Disease Progression in Cerebral X-linked Adrenoleukodystrophy based on MR Imaging: The Role of Contrast Enhancement and Location of Brain Lesion

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Abstract: X-linked adrenoleukodystrophy (X-ALD) has many variations with outcomes that range from no deficits to death. The purpose of this study was to evaluate the role of MR Imaging findings on MR disease progression in male X-ALD patients. The population included 140 X-ALD patients with multiple positive MRI exams. Perilesional contrast enhancement and three main anatomic patterns were evaluated (posterior disease, anterior disease, and isolated projection fibers). Our results showed statistically significant differences in MR progression of disease between different anatomic patterns, and between patients with and without perilesional contrast enhancement. These results should help with individual patient management.

Introduction: X-linked adrenoleukodystrophy (X-ALD) is a genetic disorder that involves the central nervous system, adrenal cortex and testes [1]. Evaluation of therapy and the selection of X-ALD patients for bone marrow transplantation (BMT) are hampered by the great variability of phenotypic expression, which ranges from the rapidly progressive childhood cerebral form to the milder adrenomyeloneuropathy in adults [2]. Neither mutational analysis nor biochemical studies are predictive of clinical course [2,3]. We have reported recently that a MRI severity score, designed specifically for X-ALD, represents a surrogate marker for brain involvement [4]. Furthermore it is recognized that different anatomic patterns of MRI changes exist and that perilesional Gadolinium enhancement has considerable predictive value.

Methods: Follow-up MR Imaging studies were performed in 140 cerebral X-ALD patients (mean age: 18.5 ±14.2, median: 12.2, range 1.7-73.8). All patients were seen at the Kennedy Krieger Institute. Data after bone marrow transplant was excluded. All exams included at least sagittal T1 weighted spin-echo imaging (TR/TE 500-600/15-25) and axial T2 weighted imaging (TR/TE 2500-3500/20-30). Gadolinium enhanced axial T1W imaging (TR/TE 500-600/15-20) were performed in 40 of these patients. Depending on the anatomical location of the primary involved area three patterns were defined (see figure 1), pattern 1: white matter in the parieto-occipital lobe and/or splenium of corpus callosum; pattern 2: white matter in the frontal lobe and/or genu of corpus callosum; pattern 3: primary involvement of fronto-pontine and/or corticospinal projection fibers. Regression analyses were performed to determine the effects of multiple factors on MRI progression.

Results: Average follow-up time was 3.51 years (from 2 months to 11.1 years). In the group that underwent contrast studies, the mean time between each follow-up exam was 1±0.8 years. 63% patients presented with pattern 1, 17% with pattern 2 and 14% with pattern 3 (see table 1). The remaining 8 patients could not be grouped to a specific pattern.

The mean progression of the MRI score per year was 3.2 for pattern 1 and 2.5 for pattern 2, but it was significantly lower, 0.4, in patients with pattern 3 (p=0.001, see figure 2). In patients with perilesional contrast enhancement, MRI progression was detected in 90% of the follow-up exams within only 3.5 (±2.5) months. In patients with pattern 1, age (p=0.006) and MRI severity score (p=0.03) at initial exam and presence or absence of perilesional contrast enhancement (p=0.001) accounted for 67% of the variability of disease progression (R2=0.67). In patients with pattern 2, MRI progression was strongly influenced by age (p=0.01) and the MRI severity score (p=0.035) at initial examination and these two factors together accounted for 58% of the variability of disease progression (R2=0.58). Only 3/19 (16%) patients with pattern 3 had an increase of the MRI severity score of greater than 2.

Conclusions: Our results demonstrate that different anatomical patterns and perilesional contrast enhancement play a significant role in prediction of disease progression and can serve as additional disease markers in the evaluation and management of X-ALD patients. These results will facilitate the evaluation of the effects of therapies, such as bone marrow transplantation.

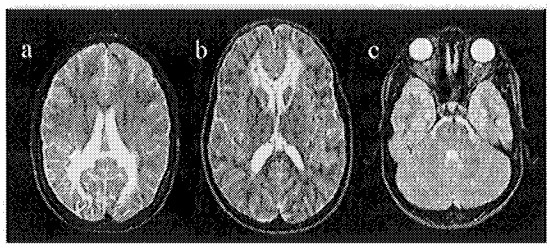

Figure1: Three different pattern recognized in male patients with cerebral X-ALD, a) pattern 1: white matter in the parieto-occipital lobe and splenium of corpus callosum, b) pattern 2: white matter in the frontal lobe and genu of corpus callosum, c) pattern 3: primary involvement of corticospinal projection fibers

	Pattern 1	Pattern 2	Pattern 3
Frequency	63%	17%	14%
	n = 88/140	n = 24 / 140	n = 20 /140

Table 1: Frequency of the three different anatomical patterns in the group of 140 X-ALD patients.

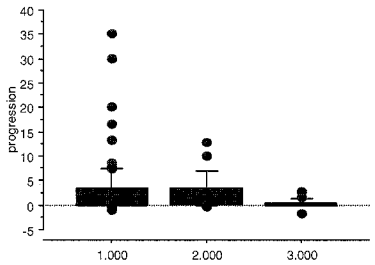

Figure 2: Rate of progression (increase of MRI severity score / number of follow-up years) in the different pattern groups 1,2 and 3.

Reference

1. Moser HW, Smith KD, Watkins PA, Powers J, Moser AB. X-Linked Adrenoleukodystrophy. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The Metabolic and Molecular Bases of Inherited Disease. Eighth Edition. New York: McGraw Hill, 2000:3257-3301.
2. Moser AB, Kreiter N, Bezman L, Lu S-E, Raymond GV, Naidu S, Moser HW. Plasma very long chain fatty acids in 3,000 peroxisome disease patients and 29,000 controls. Ann Neurol 1999;45:100-10.
3. Smith KD, Kemp S, Braiterman LT, Lu JF, Wei HM, Geraghty M, Stetten G, Bergin JS, Pevsner J, Watkins PA. X-linked adrenoleukodystrophy: genes, mutations, and phenotypes. Neurochem Res 1999; 24:521-535
4. Moser HW, Loes DJ, Melhem ER, et al. X-linked adrenoleukodystrophy: Overview and prognosis as a function of age and brain Magnetic Resonance Imaging abnormality. A study involving 372 patients. Neuropediatrics 2000;31:227-239.

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