HHS Public Access

Author manuscript

Bone Marrow Transplant. Author manuscript; available in PMC 2015 August 24.

Published in final edited form as:

Bone Marrow Transplant. 2012 October ; 47(10): 1377–1378. doi:10.1038/bmt.2012.33.

No evidence for the reversal of adrenal failure after hematopoietic cell transplantation in X-linked adrenoleukodystrophy

A Petryk[1], **LE Polgreen**[1], **S Chahla**[1], **W Miller**[2], and **PJ Orchard**[2]

[1]Division of Pediatric Endocrinology, University of Minnesota Amplatz Children's Hospital, Minneapolis, MN, USA

[2]Division of Pediatric Blood and Marrow Transplantation, University of Minnesota Amplatz Children's Hospital, Minneapolis, MN, USA

X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder characterized by accumulation of saturated very long-chain fatty acids (VLCFA) primarily in the adrenal cortex, central nervous system and testes. ALD results from mutations in the ABCD1 gene, which encodes a peroxisomal membrane transport protein.[1] The link between peroxisomal dysfunction and accumulation of VLCFA is not completely understood. Although impaired peroxisomal β-oxidation of VLCFA has been shown to have a role, mechanisms independent of the peroxisomal β-oxidation have also been proposed.[2]

The severity and tempo of progression of end-organ involvement vary among patients. Neurological disease is the most devastating manifestation, presenting either during childhood as rapidly progressive cerebral ALD or during adulthood as adrenomyeloneuropathy, a slowly progressive disease of the spinal cord, or both. Adrenal insufficiency (AI), either subclinical or overt, is found in the majority of patients with ALD, and may be present in up to 92% of children with cerebral disease.[3]

Hematopoietic cell transplantation (HCT) is the only treatment definitively shown to halt neurological disease progression if performed early in the disease process.[4] Much less is known about the effects of HCT on adrenal function. The goal of this study was to examine if HCT can preserve normal adrenal function or reverse AI in ALD patients.

We conducted a retrospective chart review of 50 consecutive patients with cerebral ALD, who were transplanted between October 2001 and September 2010 at the University of Minnesota and survived more than a year after HCT. The diagnosis of cerebral ALD was based on the presence of increased plasma VLCFA levels and characteristic white matter changes on MRI.[5] A pre-transplant diagnosis of AI was made at either the referring institutions or at our institution as recently published.[5] A group of 20 ALD patients, who returned for a follow-up visit, had a low-dose Cosyntropin (synthetic adrenocorticotropic

petry005@umn.edu.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

hormone (ACTH) 1 - 24) stimulation test 1 - 7 years post HCT (one patient did not proceed with the stimulation test because a random ACTH level was markedly elevated at 1749 pg/mL). Cortisol level was measured at baseline and + 15, + 30, and + 60 min after i.v. administration of 1 mcg of Cosyntropin,[5] with AI diagnosed if the peak stimulated cortisol level was less than 20 mg/dL. A low-dose ACTH stimulation test was chosen because it is more sensitive for the diagnosis of subclinical AI than a standard dose (250 mcg) test. None of the patients were receiving supraphysiologic doses of corticosteroids for GVHD at the time of ACTH stimulation testing. For patients on physiological replacement hydrocortisone doses, the morning dose was withheld before the test. The study was approved by the University of Minnesota Institutional Review Board.

Characteristics of the study population are shown in Table 1. Of the 20 evaluable patients surviving 1 year post HCT, 16 patients manifested AI before HCT, and none of these showed any recovery of adrenal function after HCT. Three of four patients that had normal adrenal function before HCT progressed to AI within 1 - 2 years after HCT. Only one patient had a normal adrenal function before and after HCT, with follow-up at 4 years. All 19 patients with AI were treated with hydrocortisone and 12 (63%) of them also required fludrocortisone treatment initiated for elevated serum renin levels (usually mild) or unstable blood pressure.

The present study, although limited by its retrospective nature and a small sample size, shows that ALD-associated AI persists after HCT performed for cerebral disease and suggests that most patients without AI before HCT will develop AI after HCT. It seems unlikely that HCT can reduce the risk of developing AI based on what is known about the pathological findings and the biological effects of HCT in this disease. In ALD, the adrenal cortex undergoes permanent atrophy. Although the mechanism is not completely understood, *in vitro* studies have shown that accumulation of VLCFA appears to alter the viscosity of the adrenocortical cell membrane, in which the *ABCD1* gene product normally resides, thus impairing binding of ACTH to its receptor.[6] As ACTH is a trophic hormone, a decrease in ACTH action would be expected to result in adrenocortical atrophy. In addition, oxidative stress from lipid peroxidation may contribute to adrenocortical cellular apoptosis.[7] As HCT does not seem to dramatically decrease plasma VLCFA burden, transplant may not alter the risk of development of adrenal disease.

Why would HCT halt the progression of neurological disease, but not adrenal disease? The pathogenesis of cerebral disease, unlike adrenal disease, also involves strong immunological and inflammatory responses, which are likely mitigated by HCT. In addition, donor-derived microglial cells of hematopoietic origin may have a role in stabilizing the process of demyelination within the central nervous system compartment.[8] There is no evidence that a similar metabolic process occurs in adrenocortical cells.

In summary, current data suggest that HCT does not reverse ALD-associated AI. Therefore, once AI is diagnosed in patients with ALD, the patients are committed to hydrocortisone treatment and do not need further ACTH stimulation testing. However, random ACTH levels should be measured annually to ensure adequate supplementation with hydrocortisone. Monitoring of electrolytes and renin levels should also continue as some

patients may require fludrocortisone. Patients who had normal adrenal function before HCT should be monitored for the development of AI by random ACTH levels. Equivocal results (elevated, but <500 pg/mL) should prompt ACTH stimulation testing.

REFERENCES

1. Mosser J, Douar AM, Sarde CO, Kioschis P, Feil R, Moser H, et al. Putative X-linked adrenoleukodystrophy gene shares unexpected homology with ABC transporters. Nature. 1993; 361:726–730. [PubMed: 8441467]
2. Berger J, Gartner J. X-linked adrenoleukodystrophy: clinical, biochemical and pathogenetic aspects. Biochim Biophys Acta. 2006; 1763:1721–1732. [PubMed: 16949688]
3. Korenke GC, Roth C, Krasemann E, Hufner M, Hunneman DH, Hanefeld F. Variability of endocrinological dysfunction in 55 patients with X-linked adrenoleucodystrophy: clinical, laboratory and genetic findings. Eur J Endocrinol. 1997; 137:40–47. [PubMed: 9242200]
4. Peters C, Charnas LR, Tan Y, Ziegler RS, Shapiro EG, DeFor T, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic cell transplantation experience from 1982 to 1999. Blood. 2004; 104:881–888. [PubMed: 15073029]
5. Polgreen LE, Chahla S, Miller W, Rothman S, Tolar J, Kivisto T, et al. Early diagnosis of cerebral X-linked adrenoleukodystrophy in boys with Addison's disease improves survival and neurological outcomes. Eur J Pediatr. 2011; 170:1049–1054. [PubMed: 21279382]
6. Whitcomb RW, Linehan WM, Knazek RA. Effects of long-chain, saturated fatty acids on membrane microviscosity and adrenocorticotropin responsiveness of human adrenocortical cells in vitro. J Clin Invest. 1988; 81:185–188. [PubMed: 2891726]
7. Powers JM, Pei Z, Heinzer AK, Deering R, Moser AB, Moser HW, et al. Adrenoleukodystrophy: oxidative stress of mice and men. J Neuropathol Exp Neurol. 2005; 64:1067–1079. [PubMed: 16319717]
8. Djukic M, Mildner A, Schmidt H, Czesnik D, Bruck W, Priller J, et al. Circulating monocytes engraft in the brain, differentiate into microglia and contribute to the pathology following meningitis in mice. Brain. 2006; 129:2394–2403. Pt 9. [PubMed: 16891321]

Table 1

Characteristics of the study population of 20 surviving ALD patients with testing for adrenal insufficiency 1 - 7 years post transplantation

Variable	Adrenal function (pre-HCT/post-HCT)		
	abnormal/abnormal	normal/abnormal	normal/normal
N	16	3	1
Age at HCT (years), mean±s.d.	7.9±2.3	10.1±0.2	8.3
Years between HCT and ACTH stimulation test mean±s.d. (range)	2.5±2.1 (1 - 7)	1.6±0.6 (1 - 2)	4 (NA)
Peak stimulated cortisol level (mg/dL) post HCT mean±s.d.	4.0±5.3	12.4±3.4	21.2
Currently on hydrocortisone (*N*, %)	16 (100%)	3 (100%)	0 (0%)
Currently on fludrocortisone (*N*, %)	9 (56%)	3 (100%)	0 (0%)
Donor type (N)			
Cord blood	7	2	0
Related marrow	7	1	1
Unrelated marrow	2	0	0
Conditioning (N)			
Myeloablative	12	2	0
Non-myeloablative	4	1	1

Abbreviations: ACTH=adrenocorticotropic hormone; ALD=adrenoleukodystrophy; HCT=hematopoietic cell transplantation; NA=not available.