

# X-linked adrenoleukodystrophy in heterozygous female patients: women are not just carriers

Adrenoleucodistrofia ligada ao X em pacientes femininas heterozigotas: mulheres não são meras portadoras

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## ABSTRACT

X-linked adrenoleukodystrophy (X-ALD) is a recessive X-linked disorder associated with marked phenotypic variability. Female carriers are commonly thought to be normal or only mildly affected, but their disease still needs to be better described and systematized. **Objectives:** To review and systematize the clinical features of heterozygous women followed in a Neurogenetics Clinic. **Methods:** We reviewed the clinical, biochemical, and neuroradiological data of all women known to have X-ADL. **Results:** The nine women identified were classified into three groups: with severe and aggressive diseases; with slowly progressive, spastic paraplegia; and with mildly decreased vibratory sensation, brisk reflexes, and no complaints. Many of these women did not have a known family history of X-ALD. **Conclusions:** Heterozygous women with X-ADL have a wide spectrum of clinical manifestations, ranging from mild to severe phenotypes.

**Key words:** adrenoleukodystrophy, X-linked disorder, heterozygous carriers.

## RESUMO

A adrenoleucodistrofia ligada ao X (ADL-X) é uma doença recessiva ligada ao X, associada à grande variabilidade clínica. Mulheres heterozigotas portadoras do gene causador da doença são consideradas, tradicionalmente, como clinicamente normais ou com fenótipo clínico muito discreto. No entanto, a apresentação clínica deste grupo necessita ser melhor caracterizada e sistematizada. **Objetivos:** Revisar e sistematizar as principais características clínicas de mulheres heterozigotas para ADL-X, seguidas em serviço de neurogenética. **Métodos:** Foram revisados os principais achados clínicos, bioquímicos e neurorradiológicos das mulheres seguidas no serviço com o diagnóstico bioquímico de ADL-X. **Resultados:** Nove mulheres foram identificadas e classificadas em três grupos: com doença grave e incapacitante; com evolução mais insidiosa e sintomas de paraparesia espástica; e com sintomas discretos apresentando diminuição da sensibilidade vibratória, reflexos vivos, mas sem queixas clínicas. A maioria dessas mulheres não possuía história familiar positiva para ADL-X. **Conclusões:** Mulheres heterozigotas para ADL-X apresentam um amplo espectro de manifestações clínicas, variando desde um fenótipo leve, subclínico até apresentações graves e incapacitantes.

**Palavras-Chave:** adrenoleucodistrofia, doença recessiva ligada ao X, portadoras heterozigotas.

X-linked adrenoleukodystrophy (X-ALD) is an X-linked recessive disorder that affects the brain white matter and that is associated with adrenal insufficiency<sup>1</sup>. The disease most commonly affects boys during early childhood and initially presents with either adrenal insufficiency or a variety of neurological manifestations, such as hyperkinetic behavior, neurological regression,

sensorineural deafness and optic atrophy, although most patients eventually develop the whole neurological picture. As white matter demyelination relentlessly progresses, the neurological status steadily becomes worse, resulting in complete disability, vegetative state, and death. Adrenomyeloneuropathy (AMN), a less severe clinical manifestation<sup>2</sup>, causes progressive myelopathy

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**Conflict of interest:** There is no conflict of interest to declare.

Received 06 January 2012; Received in final form 1 March 2012; Accepted 19 March 2012

that predominantly affects the corticospinal tract in the lower limbs of adolescents and young adult males. This condition is frequently mistakenly diagnosed as multiple sclerosis (MS)<sup>3</sup>. In such patients, the presence of adrenal dysfunction strongly suggests AMN<sup>4</sup>.

Although women carriers are usually considered normal or only very mildly affected, it has, in fact, been observed that at least half of the heterozygous females present neurological manifestations that vary in severity from mild hyperreflexia and vibratory sense impairment, with little or no functional disability to severe spastic paraparesis that requires a wheelchair<sup>5</sup>. As in males, females show no correlation between clinical severity and very long chain fatty acids (VLCFA) blood levels<sup>6</sup>. It seems, however, that there is a correlation between the skewing of the X chromosome and the specific mutation harbored by the patient<sup>6</sup>. Adrenal insufficiency has also been rarely detected in heterozygotes<sup>5-7</sup>.

To date, there are no systematic studies that address the prevalence of neurological and adrenal dysfunctions in ALD female heterozygotes. Additionally, their clinical characteristics have not been properly documented. In this report, we review the clinical features of the heterozygous women who were followed in our Neurogenetics Division, Clinics Hospital, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, in São Paulo.

## METHODS

In this study, we have included all females with VLCFA profiles showing increased C26:C22 and C24:C22, regardless of their clinical status or family history, followed in our hospital. They were submitted to a detailed clinical examination, nerve conduction studies (NCS), and brain/spinal cord magnetic resonance imaging (MRI). They all provided an informed consent (Clinics Hospital, School of Medicine of Ribeirão Preto, n. 3172/2009).

## RESULTS

Nine women showed abnormal VLCFA profiles compatible with a heterozygous state for X-ALD.

Their clinical manifestations suggest the existence of three distinct groups (Table): with a severe and aggressive neurological disease, mimicking the male X-ALD phenotype; with a slowly progressive spastic paraparesis; and with no complaints, having only mild abnormalities detected on neurological examination, including decreased vibratory sensation and brisk reflexes, with no apparent progression. There was no difference between the three groups with respect to the biochemical profile.

The first group consisted of three patients who presented with neurological regression and white matter abnormalities. They exhibited mental impairment, cerebellar ataxia, and spastic paraplegia. Psychotic behavior was noted in the most severely affected girl, who also presented seizures. Two patients presented learning disabilities before the physical manifestations onset. The brain MRI of patient 1 was virtually identical to the pattern found in males with ALD of childhood onset (Fig 1). Patient 2 was initially diagnosed with childhood onset MS and was treated accordingly (Fig 2).

In the second group, four patients showed spastic paraparesis as the main symptom. Two of them were mother and daughter, who were initially diagnosed as having autosomal dominant hereditary spastic paraplegia. The daughter's manifestations appeared in the second decade of life, whereas the mother developed symptoms in her forties. In this group, the symptoms were slowly progressive, but they were considered debilitating mainly due to the presence of bladder incontinence. Mood disorder was observed in three patients. Interestingly, only one patient had a known family history (son and brother) of ADL. Their brain MRI was initially normal, but mild abnormalities of the subcortical white matter were later developed.

In the third group, two patients were diagnosed exclusively due to their positive family history. They both reported

**Table.** Manifestations of heterozygous females with X-ALD.

Characteristics	Patients								
	01	02	03	04	05	06	07	08	09
Age of onset	7y	10y	12y	41y	20y	32y	41y	30y	35y
Dementia	+	+	+	-	-	-	-	-	-
Gait disturbance	+	+	+	+	+	+	+	-	-
Hyperreflexia in legs	+	+	+	+	+	+	+	+	+
Distal sensory impairment	+	+	+	+	+	+	+	+	+
Clinical fluctuation	-	-	-	-	-	-	-	-	-
Adrenal insufficiency	-	-	-	-	-	-	-	-	-
Abnormal NCS	-	-	-	-	-	-	-	-	-
Abnormal BAER	-	-	-	-	-	-	-	-	-
Brain MRI abnormalities	+	+	+	+	+	-	-	+	-
Abnormal spinal cord MRI	-	-	-	-	-	-	-	-	-

NCS: nerve conduction studies; BAER: brainstem auditory evoked response; MRI: magnetic resonance imaging.

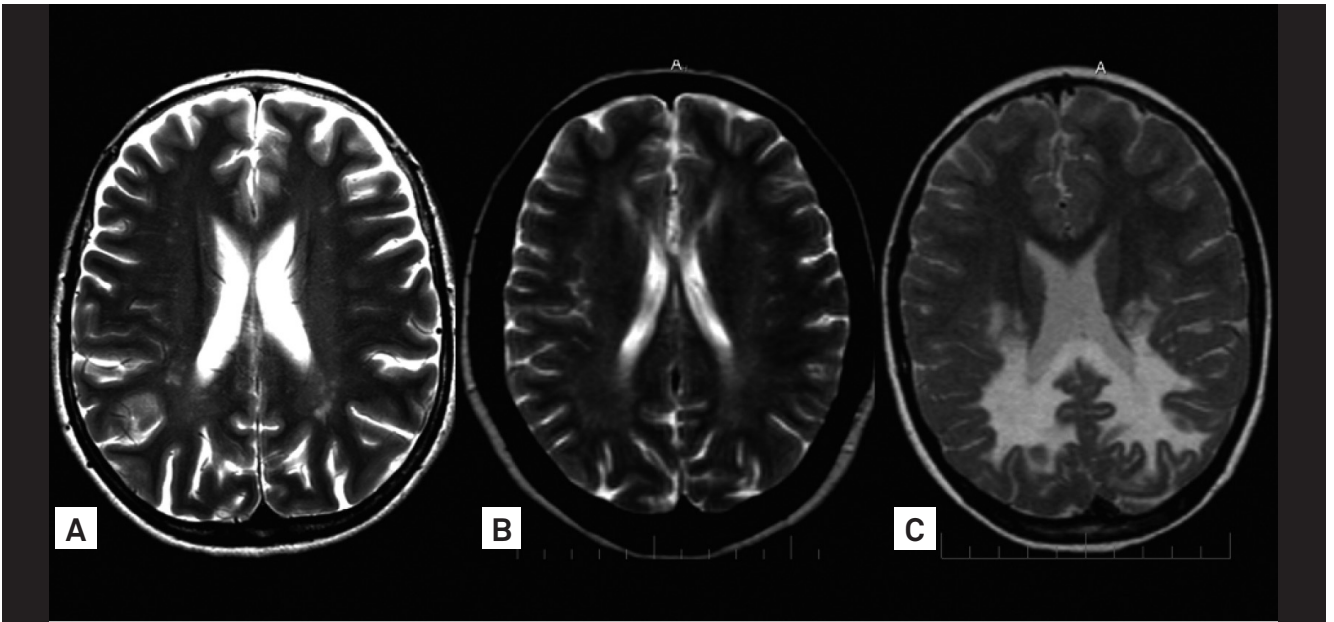


Fig 1. Characteristic patterns of symmetrical enhanced T-2 signal in the parieto-occipital region with contrast enhancement, similar to the one found in boys with the classical cerebral form of X-ALD.

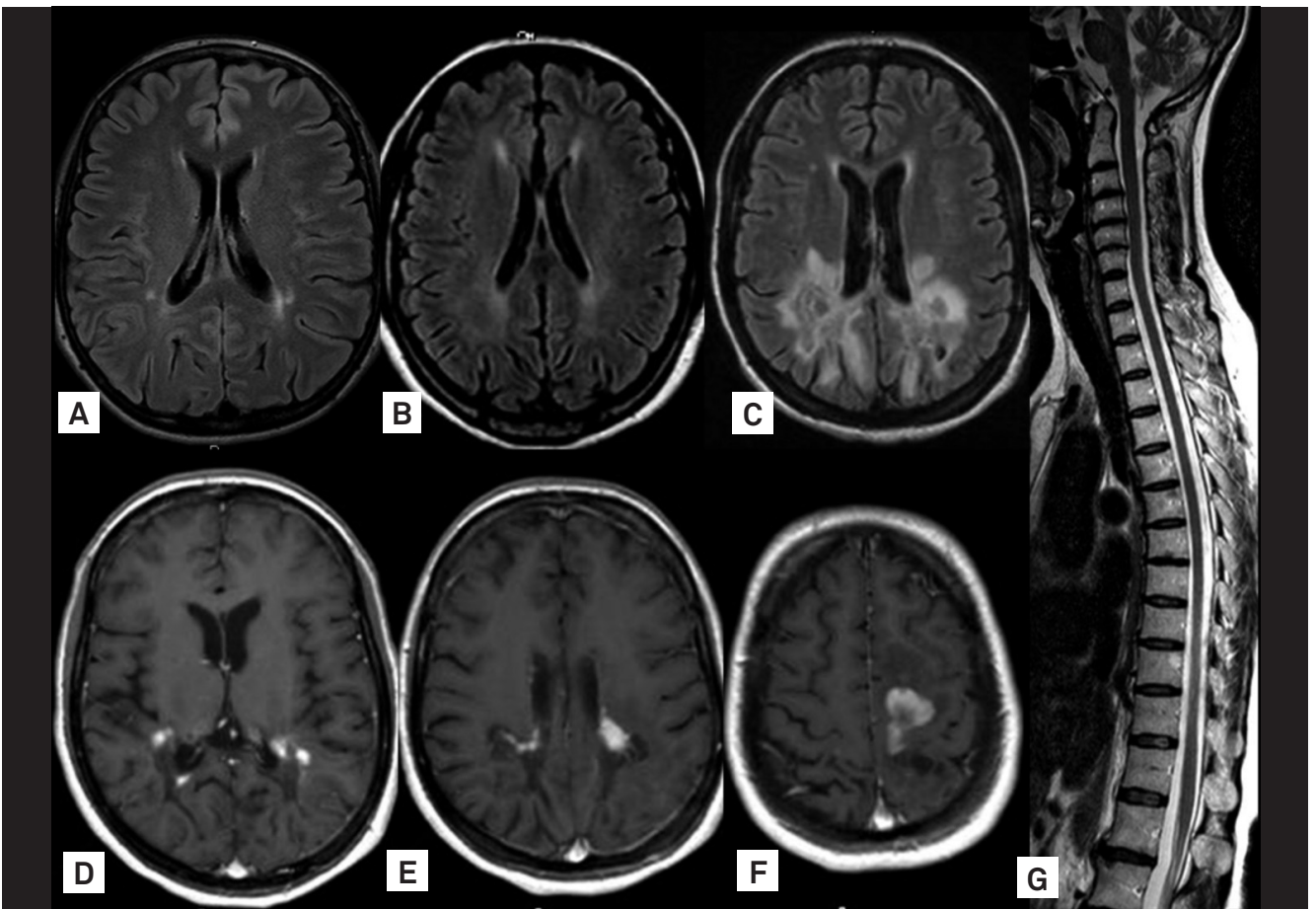


Fig 2. Severe periventricular demyelination with enhancement after contrast. This patient was misdiagnosed as childhood form of multiple sclerosis.

“cramps” and occasional discomfort when walking long distances. On examination, vibration was mildly decreased distally in the lower limbs, and tendon jerks were brisk at knees and ankles.

Karyotype (G-banding) analysis was performed in these patients, but no abnormalities were found in 100 metaphases. Endocrinological, ophthalmological, and audiometric evaluations, NCS and spinal cord MRIs were all normal.

## DISCUSSION

The phenotype of X-ALD varies widely among affected patients, even within the same family, but five major clinical subtypes have been identified in affected males<sup>8</sup>. These include childhood cerebral ALD, the most common phenotype, which affects 48% of male patients under 11 years-old; AMN, the next most common form (26%), which affects men over 21 years-old; the adolescent cerebral form (5%), which is observed between the ages of 11 to 21 years; Addison's disease without neurological involvement (11%); and the adult cerebral form (3%). Additionally, there are reports of a rare olivopontocerebellar atrophy presentation that affects mainly adults with late-onset manifestations of X-ADL<sup>9</sup>.

Neurological manifestations in ALD heterozygous females were previously thought to be relatively uncommon. However, data from the Kennedy Institute<sup>10</sup> showed that 15 to 20% of these patients develop symptomatic spastic paraparesis. In addition, neurological examination of these women showed that almost 55% of them had at least mild neurological abnormalities. This spectrum of manifestations resembled our patients from the first and second groups. Such manifestations were somewhat similar to males with AMN but were milder, slowly progressive, and of late onset. Adrenal dysfunction was extremely rare in female patients.

In our patients, stiffness and clumsiness in the legs were usually the first symptoms to appear (90%). The most common clinical signs were hyperreflexia (100%), spastic

paraparesis (76%), and impaired sense of vibration (88%). Neuropathy was not observed in our series of patients, although it was presented in other series<sup>11</sup>. Two of our patients from the second group developed a late and incapacitating sphincter disturbance. Cerebral involvement is considered uncommon in female carriers<sup>12</sup>, but three of our patients presented cerebral demyelination, and two developed severe neurological regression. Fluctuating manifestations and adrenal dysfunction were not observed in our cohort<sup>5</sup>.

The diagnosis of ALD is rarely made in women without an affected male relative. It is possible that many patients are initially misdiagnosed as having MS, until a family history of ALD is detected<sup>3</sup>. Interestingly, only three women in our cohort had a positive family history, suggesting that women, even those with mild evidence of bilateral corticospinal tract and/or decreased vibration perception in the lower limbs, should have their VLCFA levels tested.

Brain MRI identify characteristic changes in the majority of males with ALD and in about 50% of those with AMN, and may even detect abnormalities in asymptomatic patients<sup>13</sup>. A total of 16% of symptomatic females may present white matter abnormalities in the internal capsule, cerebral peduncle, and optic radiation<sup>10</sup>. In general, our patients showed only very mild abnormalities; although those with serious neurological regression showed multiple areas of cerebral demyelination (Fig 1 and 2). In our patients, MRI of the spinal cord was always normal, in opposition to previous reports suggesting that a decreased spinal cord diameter could be a marker of the onset of symptoms in heterozygous females<sup>12</sup>.

At present, there is no proven prevention or curative therapy for ALD in female carriers, and none of our patients received a specific therapy<sup>14</sup>. In addition to a supportive follow-up with no unnecessary investigation, a proper genetic counseling may be extremely useful for these patients and their families<sup>15</sup>. The wide range of clinical variability, which seems to be associated with ADL female carriers, should prompt interested clinical investigators to organize a multi-center systematic study to better define the associated clinical spectrum.

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