Objectifs. Décrire des anomalies cérébrales subtiles visibles en IRM chez des patients adultes atteints d’adrénomyéloneuropathie (AMN). Les symptômes sont caractérisés par un déficit sensoriel périphérique, des troubles pyramidaux et une dysfonction du système nerveux autonome. Les complications de l'ADL incluent une dystrophie musculaire progressive, une dégénérescence et des anomalies lipidiques de l'amygdale et du noyau caudé. L'ADL est une maladie progressive qui s'accompagne de symptômes cliniques comparables à ceux de l'AMN.

Matériels et méthodes. Étude rétrospective de données acquises prospectivement dans le cadre d'un essai thérapeutique (Riluzole) de 66 adultes atteints d’AMN sans lésion cérébrale patente en IRM. Chaque patient a eu une IRM cérébrale à l’inclusion (T1, T2 et FLAIR, spectroscopie). Après validation préalable d’une grille par 3 lecteurs différents, la lecture des IRM a été effectuée consensuellement selon une échelle semi-quantitative.

Résultats. L’analyse préliminaire a confirmé les anomalies de signal des faisceaux cortico-spiinaux chez 36 patients (54,6%). D’autres anomalies subtiles ont été mises en évidence : aspect « délai » de la SB à prédominance pariéto-occipitale avec hypersignal modéré, en plage chez 36 patients (54,6 %), hypersignal des fibres ponto-cérébelleuses en T2 et FLAIR chez 25 patients (41,7 %). L’augmentation des rapports Cho/Cr et mI/Cr décrite dans la littérature a été confirmée.

Conclusion. Cette étude rétrospective permet la description d’un profil AMN en IRM chez des patients ne présentant pas d’anomalie de la substance blanche et du corps calleux.

Mots-clés : Adrénomyéloneuropathie. IRM cérébrale, spectroscopie.

Brain MRI was obtained at the time of enrollment and every 3 months during the trial. All exams were performed on 2 magnets using a similar protocol: sagittal T1W, axial T2W, FLAIR and diffusion-weighted, coronal FLAIR images along with single voxel spectroscopy of the left parietal periventricular white matter. Spectroscopic data included the three main ratios: N-acetylaspartate (NAA)/creatine, choline (Cho)/creatine, and myo-inositol (mI)/Cr. All three metabolites were compared to reference values (table I) (7).

All initial MRI examinations were reviewed (n=66) using a list of criteria established by 4 physicians (3 radiologists including 2 experienced neuroradiologists and 1 neuroradiologist with international recognition for ALD) (table II). This review grid included classical brain abnormalities described with AMN as well as newer findings observed during review of patient imaging charts. Signal abnormalities were graded between 0 (normal) and 2 based on their relative intensity compared to normal contralateral brain parenchyma on the same image. After a preliminary independent review of one third of the examinations by 3 reviewers to confirm the value of the criteria and the absence of significant interobserver variability, the review of all MRI examinations was performed by consensus of all 3 reviewers.

### Results

Based on the set of criteria defined in the hospital clinical research program in 2001, 66 patients were included in the study. Currently, 46 patients (69.7%) have completed the clinical trial while 5 patients are still enrolled, 1 at month 12 and 4 at month 24. Fifteen patients, or about 25% of subjects, were terminated from the clinical trial prior to completion, most frequently based on a decision by the lead investigator (73.3%) due to poor compliance with the research protocol. Two patients died from unrelated infections and two patients developed progressive disease requiring termination from the clinical trial.

The male/female ratio was 2.3 and the mean age of patients was 40.2 years. The mean age for males and females was 35 years and 52.1 years respectively.

### MRI images

Review of MR images in 66 cases showed:

- signal abnormalities of corticospinal tracts beyond the posterior limb of the internal capsules in 54.6% (n=36) of cases. This mainly occurs at the superior portion of the corticospinal tracts at the level of the corona radiate (n=29 or 53%) and less frequently lower down at the cerebral peduncle level (n=17 or 19%) (fig. 1). Combined superior and inferior involvement was noted in 28% of cases (n=10). Involvement was always bilateral and symmetrical with moderate signal intensity (grade 1) in 91.7% of cases.
- III-defined patchy areas of increased FLAIR and T2W signal intensity, mainly in the parieto-occipital white matter with periventricular extension and preservation of subcortical U-fibers (fig. 2). The hyperintensity was graded 1 or 2 relative to parieto-occipital cortex (table II). Such abnormalities were present in 36 patients (54.6%) with frontal extension, anterior to the central sulcus, in 6 patients (16.7%) (fig. 3). Parieto-occipital white matter involvement was always present. Isolated frontal white matter involvement was not observed. The signal intensity was moderate (grade 1) in 83.3% of cases.
- T2W and FLAIR hyperintensity of ponto-cerebellar fibers (fig. 4 and 5) were observed in 25 patients (41.7%), with moderate signal intensity (grade 1) in 81.7% of cases.

### MR Spectroscopy

MR spectroscopy obtained in 59 patients showed elevated Cho/Cr ratios at both TE values (SD 0.19 and 0.22) and mI/Cr ratios (SD 0.20) (table III). The NAA/Cr ratios remained within normal range at both TE values.

### Discussion

Currently, no effective treatment is available for AMN. Allogeneic bone marrow transplant is not offered to patients with AMN due to the high risks associated with the procedure. Diets with low levels of VLCFA have not shown benefits for patients with cerebral ALD or AMN (8-10). The purpose of the clinical trial was, on one hand, to assess the value of riluzole, a neuroprotector and glutamate release inhibitor, a drug that has shown some efficacy in the management of amyotrophic lateral sclerosis, and, on the other hand, to evaluate for the presence of focal brain abnormalities on conventional MRI and MT spectroscopy during such a clinical trial. The female ratio and higher age of female patients are consistent with reports in the literature. A diagnosis of ALD, irrespective of phenotype, is more frequently made in males, usually young adults for AMN. However, this diagnosis should be
considered in adult females presenting with myelopathy, even in the absence of family history, because about half of carrier females over 40 years of age present some clinical symptoms (11). The features of AMN on conventional MR imaging are well described in the literature. White matter lesions are described in the internal capsules and frontal white matter, best depicted on FLAIR images (6). MR imaging of the spine is typically normal or shows cord atrophy of variable degree, without correlation to the severity of clinical impairment.

MR imaging of the brain typically is normal in patients with pure AMN (1, 5). The evaluation of a population of patients with AMN without classical brain lesions on MRI in the setting of a clinical trial provided us with the opportunity to identify additional subtle brain abnormalities including moderate hyperintensity of the ponto-cerebellar fibers and establish the frequency of abnormalities previously described in the literature. The subtle nature of some of these abnormalities has raised questions with regards to their true existence versus variants of normal and to their significance.

For example, regions of signal abnormality involving the corticospinal tracts are difficult to interpret, especially at the posterior limbs of the internal capsules due to normal variations related to anisotropy. Based on the evaluation grid, signal abnormalities of the corticospinal tracts were considered present when they involved the cerebral peduncles inferiorly or the centrum semiovale superiorly, above the ventricles. In order to avoid variations due to windowing factors, the degree of hyperintensity of the corticospinal tracts was arbitrarily compared to the insular cortex (table II). Using these criteria, signal abnormalities of the corticospinal tracts were recorded in 54.6% of cases, similar to previous reports from the literature (4, 12).

The presence of patchy areas of moderate hyperintensity, ill-defined and symmetrical, of the periventricular posterior parieto-occipital white matter has previously been reported (13). This was recorded in 55% of cases. In our patient population, the parieto-occipital white matter was always involved with occasional frontal white matter involvement. The distribution of these white matter lesions is fairly similar to that observed with ALD (14), but the degree of signal alteration is different and the corpus callosum was always spared in our patients with AMN (exclusion criteria). This white matter pallor raises the possibility of early demyelination, a hypothesis that would be supported by spectroscopy results characterized by elevated choline, a marker of cell membrane turnover, usually increased in patients with cell proliferation or demyelination. However, NAA, a neuronal marker (7), usually reduced in cerebral ADL (3, 4, 13, 14), was normal in our study. The absence of reduced NAA levels could indicate that the washed out appearance of the cerebral white matter could relate to demyelination without neuronal loss in patients with AMN (15).

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**Table III**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Short TE</th>
<th>Long TE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NAA/Cr</td>
<td>Cho/Cr</td>
</tr>
<tr>
<td>Mean (n=59)</td>
<td>1,71</td>
<td>1,18</td>
</tr>
<tr>
<td>Standard deviation (n=59)</td>
<td>0,27</td>
<td>0,19</td>
</tr>
</tbody>
</table>
Symmetrical areas of patchy moderate hyperintensity, typically at the pontocerebellar fibers, were observed in 42% of our patients. This non-specific finding has not previously been described in patients with AMN. Cerebellar white matter abnormalities occur in 3 to 29% of patients with ADL (12, 15). Pontine involvement usually affects pyramidal fibers, without male predilection. The presence of subtle abnormalities described here (washed out appearance of the cerebral white matter and hyperintense ponto-cerebellar fibers) do not seem to be associated with a pejorative clinical course since none of our patients with these findings manifested central neurological signs observed in AMN with brain involvement during the 36-month course of the clinical trial. Also, these lesions were not more frequent in males, even though cerebral phenotypes are more frequent in males (1, 4).

**Conclusion**

The purpose of this study was to describe brain abnormalities on MRI in patients with pure AMN without classical brain lesions. These abnormalities (subtle hyperintensity of pyramidal tracts and pontocerebellar fibers, washed out appearance of the parieto-occipital cerebral white matter) could correspond to early lesions of demyelination without association with disease progression. Therefore, the presence of these lesions on MRI does not currently affect patient management.
Fig. 4:  
\(a-b\) Moderate grade I signal of the ponto-cerebellar fibers (arrowheads) (signal inferior to cerebellar cortex).

Fig. 5:  
\(a-b\) Grade II signal of the ponto-cerebellar fibers (arrowheads) (signal superior to cerebellar cortex).

References