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Life-threatening arrhythmic presentation in patients with arrhythmogenic cardiomyopathy before and after entering the genomic era; a two-decade experience from a large volume center☆

Christine Rootwelt-Norberg [a,b], Øyvind H. Lie [a,b,c], Lars A. Dejgaard [a,b,c], Monica Chivulescu [b], Ida S. Leren [a,b,c], Thor Edvardsen [a,b,c], Kristina H. Haugaa [a,b,c,*]

[a] Department of Cardiology, Oslo University Hospital, Rikshospitalet, PO Box 4950, Nydalen, 0424 Oslo, Norway
[b] Center for Cardiological Innovation, Oslo University Hospital, Rikshospitalet, Domus Medica 4 (DM4), PO Box 4950, Nydalen, 0424 Oslo, Norway
[c] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, PO Box 1171, Blindern, 0318 Oslo, Norway

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ABSTRACT

Background: Arrhythmogenic cardiomyopathy (AC) is an inheritable progressive heart disease with high risk of life-threatening ventricular arrhythmia (VA). We aimed to explore the prevalence of VA as presenting event in patients with AC over two decades, symptoms preceding VA and compare the clinical presentations and rate of AC-diagnosis over time.
Methods: We included consecutive AC-patients from our tertiary referral center. We recorded clinical history, VA (aborted cardiac arrest, sustained ventricular tachycardia or appropriate implantable cardioverter-defibrillator therapy), cardiac symptoms preceding VA in AC, and compared the history of patients diagnosed before and after implementation of genetic testing.
Results: We included 179 consecutive AC-patients and mutation-positive family members (95 [53%] probands, 84 [45%] female, 49 ± 17 years), 33 (18%) diagnosed before and 146 (82%) after genetic testing became available. VA led to the AC-diagnosis in 46 (26%), and was less prevalent after implementation of genetic testing (17[52%] vs. 29[20%], $p < 0.001$), also when adjusted for proband status (Adjusted OR 2.7, 95% CI 1.1–6.7, $p = 0.03$). Yearly rate of AC-diagnosis increased after implementation of genetic testing in probands (2.7 ± 1.3 vs. 6.8 ± 4.3, $p = 0.01$) and family members (0.7 ± 1.1 vs. 7.7 ± 5.9, $p = 0.002$). Most patients with VA (92%) reported cardiac symptoms prior to event, and exercise-induced syncope was the strongest marker of subsequent VA (Adjusted OR 5.3, 95% CI 1.7–16.4, $p = 0.004$).
Conclusion: VA led to AC-diagnosis in 46% of probands and was preceded by cardiac symptoms in the majority of cases. Yearly rate of AC-diagnoses increased after the implementation of genetic testing and life-threatening presentation of AC-disease seemed to decrease.

1. Introduction

Arrhythmogenic cardiomyopathy (AC) is an inheritable, progressive heart disease caused by dysfunctional cardiac desmosomes, resulting in myocardial necrosis, fibrofatty replacement, impaired cardiac function, and high risk of life-threatening ventricular arrhythmia [1]. Ventricular arrhythmia has been reported as a common first manifestation of AC affecting more than half of probands [2–5], with sudden cardiac death as a feared presenting event [6]. Sudden cardiac death is more frequently a presenting symptom than a later symptom of the disease [2,7]. This indicates that once the AC-patient is diagnosed, treated and monitored, the mortality is relatively low, ranging from 1.5 to 6% [2,8,9]. Therefore, identification of risk individuals and early diagnosis are vital to prevent sudden death. Ventricular arrhythmia as presenting event of AC is difficult to prevent in patients without family history. However, ventricular arrhythmia may be preceded by warning symptoms which could facilitate early diagnosis if recognized. Data on warning symptoms before ventricular arrhythmia in AC are diverging [4,6,8,10–12].

The era of genetic testing has shifted the patient population towards more mutation-positive family members with no or early disease,

Abbreviations: AC, arrhythmogenic cardiomyopathy; ICD, implantable cardioverter defibrillator; VA, ventricular arrhythmia; VF, ventricular fibrillation.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Department of Cardiology, Oslo University Hospital, Rikshospitalet, Sognsvannsveien 20, 0372, PO Box 4950, Nydalen, 0424 Oslo, Norway.
E-mail addresses: christine.rootwelt@rr-research.no (C. Rootwelt-Norberg), oyvind.haugen.lie@rr-research.no (Ø.H. Lie), lars.andreas.dejgaard@rr-research.no (L.A. Dejgaard), thor.edvardsen@medisin.uio.no (T. Edvardsen), kristina.haugaa@medisin.uio.no (K.H. Haugaa).

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providing us with the opportunity to study early disease and the responsibility to prevent the most unwanted events. Whether the first presentation of AC has changed since the implementation of genetic testing and the increased awareness of the disease has not been explicitly studied.

We aimed to explore the prevalence of ventricular arrhythmia and ventricular arrhythmia as first disease manifestation in AC-patients during two decades and to report any preceding symptoms.

2. Methods

2.1. Study population and design

Patients diagnosed with AC at the Department of Cardiology, Oslo University Hospital, Rikshospitalet, were consecutively included in a cohort study from 1997 to 2017. To assess changes in clinical presentation over time, data were analyzed in two separate cohorts; patients diagnosed between January 1st 1997–December 31st 2006 and between January 1st 2007–February 1st 2017. Genetic testing became available in Norway in 2007 and the second cohort was therefore consecutively genetically tested, while the first cohort was tested retrospectively.

All patients met 2010 Task Force Criteria [13] for definite, borderline or possible AC-diagnosis. These diagnostic criteria were applied retrospectively for patients identified before 2010. Probands, defined as individuals without known family history of AC who were seeking medical attention due to clinical manifestations of potential AC-disease, were screened for pathogenic mutations. Mutation-negative probands were only included if a definite AC-diagnosis was fulfilled by the 2010 Task Force Criteria, and their family members were not included. Mutation-positive family members of mutation-positive probands were included. Patients with cardiopulmonary comorbidities were excluded. All underwent clinical examination [14], and AC associated medication was recorded. Clinical characteristics, age at first contact and arrhythmic events were recorded. First contact was defined as first AC-evaluation at our center. All participants underwent a structured interviewed about symptoms and first disease manifestation. Written informed consent was obtained from every patient. The study conforms to the Declaration of Helsinki and was approved by the Regional Medical Ethics Committee of South-Eastern Norway.

2.2. Ventricular arrhythmia as first disease manifestation

Ventricular arrhythmia was defined as sustained ventricular tachycardia (VT) documented on 12 lead electrocardiogram or 24 hour Holter recordings, ventricular fibrillation, appropriate implantable cardioverter defibrillator (ICD) therapy (anti-tachycardia pacing or shock) or aborted cardiac arrest. Sustained VT was defined as runs of ventricular beats ≥100 beats per minute lasting longer than 30 s or requiring intervention earlier due to hemodynamic instability [15]. Aborted cardiac arrest was defined as avoided sudden cardiac death by cardio-pulmonary resuscitation and/or defibrillation. Appropriate ICD-therapy was defined as anti-tachycardia pacing or shock therapy for documented VT or VF. Exercise-induced arrhythmic event was defined as ventricular arrhythmia occurring during or within 30 min after exercise. Ventricular arrhythmia was defined as the presenting event if it led to clinical evaluation for cardiac disease in a previously undiagnosed patient.

2.3. Cardiac symptoms

All medical records were reviewed, and cardiac symptoms were recorded. If symptoms were not explicitly documented or timed in relation to arrhythmic event, subjects were contacted by telephone for a structured interview. Cardiac symptoms were defined according to current guidelines, including dyspnea, chest pain, palpitations, dizziness, pre-syncope and suspected cardiac syncope [16]. In patients with history of ventricular arrhythmia, only symptoms before the first documented arrhythmic event were registered. Consequently, all symptoms were registered in patients without prior ventricular arrhythmia.

2.4. Genetic testing

Genetic testing for AC was introduced in Norway in 2007. Genomic DNA was isolated from peripheral blood and analyzed as part of the diagnostic workup. Genes encoding plakophilin-2 (PKP2, GenBank: X97675.1), desmocollin-2 (DSC2, GenBank: X56807.1), desmoglein-2 (DSG2, GenBank: Z26317.1), desmoplakin (DSP, GenBank: J05211.1) genes and 29 of the 105 exons of the ryanodine receptor-2 (RYR2, GenBank: X91869.1) were screened for pathogenic mutations. Family members of probands with definite diagnosis variants of uncertain significance were only included if family history was present as previously described [17,18].

2.5. Statistics

Values were expressed as mean ± standard deviations or frequencies with percentages, and were compared by Student's *t*-test, chi-square test or Fisher's exact test as appropriate (SPSS 21.0, SPSS Inc., Chicago, Il, USA). To assess the value of cardiac symptoms as markers of ventricular arrhythmia, we performed multivariable logistical regression including potentially confounding variables (sex and age). To assess the prevalence of ventricular arrhythmia as presenting event in patients diagnosed before and after implementation of genetic testing in 2007, multivariable logistical regression analyses was adjusted for proband status. p-Values were two-sided, and values <0.05 were considered significant.

3. Results

3.1. Study population

In total, 192 patients were eligible for inclusion, of which 13 (7%) patients were excluded (10 with heart or lung comorbidities, and 3 were lost to follow-up). Consequently, we included 179 patients (Table 1). Ventricular arrhythmia occurred in 80 patients (45%) at age 41 ± 15 years, and 10% of patients had experienced aborted cardiac arrest. Thirty-three patients (18%) were diagnosed before 2007 and 146 (82%) from 2007, when genetic testing was introduced (Table 2). Genetic analyses were performed in 88 of 95 probands. Forty-five (51%) of the genetically tested probands were mutation-positive, and 84 mutation-positive family members were identified by genetic cascade screening. Importantly, the number of probands diagnosed per year increased after the introduction of genetic testing in 2007 (from 2.7 ± 1.3 per year to 6.8 ± 4.3 per year, p = 0.01). Furthermore, as expected, the mean number of identified family members per proband increased after 2007 (p = 0.04) (Table 2). Of the 129 mutation positive, the genes affected were 110 (85%) PKP2, 9 (7%) DSP, 8 (6%) DSG2 and 2 (2%) DSC2.

3.2. Prevalence of ventricular arrhythmia as presenting event in AC

Ventricular arrhythmia led to AC-diagnosis in 46 (26%) patients (44 [46%] probands and 2 [2%] mutation-positive family members, Table 1). Ventricular arrhythmia as presenting event occurred as aborted cardiac arrest in 28%, and the arrhythmic event was exercise-induced in 74%. We observed no sex differences in prevalence of ventricular arrhythmia as presenting event (21% females vs. 29% males, p = 0.22), and no sex difference in arrhythmic events in probands

Table 1
Clinical characteristics of 179 AC-patients.

	All n = 179	Probands n = 95	Family members n = 84	p-Value
Age, years	42 ± 17	45 ± 15	38 ± 18	0.01
Female, n(%)	80 (45)	34 (36)	46 (55)	0.01
Electrocardiography				
Epsilon, n(%)	19 (11)	17 (18)	2 (2)	0.001
Major TWI, n(%)	54 (30)	43 (45)	11 (13)	<0.001
Minor TWI, n(%)	19 (11)	10 (11)	9 (11)	0.99
TAD >55 ms, n(%)	17 (9)	12 (13)	5 (6)	0.12
Abnormal SAECG, (n = 150) n(%)	85 (47)	54 (57)	31 (37)	<0.001
Ventricular arrhythmia				
Presenting event VA, n(%)	46 (26)	44 (46)	2 (2)	<0.001
- ACA	13 (7)	13 (14)	0 (0)	<0.001
- VT	33 (18)	31 (33)	2 (2)	<0.001
- Exercise-induced VA	32 (18)	30 (33)	2 (2)	<0.001
Age at presenting event VA, years	41 ± 16	42 ± 16	28 ± 15	0.24
Total VA, n(%)	80 (45)	75 (79)	5 (6)	<0.001
- ACA	18 (10)	18 (19)	0 (0)	<0.001
- VT	62 (35)	59 (62)	3 (4)	<0.001
- ICD therapy	53 (30)	48 (51)	5 (6)	<0.001
- Exercise-induced VA	50(30)	47 (53)	3 (4)	<0.001
Age at VA, years	41 ± 15	41 ± 15	41 ± 17	0.99
Medication, n(%)	82 (46)	65 (68)	17 (20)	<0.001
- Beta blocker	59 (33)	45 (43)	14 (17)	<0.001
- Sotalol	14 (8)	13 (14)	1 (1)	0.002
- Flecainide	5 (3)	4 (4)	1 (1)	0.22
- Amiodarone	6 (4)	5 (5)	1 (1)	0.13

Values are mean ± SD if not stated otherwise. p-Values by unpaired Student's *t*-test, chi-square or Fisher's exact test as appropriate. AC = arrhythmogenic cardiomyopathy; ACA = aborted cardiac arrest; ICD = implantable cardioverter defibrillator; SAECG = signal averaged electrocardiogram; TAD = terminal activation duration; TWI = T-wave inversion, VA = ventricular arrhythmia; VT = ventricular tachycardia.

Table 2
Clinical characteristics of AC-patients diagnosed before and after the introduction of genetic testing program.

	Diagnosed before 2007, n = 33	Diagnosed from 2007, n = 146	p-Value
Age, years	39 ± 16	42 ± 17	0.29
Female, n(%)	14 (42)	66 (45)	0.77
Proband, n(%)	26 (79)	69 (47)	0.001
Yearly rate of diagnosis probands, n	2.7 ± 1.3	6.8 ± 4.3	0.01
Yearly rate of diagnosis family members, n	0.7 ± 1.1	7.7 ± 5.9	0.002
Yearly number of diagnosed family members per proband, n	0.4 ± 0.7	3.0 ± 3.2	0.04
Definite AC, n(%)	24 (73)	79 (54)	0.05
Presenting event VA, n(%)	17 (52)	29 (20)	<0.001
- Presenting event ACA	3 (9)	10 (7)	0.71
- Presenting event sustained VT	14 (42)	19 (13)	<0.001
Total VA, n(%)	28 (85)	52 (36)	<0.001
- Total ACA	3 (9)	15 (10)	0.88
- Total sustained VT	23 (70)	39 (27)	<0.001
- Total ICD therapy	18 (55)	35 (24)	0.001
Presenting event exercise-induced VA, n(%)	12 (38)	20 (14)	0.002
Exercise-induced VA, n(%)	19 (58)	31 (21)	<0.001
Probands only	n = 26	n = 69	
Age, years	42 ± 15	46 ± 15	0.25
Female, n(%)	12 (46)	22 (32)	0.20
Presenting event VA, n(%)	15 (58)	29 (42)	0.17
- ACA	3 (12)	10 (14)	1.0
- Sustained VT	12 (46)	19 (28)	0.08
- Exercise-induced VA	10 (40)	20 (30)	0.36
All VA, n(%)	25 (96)	50 (72)	0.01
- ACA	3 (12)	15 (22)	0.38
- VT	20 (77)	38 (55)	0.07
- ICD therapy	15 (58)	33 (48)	0.39
- Exercise-induced VA	16 (62)	31 (45)	0.07

Values are mean ± SD if not stated otherwise. p-Values by unpaired Student's *t*-test, chi-square or Fisher's exact test as appropriate. AC = arrhythmogenic cardiomyopathy; ACA = aborted cardiac arrest; ICD = implantable cardioverter defibrillator; VA = ventricular arrhythmia, VT = ventricular tachycardia.

only (76% females vs. 80% males, p = 0.66), nor in separate analyses of definite AC only (24% females vs. 32% males, p = 0.36). Furthermore, we observed no difference between the prevalence of ventricular arrhythmia as presenting event in mutation positive and mutation negative probands (54% mutation positive vs. 39% mutation negative, p = 0.13).

In patients diagnosed with AC before 2007 (n = 33), 17 patients (52%) presented with ventricular arrhythmia compared to 29 patients (20%) diagnosed with AC from 2007 (n = 146, p < 0.001), Table 2. However, there was a higher proportion of family members in the cohort diagnosed from 2007 (7/33 (21%) vs. 77/146 (52%), p < 0.01). Comparing only probands before and after implementation of genetic testing, 58% of probands presented with ventricular arrhythmia before 2007, compared to 42% of probands diagnosed from 2007 (p = 0.17, Table 2). In logistic regression analysis adjusted for proband status, odds of ventricular arrhythmia as presenting event was higher in patients diagnosed before 2007 than in those diagnosed from 2007 (OR 2.7, 95% CI 1.1–6.7, p = 0.03). Furthermore, when evaluating only patients presenting with definite AC, more patients presented with ventricular arrhythmia before than after 2007 (43% vs. 23%, p = 0.03). This was also the case for age-related risk of ventricular arrhythmia as presenting event in Cox regression analysis (HR 2.9, 95% CI 1.2–6.3, p = 0.009, Fig. 1).

Importantly, no family members (0 of 77) had experienced ventricular arrhythmia pre-diagnosis after the implementation of genetic testing, while 2 of 7 (29%) family members in the first cohort presented with ventricular arrhythmia (p = 0.006). The two family members who had experienced ventricular arrhythmia before the diagnosis was made were a 38 year old male with several episodes of exercise-induced ventricular arrhythmia with assumed myocarditis. He had a relative who was diagnosed with AC, and was later genetically diagnosed with AC by cascade genetic screening. The other family member was a 17 year old male with ventricular arrhythmia during exercise. He had positive family history of AC, but was not diagnosed with AC at time of the event. He was found to be mutation-positive when genetic testing became available.

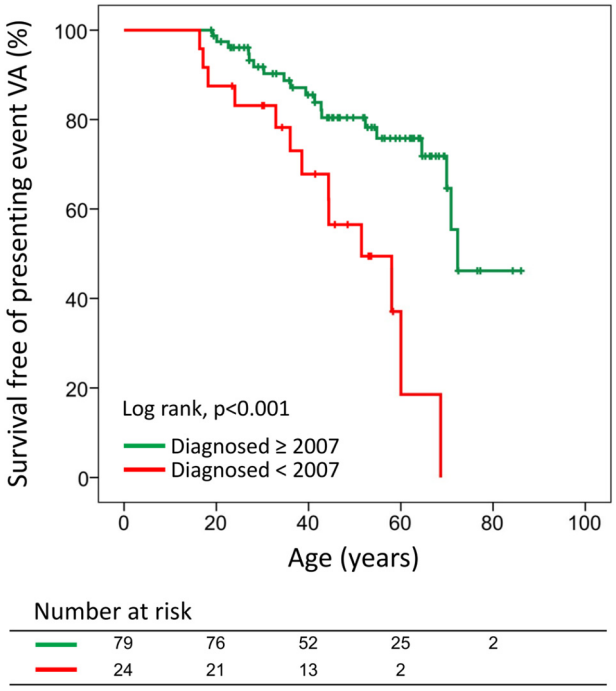

Fig. 1. Curves of estimated age-adjusted survival free from VA as presenting event in 103 patients presenting with definite AC, grouped by time of diagnosis before (n = 24) and after (n = 79) the introduction of genetic testing program in 2007. AC = arrhythmogenic cardiomyopathy; VA = life-threatening ventricular arrhythmia.

From 2007, 3 mutation-positive family members experienced ventricular arrhythmia, all of them during treatment and follow-up at our clinic. Two had a primary preventive ICD and received appropriate therapy, while the third was treated with anti-arrhythmic medications when he experienced stable VT during exercise.

The occurrence of aborted cardiac arrest as presenting event did not differ before and from 2007 (3 (9%) patients vs. 10 (7%) patients, p = 0.71). The total occurrence of arrhythmic events was lower in the cohort diagnosed from 2007 compared to those diagnosed before 2007 (p < 0.001), also when comparing probands only (p = 0.01, Table 2).

3.3. Symptoms

Cardiac symptoms were common in all patients, but more prevalent in patients who later experienced ventricular arrhythmia than in patients without arrhythmic event (Table 3). Independent markers of

Table 3
Clinical characteristics and cardiac symptoms of 179 AC-patients without and with VA.

	No VA n = 99	VA n = 80	p-Value	Adjusted OR (95% CI)	p-Value
Age at baseline, years	40 ± 18	44 ± 15	0.16	1.0 (1.0–1.0)	0.13
Female, n(%)	53 (54)	27 (34)	0.008	0.4 (0.2–0.8)	0.007
Any symptom, n(%)	72 (73)	70 (92)	0.001	4.4 (1.7–11.6)	0.003
Dyspnea, n(%)	10 (10)	8 (11)	0.94		
Chest pain, n(%)	17 (18)	25 (33)	0.02	1.9 (0.9–4.0)	0.09
Palpitations, n(%)	56 (57)	50 (68)	0.13		
Dizziness, n(%)	32 (33)	39 (55)	0.005	2.6 (1.3–4.9)	0.005
Pre-syncope, n(%)	26 (27)	32 (44)	0.02	2.5 (1.2–4.9)	0.01
Syncope, n(%)	23 (23)	24 (31)	0.24		
Exercise-induced syncope, n(%)	5 (5)	13 (16)	0.01	5.3 (1.7–16.4)	0.004

Values are mean ± SD if not stated otherwise. Symptoms are step-wise adjusted for age at first contact and sex. p-Values by unpaired Student's *t*-test, chi-square or Fisher's exact test as appropriate. AC = arrhythmogenic cardiomyopathy; OR = odds ratio; VA = ventricular arrhythmia.

ventricular arrhythmia were dizziness, pre-syncope and exercise-induced syncope. Syncope <1 year before diagnosis had occurred in 10 patients, and all of them had documented ventricular arrhythmia within one year after syncope (13% of patients with subsequent event vs. 0% without event, $p < 0.001$). Syncope between 1 and 10 years before diagnosis and syncope >10 years before diagnosis were not associated with later ventricular arrhythmia (8% vs. 6%, $p = 0.70$, and 9% vs. 18%, $p = 0.07$, respectively). We observed no differences in the prevalence of symptoms in patients diagnosed before or after introduction of genetic testing (88% vs. 80%, $p = 0.31$), between the sexes (82% females vs. 80% males, $p = 0.73$) or between mutation positive and mutation negative probands (98% vs. 91%, $p = 0.36$). Lastly, there was no difference in symptoms in patients before aborted cardiac arrest and before other types of ventricular arrhythmia (93% vs. 92%, $p = 0.83$).

4. Discussion

Ventricular arrhythmia was a highly prevalent presenting symptom in AC, occurring in nearly half of AC-probands, reflecting the high risk of life-threatening arrhythmia as the first disease manifestation. The yearly rate of AC-diagnosis increased after implementation of genetic testing and the incidence of arrhythmic events as presenting event seemed to decrease, also when adjusted for the higher fraction of family members identified in the latter decade. Almost all patients were symptomatic before the first ventricular arrhythmia occurred, suggesting that warning symptoms of subsequent life-threatening arrhythmia were common.

4.1. Prevalence of ventricular arrhythmia as presenting event and changes in diagnostic rate after implementation of genetic testing

In a quarter of all subjects, and in almost half of AC-probands, ventricular arrhythmia led to the diagnosis of AC. This emphasizes that AC is a malignant disease, often manifesting dramatically in presumably healthy individuals. Our results indicated that the incidence of life-threatening ventricular arrhythmia as presenting event seemed to be lower in patients diagnosed with AC during the latter decade. The analyses were limited by the relatively sparse number of family members identified before implementation of genetic testing. After implementation of genetic testing in 2007, the yearly rate of AC-diagnosis increased both in probands and particularly in family members and the number of diagnosed family members per proband increased, highlighting the effect of family genetic testing on AC-diagnosis. Mutation-positive family members have inherently lower risk of ventricular arrhythmia. Still, our data, though not conclusive, may indicate a lower incidence of life-threatening arrhythmic presentation in recent years also when considering the higher fraction of family members. This tendency may be explained by the implementation of the 2010 Task Force Criteria and increased disease awareness among cardiologists in our region due to available genetic testing, leading to earlier diagnosis and closer follow-up of patients at risk.

None of the family members diagnosed by genetic family screening had experienced ventricular arrhythmia before evaluation at our center, in contrast to 2 of 7 family members in the early cohort. All family members who experienced ventricular arrhythmia after genetic screening had either a primary prevention ICD or were treated with anti-arrhythmic medication. These findings support the idea that genetic testing and subsequent follow-ups are beneficial in preventing ventricular arrhythmia as presenting symptom with subsequent physical and psychological traumatizing events [19]. Further studies of larger populations are necessary to confirm this finding. Importantly, incidence of ventricular arrhythmia as presenting event in the latter decade was still considerable with 20% in all individuals diagnosed with AC, and as many as 42% of probands. Dramatic and life threatening events are difficult to predict and prevent in probands, and these numbers underline the challenge of identifying all patients at risk.

The total prevalence of arrhythmic events was lower in the subgroup of probands diagnosed from 2007, indicating that probands diagnosed during the latter decade are more frequently diagnosed by imaging or other symptoms than ventricular arrhythmia. The incidence of aborted cardiac arrest as presenting symptom did not change in the last decade, and occurred in 7% of AC-patients from 2007. Half of these were competitive athletes, and could possibly have been identified by athlete screening. The other half had no known environmental risk factor for malignant presentation and represents a nearly impossible patient population to identify without population screening.

4.2. Warning symptoms

Cardiac symptoms were frequent, and ventricular arrhythmia had rarely occurred without preceding symptoms. Our result showed a higher frequency of preceding cardiac symptoms with 92% compared with previous studies of AC-patients, reporting symptoms in 41–51% of AC-patients before arrhythmic event [4,8,11,20]. These findings suggest that cardiac symptoms are common during the development of AC, and highlight the importance of a detailed symptom anamnesis in AC family members.

Exercise-induced syncope was the strongest marker of later ventricular arrhythmia, which is in concordance with previous studies [6]. Six patients who presented with ventricular arrhythmia had experienced exercise-induced syncope prior to this event. These cases of malignant presentation of AC-disease might potentially have been prevented if the exercise-induced syncope had led to clinical evaluation for heart disease. Furthermore, the more unspecific symptoms dizziness and pre-syncope were also independent markers of ventricular arrhythmia. This underlines that a wide range of symptoms should be addressed when evaluating AC-patients, with special emphasis on recent syncope and exercise-induced syncope. Based on these findings, AC-subjects should be informed to contact their cardiologist in case of change or increase in symptoms, and patients with exercise-induced syncope should be carefully examined for phenotypical signs of AC.

Cardiac symptoms were common also in AC-patients without ventricular arrhythmia and therefore limited the value of symptoms as a warning marker for arrhythmic events in known AC-patients.

4.3. Sex differences

Male sex has been reported as a risk factor for ventricular arrhythmia in several previous studies [8,9,21]. Our data suggested that although disease was more penetrant in men, and in line with other studies [12,22,23], women and men had similar risk of experiencing life-threatening ventricular arrhythmia as early disease manifestation. Female probands had similar risk as male probands for ventricular arrhythmia, and therefore, females with overt AC should not be regarded as having lower risk for arrhythmic events than males.

4.4. Limitations

This is a cohort study with retrospective and cross-sectional elements, with inherent limitations. All patients were included from a tertiary care center, which may be associated with selection bias. The single center design may have limited the external validity of the results. Information collected by structured interview may have been influenced by patient recall bias. We recorded the time from first syncope to ventricular arrhythmia as presenting event. It would be interesting to investigate the time from first cardiac symptom to ventricular arrhythmia, but this was not possible due to profound recall bias for unspecific and less alarming symptoms (palpitations, dizziness etc.).

Our study assessed clinical presentation of AC-disease over time. AC-disease presentation was influenced by a variety of factors, including introduction of genetic testing and change in clinical practice due to introduction of 2010 Task Force Criteria, among others.

5. Conclusion

In almost half of all AC-probands, a life-threatening ventricular arrhythmia led to their first evaluation for AC. These events were frequently exercise-induced and preceded by cardiac symptoms, such as recent syncope and exercise-induced syncope, indicating that warning symptoms may be more common in this patient population than previously reported. After implementation of genetic testing, the yearly rate of diagnosed probands and family members with AC increased, while the risk of ventricular arrhythmias as presenting event seemed to decrease. This may be attributable to a variety of factors including implementation of 2010 Task Force Criteria, increased AC-disease awareness, identification of individuals at risk and a thorough follow-up program including preventive measures.

Conflict of interest

The authors have no conflict of interests to declare.

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