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Cardiac manifestations in Finnish Gelsolin Amyloidosis Patients

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Abstract

Introduction: Finnish gelsolin amyloidosis (AGel amyloidosis) is an inherited systemic amyloidosis with well-known ophthalmological, neurological and cutaneous symptoms. Additionally, cardiomyopathies, conduction disorders and need of cardiac pacemakers occur in some patients. This study focuses on electrocardiographic (ECG) findings in AGel amyloidosis and their relation to cardiac magnetic resonance (CMR) changes. We also assessed whether ECG abnormalities were associated with pacemaker implantation and mortality.

Materials and methods: In this cohort study, 51 genetically verified AGel amyloidosis patients (mean age 66 years) without cardiac pacemakers underwent 12-lead ECG and CMR imaging with contrast agent in 2017. Patients were followed-up for 3 years.

Results: Conduction disturbances were found in 22 patients (43%). 9 (18%) presented with first-degree atrioventricular block, 6 (12%) with left anterior hemiblock, 7 (14%) with left or right bundle branch block and 2 (4%) with non-specific intraventricular conduction delay. Low QRS voltage was present in 2 (4%) patients. Late gadolinium enhancement (LGE) concentrating on the interventricular septum and inferior parts of the heart was present in 19 (86%) patients with conduction abnormalities. During the follow-up, only one patient received a pacemaker, and one patient died.

Discussion: Conduction disorders and septal LGE are common in AGel amyloidosis, whereas other ECG and CMR findings typically observed in most common cardiac amyloidosis types were rare. Septal pathology seen in CMR may interfere with the cardiac conduction system in AGel amyloidosis, explaining conduction disorders, although pacemaker therapy is rarely required.

Keywords: Finnish gelsolin amyloidosis, Meretoja's disease, electrocardiography, conduction disease, cardiac magnetic resonance

Abbreviations:

AGel amyloidosis – Finnish type of hereditary gelsolin amyloidosis

AL amyloidosis – Immunoglobulin light-chain amyloidosis

ATTR amyloidosis – Transthyretin amyloidosis

AV – Atrioventricular

CMR – Cardiac magnetic resonance imaging

ECG – Electrocardiographic, electrocardiogram

GSN – Gelsolin

LAHB – Left anterior hemiblock

LBBB – Left bundle branch block

LGE – Late gadolinium enhancement

LVH – Left ventricular hypertrophy

RBBB – Right bundle branch block

Introduction

The Finnish type of hereditary gelsolin amyloidosis (AGel amyloidosis or Meretoja's disease) is a systemic amyloidosis with an autosomal dominant, fully penetrant inheritance pattern [1,2]. The disease is usually caused by a c.640G>A, or less commonly a c.G640G>T, mutation in the gelsolin (GSN) gene. This leads to the abnormal processing of the variant GSN molecule, its misfolding, and ultimately to gelsolin-derived amyloid accumulation in various tissues. As a part of the Finnish disease heritage, patients are primarily found in Finland, although the disease has also been reported in other countries [2]. AGel amyloidosis is conventionally characterized by ophthalmological, neurological and cutaneous symptoms that patients generally notice in middle age, although the disease manifests already earlier, commonly under the age of 30, with corneal lattice dystrophy [2,3]. In addition, AGel amyloid deposits have been identified in the heart in histological studies [4,5] and myocardial involvement in AGel amyloidosis has also been demonstrated with magnetic resonance imaging [6].

Other amyloid diseases have also been shown to lead to cardiac amyloid depositions, immunoglobulin light-chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) being the most common [7], with varying clinical manifestations. Low voltage and pseudoinfarction pattern represent the classic electrocardiographic (ECG) findings of cardiac amyloidosis [7], but atrial fibrillation and atrioventricular and intraventricular conduction disturbances are also often seen in AL and ATTR amyloidoses [8]. Although clinically significant cardiomyopathy in AGel amyloidosis appears to be rare [9], some small case series have reported cardiac involvement and cardiac conduction

defects [1,2,10-13]. The prevalence of cardiac pacemakers has been higher in AGel amyloidosis patients compared with the general population [3].

Using a comprehensive patient series, this study aimed to investigate cardiac manifestations associated with AGel amyloidosis and to evaluate the relationship between ECG findings and cardiac magnetic resonance (CMR) findings. In addition, we assessed the need for pacemaker therapy and all-cause mortality in these patients.

Materials and Methods

The local ethics committee and the institutional review board of the Helsinki University Hospital approved this study. Patients were selected from the Finnish gelsolin amyloidosis patient registry (FIN–GAR), which was established in 2013 [3]. Informed consent was obtained from each patient before the investigations. A total of 51 genetically confirmed AGel amyloidosis patients aged ≥ 50 years were included in the study, with the following exclusion criteria: implanted cardiac pacemaker, claustrophobia, and metal instruments in the body which could interfere with CMR. The age-criteria was set to ≥50 years of age due to the late onset of symptoms and slow disease progression [3].

All study subjects underwent a clinical examination by the same physician (T.M.) at Helsinki University Hospital 2017. Study subjects were first interviewed on their general health status, cardiac events and symptoms, medications and possible previous diagnoses and family history of cardiac pacemakers. Cardiovascular examination focused on signs of cardiac pathology, and an orthostatic test was performed. For all

patients, survival status and clinical history, including pacemaker implantation, was obtained from medical records and/or by telephone contact in October 2020.

ECGs were measured and analysed by an experienced physician (A.H.). A low QRS voltage was defined as QRS amplitude ≤0.5 mV in all limb leads or ≤1.0 mV in all precordial leads. Poor R wave progression was defined as R wave amplitude ≤3.0 mm in V3 and RV2 ≤ RV3 and no left bundle branch block (LBBB) or left ventricular hypertrophy (LVH) present. Pseudo-infarction pattern was defined as pathological Q-waves in two contiguous leads, and no LBBB or LVH [14] . LVH on ECG was assessed using the Sokolow–Lyon and Cornell voltage criteria. The American Heart Association's (AHA) recommendations were used for the interpretation of intraventricular conduction disturbances [15] . First-degree atrioventricular (AV) block was defined as PR interval >200 ms.

The structure and function of the heart were studied using CMR with cine imaging and late gadolinium enhancement (LGE) assessment. CMR methods and results have previously been described in more detail (one patient was excluded from the earlier extensive CMR analyses because of suboptimal image quality, but LGE and LVH findings of this patient have been included in the present study) [6]. Anatomical LVH was defined as left ventricular wall thickness >12mm, and severe LVH as wall thickness ≥15mm.

Results

Clinical and electrocardiographic characteristics

In total, 51 patients (67% female) took part in this study. The mean age was 66 (range 50–77 years). Table 1 summarises the data on clinical and ECG findings. Conduction abnormalities were present in a total of 22 patients (43%) on ECG. Altogether, 9 (18%) patients had first-degree AV block, 6 (12%) left anterior hemiblock (LAHB), 4 (8%) right bundle branch block (RBBB), 3 (6%) LBBB and 2 (4%) non-specific intraventricular conduction delay (IVCD). Two patients (4%) had both first-degree AV block and LAHB. LVH on ECG was present in 7 patients (14%). Low QRS voltages were found in 2 patients (4%), both in the limb leads. 16 (31%) patients had a normal ECG (none of the abnormal findings presented in Table 1). When divided into two groups based on age (cut-off 65 years), conduction abnormalities were more prevalent in the older age group (Table 2).

Correlation of imaging findings with the electrocardiogram

All study patients underwent CMR, with mean left ventricular ejection fraction (LVEF) of 61±7%. LGE was present in 19 (86%) of the patients with conduction abnormalities and in 50% with normal ECG and was almost solely concentrated on the ventricular septum and inferior left ventricle (Figure 1). Cross-sectional data on LGE and conduction abnormalities are presented in Table 3. Among patients with LGE, 45% presented with first-degree AV-block or prolonged QRS duration, compared with 8% of those without LGE present. Altogether, abnormal ECG findings were present in 79% of subjects with LGE in CMR and 38% of subjects without LGE in CMR.

A total of 29 patients (57%) had LVH >12mm in CMR, 11 (22%) with severe LVH ≥15mm. In most cases hypertrophy was confined to the ventricular septum. Nine (31%) of these patients with ventricular hypertrophy did not have a hypertension diagnosis.

Only 5 (17%) patients with increased wall thickness in CMR presented with ECG signs of LVH. Conversely, 5 (71%) of the 7 patients with LVH on ECG also had a thickened ventricular wall in CMR.

Follow-up

During the 3-year follow-up, one cardiac pacemaker was implanted and one patient underwent ongoing cardiac investigations due to recurrent syncope. One case of new atrial fibrillation and LBBB appeared in the study population. One patient had deceased.

Discussion

In this study, we present ECG findings in AGel amyloidosis patients and their correlation with structural changes in CMR. Atrioventricular and intraventricular conduction disorders represented a common ECG manifestation in AGel amyloidosis, and these ECG abnormalities correlated strongly with LGE findings in CMR imaging. However, despite high prevalence of conduction abnormalities and LGE, advanced conduction disease necessitating pacemaker therapy was rare at three years.

Conduction abnormalities alongside low voltage and pseudo-infarction patterns on ECG are characteristic findings in cardiac amyloid diseases [7]. While low voltage and pseudo-infarction patterns on ECG were rare in AGel amyloidosis, conduction abnormalities were relatively common. In the present study, LAHB, RBBB and LBBB were present in 12%, 8% and 6% of patients respectively, which was significantly higher than the reported prevalence of LAHB, RBBB and LBBB, 2% each, in an elderly Finnish general population [16]. Similarly, first-degree AV-block (PR-interval

>200ms) was a common finding, present in 18% of AGel amyloidosis patients, which is three times more than the 6% prevalence of prolonged PR-interval in the general population aged ≥60 years [18], although the use of beta blocker medication among AGel amyloidosis patients could have influenced these numbers.

In the general population, intraventricular conduction disorders are also associated with adverse prognoses [17]. Similarly, based on a recent meta-analysis, PR-interval prolongation seemed to be associated with mortality, heart failure and atrial fibrillation [18], although in some younger study populations first degree AV block seems to be a benign phenomenon [19]. In AGel amyloidosis, an increased prevalence of cardiac pacemakers (4% in a sample with a mean age of 62 years) has been described [3] and several case reports regarding conduction disturbances [1,2,10-13] have been published. However, in the present study only one of the 51 patients died, and one pacemaker was implanted during the 3-year follow-up, suggesting a relatively benign course of the conduction abnormalities in AGel amyloidosis.

In other types of cardiac amyloidosis, conduction disorders are even more commonly encountered. In a study comparing various types of biopsy-proven systemic amyloidosis with echocardiographic evidence of cardiac involvement, AL amyloidosis had the respective prevalences of LAHB, RBBB and LBBB 29%, 19% and 4% (mean age 60 years), hereditary ATTR amyloidosis 30%, 12% and 7% (mean age 52 years), and wild-type ATTR amyloidosis 20%, 13% and 40% (mean age 76 years). In the same study, the prevalence of first-degree AV-block in AL amyloidosis, hereditary ATTR amyloidosis and wild-type ATTR amyloidosis was 18%, 25% and 33% respectively [8]. Thus, compared to AGel amyloidosis, the prevalence of conduction disorders in

other cardiac amyloidoses seem to be generally higher, though the frequency and severity of cardiac conduction disorders in cardiac amyloid diseases varies depending on the duration of the disease. AGel amyloidosis typically manifests at the age of 25-30 with ophthalmological signs, followed later by other symptoms generally noticed by the patients in their 50s or 60s [2,3]. Thus, the patient cohort in this study (age range 50-77) represents a fairly advanced stage of the disease and increasing prevalence of conduction defects was seen especially in patients aged ≥65 years.

CMR is a useful test for diagnosing cardiac amyloidosis, with 86% sensitivity and 92% specificity in AL and ATTR amyloidosis [20]. However, in this cohort of AGel amyloidosis patients CMR findings have been shown to differ from those of typical cardiac amyloid disease. Local LGE was common (noted in 75% of the patients), but it concentrated mainly on the ventricular septum and inferiorly [6], rather than globally and subendocardially as in AL amyloidosis, or transmurally like in ATTR amyloidosis [21]. The septal pathology could possibly represent the underlying cause of the high prevalence of conduction disease among AGel amyloidosis patients, as the ventricular septum comprises an important part of the electrical conduction system of the heart. In these patients, there was a noteworthy association between LGE and conduction abnormalities. Nearly half of the patients with LGE had a first-degree AV-block or prolonged QRS duration, compared to less than 10% of those without LGE. The underlying cause of LGE in AGel amyloidosis requires histological verification, as it could be due to any process expanding the interstitial space, for example interstitially accumulating amyloid protein or fibrosis. In a previous histopathological autopsy study, AGel amyloid deposits in the heart were demonstrated in all study subjects, but only in minor amounts and co-localized with excess fibrosis in every case [5]. So far,

the pathophysiology behind conduction alterations in cardiac amyloidosis remains unclear. Results from previous studies are conflicting, some favouring amyloid infiltration of the conduction system [22,23] and others suggesting fibrosis and atrophy [24] or cardiac sympathetic denervation to be the cause [12].

In addition to septal LGE, thickness of the ventricular septum was increased in the majority of patients [6]. The increased wall thickness could be due to myocardial hypertrophy, as hypertension was relatively prevalent among the patients. However, it could also be due to infiltrative processes, such as interstitial accumulation of AGel or fibrous tissue, as ventricular wall thickness was also increased in many patients without hypertension. Interestingly, while increased left ventricular thickness in CMR was a common finding in AGel amyloidosis, this was rarely reflected as LVH in the ECG of these patients. This can be due to different sensitivities of the methods or partially different mechanisms behind anatomical and electrical LVH [25]. On the other hand, increased wall thickness combined with low or normal QRS voltage is a typical finding in cardiac amyloidosis [7].

Limitations

Although a 51-patient series for a rare disease is a satisfactory sample size, a larger cohort with a matched control group would have been ideal. In addition, cardiac biomarkers, such as N-terminal propeptide of brain natriuretic peptide and troponin, which have been shown to be elevated in AL and ATTR cardiac amyloidoses [26], were not measured. While CMR is the gold standard in imaging, echocardiography could have provided more specific data on diastolic function, shown to be commonly impaired in cardiac amyloidosis [26]. Myocardial LGE represents a non-specifically

expanded interstitial space and without a histological examination it cannot be confirmed to represent amyloid or fibrosis. This study covers only AGel amyloidosis patients aged 50–77 years and some of the patients with probably the most remarkable cardiac involvement were likely excluded from this study due to having a pacemaker, which may have led to underestimating the prevalence of conduction disease in these patients.

Conclusions

In AGel amyloidosis patients, conduction abnormalities were common and there was a notable association between conduction defects and septal LGE in CMR, possibly explaining the high prevalence of conduction abnormalities. By contrast, low QRS voltage and pseudoinfarction pattern on ECG, typical in other cardiac amyloidoses, were rare in AGel amyloidosis. Although advanced conduction defects necessitating pacemaker therapy were rarely observed during this study, follow-up of these patients from middle age onwards, possibly involving CMR, may be indicated for early detection of conduction disease.

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Table 1. Clinical and electrocardiographic (ECG) findings in AGel amyloidosis patients (n=51).

Parameter	Value
Clinical findings	
Age, yrs	66 ± 6
Female	34 (67%)
Systolic blood pressure, mmHg	149 ± 22
Diastolic blood pressure, mmHg	90 ± 8
Hypertension	33 (65%)
Coronary heart disease	2 (4%)
History of syncope	3 (6%)
Orthostatic hypotension	14 (27%)
Arrhythmia symptoms	21 (41%)
Beta blocker medication	15 (29%)
First-degree relative with AGel amyloidosis and pacemaker	6 (12%)
Electrocardiographic findings	
Heart rate, bpm	68 ± 11
PR interval, ms	175 ± 31
QRS duration, ms	101 ± 19
QRS duration >120 ms	7 (14%)
QTc duration, ms	437 ± 28
Atrial fibrillation	1 (2%)
Atrial premature beats	5 (10%)
Ventricular premature beats	3 (6%)
Low QRS voltage	2 (4%)
Poor R wave progression	7 (14%)
Pseudo-infarction pattern	2 (4%)
LVH	7 (14%)
Conduction disturbances	22 (43%)
First-degree AV block*	9 (18%)
LAHB	6 (12%)
RBBB	4 (8%)
LBBB	3 (6%)
IVCD	2 (4%)

IVCD = intraventricular conduction delay; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; RBBB = right bundle branch block; QTc = corrected QT interval

Data are presented as n (%) or mean ± SD.

* PR >200ms. No cases of 2nd or 3rd degree AV-block were observed. 2 patients had 1-degree AV block and LAHB

Table 2. Prevalence of conduction disturbances in two age groups: <65 years (n=25, median 61 yrs) and ≥65 yrs (n=26, median 71 yrs).

Parameter	Age 50-65 yrs n (%)	Age ≥65 yrs n (%)
Abnormal conduction*	8 (32%)	16 (62%)
First-degree AV block	3 (12%)	6 (23%)
LAHB	2 (8%)	4 (15%)
RBBB	1 (4%)	3 (12%)
LBBB	0 (0%)	3 (12%)
IVCD	2 (8%)	0 (0%)

IVCD = intraventricular conduction delay; LAHB = left anterior hemiblock; LBBB = left bundle branch block; RBBB = right bundle branch block
*PR >200ms, LAHB, LBBB, RBBB or IVCD

Table 3. Cross-sectional data on conduction disorders and late gadolinium enhancement (LGE vs. no LGE) *.

	First-degree AV-block or QRS > 110ms	First-degree AV-block	LAHB	RBBB	LBBB	IVCD
LGE (n=38)	17 (45%)	8 (21%)	4 (11%)	4 (11%)	3 (8%)	2 (5%)
No LGE (n=13)	1 (8%)	1 (8%)	2 (15%)	0 (0%)	0 (0%)	0 (0%)

IVCD = intraventricular conduction delay, LAHB = left anterior hemiblock, LBBB= left bundle branch block, RBBB= right bundle branch block

*Two patients had both first-degree atrioventricular block and left anterior hemiblock.

Data are presented as n (%)

Figure captions

Figure 1. Cardiac magnetic resonance (CMR) images of a 77-year-old male with AGel amyloidosis and both first-degree atrioventricular block and left anterior hemiblock. The short-axis cine image shows hypertrophic basal interventricular septum (a) and intramyocardial patchy late gadolinium enhancement in the same area (b).

RV = right ventricle; LV = left ventricle