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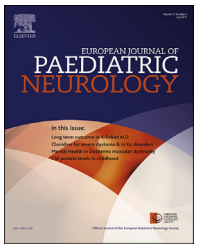

Original article

Long-term outcome of patients with X-linked adrenoleukodystrophy: A retrospective cohort study

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ABSTRACT

Background: X-linked adrenoleukodystrophy (X-ALD) is a peroxisomal disorder associated with leukodystrophy, myeloneuropathy and adrenocortical insufficiency. We performed a retrospective cohort study to evaluate long-term outcome of patients with X-ALD.
Method: All patients with X-ALD diagnosed between 1989 and 2012 were included. Electronic patient charts were reviewed for clinical features, biochemical investigations, molecular genetic testing, neuroimaging, long-term outcome and treatment.
Results: Forty-eight patients from 18 unrelated families were included (15 females; 33 males). Seventeen patients were symptomatic at the time of the biochemical diagnosis including 14 with neurocognitive dysfunction and 3 with Addison disease only. Thirty-one asymptomatic individuals were identified by positive family history of X-ALD. During follow-up, eight individuals developed childhood cerebral X-ALD (CCALD), one individual developed adrenomyeloneuropathy (AMN), six individuals developed Addison disease only, and five individuals remained asymptomatic. Direct sequencing of *ABCD1* confirmed the genetic diagnosis in 29 individuals. Seven patients with CCALD underwent

Abbreviations: AI, adrenal insufficiency; ACTH, adrenocorticotropin; CCALD, childhood cerebral X-ALD; FSIQ, full scale intelligence quotient (IQ) score; HSCT, hematopoietic stem cell transplantation; MRSS, Moser–Raymond severity score; MRS, magnetic resonance spectroscopy; MRI, magnetic resonance imaging; NAA, N-acetylaspartate; PIQ, performance intelligence quotient; VLCFA, very long chain fatty acid; VMI, visual-motor integration; WISC-IV, Wechsler Intelligence Scale for Children, fourth edition; WAIS-IV, Wechsler Adult Intelligence Scale, fourth edition; WPPSI-III, Wechsler Preschool and Primary Scale of Intelligence, third edition; X-ALD, X-linked adrenoleukodystrophy.

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hematopoietic stem cell transplantation (HSCT). Nine patients lost the follow-up. There was no correlation between clinical severity score, Loes score and elevated degree of elevated very long chain fatty acid (VLCFA) levels in CCALD.

Conclusion: Our study reports forty-eight new patients with X-ALD and their long-term outcome. Only 35% of the patients presented with neurological features or Addison disease. The remaining individuals were identified due to positive family history. Close monitoring of asymptomatic males resulted in early HSCT to prevent progressive lethal neurodegenerative disease. Identification of patients with X-ALD is important to improve neurodevelopmental outcome of asymptomatic males.

1. Introduction

X-linked adrenoleukodystrophy (X-ALD) (OMIM #300100) is a peroxisomal disorder caused by mutations in *ABCD1*. It is inherited as an X-linked trait. X-ALD results in impaired β-oxidation of very long chain fatty acids (VLCFAs) in peroxisomes resulting in accumulation of VLCFA in plasma, central nervous system and adrenal glands. The biochemical hallmark of the X-ALD is elevated saturated hexacosanoic

Table 1 – Demographics, phenotype, MRSS, Loes score, and choline to N-acetylaspartate ratio in brain MRS of male patients with X-ALD ($n = 33$).

Patient ID/initial age/ duration of follow-up	Phenotype initial → follow-up	MRSS system initial → follow-up	Loes score initial → follow-up	Chol/NAA ratio	Treatment
1/9.6 yrs/15.3 yrs	Asymp → Asymp	0 → 0	0 → 0	N → N	None
2/12.5 yrs/2 mo	Asymp → Addison only	0 → 0	0 → 0	N → N	LO/AS
3/27 mo/10.6 yrs	Asymp → Addison only	0 → 0	0 → 0	N → N	AS
4/8 yrs/18 yrs	Asymp → Addison only	0 → 0	0 → 0	N → N	CoQ10
5/4.7 yrs/9.4 yrs	Asymp → Addison only	0 → 1	0 → 0	NA → NA	AS/CoQ10
6/5 yrs/11.1 yrs	Asymp → Addison only	0 → 1	0 → 0	N → N	CoQ10
7/12 yrs/8.2 yrs	Asymp → Addison only	0 → 1	0 → 0	N → N	AS
8/4.7 yrs/16.11 yrs	Asymp → AMN	1 → 2	0 → 0	↑ → N	LO/CoQ10
9/6 yrs/13.5 yrs	Asymp → CCALD + AI	0 → 2	1 → 3	NA → NA	AS/HSCT
10/2 yrs/4.5	Asymp → CCALD + AI	0 → 1	0 → 1	↑ → N	AS/HSCT
11/4 yrs/10.4 yrs	Asymp → CCALD	0 → 0	0 → 12	↑ → N	HSCT/Coq10
12/8.11 yrs/5 yrs	Asymp → CCALD + AI	0 → 0	0 → 3	NA → NA	AS/HSCT
13/7 yrs/2 mo	Asymp → CCALD + AI	9 → 9	18.5 → NA	NA → NA	AS
14/12 yrs/1 mo	Asymp → CCALD	6→NA	14 → NA	NA → NA	Other[a]
15/9 yrs/11 mo	Asymp → CCALD + AI	4 → 8	13 → NA	NA → NA	AS
16/8.7 yrs/14 mo	Asymp → CCALD	0 → 0	0 → NA	NA → N	LO
17/4.3 yrs/2,7	CCALD → CCALD	NA → NA	11 → 15	NA → NA	LO
18/4.8 yrs/12.5 yrs	CCALD → CCALD	NA → 11	1 → 15	NA → NA	LO/HSCT
19/6.1 yrs/1 yrs	CCALD + AI → CCALD + AI	3 → NA	1 → 2	NA → NA	AS/HSCT
20/8 yrs/7 mo	CCALD → CCALD	7 → 7	14.5 → NA	↑ → NA	CoQ10
21/7.4 yrs/4 mo	CCALD → CCALD	4 → NA	13 → NA	↑ → N	Other[a]
22/6.6 yrs/3.7 yrs	CCALD + AI → CCALD + AI	13 → 13	16.5 → NA	↑ → NA	AS
23/7.8 yrs/1.2 yrs	CCALD → CCALD	5 → 6	14 → NA	NA → NA	LO
24/9 yrs/3.6 yrs	CCALD → CCALD	8 → 19	18 → NA	NA → NA	CoQ10
25/7.6 yrs/5.7 yrs	CCALD + AI → CCALD + AI	3 → 6	12 → 8	↑ → N	AS/HSCT/CoQ10
26/5 yrs/2 mo	CCALD → CCALD	1 → NA	NA → NA	NA → NA	None
27/7 yrs/1 mo	CCALD → CCALD	3 → NA	NA → 15	NA → NA	Other[a]
28/20.1 yrs/9.4 yrs	ACALD → ACALD	NA → NA	NA → 13.5	NA → NA	NA
29/39 yrs/15.3 yrs	Addison only → AMN + AI	1 → 1	NA → NA	NA → NA	AS
30/9.2 yrs/0.5 mo	Addison only → CCALD	0 → NA	0 → 8	NA → NA	AS
31/23 yrs/7 mo	Addison only → AMN + AI	0 → NA	NA → NA	NA → NA	AS
32/6 mo/NA	Asymp → No FU	0 → NA	NA → NA	NA → NA	NA
33/34 yrs/NA	Asymp → No FU	0 → NA	NA → NA	NA → NA	NA

Abbreviations: ACALD: adult cerebral adrenoleukodystrophy; AI: adrenal insufficiency; AMN: adrenomyeloneuropthy; AS: adrenal substitution; Asymp: asymptomatic; CCALD: childhood cerebral adrenoleukodystrophy; CoQ10: co-enzyme Q10; Chol: choline; LO: Lorenzo's oil; mo: month; MRSS: Moser–Raymond severity scoring; N: normal; NA: not available; NAA: N-acetylaspartate; yrs: years; X-ALD: X-linked adrenoleukodystrophy; ↑: increased ratio of Chol/NAA; FU: follow-up.

[a] Other treatment included anticonvulsants and/or vitamins and/or pain medication and/or immunosuppressive therapy.