Cognitive Functions in Adult-Onset Phenotypes of X-Linked Adrenoleukodystrophy

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Objective: X-linked adrenoleukodystrophy (X-ALD) is a rare genetic disorder characterized by progressive demyelination ranging from mild myelopathic forms (adrenomyeloneuropathy [AMN]) to severe cerebral variants (adult cerebral adrenoleukodystrophy [ACALD]). The aim of this study was to compare cognitive function in adult-onset X-ALD phenotypes.

Methods: Cognitive function in various domains (intelligence, attention, memory, executive function, and processing speed) was assessed in 172 adults (117 with AMN, 30 with arrested ACALD, and 25 with acute ACALD) using comprehensive neuropsychological batteries. Phenotype differences were examined by analyses of variance.

Results: X-ALD phenotypes significantly differed in nonverbal intelligence, sustained attention, verbal encoding, nonverbal recognition, and processing speed (ps < 0.050). No group differences emerged regarding verbal intelligence, verbal retrieval and recognition, and executive function (ps > 0.050). Specifically, patients with acute ACALD showed severe cognitive deficits compared to AMN and normal data, with largest effects on processing speed. Contrary, cognition was overall intact in patients with AMN, independent of sex and corticospinal tract involvement, and those with arrested ACALD showed mild cognitive dysfunction, particularly in verbal encoding and processing speed.

Interpretation: Cerebral demyelination in patients with X-ALD causes white matter dementia, mainly characterized by an extreme slowdown in processing speed associated with deficits in attention and learning. Most patients with AMN show intact cognitive function. Future prospective, longitudinal studies with more sensitive imaging techniques are required to clarify whether early mild cognitive dysfunction found in some patients with AMN may be associated with subtle myelin abnormalities that do not yet appear as white matter lesions on cerebral MRI (cMRI) but have the potential to serve as early predictors of later cerebral progression.

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X-linked adrenoleukodystrophy (X-ALD) is a rare white matter disorder caused by mutations in the ABCD1 gene. Adult-onset X-ALD phenotypes vary widely, ranging from slowly progressive myelopathic variants with chronic degeneration of the long tracts in the spinal cord, clinically manifested as spastic paraparesis, sensory ataxia, bladder and sexual dysfunction (adrenomyeloneuropathy [AMN]), to severe cerebral forms characterized by rapidly progressive inflammatory demyelination in the brain (adult cerebral ALD [ACALD]).1 If not arrested by hematopoietic stem cell transplant (HSCT),2 acute ACALD rapidly leads to vegetative states and death within years.3 In some cases, acute cerebral inflammation in ACALD spontaneously arrests and remains stable over years without treatment for reasons not yet clarified (arrested ACALD).4 Although the gene
defect is inherited X-linked, up to 80% of heterozygous women develop AMN symptoms during their lifetime. Unlike men, AMN in women starts at a higher age, progresses slower, and usually shows no cerebral involvement (ACALD < 1%).

To date, research on cognitive function in adult-onset X-ALD phenotypes is still scarce, but of importance for planning patients’ symptomatic treatment and predicting disease progression, as shown in childhood X-ALD and metachromatic leukodystrophies. A recent study suggested intact general cognitive function (ie, language, verbal and nonverbal memory, visuoconstruction, executive function, and psychomotoric speed) in 33 male patients with AMN with no or minimal cerebral magnetic resonance imaging (cMRI) anomalies. Only word fluency (ie, verbal processing speed) was significantly lower (mean T value = 45.7 ± 8.9), but not below average in this sample compared to normal data. However, in another study, group differences in processing speed, visuoconstruction, visual memory, and verbal recall emerged when comparing patients with pure AMN (n = 32–48) versus patients with acute ACALD (n = 19–33), with the latter significantly performing worse. Notably, impairment in patients with X-ALD across cognitive domains was positively associated with the degree of brain involvement detected in cMRI. Although a subset of male patients with pure AMN were found to show below-average performance compared to healthy patients, studies did not reveal consistent impairments in a particular cognitive domain.

Due to the lack and heterogeneity of previous findings, this study aimed to compare adults with AMN, acute ACALD, and, for the first time, arrested ACALD regarding their functional level across different cognitive domains (intelligence, attention, verbal and nonverbal learning and memory, executive function, and processing speed) using comprehensive and computerized neuropsychological tests. Associations between the localization of cerebral white matter lesions found in cMRI and specific cognitive deficits were examined in an exploratory manner. Based on previous evidence, it was hypothesized that cerebral involvement in X-ALD is reflected by cognitive decline that ranges from mild cognitive dysfunction (MCD) to white matter dementia (WMD) with increasing severity and is mainly characterized by cognitive slowing, executive dysfunction, memory retrieval dysfunction, sustained attention deficits, and visuospatial impairment. Particularly slowdown in processing speed, a core feature of WMD, was expected to be more pronounced in patients with acute ACALD than arrested ACALD, independent of the localization of white matter lesions. In contrast, patients with pure AMN were expected to show overall intact cognitive function compared to age-, sex-, and education-based healthy patients.

Materials and Methods

Study Population

Data of this cross-sectional study were collected during patients’ regular follow-up examinations in the Leukodystrophy Outpatient Clinic of the University Hospital Leipzig and the Hospital Hubertusburg in Wermsdorf, Germany, between the years 2010 and 2020 and retrospectively analyzed. The study protocol was approved by the Ethical Committee at the Medical Faculty, Leipzig University (591/20-ek). Patient’s data were only included if (1) adult-onset X-ALD was genetically verified, (2) patients had never received an HSCT, and (3) neuropsychological test scores and cMRI results were available for the same visit point, allowing a clear assignment to a specific X-ALD phenotype (ie, pure AMN, arrested ACALD, and acute ACALD). Due to differences in institutional equipment and protocols (eg, use of intelligence tests at baseline assessment, but not at regular follow-up visits), innovations in testing over time (eg, replacement of paper-pencil tests with computerized versions), and omission of individual tests (eg, lack of compliance, motoric abilities, or comprehension of test instructions in severely affected patients), not all included patients received the complete and same test battery, resulting in varying sample sizes for each neuropsychological test analyzed. Specifically, the complete test battery, which was defined as covering the cognitive domains of attention, learning and memory, executive function, and processing speed with at least one test, was performed in 59 patients, whereas one cognitive domain (mainly executive function or attention) was not assessed in 84 patients and ≥ 2 domains were missing in 29 patients.

Phenotype Assignment and White Matter Lesion Pattern

The cMRI images were rated by independent radiologists with expertise in X-ALD-specific white matter anomalies. The X-ALD MRI Severity Scale (Loes Score; range = 0–34, with higher scores indicating greater severity) was used in order to quantify the severity of cerebral involvement based on the localization and extent of lesions and the presence of focal and/or generalized atrophy found in patient’s cMRI. Patients with Loes Score > 0 were additionally categorized into 5 groups based on their cMRI lesion pattern: parieto-occipital, frontal, corticospinal tract, cerebellar, or concomitant parieto-occipital and frontal pattern, as described previously. Based on Loes Score, the pattern of white matter involvement, and the clinical syndromes, patients were classified into 3 phenotypes: pure AMN, arrested ACALD, and acute ACALD. All patients of the present sample showed a normal grey matter appearance and 27 patients had white matter lesions that were not specific for X-ALD (mainly nonspecific, likely microvascular signal abnormalities, n = 24).

Pure AMN. The pure AMN phenotype usually is clinically defined in patients with myelopathy without clinical evidence of cerebral involvement. However, in some patients, noncontrast enhancing corticospinal tract (CST) involvement is detected by cMRI. It still remains unclear whether CST involvement without contrast enhancement...
is a feature of AMN or a marker of early ACALD. To investigate the impact of CST involvement on cognitive function, patients with pure AMN were subdivided in a pure AMN phenotype without radiological abnormalities (Loes Score = 0) and a pure AMN phenotype with involvement of the CST (Loes Score < 2) but no cerebral contrast enhancement.

**Arrested ACALD.** Patients with demyelination of the white matter (ie, Loes Score ≥ 2) but without cerebral contrast enhancement were defined as diagnosed with arrested ACALD.

**Acute ACALD.** Patients with inflammatory cerebral lesions indicated by contrast enhancement were phenotyped as acute ACALD.

**Intelligence**
The Multiple Choice Vocabulary Test (MWT) was used for screening pre-morbid verbal intelligence. The MWT consists of 37 word lines. In each line, patients have to identify a colloquially or educationally known word from the German language among 4 meaningless words. The Performance Test System – Subtest 3 (LPS-3) was applied for evaluating nonverbal intelligence, that is, abstract-logical thinking. The LPS-3 consists of 40 rows representing 8 geometric figures. Within a time limit of 5 minutes, patients have to cross out the figure in each row that does not fit the logic of the row.

**Cognitive Functions**

**Attention.** Selective sustained attention for visual stimuli was either evaluated by the computerized attention test (Attention Functions Battery – Selective Attention [WAFS]) of the Vienna Test System version 7 (VTS) or by using the paper and pencil version of the d2 Test of Attention. In the WAFS, patients have to respond as quickly as possible to visual stimuli by key press while ignoring preceding auditory stimuli. The d2 Test of Attention consists of 14 test lines of 47 characters, in which target stimuli (letter “d” with 2 dashes) have to be detected among several distractors. Both processing speed (time limit of 20 seconds per line) and processing quality (discrimination of visual stimuli) are considered in evaluating patients’ test performance.

**Verbal Learning and Memory.** Learning and recall of verbal stimuli was either assessed by the computerized Verbal Learning Test (VLT) of the VTS or by applying the German version of the Auditory Verbal Learning Test (AVLT). In the VLT, patients are presented with neologisms one after the other and they decide in each case whether this combination of letters has been seen before or is new (verbal recognition). In the AVLT, patients are read 15 real words in 5 repetitions, which have to be actively recalled from memory after each repetition (verbal encoding) and after a 30-minute delay (verbal retrieval).

**Nonverbal Learning and Memory.** Nonverbal recognition of geometric or irregularly shaped figures was evaluated by using the computerized Non-Verbal Learning Test (NVLT) of the VTS. Analogous to the VLT, patients are shown figures one after the other and they must decide in each case whether the figure has already been seen or is being presented for the first time.

**Executive Function.** Computerized neuropsychological tests, run by the VTS, were applied to evaluate working memory (Corsi Block-Taping-Test [CORSI]), reading and naming interference (Stroop Interference Test [STROOP]), and cognitive flexibility (5-Point-Test [5-POINT]). In the CORSI, 9 blocks are arranged on a computer screen and a sequence of blocks is tapped, with the length of the sequence increasing during the test. Patients are required to tap the blocks in the same previously shown sequence on each trial. In the STROOP, patients must either name written color words while ignoring the antagonistic color of the ink in which they are printed (reading interference), or name the ink color while ignoring the written word (naming interference). In both subtests, performance is evaluated based on patients’ response times and error rates. In the 5-POINT, squares, each consisting of a fixed pattern of 5 symmetrically arranged dots, are presented. Patients are required to produce as many different patterns as possible within 2 minutes of testing time by connecting the dots in each square with one or more straight lines.

**Processing Speed.** Nonverbal processing speed was assessed by the oral version of the Symbol Digits Modalities Test (SDMT), which asks patients to assign the correct digits to specific symbols within 90 seconds. Verbal processing speed was evaluated with both formal-lexical and semantic-categorical subtests of the Regensburger Word Fluency Test (RWT). In the RWT, patients must name as many words as possible with a specific initial letter (eg, “S”; formal-lexical) or from a specific category (eg, animals; semantic-categorical) within 2 minutes of test time.

**Neurological Impairment**
Two scoring systems were used to rate patient’s neurological impairment: the Expanded Disability Status Scale (EDSS, range = 0–10), originally developed for rating neurological deficits in multiple sclerosis, and the disorder-specific Adult Adrenoleukodystrophy Clinical Score (AACS, range = 0–24), assessing motor, bladder, sensory, and cerebral functions in
Adults with X-ALD. In both scales, higher scores indicate greater neurological impairment.

**Statistical Analysis**

Patients’ raw data of neuropsychological tests were transformed to standardized values (i.e., intelligence quotient [IQ] for MWT and LPS-3, otherwise T values) according to age-, sex-, and/or education-based norms. The analysis included 3 steps. First, chi-squared tests and analyses of variance (ANOVA) were performed to compare X-ALD phenotypes (pure AMN, arrested ACALD, and acute ACALD) regarding sociodemographic variables (age, sex, and education), neurological impairment (EDSS and AACS), and cognitive test performance across different domains. To control for the effects of sex and CST involvement on cognitive function in AMN, ANOVAs were repeated in men versus women and men with versus without CST involvement of the pure AMN group. Post hoc tests with Bonferroni correction were conducted to examine pair-wise differences if omnibus tests were significant. Welch’s ANOVAs and Games-Howell’s post hoc tests were used when homogeneity of variance was violated in ANOVAs. Second, differences in test performance of patients with Loes Scores > 0 were described as a function of the localization of white matter lesions detected in cMRI scan, although statistical significance tests were not conducted due to insufficient sample size and test power. Third, two-tailed Pearson correlation analyses were performed to determine associations between the degree of cerebral involvement found on patients’ cMRI (Loes Score) and neuropsychological test scores, and to detect intercorrelations between different neuropsychological tests in the total sample.

All statistical analyses were conducted using SPSS version 24.0 and a two-tailed significance level was set at $\alpha = 0.050$.

**Results**

**Sample Description**

The total sample consisted of 172 patients with adult-onset X-ALD (mean age = 44.1 ± 13.4 years, range = 18–80) of which 117 patients (68.0%) were clinically phenotyped as having pure AMN, 30 patients (17.5%) as having arrested ACALD, and 25 patients (14.5%) as having acute ACALD. Sociodemographic and neurological differences between phenotypes are displayed in Table. Groups differed significantly in terms of sex ($p < 0.001$), with only men showing brain involvement (i.e., arrested ACALD and acute ACALD). No group differences were detected regarding age ($p = 0.072$) and education ($p = 0.055$).

| TABLE. Sociodemographic and Neurological Description of X-Linked Adrenoleukodystrophy Phenotypes |
|-----------------------------------------------|---------------------------------|---------------------------------|---------------------------------|------------------|------------------|
| Pure AMN (n = 117) | Arrested ACALD (n = 30) | Acute ACALD (n = 25) | **Chi-square test** | **df** | **V** |
| Socio-demographics | | | | | |
| Sex (M) | 70 (59.8)a | 30 (100.0)b | 25 (100.0)b | 30.401c | 2, 172 | 0.42 |
| Education (school yr) | | | | | |
| ≤8 | 18 (15.4) | 12 (40.0) | 6 (24.0) | 9.253 | 4, 172 | 0.16 |
| 9–11 | 59 (50.4) | 11 (36.7) | 10 (40.0) | | | |
| ≥12 | 40 (34.2) | 7 (23.3) | 9 (36.0) | | | |
| M (SD) | M (SD) | M (SD) | F | df | $\eta^2$ |
| Age (yr) | 45.3 (13.6) | 44.4 (13.4) | 38.5 (11.4) | 2.676 | 2, 169 | 0.03 |
| Symptom scores | | | | | |
| EDSS (0–10) | 4.0 (2.1)a | 4.9 (2.1)b | 5.3 (1.8)b | 5.734d | 2, 168 | 0.06 |
| AACS (0–24) | 5.1 (3.5)a | 7.7 (3.9)b | 9.9 (5.0)b | 19.327c | 2, 168 | 0.19 |

Effect sizes ($\eta^2$ or Cramer’s V) were interpreted as small (0.01 or 0.10), medium (0.06 or 0.30), or large (0.14 or 0.50). AACS = Adult Adrenoleukodystrophy Clinical Score; ACALD = Adult Cerebral Adrenoleukodystrophy; AMN = Adrenomyeloneuropathy; EDSS = Expanded Disability Status Scale. $a$,b Indicate significant differences between phenotypes after post-hoc comparisons with Bonferroni corrections; e.g., “a” in AMN and “b” in arrested ACALD indicate significant differences between these two groups. $^c$ p < 0.001. $^d$ p < 0.01.
As displayed in Table S3, the acute ACALD phenotype showed decreased performance in attention measured by d2 ($p = 0.014$) and nonverbal recognition ($p = 0.022$) compared to the pure AMN phenotype, whereas no significant group differences emerged between pure AMN and arrested ACALD or arrested and acute ACALD ($p ≥ 0.050$) with respect to these domains. Nonverbal intelligence ($p = 0.001$), verbal encoding ($p < 0.001$), and verbal processing speed ($p ≤ 0.001$) were significantly greater impaired in patients with arrested and acute ACALD compared to patients with pure AMN, whereas patients with arrested versus acute ACALD did not differ in these domains ($p ≥ 0.050$). Nonverbal processing speed was significantly more impaired in patients with acute ACALD compared to the patients with pure AMN and patients with arrested ACALD ($p < 0.001$), who did not differ in this regard ($p ≥ 0.050$). Mean performance on tests assessing attention (d2), verbal encoding, and verbal and nonverbal processing speed was below average compared to the norm (T < 40) only in patients with acute ACALD, whereas patients with pure AMN and patients with arrested ACALD achieved mean group scores within the normal range. No phenotype differences emerged regarding verbal intelligence ($p = 0.442$), attention measured by WAFS ($p = 0.479$), verbal retrieval ($p = 0.088$), verbal recognition ($p = 0.893$), and executive function ($p = 0.207–0.764$). ACALD-specific cognitive impairment correlated positively with patients’ white matter lesion burden assessed by Loes Score, with largest effects emerging in verbal encoding (AVLT) and processing speed (SDMT and RWT).

Concerning sex effects on cognitive function in the pure AMN phenotype (Table S4), ANOVAs revealed higher performance in nonverbal intelligence ($p = 0.005$) and working memory ($p = 0.017$) tests in patients with AMN in men compared to women, whereas women performed significantly better in verbal encoding ($p = 0.011$) and semantic-categorical word fluency ($p = 0.022$). No other sex differences in cognitive performance were found in AMN ($p > 0.050$).

In the current sample, 11 male patients of the pure AMN phenotype showed noncontrast enhancing CST involvement in their cMRI. As presented in Table S5, no significant group differences were found when comparing neuropsychological test performance across different cognitive domains between male patients with pure AMN without versus with CST involvement ($p = 0.268–0.989$).

Descriptive comparison of neuropsychological test scores depending on the specific white matter lesion pattern found in cMRI in patients with Loes Score > 0 are displayed in Table S1 (Online Supplementary Material). Processing speed appeared to be a cognitive domain impaired in all patients with X-ALD with Loes Score > 0, independent of the localization of the white matter lesion. Only patients with mere CST involvement exhibited unremarkable general cognition with mildly reduced processing speed in the lower normal range. Patients with parieto-occipital and concomitant parieto-occipital and frontal lesion pattern additionally showed deficits in sustained attention and verbal encoding. Impaired executive functions appeared to be more of a core feature in patients with frontal and cerebellar lesion pattern; however, interpretation is limited due to small sample sizes.

Intercorrelations between neuropsychological test results within the total sample are shown in Table S2 (Online Supplementary Material). In particular, nonverbal (SDMT) and verbal processing speed (RWT) were highly correlated with the performance in tests assessing nonverbal intelligence (LPS-3), sustained attention (d2), and verbal encoding (AVLT).

The present study provides support for a progressive cognitive decline in X-ALD patients with cerebral demyelination (ie, acute ACALD), clinically manifested by a severe slowdown in processing speed$^{31}$ that is associated with further deficits specifically in the domain’s attention and verbal encoding. Patients with arrested ACALD showed a slight decrease in these domains compared to normal data and differed significantly from patients with AMN by impaired verbal encoding and verbal processing speed. Whereas the cognitive profile in arrested ACALD is best described as MCD, the severity of the deficits found in acute ACALD justify its classification as WMD.$^{12}$ As hypothesized, patients with pure AMN showed overall unimpaired cognitive function compared to the healthy patient. Of note, the small proportion of patients with impaired test results in this group was not consistently explained by male sex or noncontrast enhancing CST involvement found on patients’ cMRI.
In accordance with the hypotheses, largest group effects were detected in neuropsychological tests measuring patients’ nonverbal (SDMT) and verbal (RWT) processing speed, with greater impairment being associated with greater demyelination in the brain (medium-to-large-sized correlations between patients’ test results and Loes score), irrespective of the localization of white matter lesions found in cMRI. These results emphasize the essential function of the white matter as a connecting link between widely distributed neural networks and as a fast information transmitter that complements grey matter information processing. Accordingly, patients with acute ACALD in the present sample also showed deficits in sustained attention assessed by d2 as well as verbal encoding.

Consistent with previous findings, no decline of general, pre-morbid intellectual abilities was found in arrested and acute ACALD. However, performance in the nonverbal IQ test LPS-3 declined with increasing cerebral involvement, resulting in patients with ACALD differing significantly from patients with AMN. This finding seems to be rooted in the LPS-3 paradigm itself, as performance in this test, additionally depends on patients’ processing speed (time limit of 5 minutes) and visuconstruction (presentation of geometric figures), a cognitive domain particularly affected in cerebral X-ALD phenotypes with demyelination in parieto-occipital regions. Indeed, most patients with Loes Score > 0 of the present sample showed a parieto-occipital white matter lesion pattern (n = 33, 50.0%), indicating that phenotype differences in LPS-3 performance may predominately result from impaired processing speed and visuconstruction rather than deficits in individuals’ abstract-logical thinking.

The impact of different test paradigms, which to varying degree tap into processing speed and visual discrimination, is also mirrored by conflicting results found in the attention tests used. Significant phenotype differences emerged in the d2 but not in the WAFS, indicating that psychomotoric speed and visual discrimination is more demanded in the d2, whereas the WAFS assesses more basal attention via reaction times and may have a lower difficulty level than the d2. Further, X-ALD phenotypes differed significantly in tests assessing verbal encoding (AVLT) and nonverbal recognition (NVLT), whereas no group effects emerged in verbal retrieval (AVLT) and verbal recognition (VLT). Accordingly, learning and memory deficits in acute ACALD are more likely to be rooted in a delayed learning process due to deficient processing speed than in difficulties in consolidating and storing new information in the long-term memory. Further, patients with acute ACALD versus patients with pure AMN and patients with arrested ACALD performed significantly worse in recognition of previously presented geometric or irregularly shaped figures (NVLT), whereas no significant group differences appeared in recognition of previously presented neologisms (VLT). This finding again underlines the potential effects of deficient visual discrimination in patients with ACALD with parieto-occipital white matter lesions.

Against expectations, no significant group differences in executive function were found in the present sample. Because deficient executive functions in acute ACALD have been reported in previous research and are typical for white matter dementia, the lack of group differences in the present study should be interpreted with caution, as little patient data were available for this domain, increasing the risk of not detecting small effects.

The assumption that declining processing speed in patients with X-ALD with cerebral involvement is associated with additional cognitive deficits in other domains is supported by the present finding that patients’ processing speed (SDMT and RWT) correlated highly with the performance in nonverbal IQ (LPS-3), sustained attention (d2), verbal encoding (AVLT), and cognitive flexibility (5-POINT) tests.

Although, in fact, only men with X-ALD can progress from pure AMN to ACALD in the course of the disease, the current study could not identify any sex differences in cognitive function in AMN that would indicate the different risk for future cerebral involvement, replicating previous results. Rather, significant sex differences in some tests of the present sample tend to reflect a general superiority of women in verbal abilities and men in nonverbal abilities.

Consistent with the study by Buermans et al., a subset of patients with pure AMN of the present sample showed impaired performance (T < 40) in some cognitive domains. Buermans and colleagues suggested that these patients with AMN are at higher risk to show cerebral involvement in the later course of the disease. However, in the current study, the percentage of male and female patients with AMN with below-average results did not differ significantly across cognitive functions. Further, no effect of CST involvement in male patients with pure AMN on cognitive functions was detected, indicating that noncontrast enhancing CST involvement is rather a feature of AMN than a precursor of later ACALD.

Descriptive comparison of cognitive functions in patients with Loes Score > 0 with different localization of cerebral demyelination revealed deficient processing speed in all patients, ranging from mild deficits within the normal range found in patients with mere CST involvement to more severe impairment in patients with parieto-occipital and concomitant parieto-occipital and frontal lesions. In addition to general deficient processing speed,
In conclusion, the onset of cerebral involvement, especially acute inflammatory demyelination in X-ALD, is indicated by a severe slowdown in patient’s processing speed, which is associated with attention and learning deficits. Cognitive decline ranges from MCD, found in arrested ACALD, to WMD, a unique cognitive profile that is a hallmark for acute ACALD. Deficits in further cognitive domains (eg, executive function and visuoconstruction) seem to be dependent on the specific location of patient’s cerebral white matter lesions. Cognitive function in patients with pure AMN seem to be generally intact in both men and women, independent of noninflammatory CST involvement. For clinical practice, the present results suggest the neuropsychological screening of patients’ processing speed, for example, by using the time-economic SDMT, as well as assessing neurological impairment using the disorder-specific AACS to rate disease progression in patients with X-ALD during regular neurological examinations.

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Author Contributions
L.S., H.R., and W.K. contributed the conception and design of the study. L.S., H.R., M.F., A.S., and W.K. contributed to acquisition, analysis, and interpretation of the data. L.S. and W.K. contributed to drafting the text and preparing the figures and tables of the manuscript.

Potential Conflicts of Interest
The authors declared no conflict of interest.

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