Mortality in patients with alpha-mannosidosis

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Background

- Alpha-mannosidosis (OMIM 248500) is a rare autosomal recessive lysosomal storage disorder (LSD) caused by mutations in the MAN2B1 gene leading to deficiency of alpha-mannosidase, involved in the breakdown of mannose-oligosaccharides[1]
- Manifestations include mental impairment, hearing loss, skeletal dysmorphism, immunodeficiency and recurrent infections[1,2]
- The severe type of the disease leads to early childhood death, while patients with milder forms can live into adulthood[2]
- There are no mortality studies to date, except individual case reports

Objective

To investigate the **age at death** and the **causes of death** in patients with alpha-mannosidosis who had not received disease-modifying treatment*

Methods

Recruitment → Questionnaire (April–May 2021) → Analysis

A total of 78 clinicians and 34 LSD patient organisations (POs) from 33 countries were invited to participate

Data were collected by a questionnaire after obtaining consent. Variables collected included: gender, year of birth, year of death, age at death, cause of death and MAN2B1 mutation#

Individuals were only included in the analysis if treatment status and cause of death were available

Results

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Responses

Clinicians response rate 53 out of 78: 67.9% → 25 deceased patients from 10 clinicians

POs response rate 20 out of 34: 58.8% → 6 deceased patients from 3 POs

16 patients excluded
No cause of death = 11
Duplicate = 1
HSCT= 4

15 Cause of death and age at death were available for **15 deceased untreated patients**

Patient demographics (n=15)

8 Countries

Table 1. Patient demographics

Sex	n (%)
Male	6 (40.0)
Female	8 (53.3)
Unknown	1 (6.7)

Year of birth: 1957–1992

Age at death

Table 2. Age at death of patients with alpha-mannosidosis

	Age at death (years)			
	Male (n=6)	Female (n=8)	Sex Unknown (n=1)	Total (n=15)
Median	47.0	43.5	18	**45.0**
Mean ±SD	44.8 ±6.6	39.6 ±15.1	18	40.3 ±13.2
Range	35–52	20–56	—	18–56

Figure 1. Year of death and age at death (years)

- Median age at death was 45 years (Table 2)
- 80% of patients (12 out of 15) died between the years 2010–2021 (Figure 1)
- One death occurred during the patient's second decade of life but **93.3%** (14 out of 15) **of deaths occurred during or after the patients' third decade of life** (≥20 years of age) (Figure 1)
- Four deaths (26.7%) were recorded during the patients' fifth decade (40–49 years of age) and four (26.7%) during the sixth decade (≥50 years) (Figure 1)
- Two female patients reached 56 years of age, the maximum age in the study population

Causes of death

Causes of death (Figure 2):

- 7 out of 15 deaths were associated with pneumonia, median age of death 49 years (mean 44.6 ±12.6, range 21–56)
- 3 out of 15 deaths were associated with cancer, median age of death 39 years (mean 36.3 ±17.2; range 18–52)

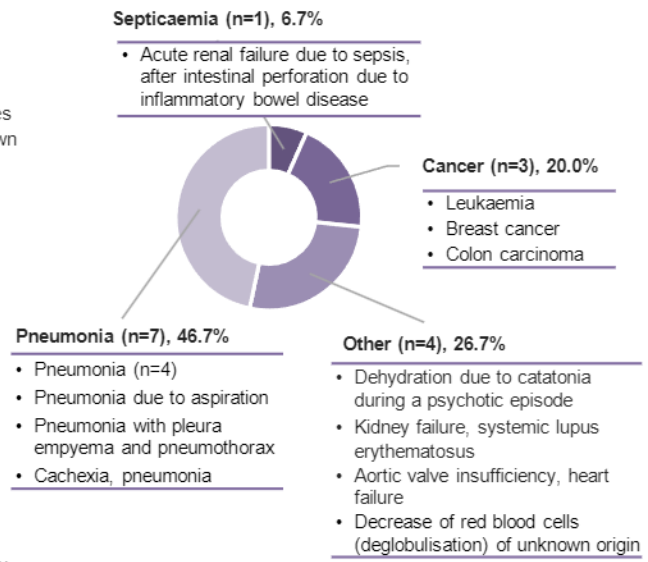

Figure 2. Causes of death

Key findings

- **Pneumonia was the most prevalent cause of death** over the past fifteen years in patients with alpha-mannosidosis in this population
- **Cancer was the second most prevalent cause of death** in this population of alpha-mannosidosis patients
- A compromised immune response to infections may explain the high incidence of infections and sepsis in this population
- Pneumonia may also be a consequence of swallowing problems associated with functional deterioration as patients get older, leading to aspiration pneumonia
- An increased risk of cancer has been reported for other LSDs but its association with alpha-mannosidosis is not known

Conclusions

Determining the causes of mortality and life expectancy in these patients is crucial to further improve our understanding of the natural history of alpha-mannosidosis.

Comorbidities identified from this study may help in the management of patients with alpha-mannosidosis.

*Patients were considered untreated if they had not received disease-modifying treatment (e.g. enzyme replacement therapy or HSCT). #This analysis presents a subset of variables. HSCT: Haematopoietic stem cell transplantation

References: 1. Malm D, Nilssen Ø. Alpha-Mannosidosis. In: Adam MP et al. (eds.) GeneReviews®). Seattle (WA): University of Washington, Seattle; 1993-2020; 2001 [updated 2019]. 2. Malm D, Nilssen Ø. Alpha-mannosidosis. *Orphanet J Rare Dis.* 2008;3:21. **Acknowledgements:** This study was sponsored by Chiesi Farmaceutici S.p.A. **Declaration:** This research was conducted in accordance with the British Healthcare Business Intelligence Association's Legal & Ethical Guidelines for Market Research. The survey study was non-interventional and all participants signed a consent form. **Disclosures:** J.B.H. has received consulting fees and/or travelling expenses by Amicus, Chiesi Farmaceutici S.p.A and Takeda; E.M.R. is employed by the Rare Disease Research Partners which supplies various professional services to Chiesi Farmaceutici S.p.A.; F.D. and A.B. are employees of Chiesi Farmaceutici S.p.A; G.C. has received advisory board fees from Chiesi Farmaceutici S.p.A.; M-L.J. and D.M. have no competing interests to declare.