Characteristics of Patients with Hereditary Transthyretin Amyloid Polyneuropathy and Chronic Idiopathic Axonal Polyneuropathy in Russia: PRIMER Study Results

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Abstract

Introduction. *Hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) is a severe progressive hereditary disease. Even with the availability of genetic testing for transthyretin (TTR) gene variants, timely hATTR-PN diagnosis remains challenging due to a great variability in its clinical presentation. Patients with hATTR-PN are often misdiagnosed with chronic idiopathic axonal polyneuropathy (CIAP).*

The ***objective of our study*** *is to describe the baseline electrophysiological, clinical, and demographic characteristics of hATTR-PN and CIAP patients and to establish patients' pre-selection criteria for genetic testing.*

Materials and methods. *Retrospective analysis was performed in 42 hATTR-PN patients and 58 CIAP patients (according to diagnosis defined in medical records from 1 January 2017 to 1 March 2024). Demographic, clinical, and electrophysiological data were collected at diagnosis. To identify factors influencing the likelihood of the hATTR-PN presence, a logistic regression model including clinically relevant variables was developed.*

Results. *The mean age of hATTR-PN and CIAP patients was 57.7 and 60.9 years, respectively. As compared with CIAP patients, those with hATTR-PN more frequently exhibited gait disturbances (64.3% vs 37.9%), autonomic (47.6% vs 12.1%), cardiac (35.7% vs 10.3%) and gastrointestinal symptoms (64.3% vs 12.1%), unintentional weight loss (45.2% vs 12.1%), and heart failure with preserved ejection fraction (26.2% vs 6.9%). Peripheral nerve conduction scores were also lower in the hATTR-PN group. In predicting hATTR-PN, the logistic regression model had a sensitivity of 91% and a specificity of 97%.*

Conclusion. *Demographic, clinical, and electrophysiological characteristics of patients with hATTR-PN and CIAP were described. Based on the screening data, it is feasible to predict hATTR-PN in CIAP patients with relatively high accuracy, sensitivity, and specificity.*

Keywords: *transthyretin amyloidosis; polyneuropathy; transthyretin; screening tool*

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Характеристики пациентов с наследственной формой транстиретиновой амилоидной полинейропатии и хронической идиопатической аксональной полинейропатией в российской популяции: результаты исследования «ПРАЙМЕР»

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Аннотация

Введение. *Наследственная транстиретиновая амилоидная полинейропатия (hATTR-PN) – прогрессирующее тяжёлое наследственное заболевание. Несмотря на доступность генетического тестирования для выявления вариантов гена транстиретина (TTR), своевременная диагностика затруднена вследствие разнообразия клинических проявлений. Частым ошибочным диагнозом является хроническая идиопатическая аксональная полинейропатия (ХИАП).*

Цель исследования *– описание исходных электрофизиологических, клинических и демографических характеристик пациентов с hATTR-PN и ХИАП и подбор критериев для отбора пациентов, которые подлежат генетическому тестированию.*

Материалы и методы. *Ретроспективный анализ проведён у 42 пациентов с hATTR-PN и 58 пациентов с ХИАП (диагноз установлен в медицинской документации с 01.01.2017 по 01.03.2024). Демографические и клинические характеристики, результаты электрофизиологического исследования были собраны на момент постановки диагноза. Клинически релевантные параметры включили в модель логистической регрессии для выявления факторов, влияющих на вероятность наличия hATTR-PN.*

Результаты. *Средний возраст составил 57,7 (hATTR-PN) и 60,9 (ХИАП) года. В группе hATTR-PN по сравнению с ХИАП чаще встречались нарушения походки (64,3 и 37,9%), вегетативные симптомы (47,6 и 12,1%), проявления со стороны сердца (35,7 и 10,3%), желудочно-кишечного тракта (64,3 и 12,1%), непреднамеренная потеря веса (45,2 и 12,1%), сердечная недостаточность с сохранённой фракцией выброса (26,2 и 6,9%), были хуже показатели проводящей функции периферических нервов. Модель логистической регрессии показала чувствительность 91% и специфичность 97% в отношении предсказания наличия hATTR-PN.*

Заключение. *Описаны демографические, клинические и электрофизиологические характеристики пациентов с hATTR-PN и ХИАП. На основании скрининговых данных возможно с хорошей точностью, чувствительностью и специфичностью предсказать наличие hATTR-PN у пациентов с ХИАП.*

Ключевые слова: *транстиретиновый амилоидоз; полинейропатия; транстиретин; скрининговый инструмент*

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Introduction

Hereditary transthyretin amyloidosis is a severe progressive multisystem disease caused by mutations in the gene encoding transthyretin (*TTR*) [1]. The *TTR* gene composed of four exons is located on chromosome 18. Over 160 *TTR* gene variants have been identified so far [2]. The majority of hATTR-PN cases (formerly referred to as Familial Amyloid Polyneuropathy) are caused by a point mutation leading to methionine-for-valine substitution at position 30 of the mature protein (Val30Met, or p.Val50Met) [3]. The mutated tetrameric TTR protein is unstable and dissociates into misfolded monomers that accumulate mainly in the heart and the peripheral nervous system, causing cardiomyopathy and progressive axonal polyneuropathy, respectively [4].

hATTR-PN is an adult-onset disease with variable penetrance and an autosomal-dominant mode of transmission [5, 6]. Accumulation of TTR amyloid fibrils in the peripheral nervous system results in rapidly progressing sensorimotor and autonomic polyneuropathy leading to patient's disability. Patients die within an average of 10 years from the onset of symptoms [7].

The prevalence of hATTR-PN per 1 million population ranges from 0.9 to 204 and 0.3 to 56 in endemic and non-endemic countries, respectively [8]. Portugal, Japan, Sweden, and Brazil are recognized as endemic countries; however, the global incidence of hATTR-PN continues to increase and cases are mainly sporadic. It is expected that the accuracy of diagnosis will improve with the expanded use of genetic testing, particularly in non-endemic regions, thereby increasing the detection of new hATTR-PN cases [1, 4, 6]. No data on the hATTR-PN prevalence in Russia are currently available. Based on available data extrapolation [9], we can assume that the estimated prevalence for Russia would be 0.32 (per 1 million population). This estimate is tentative and is based on the lowest prevalence rates in other countries.

Timely hATTR-PN diagnosis is challenging mainly due to a great variability in symptoms, with signs of damage not only to peripheral nerves, but also to many internal organs and systems. Clinical presentation of hATTR-PN often mimics that of other, more prevalent, diseases [10]. Hence, the early diagnosis of this rare disease poses a significant challenge for a neurologist practicing in non-endemic areas. In these areas, hATTR-PN is suspected in only 26–38% of initial evaluations [5]. A delay in diagnosis can be as long as 3–4 years, which directly affects the functional and vital prognosis for patients.

The symptom complex of chronic symmetric sensorimotor or peripheral neuropathy associated with hATTR-PN is non-specific. Neurological disturbances similar to these may accompany a variety of conditions, each with the potential for misdiagnosis [11]. Initial hATTR-PN misdiagnoses commonly include chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), lumbar spinal stenosis, diabetic polyneuropathy, carpal tunnel syndrome (CTS), paraneoplastic polyneuropathy, paraproteinemic polyneuropathy, and, more rarely, inherited polyneuropathy, and amyotrophic lateral sclerosis [10]. To date, patients with hATTR-PN are often misdiagnosed with chronic idiopathic axonal polyneuropathy (CIAP), which is a peripheral nerve disease of uncertain etiology. In Russia, such patients are usually diagnosed with polyneuropathy of unspecified or

mixed etiology. CIAP is diagnosed in 20–30% of patients with polyneuropathy. The disease is slowly progressive and most patients remain ambulatory with mild to moderate disability, but the quality of life is affected in all patients [12].

In patients without a family history of amyloidosis who present with progressive idiopathic axonal polyneuropathy or atypical CIDP, current guidelines suggest that the diagnosis of hATTR-PN should be considered first. Red flag symptoms and manifestations are autonomic dysfunction, early gait disturbances, gastrointestinal manifestations, CTS or a history of surgically corrected bilateral CTS, concomitant cardiac abnormalities, or unexplained weight loss [5]. In patients with such red flag symptoms, genetic testing should be performed to establish mutation status of the *TTR* gene.

We conducted a present multicenter observational study to define the baseline electrophysiological, clinical, and demographic characteristics of the patients diagnosed with hATTR-PN and CIAP in Russia. The secondary objective of this study was to develop a screening tool to preselect patients with axonal polyneuropathy for the *TTR* gene sequencing to detect its variants.

Materials and Methods

Study Design and Population

A multicenter, non-interventional, observational, retrospective study with secondary data collection was conducted at four institutions specialized in neurology and located in Russia:
- Research Center of Neurology (Moscow);
- M. Sechenov First Moscow State Medical University (Sechenov University, Moscow);
- Medical Center "Reavita Med SPb" (Saint Petersburg);
- Republican Clinical Hospital of the Ministry of Health of the Republic of Tatarstan (Kazan).

Given its non-interventional design, this study did not interfere with routine clinical practice or procedures and examinations of the patients. All the examinations were conducted in accordance with the standard clinical practice protocols of the study sites and their findings were retrospectively obtained from medical records.

The study included adult patients with a confirmed diagnosis of hATTR-PN or CIAP, as per primary medical records, who met the following inclusion criteria:
- hATTR-PN or CIAP diagnosis or its equivalents: polyneuropathy of unspecified etiology, polyneuropathy of mixed etiology (patients with axonal polyneuropathy carrying a pathogenic *TTR* gene mutation were classified as having hATTR-PN);
- hATTR-PN or CIAP was diagnosed between 1 January 2017 and 1 March 2024;
- at least 1 month between the hATTR-PN or CIAP diagnosis and study inclusion date;
- age of ⩾ 18 years at hATTR-PN or CIAP diagnosis.

Non-inclusion criterion was participation in any clinical trial of an investigational product from the date of hATTR-PN or CIAP diagnosis until the end of the retrospective follow-up period.

Due to retrospective design of the study, no written informed consent was required. All data were collected retrospectively and anonymously from the medical records available in the study sites.

Data Collection

This study was conducted using secondary data. Authorized and duly trained study site staff transferred all protocol-required data from medical records available at the study sites to the electronic Case Report Form (eCRF) developed for each patient included into the study. All the patients were identified by a unique code in their eCRF, which included no data allowing the identification of the patient's identity.

The retrospective data collection started on 23 January 2023 and ended on 27 June 2024. The database was closed on 18 July 2024.

A patient was enrolled in the study once the investigator deemed a patient eligible and decided to input the patient's data into the eCRF. Patients were enrolled in the study consecutively, beginning with the earliest diagnosis of hATTR-PN or CIAP and continuing to the later date, within the pre-specified period from 1 January 2017 to 1 March 2024. Retrospective follow-up began on the date of diagnosis of hATTR-PN or CIAP and continued until the patient was enrolled in the study, died or was lost to follow-up, whichever occurred first. Thus, if patients died or were lost for retrospective follow-up at the study site, their data were also included in the study.

The data obtained were based on three consecutive patient's visits during the retrospective data collection period, which were carried out as a part of routine clinical practice and registered in the medical records. We collected all available data from these visits during the retrospective follow-up period, even if the data were not fully available at the time of any visit.

Once a patient was recognized eligible and thus included in the study, we collected their baseline demographic, electrophysiological, and clinical characteristics and other baseline data (medical history, comorbidities, etc.) registered at hATTR-PN or CIAP diagnosis (this time point was designated as Visit 1). The changes in the selected endpoints were evaluated at the two subsequent follow-up visits (Visit 2 and Visit 3) relative to the baseline assessment at Visit 1.

Statistical analysis

Considering that hATTR-PN is a rare condition (with a prevalence of about 0.32 cases per 1 million in Russia), the sample size was established based on the available number of patients diagnosed with hATTR-PN. The planned sample size included approximately 50 patients with hATTR-PN and a similar number of patients with CIAP, for a total of 100 patients.

Statistical data processing was performed using R-Studio v. 2023.06.1 software and the R programming language v. 4.2.2. The results are presented using descriptive statistics for all patients included in the analysis (full analysis set) and for each group (mean and standard deviation, absolute frequencies, and percentages).

In intergroup analysis of demographic, clinical, and electrophysiological characteristics, Fisher's exact test or Pearson's χ^2 test were used to compare qualitative variables, and Student's test or Wilcoxon–Mann–Whitney test were used for quantitative variables (depending on the distribution patterns).

A logistic regression model was used to detect the factors impacting the likelihood of hATTR-PN diagnosis. This model included clinically relevant variables. Based on this model, a screening tool for patients with axonal polyneuropathy was developed, which allows to preselect them for the *TTR* gene sequencing.

Results

Clinical and demographic characteristics of patients

The study included 42 hATTR-PN patients as per medical records and 58 patients with CIAP diagnosed according to medical records (or its equivalents – polyneuropathy of unspecified etiology, polyneuropathy of mixed etiology) in 4 clinical centers in Russia. All 100 patients were included in the analysis set. Two patients were deceased at the time of inclusion (both from hATTR-PN group, with the cause of death unknown).

Baseline demographic and clinical characteristics of patients are presented in Table 1. The study sample was represented

Table 1. Baseline demographic and clinical characteristics of patients

Parameter	hATTR-PN (*n* = 42)	CIAP (*n* = 58)	*p*
Age, years	57.7 ± 12.8	60.9 ± 11.9	0.201
Male	24 (57.1%)	23 (39.7%)	0.127
Female	18 (42.9%)	35 (60.3%)	
Federal district (region of residence):			0.020
Central	17 (40.5%)	25 (43.1%)	
Northwestern	10 (23.8%)	19 (32.8%)	
Volga	10 (23.8%)	4 (6.9%)	
Southern	3 (7.1%)	2 (3.5%)	
North Caucasian	1 (2.4%)	1 (1.7%)	
Ural	1 (2.4%)	0 (0%)	
unknown	0 (0%)	7 (12.1%)	
Body mass index, kg/m^2	22.6 ± 5.0	27.4 ± 4.0	< 0.001
Underweight (Body mass index < 18.5 kg/m^2)	2 (4.8%)	0 (0%)	0.317
History of excessive alcohol use	4 (9.5%)	3 (5.2%)	0.669
Family history:			
premature cardiovascular death (age < 50) in close relatives	4 (9.5%)	0 (0%)	0.058
heart failure in close relatives	7 (16.7%)	2 (3.4%)	0.033
progressive polyneuropathy in close relatives	22 (52.4%)	7 (12.1%)	< 0.001

Continuation of the Table 1

Parameter	hATTR-PN (*n* = 42)	CIAP (*n* = 58)	*p*
Time from symptom onset to polyneuropathy diagnosis, years:			0.166
number of valid cases	40	58	
M ± SD	2.48 ± 3.33	2.03 ± 3.11	
median	1.5	1.0	
Time from polyneuropathy symptom onset to hATTR-PN or CIAP diagnosis, years:			0.088
number of valid cases	40	58	
M ± SD	3.10 ± 3.26	2.45 ± 3.21	
median	2.0	1.0	
Time from polyneuropathy diagnosis to hATTR-PN or CIAP diagnosis, years:			0.170
number of valid cases	42	54	
M ± SD	0.64 ± 1.32	0.39 ± 1.29	
median	0	0	
Chronic sensory or sensorimotor polyneuropathy*	–	55 (94.8%)	–
Chronic progressive polyneuropathy*	–	3 (5.2%)	–
Initially suggested polyneuropathy etiology, as per physician opinion**:			
number of valid cases	40	45	
diabetes mellitus	0 (0%)	2 (4.4%)	0.497
alcohol-related	0 (0%)	0 (0%)	–
toxicity-related	0 (0%)	2 (4.4%)	0.497
other hereditary factors	26 (65.0%)	4 (8.9%)	< 0.001
vitamin deficiency	0 (0%)	4 (8.9%)	0.120
immunity-related	2 (5.0%)	6 (13.3%)	0.275
hematology-related	1 (2.5%)	0 (0%)	0.465
infection-related	0 (0%)	0 (0%)	–
idiopathic	9 (22.5%)	19 (42.2%)	0.104
other causes***	4 (10.0%)	11 (24.4%)	0.153
TTR-gene sequencing:			< 0.001
performed, gene mutation (gene variant) detected	38 (90.5%)	–	
performed, no gene mutation (gene variant) detected	–	9 (15.5%)	
no data available in patient's medical record	4 (9.5%)	49 (84.5%)	
TTR-gene variants detected**** (*n* = 38):			
NM_000371.4(TTR):c.148G>A (p.Val50Met)	20 (52.6%)	–	–
NM_000371.4(TTR):c.379A>G (p.Ile127Val)	6 (15.8%)	–	

End of the Table 1

Parameter	hATTR-PN (*n* = 42)	CIAP (*n* = 58)	*p*
NM_000371.4(TTR):c.220G>C (p.Glu74Gln)	4 (10.5%)	–	
NM_000371.4(TTR):c.368G>A (p.Arg123His)	1 (2.6%)	–	
NM_000371.4(TTR):c.200G>C (p.Gly67Ala)	1 (2.6%)	–	
NM_000371.4(TTR):c.323A>G (p.His108Arg)	1 (2.6%)	–	
NM_000371.4(TTR):c.233T>A (p.Leu78His)	1 (2.6%)	–	
NM_000371.4(TTR):c.157T>A (p.Phe53Ile)	1 (2.6%)	–	
NM_000371.4(TTR):c.179C>A (p.Thr60Asn)	1 (2.6%)	–	
NM_000371.4(TTR):c.272T>C (p.Val91Ala)	1 (2.6%)	–	
gene variant is not specified in patient's medical record	1 (2.6%)	–	
Heart failure with preserved ejection fraction	11 (26.2%)	4 (6.9%)	0.016
Hypertension with predominant cardiac involvement	5 (11.9%)	19 (32.8%)	0.018
Systolic blood pressure, mm Hg:			0.006
number of valid cases	25	34	
M ± SD	114.7 ± 17.7	127.4 ± 15.5	
Diastolic blood pressure, mm HG:			0.016
number of valid cases	25	34	
M ± SD	72.4 ± 10.7	80.2 ± 10.8	
Heart rate, bpm:			0.911
number of valid cases	28	34	
M ± SD	72.8 ± 9.7	73.1 ± 9.3	

Note. *The parameter was assessed only in patients with CIAP. **Missing data were not included in the analysis due to unequal distribution of patients whose data was missing; a patient could have more than 1 variant etiology indicated. ***Other etiology encompassed depression with anorexia, radiation therapy, hypothyroidism, hereditary conditions, chemotherapy, deficit-, dysmetabolic-, and inflammatory-related conditions. ****Gene variant names according to HGVS (Human Genome Variation Society) nomenclature.

by patients from six federal districts. Almost half of them (42/100) resided in the Central Federal District. The mean age of the patients at diagnosis (Visit 1) was 57.7 ± 12.8 years in the hATTR-PN group and 60.9 ± 11.9 years in the CIAP group ($p = 0.201$). The hATTR-PN group was predominantly male (57.1%) and the CIAP group was predominantly female (60.3%; $p = 0.127$). There were no statistically significant intergroup differences for age and sex, whereas the groups differed in body mass index (BMI): in the hATTR-PN group BMI was lower (22.6 ± 5.0 kg/m^2 vs 27.4 ± 4.0 kg/m^2 in the CIAP group; $p < 0.001$). There were also two (4.8%) patients in the hATTR-PN group with BMI < 18.5 kg/m^2 (0% in the CIAP group).

According to medical records, the most frequent (> 50%) clinical manifestations of polyneuropathy at hATTR-PN or CIAP diagnosis (Visit 1) in the hATTR-PN group were sensory (88.1% of patients), motor (85.7%), gastrointestinal (64.3%), and autonomic symptoms (47.6%). In the CIAP group, the most frequent (> 50%) clinical manifestations were sensory (82.8%) and motor (67.2%) symptoms. Some polyneuropathy manifestations were reported significantly more often in the hATTR-PN group compared with the CIAP group. These included gait disturbances such as walking imbalance, foot weakness, unsteadiness, and coordination disorders (64.3 vs 37.9%; p = 0.016), gastrointestinal (64.3 vs 12.1%; $p < 0.001$) and autonomic symptoms (47.6 vs 12.1%; $p < 0.001$), unintentional weight loss (45.2 vs 12.1%; $p < 0.001$), and heart failure (23.8 vs 1.7%; $p = 0.001$; see Table 2).

In the hATTR-PN group compared with the CIAP group, there were significantly more patients with HFpEF as per their medical record (11 [26.2%] vs 4 [6.9%], $p = 0.016$). Ejection fraction considered preserved at ⩾ 50% (Table 1).

Table 2. Clinical manifestations of polyneuropathy at hATTR-PN or CIAP diagnosis

Clinical manifestations	hATTR-PN (*n* = 42)	CIAP (*n* = 58)	*p*
Sensory symptoms:	37 (88.1%)	48 (82.8%)	0.575
paresthesia	22 (52.4%)	26 (44.8%)	0.587
hypoalgesia/analgesia	11 (26.2%)	13 (22.4%)	0.842
neuropathic pain	21 (50.0%)	25 (43.1%)	0.631
Balance disorder	25 (59.5%)	22 (37.9%)	0.053
Motor symptoms:	36 (85.7%)	39 (67.2%)	0.061
muscular weakness	28 (66.7%)	30 (51.7%)	0.197
gait disturbances (walking imbalance, foot weakness)	27 (64.3%)	22 (37.9%)	0.016
Gastrointestinal symptoms:	27 (64.3%)	7 (12.1%)	< 0.001
diarrhea	11 (26.2%)	1 (1.7%)	< 0.001
constipation	6 (14.3%)	0 (0%)	0.004
switching between diarrhea and constipation	5 (11.9%)	0 (0%)	0.011
persistent nausea and vomiting	3 (7.1%)	0 (0%)	0.071
early satiety	0 (0%)	0 (0%)	–
Autonomic symptoms:	20 (47.6%)	7 (12.1%)	< 0.001
orthostatic hypotension	17 (40.5%)	3 (5.2%)	< 0.001
sweating disorders	9 (21.4%)	1 (1.7%)	0.002
dysuria	8 (19.1%)	4 (6.9%)	0.116
sexual dysfunction	4 (9.5%)	0 (0%)	0.029
Unintentional weight loss	19 (45.2%)	7 (12.1%)	< 0.001
Cardiac disorders:	15 (35.7%)	6 (10.3%)	0.005
heart failure	10 (23.8%)	1 (1.7%)	0.001
arrhythmias	5 (11.9%)	4 (6.9%)	0.486
heart block	3 (7.1%)	3 (5.2%)	0.694
Central nervous system disorders:	9 (21.4%)	10 (17.2%)	0.788
ataxia	5 (11.9%)	6 (10.3%)	1.000
seizures	2 (4.8%)	3 (5.2%)	1.000
progressive dementia	0 (0%)	1 (1.7%)	1.000
headache	0 (0%)	0 (0%)	–
Eye disorders:	7 (16.7%)	5 (8.6%)	0.350
abnormal changes in fundus blood vessels	4 (9.5%)	1 (1.7%)	0.158
vitreous opacities	3 (7.1%)	3 (5.2%)	0.694
glaucoma	1 (2.4%)	0 (0%)	0.420
pupil abnormalities	0 (0%)	0 (0%)	–
dry eyes	1 (2.4%)	1 (1.7%)	1.000
Carpal tunnel syndrome	8 (19.0%)	4 (6.9%)	0.116
Renal disorders:	4 (9.5%)	3(5.2%)	0.449
renal failure	4 (9.5)	2 (3.5%)	0.235
proteinuria	1 (2.4%)	0 (0%)	0.420
Lumbar spinal stenosis	2 (4.8%)	1 (1.7%)	0.571
Biceps tendon rupture	1 (2.4%)	2 (3.5%)	1.000

CTS was diagnosed in 8 (19.0%) hATTR-PN patients and 4 (6.9%) CIAP patients. Two patients in each group had a history of surgically corrected CTS.

Other Comorbidities

In the hATTR-PN group, the most common (> 10%) comorbidities were chronic gastritis – in 8 (19.1%) patients; hypertension with predominant cardiac involvement – in 5 (11.9%), and chronic heart failure – in 5 (11.9%) patients. In the CIAP group, the most common (> 10%) comorbidities were hypertension with predominant cardiac involvement – in 19 (32.8%) patients, chronic gastritis – in 12 (20.7%), osteochondrosis – in 6 (10.3%), and varicose veins of lower limbs – in 7 (12.1%) patients. Statistically significant differences were detected for hypertension with predominant cardiac involvement (p = 0.018) and varicose veins of lower limbs (p = 0.020).

Treatment

Thirty-three (78.6%) patients in the hATTR-PN group and 47 (81.0%) patients in the CIAP group received medicines to treat their primary disease (p = 0.804). Namely, tafamidis was prescribed to 18 (42.9%) hATTR-PN patients. Fourteen (33.3%) hATTR-PN patients and 29 (50%) CIAP patients received medicines to treat their concomitant disease (p = 0.107).

Polyneuropathy dysfunction scores

The following polyneuropathy disability score (PND) is used to evaluate the impact of polyneuropathy on locomotion [13]:
- PND 0 – no impairment;
- PND I – sensory disturbances, preserved walking capability;
- PND III – impaired walking capability but ability to walk without a stick or crutches;
- PND IIIA – walking only with the help of one stick or crutch;
- PND IIIB – walking with the help of two sticks or crutches;
- PND IV – patient confined to a wheelchair or bedridden.

In the hATTR-PN group, 16 (38.1%) patients had PND I, 9 (21.4%) – PND II, 6 (14.3%) – PND IIIA, 4 (9.5%) – PND IIIB, and 4 (9.5%) – PND IV; 3 (7.1%) patients had no PND score data in their medical records. In the CIAP group, 31 (53.5%) patients had PND I, 12 (20.7%) – PND II, 6 (10.3%) – PND IIIA, 3 (5.2%) – PND IIIB, and 2 (3.5%) – PND IV; 4 (6.9%) patients had no PND score data in their medical records. In either group, there were no patients with PND 0. No statistically significant intergroup differences in PND scores were detected (p = 0.577).

Modified Rankin Scale

The modified Rankin Scale, mRS is a universal tool to measure the degree of disability [14].

A single mRS grade should be assigned based on the following criteria:
0 – no symptoms;
1 – no significant disability despite symptoms: able to carry out all usual duties and activities;
2 – slight disability: unable to carry out all previous activities but able to look after own affairs without assistance;
3 – moderate disability: requiring some help, but able to walk without assistance;
4 – moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance;
5 – severe disability: bedridden, incontinent, and requiring constant nursing care and attention;
6 – dead.

MRS scores were available in medical records of 42 hATTR-PN patients and 56 CIAP patients. In the hATTR-PN group, the mean mRS score was significantly higher than that in the CIAP group (2.50 ± 1.35 vs 1.82 ± 0.92; p = 0.014). mRS scores ranged from 1 to 5 in the hATTR-PN group and from 1 to 4 in the CIAP group, with a median of 2.5 and 2.0, respectively. Thus, hATTR-PN patients were characterized by more severe functional impairment.

INCAT disability score

The INCAT (Inflammatory Neuropathy Cause and Treatment) disability score is widely used for assessment of activity limitation in CIDP patients. A Russian version of the INCAT scale is developed [15]. The 5-point INCAT score is meant for separate assessment of upper and lower limb function, with 0 representing no disability and 5 representing no limb function, and a 10-point INCAT total score as the sum of points for upper and lower limbs.

In the hATTR-PN group, lower limb INCAT scores were 1.38 ± 1.41 vs 1.19 ± 1.21 in the CIAP group (difference statistically insignificant). The number of patients with data available for analysis was 39 in the hATTR-PN group and 53 in the CIAP group. Differences were identified for upper limb INCAT scores: 1.36 ± 1.16 vs 0.54 ± 0.80, respectively (p = 0.001; number of patients with data available for analysis: 39 in the hATTR-PN group and 48 in the CIAP group) and for INCAT total scores: 2.74 ± 2.36 vs 1.57 ± 1.60, respectively (p = 0.021; number of patients with data available for analysis: 39 in the hATTR-PN group and 47 in the CIAP group). Thus, activity limitations, including those associated with upper limbs, were more pronounced in hATTR-PN patients than in CIAP patients.

Electrophysiological findings

Results of nerve conduction studies (NCS) performed at diagnosis presented in Table 3. Patients with hATTR-PN generally had worse peripheral nerve conduction function compared

Table 3. Results of nerve conduction study

Nerve	Parameter	hATTR-PN			CIAP			
		n	mean	SD	*n*	mean	SD	*p*
Median nerve	mV	15	3.70	3.28	20	8.96	12.37	0.012
	ms	15	6.39	2.68	20	4.98	2.61	0.129
	m/s	15	48.64	8.50	19	55.02	8.80	0.040
	μV	6	9.11	12.76	13	16.12	9.61	0.267
	SNCV at wrist level, m/s	6	41.27	14.40	13	55.75	12.63	0.064
Peroneal nerve	mV	8	2.95	2.61	16	3.12	2.63	0.883
	ms	8	5.41	1.64	13	5.76	4.93	0.818
	m/s	8	44.06	9.82	14	43.06	10.58	0.825
Superficial peroneal nerve	μV	2	5.80	3.96	4	3.08	2.39	0.500
	m/s	2	41.80	8.20	4	47.45	8.44	0.509
Sural nerve	μV	2	15.50	7.78	6	4.17	2.60	0.278
	m/s	2	43.40	3.39	6	47.88	9.44	0.365
Tibial nerve	mV	8	4.64	5.58	15	3.40	3.08	0.574
	ms	9	6.49	3.39	14	6.84	6.42	0.867
	m/s	9	42.80	7.77	13	40.25	7.07	0.443
Ulnar nerve	mV	13	4.97	3.42	17	6.84	1.90	0.094
	ms	13	4.55	2.54	17	4.47	3.08	0.217
	m/s	13	44.12	8.03	15	52.95	7.39	0.006
	μV	9	9.97	9.33	12	12.07	8.45	0.601
	m/s	9	44.44	12.72	12	50.89	9.74	0.225

Note. DML — distal motor latency. The number of patients with non-zero values of these parameters is indicated.

with CIAP patients. The greatest intergroup differences were observed for the median, sural, ulnar and superficial peroneal nerves. The following parameters were statistically significantly lower in the hATTR-PN group compared with those in the CIAP group: the compound muscle action potential (CMAP) of the median nerve: 3.70 ± 3.28 mV vs 8.96 ± 12.37 mV (p = 0.012); the motor nerve conduction velocity (MNCV) of the median nerve: 48.64 ± 8.50 m/s vs 55.02 ± 8.80 m/s (p = 0.040) and MNCV of the ulnar nerve: 44.12 ± 8.03 m/s vs 52.95 ± 7.39 m/s (p = 0.006), respectively.

Additionally, there were intergroup differences in the number of patients in whom it was not possible to record a response during the nerve conduction study . Statistically significant intergroup differences were found for the sensory nerve action potential (SAP) of the superficial peroneal nerve and sural nerve: in 8 hATTR-PN patients (19.1%) vs 1 (1.7%) CIAP patient; p = 0.004 for both nerves) and for sensory nerve conduction velocity (SNCV) of the superficial peroneal nerve and sural nerve: in 7 hATTR-PN patients (16.7%) vs 1 (1.7%) CIAP patient; p = 0.009 for both nerves).

Changes in clinical and electrophysiological characteristics over time

The exploratory objective of the study was to assess the changes in clinical and electrophysiological characteristics of the patients from the date of hATTR-PN or CIAP diagnosis to Visits 2 and 3 of the retrospective follow-up. The assessment was challenging because of the significant number of patients with missing data. Noteworthy, during the retrospective dynamic follow-up period, a decrease in PND scores from baseline to Visit 2 was detected in 2 (4.8%) hATTR-PN patients compared to none in the CIAP group. By Visit 3, the number

Table 4. Prognostic value of the hATTR-PN diagnosis predictors in a logistic regression model

Factor	Significance score
Other hereditary factors (of polyneuropathy etiology)	3.05
Body mass index	2.65
History of hypertension with predominant cardiac involvement	1.89
Cardiac manifestations	1.25
Median nerve, CMAP	1.14
Heart failure in close relatives	1.14
Median nerve, MNCV	0.93
Diastolic blood pressure, mm Hg	0.87
Heart failure with preserved ejection fraction	0.78
Gastrointestinal symptoms	0.73
Ulnar nerve, MNCV	0.63
INCAT total score	0.56
Upper limb INCAT score	0.56
Autonomic symptoms	0.41
Progressive polyneuropathy in close relatives	0.38
mRS score	0.31
Systolic blood pressure, mm Hg	0.27

of patients with decreased PND score was 3 (7.1%) in the hATTR-PN group and 1 (1.7%) in the CIAP group. These data may indicate a more rapid progression of neurological impairment in hATTR-PN patients.

Pre-selection of patients eligible for genetic testing for hATTR

Variables influencing disease prediction were included in a logistic regression model for assessment of the likelihood of hATTR-PN or CIAP diagnosis. To identify the factors that most contribute to the prediction of the diagnosis, the variables were scored according to their significance in the model (Table 4). Variables that were considered clinically insignificant (certain comorbidities and aspects of neurological examination, etc.) were excluded from the model. This model demonstrated a predictive accuracy of 94%, a sensitivity of 91%, and a specificity of 97% for the likelihood of hATTR-PN diagnosis. The AUC (area under the ROC curve displaying the trade-off between sensitivity and specificity) was 0.96. Based on these findings, we developed a screening tool that considers factors indicating the likelihood of hATTR-PN in a patient.

Discussion

Hereditary transthyretin amyloidosis with polyneuropathy is a rare disease. Timely diagnosis of hATTR-PN is challenging due to a great variability of clinical manifestations that can be mistaken for those of other neurological diseases.

In this non-interventional, observational, retrospective study with secondary data collection, we described the baseline (at diagnosis) electrophysiological, clinical, and demographic characteristics of hATTR-PN and CIAP patients in Russia. Additionally, the obtained data allowed us to develop a screening tool predicting the likelihood of hATTR-PN diagnosis. A hATTR-PN or CIAP diagnosis was documented in primary medical records.

No statistically significant differences for age and sex were observed between hATTR-PN and CIAP groups. Mean age at diagnosis was approximately 60 years in both groups. Results of routine genetic testing were available in medical records of 90% of hATTR-PN patients (38/42). Val30Met/Val50Met (p.Val50Met) mutation was detected in 53% cases, which corresponds to previously published data [1, 7].

The study revealed fundamental differences between hATTR-PN and CIAP patients, which are typical for the Russian population. Hereditary factors are known to be one of the red flags for suspected transthyretin amyloidosis. In this study, the proportion of patients with polyneuropathy of hereditary origin, as assessed by the physician, was significantly greater in the hATTR-PN group compared with the CIAP group (65% vs 8.9%). In the hATTR-PN group compared with the CIAP group, there was also a higher incidence of heart failure in close relatives (16.7% vs 3.4%) and progressive polyneuropathy in close relatives (52.4% vs 12.1%).

Patients with hATTR-PN more often exhibited gait disturbances (64.3% vs 37.9%), autonomic (47.6% vs 12.1%), cardiac (35.7% vs 10.3%), and gastrointestinal (64.3% vs 12.1%)

symptoms, unintentional weight loss (45.2% vs 12.1%), and heart failure with preserved ejection fraction (26.2% vs 6.9%) compared with CIAP patients. Intergroup differences in the history of CTS (this syndrome is often associated with early- or late-onset hATTR-PN due to local deposits of amyloid in the palmar carpal ligament) did not reach the level of statistical significance. However, in the hATTR-PN group, CTS incidence was higher than that in the CIAP group (19.0% vs 6.9%). These findings are also confirmed by results of a nerve conduction velocity (NCV) test for the median nerves, which showed a significant decrease in the M-wave amplitude at distal stimulation, and slowing of NCV in the forearms in hATTR-PN patients compared to CIAP patients (Table 3).

Patients with hATTR-PN had lower mean systolic and diastolic blood pressure values (approximately 10 mm Hg lower than in the CIAP group), suggesting that arterial hypotension may be considered an autonomic symptom of hATTR-PN. Further, hATTR-PN patients generally exhibited more severely impaired peripheral nerve conduction compared to CIAP patients.

In the study with similar design (n = 90) conducted in Italy by S. Tozza et al., hATTR-PN patients, compared with CIAP patients, more often presented with motor symptoms (86 vs 54%) and a CTS history (57% vs 24%) as polyneuropathy manifestations. Intergroup differences for gait disturbances did not reach statistical significance [16]. In another study conducted by J.K. Warendorf et al., hATTR-PN patients, compared with CIAP patients, more often had bilateral CTS (80.0% vs 23.9%), cardiac involvement (60.0% vs 2.2%), family history suggestive of hATTR (86.7% vs 12.0%), and autonomic symptoms (86.7% vs 51.1%) [17].

We identified the factors contributing to the likelihood of hATTR-PN diagnosis using a logistic regression model with predictive sensitivity of 91% and specificity of 97%. Based on the model, we developed a screening tool to pre-select patients with axonal polyneuropathy eligible for *TTR* gene sequencing. Modeling results demonstrate high levels of predictive accuracy, sensitivity, and specificity for this screening tool in assessing the likelihood of an hATTR-PN diagnosis, enabling the pre-selection of patients with axonal polyneuropathy for genetic testing.

The study presented in this article confirmed the variability of clinical manifestations of polyneuropathy in hATTR-PN patients [18], which makes the differential diagnosis of this disease quite challenging. At the same time, early diagnosis and timely treatment help slow down the progression of neurological and other signs of the disease, confirming the relevance of the comparative data obtained and the screening tool developed. Nowadays, all necessary methods for screening of hATTR patients are available in Russia — first of all, genetic testing. Therefore, timely referral of patients to specialized institutions is of key importance for early diagnosis, which is most effective in improving the disease course.

Strengths and limitations of the study. This study was conducted in the study sites focusing on the management of hATTR-PN patients, which allowed a comprehensive retrospective assessment of their clinical and electrophysiological characteristics. The study included a selected group (cohort) of hATTR-PN or CIAP patients according to the inclusion/non-inclusion criteria. The sample size was limited by the available number of patients diagnosed with hATTR-PN. The patients enrolled in the study were diagnosed with hATTR-PN or CIAP at a pre-specified time interval. This time limitation was essential to evaluate the patients' characteristics over the past several years (since 2017), as standard clinical practices and the required data may have significantly changed over time. In the non-interventional study design, all procedures that yielded results collected from primary medical records are to be the part of standard clinical practice. Hence, there were missing data in the statistical analyses due to their absence in the medical records, particularly for follow-up visits after diagnosis. At the same time, baseline data (at diagnosis) were almost complete. In an observational study, it is impossible to standardize procedures and management of patients, which naturally leads to heterogeneity in the data obtained from the study sites. However, given that the study sites underwent thorough selection for the purposes of this study, this limitation can be considered insignificant. To assess functional impairment in hATTR-PN and CIAP patients, we used INCAT scores originally developed for CIDP, which is another form of polyneuropathy. The Russian version of INCAT scale is developed and validated only for CIDP, not for hATTR-PN or CIAP. Taking into account that CIDP is the first to rule out in the hATTR-PN differential diagnosis, which reflects the similarity of their clinical symptom complexes, this choice of evaluation scale was considered appropriate. Moreover, it was important to evaluate functional impairment in both the lower and upper limbs, as the median nerve is more commonly affected in hATTR-PN patients, which was confirmed by intergroup differences: severity and disability were more pronounced in hATTR-PN patients than in CIAP patients.

Additionally, to minimize data heterogeneity, a standardized data collection form (eCRF) was created and introduced across all the study sites. Detailed instructions for data collection and assessment were also provided to all investigators.

Conclusion

In this study, we described demographic, clinical, and electrophysiological characteristics collected at diagnosis for hATTR-PN and CIAP patients in Russia. Patients with hATTR-PN more often exhibited autonomic, cardiac, and gastrointestinal symptoms, gait disturbances, unintentional weight loss, heart failure with preserved ejection fraction, and declined peripheral

nerve conduction. Based on the results of clinical and electrophysiological tests (screening data), we demonstrated high predictive accuracy, sensitivity and specificity of the screening tool for the likelihood of an hATTR-PN diagnosis in patients with axonal polyneuropathy. Based on the screening tool scores, the patients can be referred for genetic testing.

Reference medical institutions for transthyretin amyloid polyneuropathy:

1. Federal medical centers:
   1) Research Center of Neurology, Moscow;
   2) A.Ya. Kozhevnikov Clinic for Nervous Diseases, E.M. Tareev Clinic of Rheumatology, Nephrology and Occupational Diseases in I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow;
   3) The Loginov Moscow Clinical Scientific Center, Moscow;
   4) N.I. Pirogov National Medical and Surgical Center, Moscow;
   5) First Pavlov State Medical University of St. Petersburg, Saint Petersburg;
   6) S.M. Kirov Medical Military Academy, Saint Petersburg;
   7) I.I. Mechnikov North-Western State Medical University, Saint Petersburg;
   8) Almazov National Medical Research Centre, Saint Petersburg.

2. Regional centers:
   1) Northern State Medical University, Arkhangelsk;
   2) Alexander-Mariinsky Regional Clinical Hospital, Astrakhan;
   3) Profimed Ltd – Siberian Medical Center, Barnaul;
   4) Primorye Regional Clinical Hospital No. 1, Vladivostok;
   5) Volgograd Regional Clinical Hospital No. 1, Volgograd;
   6) Medical Center “Healthy Child”, Voronezh;
   7) Voronezh Regional Clinical Hospital No. 1, Voronezh;
   8) Grozny Clinical Hospital No. 4, Grozny;
   9) Sverdlovsk Regional Clinical Hospital No. 1, Ekaterinburg;
   10) Medical Association “New Hospital”, Ekaterinburg;
   11) First Regional Clinical Hospital, Izhevsk;
   12) Irkutsk Regional Clinical Hospital, winner of the “Mark of the Honor” award, Irkutsk;
   13) M.N. Sadykov City Clinical Hospital No.7, Kazan;
   14) Medical Center for Vascular diseases “Impuls-Angio”, Kazan;
   15) Republican Clinical Hospital, Kazan;
   16) Kaliningrad Regional Clinical Hospital, Kaliningrad;
   17) Kaluga Regional Clinical Hospital, Kaluga;
   18) S.V. Belyaev Kuzbass Regional Clinical Hospital, Kemerovo;
   19) Research Center of Cardiology and Neurology, Kirov;
   20) Prof. S.V. Ochapovsky Regional Clinical Hospital No. 1, Krasnodar;
   21) Regional Clinical Hospital No. 2, Krasnodar;
   22) Regional Clinical Hospital, Krasnoyarsk;
   23) Lipetsk Regional Clinical Hospital, Lipetsk;
   24) A.V. Vishnevsky Republican Clinical Hospital, Makhachkala;
   25) The Loginov Moscow Clinical Scientific Center, Moscow;
   26) M.F. Vladimirsky Moscow Regional Research Clinical Institute, Moscow;
   27) N.A. Semashko Regional Clinical Hospital, Nizhny Novgorod;
   28) State Novosibirsk Regional Clinical Hospital, Novosibirsk;
   29) EZRAMED Clinic Ltd, Omsk;
   30) Regional Clinical Hospital No. 2, Orenburg;
   31) Penza Institute for Advanced Medical Education – branch of the Russian Medical Academy of Continuing Professional Education, Penza;
   32) Perm Regional Clinical Hospital, Perm;
   33) Medical Center “Beauty and Health Philosophy”, Perm;
   34) Rostov State Medical University, Rostov-on-Don;
   35) Regional Consultative and Diagnostic Centre, Rostov-on-Don;
   36) Rostov Regional Clinical Hospital, Rostov-on-Don;
   37) V.D. Seredavin Regional Clinical Hospital, Samara;
   38) City Multidisciplinary Hospital No. 2, Saint Petersburg;
   39) V.I. Razumovsky Saratov State Medical University, Saratov;
   40) Stavropol Regional Clinical Hospital, Stavropol;
   41) Tula Regional Clinical Hospital, Tula;
   42) Regional Treatment and Rehabilitation Centre, Tyumen;
   43) Regional Clinical Hospital No. 1, Tyumen;
   44) Ulyanovsk Regional Clinical Hospital, Ulyanovsk;
   45) Republican Center of Medical Genetics, Ufa;
   46) G.G. Kuvatov Republican Clinical Hospital, Ufa;
   47) Psychology and Childhood Development Centre “Psylogia”, Khabarovsk;
   48) Regional Clinical Hospital, Khanty-Mansiysk;
   49) Chelyabinsk Regional Clinical Hospital, Chelyabinsk;
   50) City Clinical Hospital No. 1, Chelyabinsk;
   51) Clinical Hospital No. 2, Yaroslavl.

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