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Е.В. Резник*[1,2,3,4], Т.Л. Нгуен[1], С.В. Борисовская[1,2], Л.В. Брылев[2], А.В. Желнин[5], Н.Е. Сексяев[6]

[1] — ФГАОУ ВО РНИМУ им. Н.И. Пирогова МЗ РФ, Москва, Россия
[2] — ГБУЗ ГКБ им. В.М. Буянова ДЗМ, Москва, Россия
[3] — ГБУЗ ГКБ им. В.П. Демихова ДЗМ, Москва, Россия
[4] — ГБУЗ ГКБ № 31 ДЗМ, Москва, Россия
[5] — ФГБОУ ВО Пермский государственный медицинский университет имени ак. Е.А. Вагнера Минздрава России, Пермь, Россия
[6] — ГБУЗ ПК «Ордена «Знак Почёта» Пермская краевая клиническая больница, Пермь, Россия

КЛИНИЧЕСКИЙ СЛУЧАЙ НАСЛЕДСТВЕННОГО ТРАНСТИРЕТИНОВОГО АМИЛОИДОЗА

E.V. Reznik*[1,2,3,4], T.L. Nguyen[1], S.V. Borisovskaya[1,2], L.V. Brylev[2], A.V. Zhelnin[5], N.E. Seksyaev[6]

[1] — Russian National Research Medical University (RNRMU) n.a. N.I. Pirogov, Moscow, Russia
[2] — City Clinical Hospital n.a. V.M. Buyanov of Healthcare Department of Moscow, Moscow, Russia
[3] — City Clinical Hospital n.a. V.P. Demikhov of Healthcare Department of Moscow, Moscow, Russia
[4] — City Clinical Hospital № 31 of Healthcare Department of Moscow, Moscow, Russia
[5] — Perm State Medical University named after Academician E.A. Wagner Ministry of Health of Russia, Perm, Russia
[6] — Perm Regional Clinical Hospital, Perm, Russia

A Clinical Case of the Hereditary Transthyretin Amyloidosis

Резюме

Введение: транстиретиновый (ATTR) амилоидоз является тяжелым редким заболеванием с широким спектром неспецифических проявлений, в т.ч. поражением периферической нервной системы и сердца. Клинический случай: пациентку 60 лет в течение 2 лет беспокоили парестезии и слабость в дистальных отделах нижних конечностей, затрудняющая ходьбу. Первоначально симптомы рассматривались как проявление дегенеративного стеноза поясничного отдела позвоночника, выполнена декомпрессионная ламинэктомия, несмотря на которую симптоматика сохранялась. На основании данных клинического и электронейромиографического обследований, диагностирована аксональная сенсомоторная полиневропатия. При генетическом тестировании 4 членов семьи (пациентки, ее старшей сестры с сыном и дочерью) выявлен вариант нуклеотидной последовательности в четвертом экзоне гена транстиретина (*Chr18: 29178562, rs148538950, NM_000371.3:c. G368A:p. Arg123His*) в гетерозиготном состоянии. При исследовании нативных препаратов жировой клетчатки живота при окраске Конго красным и исследовании в поляризованном свете в единичных полях зрения выявлены микродепозиты амилоида, grade CR 1+ (минимальные отложения). При эхокардиографии выявлено утолщение стенок левого желудочка с нормальными конечнодиастолическим размером и объемом и сохраненной фракцией выброса, дилатацией левого предсердия, умеренной легочной гипертензией и диастолической дисфункцией типа 1. Пациентке рекомендовано начать специфическую антиамилоидную терапию — тафамидис. Заключение. У больных с поражением периферической нервной системы и утолщением стенок левого желудочка неясной этиологии необходимо комплексное обследование для своевременной диагностики и адекватной терапии амилоидной полинейропатии и кардиомиопатии.

Ключевые слова: *амилоидная кардиомиопатия, амилоидоз сердца, транстиретин, транстиретиновая семейная амилоидная полинейропатия, TTR-FAP, ATTR амилоидоз, ATTP-амилоидоз*

*Контакты: Елена Владимировна Резник, e-mail: elenaresnik@gmail.com
*Contacts: Elena V. Reznik, e-mail: elenaresnik@gmail.com
ORCID ID: https://orcid.org/0000-0001-7479-418X

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Abstract

Introduction: Transthyretin (ATTR) amyloidosis is a severe rare disease with wide range of characters without specific symptoms including the damage to the peripheral nervous system and cardiac involvement. Case report: A 60-year-old female patient represented with weakness and paresthesia in the distal parts of the lower limbs, impeding walking for 2 years. Initially, symptoms were considered as a manifestation of degenerative stenosis of the lumbar spine, decompressive laminectomy was performed but the symptoms after surgical treatment persisted. Based on data from clinical and electroneuromyographic examinations, axonal sensorimotor polyneuropathy was diagnosed. Genetic testing of the patient, her elder sister, son and daughter using the Sanger sequencing method detected a variant of the nucleotide sequence in the fourth exon of the transthyretin gene (*Chr18: 29178562, rs148538950, NM_000371.3: c.G368A: p. Arg123His*) in the heterozygous state. A subcutaneous fatty tissue biopsy of abdominal wall with a Congo red stain and polarized light examination revealed amyloid microdeposits, grade CR 1+ (minimal deposits), confirmed the diagnosis of familial ATTR-amyloidosis. Echocardiography revealed concentric left ventricular wall thickening with normal end diastolic size and volume, preserved ejection fraction, left atrial enlargement, pulmonary hypertension and type 1 diastolic dysfunction. Specific anti-amyloid therapy — tafamidis was prescribed. Conclusion: In patients with peripheral polyneuropathy and left ventricular hypertrophy of unknown etiology, a complex examination is necessary for the timely detection and treatment of amyloid polyneuropathy and cardiomyopathy.

Key words: *asymptomatic cardiomyopathy, cardiac amyloidosis, transthyretin, transthyretin familial amyloid polyneuropathy, TTR-FAP, ATTR amyloidosis*

Conflict of interests

The authors declare no conflict of interests

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ATTR — transthyretin amyloidosis, BP — blood pressure, ECG — electrocardiogram, EchoCG — echocardiography, GFR — glomerular filtration rate, CHF — chronic heart failure, CHFpEF — CHF with preserved LVEF, HR — heart rate, LV — left ventricle, LV EF — left ventricle ejection fraction, TAVI — transcatheter aortic valve replacement

Introduction

Amyloidoses are a group of diseases with the specific feature of extracellular deposition of a specific glycoprotein (amyloid) in tissues and organs [1]. Amyloid infiltration of tissues and organs can result in their enlargement, damage/death of their cells and impaired functioning [2].

For clinical purposes, local and systemic (generalized) types of amyloidosis can be identified. Local types of amyloidosis are characterized by the involvement of one organ. Systemic types are characterized by the involvement of many organs and systems [3].

Modern classification of amyloidosis is based on the principle of the specificity of the main fibrillar protein of amyloid (36 different types of amyloidosis are known today). In the name of an amyloid type, the first letter is the capital letter A, which stands for “amyloid”, followed by the designation of a specific amyloid fibrillar protein — A (amyloid A protein), L (immunoglobulin light chains), TTR (transthyretin), etc. [2, 4].

Transthyretin (TTR) is a carrier protein of thyroxine (T4) and complex retinol-binding protein/vitamin A. Transthyretin is a tetramer; it consists of four identical subunits. About 95% of transthyretin is produced in the liver. Less than 5% of transthyretin is synthesized in the vascular plexus of the brain and retinal pigment epithelium. Less than 1% of thyroxine in serum is transported by transthyretin protein (99% of thyroxin is transported by thyroxine-binding globulin and albumin). Most of circulating transthyretin is unconjugated [5–7].

ATTR amyloidosis is a type of amyloidosis with pathogenesis based on the destabilization (improper folding) of transthyretin tetramer and deposition of incorrectly folded transthyretin monomers in tissues [8]. ATTR amyloidosis includes familial (mutant, hereditary) amyloidosis, which is inherited in an autosomal dominant manner with incomplete penetrance, and systemic senile amyloidosis ("wild", i.e., its phenotype most frequently observed in the natural population; its signs are determined by "normal" (non-mutant) alleles; it is called "cardiac Alzheimer's disease") with no mutations in transthyretin gene [2].

"Wild" ATTR amyloidosis affects 20–30% of people aged 80+, which suggests the existence of age-related triggers of amyloidosis; it is often found in patients with chronic heart failure (CHF) with preserved left ventricular ejection fraction (LV EF — CHFpEF) and degenerative aortic stenosis [9].

Hereditary ATTR amyloidosis is the result of a mutation in the gene (located on 18q chromosome and consisting of 4 exons) that encodes transthyretin, which leads to the replacement of amino acids in its molecule [10]. Today, there are more than 140 different mutations in the transthyretin gene; most of them are amyloidogenic, and only about ten are not [10, 11]. Most patients are heterozygotes; therefore, they have not only mutant but also normal non-mutant transthyretin. The phenotype of ATTR amyloidosis can be predominantly neurological, or predominantly cardiological, or mixed. Val-30Met mutation is the most frequent cause of amyloid polyneuropathy; however, its late onset may be manifested by cardiomyopathy. The most common mutation in ATTR amyloidosis in the world is *Val122Ile*, with predominating cardiological symptoms; it is observed in 3–4% of African Americans with different clinical manifestations, 10% of African Americans aged 60+ develop CHF. Patients with *Thr60Ala* mutation have a mixed phenotype; it is found in 1% of the population of the North-West of Ireland [6, 12–15]. A. Ya. Gudkova et al. examined 257 patients with CHF in the North-West region of Russia, where a relatively high mutation rate (4.6%) in the transthyretin gene was detected [10]. Only half of the cases, specifically of ATTR-Val30Met amyloidosis, have a typical clinical picture [10].

For a long time, hereditary ATTR amyloidosis was considered an endemic disease (in Portugal, Japan, Sweden, Brazil), with a prevalence of 1/1,000. Over time, reports of ATTR amyloidosis began to come from many countries outside of the endemic areas [16]. The number of patients in the world is currently about 50,000 [17].

Damage to the nervous system in cases of ATTR amyloidosis is represented by symptoms of peripheral neuropathy and autonomic dysfunction [3]. Clinical signs of neuropathy are caused by the degeneration of the myelin sheath of nerves and the compression of the nerve trunks by amyloid deposits and ischemia as a result of amyloid deposits in the walls of blood vessels. In most cases, there is a symmetric distal neuropathy with steady progression. The debut of nervous system impairment includes mainly sensory disturbances, primarily pain and temperature sensitivity, later vibrational and positional sensitivity, then motor disorders. Trophic disorders are manifested by weight loss. The earliest symptoms of neuropathy are paresthesias or painful dysesthesias (numbness). Lower limbs are involved in the pathological process more often than upper limbs and often cause problems with walking [3]. Dysfunctions of the autonomic nervous system often manifest with orthostatic arterial hypotension, sometimes with fainting, diarrhea, impaired bladder function, impotence in men [3]. There may also be signs of damage to the central nervous system: progressive dementia, headache, ataxia, seizures, spastic paresis, stroke-like episodes [17].

Cardiac damage with ATTR amyloidosis starts with amyloid depositions in the myocardium, continuously progresses to CHF, and leads to a progressive decrease in LVEF and patient death [7, 18]. Cardiac amyloidosis can cause various rhythm and conduction disturbances: atrial fibrillation, supraventricular tachycardia, ventricular pre-excitation syndrome, heart blocks, and sinus node weakness syndrome [19]. Amyloid can deposit on heart valves and lead to regurgitation or valve stenosis. The highest prevalence of amyloid was found in patients with aortic valve stenosis (74%); less often, amyloid was found in cases of mitral stenosis and insufficiency (28.6 and 29.2%, respectively), even less often — with aortic regurgitation (10.5%) [20].

Renal damage is also observed in patients with hereditary ATTR amyloidosis [3]. Amyloid nephropathy usually has clinical manifestations of isolated proteinuria and is characterized by a steadily progressive course with successively changing stages: proteinuric, nephrotic, chronic renal failure. Nephrotic syndrome and large kidneys persist even with the development and progression of renal failure. In the cases of nephrotic syndrome, antithrombin III deficiency is often observed along with the increased risk of thrombosis [3].

Damage to the gastrointestinal tract is often associated with amyloidosis; it can be manifested by nausea, vomiting, early satiety, diarrhea, constipation, alternating diarrhea and constipation, inadvertent weight loss due to secondary malabsorption. The following can be possible causes of diarrhea: 1) amyloid infiltration of the intestinal wall, including villi, and 2) intestinal autonomic plexus dysfunction [3].

A rare manifestation of amyloidosis described for ATTR types is eye damage (opacification of the vitreous body that leads to a gradual loss of vision; obstruction of the lacrimal canal that can lead to chronic open-angle glaucoma, conjunctival vascular anomalies, pupil abnormalities) [3].

Urogenital disorders are rare but can develop with ATTR-amyloidosis and manifest in men in the form of erectile dysfunction [3].

Since hereditary and "wild" ATTR amyloidosis are considered rare and usually manifest with heterogeneous symptoms similar to those of other more common diseases, their diagnosis presents a challenge. The primary sign of amyloidosis on the ECG is low QRS voltage (<0.5 mV in limb leads and/or <1.0 mV in precordial leads) [21]. A combination of low voltage on the ECG and echocardiographic signs of a large mass of myocardium is considered a typical diagnostic sign. It is believed that there is a true myocardial hypertrophic response to transthyretin infiltration that is not observed in AL amyloidosis (LV hypertrophy only due to amyloid deposition — pseudohypertrophy) [18]. QS complex, at least, in two chest leads without specific changes in repolarization ("pseudo-infarction pattern") can be observed in some patients [3]; T inversion or ST segment depression in lateral chest leads is rare but is sometimes recorded. HM ECG can help detect episodes of ventricular and supraventricular arrhythmias in many asymptomatic patients. Another sign is a decrease or absence of heart rhythm variability, which indicates autonomic nervous dysfunction [21].

Echocardiography (EchoCG) is considered the best method for detecting signs of amyloid cardiomyopathy; it can be used to diagnose symmetrical thickening of ventricular walls (>12 mm) with no reason for LV hypertrophy, especially thickening of the free wall of RV, normal LV size in diastole, increased size in systole. LV wall thickness >15 mm is rare in hypertensive disease. Therefore, if patients have thickened ventricular walls for no apparent reason, or severe LV hypertrophy, even with AH, a mismatch between increased LV mass and low QRS voltage on ECG should raise suspicion of cardiac amyloidosis. Echocardiography also reveals atrial dilatation, thickening of valves with blood regurgitation, effusion in the pericardial cavity, signs of diastolic myocardial dysfunction (the most typical restrictive type of diastolic dysfunction with E/A ratio of more than 2), diffuse or local LV hypokinesis [22]. Myocardial granularity or luminescence is quite common (26%) but may not be constant in the same patient; LV EF is often within normal, but it can significantly decrease in the terminal stage of the disease [3, 22]. ECG and EchoCG parameters independently have low sensitivity and specificity, which raises the question of the combination of various parameters of these methods for the diagnosis of cardiac amyloidosis. Caroll J. D et al. suggested using the ratio of the voltage sum to the cross-sectional area of the heart as a criterion for screening amyloid cardiomyopathy, which enabled the diagnosis of amyloid cardiomyopathy with a higher probability. This ratio also correlates well with clinical symptoms and death outcomes. [23]. Reference values of this parameter are to be determined.

Scintigraphy, single-photon emission computed tomography (99mTc pyrophosphate, 3,3-diphosphono-1,2-propane dicarboxylic acid (DPD) and hydroxymethylene diphosphonate — HMDP) are non-invasive methods with very high specificity (>99%) and sufficient sensitivity (86%); they can be used to diagnose ATTR amyloidosis and eliminate the need for endomyocardial biopsy [5, 24, 25].

Genetic testing in patients with clinical symptoms and family history is enough to diagnose ATTR-amyloidosis. Precise identification of the mutation via genetic testing helps to assess the prognosis and effectiveness of treatment [24, 26]. A biopsy with immunohistochemistry test with anti-transthyretin antibodies may also be used to confirm the diagnosis.

In cases of amyloidosis, there may be an increase in the levels of troponin T/I and N-terminal pro-brain natriuretic peptide (NT-proBNP); they are not specific, but the degree of increase correlates with the severity of cardiac amyloidosis [3].

Cardiac ATTR amyloidosis is often not diagnosed or is misdiagnosed as hypertrophic CMP, or CHFpEF with unknown etiology. The true prevalence of cardiac ATTR amyloidosis is unclear and probably higher than previously thought. Some recent studies demonstrate a higher prevalence: in 13% of patients with CHFpEF, a "wild" type of ATTR amyloidosis was confirmed [27], in 5% of patients with hypertrophic cardiomyopathy — a mutant type of ATTR amyloidosis [28]. Among 101 patients aged 86 ± 5 years (43% male subjects) with severe symptomatic aortic stenosis who underwent transcatheter aortic valve replacement (TAVI), 13.9% had ATTR amyloidosis [29]. According to Castano A. et al., 16% of patients undergoing TAVI (151 patients, 84 ± 6 years) had ATTR amyloidosis [30]. The figure was 6% in patients aged 65+ with aortic stenosis who underwent surgical replacement of the aortic valve [31].

Colleagues from Heart Failure Bridge Clinic (J. Hopkins Clinic) proposed and implemented screening criteria for cardiac amyloidosis in patients with CHF, as well as its diagnostic algorithm:

1. Age 50+ years
2. Thickness of interventricular septum (T_{IVS}) ≥1.2 cm
3. BMI ≤30 kg/m^2
4. Low voltage on ECG
5. Central or peripheral neuropathy, carpal tunnel syndrome

If a patient has ≥2 of these criteria, the diagnostic procedure should be started in order to exclude/confirm cardiac amyloidosis (**Fig. 1**) [32].

For timely diagnosis of ATTR amyloidosis in patients with peripheral polyneuropathy, it is recommended to use the algorithm shown in Figure 2.

The average life expectancy after the onset of the clinical symptoms of ATTR amyloidosis is 6–12 years; the common cause of death is heart damage. Hereditary ATTR amyloidosis was previously considered an incurable disease. In the 1990s, liver transplantation was used for the management of ATTR amyloidosis; then, stabilizers of transthyretin tetramers (diflunisal, tafamidis) were introduced into clinical practice; agents affecting mRNA (patisiran, inocerten) have recently been studied. In this regard, early diagnosis and timely initiation of therapy become extremely relevant in the cases of ATTR amyloidosis.

Here is a description of a patient with hereditary ATTR amyloidosis that debuted in the form of peripheral polyneuropathy with subsequent asymptomatic heart damage.

Patient N., female, a resident of Perm Krai, felt paresthesias from the age of 58; within two years, weakness in the distal parts of lower extremities increased, making walking difficult**.** Past diseases included just childhood infections. She denied having arterial hypertension, diabetes mellitus, acute cerebrovascular accident, history of acute myocardial infarction, smoking, alcohol abuse, and allergic reactions. There were no signs of autonomic dysfunction. Height 168 cm, weight 90 kg, stable over the past 5 years. The symptoms were initially considered a manifestation of degenerative stenosis of the lumbar

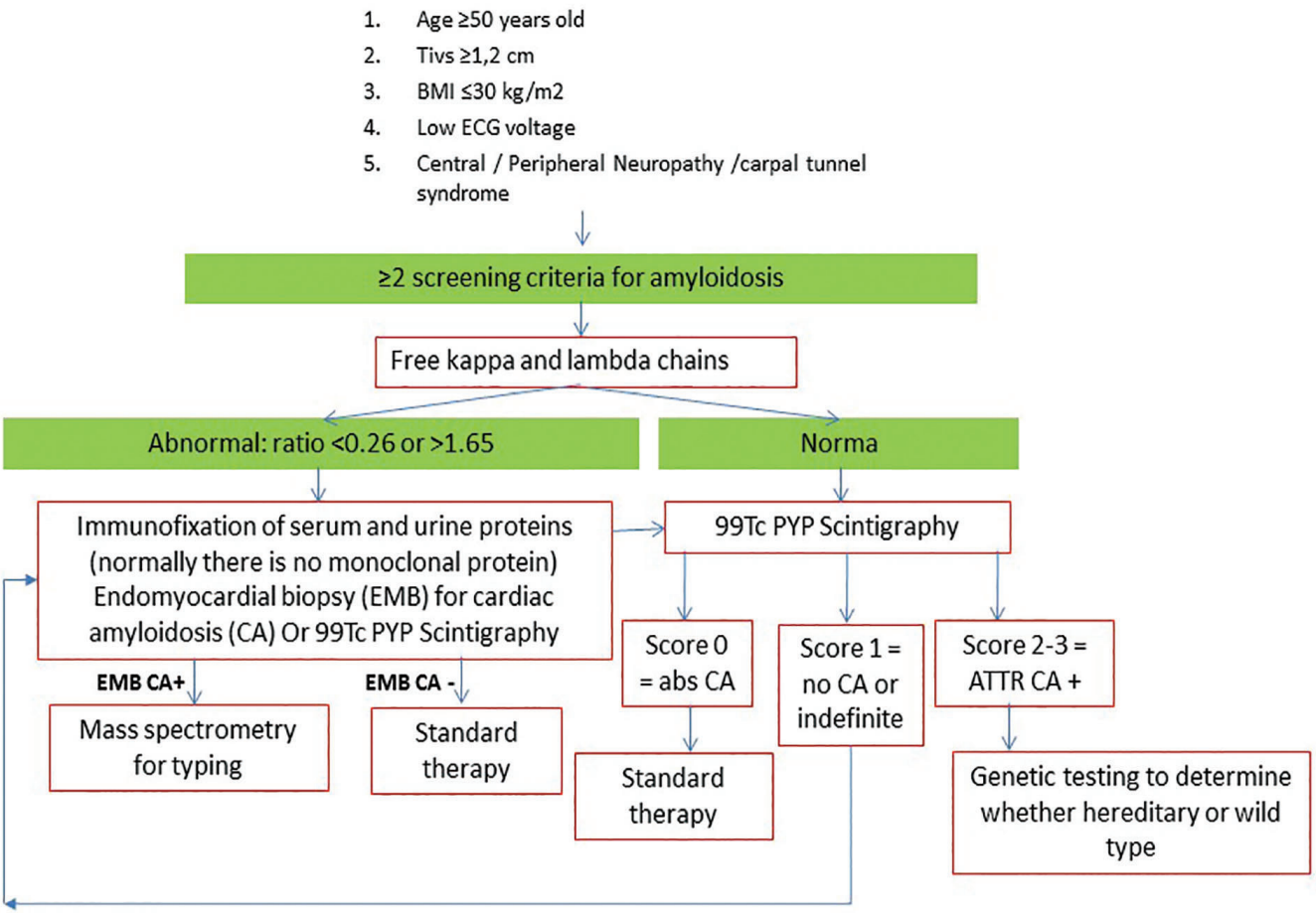

Figure 1. *Algorithm for the diagnosis of heart amyloidosis in CHFsPV*

CHFsFV — chronic heart failure with preserved ejection fraction; CA EMB: endomyocardial biopsy for cardiac amyloidosis; 99mTc-PYP- 99mtechnetium pyrophosphate [Fajardo J, Cummings A, Brown E, et al. (2019) Clinical pathway to screen for cardiac amyloidosis in heart failure with preserved ejection fraction. Amyloid 26:166–167. doi: 10.1080/13506129.2019.1583178]

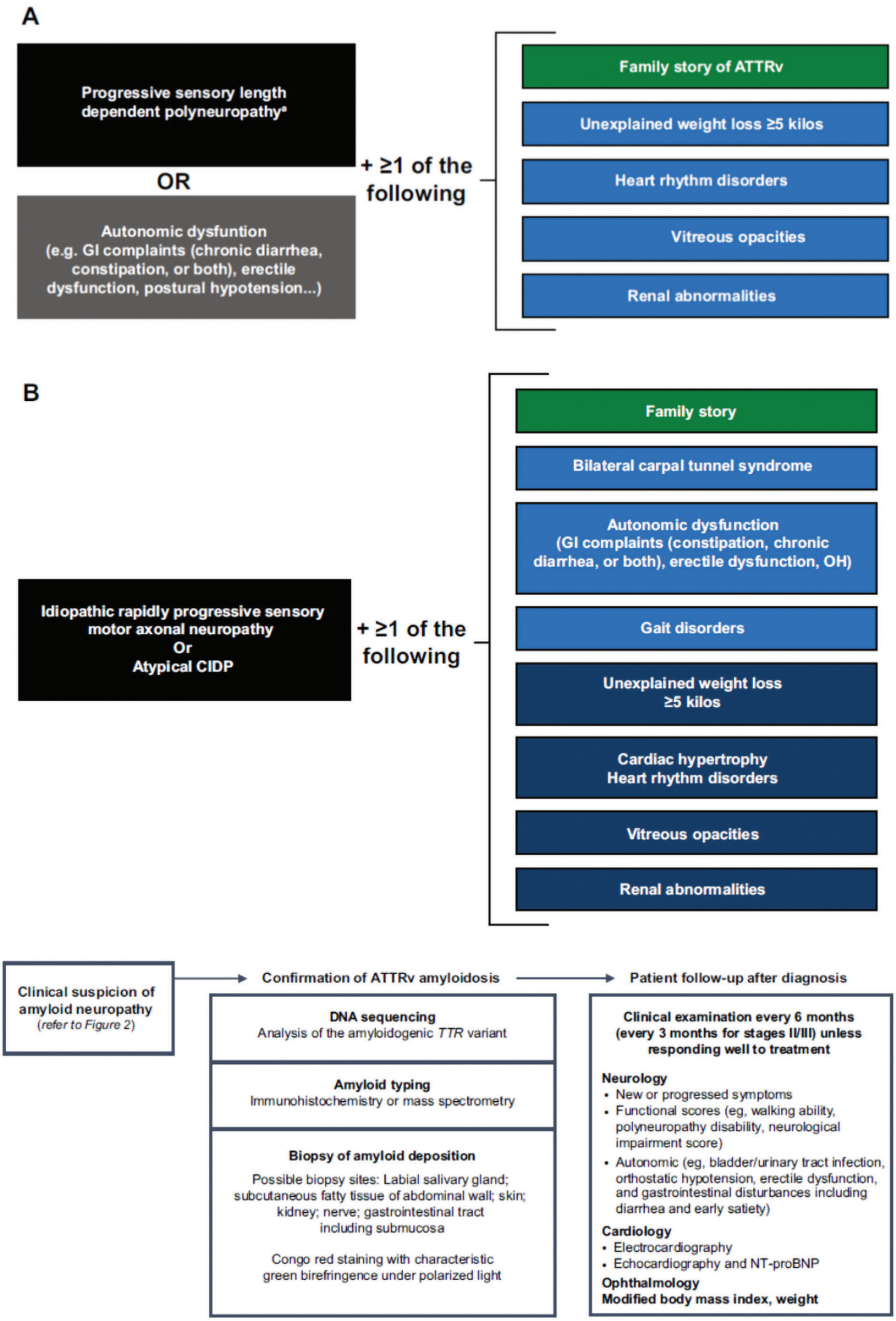

Figure 2. *Suspicion index for diagnosis of ATTRv amyloidosis with PN*

A — in endemic areas, B — in nonendemic areas. ATTRv hereditary transthyretin amyloid amyloidosis, CIDP chronic inflammatory demyelinating polyneuropathy, GI gastrointestinal, OH orthostatic hypotension. aNo diabetes, no alcohol abuse, vitamin B12 deficiency [15, 33]

spine; decompression laminectomy was performed. As symptoms remained after surgical treatment, the patient was referred to the Regional Neurological Center. Neurological status demonstrated signs of lower peripheral, predominantly distal, paraparesis (gait disturbance of "steppage" type — from French "steppage" — trotting, peroneal gait, atrophic changes, decreased tonus and muscle strength to 4 points in the proximal and to 3 points in the distal muscles of lower extremities), sensitive disorders of polyneural type (symmetrical superficial and deep hypesthesia in the distal parts of lower extremities, inhibition of deep reflexes, severe atactic syndrome with a sensitive component). Based on the clinical data and electroneuromyographic examination results, the diagnosis of axonal sensorimotor polyneuropathy was established.

Genetic testing was conducted in the patient and then her relatives to exclude the amyloid etiology of polyneuropathy. **Genetic testing** in the patient, her elder sister, son and daughter using the Sanger sequencing method revealed the nucleotide sequence variant in the fourth exon of the transthyretin gene in the deoxyribonucleic acid test sample (*Chr18: 29178562, rs148538950, NM_000371.3:c.G368A:p. Arg123His*) in heterozygous state (**Fig. 3**).

Histological results: Biopsy specimens from different parts of the gastrointestinal tract stained with red Congo and examined in polarized light revealed no amyloid deposits. Biopsy specimens of abdominal subcutaneous adipose tissue stained with red Congo and examined in polarized light revealed amyloid microdeposits, CR 1+.

ECG (**Fig. 4**) showed sinus rhythm, heart rate (HR) of 68 beats per minute, normal position of QRS axis and normal voltage of QRS complex (above 5 mm in leads from extremities and above 10 mm in precardial leads), abnormal Q wave in lead III lasting for 40 ms, amplitude 0.3 mV = ½ R.

Holter ECG monitoring revealed sinus rhythm with frequency; average heart rate of 79 beats/min during daytime, 67 beats/min at night and 75 beats/min for the whole measurement period; maximum heart rate of 145 beats/min, minimum — 51 beats/min; 8 ventricular extrasystoles, 10 supraventricular extrasystoles, including 3 of bigeminia type, 1 paired, 1 run of supraventricular tachycardia of 3 complexes. No pauses registered. During the monitoring, painless episodes of horizontal and oblique ST segment depression were registered, up to –0.12 mV lasting for 78 seconds, during daytime.

Daily monitoring of blood pressure (BP): Mean systolic BP 115 and 112 mm Hg, mean diastolic BP 75 and 73 mm Hg in daytime and at night, respectively; degree of night decrease in systolic blood pressure is 2%, in diastolic blood pressure — 3% (non-dipper).

Complete blood count: Hemoglobin concentration 127 g/l, red blood cell count 4.45×10^{12}/l, platelet count 303×10^{9}/l, WBC 6.7×10^{9}/l, erythrocyte sedimentation rate 12 mm/h.

Biochemical blood test: Aspartate aminotransferase — 21 IU/l (5~34), alanine aminotransferase — 16 IU/l (0~32), total creatine phosphokinase — 138 IU/l (21~215), its MV fraction — 14.30 IU/l (0,00~25.00), total lactate dehydrogenase — 613 IU/l (225~450), gamma glutamyl transpeptidase — 20 IU/l (9~39), alkaline phosphatase — 148 IU/l (64~306), alpha-amylase — 76 IU/l (0~220), total protein — 67 g/l (65~85), albumin — 42 g/l (35~55), albumin — 61.34% (54.40~69.66), alpha 1-globulin — 3.20% (2.63~5.03), alpha 2-globulin — 6.44% (4.87~10.48), beta 1-globulin — 7.08% (5,35~9.19), beta 2-globulin — 6.37% (2.38~7.11), gamma-globulin — 15.57% (9.69~18.90), uric acid — 332 mmol/l (184~464), urea — 4.80 mmol/l (2.50~8.33), creatinine — 58 μmol/l (53~88), iron — 21.5 μmol/l (9.0~30.4), OZHSS — 51.5 μmol/l (44.7~80.6), sodium — 141.0 mmol/l (130.5~156.6), potassium — 4.30 mmol/l (3.44~5.30),

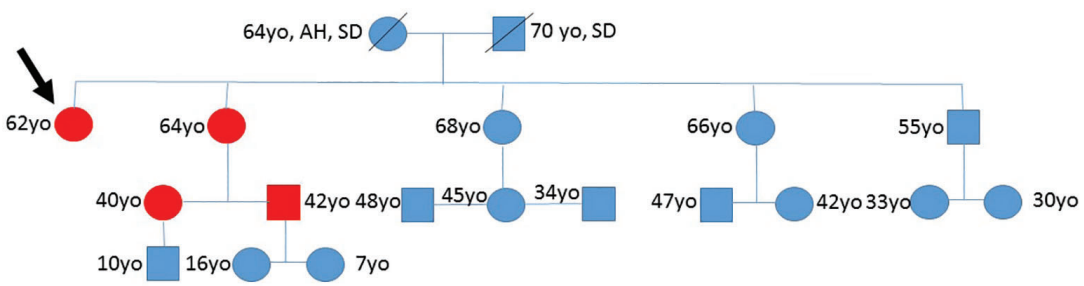

Figure 3. *Pedigree of the patient. Women are indicated by a circle, men by a square. Family members with an identified mutation are shown in red, and unexamined family members are shown in blue (examination is planned). The numbers indicate the age. AH — a history of arterial hypertension, SD — sudden death, yo — years old*

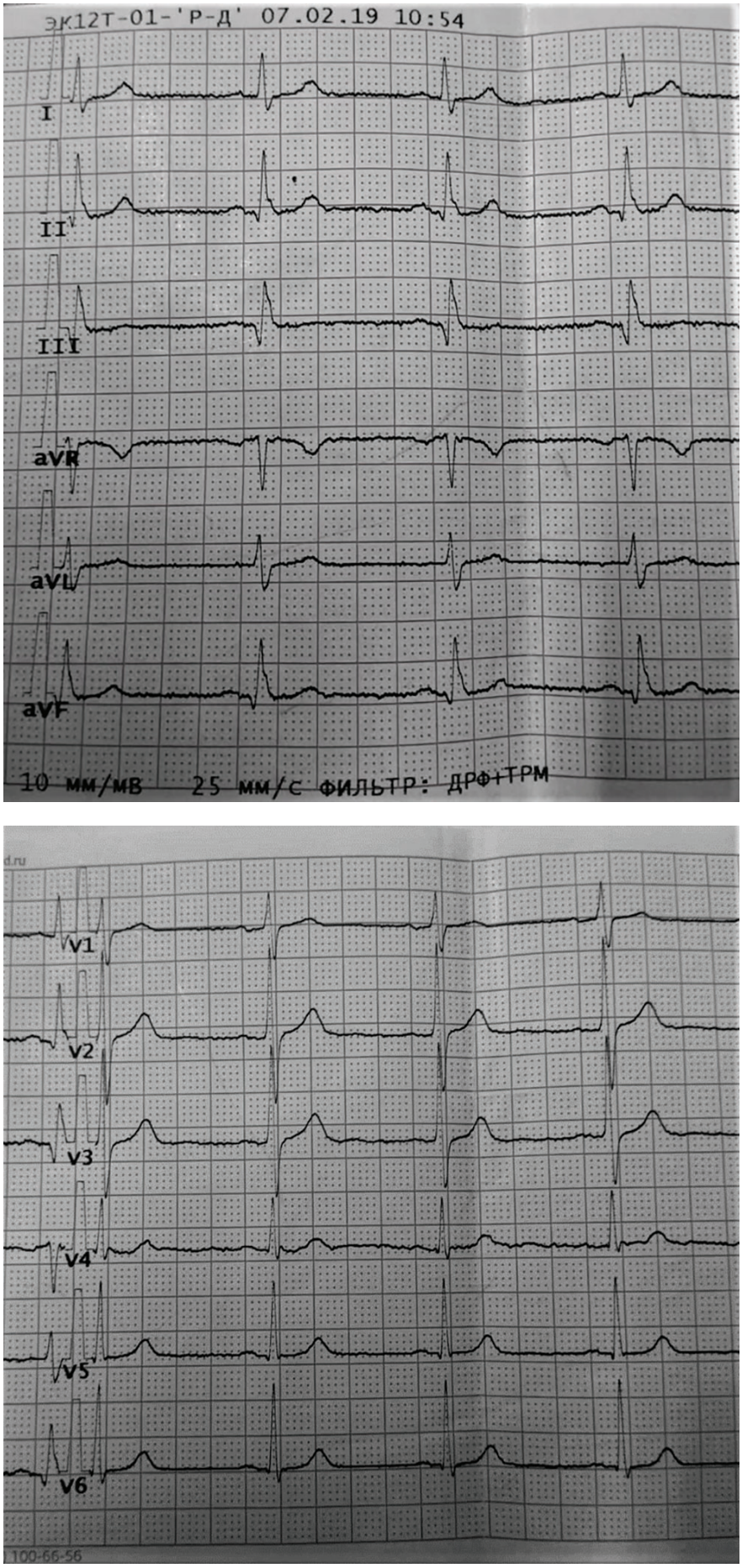

Figure 4. *Patient's Electrocardiogram*

calcium — 2.04 mmol/l (1.90~2.75), chlorides — 107 mmol/l (95~110), phosphorus — 1.20 mmol/l (0,78~1.65), total bilirubin — 9.0 μmol/l (1.7~20.5), direct bilirubin — 2.00 μmol/l (0.86~5.00), c-reactive protein — 0.9 mg/l (0.1~7.0), d-dimer — 152.0 ng/ml (64.0~550.0), fibrinogen — 2.26 g/l (1.80~3.50), prothrombin according to Quick — 103.50% (70.00~130.00), international normalized ratio — 0.980 (0.850~1.150), thrombin time — 20.8 sec (14.0~21.0), activated partial thromboplastin time — 31.20 sec (26.00~36.00).

Estimated glomerular filtration rate (GFR, CKD-EPI) was 96.2 ml/min/1.73 m^2.

Clinical urine test results are within normal.

Ultrasound examination of abdomen and retroperitoneal space: diffuse changes in enlarged liver (craniocaudal size of left lobe 120 mm, its thickness — 74 mm, vertical oblique size of right lobe — 172 mm, its thickness — 130 mm), pancreas, calculi (up to 6 mm) in gallbladder; spleen is not enlarged, 96 × 40 mm; diffuse changes in the parenchyma of both kidneys, cyst of the renal sinus of left kidney; hypoechoic (8 × 5 mm) lesion of the right lower parathyroid gland; diffuse changes in thyroid gland; enlarged cervical lymph nodes on both sides up to 13 mm, with reduced echogenicity, with a thickness of cortical layer 1 mm, with no signs of hypervascularization during color Doppler mapping.

Despite the fact that the patient had no history of AH and there were no reasons for overloading heart chambers with volume and/or pressure, **echocardiography** showed left ventricular concentric hypertrophy with interventricular septum thickness of 13.8 mm, posterior wall of 13.8 mm, preserved ejection fraction (55%), left atrial dilatation (35 ml/m^2), pulmonary hypertension (systolic pressure in pulmonary artery 38 mm Hg) and diastolic dysfunction of type 1 (E/A in transmissible flow = 0.76), mitral regurgitation grade 2, tricuspid regurgitation grade 2, pulmonary regurgitation grade 1.

The patient was prescribed specific anti-amyloid therapy with tafamidis.

Discussion

In this clinical case, the disease onset was with neurological symptoms. The diagnosis was clinically suspected and confirmed by molecular genetic analysis of the transthyretin gene, which revealed c.G368A:p.Arg123His mutation, and by amyloid biopsy samples of abdominal subcutaneous adipose tissue. A similar mutation was detected in the sister and two nephews of the patient. This revealed an autosomal dominant type of inheritance. The father and mother of the patient died at 70 and 64 years, respectively. In connection with living in a rural area of one of the regions of the Russian Federation, no intravital examination of parents was carried out; there are no accurate autopsy data on diseases and causes of death. It is recommended to examine two more sisters and a brother of the patient for timely diagnosis of possible amyloidosis and the beginning of treatment.

Cardiac amyloidosis should be diagnosed both with the detection of amyloid infiltration by endomyocardial biopsy and with a thickening of the left ventricular wall >12 mm in the absence of AH or other reasons for left ventricular hypertrophy if amyloid extracardiac localization is detected [2]. Cardiological examination of the described patient revealed thickening of LV myocardium wall, single ventricular and supraventricular extrasystoles, including these of bigeminia type, paired, run of supraventricular tachycardia, painless episodes of ST segment depression. Unfortunately, no cardiac magnetic resonance imaging and DPD scintigraphy were performed for technical reasons. It is recommended to carry out these procedures in the future, with an assessment of the parameters during therapy. This requires the widespread implementation of these examination methods throughout the Russian Federation and the inclusion of these methods in state guarantee programs for patients with amyloidosis. Nonetheless, even the available data are sufficient to diagnose cardiac amyloidosis in the presented patient.

Hereditary ATTR amyloidosis is one of the most serious hereditary polyneuropathies with onset in adulthood and a progressive course. In non-endemic areas, the diagnosis is usually established within 3-4 years. In our patient, about two years passed from the onset of clinical manifestations to the diagnosis.

The c.G368A:p.Arg123His mutation found is extremely rare. There were no patients with this mutation in the THAOS registry of patients with ATTR amyloidosis [6, 14, 33]. This mutation was detected in one out of 298 patients with thickening of LV myocardium in France, but there was no evidence of amyloid deposition in biopsy specimens of salivary glands, nerves and kidneys, and scintigraphy, and the patient refused endomyocardial biopsy [28]. This was the first description of the mutation in this patient described by us (http://amyloidosismutations.com). Prior to this, another amyloidogenic mutation in the given position of transthyretin was described — c.Arg123Ser [34].

Conclusion

A case of transthyretin-related familial amyloid polyneuropathy and cardiac amyloidosis associated with a rare c.G368A:p.Arg123His mutation was presented. For the timely diagnosis and adequate management of

this disease, a kind of "amyloid alertness" is required. Implementation of modern approaches to the diagnosis and management of amyloidosis will improve the quality and increase the life expectancy of patients with this disease.

Вклад авторов:

Все авторы внесли существенный вклад в подготовку работы, прочли и одобрили финальную версию статьи перед публикацией

Резник Е.В. (ORCID http://orcid.org/0000-0001-7479-418X): описание клинического случая, обзор литературы, идея, организация работы

Нгуен Т.Л. (ORCID http://orcid.org/0000-0002-8856-4542): подготовка материалов для описание клинического случая, обзор литературы, идея, организация работы

Борисовская С.В. (ORCID https://orcid.org/0000-0007-9365-1472): ведение больной, предоставление материалов обследований

Брылев Л.В. (ORCID https://orcid.org/0000-0003-2314-6523): ведение больной, предоставление материалов обследований, описание неврологического статуса

Желнин А.В. (ORCID https://orcid.org/0000-0003-1436-6145): ведение больной, предоставление материалов обследований, описание неврологического статуса

Сексяев Н.Е. (ORCID https://orcid.org/:0000-0001-5088-2855): ведение больной, предоставление материалов обследований, описание неврологического статуса

Author Contribution:

All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

Reznik E.V. (ORCID http://orcid.org/0000-0001-7479-418X): case description, literature review, idea, work organization

Nguen T.L. (ORCID http://orcid.org/0000-0002-8856-4542): case description, literature review

Borisovskaya S.V. (ORCID https://orcid.org/0000-0007-9365-1472): patient management, provision of examination materials

Brilev L.V. (ORCID https://orcid.org/0000-0003-2314-6523): patient management, provision of examination materials, neurological part of case description

Zhelnin A.V. (ORCID https://orcid.org/0000-0003-1436-6145): patient management, provision of examination materials, neurological part of case description

Seksyaev N.E. (ORCID https://orcid.org/:0000-0001-5088-2855): patient management, provision of examination materials, neurological part of case description

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