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Changes in the perceived epidemiology of amyloidosis: 20 year-experience from a Tertiary Referral Centre in Tuscany

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ABSTRACT

Background: Amyloidosis is considered a rare heterogeneous condition comprising different entities. Epidemiological data are limited and often controversial. We aimed to examine epidemiological changes in amyloidosis diagnosed over a 20-year period at a tertiary referral centre for amyloidosis.
Methods: We retrospectively reviewed medical files from all patients diagnosed with amyloidosis between January 2000 and December 2019, at Careggi University Hospital, Florence, Italy.
Diagnosis of amyloidosis was performed as per current clinical practice and scientific evidence at the time of patient evaluation.
Results: We reported data on 654 consecutive patients: 274 (42%) wild type transthyretin amyloidosis (wtATTR), 68 (10%) genetic variant amyloidosis (vATTR), 281 (43%) light-chain amyloidosis (AL) and 31 (5%) serum amyloid A amyloidosis (AA). With limited fluctuations, the absolute number of new AL diagnosis increased during the 20-year period. wtATTR was unrecognized before 2009 but represented by far the most common aetiology at the end of the observation period. AA represented a residual diagnosis throughout the entire examined period.
Conclusions: Following a rapid and marked increase in the number of new diagnoses over the last decade, ATTR represents by far the most common type of amyloidosis in our regional centre. These data contrasts with recent reports from national referral institutions and may help shed light on the epidemiology of the disease at the community level.

1. Introduction

Amyloidosis is a heterogeneous condition comprising different entities with diverse pathophysiology [1]. Light-chain amyloidosis (AL) AL is caused by deposition of insoluble amyloid fibrils derived from misfolding of monoclonal immunoglobulin light chains usually produced by a plasma cell clone [2]. Transthyretin amyloidosis (ATTR) ATTR is caused by deposition of amyloid fibrils resulting from misfolded tetrameric transthyretin precursors both wild-type (wtATTR) or caused by a genetic variant (vATTR) [3]. Serum amyloid A amyloidosis (AA) is a very rare form due to acute phase plasma protein deposition, complicating chronic inflammatory diseases or infections [4].

Each of these entities is considered rare and epidemiological estimates are limited and difficult to obtain, as referral bias and evolving diagnostic strategies may provide radically different profiles in different settings.

The last two decades have been particularly relevant for TTR amyloidosis, following the introduction of two major advances in the diagnostic process (Fig. 1): bone scan scintigraphy in 2005 [5] associated with the decryption of its clinic usefulness in 2008 [6] (allowing non-invasive, specific identification of ATTR) and Gilmore's algorithm in April 2016 [7] (which included the use of the bone scan in a systematic approach).

Recently, a large series from a nation dedicated centre in the UK reported AL amyloidosis as the most common type of amyloid disease [8], accounting for the majority of referrals. However, this aspect remains controversial in the light of increasing recognition of ATTR (particularly wild type) in the population. In the present study, we, therefore, aimed to examine epidemiological changes in different subtypes of

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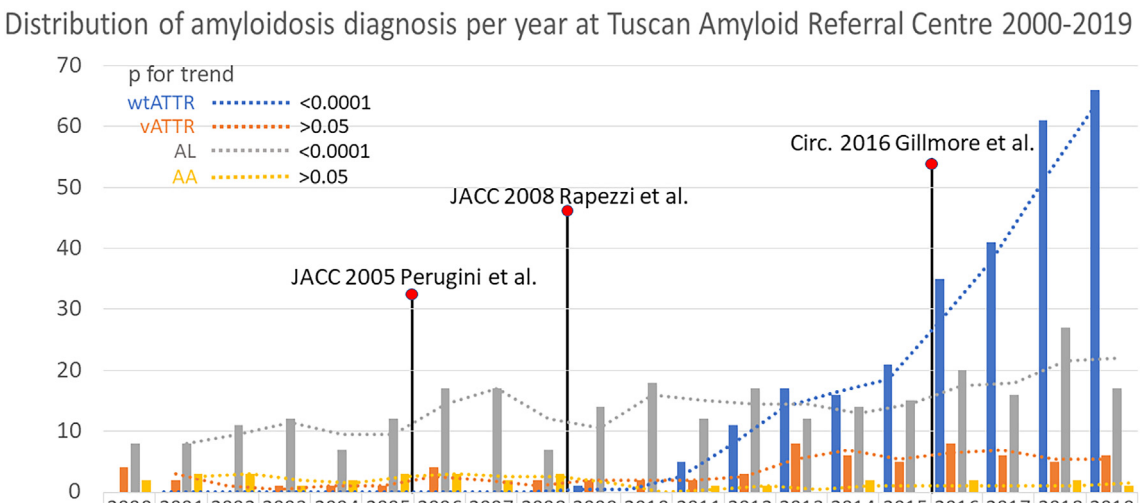

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
wtATTR	0	0	0	0	0	0	0	0	0	1	0	5	11	17	16	21	35	41	61	66
vATTR	4	2	0	1	1	1	4	0	2	2	2	2	3	8	6	5	8	6	5	6
AL	8	8	11	12	7	12	17	17	7	14	18	12	17	12	14	15	20	16	27	17
AA	2	3	3	1	2	3	3	2	3	0	0	1	1	0	2	0	2	0	2	1

Fig. 1. Diagnoses of Amyloidosis over a 20-year period at Careggi University Hospital, tertiary referral centre for amyloidosis. Figure shows number of diagnosis of different subtypes of amyloidosis per year, from 2000 to 2019. Dashed lines show diagnosis moving average trend lines for each amyloidosis subtypes. Wild type transthyretin-associated amloidosis (wtATTR) and light chain amyloidosis (AL) number of diagnosis increased significantly during study period (p for trend < 0.0001). Abbreviations: AA serum amyloid A amyloidosis, AL light chain amyloidosis, vATTR genetic variant transthyretin-associated amloidosis, wtATTR wild type transthyretin-associated amloidosis.

amyloidosis diagnosed over a 20-year period (January 2000–December 2019) at Careggi University Hospital, a multidisciplinary referral centre for amyloidosis, serving Tuscany and in particularly the Florence metropolitan area.

2. Methods

Medical files from all patients diagnosed with amyloidosis between January 2000 and June 2019, at Careggi University Hospital, were retrospectively evaluated.

Diagnosis of ATTR was performed as per current clinical practice and scientific evidence, and namely based on biopsy demonstration of ATTR deposit in an involved organ, analyzed by immunochemistry or immune-electron-microscopy. After April 2016 diagnosis of ATTR-CA was also performed according to the non-invasive diagnostic algorithm suggested by Gilmore et al. [7] and as described elsewhere [9]. A further distinction between vATTR or wtATTR was performed by the presence/absence of a pathogenic mutation at the ATTR gene sequencing. Genetic counselling and genetic analysis were performed in all ATTR patients.

Diagnosis of AL amyloidosis was confirmed by biopsy of abdominal fat pad or of an involved organ with amyloid deposits characterised as AL type by immunohistochemistry, optic/immunoelectron microscopy or proteomics.

Due to the retrospective nature of this study, informed consent was waived for patients who had died or were lost to follow-up. Otherwise, all subjects provided written informed consent that was approved by the institutional review board.

2.1. Statistical analysis

Absolute numbers and percentages were computed to describe the patient population. Continuous variables were presented as means (± standard deviation) or as medians (with inter-quartiles ranges) respectively when normally and non-normally distributed. Continuous variables were compared by Student's t-test and categorical variables using the Chi-square or the Fisher's exact test, as appropriate. P-values < 0.05 were considered significant. All statistical analyses were performed using SPSS statistics 21.0 for Windows.

3. Results

We report data on 654 consecutive patients who received a diagnosis of amyloidosis over the period January 2000–December 2019. All patients were evaluated at Careggi University Hospital, Florence, Italy. The majority of patients (77%) were from the Florence metropolitan area (1,004,298 inhabitants, data from *National Institute of Statistics* (ISTAT) census date: 31st December 2019) [10], 19% were from different cities in Tuscany region and the remaining 4% from other Italian regions.

The cohort comprised 274 (42%) wtATTR, 68 (10%) vATTR, 281 (43%) AL and 31 (5%) AA.

Mean age at diagnosis was 79 ± 6 years in wtATTR (89% males), 72 ± 11 years in vATTR (74% males), 69 ± 9 years in AL (54% males), 63 ± 13 in AA (32% males). Main baseline clinical characteristics in different amyloidosis subtypes are reported in Table 1.

In 2009, our institution extended the use of bone tracer scintigraphy to amyloidosis diagnosis.

In ATTR patients bone tracer scintigraphy identified grade 1 Perugini score in 30 (9%) patients, grade 2 in 114 (33%) patients and grade 3 in 193 (56%) patients (Table 1).

Concomitant presence of monoclonal gammopathy or significantly altered free light chain ratio was identified in 54 (16%) of ATTR patients. In these cases, ATTR diagnosis was performed by tissue biopsies with evidence of TTR deposits.

Before the publication of Gilmore's algorithm in April 2016, 123/128 (96%) ATTR patients underwent tissue biopsy (the remaining 4% were diagnosed because of positive genetic test and amyloid-related polyneuropathy), whereas, after April 2016, biopsy was performed in 30/214 (14%) of ATTR patients ($p = 0.001$).

Since the introduction of bone tracer scintigraphy for ATTR diagnosis, baseline patients characteristics changed over time. During years

Table 1
Data on 654 consecutive patients collected from a 20-year experience at Careggi University Hospital, amyloidosis referral centre, Florence, Italy. Main baseline clinical characteristics in different amyloidosis subtypes.

	wtATTR (n = 274)	vATTR (n = 68)	AL (n = 281)	AA (n = 31)
Demographic data				
Male (n, %)	244 (89%)	50 (74%)	151 (54%)	10 (32%)
Age (years)	79 ± 6	72 ± 11	69 ± 9	63 ± 13
BSA (m^2)	1.8 ± 0.1	1.8 ± 0.1	1.7 ± 0.1	1,7 ± 0.1
Bone scintigraphy				
Delay to diagnosis (months)	4 (2−11)	7 (2–19)	7 (0–124)	4 (0−10)
Perugini 0 (n, %)	0	4 (5%)	NA	NA
Perugini I (n, %)	25 (9%)	5 (7%)	NA	NA
Perugini II (n, %)	90 (33%)	24 (36%)	NA	NA
Perugini III (n, %)	159 (58%)	35 (52%)	NA	NA
Clinical characteristics				
Carpal tunnel (n, %)	170 (62%)	34 (50%)	NA	NA
Amyloidosis cardiac involvement (n, %)	274 (100%)	65 (96%)	198 (70%)	8 (25%)
Amyloidosis renal involvement (n, %)	No	No	119 (42%)	22 (72%)
Neurologic Involvement	11 (4%)	15 (22%)	60 (22%)	1 (3%)
AF at first ECG (n, %)	71 (26%)	16 (24%)	28 (10%)	1(3%)
Need for PM or ICD before or after amyloidosis diagnosis (n, %)	60 (22%)	17 (26%)	8 (3%)	0
History of HTN (n, %)	178 (65%)	34 (50%)	106 (38%)	10 (32%)
SAP (mmHg)	124 ± 16	122 ± 18	118 ± 21	123 ± 14
DAP (mmHg)	73 ± 11	72 ± 11	71 ± 11	71 ± 8
CAD (n, %)	52 (19%)	7 (11%)	14 (5%)	1 (3%)
NYHA 1 (n, %)	46 (17%)	9 (13%)	87 (31%)	24 (80%)
NYHA 2 (n, %)	148 (54%)	40 (58%)	104 (37%)	5 (16%)
NYHA 3 (n, %)	77 (28%)	18 (27%)	67 (24%)	1 (4%)
NYHA 4 (n, %)	3 (1%)	1 (2%)	23 (8%)	0
Blood sample and prognostic scores				
eGFR (mL/min)	63 ± 22	71 ± 25	64 ± 30	40 ± 35
NT-pro-BNP (pg/L) (data available for 589 patients)	3203 (1282–6156)	2926 (1549–4893)	6658 (20–77,753)	3050 (102–13,500)
Troponin I (ng/mL)	0.07 (0.04–0.13)	0.08 (0.05–0.20)	0.18 (0.01–5.22)	0.03 (0.02–0.08)
SAA (mg/dl)	NA	NA	NA	57 (1,1–179)
Gillmore score				
1 (n, %)	121 (44%)	30 (45%)	NA	NA
2 (n, %)	109 (40%)	27 (38%)		
3 (n, %)	44 (16%)	11 (17%)		
Mayo 2004 European score (Data available for 196 patients)				
I (n, %)	NA	NA	43 (22%)	NA
II (n, %)			63 (32%)	
IIIa (n, %)			47 (24%)	
IIIb (n, %)			43 (22%)	
Echocardiography				
IVS (mm)	17 ± 2	17 ± 3	13,7 ± 3	12 ± 3
LVEDV (mL)	91 (75–108)	89 ± 25	78 (40–102)	88 ± 21
EF (%)	55 (46–62)	50 ± 12	57 (20–82)	57 (26–71)
LA volume (mL)	92 ± 31	82 ± 52	71 ± 26	NA
E/e'	17 ± 6	19 ± 6	16 ± 7	9 ± 5
TAPSE (mm)	18 ± 5	16 ± 4	19 ± 5	23 (19–23)
sPAP (mmHg)	47 (28–65)	38 ± 11	34 ± 12	27 (22−32)
Moderate or severe aortic stenosis (n, %)	21 (7%)	4 (6%)	3 (1%)	0
Survival				
Median survival (months)	54 (48–60)	51 (44–57)	22 (18–25)	48 (21–74)

Abbreviations: AF = atrial fibrillation; AL = light-chain amyloidosis; BSA = body surface area; CAD = coronary artery disease; DAP = diastolic arterial pressure; EF = ejection fraction; eGFR = estimated glomerular filtration rate; HTN = hypertension; ICD = implantable cardiac defibrillator; IVS = interventricular septum; LA = left atrium; LVEDV = left ventricular end diastolic volume; NT-pro-BNP=; NYHA = New York heart association; PM = pacemaker; SAA serum A Amyloid protein; SAP = systolic arterial pressure; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; vATTR = genetic variant amyloidosis; wtATTR = wild type transthyretin amyloidosis;
Amyloidosis scores:
Gillmore score [21] = is a prognostic staging system applicable to patients with both wtATTR and vATTR, Stage I was defined as NT-pro-BNP ≤3000 ng/L and eGFR ≥45 mL/min, Stage III was defined as NT-pro-BNP >3000 ng/L and eGFR <45 mL/min, and the remainder were Stage II.
Mayo2004/European [19] = is a prognostic score system applicable to patients with AL: Stage I was defined as NT-pro-BNP ≤ 332 ng/L and TnI. ≤ 0.1 ng/mL; Stage II one marker >cut-off; Stage IIIa both markers > cut-off but NT-pro-BNP ≤ 8500 ng/L; Stage IIIb Tn I. > 0.1 ng/mL but NT-pro-BNP >8500 ng/L.
Perugini score [20] = is a semi-quantitative method of scoring cardiac uptake following bone tracer scintigraphy, grade 0: no cardiac uptake and normal bone uptake, grade 1: cardiac uptake which is less than bone uptake, grade 2: cardiac uptake with intensity similar to or greater than bone uptake, grade 3: cardiac uptake with much reduced or absent bone signal.

we recorded a progressive decrease in delay from symptoms onset and diagnosis from a median of 7 (2–19) months to 4 (2−12) months ($p = 0.010$); New York Heart association functional class III or IV decreased from 45% to 23% ($p = 0.001$); echocardiographic ejection fraction increased from 50% ± 12 to 54% ± 10 ($p = 0.02$), tricuspid annular plane systolic excursion increased from 16 ± 3 mm to 18 ± 5 ($p = 0.02$). Whereas no meaningful difference was recorded during years for gender, age at diagnosis, Perugini score, NTproBNP level, Gillmore score, echocardiographic wall thickness, left ventricular volume, diastolic function and estimated systolic pulmonary pressure.

AL patients demonstrated a prevalence of λ free light chains (75%) over *K* free light chain (25%); Bence Jones proteinuria was positive in

196 (70%) of AL individuals. All AL patients had amyloid positive tissue biopsy during the diagnostic process: 244 (87%) fat pad, 25 (9%) renal, 6 (2%) minor salivary gland, 6 (2%) cardiac, 6 (2%) bone marrow biopsy. Few patients underwent tissue biopsy in more than 1 organ.

AA diagnoses were limited to few individuals manifesting severe and chronic inflammatory conditions lasting several years, mainly rheumatological diseases. AA deposits most commonly involved kidneys and liver. All patients had at least fat pad or involved organ (predominantly renal) biopsy.

3.1. Perceived incidence of ATTR over the study period

Fig. 1 shows the trend of specific amyloidosis diagnoses over the study period. With limited fluctuations, the absolute number of new AL diagnoses increased during the 20-year period (p for trend $<$ 0.0001) with a mean number of diagnoses per year of 14 $\pm$ 5 cases (Fig. 1).

Notably, no wtATTR was recognized before 2009, i.e. before the clinical introduction of bone scintigraphy, but represented by far the most common aetiology at the end of the observation period in 2019 (73% of total amyloidosis cases in that year, Fig. 1). The increase in wtATTR accounts almost entirely for the increased in referrals over the second half of the last decade of the observational period (p for trend $<$ 0.0001).

Conversely, the number of new vATTR diagnoses never exceeded 8 cases per year and showed limited fluctuations (p for trend $>$ 0.05) (Fig. 1). AA, a rarer form associated with chronic inflammatory conditions, represented a residual diagnosis (≤3 cases per year throughout all the examined period, p for trend $>$ 0.05) (Fig. 1).

4. Discussion

We reported data from a 20-year experience at Careggi University Hospital, amyloidosis referral centre, serving Tuscany and particularly the Florence metropolitan area. During this time, the number of new diagnoses per annum increased from 14 in 2000 to 90 in 2019 (Fig. 1). In parallel, the perceived epidemiology of amyloidosis at our centre has substantially changed over the past two decades. Notably, the number of new AL diagnoses, with some fluctuation, significantly increased, mainly driven by increased referral from surrounding cities or regions, as recently described by our group [11].

Conversely, we recorded an almost exponential growth in ATTR diagnoses, with the wild type subtype in older individuals accounting almost entirely for the growing pattern of amyloidosis diagnosis over the last 20 years. While wtATTR patients were almost undiagnosed before 2010, they reached 73% of all diagnoses in 2019 (Fig. 1).

Such trend likely reflects increased awareness among referring physicians as well as advances in diagnostic accuracy; however, it is also a reflection of the considerable diffusion of the disease in the community, previously unrecognized.

Recent data suggest that ATTR is overlooked as a cause of common cardiovascular conditions. The real prevalence of ATTR is likely to be higher than what has been described so far, especially in older individuals [12,13], among individuals diagnosed with heart failure [14] and aortic stenosis [15–17].

The improvement in the diagnostic yield, redefining the epidemiology of this condition, is largely due to an increased awareness (campaigns following development of drugs in international trials) as well as easy and widespread access to bone scintigraphy, which represents a non-invasive gold-standard for diagnosis.

Our data differ markedly from recent reports from national referral centres in which AL has been reported as the increasingly most common type of amyloidosis [8]. Such discrepancy may be largely explained by different referral patterns. AL patients are younger, have a potentially treatable underlying disease and are therefore highly motivated to travel to a national referral centre, compared with patients with wtATTR who are generally old and have long been regarded as orphan of viable treatment options. Our centre more closely reflects the state of things at the community level and therefore intercepts the real incidence of the different amyloid subtypes.

A degree of referral bias has unavoidably occurred also at our institution, following the increasingly established reputation of our center in the region. This is exemplified by the limited but significant increase in overall AL diagnoses, contrasting with the stable rate of new local patients [11]. However, this bias with regard to ATTR is plausibly small and expected to have limited impact on the present results since, even in most recent years ATTR patients from the metropolitan area constituted $>$ 80% of the study cohort. Therefore, our data remain strongly representative of the local epidemiology.

An increased awareness of amyloidosis following the recent spur of research initiatives and successful clinical trials, that changed the erroneous dogma that ATTR is an untreatable disease, has triggered diagnostic processes at peripheral hospitals and clinics, leading to increased referral rates of previously unrecognized wtATTR which clearly emerges from the study as the most prevalent form of amyloidosis.

Whereas vATTR, AA and AL are multisystemic diseases, since they generally affect younger individuals, they are more prone to be correctly identified and not underestimated, therefore these subtypes of amyloidosis diagnoses are more likely to remain stable across the years. Conversely a recent study from 2 European amyloidosis centres showed that 35% of wtATTR patients had been previously misdiagnosed with other conditions [18]. wtATTR has been a neglected diagnosis for a long time: we are likely facing the tip of an iceberg whose real dimensions are not known.

Our data have a potential clinical impact as the planning of resources and screening programs for cardiac amyloidosis will unavoidably depend on reliable epidemiological data. Even more notable is the fact that accurate estimates of the prevalence of amyloidosis subtypes may have direct implication for the pricing of novel agents: this need to consider the true numbers which will determine the ultimate economic burden for the community.

5. Conclusions

ATTR likely remains an underdiagnosed disorder. wtATTR showed an almost exponential increase in the number of new diagnoses in the last decade and our data suggests that ATTR overall is the most common type of amyloidosis. The increase in disease awareness and the availability of a non-invasive diagnostic algorithm have started to unveil the real epidemiological burden of a disease too long considered untreatable and rare.

The commitment of the next years should be to improve our knowledge of ATTR epidemiology and continue pursuing the goal of prompt diagnosis in order to start disease-modifying treatment in early stages of the disease.

Declaration of Competing Interest

None declared.

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