Subtle brain abnormalities in adrenomyeloneuropathy

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Abstract

Purpose. To describe subtle brain abnormalities detected on MRI in adult patients with adrenomyeloneuropathy (AMN).

Materials and methods. Retrospective evaluation of data acquired prospectively as part of a clinical trial (Riluzole) in 66 adult patients with AMN without obvious brain lesion on MR. All patients underwent brain MR including T1W, T2W, FLAIR and spectroscopy. After a review had been validated by three different reviewers, review of MR images was performed by consensus using a semi-quantitative scale.

Results. Preliminary analysis of MR images confirmed the presence of signal abnormalities involving the corticospinal tracts in 36 patients (54.6%). Additional subtle abnormalities were also detected: white matter palor, mainly parieto-occipital in location, with patchy hyperintensity in 36 patients (54.6%), hyperintense pontocerebellar fibers on T2W and FLAIR in 25 patients (41.7%). The presence of elevated Cho/Cr and mI/Cr ratios, described in the literature, were confirmed.

Conclusion. This retrospective study allows the description of an AMN pattern on MRI in patients without white matter or callosal abnormalities.

Key words: Adrenomyeloneuropathy. MR. Brain. Spectroscopy.

Patients and methods

Retrospective analysis of data acquired in the setting of a prospective longitudinal study performed between December 1999 and December 2005 at the Hopital St-Vincent de Paul in Paris. The purpose of the longitudinal study was a clinical trial of 36 months of the drug Rilozole for patients with AMN.

Inclusion criteria for the clinical trial for male and female patients included: age between 14 and 60 years, able to comprehend the information provided about the protocol, and diagnosis of AMN based on 3 criteria: pyramidal symptoms of the lower extremities, elevated VLCFA, and abnormality of at least one evoked potential, auditory or somesthetic.

Patients with progressive disease, disability score equal to or superior to 6.5 on the EDSS scale, and abnormalities at initial brain MRI except for the presence of T2W hyperintense signal (5, 6) along the pyramidal tracts (pons, midbrain, and internal capsules) or pallor of the white matter along the posterior convexities.

Clinical manifestations are different from ADL and are characterized by cord symptoms with severe spastic paraparesis, proprioceptive sensory deficits, bladder dysfunction and moderate peripheral neuropathy. A demyelinating brain lesion eventually develops in 30-40% of adults (1-4). The purpose of this paper is to describe subtle brain lesions detected on MRI in patients with AMN as part of a clinical trial in a patient population with AMN without “classical” brain lesion.


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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 myoinositol (mI)/Cr. All three metabolites were compared to reference values (table 1) (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 neurologist 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 3 at 24 months. 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 rifuzole, 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 myopathy, 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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<th>Table III Spectroscopy results (n=59) on initial MRI examination.</th>
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<td>Patient</td>
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<td>Mean (n=59)</td>
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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 pontocerebellar 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.
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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


