EPH153

Clinical Characterization and Healthcare Resource Utilization in Adrenoleukodystrophy: A Nationwide Retrospective Cohort Using Swedish National Registries

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Objectives

The aim of this study was to utilize Swedish population-based health registries to identify and characterize patients diagnosed with adrenoleukodystrophy (ALD), and to describe the disease burden associated with cerebral ALD (cALD) and treatment with allogeneic hematopoietic stem cell transplantation (allo-HSCT).

Background

Adrenoleukodystrophy (ALD) is a rare X-linked degenerative syndrome affecting the nervous system and the adrenal cortex. Due to its rarity (approx. 1 in 20,000 newborns), data on ALD is limited. Cerebral ALD (cALD) is the most severe form of the disease with onset typically in early childhood. cALD is characterized by progressive loss of neurological and cognitive function and early mortality, and represents approximately 35% of all ALD cases. Currently, the only treatment option for ALD patients is allo-HSCT, indicated for cALD patients diagnosed early in disease progression. cALD is a target for emerging gene therapies, however, information on disease burden, treatment patterns, and outcomes for cALD patients are limited [1-3].

Sweden's nationwide health registries, linkable via unique national personal IDs, offer the opportunity to identify and characterize patient populations with e.g., rare diseases. This study utilizes Sweden's health registries to better understand the unmet medical need of ALD patients.

Methods

This retrospective cohort study was conducted using linked Swedish health registry data from

- the National Patient Registry,
- the National Cause of Death Registry, and
- the National Prescribed Drug Registry.

All male patients diagnosed with ALD (ICD-10-SE: E71.3D) between 2001-01-01 and 2019-06-30 were included. Patients were followed from index date (first ALD diagnosis) until death or end of follow-up (2019-12-31). Amongst patients with an ALD diagnosis, cALD was defined based on treatment or symptom proxy definitions as a cALD-specific ICD-10 code is lacking in Sweden:

- Exposure to allo-HSCT, and/or
- Diagnosis record of at least one cALD-associated symptom (see Table 2)

Descriptive statistics were used to assess ALD patient characteristics. For cALD patients who underwent allo-HSCT, treatment patterns (corticosteroid and immunosuppressant dispensations), incidence of infection (ICD-10-SE A00-B99) and adrenal morbidities (ICD-10-SE E27.1-4,8-9), and healthcare resource utilization (time in inpatient/outpatient specialized care) were described. Overall survival was analyzed using the Kaplan-Meier estimate.

Results

Overall, 40 male ALD patients were identified in Sweden between 2001-2019. 33 males displayed treatment or symptoms indicative of cALD. Among cALD patients, 6 (18%) received allo-HSCT, while 27 (82%) were identified based on cALD-associated symptoms only (Figure 1).

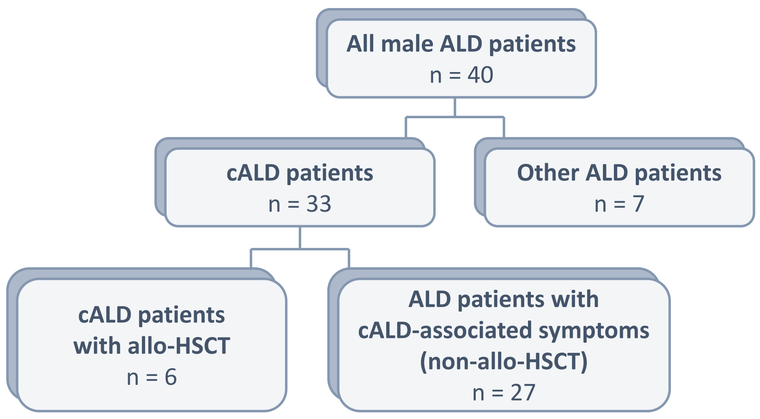

FIGURE 1. Patient stratification and patient numbers
Clinicians from the Center for Allogeneic Stem Cell Transplantation (CAST) at Karolinska Hospital, which performs most if not all Swedish ALD allo-HSCTs, confirmed that n=6 is also in the range of ALD allo-HSCTs they have registered.

The median age at diagnosis was 7.5 years for cALD patients who received allo-HSCT, 29.0 years for ALD patients with cALD-associated symptoms but without allo-HSCT, and 33.0 years for the other ALD patients. Median time from ALD diagnosis to allo-HSCT was 2.5 months (Table 1).

	cALD patients with allo-HSCT	ALD patients with cALD-associated symptoms (non-allo-HSCT)	Other ALD patients
Total number, n (% of all)	6 (15%)	27 (67.5%)	7 (17.5%)
Age at first ALD diagnosis in years, Median (IQR)	7.5 (4.5-26.3)	29.0 (11.0-49.5)	33.0 (27.0-45.5)
Age at first cALD symptoms in years, Median (IQR)	5.5 (3.3-26.5)	37.0 (13.0-46.0)	n.a.
Time from first ALD diagnosis to allo-HSCT in months, Median (IQR)	2.5 (1.3-15.8)	n.a.	n.a.
Follow-up time in years, Median (IQR)	10.0 (6.8-11.0)	11.0 (4.5-14.0)	3 (2.5-5.5)

TABLE 1. Patient characteristics of ALD patients
n.a.: not applicable

Common clinical manifestations of cALD included musculoskeletal problems, hearing loss/visual impairment, and behavioral issues (Table 2).

Incidence of cALD-associated symptoms at first ALD diagnosis (look-back-period from first ALD diagnosis to 2001), n (% of all)	**cALD patients with allo-HSCT** (n=6)	**ALD patients with cALD-associated symptoms (non-allo-HSCT)** (n=27)
Behavioral problems (F00-F99)	<3	5 (18.5%)
Hearing loss / Eye diseases (H00-H52; H55-H95)	3 (50%)	9 (33.3%)
Visual impairment / Blindness (H53-H54)	<3	0
Engagement of the musculoskeletal system (M00-M99)	0	11 (40.7%)
Difficulties to swallow (R13)	0	<3
Aphasia and similar conditions (R47-R49)	0	<3
Seizures (R56.8)	0	<3

TABLE 2. Diagnosis records of cALD-associated symptoms among all likely cALD patients.
Additional proxy CALD definitions were also considered; however, no records were identified for prescription of wheelchair (KVÅ GA023), diseases in the urinary organ incl. incontinence (N39.3, N39.4), and tube feeding (KVÅ DV065).

Among cALD patients who underwent allo-HSCT, all 6 patients (100%) had diagnoses indicative of infection and adrenal morbidities after allo-HSCT. Pharmacy drug dispensations indicated that most patients received systemic corticosteroids and/or immunosuppressive treatment for the first five years after allo-HSCT (Table 3).

	cALD patients who underwent allo-HSCT			
Follow-up year (after allo-HSCT)	**Patients in follow-up**, n	**Patients with corticosteroid dispensation**, n	**Patients with immunosuppressive dispensation**, n	**Patients receiving extracorporeal photopheresis (ECP)**, n
1	6	4	5	0
2	6	5	<3	0
3	6	6	0	0
4	6	6	0	0
5	4	3	0	0

TABLE 3. Treatment of cALD patients with allo-HSCT

In the 2nd and 3rd follow-up year after transplant, cALD patients who underwent allo-HSCT spent on average 20.4 and 23.4 days in secondary healthcare, respectively (Table 4).

	cALD patients who underwent allo-HSCT			
Follow-up year (after allo-HSCT)	**Patients in follow-up**, n	**Total time spent in healthcare**, days per year	**Time spent in inpatient healthcare**, days per year (% of total time)	**Time spent in outpatient healthcare**, days per year (% of total time)
1	6	103.3	66.8 (65%)	36.6 (35%)
2	6	20.4	1.2 (6%)	19.2 (94%)
3	6	23.3	12.4 (53%)	11.0 (47%)
4	6	18.1	8.8 (49%)	9.3 (51%)
5	4	10.5	0.8 (7%)	9.7 (93%)

TABLE 4. Healthcare resource utilization (HRU) of cALD patients with allo-HSCT
For total time in care, days where inpatient and outpatient care occurred on the same day were counted only once.

Median 5-year overall survival rate was 100% for CALD patients who received allo-HSCT and 92% for non-transplanted ALD patients with cerebral symptoms (Figure 2).

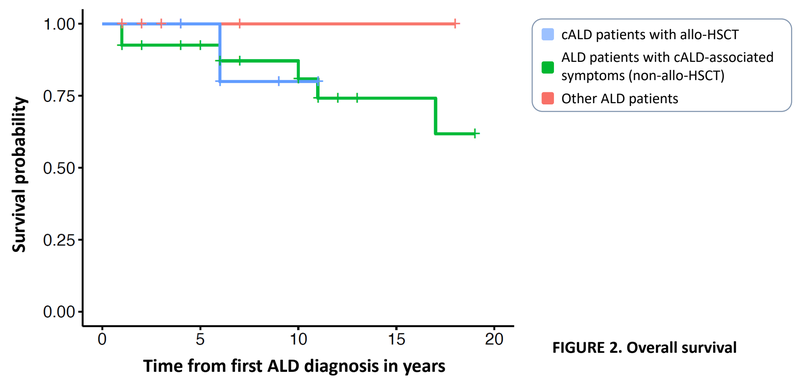

FIGURE 2. Overall survival

Conclusions

- Swedish population-based health registries can be used to identify and characterize ALD patients and describe treatment outcomes for cALD patients who underwent allo-HSCT.
- While previous studies estimate that cALD represents approx. 35% of all ALD cases, in the current study only 15% of ALD patients underwent allo-HSCT. Median diagnosis age was 7.5 years for cALD patient who underwent allo-HSCT, compared to 27 years for ALD patients with cerebral symptoms. Improved awareness and early diagnosis is important to enable timely intervention to limit disease progression.
- Allo-HSCT is associated with significant morbidity including ongoing need for immunosuppressant treatment, high incidence of infection and ongoing healthcare need. Novel treatment options with improved safety profiles that limit disease progression will be important for cALD patients.
- The proxy definition for cALD based on treatment and symptoms records is necessary in Swedish registry data due to the lack of a cALD-specific ICD-10 code. While allo-HSCT is a reliable indicator for treated cALD patients, a symptom-based definition to identify the untreated cALD patients may suffer from registry underreporting of symptoms or diagnoses independent of ALD, and therefore limits the extent of cALD population characterization in a registry setting.

References

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