Hospitalizations, Clinical Characteristics and Mortality in Adults with Adrenomyeloneuropathy (AMN): A Retrospective Study

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INTRODUCTION

- X-linked adrenoleukodystrophy (X-ALD) is a genetic, metabolic condition with an incidence of 1:16,800 caused by a *ABCD1* gene mutation.[1,2]
- Males with the mutation develop adrenomyeloneuropathy (AMN) in adulthood. Symptom onset is typically observed around the late 20s to 30s. Women may also develop symptoms, though onset is observed later in life.[3-5]
- AMN is neurodegenerative – characterized by progressive myeloneuropathy that causes spastic paraparesis, sensory ataxia, incontinence, and sexual dysfunction. Eventually walking is severely affected and mobility is impaired.[3,6-8]
- There are currently no effective treatments in stabilizing or reversing the progression of AMN. Moreover, suggested and practiced care varies based on the symptoms experienced by each person.[9]
- AMN's impact on healthcare resource utilization (HRU) and mortality is unknown.

Objectives

- The study objectives were to examine clinical characteristics, hospitalizations, and mortality in adults with AMN in the US.

Methods

- Comorbidities and hospitalizations were assessed using commercial insurance claims from IQVIA's PharMetrics Plus database (1/01/2006-6/30/2021) via a retrospective cohort study. Mortality rates and age at death were assessed in the Medicare Limited Dataset (LDS; 1/1/2016-12/31/2020).
- Patient selection: Study patients had ≥1 inpatient or ≥2 outpatient claims with an AMN diagnosis (ICD-10-CM: E71.52x; ICD-9-CM 277.86), no evidence of childhood cerebral adrenoleukodystrophy or other peroxisomal disorders, or pregnancy related diagnoses. Commercially insured patients were age 18-64y and 1:4 propensity score matched on demographic characteristics and enrollment time to individuals without AMN. Medicare patients were age-eligible (≥65y) and disability-eligible (age<65y).
- Study Period and Index: Commercially insured patients were followed from the month of their first observed AMN diagnosis (index date) until they were disenrolled from their insurance plan. Individuals with Medicare coverage were followed for the 5-year period.
- Study Measures: Hospitalizations were measured as the average number of healthcare encounters per patient per year (PPPY). Mortality was measured as the proportion of patients who died in a 5-year period among those with Medicare coverage and as the average age at death among Medicare enrollees who died.
- Analyses: Descriptive univariate analyses (mean ± standard deviation and counts [percentages]) and bivariate analyses (Mann-Whitney U/ Student's t-test and Fisher's Exact/Chi-squared tests) assessed for differences between cases and controls. All statistical analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC) and R 2022.02, assuming a two-tailed test of significance and an alpha level set a-priori at 0.05.

Table 1: Patient Demographics

	Females		Males	
Characteristic	AMN Patients (N=503)	Controls (N=1,689)	AMN Patients (N=303)	Controls (N=1,037)
Follow-up months	18.9 ± 19.74	22.4 ± 22.50	29.0 ± 27.69	30.1 ± 25.34
Age (mean ± SD)	35.0 ± 11.56	34.8 ± 11.41	35.1 ± 13.81	35.2 ± 13.33
Age 18-35 (n, %)	322 (64.0%)	1,069 (63.3%)	171 (56.4%)	585 (56.4%)
Age 36-51 (n, %)	116 (23.1%)	425 (25.2%)	81 (26.7%)	275 (26.5%)
Age 52-64 (n, %)	65 (12.9%)	195 (11.5%)	51 (16.8%)	177 (17.1%)

Results

Demographics and Comorbidities

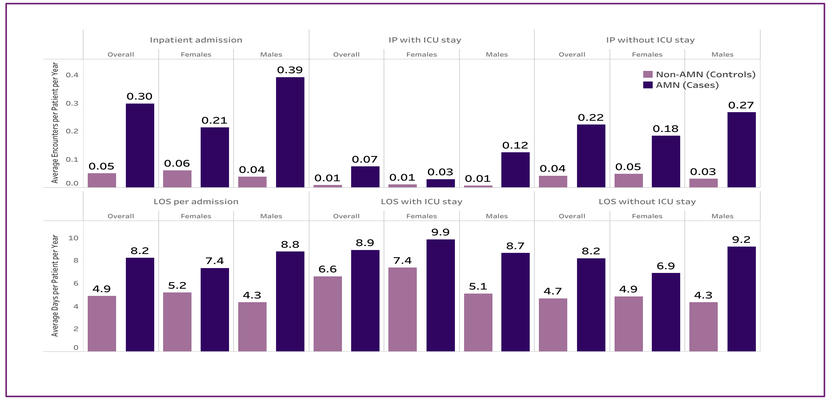
- A total of A total of 806 commercially insured individuals (Males: 303; Females: 503) met inclusion criteria.
- Matched controls ((Males: 1,037; Females: 1,689) were similar to AMN cases on demographic characteristics and follow-up time period. Mean age was approximately 35y for female and male patients and controls, with the majority age 18-35y (**Table 1**).
- Compared with controls, AMN patients had a significantly greater comorbidity burden as measured by the Charlson Comorbidity Index (CCI: 0.46±1.11 vs. 0.17±0.65, (p <0.001). Hemiplegia/paraplegia and non-diabetic neuropathy were expected comorbid conditions in AMN patients (**Table 2**).

Table 2: Patient Comorbidities

	Females		Males	
Comorbidities (within the follow up window)	AMN Patients (N=503)	Controls (N=1,689)	AMN Patients (N=303)	Controls (N=1,037)
Charlson Comorbidity Index (mean, SD)	0.34±0.94	0.16±0.63	0.67±1.33	0.19±0.68
Non-Diabetic Neuropathy (n, %)	40 (8.0%)	13 (0.8%)	33 (10.9%)	6 (0.6%)
Hemiplegia or Paraplegia (n, %)	16 (3.2%)	<5	33 (10.9%)	<5
Chronic Pulmonary Disease (n, %)	30 (6.0%)	60 (3.6%)	19 (6.3%)	27 (2.6%)
Diabetes (n, %)	12 (2.4%)	52 (3.1%)	18 (5.9%)	54 (5.2%)
Liver Disease (n, %)	16 (3.2%)	15 (0.9%)	17 (5.6%)	8 (0.8%)
Peripheral Vascular Disease (n, %)	11 (2.2%)	8 (0.5%)	14 (4.6%)	9 (0.9%)
Cerebrovascular Disease (n, %)	12 (2.4%)	5 (0.3%)	13 (4.3%)	6 (0.6%)
Cancer (n, %)	10 (2.0%)	17 (1.0%)	13 (4.3%)	14 (1.4%)
Renal Disease (n, %)	6 (1.2%)	6 (0.4%)	9 (3.0%)	6 (0.6%)
Congestive Heart Failure (n, %)	5 (1.0%)	6 (0.4%)	7 (2.3%)	<5
Rheumatic Disease (n, %)	9 (1.8%)	19 (1.1%)	<5	<5
Multiple Sclerosis ((n, %)	7 (1.4%)	5 (0.3%)	<5	<5
Diabetic Neuropathy (n, %)	<5	5 (0.3%)	<5	6 (0.6%)

*Measures with <5 patients masked for patient confidentiality; all differences between AMN and non-AMN statistically significant at p<0.05 except for Rheumatic Disease, Diabetes, and Diabetic Neuropathy

Figure 2: Inpatient Admission Rates and Length of Stay (LOS)*



* Differences in estimates between AMN and non-AMN are all statistically significant at p<0.05

Hospitalizations

- A larger proportion of AMN patients had at least one hospital admission, compared to controls (Females: 23.2% vs. 7.2%; Males: 32.0% vs. 6.1%; both P <0.05)
- Rates of hospitalization with and without ICU stays differed significantly between AMN patients and controls overall and for females and males (p <0.05) (**Figure 2**).
- Length of stay (LOS) also differed significantly between AMN patients and controls, p <0.05 (**Figure 2**).

Mortality

- Mortality rates were significantly higher for both female and male AMN patients with Medicare coverage, compared with all Medicare enrollees, p <0.001 (**Figure 3A**).
- The average age at death was significantly younger for AMN patients compared with all Medicare enrollees – for females (≥65y) and males (18-64y), p <0.05 (**Figure 3B**).
- Patients may be age-eligible for Medicare coverage (aged ≥65y) or disability-eligible (aged <65y), which limits the generalizability of the findings.

Figure 3: Mortality

Figure 3A: Mortality Rates*

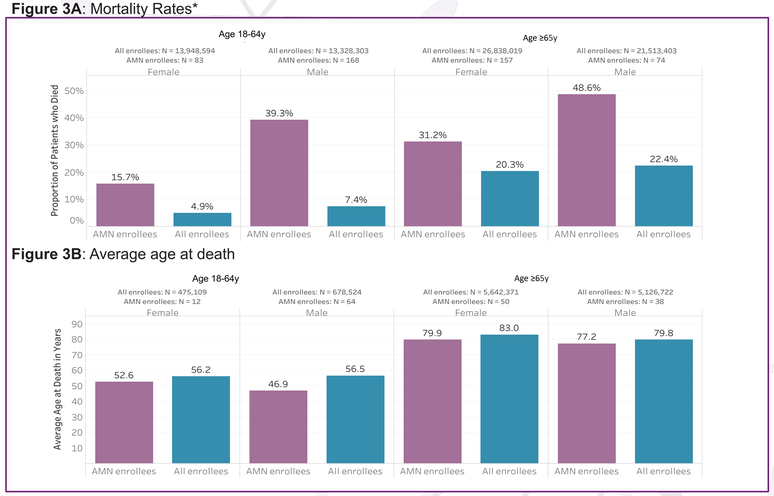


Figure 3B: Average age at death

* All differences in mortality rates between AMN and non-AMN statistically significant at p<0.05; age at death statistically significant for AMN patients vs. controls aged <65y at p<0.05

CONCLUSIONS

- There is a substantial burden of disease in both men and women with AMN but particularly in men, as expected.
- Higher rates of HRU are consistent with earlier disease onset in men.
- An increased comorbid burden, greater HRU, and, in some patient groups, higher mortality rates, are present for in both sexes
- Better understanding of comorbidity and mortality drivers in both men and women with AMN is needed to improve health outcomes.

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