Published in final edited form as:
*Eur J Pediatr*. 2011 August ; 170(8): 1049–1054. doi:10.1007/s00431-011-1401-1.

# Early Diagnosis of Cerebral X-linked Adrenoleukodystrophy in Boys with Addison's Disease Improves Survival and Neurological Outcomes

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## Abstract

Approximately one-third of boys with X-linked adrenoleukodystophy (X-ALD) develop an acute, progressive inflammatory process of the central nervous system, resulting in rapid neurologic deterioration and death. Hematopoietic cell transplantation (HCT) can halt the progression of neurologic disease if performed early in the course of the cerebral form of X-ALD. We describe a retrospective cohort study of 90 boys with X-ALD evaluated at our institution between 2000 and 2009, to determine if early diagnosis of X-ALD following the diagnosis of unexplained adrenal insufficiency (AI) improves outcomes. We describe 7 cases with a delay in the diagnosis of X-ALD, and compare their outcomes to 10 controls with the diagnosis of ALD made within 12 months following diagnosis of AI. At the time of evaluation for HCT, boys with a delay in the diagnosis of X-ALD had more extensive cerebral involvement and more limited functioning. These boys also were 3.9 times more likely to die, and had significant advancement of cerebral disease after HCT, compared to boys with a timely diagnosis of X-ALD.

**Conclusion—**Early diagnosis of cerebral X-ALD following the diagnosis of unexplained AI, and subsequent treatment with HCT, improves both neurological outcomes and survival in boys with cerebral X-ALD.

### Keywords

adrenoleukodystrophy; adrenal insufficiency; Addison's disease; hematopoietic cell transplantation

## Introduction

X-linked adrenoleukodystrophy (X-ALD), MIM ID #300100, is a peroxisomal disorder affecting the adrenal cortex, the central nervous system, and testicular function [12,13]. The incidence in males with X-ALD in the U.S. is estimated to be 1:21,000 [4]. There is a broad phenotype of X-ALD, which ranges from the childhood cerebral form characterized by rapid

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**Conflict of interest**.

The authors declare no financial relationship with the organization that sponsored the research.

progression to a vegetative state or death within 1–2 years (31–35%), to the slowly progressive adrenomyeloneuropathy (AMN) in adults (40–46%) [3,15].

The rapidly progressive childhood cerebral form is the most severe phenotypic variant of X-ALD, with a peak incidence at 4–7 years of age [10]. The most common initial problem is intellectual deterioration, secondary to impaired auditory and visual processing in brain [3]. Early allogeneic hematopoietic cell transplantation (HCT) has been reported to arrest progression of the inflammatory changes in boys who are diagnosed in the early phase of neurologic involvement associated with the cerebral form of the disease [2,8,11,17,20]. Primary adrenal insufficiency (AI), or Addison's disease, may precede overt neurological involvement, particularly when X-ALD manifests at a younger age [1,5–7]. AI is common in boys with X-ALD, with an estimated prevalence of 43% in asymptomatic affected boys [5].

X-ALD is likely under-diagnosed in boys with AI [4], and in one study 83% of boys with unexplained AI did indeed have X-ALD [18]. The diagnosis of X-ALD is reliably established by characteristic abnormalities in fasting saturated very long chain fatty acids (VLCFA) profile in serum samples from affected patients. Our hypothesis was that prompt VLCFA testing in boys newly diagnosed with unexplained primary AI would improve clinical outcomes by preventing delay in the diagnosis and treatment of cerebral X-ALD. Therefore, we completed a retrospective cohort study of boys with X-ALD who were referred to the University of Minnesota Amplatz Children's Hospital for evaluation for possible treatment with HCT to determine the clinical implications of delayed diagnosis of X-ALD in boys presenting with AI.

## Methods

We reviewed the medical records of 90 boys with cerebral X-ALD referred to the University of Minnesota Amplatz Children's Hospital for possible treatment with HCT, from January 2000 to August 2009. Subjects were labeled "late diagnosis" if the diagnosis of X-ALD was made *more* than 12 months after the diagnosis of AI and "early diagnosis" if the diagnosis of X-ALD was made 12 months or *sooner* after the diagnosis of AI. All HCT-related data were obtained from the University of Minnesota Pediatric Blood and Marrow Transplantation Database. The transplant procedures and retrospective chart review were approved by the University of Minnesota Institutional Review Board.

Laboratory evaluation of X-ALD and AI in each patient was done at the request of both outside physicians and members of the HCT team. In general, adrenocorticotropin hormone (ACTH) levels (Chemiluminescent immunoassay) above 80 pg/mL were considered to be suggestive of AI and greater than 500 pg/mL were diagnostic of AI 5]. Unless previously diagnosed with adrenal insufficiency, cortisol levels were measured after intravenous administration of 1 mcg cosyntropin, a synthetic derivative of ACTH, to assess pre-transplant adrenal function. AI was confirmed if peak cortisol level was less than 20 mg/dL after stimulation testing. In order to confirm X-ALD, VLCFA levels were measured by capillary gas chromatography/mass spectroscopy of pentafluorobenzyl bromide fatty acid esters (Kennedy Krieger Institute, Peroxisomal Diseases Laboratory). The diagnosis of cerebral X-ALD was based on the presence of increased VLCFA in blood samples and characteristic white matter changes on MRI. The extent and severity of cerebral demyelination was determined by T2 MRI analysis and graded per the method described by Loes [9]. Clinical neurologic involvement for all subjects was determined by retrospective chart review and graded according to the scale devised by Moser et al [16]. A score of "0" is "normal", so that any score > 0 already indicates significant neurological involvement.

The patients treated with transplantation received a fully myeloablative preparative regimen consisting of cyclophosphamide 120 mg/kg (60 mg/kg × 2 doses) and 1200 cGy of total body irradiation [TBI], or cyclophosphamide 200 mg/kg (50 mg/kg × 4 doses) and 12.8 mg/kg of intravenous busulfan (0.8 mg/kg/dose × 16 doses). Alternatively, in some advanced cases a reduced intensity preparative regimen was used. This regimen consists of Campath-1H (0.3 mg/kg × 5 doses), clofarabine (40 mg/m$^2$ × 5 doses), a single dose of melphalan (140 mg/m$^2$), and 200 cGy of TBI.

Differences in outcomes between early and late diagnosis were analyzed using Student's t-test, and within group differences, from before HCT to after HCT, using paired t-tests (SAS 9.2).

## Results

### Population

Ninety patients, consecutively evaluated at the University of Minnesota for treatment of X-ALD with HCT, were included. Of these, the first indicator of X-ALD was AI in 17 (19%), MRI and/or neurologic changes in 52 (58%), and a family history in 21 (23%). The frequency of X-ALD phenotypes were: 2% AI only, 12% cerebral disease only, 86% AI and cerebral disease, and 0% AMN. AI was the presenting sign in 38% of the entire cohort. Of the boys with cerebral disease, AI was the presenting sign in 40%. Of the boys with AI, AI was the presenting sign in 19% (Fig. 1). Seven patients were identified as having a delay in diagnosis of X-ALD (> 12 months after diagnosis of AI). All seven patients had neurological symptoms of cerebral ALD at the time of diagnosis and six of these patients were only diagnosed with ALD because of neurological symptoms which prompted MRI. Five of the boys in the delayed cohort were eligible for treatment with HCT; cerebral disease was too advanced in two boys to recommend treatment with HCT. Ten patients had a more timely diagnosis of X-ALD (≤ 12 months after diagnosis of AI) and were therefore included in the "early diagnosis" group. All patients diagnosed with ALD because of family history did develop AI (n=21) and 81% (n=17) developed AI before cerebral changes were identified in MRI. The majority of patients (57%, n=52) were diagnosed with X-ALD because of neurological and MRI changes, however, within 2 months after their diagnosis of X-ALD, 60% (n=31) of these boys were diagnosed with AI.

Comparison of MRI severity scores, functional scores, and survival in the "delayed diagnosis" versus "early diagnosis" groups is detailed in Table 1. Overall, the age at presentation of AI was no different between the boys with a late diagnosis of X-ALD and those with an early diagnosis of X-ALD. There was no difference in the age of diagnosis of X-ALD or the time to HCT after diagnosis of X-ALD. MRI severity scores revealed more extensive cerebral disease and more areas of impaired functioning (higher functional scores) in "delayed diagnosis" compared to "early diagnosis" prior to HCT (Table 1). There was a significant worsening of MRI severity score (mean ± SEM: 3.8 ± 0.5; P = 0.002) and functional score (9.9 ± 3.0; P = 0.02) in "delayed diagnosis" from before HCT to after HCT. There was a non-significant trend toward worsening MRI severity scores (3.1 ± 1.6; P = 0.10) and functional scores (6.5 ± 3.1; P = 0.07) in "early diagnosis" from before to after HCT (Fig. 2). The MRI severity and functional scores were measured at the same time for both the initial evaluation and most recent evaluation. The time interval between the initial and the most recent MRI and functional score testing ranged from 3–55 months in the "delayed diagnosis" group and 2–83 months in the "early diagnosis" group; the mean time interval was not significantly different between the groups (mean ± SEM: late diagnosis 21.6 ± 10.2 months, early diagnosis 32.4 ± 11.0 months; P value = 0.52).. The MRI score remained higher in the "late diagnosis" than the "early diagnosis" group at most recent evaluation, approaching statistical significance (15.8 vs 9.8, p=0.09). For the entire study

period, the relative risk for death in boys with a late diagnosis was 3.9 (95% CI: 0.5–29.6) times greater than in boys with an early diagnosis.

## Discussion

We provide evidence that boys diagnosed with unexplained AI, who had a delay in the diagnosis of X-ALD for greater than 12 months after the diagnosis of AI, had overall decreased survival, more advanced cerebral disease at the time of evaluation for HCT, and more progression of disease after treatment with HCT, compared to boys diagnosed with X-ALD at the time of AI diagnosis. Our data support the critical importance of testing all boys with unexplained AI for X-ALD to detect neurological disease early, because the lost neurological function cannot be regained by HCT.

Although autoimmune and infectious diseases are more common causes of AI in boys worldwide, X-ALD is highly prevalent in boys with unexplained AI. In 1990, Sadeghi-Nejad and Senior reported that 5 of 8 adult men (63%) with unexplained AI diagnosed in childhood had X-ALD [19]. In 2002, Ronghe et al. found that 83% of boys (n=12) with unexplained AI in southwest England had X-ALD [18]. AI is a prominent component of X-ALD, diagnosed among 88% of our cohort, therefore the diagnosis of unexplained AI merits VLCFA testing to rule out the X-ALD.

AI may be the only clinical manifestation of X-ALD before the onset of cerebral disease is apparent. Korenke *et al.* noted that endocrinological symptoms preceded neurological symptoms in 92% of children with cerebral X-ALD with an onset of symptoms before 6 years of age, and 63% with onset of symptoms before 15 years of age [7]. Dubey et al. reported that 80% of boys with asymptomatic X-ALD had borderline (37%) or overt (43%) adrenal insufficiency [5]. If we assume that those diagnosed with X-ALD because of family history were more closely monitored for AI and neurological symptoms then within that subset of patients we confirm that endocrinological symptoms preceded neurological symptoms in the majority (80%) of X-ALD. For the entire cohort, AI was the first symptom of X-ALD in 38% of patients. This is much lower than the 63% reported by Korenke et al for boys with a similar age of onset of symptoms (before 15 years) [7], and likely due to the referral bias in our cohort for boys with cerebral disease. Within the group of boys with cerebral disease, AI was the presenting sign in 40%, which *is* the similar to that reported by Moser et al (39%) [14] and Korenke et al (29%) [7].

If performed early in the disease process, HCT can stabilize the progression of X-ALD, preventing the devastating neurological outcomes. Mahmood et al. found that 53% of boys with mild cerebral involvement who survived transplant remained neurologically stable five years after HCT compared to only 6% in the untreated group [11]. Moreover, the probability of 5-year survival increased from 54% to 95% in boys with early stage cerebral X-ALD who were treated with HCT [11]. Shapiro et al. followed 18 boys who received HCT at early stage X-ALD and described remarkable benefits as well - 44% of patients returned to mainstream school without additional support, motor function stabilized or improved in 56% of patients, verbal intelligence stabilized for 61% of patients, and performance testing improved or stabilized in 39% of patients [20]. However, despite novel therapies which show promise, such as treatment with N-acetyl-L-cysteine before and after transplant [21], the outcome from delayed therapy is far from optimal. Severe demyelination prior to HCT, reflected by the MRI severity score > 9, is associated with continued progression of neurological disease and decreased survival after HCT [2,11]; our findings support this as the mean MRI severity score at initial evaluation for the “late diagnosis” group, who had on average more progression of disease than the “early diagnosis” group, was >9, while the mean MRI severity score at initial evaluation for the “early diagnosis” group was <9. Our

comparison of the functional scores and MRI severity scores confirms the significant worsening of neurological outcomes in the “late diagnosis” group. Furthermore, the relative risk for death was 3.9 times greater in boys with a delayed diagnosis compared to those with no delay in the diagnosis of ALD. Therefore, early diagnosis of cerebral disease is imperative for improving survival and stabilizing neurological disease in boys with X-ALD.

This retrospective study is limited by a small sample size and potential sampling bias. The cohort was referred to an academic BMT center, which most likely increased the disease severity of the reported group; for example the prevalence of cerebral disease in our cohort was 98% compared to 66% in boys with onset of symptoms before 15 years of age reported by Korenke et al [7]. We have no means of capturing boys diagnosed with AI who were never diagnosed with X-ALD and remained healthy. However, this does not detract from the importance of using AI as a clue to diagnosis of cerebral X-ALD early in its course, since early diagnosis improves neurological outcomes and survival, as previously discussed and described in this report. In addition, this is a retrospective study that relies on data from medical records which may be incomplete.

In conclusion, a delay in the diagnosis of X-ALD after the diagnosis of unexplained AI results in decreased survival, more cerebral involvement at the time of evaluation for HCT, and progression of disease after treatment with HCT. It is critical to test for X-ALD in boys diagnosed with unexplained AI, given the increased survival and likely improved outcome of cerebral X-ALD treated with early HCT. If testing reveals an elevation in VLCFA consistent with X-ALD, additional assessments including a brain MRI and neurological and neuropsychological evaluations should be ordered to assess for cerebral involvement.

## Acknowledgments

This work was partially funded by the Children’s Cancer Research Fund, Minneapolis, MN (J.T., P.O.), NIH 5K12RR023247-05 (L.P.), and the Minnesota Medical Foundation (J.T.). Dr. William Krivit and Dr. Hugo Moser for their pioneering work in the field of ALD, and Dr. Lawrence Charnas for his helpful comments.

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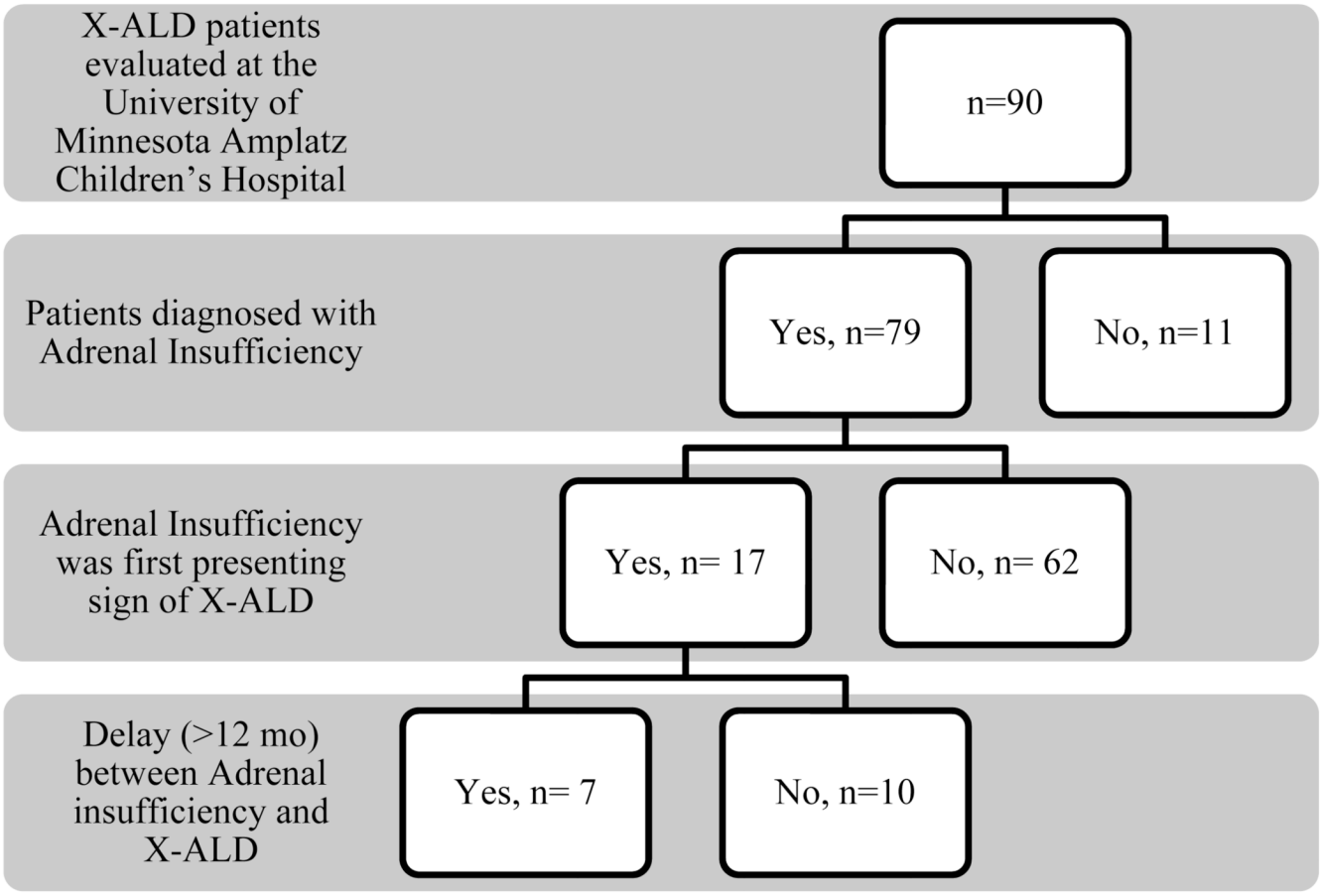


**Fig. 1.**
Identification of patients with "delayed diagnosis" versus "early diagnosis" of X-ALD.

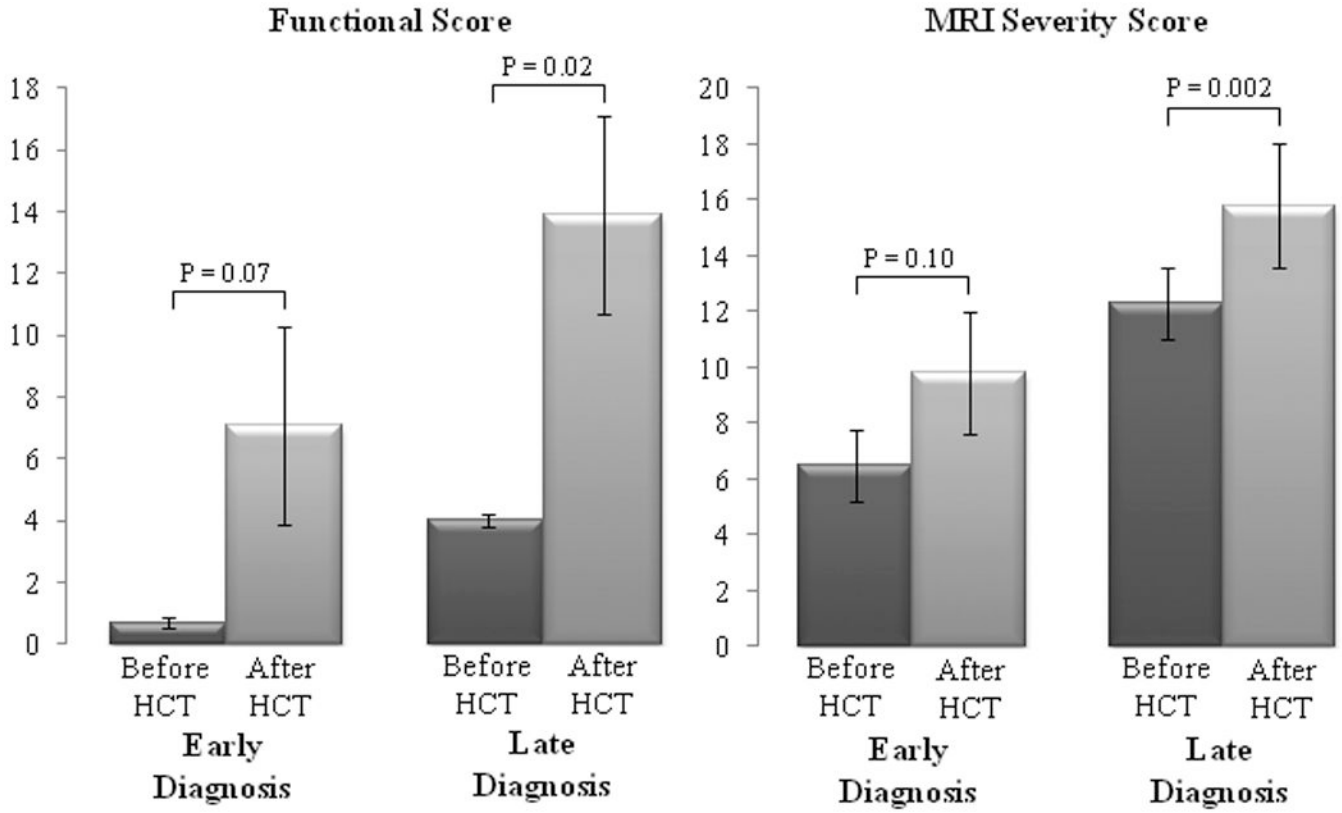


**Fig. 2.**

Change in MRI severity score and functional assessment from before HCT to after HCT. Mean with standard error bars are presented.

**Table 1**

Comparison of outcomes between boys with late diagnosis of X-ALD and boys with early diagnosis of X-ALD.

| | | Age at AI Diagnosis (yrs) | Age at X-ALD Diagnosis (yrs) | Time to X-ALD Diagnosis after AI Diagnosis (yrs) | Age at HCT (yrs) | Time to HCT after Diagnosis of X-ALD (yrs) | MRI Severity Score at Initial Evaluation | Most Recent MRI Severity Score | Change in MRI Severity Score | Neurologic Function Score at Initial Evaluation | Most Recent Neurologic Function Score | Change in Neurologic Function Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Late** | **1** | 12.1 | 22.1 | 10 | 22.4 | 0.3 | 16 | 20 | 4 | 1 | 13 | 12 |
| **Diagnosis** | **2** | 3.3 | 6.6 | 3.3 | 6.9 | 0.3 | 7 | 12 | 5 | 0 | 0 | 0 |
| | **3** | 4.8 | 7.1 | 2.3 | 7.8 | 0.7 | 10 | 13.5 | 3.5 | 2 | 8 | 6 |
| | **4** | 3.3 | 5.3 | 2 | 5.9 | 0.6 | 16.5 | 21 | 4.5 | 12 | 25* | 13 |
| | **5** | 6.4 | 8.3 | 1.9 | 8.4 | 0.1 | 10.5 | 12.5 | 2 | 0 | 1 | 1 |
| | **6** | 7.5 | 8.9 | 1.4 | NA | NA | N/A | NA | NA | 10 | 25* | 15 |
| | **7** | 3.8 | 10.5 | 6.7 | NA | NA | 14 | NA | NA | 3 | 25* | 22 |
| | **Mean** | 5.9 | 9.8 | **3.9** | 10.3 | 0.4 | **12.3** | 15.8 | 3.8 | **4.0** | 13.9 | 9.9 |
| **Early** | **1** | 6.3 | 6.3 | 0 | 6.7 | 0.4 | 9 | 22 | 13 | 1 | 15 | 14 |
| **Diagnosis** | **2** | 5.2 | 5.2 | 0 | 10.2 | 5.0 | 5 | 7 | 2 | 1 | 0 | −1 |
| | **3** | 3.8 | 3.8 | 0 | 7.1 | 3.3 | 2 | 2 | 0 | 0 | 0 | 0 |
| | **4** | 5.2 | 5.5 | 0.3 | 6.5 | 1.0 | 6.5 | 13 | 6.5 | 0 | 6 | 6 |
| | **5** | 8.4 | 8.4 | 0 | 8.8 | 0.4 | 11.5 | 12.5 | 1 | 1 | 25* | 24 |
| | **6** | 6.8 | 6.8 | 0 | 7.3 | 0.5 | 9 | 9 | 0 | 1 | 9 | 8 |
| | **7** | 6.3 | 6.5 | 0.2 | 7.5 | 1.0 | 0 | NA | NA | 2 | NA | NA |
| | **8** | 6.8 | 7 | 0.2 | NA | NA | 11 | NA | NA | 0 | NA | NA |
| | **9** | 4.7 | 5.3 | 0.6 | 5.3 | 0 | 9 | 10 | 1 | 1 | 2 | 1 |
| | **10** | 6.8 | 7.3 | 1.0 | 8.2 | 0.4 | 2 | 3 | 1 | 0 | 0 | 0 |
| | **Mean** | 6.0 | 6.3 | **0.2** | 7.5 | 1.3 | **6.5** | 9.8 | 3.1 | **0.7** | 7.1 | 6.5 |
| | **p-value** | 0.90 | 0.07 | **0.00** | 0.25 | 0.25 | **0.01** | 0.09 | 0.73 | **0.05** | 0.22 | 0.45 |

NA = not applicable; N/A = not available, AI = adrenal in sufficiency; X-ALD = X-linked adrenoleukodystrophy; HCT = hematopoietic cell transplantation

*Subject died; assumed score to = 25 (most severe) fort-test analysis.