X-linked adrenoleukodystrophy: Clinical course and minimal incidence in South Brazil

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Abstract

X-linked adrenoleukodystrophy is a genetic disease that affects the degradation of very long-chain fatty acids. In male patients, common pictures are the cerebral form (CALD), myeloneuropathy (AMN), and Addison-only. Objective: To describe the clinical course of affected male patients from South Brazil between 1993 and 2007. Methods: Affected male patients and their maternal lineages were studied from a clinical, neurological and biochemical standpoint. Results: Eighty-three male patients from 30 families were biochemically evaluated: 51 were affected. 27/51 (54%) presented the cerebral form; 11/51 had AMN (22%); 5 had Addison-only (10%), and 8 (16%) were asymptomatic. Between 2002 and 2006, the minimal incidence was 1:35,000 males in our State (South Brazil). Forty-three affected individuals were followed for 5.4 ± 3.7 years. Of 10 boys detected at early stages, three developed CALD. These three boys and another five CALD at baseline were referred to hematopoietic stem cell transplantation. Seven transplants were carried out, 5 with good clinical evolution after 2.2 years post-transplant. The non-transplanted case was later defined as a stable cerebral form. Discussion: Among the present families, the observed cases were comparable to the 50% expected by Mendelian segregation. Based on the natural history, the number of cases that developed CALD was similar to the expected. Transplants were successful in 70% of cases. The occurrence of a stable cerebral form pointed to an urgent need for better markers of active cerebral disease.

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1. Introduction

X-linked adrenoleukodystrophy (X-ALD – OMIM 300100) is a peroxisomal disorder that affects the nervous system’s white matter and the adrenal cortex.
Incidence figures vary around 1:42,000 for hemizygotes [1]. Three main phenotypes are seen in males. The earliest one is the “Addison disease only” (Addison-only), when a boy presents with primary adrenocortical insufficiency between the age of 2 years and adulthood; the majority of these patients evolve to one of the remaining clinical types. The second and most severe phenotype is the cerebral form (CALD), which most commonly manifests between the ages of 4 and 8 years. Initially resembling attention deficit disorder, it is followed by progressive impairment of cognition, behavior, sight, hearing, and motor function, leading to total disability within 2 years. The third phenotype, adrenomyeloneuropathy (AMN), most commonly manifests in the late twenties as progressive paraparesis, sphincter disturbances, and sexual dysfunction; all symptoms worsen over decades. In male patients, AMN and CALD together account for more than 80% of clinical forms of ALD. Approximately 50% of carrier females develop AMN-like manifestations but have later onset (age 35 years or later) and milder disease than do affected males [2].

ALD is caused by mutations in the ABCD1 gene that encodes a peroxisomal membrane located ABC half transporter named ALDP. Mutations in ALDP result in elevated levels of very long-chain fatty acids (VLCFA). Plasma VLCFA analysis is still the best initial biomarker for X-ALD in males, for whom it brings unambiguous diagnosis. In obligate carriers, VLCFA levels can be normal in around 20% of cases; this means that mutation analysis is the most reliable method for the identification of other heterozygotes [2].

Therapeutic options for X-ALD are limited and can change as the phenotype evolves. Patients with adrenocortical insufficiency should receive adrenal steroid replacement. In boys and adolescents with early-stage cerebral involvement, hematopoietic stem cell transplantation (HSCT) can provide long-term stabilization and even reversal of symptoms [3,4]. However, the procedure leads to clinical benefits only at an early stage of cerebral demyelination. At present, patients with performance IQ of 90 or more are candidates to HSCT, because lower IQ levels are associated with HSCT complications and early death. Moreover, boys with few neurological findings – with scores of less than 10 on the 34-point ALD MRI Loes severity scale – have a survival probability of 92% after HSCT [3,5], and seem to have a better long-term neurological outcome [4]. Lorenzo’s oil (LO) is a 4:1 mixture of glyceryl trioleate and glyceryl trirurate that normalizes VLCFA levels in the plasma of X-ALD patients [6]. This biochemical response is not associated with a clinical benefit [7]. A recent long-term open label study has suggested that LO could have a partial preventive effect in asymptomatic boys whose brain MRIs were normal and whose VLCFA normalized after therapy [8]. Recent publications reviewed all these issues [9,10].

These therapeutic strategies have been tested since the 1990s. Papers on safety and efficacy have successively changed the panorama. In the same period, in the south of Brazil, the availability of the biochemical diagnosis became more or less universal to cases and families with suspected X-ALD [11].

Our aim was to report the males detected in our Hospital in a 15-year period, giving emphasis to the proportion of male phenotypes, the progression of these phenotypes, and the short-term follow-ups of the boys who underwent HSCT in this period.

2. Methods

2.1. Clinical evaluation and classification

Index cases were referred for genetic evaluation due to suspicion of ALD. Measurements of VLCFA were performed by gas chromatography in our lab. The diagnosis of ALD was established when high concentrations of hexacosanoic acid (C26:0) and increase in the hexacosanoic versus docosanoic acid (C26:00/C22:00) and/or tetracosanoic versus docosanoic acid (C24:00/C22:00) ratios were found in plasma [12]. Positive cases were then followed and managed as indicated at the time. Each male carrier underwent two investigations: an individual clinical evaluation and the family history collection.

The individual clinical evaluation included medical history, physical and neurological examination, and ancillary tests. The objective was to detect any neurological syndrome at baseline. Male patients with a biochemical diagnosis were classified in four phenotypes as follows: CALD, AMN, Addison-only, and asymptomatic.

Two possibilities defined the phenotype as CALD: (1) clear encephalic signs: hemisindrome (hemiparesias, hemihypoesthesias, hemianopsias), amaurosis, cognitive deterioration (aphasias, acalculias, agnosias, apraxias, etc), axial and appendicular cerebellar syndromes and cranial nerve lesions, or (2) demyelinating lesions in neuroimaging exams of the encephalus.

AMN phenotype was defined if findings (1) and (2) described above were absent and if the following were present: (3) symmetric pyramidal signs, and/or (4) distal sensitive loss with bilateral symmetric and neuropathic pattern, and/or (5) neurophysiologic signs of peripheral neuropathy, or lesion of the ascending tract (in SSER or SSEP).

Addison-only phenotype was characterized by the absence of findings (1)–(5) in individuals with (6) frank or subclinical adrenal insufficiency (positive stimulation test with ACTH).
Finally, the asymptomatic phenotype was characterized as the absence of any the following findings: (1)–(6).

Family history was based on the information given by the affected individual or his relatives. Maternal lineages were studied, and all male patients received an a priori classification up to the third generation (generations of the affected individual, of his mother and of his grandmother). Male relatives who were evaluated and performed the dosages of VLCFA were classified in the same way as was done for the index cases, as described above in the item “individual evaluation”. Among these relatives, there were (a) non-affected (with normal VLCFA), (b) asymptomatic ALD, (c) Addison-only ALD, (d) AMNs, and (e) CALD. Male relatives who did not have their dosages of VLCFA taken were those who were (f) deceased with a history of a neurological condition suggestive of a cerebral form (called “likely CALD”), or (g) asymptomatic male patients who either refused to be evaluated or with whom we lost contact; these were called “unknown status”.

2.2. Management

Management followed international recommendations [9,10]. After diagnosis, patients and/or their parents underwent genetic counseling. All individuals at risk of being carriers of the gene – men and women – were identified in their family pedigree. The need to measure the VLCFA of these people was insistently informed to the consultants. All cases analyzed biochemically were called to receive their results (normal or altered), and all new positive cases detected received the recommended management at the time of their diagnosis. Since 2008, DNA sequencing of the ABCD1 gene has been done in our lab. When a mutation was detected in an index case, direct analysis was also offered to the women of the same family. These results will be published elsewhere.

Management of male patients followed our local protocol for ALD (Fig. 1). All individuals were referred for endocrine evaluation; patients with adrenal insufficiency received hormonal repossession.

Until 2001, all carriers (asymptomatic, Addison-only, AMN, and CALD) were prescribed LO, at the dosage of 2 ml/kg/day, and were followed for adverse effects. Since 2001, only non-cerebral cases have received this prescription in an attempt to prevent cerebral involvement (Moser, personal communication, at the time). CALD patients stopped receiving this prescription [7].

Since the beginning, all cases that presented CALD, be it at baseline or at follow-up, were evaluated as to the possibility of receiving HSCT. The exclusion criteria have been a performance intelligence quotient (PIQ) equal to or smaller than 80, since in these cases post-transplant mortality made the procedure unjustifiable [3].

2.3. Statistical analysis

Means between groups were analyzed using Student’s t or Mann–Whitney’s U test according to the distribution of variables. Categorical variables were analyzed using chi-square test. All tests were two-tailed; p values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS 14.0 for Windows.

3. Results

3.1. General description of families

Thirty families were seen between 1993 and 2007. Twenty-one came from the state of Rio Grande do Sul; the remaining came from different parts of Brazil. Mixed ancestries were the norm.

Index cases were 24 CALD, 2 Addison-only, 3 AMN, and one asymptomatic female patient, who was seen due to her previous family diagnosis performed elsewhere.

To the 29 male index cases, the family investigation added another 32 non-affected (with normal dosages of VLCFA); 35 with unknown status (without VLCFA exam); 34 deceased due to a neurological picture; and 22 male patients with some form of ALD (biochemically confirmed). The observed phenotypes and the expected ones are described in Table 1. Fig. 2 illustrates one family pedigree, as an example of phenotypic variability found in kindreds.

Therefore, in three generations of 30 families, 152 men were identified: 85/152 were either confirmed or likely carriers of ALD; 32/152 were non-carriers, and 35/152 had an unknown status.

Between 1993, year of the first diagnosis, and June 2007, 43 individuals with ALD entered the cohort followed up (29 index cases and 14 additional cases). Their mean ± SD follow-up was of 5.44 ± 3.7 years.

In latter years, between 2002 and 2006 (a 5-year interval), 17 carriers were diagnosed; of these, 13 came from Rio Grande do Sul. In the same period, 450,000 males were born in this region, which gives a minimal incidence of ALD as 1 per 35,000 male newborns.

The clinical course and the conversion to a new phenotype could be documented in cases that returned to two or more follow-ups, that is, in the ALD cohort. In the ALD cohort (43 cases), we found different rates between phenotypes before and after the mean follow-up of 5.44 ± 3.7 years. CALD and AMN numbers were maintained approximately unchanged at the expense of the decreasing numbers of asymptomatic and Addison-only cases. All 11 deaths (at 10 ± 1 year of age) were due to CALD (Fig. 3, or Table 3).
3.2. Phenotypes

After family investigation, 8 asymptomatic ADL individuals were found. Among them, there were two exceptional circumstances, that is, an early diagnosis (at 8 months of age) and two losses about whom we did not get any clinical information. The remaining cases had a mean ± SD age at diagnosis of 5.8 ± 3 years (variation: 3–11 years). The follow-ups of asymptomatic cases are described in Fig. 3 (or Table 3). In 2.85 years, 3 of the 6 asymptomatic cases became Addison-only. Later, one of these Addison-only individuals developed CALD.

Five patients – 2 of them were index cases – were identified as Addison-only at baseline. Mean ± SD age at diagnosis was of 7 ± 1.2 years (range: 5–15). Their evolutions are described in Fig. 3 (or Table 3). At the end of the present observation, other 3 men, previously non-affected, converted to Addison-only. Two of the total 7 Addison-only boys later evolved to CALD.

Only 3 of 30 families were detected by the AMN index cases. Besides these, another 8 cases were recog-
nized from the family history. Thus, there were 11 AMN cases (6 followed; Fig. 3 or Table 3). Almost all of them had adrenal insufficiency. Mean ± SD age at diagnosis and follow-ups were of 30 ± 7.7 and 5 ± 3.1 years, respectively.

Thirty CALD patients were followed (Fig. 3 or Table 3, and Table 2). Twenty-seven had this phenotype at baseline (24 were index cases), and 3 were boys who entered the follow-up after their family investigation either as asymptomatic or as Addison-only and who evolved to cerebral forms during a mean follow-up of approximately 2 years. MRIs of one of those individuals are illustrated in Fig. 4. Different ages at entrance in the cohort were found for CALD diagnosed at baseline and during follow-up (8.8 ± 3.4 versus 6 ± 1 yr, \( p = 0.03 \)); this difference disappeared when ages at the diagnosis of cerebral involvement were compared (8.8 ± 3.4 versus 8 ± 1, ns).

Only 5 of 27 CALDs at baseline met the criteria to perform HSCT; the other 22 had arrived too late. Two CALDs at baseline were adolescents. Both presented specific characteristics. The first CALD adolescent presented simultaneously with AMN (spastic paraparesia and decreased nerve conduction velocities); he underwent HSCT (case d, Table 2).

The second CALD adolescent was 17 years old at diagnosis. This patient did not agree to undergo the procedure but has been followed up to the present date (2008). His neurological examination showed an action tremor and dysdiadochokinesia in the left arm; his total, verbal, and performance IQ were respectively 108, 122, and 88. This patient has remained stable in 2 years of follow-up.

Table 1
Characterization of the men detected in the 30 ALD families in three generations recalled. Comparison of the observed phenotypes with those found in the literature.

<table>
<thead>
<tr>
<th>Male alive at baseline</th>
<th>Comparison with the expected, mendelian proportion of males</th>
<th>Proportions of observed phenotypes in the affected males (versus data from literature)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Expected</td>
<td>Observed</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>50% (^a)</td>
<td>61.5%</td>
</tr>
<tr>
<td>Addison-only</td>
<td>5</td>
<td>10% (10–15%)</td>
</tr>
<tr>
<td>AMN</td>
<td>11</td>
<td>22% (40%)</td>
</tr>
<tr>
<td>Cerebral forms</td>
<td>27</td>
<td>54% (35–40%)</td>
</tr>
<tr>
<td>Unknown status (losses)</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Non-carriers</td>
<td>50% (^b)</td>
<td>38.5%</td>
</tr>
<tr>
<td>Total</td>
<td>( p = 0.04 ), chi-square</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) This proportion is in accordance to the independent segregation of gametes. However, a smaller proportion of carriers alive could be expected, since ALD strongly reduces the survival of affected males.

\(^b\) Only the examined individuals were included in chi-square Table; men with unknown status were not taken into account.

Fig. 2. Family 10, an example of phenotypic variability found in ALD kindreds, with sequential individual diagnoses since 1999.
successive, annual MRIs remained unchanged, showing a parieto-occipital pattern of involvement and a Loes score of 7. For these reasons, this case was eventually defined as “stable cerebral form”.

On their turn, all three individuals that developed CALD during medical follow-up were referred for HSCT. CALD follow-ups are described in Table 2, and the post-HSCT evolution is described below. In Fig. 4, serial MRIs of case g (Table 2) showed the appearance of white matter lesions in Flair sequence 4b, its worsening during the search for a HSCT donor (4d and 4e), and its stable appearance 5 months after the procedure (4f).

Therefore, there were two distinct groups of indications for HSCT as follows: those five CALD at baseline, and those three patients who converted to CALD during follow-up. Mean ± SD ages at HSCT in these groups were respectively 14.2 ± 3.2 and 8.6 ± 2.5 years (p < 0.05).

The great majority of cases diagnosed as CALD and who did not receive the indication for HSCT abandoned follow-up between 2 and 3 years after their first appointment.

3.3. Managements: Lorenzo’s oil and HSCT

Ten boys aged 3–15 years were prescribed LO for the prevention of the cerebral form. Their age at the beginning of this preventive treatment was of 6.6 ± 3 years, and their follow-up was of 6.6 ± 3.7 years. However, LO usage was erratic due to the lack of its dispensing by the health system. Periods of 2–6 months of use were interchanged with periods of 6 or more months without the medication.

Three of these 10 boys and adolescents ended up developing CALD (see Fig. 2 or Table 3). Mean age at entering the study was similar between the boys who remained stable (6.6 ± 5.3) and the boys who evolved to CALD (6 ± 1).

Eight boys received the indication, and seven have already preformed HSCT. Their evolution is briefly described in Table 2. Age (mean ± SD) at transplant was 11.9 ± 4 years. Aspects of the procedure and post-transplant follow-up of case “a” have been previously described [13]; the remaining will be published separately in a near future.
### Table 2
Evolution of the 30 cases characterized as cerebral ALD, with special attention to those who performed HSCT.

<table>
<thead>
<tr>
<th>Picture at baseline</th>
<th>Age at diagnosis, in years (mean ± SD)</th>
<th>Follow-up (mean ± SD)</th>
<th>Outcome</th>
<th>HSCT Performed</th>
<th>Age at transplant (years)</th>
<th>Type</th>
<th>Chimerism (%)</th>
<th>GVHD</th>
<th>Post-HSCT follow-up in 2008, in years</th>
<th>Loes at transplant</th>
<th>Loes at the end of observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALD 27 cases</td>
<td>8.8 ± 3.4</td>
<td>4.6 ± 3</td>
<td></td>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 cases</td>
<td>Case a: 14</td>
<td>Unrelated 100</td>
<td>No</td>
<td>7</td>
<td>7.5</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Case b: 12</td>
<td>Unrelated 100</td>
<td>Yes. Cerebral deterioration</td>
<td></td>
<td>Deceased after 12 months due to GVHD</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Case c: 11</td>
<td>Unrelated 100</td>
<td>No</td>
<td>3</td>
<td>6</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Case d: 19</td>
<td>Related (paternal uncle) 100</td>
<td>No</td>
<td>0.6</td>
<td>2</td>
<td>4.5</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic or Addison-only, or AMN 3 cases</td>
<td>Baseline: 6 ± 1</td>
<td>Since baseline: 4 ± 1.7</td>
<td>3 followed up in 2008</td>
<td>3 cases</td>
<td>Case e: 6</td>
<td>Unrelated</td>
<td>Graft failure</td>
<td>No</td>
<td>Deceased after 12 months due to bone marrow aplasia</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Age at conversion to CCALD: 8 ± 1</td>
<td>Time to convert to CALD: ±2 years</td>
<td>Mean ± SD age at HSCT: 8.7 ± 2.5</td>
<td>Case f: 10</td>
<td>Related (sister) 100</td>
<td>No</td>
<td>1.3</td>
<td>2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total mean ± SD (range) 8.5 ± 3.3 (4–18)</td>
<td>4.5 ± 2.8 (1–13)</td>
<td>–</td>
<td>11.8 ± 4</td>
<td></td>
<td>–</td>
<td>0.9 ± 0.4</td>
<td>2.2 ± 2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05.*
4. Discussion

Cerebral X-ALD is a rapidly progressive demyelinating disease that leads to severe disability, dementia, and death over months to years. Diagnosing a new ALD case brings at least two important challenges to physicians. First, offering the best possible treatment to each individual case and, second, preventing new cerebral forms in the maternal family.

This retrospective cohort reports the results of 15 years of both efforts.

The prevention of new cerebral forms can be achieved either through genetic counseling or neonatal screening. In Brazil, where no screening tests for ALD are done, prevention of CALD depends only on newly diagnosed families and proper genetic counseling. In an ideal clinical picture, all males at risk are analyzed. And 50% of them will carry the gene, whereas 50% will not. Unfortunately, 35 men of the present pedigrees were lost. Although mainly adults, these losses were very worrying. One can speculate how many of them would be actually carriers. The proportion of affected and non-affected men in a given family or group of families can give us a clue about it; and about the coverage and effectiveness of our diagnostic practice. In 30 families, with three generations under study, 152 men were reported among sibships, of which 85 were almost certainly affected. This number practically covered the expected rate of carriers due to meiotic segregation. As a result, almost all the remaining 67 men would be expected to be non-carriers, that is, the 32 effectively characterized as non-carriers plus the 35 missing men. It is impossible to state with certainty that these 35 losses were mostly non-carriers. Even if Mendelian probabilities foresee this as a good interpretation, there is no way to prove this speculation.

The rate of phenotypes observed gave us two divergent pieces of information. First, our cohort showed the exact expected proportions of asymptomatic and Addison-only forms as found in the literature (Table 1). This result suggests that the data collection of this cohort was adequate. Second, the proportion of CALD and AMN were different from those found elsewhere. AMN cases seemed to be lacking. Given that the majority of phenotypes concentrated in the earlier forms (asymptomatic, Addison-only and CALD), one possible
explanation would be the young age of our ALD cohort. Nonetheless, the possibility that CALD phenotype was indeed more frequent than others in our population should wait for more studies to be excluded.

In the present cohort, entrances gave us the estimate of the minimal incidence in our State as being 1:35,000 (or 2.8:100,000) males. Using the same strategy, based on the number of ALD cases identified and the number of live births, Kirk et al. (1998) and Ruiz et al. (1998) [14,15], respectively, arrived at a minimum incidence of 1.6 per 100,000 live births in Australasia and Spain, a number that increased to 1:42,000 in a comprehensive study conducted in the USA [1]. Our minimal incidence was therefore similar to the numbers published by others.

Withdrawal after the first appointments reflect the countless difficulties found in the Health System of a developing country. All of the following were factors that contributed to the decrease in number of cases identified and followed up: low levels of suspicion among clinicians in the early years of the cohort; difficult access to the biochemical diagnosis and to the reference center, located in the extreme south of the country; difficulty to obtain biochemical follow-ups and Lorenzo’s oil at the beginning of the cohort; resistance to accept the bad prognosis for the index case, which is almost always a CALD.

Since the publication by Moser et al. [8], the use of LO has become recommended for the prevention of cerebral evolution. It was estimated that, among male carriers, 35–40% at some point present central demyelination and that, among those who used the formula, this rate decreased to 24%. In our small series of 10 asymptomatic cases or Addison-only who received LO, three evolved to demyelination. We were not able to attribute any effect in favor or against LO, however. LO usage was very irregular in the present cohort. This medication is imported and dispensed by the State Health System. Very long periods between imports have produced long periods in which there was a lack of LO for all patients.

Both those ALD boys who remained without neurological damage and those who developed CALD started treatment on average at the age of 6 years and were followed up for 4.2 ± 2.2 years. So the two outcomes – being free of cerebral symptoms or developing CALD – could not be foreseen due to the different ages at entry. Later, ages at onset of Addison-only and of CALD phenotypes were again almost the same, or 7.3 (three individuals) and 7.7 years (another three individuals), respectively.

All 3 cases followed up and who developed central demyelination underwent HSCT. On the other hand, only 5 of the 24 boys and adolescents who already presented cerebral involvement at diagnosis received this referral.

HSCT is the only efficient treatment to interrupt the demyelinating course of CALD, in the early cerebral forms. Cases with a performance IQ below 80 or 90 have a reduced survival after HSCT; this is the cutoff below which the transplant is not indicated [3]. Nevertheless, the aim of HSCT is much more than to guarantee sur-
vival. Its ultimate objective is to prevent neurological handicaps. Cases with broad demyelination, generally associated to a Loes score equal to or above 10, have presented worse outcomes [3,4].

Of the seven transplanted cases, only one had a Loes score above 10. It was exactly this case that after transplant developed massive demyelination secondary to a graft disease versus host and evolved to a persistent vegetative state and death.

In contrast, five of seven transplanted boys (70%) showed apparently good responses to treatment, being stable 2 ± 2.8 years after HSCT. Although this is a short time after HSCT, it is already enough to show that the post-HSCT CALD did not reach the rate of progression seen in non-treated boys.

Stable cerebral forms have been mentioned very few times in the literature of ALD. A patient is said to present a stable cerebral disease if he shows MRI and neuropsychological abnormalities at diagnosis, with no evidence of neuroradiological and neuropsychological deterioration in follow-ups [16]. Stable cerebral disease constitutes a real problem in terms of management decision, especially because it is only recognized if transplant is not performed. This happened in the Storage Disease Consortium in the US and Canada [16]. Of CALD patients recruited in 1991 and 1992, five were not transplanted, and on a subsequent follow-up two were totally stable and alive after 8 years. A similar evolution occurred with one of our CALD patients. Because he was an adolescent, he had a little more autonomy and postponed his inclusion in the transplant program for 1 year, actively refusing it thereafter. His lack of adherence did not prevent him from performing new MRIs, which showed stable lesions. In face of this stability and the absence of impregnation of gadolinium on borders, we concluded that this patient in fact was not indicated to perform HSCT.

This case raised the question of looking for better markers of active cerebral disease in order to avoid unnecessary procedures in unsuspected stable cerebral forms.

Moreover, the moment HSCT is indicated can also be subject to a “mis-selection bias”. The CALD forms which developed during the follow-up visits had a mean age of conversion of 8 ± 1 years (mean age at HCT was 8.6 ± 2.5). In contrast, all CALD at baseline who received HSCT indication were on their late childhood or adolescence (mean age of 11.7 ± 4.1 years; mean age at HCT 14.2 ± 3.2 years), when cerebral involvement tends to progress more slowly. We cannot be sure whether or not there were other stable cerebral forms among these older boys. HSCT turns out to be rather an urgency, mainly in individuals with unknown previous clinical pictures, and the dilemma between indicating or postponing HSCT has no clear answer at this moment.

We concluded that the genetic counseling of ALD families has made the early diagnosis of the cerebral form in boys possible. We also concluded that an agile transplant program provides relatively fast and efficient procedures. Our short-term rate of success after transplant was 5 in 7 cases, or 70%. Finally, we concluded that more elaborate neuroimaging exams, including spectroscopy and the use of gadolinium, should be tested as markers of disease activity in order to avoid that the so-called stable cerebral forms be transplanted perhaps unnecessarily.

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