Journal of Endocrine Disorders

Open Access

Austin Publishing Group

Research Article

Adrenal Insufficiency in Male Patients with Adrenoleukodystrophy; A Retrospective Analysis of an Institutional Database

Zekarias K[1*]; Salim M[2]; Tessier KM[3]; Radulescu A[4]

[1]Department of Medicine, Division of Diabetes, Endocrinology and Metabolism, University of Minnesota, USA

[2]Department of Medicine, Division of Diabetes, Endocrinology and Metabolism, University of Minnesota, USA

[3]Biostatistics Core, Masonic Cancer Center, University of Minnesota, USA

[4]Department of Medicine, Division of Diabetes, Endocrinology and Metabolism, University of Minnesota, USA

***Corresponding author: Zekarias K**

Department of Medicine, Division of Diabetes, Endocrinology and Metabolism, University of Minnesota, 420 Delaware St SE, MMC 101, Minneapolis, MN, USA.
Tel: 414-266-6750
Tel: 612 624 5150, Fax: 612 626 3133;
Email: kzekaria@umn.edu

Received: May 18, 2024
Accepted: June 11, 2024
Published: June 18, 2024

Abstract

Introduction: Adrenoleukodystrophy (ALD) patients exhibit three primary clinical phenotypes: primary adrenal insufficiency, adrenomyeloneuropathy, and cerebral demyelination due to the accumulation of saturated very long-chain fatty acids in the adrenal cortex and central nervous system white matter and axons. We investigated the prevalence of Adrenal Insufficiency (AI) and mineralocorticoid deficiency in male ALD patients.

Methods: A retrospective chart review of electronic medical records was conducted for all ALD patients at a single institution between January 1, 2011, and December 6, 2021.

Results: Of the 437 ALD patients, 82% were males and 18% were females. Sixty (213/358) percent of male ALD patients had adrenal insufficiency, with 39% (84/213) of them receiving mineralocorticoid replacement therapy.

Conclusion: Adrenal insufficiency is highly prevalent in ALD patients, with approximately 40% of those with AI and ALD receiving mineralocorticoid replacement therapy. This study represents the second investigation into the prevalence of mineralocorticoid treatment utilization among males diagnosed with both ALD and AI. Further research is warranted to delineate the characteristics of patients predisposed to developing mineralocorticoid deficiency within the context of ALD and AI.

Keywords: Adrenoleukodystrophy; Neurodegenerative disorder; ALD; Adrenal insufficiency; Mineralocorticoid deficiency.

Introduction

Adrenoleukodystrophy (ALD) is a neurodegenerative disorder that affects both the white matter and axons of the central nervous system, as well as the adrenal cortex, due to the accumulation of saturated Very Long-Chain Fatty Acids (VLCFA) [1-3]. It is an X-linked inherited disorder caused by a defective gene, ABCD1, located on Xq28. (2) Male patients with ALD typically manifest three primary clinical phenotypes: adrenal insufficiency (AI), adrenomyeloneuropathy (AMN), and cerebral demyelination (cerebral ALD) [2]. While progressive spinal cord disease can develop in women with ALD, AI and cerebral ALD are rare in this population, occurring in less than 1% of cases [4-6].

Huffnagel and colleagues reported a lifetime prevalence of adrenal insufficiency in male ALD patients of approximately 80% [7]. This underscores the importance of age-based regular screening for AI in this demographic. Accumulation of VLCFA is associated with cell death, particularly affecting the zona reticularis and zona fasciculata of the adrenal cortex, while sparing the zona glomerulosa [6-8].

Elevated Adrenocorticotropic Hormone (ACTH) and impaired cortisol response to ACTH administration are the primary biochemical indicators of primary AI, often preceding clinical symptoms by two years [9,10]. Mineralocorticoid deficiency is less frequently observed in ALD patients due to the relative sparing of the zona glomerulosa [6]. This study aimed to analyze the prevalence of AI in ALD patients and assess the utilization of mineralocorticoid treatment in those with AI and ALD.

Citation: Zekarias K, Salim M, Tessier KM, Radulescu A. Adrenal Insufficiency in Male Patients with Adrenoleukodystrophy; A Retrospective Analysis of an Institutional Database. J Endocr Disord. 2024; 9(1): 1051.

Methods

We conducted a retrospective analysis of Electronic Medical Records (EMR) spanning from January 1, 2011, to December 6, 2021, encompassing all patients diagnosed with ALD. Approval for the study protocol (Study00014492) was obtained from the Institutional Review Board. Data extraction was facilitated by the informatics consulting services of the Clinical and Translational Science Institute and securely maintained within the Academic Health Center Secure Data Environment.

All patients who provided consent for EMR research were included. Individual chart reviews were performed to confirm ALD diagnoses, utilizing VLCFA results, genetic assessments, or documented diagnoses in medical history or visit notes. Diagnosis of Adrenal Insufficiency (AI) was ascertained through thorough chart reviews, confirming documented diagnoses in medical history or progress notes.

Statistical Method

Demographic data for all ALD patients and those with AI were summarized using descriptive statistics. Statistical analyses involved Wilcoxon rank-sum tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. Data analysis was conducted using R (version 4.1.2, R Core Team) [11].

Results

Out of 437 patients with ALD, 82% (358/437) were males and 18% (79/437) were females. Table 1 provides demographic details of male patients with ALD. The median age among male patients with ALD was 14, ranging from 0 to 92 years. Among male ALD patients, 65% identified White, 6% Asian, 2% American Indian or Alaska Native, 1% more than one race, while race was unknown in 27%.

Sixty percent (213/358) of male patients with ALD had a diagnosis of AI. Steroids medications prescribed for patients with AI and ALD included hydrocortisone (190/213), prednisone (38/213), dexamethasone (66/213), and other (33/213). Thirty nine percent (84/213) of patients with AI and ALD were on mineralocorticoid replacement therapy.

Table 1: Comparison of demographics by Adrenal Insufficiency (AI) for male patients with adrenoleukodystrophy.

Variable	All ALD[2] male patients (N=358)	Diagnosis of AI[3] (N=213)	No diagnosis of AI[2] (N=145)	P-value[1]
Age, median (range)	14.0 (0.0, 92.0)	16.0 (1.0, 68.0)	11.0 (0.0, 92.0)	<0.001
Race, n (%)				
White	231 (64.5%)	142 (66.7%)	89 (61.4%)	0.54
Asian	20 (5.6%)	10 (4.7%)	10 (6.9%)	
AI or AN	6 (1.7%)	2 (0.9%)	4 (2.8%)	
More than 1 race	3 (0.8%)	2 (0.9%)	1 (0.7%)	
Unknown	98 (27.4%)	57 (26.8%)	41 (28.3%)	
Ethnicity, n (%)				
Hispanic or Latino	28 (7.8%)	15 (7.0%)	13 (9.0%)	0.154
Not Hispanic or Latino	266 (74.3%)	166 (77.9%)	100 (69.0%)	
Unknown	64 (17.9%)	32 (15.0%)	32 (22.1%)	

[1]Wilcoxon rank-sum test was used for age. Chi-square or Fisher's exact tests were used for categorical variables.
[2]ALD: Adrenoleukodystrophy.
[3]AI: Adrenal Insufficiency;

Discussion

This chart review study, utilizing EMR data, provides a descriptive analysis of AI prevalence among ALD patients and the utilization of mineralocorticoid therapy in this group. Our findings suggest a lower AI prevalence compared to studies relying on biochemical evidence, potentially because biochemical abnormalities precede clinical symptoms by two years [7,9,10]. Furthermore, the introduction of newborn screening programs for ALD, recommended by the US Department of Health and Human Services, has been underway in recent years [12]. This might have led to a larger population of young ALD patients who have not yet developed AI.

Approximately 40% of AI and ALD patients received mineralocorticoid replacement therapy, which could be due to the preferential VLCFA accumulation in the adrenal cortex, sparing the zona glomerulosa. While our study benefits from a large patient database, AI diagnosis based on medical chart documentation rather than biochemical evidence may underestimate prevalence.

In conclusion, AI prevalence remains high among male ALD patients, with approximately 40% of those with both conditions receiving mineralocorticoid replacement therapy. Our study represents the second attempt to quantify mineralocorticoid treatment prevalence in males diagnosed with both ALD and AI. Further research is necessary to identify individuals at risk of developing mineralocorticoid deficiency in the context of ALD and AI.

References

1. Engelen M, Kemp S, de Visser M, van Geel BM, Wanders RJA, Aubourg P, et al, X-linked adrenoleukodystrophy (ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis. 2012; 7: 51.

2. Kemp S, Huffnagel IC, Linthorst GE, Wanders RJ, Engelen M. Adrenoleukodystrophy - neuroendocrine pathogenesis and redefinition of natural history. Nat Rev Endocrinol. 2016; 12: 606-15.

3. Wanders RJ, van Roermund CW, Lageweg W, Jakobs BS, Schutgens RB, Nijenhuis AA, et al. X-linked adrenoleukodystrophy: biochemical diagnosis and enzyme defect. J Inherit Metab Dis. 1992; 15: 634-44.

4. Huffnagel IC, Dijkgraaf MGW, Janssens GE, van Weeghel M, van Geel BM, et al. Disease progression in women with X-linked adrenoleukodystrophy is slow. Orphanet J Rare Dis. 2019; 14: 30.

5. Engelen M, Barbier M, Dijkstra IME, Schur R, de Bie RMA, Verhamme C, et al. X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. Brain. 2014; 137: 693–706.

6. Habekost CT, Schestatsky P, Torres VF, de Coelho DM, Vargas CR, Torrez V, et al. Neurological impairment among heterozygote women for X-linked Adrenoleukodystrophy: a case control study on a clinical, neurophysiological and biochemical characteristics. Orphanet J Rare Dis. 2014; 9: 6.

7. Huffnagel IC, Laheji FK, Aziz-Bose R, Tritos NA, Marino R, Linthorst GE, et al. The Natural History of Adrenal Insufficiency in X-Linked Adrenoleukodystrophy: An International Collaboration. J Clin Endocrinol Metab. 2019; 104: 118–126.

8. Galea E, Launay N, Portero-Otin M, Ruiz M, Pamplona R, Aubourg P, et al. Oxidative stress underlying axonal degeneration in adrenoleukodystrophy: A paradigm for multifactorial neurodegenerative diseases? Biochim Biophys Acta. 2012; 1822.

9. Blevins LS, Shankroff J, Moser HW, Ladenson PW. Elevated plasma adrenocorticotropin concentration as evidence of limited adrenocortical reserve in patients with adrenomyeloneuropathy. J Clin Endocrinol Metab. 1994; 78: 261–5.

10. Dubey P, Raymond GV, Moser AB, Kharkar S, Bezman L, Moser HW. Adrenal insufficiency in asymptomatic adrenoleukodystrophy patients identified by very long-chain fatty acid screening. J Pediatr. 2005; 146: 528–32.

11. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2021.

12. Kemper AR, Brosco J, Comeau AM, Green NS, Grosse SD, Jones E, et al. Newborn screening for X-linked adrenoleukodystrophy: evidence summary and advisory committee recommendation. Genet Med. 2017; 19: 121-126.