiogram and Echocardiogram findings.

	LO-V30M		EO-V30M		p-Value
	n/N	%	n/N	%	
Electrocardiogram					
Rhythm abnormalities, %	3/15	20.0	6/38	15.8	0.7010
Conduction abnormalities, %	13/15	86.7	28/36	77.8	0.7027
First degree AV block,%	3/15	20.0	11/26	42.3	0.1860
Abnormalities in morphology, %	1/13	7.7	6/36	16.7	0.6577
Low voltage, %	2/15	13.3	1/43	2.3	0.1611
ST Segment – T wave abnormalities, %	6/15	40.0	6/36	16.7	0.1440
Echocardiogram					
IVS thickness, mm	13	14 ± 3	29	9 ± 2	< 0.0001
PW thickness, mm	13	13 ± 2	29	9 ± 1	< 0.0001
Left atrial size, mm	13	39 ± 7	29	32 ± 4	< 0.0001
LVIDd, mm	13	45 ± 7	29	43 ± 7	0.5858
Ejection fraction, %	13	64 ± 14	29	61 ± 14	0.5463

Values are % or mean ± SD. LO-V30M = Late-onset Val30Met Transthyretin Amyloidosis; EO-V30M = Early-onset Val30Met Transthyretin Amyloidosis IVS = interventricular septum; PW = posterior wall; LVIDd = left ventricular internal dimension in diastole;

population and while it presents with a more severe phenotype than early-onset ATTRv-PN, it is more frequently misdiagnosed, and delays in diagnosis are more common. Brazilian LO-V30M ATTRv-PN subjects tend to be more likely to suffer from more severe neurologic and cardiac impairments, but are less likely to experience autonomic symptoms. Late-onset subjects presented with similar impairment of both small and large fibers compared to early-onset subjects who presented with mainly small fiber neuropathy involvement. Brazilian Late-onset V30M ATTRv-PN seems to have similar characteristics to Late-onset V30M patients from other parts of the world. We hope the characterization and recognition of late-onset ATTRv-PN in Brazil will enable earlier recognition and improve patient treatment and outcomes.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2019.05.030.

Declaration of interest

Marcia Waddington-Cruz received honorarium from NHI, Prothena, FoldRx, Ionis, Pfizer, Alnylam, and Genzyme for travel expenses related to presentations at medical meetings, for acting as a principal investigator in clinical trials, and as a consultant member. Rajiv Mundayat is an employee of Pfizer and holds stock and/or stock options. No other author reports a conflict of interest.

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