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Phenotype variability and therapeutic response to Patisiran in patients with hereditary transthyretin amyloidosis: a Belgian real-world experience

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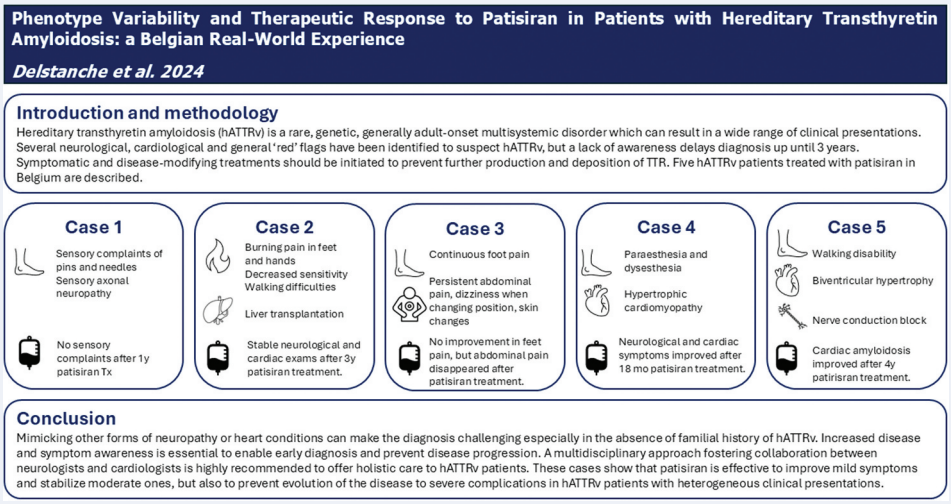
ABSTRACT

Introduction: Hereditary transthyretin amyloidosis (hATTRv) is a rare, genetic, adult-onset, multisystemic disorder which can affect diverse organs, including peripheral nerves, heart, kidneys, gastrointestinal tract, liver, skin and eyes. Currently, several disease-modifying treatments for hATTRv are available in Belgium including the TTR stabilizer tafamidis and TTR mRNA silencers patisiran and vutrisiran. Patisiran contains a small interfering RNA encapsulated into a lipid nanoparticle to deliver to hepatocytes, the main source of TTR protein production, thereby reducing TTR production.

Methods: We report and discuss five cases of hATTRv in different clinical scenarios that were successfully managed with patisiran, highlighting our real-world clinical practice.

Results: These cases illustrate that patisiran is effective to improve mild symptoms and stabilize the moderate ones. The cases also highlight the importance of red flags recognition to allow early diagnosis and treatment to prevent further disease progression.

Conclusion: Due to the multisystemic nature of the disease and its heterogeneous clinical presentation, close collaboration between neurologists and cardiologists is highly recommended, ideally within a multidisciplinary amyloidosis team, to provide holistic care in hATTRv patients.



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Introduction

Hereditary transthyretin amyloidosis (hATTRv) is a rare, genetic, generally adult-onset, multisystemic disorder which can affect the peripheral nerves, heart, kidneys, gastrointestinal tract, liver, skin, and eyes [1,2]. hATTRv is caused by pathogenic variants in the transthyretin (*TTR*) gene resulting in misfolded TTR protein aggregates accumulating as insoluble amyloid fibrils in multiple organs, ultimately disrupting normal tissue structure and function [3].

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

hATTRv can result in a wide range of clinical presentations differing in age at onset, organ involvement, and disease severity, depending on the underlying pathogenic *TTR* variant [4]. The clinical presentation can be predominantly cardiac (32%), predominantly neurologic (39%) or a mixed phenotype (25%) [5]. In the presence of a predominantly cardiac variant (e.g. V142I), patients will first present with an infiltrative cardiomyopathy (hATTRv-CM) (leading to ventricular hypertrophy, heart failure, arrhythmia, and conduction blocks), usually with various levels of length-dependent axonal sensory-motor polyneuropathy (hATTRv-PN), initially affecting the small fibres. In terms of symptomatology of familial amyloidotic polyneuropathy (FAP), four (0-III) Coutinho stages of hATTRv are distinguished [6]. Patients with stage 0 disease are asymptomatic, patients with stage I (mild) disease are ambulatory, patients with stage II (moderate) disease are ambulatory but require assistance and/or have involvement of the upper limbs, and patients with stage III (severe) disease are wheelchair-bound or bedridden [7]. In a predominantly neurological variant, the length-dependent axonal sensory-motor polyneuropathy usually precedes the development of a cardiomyopathy, depending also on the age of onset. Autonomic dysfunction is highly prevalent in patients with hATTRv-PN leading to orthostatic hypotension, recurrent urinary tract infections, constipation, sexual dysfunction and sweating abnormalities [4]. As ATTR can accumulate in many diverse organs, clinicians should be aware and also investigate for ocular involvement, nephropathy and gastrointestinal manifestations [4,8,9]. The progressive morbidity of hATTRv leads to functional disability, reduced quality of life, and increased mortality [10].

Several neurological, cardiological and general 'red flags' have been identified to suspect hATTRv. hATTRv diagnosis is confirmed following a genetic test identifying a heterozygous *TTR* gene variant [2,11]. Nevertheless, due to a lack of awareness and the challenge of identifying hATTRv, the diagnostic delay can exceed 3 years due to a negative family history, heterogeneity in presentation at onset and more complex differential diagnosis in cases mimicking other forms of neuropathy (e.g. chronic inflammatory demyelinating polyneuropathy) or other heart conditions (e.g. atrial fibrillation and aortic stenosis) [12,13].

At diagnosis, symptomatic therapy and disease-modifying treatments should be initiated to prevent further production and deposition of TTR. Currently, the disease-modifying treatment tafamidis (TTR stabilizer; FAP stage I); patisiran and vutrisiran (both TTR mRNA silencers; FAP stage I-II) are available in Belgium for symptomatic patients. Several other disease-modifying treatments are under development including other TTR stabilizers, TTR mRNA silencers, TTR fibril disruptors, inhibitors of TTR fibril seeding and gene therapy [2,14,15]. Orthotopic liver transplantation (OLT) is currently no longer used as a first-line approach, due to the emergence of drugs, the lack of organs and the absence of absolute disease control with high morbidity [16].

Patisiran contains a small interfering RNA (RNAi) encapsulated into a lipid nanoparticle to deliver to hepatocytes, the primary source of TTR protein production, resulting in a reduction of TTR protein (wild type as well as mutated) in the serum leading to a reduction of amyloid deposits. In the APOLLO study, hATTRv-PN patients showed significant improvement in polyneuropathy scores and quality of life at 18 months [17–19]. The APOLLO-B study showed preserved functional capacity in patients with hATTRv cardiac amyloidosis after administration of patisiran over a period of 12 months [20].

In this publication, we describe five hATTRv patients treated with patisiran in Belgian Neuromuscular Reference Centres (NMRC). All patients gave written informed consent to the publication of their clinical data in anonymous form for scientific and educational purposes.

Case presentations

Case 1: hATTRv patient with slowly progressing mild sensory polyneuropathy

A 52-year-old Caucasian man of Belgian descent presented in December 2016 with sensory complaints of pins and needles in both feet symmetrically. He had no decrease in muscle strength or balance problems. He had a stable weight, and no genito-urinary, gastrointestinal, sweating, visual or cardiovascular complaints. He denied alcohol abuse, took no drugs, and suffered from no other diseases. Clinical examination showed decrease in pinprick and temperature testing in both forefeet and soles. Vibration sense, position sense, reflexes, and trophism were normal and he had no foot deformities. Electroneuromyography (EMG) was normal, and blood tests did not identify a cause for neuropathy. His father had been diagnosed prior with hATTRv-PN (c.148 G>A (p.Val50Met) in *TTR*), with severe axonal neuropathy (FAP stage II rapidly evolving to stage III) and undefined cardiac rhythm- and conduction disturbances. Genetic testing confirmed the familial *TTR* pathogenic variant in the patient. Cardiac exams were normal. The patient did not fulfil Belgian reimbursement criteria for tafamidis (no EMG abnormalities) and refused symptomatic neuropathic pain treatment.

In 2018–2019, more severe and proximal tingling in the feet, combined with intermittent tingling in the fingers arose. There were no signs of autonomic or motor nerve dysfunction. EMG revealed a symmetric sensory axonal neuropathy with moderate (sural nerves) to mild (median and ulnar nerves) sensory

nerve action potential (SNAP) amplitude reduction. The transthoracic echocardiogram (TTE) remained normal, and a ^{99m}Tc-MDP-bone scan identified no sign of amyloid deposition in the myocardial tissue. The patient met the patisiran reimbursement criteria, which was initiated in February 2020.

One year later, he had no sensory complaints in the hands and the complaints in the feet had improved in severity with a reduced area of skin sensory abnormality. Nerve Conduction Velocity studies (NCV) showed normal SNAP amplitude in the hand, and mildly reduced SNAP amplitudes over both sural nerves, with normal motor nerve conduction studies and electromyography. Since then, he continued patisiran treatment and remains stable at the neurological, cardiologic, nephrological and ophthalmologic level.

Case 1: Discussion

A patient with the p.Val50Met *TTR* mutation with a familial history of hATTRv presented with symptoms of small fibre neuropathy. Two years later he developed a sensory polyneuropathy, FAP stage I, and patisiran treatment was started. After one year of treatment the patient no longer experienced sensory complaints and showed an improvement of NCV values. Since then, he remained stable at all points.

This case highlights the importance of an early diagnosis of hATTRv to start early treatment. When a patient presents with hATTRv, genetic counselling of family members should be undertaken to identify *TTR* gene variant carriers through cascade genetic counselling and testing, enabling regular follow-up to initiate treatment as soon as first symptoms appear and providing timely presymptomatic diagnostic advice [21].

Case 2: hATTRv patient with polyneuropathy showing significant clinical decline after liver transplantation with good response on patisiran

A 71-year-old Portuguese male experienced first symptoms in 2008 at the age of 57 years. Symptoms at onset were burning pains in feet and hands, decreased sensitivity in feet and distal legs, and walking difficulties. Symptoms were progressively increasing. Furthermore, he suffered from malleolar oedema, orthostatism, palpitations and a 7 kg weight loss over the past year.

Neurological examination showed a broad-based sensory ataxic gait, and impossibility to heel walk due to a bilateral foot dorsiflexor paresis of 4/5 at the Medical Research Council (MRC) scale. The patient showed hypoesthesia in feet and distal legs with proximodistal gradient, and decreased vibration and temperature sense in feet and distal legs. Deep tendon reflexes were absent in the lower limbs and weak in the upper limbs. Blood testing excluded potential causes of polyneuropathy. NCV revealed a severe chronic sensory-motor axonal polyneuropathy and a superimposed sensory-motor carpal tunnel syndrome at the right side. Autonomic function tests were abnormal. Sural nerve biopsy showed Congo red positive deposits.

The symptoms and family history have led to a genetic analysis of the *TTR* gene, which identified the pathogenic variant c.148 G>A (p.Val50Met), confirming the diagnosis of hATTRv-PN.

Episodes of bradycardia and tachyarrhythmias (non-sustained ventricular tachycardia) were detected, resulting in a pacemaker implantation. TTE revealed a normal left ventricular ejection fraction (LVEF) of 78%, but a slight concentric muscle hypertrophy. No other organs were affected.

Because of rapidly progressive symptoms, an OLT was performed in 2009. During the next 11 years, the patient was clinically stable and showed unchanged results at NCV studies and cardiac exams. However, at 69 years of age the patient developed progressively increasing neurological and cardiac symptoms. He had decreased fine motor hand skills and experienced increasing walking difficulties, resulting in decreased walking distance and in the use of a walking stick. Autonomic symptoms including orthostatism, erectile dysfunction and constipation were present. This clinical deterioration was confirmed by NCV studies and cardiac exams. TTE revealed increased concentric muscle hypertrophy, with normal LVEF of 60%. A myocardial biopsy showed Congo red positive deposits.

In 2021 the patient started treatment with patisiran intravenously every three weeks. To date, the patient shows a stable clinical neurological examination, NCV and cardiac exams, and normal ophthalmological examination.

Case 2: Discussion

OLT in hATTRv patients have proven to have a major survival benefit, but OLT outcomes highly depend on the *TTR* variant and disease characteristics [22]. Late-onset hATTRv patients with a p.Val50Met mutation have been associated with worse post-OLT outcomes [22]. After OLT, hATTRv patients often experience disease progression, partially due to a continuous production and deposition of wild type TTR and misfolding of wild type TTR depositing on existing amyloid foci [22]. Patisiran treatment has shown to suppress the production of both mutated and wild type TTR, significantly delaying the progression of neuropathy [23,24]. This case shows that patisiran is effective in patients experiencing a significant clinical decline after a liver transplantation.

Case 3: hATTRv patient with autonomic symptoms responding to patisiran treatment

A 50-year-old Pakistani man experienced first symptoms at 43 years. Symptoms at onset were continuous foot pain, predominantly in the heels. Treatment with methylprednisolone locally injected for Fasciitis plantaris was initiated, without any clear benefit. Five years later, a small fibre neuropathy was suspected due to the persistence of the complaints and a normal neurological examination. In that context, and even if the insulin-dependent type 2 diabetes could be the cause of the small fibre neuropathy, a genetic analysis of the *TTR* gene was performed and identified the pathogenic variant c.424 G>A (p.Val142Ile), confirming the diagnosis of hATTRv. The family history was negative for neurological diseases, but his father died from an undefined heart disorder.

The patient was referred to a NMRC for follow-up and treatment. EMG showed normal sensory and motor action potential amplitudes and laser-evoked potentials, but an absent sympathetic cutaneous response was observed on the feet but not on the hand confirming the small fibre polyneuropathy. A ^{99m}Tc-MDP-bone scintigraphy showed no signs of cardiac amyloidosis (Perugini 0). The cardiologist consultation and echography did not add further arguments for cardiac amyloidosis. No other organs were involved.

Treatment with 20 mg tafamidis was started with pregabalin for the management of dysesthesia. The patient developed a worsening of gastrointestinal pain resulting in treatment discontinuation.

One and a half year after treatment interruption, the patient presented with a worsening of the disease including burning pain in the feet, dizziness when changing position and persistent abdominal pain. The patient reported skin changes and xerostomia. Neurological examination revealed hypoesthesia in feet with proximodistal gradient and hypopallesthesia in the toes. Deep tendon reflexes were decreased in the lower limbs. NCV showed a mild motor axonopathy and decreased sural SNAPs. A gastrointestinal examination showed liver cytolysis and steatosis from metabolic origin and gastroparesis.

Due to the clinical and electrophysiological degradation, patisiran treatment was initiated intravenously every three weeks and was well tolerated. Since then, no improvement in the feet pain was reported, but the abdominal pain disappeared.

Case 3: Discussion

Symptoms of autonomic dysfunction are often present in the early stages of hATTRv. These symptoms can precede the onset of sensory motor impairment for many years, substantially impacting the patients' quality of life and survival [8,25–27]. This case shows that hATTRv patients presenting with dysautonomic signs could be stabilised by patisiran.

As early dysautonomic symptoms are often overlooked and identified retrospectively after other non-dysautonomic symptoms occurred, identification of these early signs is essential and should prompt for (small fibre) neuropathy or signs of cardiac amyloidosis, thereby fostering early diagnosis and treatment of hATTRv [26].

Case 4: Severely affected hATTRv patient with mixed phenotype

A 64-year-old Portuguese woman presented in December 2020 with ascending paraesthesia and dysesthesia for 2 years. For a few months, she had experienced distal muscle weakness in four limbs and reported gait disturbance. She also had dyspnoea (NYHA class II), orthostatic hypotension and a 20 kg weight loss over 6 months.

Clinical examination showed distal amyotrophy and muscular weakness (3/5 on MRC scale) in all limbs following a proximodistal gradient, combined with an ataxic, dropped foot gait. Sensory examination showed gloves and socks tactile hypoesthesia, apallesthesia of lower limbs and hypopallesthesia of upper limbs. Reflexes were absent on lower limbs and decreased on upper limbs. EMG revealed a length-dependent sensorimotor axonal polyneuropathy with severe reductions in SNAPs and compound muscle action potential (CMAP) of the 4 limbs. A ^{99m}Tc-MDP-bone scintigraphy (MDP-SPECT) showed signs of cardiac amyloidosis (Perugini 3). TTE demonstrated hypertrophic cardiomyopathy with end-diastolic thickness of around 13 mm and a thickness of valvular leaflets (Figure 1). The LVEF was 46% and a scintillating appearance of the myocardium was described. The left ventricular (LV) strain analysis showed a decrease of the global longitudinal LV strain (less than −14.5%) with a typical image on the bullseye map (preservation of apical longitudinal strain with severely abnormal basal and mid longitudinal strain) (Figure 2). The cardiac magnetic resonance imaging (MRI) showed late contrast enhancement of myocardium and subendocardium such as asymmetric hypertrophy of interventricular septum (13.5 mm) (Figure 3).

hATTRv was suspected and confirmed with the c1.248 G>A (p.Val50Met) mutation on the *TTR* gene.

This FAP stage II patient initiated patisiran treatment in April 2021. After 18 months of treatment, the neurological symptoms improved, and the grip strength increased from 3.1 to 5.02KgW on the right hand and 4.6 to 7.45KgW on the left hand. The 6 minutes walking test increased from 141 m with a walking stick to 209 m without any support. A decrease of orthostatic hypotension symptoms was also recorded. The NCV remained unchanged. Cardiac

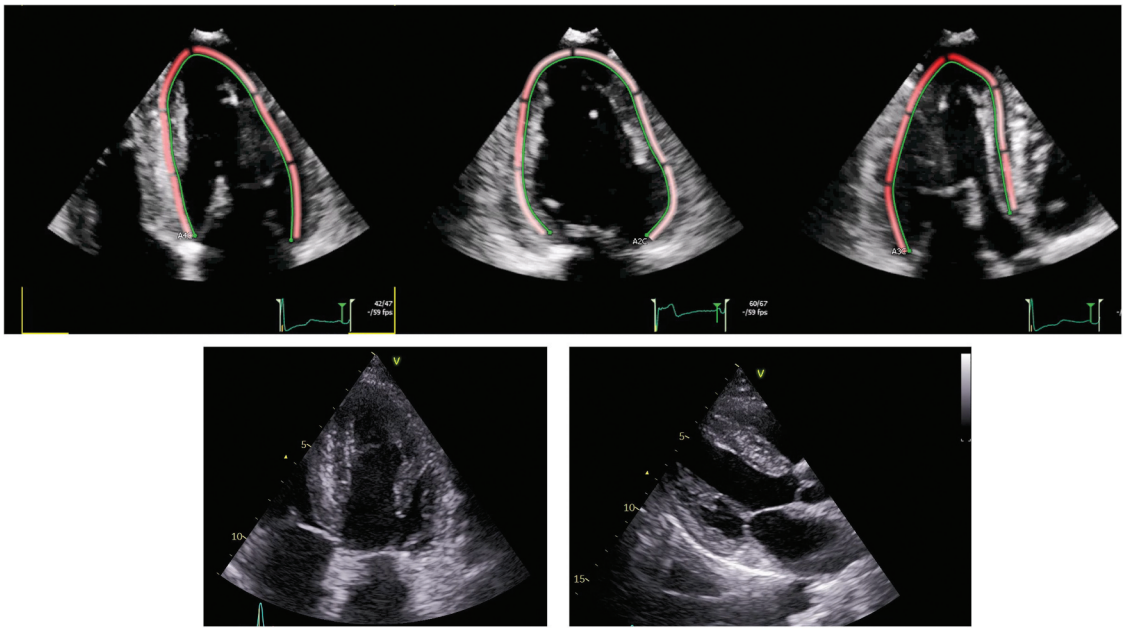

Figure 1. Transthoracic echocardiogram Hypertrophic cardiomyopathy with end-diastolic thickness of around 13 mm and a thickness of valvular leaflets. A scintillating appearance of the myocardium is also shown.

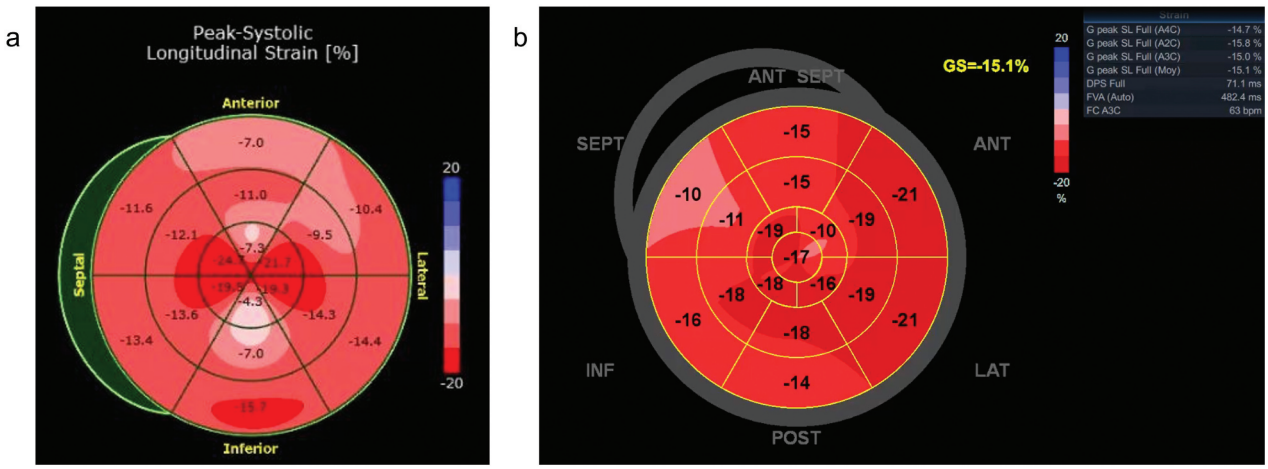

Figure 2. Longitudinal strain (a) at diagnosis: severely affected longitudinal strain on basal and mid-lv (b) After 2 years of treatment: diffuse improvement of longitudinal strain on basal and mid-lv.

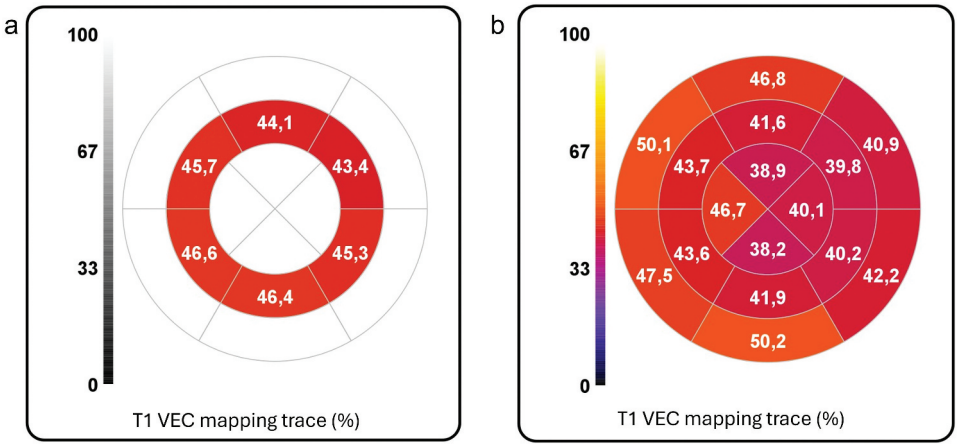

Figure 3. Extracellular volume (ECV) from heart MRI (a) at diagnosis: increased ECV on mid-lv (b) After 2 years of treatment: regression (−8%) of the ECV.

symptoms improved including reduced dyspnoea. Cardiac examination with MRI revealed regression of LV hypertrophy as measured by reduced septum in diastole (11 mm versus 13.5 mm) and a diminished ventricular contrast enhancement.

Case 4: Discussion

This report highlights the efficacy of patisiran on mixed phenotype hATTR patients even in those more severely affected according to the FAP classification. The involvement of both cardiac and neurological impairment associated with dysautonomic signs must prompt *TTR* analysis. Cardiac involvement in hATTRv-PN patient impacts prognosis rapidly and drastically with median post-diagnosis survival time of 3.4 year [28]. Despite tremendous advances in the field of amyloidosis in the last years driven by improved disease detection, and access to targeted therapy, residual mortality and morbidity remain high, defining a need for further drug development [29,30]. As for patients in FAP stage I, more severely affected hATTRv patients could benefit from patisiran treatment even if the recovery of the function is less obvious as described in this report [18].

This report also highlights the need for functional evaluation and of patient reported outcomes during the follow-up as EMG could not show any improvement under treatment.

Case 5: hATTRv patient mimicking chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) with persistent conduction blocks

A 73-year-old male complained of distal paraesthesia in the four limbs from the age of 54 years. He progressively developed gait unsteadiness, walking disability, and limitations to climb stairs. His past medical history consisted of paroxysmal atrial fibrillation alternating with sinusal bradycardia leading to pacemaker implantation. He also presented with LV hypertrophy, cataracts, bilateral carpal tunnel syndrome and a narrow lumbar canal.

Clinical examination showed lower limbs distal amyotrophy, positive Romberg's sign, diminished distal pallesthesia, but preserved reflexes.

Blood tests were normal. EMG revealed a progressive axonal length-dependent sensory-motor polyneuropathy. Electrocardiogram showed a bicameral pacemaker-trained rhythm with left block branch and no apparent peripheral micro-voltage. TTE displayed a biventricular hypertrophy, with aortic and mitral valve thickening, interatrial septum thickening and impaired global longitudinal strain with relatively preserved apical deformation. DPD-SPECT identified a Perugini grade 3 myocardial tracer uptake in the absence of circulating paraprotein, leading to the suspicion of cardiac TTR amyloidosis.

The genetic analysis of the *TTR* gene sequencing confirmed the diagnosis due to the c.148 G>A (p. Val50Met) pathogenic variant. Patisiran treatment (0.3 mg/kg every 3 weeks) was initiated at the age of 70. After six months of treatment, an obvious improvement in walking ability, balance, and the release of using a banister to climb stairs was observed.

During electrodiagnostic follow-up, demyelinating features were identified including nerve conduction blocks on common compression sites. A partial definite motor conduction block of the right median nerve was found at the age of 72 years, 2 months (Figure 4(a)). This motor conduction block showed persistence as similar findings were also demonstrated at 73 years (month 0, 4, and 8). At 73 years and 8 months, a partial definite motor conduction block was also found at the left median nerve (Figure 4(b)), as well as on both ulnar nerves. At the age of 73, the electrodiagnostic features fitted with chronic inflammatory demyelinating polyradiculoneuropathy EFNS/PNS CIDP criteria [31].

At the age of 74, his walking disability worsened due to a lumbar spinal stenosis recurrence. Lumbar decompression surgery of the posterior mass identified at the S1 level by MRI led to a clear clinical

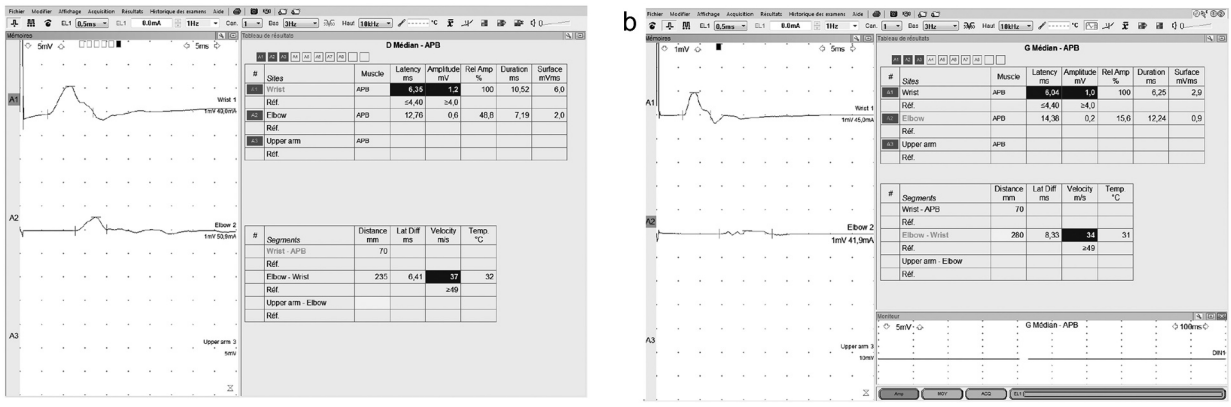

Figure 4. Median and ulnar partial definite motor conduction blocks. Picture (a) shows a partial definite motor conduction block on the right median nerve at the age of 72 years, 2 months. Picture (b) shows partial definite motor conduction blocks on left median nerve at the age of 73 years.

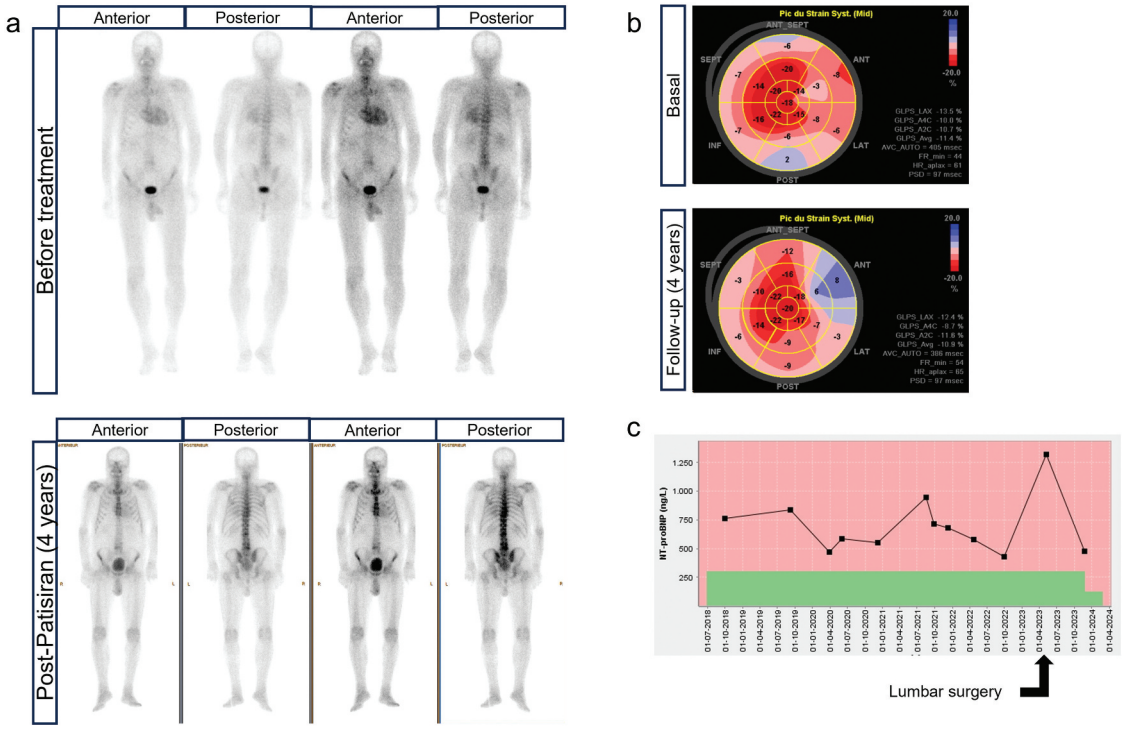

Figure 5. (a) DPD-bone tracer uptake (from Perugini grade 3 to grade 1) (b) no overt change in global longitudinal strain (c) a mild improvement in cardiac NT-proBNP levels.

improvement. Pathological examination confirmed the presence of amyloid deposits and of amyloidoma.

After 4 years of patisiran treatment, cardiac amyloidosis improved as observed by a drastic diminution of DPD-bone tracer uptake (from grade 3 to grade 1; Figure 5(a)), with no overt change in global longitudinal strain (Figure 5(b)). Additionally, a mild improvement in cardiac NT-proBNP levels was observed (Figure 5(C)). No ECV measures are available for this patient. Clinically, there was no overt heart failure event, nor cardiac hospitalization, apart from a transient clinical deterioration at the time of lumbar surgery.

Case 5: Discussion

This report illustrates the long diagnostic pathway in hATTRv patients presenting with unexplained neuropathy and the need to rule out hATTRv, especially in CIDP-like patients when red flags are present [32]. Additionally, the presence of a spinal stenosis related to a lumbar amyloidoma is an overlooked condition in hATTRv (30% of spinal stenosis with high-grade amyloid deposits [33]) despite its disability potential and therapeutic access [34].

This report also illustrated a clear functional motor improvement after patisiran initiation, and the subsequent NT-proBNP level improvements showed benefits on the cardiac prognosis as previously described [35].

Conclusion

This paper shows the impact of patisiran on five hATTRv cases in Belgium, highlighting the effect of patisiran in patients with heterogeneous clinical disease presentations. Mimicking other forms of neuropathy or heart conditions can make the diagnosis challenging especially in the absence of a familial history of hATTRv.

Multiple misdiagnoses (e.g. CIDP and idiopathic axonal polyneuropathy) are often made before the final hATTRv diagnosis [32]. In axonal polyneuropathy, one major finding in favour of hATTRv-PN is the association of a sensory polyneuropathy, typically accompanied by autonomic dysfunction and carpal tunnel syndrome [36], very early in the course of the disease [26]. If the degradation of a CIDP patient's symptoms is rapid and not controlled under standardised treatment for CIDP, one should search for a *TTR* pathogenic variant [37].

In hATTRv-CM patients, cardiologists should not stick to diagnosis of heart failure with preserved ejection fraction (HFpEF) (which is a syndrome and not a definitive diagnosis), but further investigate the patient until a definitive diagnosis is made. They should be helped by asking the patient for the presence of a carpal tunnel syndrome, lumbar tunnel stenosis and dysautonomic signs.

The development of guidelines [32], 'red flags' [2,14,38], and the establishment of non-biopsy criteria [14,32] have led to an increased rate of diagnosis and patients referred for therapies. Increased

disease and symptom awareness is essential to enable early diagnosis and prevent disease progression. The multisystemic nature of the disease stimulates the physicians to look beyond their own specialty and consider a multidisciplinary approach. A close collaboration between neurologists and cardiologists is therefore highly recommended, ideally within an amyloidosis team to offer holistic care for hATTRv. Physicians must also be aware of autonomic dysfunction. Even without standardized exploration to evaluate dysautonomia in this disease, an electrodiagnostic exploration could support confirmation of dysautonomia. Genetic analysis of the *TTR* gene should be performed for confirmation.

Early diagnosis is essential as earlier treatment is correlated with a better improvement of the patient [39]. Over the last decade several disease-modifying treatments became available that benefit patients with different mutations and at different disease stages. Patisiran is a RNAi silencer, which has shown efficacy and safety in hATTRv patients with neurological as well as cardiovascular symptoms. As demonstrated in the different cases, patisiran has shown promising results in stabilizing or improving the condition in many patients. In a Belgian study, 8 out of 9 patients for which follow-up data was available showed stable or improved neurological or cardiological parameters after patisiran treatment [40]. However, not all patients respond equally to the treatment. In the APOLLO trial, 74% of patients showed stabilization of neuropathy, while 51% experienced improved quality of life [21]. Despite these positive outcomes, some patients still experience disease progression, albeit potentially at a slower rate than the natural course. Further research is needed to understand the characteristics of non-responders and to optimize treatment strategies for all hATTRv patients.

It also needs to be highlighted that while patisiran offers clinical benefits, imaging parameters may not always clearly reflect improvements. For example, a post-hoc analysis of the APOLLO-B study demonstrated that patisiran-treated patients had improved odds of no disease progression compared to placebo, with benefits in clinical, functional, and biomarker parameters [41]. However, imaging assessments showed only a favorable trend without statistical significance [41]. This further emphasizes the need for clinicians to also consider clinical and functional outcomes when assessing treatment efficacy. A comprehensive, patient-centered evaluation, combining clinical observations and functional assessments in combination with the outcomes of imaging, should guide clinical decision-making.

To conclude, the cases that are described showed that patisiran is effective to improve mild symptoms and stabilise moderate ones, but also to prevent evolution of the disease to severe complications in hATTRv patients with heterogeneous clinical presentations.

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Author contributions

KGC, JLDB and VV wrote their clinical case. SD and PT, and AB and GR joined efforts to write a case manuscript with mixed phenotypes. SD and AB wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

Informed consent

Written informed consent was obtained from each patient prior to publication. In accordance with the editorial policies, written informed consent was obtained to publish the details from the affected individual (or their parents/guardians if the participant is not an adult or unable to give informed consent; or next of kin if the participant is deceased). Informed consents can be provided upon request.

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