Evolution of Phenotypes in Adult Male Patients with X-Linked Adrenoleukodystrophy

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Our objective was to study the phenotype evolution of X-linked adrenoleukodystrophy (X-ALD) and the relation between axonal degeneration and cerebral demyelination. Although different X-ALD phenotypes are recognized, little is known about their evolution. Neuropathological and electrophysiological studies have shown that X-ALD is a disease with mixed features of axonal degeneration, leading to myeloneuropathy, and a severe inflammatory reaction in the cerebral white matter, resulting in demyelination. Retrospectively, 129 men with X-ALD were studied who were 1) at least 20 years presently or at the time of death, and 2) regularly monitored. Phenotype assignments were made at diagnosis and at present, or at death, using medical history and findings of neurological examination. Handicap was studied with the modified Rankin scale, and cerebral abnormalities with the X-ALD MRI severity (Loes) score. The mean follow-up interval was 10.1 ± 5.0 years. Among 32 patients neurologically asymptomatic at diagnosis, 16 (50%) developed neurological deficits. Among 68 adrenomyeloneuropathy (AMN) patients initially without clinical brain involvement, 13 (19%) additionally developed cerebral demyelination. In a subset of 60 AMN patients, a moderate handicap evolved over a period of 16.2 ± 8.9 years. Among 13 AMN patients with additional definite or probable cerebral involvement at diagnosis, eight died and one remained in a vegetative state. Most of the 16 patients with the cerebral phenotypes deteriorated. There is a high risk for adult neurologically asymptomatic patients to develop neurological deficits and for AMN patients to develop cerebral demyelination. Axonal degeneration and cerebral demyelination emerge in X-ALD independently of each other. This may have implications for the phenotype classification, the search for modifying factors, and the development and evaluation of new therapies.

X-linked adrenoleukodystrophy (X-ALD) is an inherited disorder of peroxisomal metabolism, characterized by impaired degradation of saturated very-long-chain fatty acids (VLCFA).1,2 The estimated birth incidence is at least 1:42,000.3 The phenotypic variability is high, with adrenomyeloneuropathy (AMN) and childhood-onset cerebral adrenoleukodystrophy (CCALD) accounting for approximately 80% of all cases.4,5 The central nervous system, adrenal cortex, and testis are most severely affected.1,2,4,5

In CCALD, a severe inflammatory reaction associated with accumulation of VLCFA in brain lipids causes cerebral demyelination.4,5 Early symptoms include attention deficit disorder, behavioral changes, impairment of visual acuity and hearing, and at a later stage seizures, dementia, bulbar dysfunction, and spastic tetraparesis. Three years after the onset of symp-
gession of symptoms in phenotypes other than CCALD and AdolCALD. Asymptomatic- and Addison-only patients can develop neurological symptoms, and some AMN patients develop additional cerebral demyelination; however, both frequency and severity of these events are unknown.

Based on neuropathological and electrophysiological findings, it has been hypothesized that, although both axonal degeneration and cerebral demyelination occur in X-ALD, these can develop independently of each other. Thus far, clinical studies to support this hypothesis are lacking.

Over the past 15 years, several experimental therapeutic trials for X-ALD have been conducted at the Kennedy Krieger Institute (KKI) and the Clinical Research Unit of the Johns Hopkins Hospital (JHH), patients being referred from all parts of the United States and beyond. We retrospectively studied the evolution of the different phenotypes and investigated the relation between axonal degeneration and cerebral demyelination based on the phenotype evolution.

Patients and Methods

Patients

Patients were selected from our X-ALD database, which is updated weekly and presently contains information on more than 1,000 pedigrees and 2,500 male patients. Patients were considered eligible for the study when they were at least 20 years of age on January 1, 2000, or at the time of death and had been monitored thoroughly as evidenced by undergoing at least two brain MRI and neurological examinations at 6 to 18 month intervals.

The database search yielded 131 eligible patients who were all evaluated for participation in therapeutic trials. One patient was excluded because his chart could not be found and another because he was under 20 years of age. Among the 129 included patients, 117 (91%) were evaluated at the KKI or JHH at least once. Detailed medical correspondence for the remaining 12 patients (9%) was available. In all patients, X-ALD was documented by elevated VLCFAs in plasma or cultured fibroblasts.

The evolution of the phenotypes was studied by grouping the patients according to their phenotype at diagnosis. Changes in patients without neurological deficits at the time of diagnosis (Addison-only and asymptomatic phenotype) and in AMN patients without clinical cerebral involvement were studied in particular. The onset of neurological symptoms, those attributable to cerebral involvement in particular, and the diagnosis of adrenocortical insufficiency were investigated after the patients had been grouped according to their most recent phenotype. Approval for the study was obtained from the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

Data Collection

The patients’ charts contained detailed information about medical history and neurological examination; most had participated in therapeutic trials. For patients with AMN, additionally standardized evaluation forms were used to document mental status (orientation, short-term memory, and affect), muscle strength (MRC scale), sensory function, reflexes, and sphincter function.

Patients were considered alive when medical correspondence, reports of telephone conversations, or letters dated January 1, 1999, or more recently (referred to as recent updates) were available. Unless it was known that they were deceased, efforts were made to contact patients or their family by telephone, and specific questions about mobility, mental function, adrenocortical function, and bladder and bowel function were asked.

Phenotype Assignment

By using the criteria listed in Table 1, patients were retrospectively phenotyped at diagnosis and at present or at the time of death from their medical history and neurological examination. For the purposes of this study only, the AMN phenotype was divided in three subgroups: AMN with symptoms clinically restricted to the spinal cord (AMN-0), AMN with symptoms of spinal cord and brain involvement (AMN-1), and AMN with symptoms of myelopathy when cerebral

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Age of Onset (yr)</th>
<th>Spinal Cord Involvement</th>
<th>Cerebral Involvement</th>
<th>Adrenocortical Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCALD</td>
<td>3–10</td>
<td>±</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>AdolCALD</td>
<td>10–20</td>
<td>±</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>ACALD</td>
<td>&gt;20</td>
<td>±</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>AMN-0</td>
<td>&gt;15</td>
<td>++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>AMN-1</td>
<td>&gt;15</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>AMN-2</td>
<td>&gt;15</td>
<td>++</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Addison-only</td>
<td>Any age</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>Any age</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

CCALD = childhood onset cerebral ALD; AdolCALD = adolescent onset cerebral ALD; ACALD = adult onset cerebral ALD; AMN = adrenomyeloneuropathy; AMN-0 = AMN without symptoms of cerebral involvement; AMN-1 = AMN with definite symptoms of cerebral involvement; AMN-2 = AMN, cerebral involvement uncertain; Addison-only = adrenocortical insufficiency without neurological involvement; Asymptomatic = mutant X-ALD gene without neurological or endocrinological deficits; ± = sometimes; + = frequently present; ++ = always present; – = absent.

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involvement could not be excluded (AMN-2). Patients who had AMN without cerebral involvement at earlier consultations but for whom recent updates were unavailable and cerebral involvement was not excluded were also phenotyped as AMN-2. When recent updates on hitherto neurologically asymptomatic patients were lacking, the patient was phenotyped as “unknown.” Brain MRI was not used to phenotype.

Neurological Symptoms and Diagnosis of Adrenocortical Insufficiency
Abnormalities of visual acuity or auditory discrimination, significant behavioral or psychiatric disturbance, rapid decrease in intellectual function, hemiparesis rapidly progressing to tetraparesis, rapidly progressive (pseudo)bulbar dysfunction, and seizures were considered signs of cerebral involvement. Disturbed gait, sensory abnormalities in the legs, and impaired function of bowel and bladder were regarded as signs of myeloneuropathy. Adrenocortical insufficiency was demonstrated by an elevated plasma level of adrenocorticotropic hormone (ACTH), with or without lowered plasma cortisol, or impaired plasma cortisol response after ACTH stimulation.

Brain MRI
Minimally, sagittal T1- and axial T2-weighted brain MR images were used to assess the severity of cerebral abnormalities at diagnosis and thereafter with the X-ALD MRI (Loes) scale.\(^1\) This 34-point scale reflects white matter abnormalities in the brain, brainstem, and cerebellum and has been used to follow the course in the cerebral phenotypes.\(^1\) A score of \(\leq 0.5\) is considered normal, and higher scores indicate cerebral demyelination. The MRIs were reviewed by one of the authors (D.J.L.), who was blinded for phenotype and genotype.

Handicap
The modified Rankin scale is used in stroke patients to measure handicap,\(^1\) but has also been used in X-ALD.\(^1\) This six-point scale was used retrospectively to study changes in handicap during follow-up: 0 = no symptoms; 1 = minor symptoms that do not interfere with life style; 2 = minor handicap, symptoms that lead to some restrictions in life style but do not interfere with the patient’s capacity to look after himself; 3 = moderate handicap, symptoms that significantly restrict life style and prevent totally independent existence; 4 = moderately severe handicap, symptoms that clearly prevent independent existence though not requiring constant attention; 5 = severe handicap, totally dependent requiring constant attention night and day. Because cerebral involvement could also result in increase of handicap without this being due to spinal cord involvement, it was noted separately whether patients manifested clinical signs of cerebral involvement.

Data Analysis
Dates of birth, death, diagnosis of X-ALD, onset of neurological symptoms, diagnosis of adrenocortical insufficiency, phenotype at diagnosis and at the time of death or at present, and Rankin score and Loes score at evaluations were collected. When the month but not the exact date of an event was known, the 15th of that month was used. When only the year was known but not the exact month, July 1 of that year was used in the calculations. When abnormalities unnoticed by the patients were found on neurological examination or during an inquiry, the date on which these were noted was entered. The follow-up interval was defined as the time between diagnosis and the most recent update (which varied from an admission to an informative telephone conversation) or as the interval between diagnosis and death. When recent updates were unavailable, the last contact with the patient was used in the calculations, and notation was made that a patient’s present status was unknown.

For the different variables, the mean and standard deviation were calculated. When the distribution was clearly non-normal, median and range are given as well. To determine the significance of the difference between means, the 95% confidence interval (95% CI) was calculated in paired and unpaired samples. Correlations between different variables were studied with simple linear regression analyses and the corresponding 95% CI.

Results
Patients
Among the 129 patients, 110 were U.S. citizens. Nine were from Canada, 3 from Germany, and 1 each, respectively, from Uruguay, France, Italy, the United Kingdom, Israel, South Africa, and Japan. All foreign patients were admitted to the KKI or JHH. The mean age at diagnosis was 27.6 ± 12.7 years. Lorenzo’s oil\(^1\) was used by 107 of the 129 patients (83%) for 2.6 ± 2.2 years (median 2.3, range 0.1–12) with quite variable compliance. Other, infrequently used experimental therapies given to patients with extensive or rapidly progressive cerebral involvement were thalidomide or β-interferon-1b (5 patients), intravenous immunoglobulin (3 patients), high-dose cyclophosphamide (1 patient), pentoxyphylline (1 patient), and bone marrow transplantation (1 patient).

Follow-Up
The mean duration of follow-up was 10.1 ± 5.0 years. The age at diagnosis and follow-up interval per phenotype are given in Table 2. Recent updates were available for 112 of the 129 patients (87%) but were lacking for 17 patients who could not be traced, including 13 U.S. residents; at diagnosis, twelve had AMN-0, two cerebral variants, and three the Addison-only phenotype. Thirty of the 129 patients (23%) were deceased by the time of this evaluation (Table 2).

Evolution of the Phenotypes
NEUROLOGICALLY ASYMPTOMATIC PATIENTS. Among the 32 men who were neurologically asymptomatic at diagnosis (24 Addison-only and 8 asymptomatic patients), 16 (50%) developed CNS involvement; at least 26 are still alive today (Table 2). Three died, one each
from ACALD, myocardial infarction, and multiple substance abuse.

**AMN PHENOTYPES.** Eighty-one patients had AMN at diagnosis (Table 2). The most frequent variant, AMN-0, was found in 68 of the 129 patients (53%). Thirteen of these 68 patients (19%) developed rapidly progressive cerebral demyelination. All 13 died, their mean survival being 2.3 ± 1.9 years (median 1.6, range 0.5–7.6) after the first manifestation of cerebral disease. Two others died of causes probably unrelated to X-ALD (1 at the age of 78 years with no apparent cause, and 1 after myocardial infarction). At least 41 of the remaining 53 AMN-0 patients are alive at present, the mean survival being 16.6 ± 7.8 years; 3 of these 41 are in their early 70s and still free of cerebral involvement but are severely handicapped. Four of the 5 patients initially diagnosed with AMN-1 have died; the fifth is in a persistent vegetative state 13.6 years after the onset of cerebral symptoms. The mean survival was 5.5 ± 5.0 years (median 3.4, range 1.3–13.6). Among the 8 patients with AMN-2, 4 developed cerebral involvement and died 3.0 ± 3.0 years (median 2.2, range 0.3–7.2) after the onset of cerebral involvement. The 4 others are still alive, but cerebral involvement could not be excluded.

Overall, 22 of the 81 men with the different AMN phenotypes (27%) developed cerebral involvement (Table 2). Their mean survival was 3.1 ± 3.1 years (median 2.0, range 0.3–13.6).

**CEREBRAL PHENOTYPES.** Sixteen of the 129 patients (12%) had one of the cerebral variants (CCALD, AdolCALD, and ACALD) at diagnosis (Table 2). Among the 10 patients alive today, the disease ceased to progress in 5. Among these 5, 1 underwent bone marrow transplantation at the age of 11 years and is alive and well 9 years later, and another was treated with high-dose cyclophosphamide at the age of 20 years and for more than 15 years did not deteriorate. The overall survival to date among these 16 men is 10.3 ± 4.0 years.

**LORENZO’S OIL.** Disease progression in patients who used Lorenzo’s oil did not differ from those neurologically asymptomatic or AMN patients who did not. All 16 patients with cerebral phenotypes at diagnosis used Lorenzo’s oil.

**Table 2. Evolution of the X-ALD Phenotypes During a Decade of Follow-Up**

<table>
<thead>
<tr>
<th>Phenotype at Diagnosis</th>
<th>Patients (n)</th>
<th>Age at Diagnosis (Mean ± SD)</th>
<th>Duration of Follow-Up (Mean ± SD)</th>
<th>Alive (n)</th>
<th>Deceased (n)</th>
<th>Status Unknown (n)</th>
<th>Additional Cerebral Disease (n)</th>
<th>Myeloneuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCALD</td>
<td>3</td>
<td>9.7 ± 1.1</td>
<td>11.8 ± 1.2</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>AdolCALD</td>
<td>9</td>
<td>16.0 ± 2.5</td>
<td>9.1 ± 3.7</td>
<td>6</td>
<td>2</td>
<td>1</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>ACALD</td>
<td>4</td>
<td>28.7 ± 9.6</td>
<td>4.1 ± 3.5</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>*</td>
<td>**</td>
</tr>
<tr>
<td>AMN-0</td>
<td>68</td>
<td>34.7 ± 10.4</td>
<td>9.9 ± 5.2</td>
<td>41</td>
<td>15</td>
<td>12</td>
<td>13</td>
<td>*</td>
</tr>
<tr>
<td>AMN-1</td>
<td>5</td>
<td>36.7 ± 6.8</td>
<td>5.1 ± 3.4</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>*</td>
</tr>
<tr>
<td>AMN-2</td>
<td>8</td>
<td>30.0 ± 10.1</td>
<td>8.0 ± 4.1</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>*</td>
</tr>
<tr>
<td>Addison-only</td>
<td>24</td>
<td>13.8 ± 4.3</td>
<td>9.7 ± 4.9</td>
<td>19</td>
<td>2</td>
<td>3</td>
<td>1</td>
<td>11</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>8</td>
<td>20.2 ± 9.3</td>
<td>11.4 ± 4.9</td>
<td>7</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>—</td>
<td>—</td>
<td>82</td>
<td>30</td>
<td>17</td>
<td>23</td>
<td>15</td>
</tr>
</tbody>
</table>

Mean (±SD) — 27.6 ± 12.7 10.1 ± 5.0 — — — — — —

CCALD = childhood onset cerebral ALD; AdolCALD = adolescent onset cerebral ALD; ACALD = adult onset cerebral ALD; AMN = adrenomyeloneuropathy; AMN-0 = AMN without symptoms of cerebral involvement; AMN-1 = AMN with definite symptoms of cerebral involvement; AMN-2 = AMN, cerebral involvement uncertain; Addison-only = adrenocortical insufficiency without neurological involvement; Asymptomatic = biochemical defect of X-ALD without neurological or endocrinological deficits; * = brain involvement or myelopathy present by definition; ** = difficult to assess.
asymptomatic. The follow-up interval (mean 10.0 years) for these 11 was comparable to the others, and their lack of findings was not simply due to a shorter evaluation interval. For five of the 129 patients studied (4%) neurologically asymptomatic at diagnosis, detailed recent updates could not be obtained, although it was known that two were alive.

Adrenocortical Insufficiency
Adrenocortical dysfunction was diagnosed in 98 of the 129 patients (76%) at a mean age of 21.9 ± 12.3 years. It was found in 13 of the 17 patients (77%) with cerebral phenotypes (CCALD, AdolCALD, ACALD) at 14.6 ± 4.7 years and in 70 of the 96 AMN patients (73%) at 25.5 ± 12.1 years. In 35 of the 70 AMN patients, adrenocortical insufficiency was diagnosed before X-ALD, in 2 both were demonstrated simultaneously, and in 33 patients dysfunction was diagnosed after X-ALD. In 24 of these 33 patients, adrenocortical insufficiency was found shortly after X-ALD was demonstrated, but 1 patient developed adrenocortical dysfunction 6.8 years after the diagnosis of X-ALD.

Brain MRI
The MRI findings at diagnosis and the X-ALD severity scores of the different phenotypes are given in Table 3. There were no correlations between the duration of symptoms and the Loes score in the cerebral phenotypes and the AMN phenotypes.

NEUROLOGICALLY ASYMPTOMATIC PATIENTS. In a patient with a Loes score of 8, subsequent brain MRIs remained unchanged over a period of 7 years, although he developed AMN-0.

AMN PHENOTYPES. The difference in the mean duration of neurological symptoms between the patients with abnormal and normal MRI findings was not significant (difference 3.2 years; 95% CI, −0.6–6.9). Thirteen patients with AMN-0 additionally developed cerebral demyelination (Fig 2). Six of these 13 men (46%) had a normal MRI at diagnosis. The durations of symptoms resulting from myelopathy in the men without and with MRI abnormalities were similar [9.7 ± 11.7 years (median 4.9, range 1.6–33) and 10.1 ± 6.1 years, respectively].

CEREBRAL PHENOTYPES. All 16 patients with one of the cerebral variants at diagnosis had extensive cerebral white matter abnormalities at diagnosis. One of the 5 patients who clinically ceased to deteriorate now has been stable with a Loes score of 8.5 for 8 years.

Progression of Handicap
Overall, the mean value of the Rankin score during follow-up increased from 1.3 ± 1.1 to 2.5 ± 1.6 (95% CI of the difference, 0.8–1.5). In the 96 patients who developed one of the AMN phenotypes, including 57 who used Lorenzo’s oil for a mean period of 2.3 ± 2.0 years (median 2.0, range 0.1–12.0), the mean score increased from 1.5 ± 1.0 to 2.8 ± 1.2 (95% CI of the

Table 3. Mean Loes X-ALD Severity Score per Phenotype at Diagnosis

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Patients (n)</th>
<th>Score ≤0.5(n)</th>
<th>Abnormal(n)</th>
<th>Mean Score Abnormal ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral</td>
<td>16</td>
<td>0</td>
<td>16</td>
<td>10.5 ± 3.9</td>
</tr>
<tr>
<td>AMN-0</td>
<td>68</td>
<td>47</td>
<td>21</td>
<td>3.0 ± 1.4</td>
</tr>
<tr>
<td>AMN-1</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>5.4 ± 2.9</td>
</tr>
<tr>
<td>AMN-2</td>
<td>8</td>
<td>1</td>
<td>7</td>
<td>7.4 ± 4.8</td>
</tr>
<tr>
<td>Addison-only or asymptomatic</td>
<td>32</td>
<td>21</td>
<td>11</td>
<td>3.2 ± 3.1</td>
</tr>
<tr>
<td>Total</td>
<td>129</td>
<td>69</td>
<td>60</td>
<td></td>
</tr>
</tbody>
</table>

Cerebral = CCALD, AdolCALD, or ACALD phenotypes; AMN-0 = AMN without symptoms of cerebral involvement; AMN-1 = AMN with definite symptoms of cerebral involvement; AMN-2 = AMN, cerebral involvement uncertain; Addison-only = adrenocortical insufficiency without neurological involvement; asymptomatic = biochemical defect of X-ALD without neurological or endocrinological deficits.
In a subset of 60 patients with AMN-0 at diagnosis studied thoroughly at our institution, the symptoms of myelopathy began at a mean age of 28.2 ± 8.1 years. At the first visit, 9.1 ± 8.2 years after the onset of symptoms, the mean of the modified Rankin score was 1.7 ± 0.9. At last admission, 16.2 ± 8.9 years after the onset of myelopathy, the mean score had increased to 2.9 ± 1.1 (95% CI of the difference, 0.8–1.6).

A mild correlation between the duration of symptoms and the Rankin score (r = 0.62, 95% CI 0.33–0.80) was found in the AMN-0 patients. No other correlations were found between other phenotypes and the Rankin score. A mild correlation existed between the Loes score and Rankin score in the patients with one of the cerebral phenotypes (r = 0.72, 95% CI 0.49–0.85).

**Discussion**

This report is the first to address the evolution of the X-ALD phenotypes in a large group of men. During a decade of follow-up, 50% (16 of 32) of the neurologically asymptomatic patients became neurologically symptomatic, and 19% (13 of 68) of the patients initially diagnosed with AMN-0 additionally developed relentlessly progressive cerebral demyelination similar to that of CCALD.

There are no reports on the onset and progression of symptoms in larger groups of adult patients with the Addison-only and asymptomatic phenotypes of X-ALD. Therefore, the natural course of these variants that constitute approximately 8% to 14% of all X-ALD patients in cross-sectional studies is not known exactly. Nevertheless, it has been assumed that there is a high risk for neurologically asymptomatic patients to develop neurological symptoms. Our findings suggest that there is at least a 50% chance that patients with the Addison-only or asymptomatic phenotypes will develop neurological deficits within a 10-year interval.

In contrast to CCALD, AMN has been portrayed as a relatively mild and slowly progressing variant of X-ALD, unless cerebral involvement occurs. However, detailed reports on both the frequency and the progression of this event are lacking. It has been assumed that the risk for cerebral involvement decreases with increasing age. Our findings indicate that AMN without cerebral symptoms can no longer be regarded as a relatively benign phenotype, even when the brain MRI at diagnosis is normal. During 10 years of follow-up, additional cerebral disease occurred in 19% of AMN patients with initial involvement clinically restricted to the spinal cord, including 6 AMN patients with normal brain MRI at diagnosis, with a survival similar to that for CCALD. Although cerebral demyelination most frequently occurs in the fourth and fifth decades, it can occur in AMN patients at any age.

Although reports on the disease progression over a period of 2 to 3 years despite treatment with Lorenzo’s
oil have been published.\textsuperscript{13,18–21} long-term follow-up studies on patients with the milder variants are lacking. We retrospectively studied handicap and its progression. Initially, the Extended Disability Status (Kurtzke) scale\textsuperscript{22} was measured, but despite the availability of very detailed information the scores were difficult to assess and prone to high variability. Therefore, it was decided to use the modified Rankin scale, a scale that has been used mainly in the study of stroke patients\textsuperscript{12,23} but also in the evaluation of Lorenzo’s oil therapy.\textsuperscript{13} Among a subset of 60 patients thoroughly monitored by our institute, we found that, approximately 16 years after the first manifestation of myeloneuropathy, AMN patients require assistance to walk and might even be confined to a wheelchair. Furthermore, the changes in the Rankin score suggested a gradual increase in handicap.

Most of the patients with the cerebral phenotypes (CCALD, AdolCALD, ACALD) have a short survival.\textsuperscript{1,2} However, surprisingly, ten patients are still alive (CCALD, AdolCALD, ACALD) have a short survival.\textsuperscript{1,2} However, surprisingly, ten patients are still alive at present, 12.6 ± 2.6 years after the onset of their symptoms, including three who stabilized without any treatment besides Lorenzo’s oil and two who did not deteriorate, one after treatment with high-dose cyclophosphamide and one after bone marrow transplantation. Although bone marrow transplantation seems to be the only treatment that may halt the progression of cerebral demyelination,\textsuperscript{24–26} it cannot be excluded that this stabilization and prolonged survival are a reflection of the natural course, the result of intense immunosuppression, or both.

Kumar et al\textsuperscript{17} have proposed that a differentiation should be made between “pure-AMN” and “AMN-cerebral.” According to their report, 54% of the AMN patients have pure-AMN, based on the observation that cerebral white matter changes are absent, and 46% have cerebral white matter abnormalities and are referred to as “AMN-cerebral” patients. Pure-AMN patients were considered to have a more favorable prognosis. Among the 81 AMN patients we studied, 48 (59%) had a brain MRI that was considered normal (Loes score of ≤0.5). This suggests that the group of AMN patients we studied was similar to the group of Kumar et al. However, no fewer than 6 of the 13 AMN patients in our study group with pure-AMN at diagnosis developed rapidly progressive cerebral disease (Fig 2). These findings indicate that the initial absence of cerebral white matter changes in AMN does not prevent subsequent rapidly progressive demyelination. Therefore, we believe that it can no longer be justified to relate a more favorable long-term prognosis to what has been referred to as “pure-AMN.” We are studying the relation between MRI findings and clinical symptoms at present and whether certain MRI abnormalities can predict when cerebral involvement will occur.

Our findings regarding the onset of symptoms resulting from myeloneuropathy in AMN are in accordance with earlier observations.\textsuperscript{1,2} Symptoms emerge predominantly in the third and fourth decades. Initial symptoms were most frequently gait disturbance, followed by sensory symptoms and urinary and bowel hesitance or incontinence.

We believe that, even though 107 of the 129 patients (83%) used Lorenzo’s oil, it most probably did not change the natural course of the disease. Lorenzo’s oil, a dietary regimen developed in 1987, is a 4:1 mixture of glyceroltrioleate and glyceroltrirucinol.\textsuperscript{14} It was found to normalize plasma VLCFA levels within weeks, and it was hoped that correction of the metabolic defect of X-ALD could halt the progression of the disease. Unfortunately, most X-ALD patients deteriorated.\textsuperscript{13,18–21} It is now well-accepted that, even if Lorenzo’s oil had a beneficial effect in patients who already demonstrated neurological deficits, it was too small to be demonstrated.\textsuperscript{15,16} Indeed, the disease progressed in most of the AMN patients, even when they used the oil. The results may be related to the observation that the dietary oils do not pass the blood–brain barrier\textsuperscript{27,28} and so could not exert their effect on the biosynthesis of VLCFA in the brain. Therefore, even if Lorenzo’s oil has some beneficial effect, the progression in comparison to untreated patients is only slightly milder at best.

It is difficult to tell whether the normal phenotypic distribution was represented in the group of patients we studied. Without doubt patients were selected; probably younger and more severely affected individuals were more keen on participating in the clinical trials in contrast to older and less severely affected patients. We compared the composition of the study group with a cross section of the patients in The Netherlands, where the distribution of the different phenotypes probably is the most complete and is less subjected to ascertainment bias. There were no significant differences between the distribution of the phenotypes in our group and the Dutch patients older than 20 years of age at present or at time of death (B.M. van Geel, unpublished data).

A severe and devastating inflammatory reaction in the cerebral white matter and consequent demyelination can occur either before, accompanying, or after the onset of symptoms resulting from myeloneuropathy. Powers and colleagues\textsuperscript{4,5,7} have reported that a severe inflammatory reaction associated with the accumulation of VLCFA causes cerebral demyelination superimposed on mild dysmyelination in CCALD and that the peripheral nerves and spinal cord are virtually intact in these young patients. On the other hand, AMN is characterized by the absence or paucity of an inflammatory reaction in the brain and spinal cord, and the spinal cord and peripheral nerves show signs of axonal degeneration and a “dying back” phenomenon,
with secondary demyelination. This is corroborated by electrophysiologic studies in AMN patients showing that the polyneuropathy probably is primary axonal, with secondary demyelinating characteristics. It has been shown that the membrane viscosity of erythrocyte membranes changes and that the function of adrenocortical cells is impaired by the incorporation of abnormal amounts of VLCFA into the cell membranes. Analogously, the excessive incorporation of VLCFA laden lipids in the axonal membranes may cause axonopathy in X-ALD. It may be that the boys with CCALD and AdolCALD are too young rather than quantitatively different from the men with AMN, insofar as the axonopathy rarely becomes manifest before 20 years of age. Our clinical findings suggest that two distinct processes occur in X-ALD, slowly progressive deterioration of axonal function (the myeloneuropathy) and a severe cerebral inflammatory reaction (the rapidly progressive cerebral demyelination).

Different phenotypes and their relative frequencies have been described, based on age of onset of symptoms and the organs principally affected. Although a phenotypic classification may seem useful, eg, to stratify patients for clinical trials, our data suggest that, until the occurrence of cerebral involvement (CCALD, AdolCALD, ACA LD, AMN with additional cerebral involvement), the other phenotypes are merely transient. The present phenotype classification does not reflect these two aspects of the pathophysiology and may need revision. Whether MRI has a predictive value in such a classification awaits further study.

It had been suggested that a modifier gene determines the phenotypic expression of X-ALD. Gradually, the search has been focused on other genes that encode for peroxisomal membrane proteins (ALDR, PMP70, PMP70R) that may form heterodimers with the X-ALD gene product, the ALDP. Our findings might have implications in the search for modifying factors; they indicate that cerebral involvement does eventually occur in a substantial proportion of AMN patients who are without clinical cerebral involvement at diagnosis, so an absolute distinction between AMN with cerebral involvement and the cerebral forms might not be possible. It is uncertain whether these modifiers are genes involved in the import or activation of VLCFA. Other possible modifying factors are immunologic or environmental; different phenotypes have been reported in monozygotic twins.

It seems unlikely that the age of onset of adrenocortical insufficiency determines the phenotypic expression. In both the cerebral variants and the AMN phenotypes, approximately 75% of the patients eventually were diagnosed with adrenocortical insufficiency. Although the differences in age at diagnosis of adrenocortical insufficiency between the patients with the cerebral variants and AMN was significant, this finding can be explained. Most patients with cerebral phenotypes were diagnosed in late childhood and early adolescence, and, once X-ALD was diagnosed, this prompted evaluation of adrenocortical function. In contrast, the adrenocortical function of AMN patients was not studied until they were diagnosed in their late 20s or early 30s. It has been reported that the risk for developing adrenocortical insufficiency is very low when the adrenocortical function is normal in patients who already have neurological deficits. On the other hand, Assies et al have reported that adrenocortical insufficiency can precede, accompany, or follow the onset of neurological symptoms, which is in accordance with our experience. Although this occurred infrequently, one patient developed adrenocortical insufficiency almost 7 years after he was diagnosed with X-ALD. Left untreated, adrenocortical insufficiency can result in serious illness and even mortality. Therefore, adrenocortical function should be tested at regular intervals in men with X-ALD, even when their adrenocortical function was originally normal or when they already have neurological symptoms.

In conclusion, we found a very high risk for neurologically asymptomatic X-ALD patients to develop neurological dysfunction and a high risk for AMN patients to develop additional devastating cerebral disease during a decade of follow-up. These findings support the hypothesis that, in this crippling and potentially lethal disease, axonal degeneration becomes more frequent and more prominent with increasing age. Additionally, devastating cerebral demyelination caused by a severe inflammatory reaction can occur at any age. Our findings may have implications for the present phenotype classification, the search for modifying factors, and the development and evaluation of new therapies.

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