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Symptom Burden and Healthcare Utilization Before Diagnosis of Transthyretin-Mediated Amyloidosis Among Medicare Beneficiaries

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BACKGROUND & OBJECTIVE

- Patients with transthyretin-mediated (ATTR) amyloidosis often experience multiple overlapping clinical manifestations with symptom variability and low disease awareness leading to diagnostic delays and misdiagnoses[1,2]
  - Depending on the variation, symptoms usually begin between 40 and 65 years of age[2-5]
- Knowledge of patient symptoms and characteristics before diagnosis may promote earlier recognition, particularly among older patients who, relative to younger patients, are predominantly affected by the disease
  - Notably, however, older patients are underrepresented in commercial insurance claims databases
- The study's objective was to examine clinical characteristics and healthcare utilization patterns among Medicare beneficiaries in the years before a diagnosis of ATTR

METHODS

Retrospective analysis using 100% Medicare Research Identifiable Files from 1/1/2011-12/31/2018

Patient Identification

Inclusion criteria

- Patients ≥68 years newly diagnosed with ATTR amyloidosis identified using a claims-based algorithm as follows:
  - Diagnosis required ≥1 inpatient or ≥2 outpatient claims with ICD-10-CM code for ATTR amyloidosis (E85.1, E85.2, E85.82) between 2016-2018 (ID period) or another amyloidosis form during ID period plus the following between 2011-2018:
    - ≥1 claim for congestive heart failure, cardiomyopathy, or neuropathy; and no chemotherapy, stem cell transplant, or light-chain amyloidosis claims
  - Study index date was defined as date of first amyloidosis claim in ID period
  - Patients had continuous Fee-for-Service (FFS) Part A/Part B and Part D enrollment 3 years before index (look-back period)

Exclusion criteria

- ICD-9/10 amyloidosis codes during look-back period or evidence of dementia at any time in the study period

Disease-free Control Group

- To serve as a reference group, an ATTR-free cohort was created from a 5% random sample of Medicare enrollees who, during the study period, had no diagnosis of amyloidosis
  - ATTR-free patients were matched 1:1 to patients with ATTR based on age, gender, region
- ATTR-free patients were assigned the same index date and had the same enrollment requirements as the matched ATTR patients

Study Measures

- Occurrence (first and any observed) of selected conditions (i.e., potential neurological manifestations) and healthcare utilization (hospitalization and emergency department/ED visits) measured during the look-back period
- Demographics and Charlson comorbidity index (CCI) measured during 1-year pre-index

RESULTS

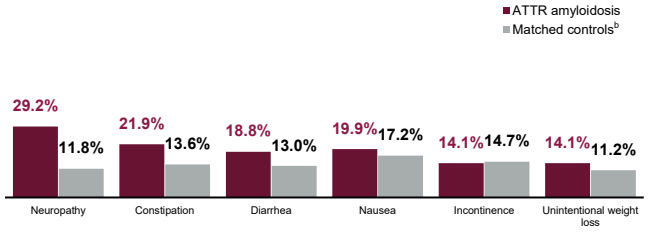
Table 1. Baseline Demographics and Comorbidities During 1-year Pre-index Period

	ATTR Amyloidosis N=552	Matched DF Controls[a] N=552	P Value
Age, year, mean (SD)	**78.3 (6.3)**	**78.3 (6.3)**	**n/a[b]**
68-69, n (%)	29 (5.3)	29 (5.3)	n/a[b]
70-74	149 (27.0)	149 (27.0)	
75-84	281 (50.9)	281 (50.9)	
85+	93 (16.8)	93 (16.8)	
Female, n (%)	**196 (35.5)**	**196 (35.5)**	**n/a[b]**
Race, n (%)			**<0.001**
White	463 (83.9)	505 (91.5)	
Black	67 (12.1)	30 (5.4)	
Other/Unknown	22 (4.0)	17 (3.1)	
Region			**n/a[b]**
Midwest	149 (27.0)	149(27.0)	
Northeast	163 (29.5)	163 (29.5)	
South	146 (26.4)	146 (26.4)	
West	94 (17.0)	94 (17.0)	
Charlson comorbidity index, mean (SD)	**3.1 (2.5)**	**2.0 (2.4)**	**<0.001**
Number of chronic conditions, mean (SD)	**5.4 (2.0)**	**4.3 (2.0)**	**<0.001**

ATTR: transthyretin-mediated; SD: standard deviation.
[a] Matched with age, gender, region.
[b] Matched exactly.

- For the 552 matched ATTR-control pairs, mean (SD) age was 78.3 (6.3) and 64.5% were male
- Mean CCI was higher among patients with ATTR vs. controls (3.1 vs. 2.0)

Figure 1. Selected Comorbidities[a] in Past 3 Years Prior to ATTR Amyloidosis Diagnosis



ATTR: transthyretin-mediated.
[a] Gastroparesis not presented due to CMS cell size suppression policy (<11).
[b] Matched with age, gender, region.

Table 2. Selected Comorbidities in Past 3 Years Prior to ATTR Amyloidosis Diagnosis

	ATTR Amyloidosis N=552	Matched DF Controls[a] N=552	P Value
Nervous System Conditions			
Neuropathy, n (%)	**161 (29.2)**	**65 (11.8)**	**<0.001**
First evidence occurred			<0.001
No evidence	391 (70.8)	487 (88.2)	
Pre Y1	48 (8.7)	15 (2.7)	
Pre Y2	42 (7.6)	22 (4.0)	
Pre Y3	71 (12.9)	28 (5.1)	
Incontinence, n (%)	**78 (14.1)**	**81 (14.7)**	**0.797**
First evidence occurred			0.482
No evidence	474 (85.9)	471 (85.3)	
Pre Y1	22 (4.0)	19 (3.4)	
Pre Y2	26 (4.7)	21 (3.8)	
Pre Y3	30 (5.4)	41 (7.4)	
Gastrointestinal Conditions			
Diarrhea, n (%)	**104 (18.8)**	**72 (13.0)**	**0.009**
First evidence occurred			0.029
No evidence	448 (81.2)	480 (87.0)	
Pre Y1	42 (7.6)	22 (4.0)	
Pre Y2	31 (5.6)	28 (5.1)	
Pre Y3	31 (5.6)	22 (4.0)	
Constipation, n (%)	**121 (21.9)**	**75 (13.6)**	**<0.001**
First evidence occurred			0.004
No evidence	431 (78.1)	477 (86.4)	
Pre Y1	51 (9.2)	29 (5.3)	
Pre Y2	38 (6.9)	25 (4.5)	
Pre Y3	32 (5.8)	21 (3.8)	
Nausea, n (%)	**110 (19.9)**	**95 (17.2)**	**0.246**
First evidence occurred			0.179
No evidence	442 (80.1)	457 (82.8)	
Pre Y1	42 (7.6)	26 (4.7)	
Pre Y2	31 (5.6)	37 (6.7)	
Pre Y3	37 (6.7)	32 (5.8)	
Unintentional weight loss, n (%)	**78 (14.1)**	**62 (11.2)**	**0.148**
First evidence occurred			0.004
No evidence	474 (85.9)	490 (88.8)	
Pre Y1	44 (8.0)	17 (3.1)	
Pre Y2	21 (3.8)	21 (3.8)	
Pre Y3	13 (2.4)	24 (4.3)	
Gastroparesis, n (%)	**--[b]**	**--[b]**	**0.094**
First evidence occurred			0.111
No evidence	550 (99.6)	545 (98.7)	
Pre Y1	--[b]	--[b]	
Pre Y2	--[b]	--[b]	
Pre Y3	--[b]	--[b]	

ATTR: transthyretin-mediated; Y: year.
[a] Matched with age, gender, region.
[b] Reported per CMS cell size suppression policy (<11).

- Selected conditions and healthcare utilization were more common during the look-back period compared to controls
  - Neuropathy (29.2% vs. 11.8%), hypotension (20.7% vs. 11.2%, not displayed)
  - Nearly half of ATTR patients experienced a selected gastrointestinal symptom of some kind (49.1% vs. 36.8%, results not displayed), including constipation (21.9% vs. 13.6%), nausea (19.9% vs. 17.2%), diarrhea (18.8% vs. 13.0%), and unintentional weight loss (14.1% vs. 11.2%)
  - Notably, for incontinence, there was no statistically significant difference between patients with ATTR and controls (14.1% vs. 14.7%; p=0.797)
  - Hospitalizations (54.0% vs. 35.5%) and ED visits (56.0% vs. 43.5%) were also more frequent among patients with ATTR vs. controls
- Evidence of selected conditions was present up to 3 years prior to diagnosis

LIMITATIONS

- Our approach to identifying patients with ATTR amyloidosis has not been validated using medical records
- The 3-year look-back period limited our ability to examine earlier manifestations of disease; however, this length was chosen in order to ensure an adequate sample size
- The study's sample did not have a higher frequency of wild-type amyloidosis (ATTRwt), as would be expected given recent availability of this code with respect to study period, and diagnosis cannot be confirmed in claims

CONCLUSIONS

- Medicare beneficiaries with ATTR amyloidosis have multiple neurological manifestations and hospitalizations before diagnosis
- Earlier and increased recognition of characteristics symptoms and utilization may facilitate earlier diagnosis and treatment

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Presented at the 2021 American Academy of Neurology Annual Meeting; April 17-22, 2021; Virtual Meeting. Poster 4800

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DISCLOSURES

- SRR, EC, and MHT are employees of Partnership for Health Analytic Research, LLC, which was paid by Akcea to perform this research.
- JP: Advisory board fees: Akcea
- JN: Financial: Pfizer, Akcea and Eidos; Grants: Pfizer. Consultant: Pfizer, Eidos, Akcea, and Alnylam.
- NF: Consulting/Speakers: honoraria-Akcea, Alnylam, Pfizer; Research support/clinical trial participation: Akcea, Alnylam, Pfizer, Eidos