NEW PERSPECTIVES IN CARDIAC AMYLOIDOSIS

PhD thesis

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1. Introduction

In the last century, especially in the previous couple of decades, our understanding of amyloid-caused diseases improved exponentially. In 2018, a new definition for amyloid was proposed: amyloid fibril refers to any cross-beta-sheet fibril. More than 30 proteins can form amyloid in the human body and damage the affected tissues. The extracellular deposition can be due to abnormal proteins (immunoglobulin light chain [AL] amyloidosis – which is acquired, hereditary amyloidosis like variant transthyretin [ATTRv] amyloidosis), the abundance of normal proteins (reactive systemic [AA] amyloidosis) and can be the result of the aging process (wild-type transthyretin amyloidosis [ATTRwt]) as well.

Systemic amyloidosis is a rare disease, except in some endemic areas. AL, AA, and ATTR (ATTRv and ATTRwt) are responsible for around 90% of cases.

AL amyloidosis is a potential complication of any plasma cell dyscrasia. The affected organ is most commonly the heart, the kidneys, the liver, and occasionally the peripheral nervous system. Macroglossia and periorbital purpura is thought to be pathognomonic.

AA amyloidosis (previously named secondary amyloidosis) is the consequence of chronic or re-occurring inflammation during which fibrils are formed from fragments of serum amyloid A protein.

ATTR amyloidosis is divided into ATTRv and ATTRwt amyloidosis. In ATTRv amyloidosis (previously called hereditary or familial amyloidosis because of its autosomal dominant inheritance), modified transthyretin (TTR), also called prealbumin, is responsible for amyloid deposition. The mainly affected organs are the heart and the peripheral nervous system. The clinical picture and the disease's course largely depend on the mutation affecting ATTR. Some relevant mutations are shown in Figure 1 (Rapezzi et al. with permission – modified). The later presented important Hungarian mutations are incorporated with a red margin.

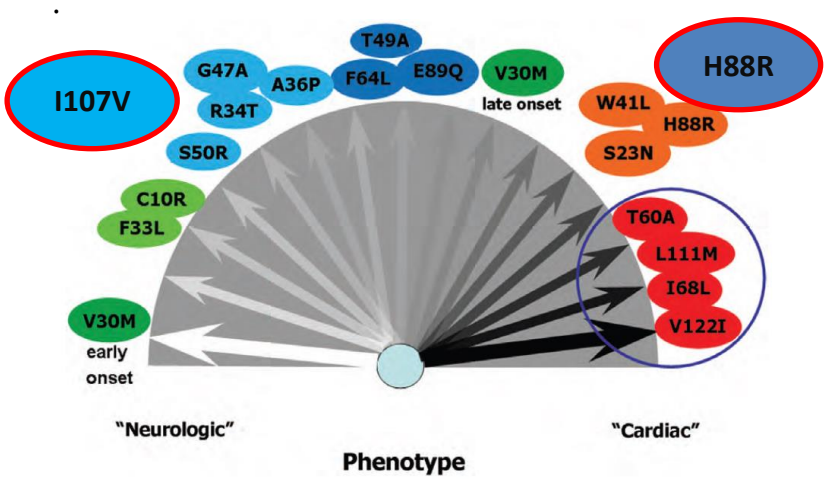

Figure 1 *Possible spectrum of genotype-phenotype correlations in transthyretin-related amyloidosis.– Rapezzi et al., with permission, modified to show the later presented important Hungarian mutations, as well.*

In ATTRwt amyloidosis, previously called senile ATTR amyloidosis, because it manifests in the elderly, transthyretin forms the beta-sheet structure that deposits in the tissues. Cardiac involvement leading to heart failure is one of the critical manifestations, and carpal tunnel syndrome (CTS) is the other. This form manifests later than ATTRv, in the 6^{th}-7^{th} decade of life.

Cardiac infiltration of amyloids, leading to restrictive heart failure with a preserved ejection fraction (HFpEF) cardiomyopathy, is a characteristic feature of AL and ATTR amyloidosis. The involvement of the heart is the primary cause of morbidity and mortality, independently of the etiology of systemic amyloidosis. The amyloid deposits in the extracellular matrix cause wall thickening, remodeling of the ventricles, and low cardiac output in the end. Atrial dilation is the consequence of locally increased pressure. Arrhythmias like atrial tachycardia or

fibrillation and conduction abnormalities are also common complications of systemic amyloidosis affecting the heart.

The diagnostic evaluation and diagnosis of cardiac amyloidosis (CA) changed a lot in recent years. Although the gold standard for the diagnosis is still the cardiac biopsy, ATTR CA diagnosis can now be established without biopsy. The first and most crucial step is the arising of suspicion upon coming across red flags like seeing low voltage on an electrocardiogram (ECG) despite thickening of the septum/posterior wall (12mm); unexplained left ventricular (LV) hypertrophy; intolerance of beta-blockers or angiotensin-converting enzyme inhibitors; history of bilateral CTS, etc. Echocardiography has a primary role in not just the diagnosis of CA but in recognizing complications, differential diagnosis, and follow-up. The term "restrictive cardiomyopathy" is often used in connection with CA because it describes the hemodynamic changes well. Concentric LV hypertrophy is the most characteristic anomaly. Above a wall thickness of 12 mm, the suspicion of CA should appear. Cardiac MR (CMR) and scintigraphy with a bone tracer have also had their fundamental role.

Previously definitive treatment of CA meant heart transplantation (HTX) if the underlying disease was treatable, meaning bone marrow transplantation in case of AL amyloidosis. CA came to the spotlight partially because of novel therapeutic options for treating ATTR CA in the last decades, like tafamidis, patisiran, and inotersen.

The prognosis of CA depends on many factors. The etiology itself is one of the most important ones. In everyday practice, the etiology, New York Heart Association (NYHA) stages for heart failure (HF), NT-proBNP, high sensitivity Troponin T, stroke volume, and wall thickness are used.

Cardiac amyloidosis and aortic stenosis (AS) have a unique connection. As a common valvular disease, AS reduces life expectancy when it becomes significant. Patients with ATTRwt CA or AL CA and those with AS have similar demographic features and echocardiographic

features like LV hypertrophy, diastolic dysfunction, or elevated LV filling pressure. CA may not be diagnosed when the patient also has AS because the abnormalities detected by echocardiography are readily explained by AS. Also, patients with concomitant AS and CA are more frequently present with a low-flow, low-gradient pattern compared to patients without CA. Assessing the severity of AS is more challenging in patients with low-flow, low-gradient AS.

2. Objectives

Assessing the co-existence of CA and AS in consecutive CA patients

1) Study the prevalence, severity, and type of AS in consecutive patients with CA
2) Evaluate the potential use of stress echocardiography in the diagnostic process

Assessing Hungarian patients with ATTRv

1) Investigate the prevalence, regional distribution, and genotypes of Hungarian patients with ATTRv
2) Study the phenotype-genotype correlation in Hungarian patients with ATTRv

3. Methods

Methods already published with my authorship are only briefly described following the guidance of the Doctoral School. For details, I refer to the publications.

We retrospectively interpreted and analyzed the available echocardiographic and clinical data of 55 consecutive CA patients between January 2009 and January 2019. CMR was routinely done for differential diagnosis and the confirmation of CA. LV longitudinal strain

analysis was done in all patients with clinical suspicion of CA after 2015. We examined segmental differences looking for "apical sparing." Also, the routine measurements for AS were done. In cases where less than 0.6 cm^2 was measured as the indexed aortic valve area, but resting echocardiography showed low-flow, low-gradient AS (LFLG AS), dobutamine stress echo was performed regardless of the LV EF to separate pseudo- and true-severe AS.

With the coordinated help of Hungarian cardiology, neurology, and rare disease centers, all genetically confirmed ATTRv patients were identified in the country retrospectively. Available clinical and epidemiological data were collected and interpreted. The primary cause of death was also processed when available. A search for publications was also performed in PubMed ((Hungary) OR (Hungarian)) AND ((TTR) OR (transthyretin)) to find further patients with ATTRv.

We established CA in the ATTRv patients according to recent recommendations based on broad consensus during our retrospective analysis. The neurologic involvement of the patients was diagnosed during complex neurologic evaluation following actual guidelines, involving the electrophysiological assessment of peripheral nerves.

4. Results

During the assessment of AS in consecutive CA patients, we performed transthoracic echocardiography at rest on 55 patients with CA between January 2009 and January 2019. Among them, 45 had AL amyloidosis, 9 had ATTR amyloidosis, and one had AA amyloidosis. The median age was 65 years. We identified 5 (9%) with moderate or severe AS. The crucial characteristics (clinical data, biomarker, and echocardiographic results) of these patients are shown in Table 1.

Table 1 *Clinical characteristics of the 55 CA patients grouped according to the presence or absence of aortic valve stenosis*

	Patients without AS (n=50)	Patients with AS (n=5)	p-value
Clinical data			
Age (years)	63.5 (58-73)	69 (68-82)	p=0.055
Male (n, %)	26 (52%)	2 (40%)	p=0.553
ATTRwt CA (n, %)	2 (4%)	1 (20%)	p=0.391
ATTRv CA (n, %)	6 (12%)	0 (0%)	p=0.485
AL amyloidosis (n, %)	41 (82%)	4 (80%)	p=0.741
AA amyloidosis (n, %)	1 (2%)	0 (0%)	p=0.909
NYHA III-IV stage (n, %)	32 (64%)	5 (100%)	p=0.278
Atrial fibrillation (n, %)	11 (22%)	1 (20%)	p=0.312
Laboratory data			
B-type natriuretic peptide (pg/ml)	606 (234-1240)	341 (77-657)	p=0.303
Troponin T (ng/L)	66 (39-104)	134 (47-215)	p=0.464
Echocardiography			
Left ventricular ejection fraction (EF) (%)	56 (43-63)	59 (51-60)	p=0.823
Septal wall thickness (mm)	16 (13-18)	17 (13-20)	p=0.578
Inferior wall thickness (mm)	15 (13-17)	15 (13-16)	p=0.780
Left ventricular end-diastolic diameter (mm)	42 (36-45)	41 (37-42)	p=0.776
E/e' (Average of lateral and septal e')	20.6 (16-24)	18.1 (16.9-20.6)	p=0.241
Lateral S'	5.5 (4-7)	6.25 (4,25-8.3)	p=0.588

Each patient with AS had severe HF with NYHA stage III or IV. There was no significant difference between the patient's clinical

characteristics with AS and CA or CA alone. Patients having AS and CA simultaneously tended to be older. The calculated aortic valve area (AVA) during baseline echo was less than 0.6cm^2/body surface area (BSA) in 3 cases. In the other 2 cases, AVA/BSA was 0.65 and 0.63 cm^2/m^2, indicating moderate AS. In the 3 cases with AVA/BSA below 0.6 cm^2/m^2, we performed stress echocardiography with dobutamine to separate true severe AS from pseudo-severe AS. The cardiac images of such a patient are presented in Figure 2. Patient characteristics who had AS and also CA are summarized in Table 2.

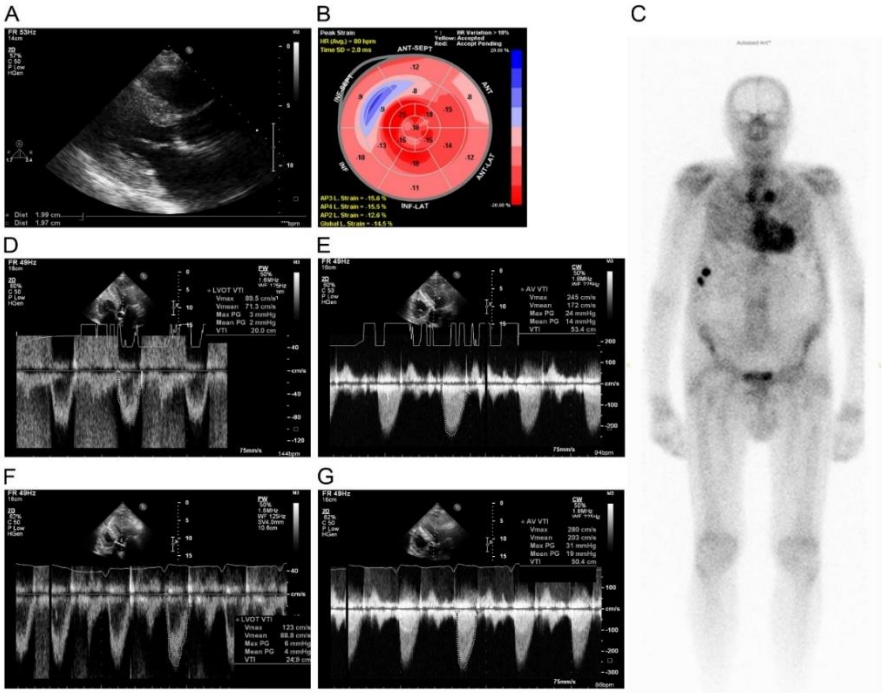

Figure 2 *Images of a patient with ATTRwt cardiac amyloidosis and low-flow, low-gradient, pseudo-severe AS. LVEF was 51%. A: TTE, parasternal long-axis view. The septum and inferior wall are 20mm thick at the end-diastole. B: Bull's eye image of the LV longitudinal strain.*

Typical apical sparing. C: PYP isotope scan, with significant take-up of the tracer in the heart: Perugini score 3. D-G: Pulsed-wave (PW) and continuous-wave (CV) Doppler images of the left ventricular outflow tract at rest and at low dose dobutamine stress test. D: Resting PW Doppler, E: Resting CW Doppler. Resting calculated AVA: 0.54 cm^2/BSA. F: PW Doppler at dobutamine test. G: CW Doppler at dobutamine test. Significant elevation in systolic volume and AVA at the dobutamine test. Calculated AVA at dobutamine test: 0.76 cm^2/BSA

During our assessment of Hungarian patients with ATTRv, we identified 36 individuals from 22 families with known pathogenic TTR mutations. Twelve were asymptomatic, and twenty-four were symptomatic at the time of the diagnosis. We found seven different pathogenic mutations summarized in Figure 3. Figure 4 shows the geographical distribution of the patients.

The clinical findings of all 24 symptomatic patients are summarized in Table 3. The twelve asymptomatic individuals were considered carriers. They were identified during family screening. We found NT-proBNP values at the time of clinical diagnosis in 15 patients. Their median value was 3511 pg/mL. Twelve patients were already dead at the time of the analysis, and one had HTX. Causes of HTX and death were the progression of heart failure (6 cases), arrhythmia (1 case), other (3 cases), or unknown (3 cases). No patients died because of progressive neuropathy. When the analysis was performed, ten patients were receiving targeted therapy for ATTRv or had received treatment earlier.

ATTRHis88Arg was the most commonly identified mutation with 10 cases. And with eight cases, ATTRIle107Val was the second most common mutation. The clinical phenotypes of the two most common Hungarian mutations are summarized and compared in Table 4.

Table 2 *Characteristics of patients with CA and AS.*

Patient's number, age (years) and sex	Type of CA	LV wall thickness (septum/posterior wall, mm) measured with echo, LVEF (%), stroke volume index (ml/m^2)	Presence of typical LGE in CMR or semiquantitative score>1 at PYP isotope scan in TTR amyloid	Cardiac biopsy positive for amyloid	Apical sparing at strain analysis. (Average apical LS/(average basal LS + mid-LS))	AVA/BSA (cm^2/m^2) and mean aortic valve gradient at rest, measured by TTE	AVA/BSA (cm^2/m^2) and aortic valve gradient during dobutamine stress echo	Final diagnosis of the type of AS
1. 66, male	AL	17/16, 48, 20	yes	DNP	yes 0.75	0.45/BSA, 13	0.45/BSA, 22	True-severe AS
2. 68, female	AL	13/13, 60, 40	DNP	DNP	yes 0.77	0.65/14	DNP	Moderate AS
3. 89, male	ATTRwt	20/20, 51, 22	yes	DNP	yes 0.81	0.54, 12	0.76, 19	Pseudo-severe AS
4. 69, female	AL	20/15, 61, 31	DNP	yes	yes 0.77	0.63, 22	DNP	Moderate AS
5. 83, female	AL	12/12, 59, 38	yes	DNP	yes 0.77	0.58, 19	0.86, 25	Pseudo-severe AS

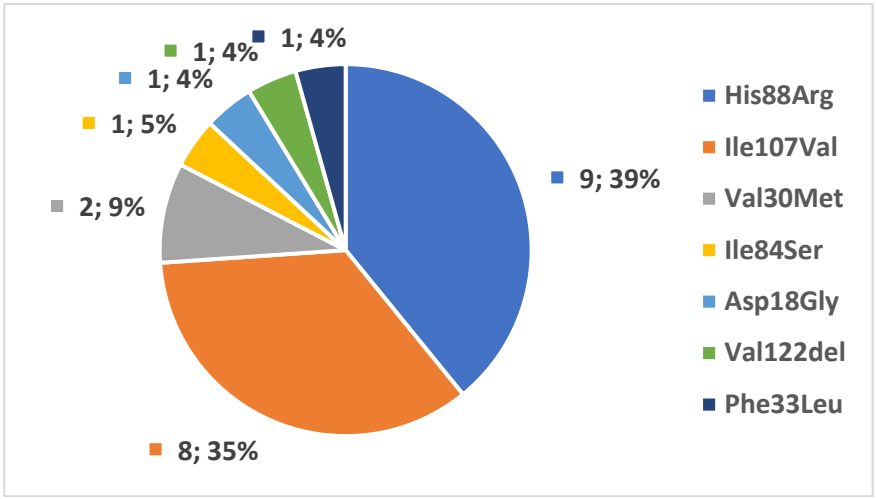

Figure 3 *Genetic spectrum of TTR mutations in Hungarian families, expressed in number and percentage of the affected families (n=23).*

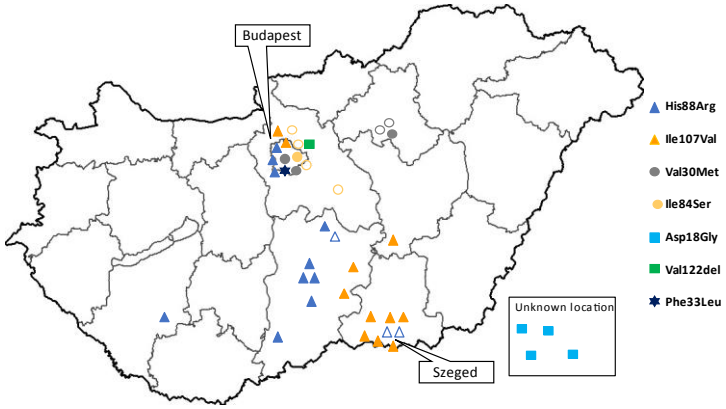

Figure 4 *Map of Hungary with the geographic distribution of different genetic subtypes of ATTRv patients (n=40). Full symbols represent symptomatic individuals, while empty symbols represent asymptomatic individuals. The four patients with unknown locations are the patients found during the literature search.*

Table 3 *Clinical characteristics of patients with symptomatic ATTRv (n=24).*

Sex		Male 18 Female 6
Age at clinical diagnosis (median)		65 years
Time to clinical diagnosis (median)		54.8 months
Initial presentation (at the time of onset of the first symptom)	cardiac	33.33% (n=8)
	neurologic	45.83% (n=11)
	mixed	12.5% (n=3)
	N/A	8.33% (n=2)
Stage of heart failure according to NYHA functional class at the time of clinical diagnosis	I.	12.5% (n=3)
	II.	33.33% (n=8)
	III.	33.33% (n=7)
	IV	8.33% (n=2)
	N/A	12.5% (n=3)
The median value of NT-proBNP at the time of clinical diagnosis		3511 pg/ml (n=15)
PND at the time of clinical diagnosis	no polyneuropathy	12.5% (n=3)
	I.	33.33% (n=8)
	II.	33.33% (n=8)
	III.	12.5% (n=3)

	IV	0% (n=0)
	N/A	8.33% (n=2)
CTS in medical history	positive history	75% (n=18)
	negative history	20.83% (n=5)
	N/A	4.16% (n=1)
Total number of patients receiving targeted pharmacological therapy		41.6% (n=10)*

NYHA: New York Heart Association – functional classification of heart failure; PND: modified polyneuropathy disability score; N/A: not available; HF: heart failure;
* 1 additional patient participates in a placebo-controlled clinical trial

Table 4 *Genotype-phenotype correlation in symptomatic Hungarian ATTRv patients with the two common mutations (ATTRHis88Arg and ATTRIle107Val)*

		ATTRIle107 Val n=8	**ATTRHis88 Arg n=10**
Number of patients with	heart failure as leading symptom	2	4*
	equally severe cardiac and neurologic symptoms	1	2
	polyneuropathy as leading symptom	5	4

Median age at clinical diagnosis	73 years	62 years
Median time from first symptoms to diagnosis	66.7 months	43.8 months
Median age at first symptoms	67.44 years	58.35 years
Median NYHA stage	III	II
Median PND stage	II	I

NYHA: New York Heart Association – functional classification of heart failure; PND: modified polyneuropathy disability score
* All patients with ATTRIle107Val and ATTRHis88Arg had mixed phenotypes, except one patient with only cardiac symptoms

5. Discussion

We found the prevalence of moderate to severe AS among consecutive, unselected CA patients to be 9%. AL CA represented the majority of our patients. The explanation for this may be that our Department at Semmelweis University specializes in cardiology and hematology.

Different authors found the prevalence of CA in AS to be 4.1 to 16% in the previous years. These studies asserted that these had ATTR CA but not AL CA. If we approach the other way around and look for AS among CA patients, we can find only a few studies. In these studies, however, the authors used ATTR CA patient registries. The co-existence of ATTR CA and AS seems to be more common than the co-existence of AL CA and AS. One plausible explanation for this is the age of the patients. Both ATTRwt and AS are strongly age-related. On the other hand, because plasma cell dyscrasia affects younger patients, the patients with AL amyloidosis will have a lower median age, which means that the co-incidence with AS decreases.

Although CA was once regarded as a rare disease, studies with HFpEF patients show that CA is unexpectedly common in this population, with a prevalence of 17 to 19%. We found that moderate to severe AS is relatively common in a CA population where 80% of patients had AL amyloidosis. This is one of the novelties in our retrospective analysis. The other novelty of our study was about the usage of dobutamine stress echocardiography in patients with low-flow, low-gradient AS, HFpEF, and CA. The dobutamine stress test is not recommended in current guidelines for patients with low-flow, low-gradient AS if they have a preserved EF. The first step, as always, is clinical suspicion, usually raised by the morphology of the aortic valve. If the AVA is below 1 cm^2, the mean pressure gradient is below 40 mmHg, and the calculated stroke volume index (< 35 ml/m^2) is low, suggesting a low-flow state, then dobutamine stress echocardiography is recommended. It can separate true-severe AS from pseudo-severe AS. AVA will increase together with the stroke volume, but the mean transvalvular gradient will not change significantly. In pseudo-severe AS, in contrast to true-severe AS, where the gradient will increase, but the AVA will stay the same. The European Society of Cardiology (ESC) guideline does not recommend the dobutamine stress test in low-flow, low-gradient AS patients if their LVEF is preserved only in those with reduced EF. One may argue from the pathophysiological point of view that only reduced LVEF can be improved by dobutamine, but it is just speculation. We also performed the dobutamine stress echo test on our three patients with severe low-flow, low-gradient AS. Their LVEF was 48, 51, and 58%. The test was diagnostic in all three cases. The significant increase in AVA in two patients clearly showed that their symptoms are caused by the CA rather than pseudo-severe AS. Our results supported the possible review of related guidelines.

Only one patient in our study had true-severe AS. He was 66 years old with NYHA stage III HF. He only survived the diagnosis by two months. AS, CA, and myeloma multiplex obviously limited his life

expectancy. It is impossible to determine how much AS or CA contributed to HF in such cases, but data suggests that both CA and AS contribute to HF and an unfavorable prognosis if they co-exist.

Based on our experience, we underline the importance of dobutamine stress echocardiography in patients with low-flow, low-gradient AS. This test identifies patients with true-severe AS who benefit from a successful aortic valve repair or transcatheter aortic valve implantation. Our findings show that low-flow, low-gradient AS patients who have CA, even with preserved EF, may benefit from this diagnostic test, as it helps to identify patients with true-serve AS, who may benefit from invasive treatment.

We also presented the first data on the prevalence, epidemiology, and geno- and phenotypes of ATTRv patients in Hungary. Apart from the endemic regions in Bulgaria with the ATTRGlu89Gln, from the Eastern and Central European regions, only Austrian data were available from a recent publication. To our best knowledge, all patients diagnosed with ATTRv were included in our analysis.

The major epidemiologic finding in our study is the identification of ATTRHis88Arg and ATTRIle107Val mutations as the most prevalent ones in Hungary. There is limited information about these mutations in the literature. In 2013, ATTRIle107Val was recognized as a mutation causing a mixed phenotype: cardiac manifestations and polyneuropathy were also present. On the other hand, ATTRHis88Arg was only described as a pathologic mutation in ATTR guidelines in 2019. The first cases of ATTRHis88Arg were recently found in Sweden in recent years. All seven identified individuals were related and originated from the same region. The leading symptom in their cases was HF, but neurologic involvement was also identified. With this mutation, we found ten patients in Hungary. The first symptom was HF in four of them, another four had polyneuropathy first, and the last two had both symptoms at onset. They all had some level of HF at the diagnosis, nevertheless. Surprisingly, in a recent Austrian study, Auer-Grumbach et al. identified six families with

ATTRHis88Arg, making it the most common variant in Austria. The common historical background of the countries may explain this co-incidence. The Austro-Hungarian Empire existed from 1867 to 1918, and its citizens mingled. As a rare mutation, ATTRHis88Arg was most likely introduced by a common ancestor to the Empire. This may be one topic for future investigation: trying to prove the theory of this founding effect.

Our other major finding comes from the phenotype-genotype analysis in the case of the above-mentioned common Hungarian mutations. One interesting finding is that ATTRIle107Val patients were almost ten years older at diagnosis, and they also had a more advanced stage of the disease: higher NYHA stage, higher PND score. This finding suggests that ATTRIle107Val is the more aggressive form of the two common Hungarian mutations. This information may have future therapeutic consequences.

The calculated prevalence of ATTRv in Hungary was 2.35 per 1 million, lower than the 5.2 cases per million in Europe, excluding the endemic regions. The clinical awareness of ATTRv improved significantly in the last decade, manifesting in the increased number of new cases. However, the disease may still be severely underdiagnosed in Hungary, which may be the reason for the discrepancy in prevalence. We illustrated the geographical distribution of the Hungarian ATTRv patients in Figure 4. The inhomogeneous distribution may highlight that the University hospitals of Szeged and Budapest specialize in amyloidosis patient care, and most patients were identified in these regions. To improve the awareness of ATTRv, I contributed to several other publications and held lectures at national congresses on the topic.

We did not evaluate mortality, prognosis, disease progression, and therapy for many reasons. Most patients were diagnosed in recent years and had a short follow-up period. Also, the patient population was inhomogeneous as far as treatment was concerned. Ten received tafamidis, one taking 61 mg (approved for ATTR cardiomyopathy), the others 20 mg (approved for stage I ATTRv polyneuropathy) daily. One

patient was in a clinical trial receiving either vutrisiran or a placebo. Among symptomatic patients, thirteen (54%) died during the follow-up period, ranging from 1 to 195 months. Median survival was not calculated due to the short follow-up period of the surviving patients.

There are some limitations to our study. Because of its retrospective nature, in some instances, data were missing. For this reason, the ATTRvAsp18Gly patients identified by the literature search were only included in the epidemiologic analysis. Regarding the lower Hungarian prevalence of ATTRv compared to non-endemic European regions, there may be undiagnosed patients present in Hungary whom we failed to identify despite the increasing awareness of this disease.

6. Conclusions

In conclusion, we found the prevalence of moderate to severe AS among consecutive, unselected CA patients to be 9%. This means that moderate to severe AS is relatively common among our CA population, where 80% of patients had AL amyloidosis. Our findings support the observation that the co-existence of ATTR CA and AS seems to be more common than the co-existence of AL CA and AS.

Based on our findings, we also concluded that dobutamine stress echocardiography has a valuable role in the diagnostic evaluation of patients with CA and AS, even though most of these patients have preserved LV EF, and the ESC guideline does not recommend this test with normal LV EF. CA patients typically have diastolic dysfunction with low stroke volume and gradients. AS is usually low-flow, low-gradient in this population and easily missed. Dobutamine stress echocardiography is a safe and helpful test to differentiate between true-severe and pseudo-severe AS in this scenario.

Our major epidemiological finding of the Hungarian ATTRv patients is that ATTRHis88Arg and ATTRIle107Val are the most prevalent mutations in Hungary. Both mutations are rare worldwide,

although ATTRHis88Arg is also common in Austria, which can be the consequence of the common historical background of our countries.

Regarding the genotype-phenotype correlation, we concluded that in ATTRIle107Val patients, polyneuropathy seems to be more dominant, although all patients had some degree of cardiac symptoms. At the same time, ATTRHis88Arg patients have an equally mixed phenotype. Our findings suggest that ATTRIle107Val is the more aggressive form of the two common Hungarian mutations.

Our work opened some new perspectives on cardiac amyloidosis.

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