Poster 1064

Healthcare Utilization, Burden of Illness, and Mortality in Adults with Adrenomyeloneuropathy (AMN): the Case for Genetic Therapies

Josh Bonkowsky[1,2], Bridget Healey[3], Naomi C. Sacks[3], Ronaé K. McLin[3], Philip Cyr[3], Eileen Sawyer[4], Christopher D. Stephen[5,6], Florian Eichler[5,6]

[1]Intermountain Healthcare, Salt Lake City, UT, [2]Division of Pediatric Neurology, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, UT, [3]Heath Economics and Outcomes Research, PRECISIONheor, Boston, MA, [4]Clinical and Medical Affairs, SwanBio Therapeutics, Boston, MA, [5]Massachusetts General Hospital, Boston, MA,[6]Harvard Medical School, Boston, MA

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.

Objective

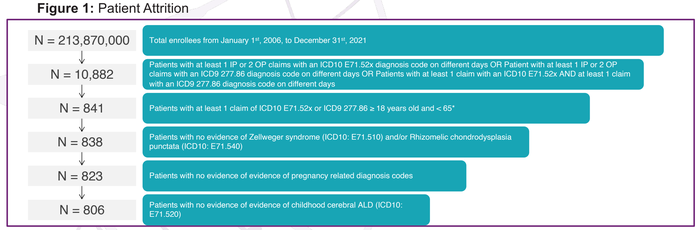
- The objective of this study was to examine, for the first time, HRU, clinical characteristics, and mortality in adults with AMN in the US.

Methods

Study Design

- HRU was 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 (1/1/2016-12/31/2020).
  - HRU was 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 those who died with Medicare coverage
- Patient selection: Individuals aged 18-64y, ≥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 (**Figure 1**). To assess for adult cerebral adrenoleukodystrophy, the distribution of utilization and costs were examined for potential associations– however this did not lead to any further exclusions.
  - AMN patients were 1:4 propensity score matched on demographic characteristics and enrollment time to individuals without AMN.
- Observation Time and Index: For both databases, patients were observed from the month of their first observed AMN diagnosis (the index date) and followed until they were disenrolled from their insurance plan.
- 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.

Figure 1: Patient Attrition



Results

Comorbidities

- Compared to controls, AMN patients had a greater comorbidity burden as measured by the CCI (0.46±1.11 vs. 0.17±0.65, p <0.001). Hemiplegia/paraplegia and non-diabetic neuropathy were expected comorbid conditions within the AMN cohort (**Table 1**).

Table 1: Patient Characteristics

Table 1. Patient Demographics– number and proportion of patients with 1+ characteristic during observation

	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%)
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
Diabetic Neuropathy (n, %)	<5	5 (0.3%)	<5	6 (0.6%)

Measures containing less than 5 patients are masked to protect patient confidentiality

Healthcare Resource Utilization

- Across all inpatient and outpatient HRU encounters, utilization rates differed significantly between AMN patients and controls – overall, by females, and by males p <.05 (**Figure 2**).
- Length of stay (LOS) also differed significantly between AMN patients and controls – overall, by females, and by males p <.05 (**Figure 2**).
  - LOS w/o ICU differed significantly between AMN patients and controls – overall and by females, p <.05 (**Figure 2**).
  - LOS w/ ICU differed significantly between AMN patients and controls – by males, p <.05. (**Figure 2**).

Figure 2A: Healthcare Resource Utilization – Inpatient

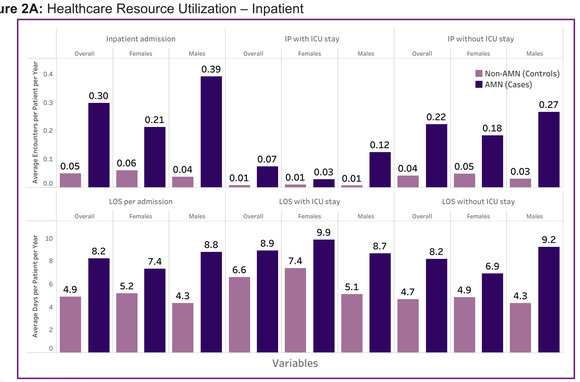
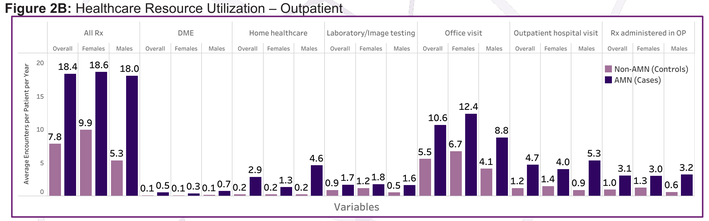


Figure 2B: Healthcare Resource Utilization – Outpatient



Mortality

- Patients may be age eligible for Medicare coverage (aged ≥65 years old) or disability eligible (aged <65 years old). The generalizability of findings are limited to AMN patients with Medicare coverage.
- Mortality rates (18-64 and 65+ years) differed significantly between AMN enrollees and All enrollees – for females and males, p <.001 (**Figure 3**).
- The average age at death differed significantly between AMN enrollees and All enrollees – for females (65+ years) and males (18-64 years), p <.05 (**Figure 3**).

Figure 3: Mortality

Figure 3A: Mortality Rate

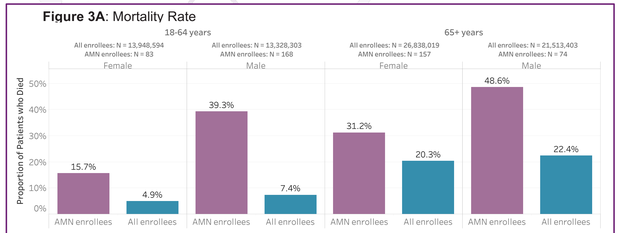
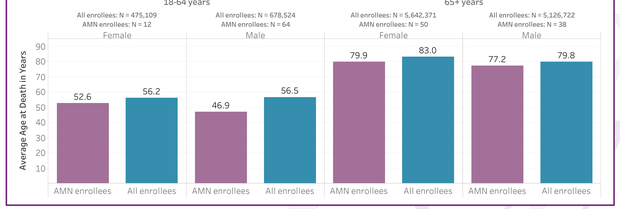


Figure 3B: Average age at death



CONCLUSIONS

- AMN confers a high burden of illness including higher HRU and, in some patient segments, higher mortality rates and earlier age at death – this burden is especially pronounced in males.
- Better understanding of comorbidity and mortality drivers in AMN is needed to improve health outcomes.

References: 1. Bezman L, Moser AB, Raymond GV, et al. Adrenoleukodystrophy: incidence, new mutation rate, and results of extended family screening. Ann Neurol. Apr 2001;49(4):512-7 2. Resende LL, de Paiva ARB, Kok F, da Costa Leite C, Lucato LT. Adult Leukodystrophies: A Step-by-Step Diagnostic Approach. Radiographics. Jan-Feb 2019;39(1):153-168. doi:10.1148/rg.2019180081 3. Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. Aug 13 2012;7:51. doi:10.1186/1750-1172-7-51 4. Kanakis G, Kaltsas G. Adrenal Insufficiency Due to X-Linked Adrenoleukodystrophy. [Updated 2018 Oct 12]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. 5. Zhu, J., Eichler, F., Biffi, A., Duncan, C.N., Williams, D. A., & Majzoub, J. A. (2020). The Changing Face of Adrenoleukodystrophy. Endocr Rev, 41(4), 577-593. https://doi.org/10.1210/endrev/bnaa013 6. Zhang YZ, G.-; Chen, W.- Pu, Z.- Song, L.- Tang, X.- Liu, Z. A novel ABCD1 G120ZA mutation in a Chinese patient with pure adrenomyeloneuropathy and literature review. Genes Dis. Sep 2021;8(5):709-714. doi:10.1016/j.gendis.2020.01.009 7. Dato C, Capaldo G, Terracciano C, et al. Late adult-onset adrenomyeloneuropathy evolving with atypical severe frontal lobe syndrome: Importance of neuroimaging. Radiol Case Rep. Mar 2019;14(3):309-314. doi:10.1016/j.radcr.2018.11.007 8. Kemp S, Berger J, Aubourg P. X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects. Biochim Biophys Acta. Sep 2012;1822(9):1465-74. doi:10.1016/j.bbadis.2012.03.012 9. Eichler F, Duncan C, Musolino PL, et al. Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy. N Engl J Med. 2017;377(17):1630-1638.

Author contributions: JB, BH, NS, RM, PC, ES, CS, and FE contributed to the design and implementation of the study, and to the interpretation of results.

Disclosures: JB has received consultant fees from Bluebird bio, Neurogene, Passage Bio,Takeda, and Autobahn; owns stock in Orchard; received research support from NIH. RM, BH, NS, and PC received employee salary from PrecisionHEOR. ES received employee salary from and owns stock in uniQure Inc; received research support from Sanofi and NIH. CS has received consultant fees from SwanBio; received research support from Sanofi. FE has received consultant fees from SwanBio, Alnylam, Origin Biosciences, Orchard, Autobahn, Bluebird; received fees from UpToDate; received research support from Bluebird, Minoryx, and Sio; owns stock in SwanBio.

Poster presented at ASGCT 2023; Los Angeles, CA, May 16, 2023

This study was sponsored by SwanBio Therapeutics Ltd