Giant Axonal Neuropathy: MRS Findings

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ABSTRACT

Giant axonal neuropathy (GAN) is a rare genetic disease of childhood involving the central and peripheral nervous systems. Axonal loss with several giant axons filled with neurofilaments is the main histopathological feature of peripheral nerve biopsies in this disease. Routine neuroimaging studies reveal diffuse hyperintensities in cerebral and cerebellar white matter. In this case report, the authors present the brain magnetic resonance spectroscopic features (normal *N*-acetylaspartate/creatine and increased choline/creatine and myoinositol/creatine ratios), which might indicate the absence of neuroaxonal loss and the presence of significant demyelination and glial proliferation in white matter, of an 11-year-old boy diagnosed with GAN.

Key words: Giant axonal neuropathy, magnetic resonance spectroscopy.

Alkan A, Kutlu R, Sigirci A, Baysal T, Altinok T, Yakinci C. Giant axonal neuropathy: MRS findings. J Neuroimaging 2003;13:371-375. DOI: 10.1177/1051228403254659

Giant axonal neuropathy (GAN) is a rare, autosomal, recessively transmitted, multisystemic neurodegenerative disorder leading to mental retardation and chronic, slowly progressive, symmetrical distal neuropathy, which causes a unique posture of the legs.[1-3] It was first described in 1972 by Asbury et al[4] and usually affects curly-haired children, but a second form without curly hair has also been described.[4,5] Affected patients usually die before the age of 30 years.[6] Pathologically, the intra-axonal accumulation of intermediate neurofilaments (NFs) leads to an increase in the diameter of axons and the progressive thinning and loss of the myelin sheath.[7]

Received December 4, 2002, and in revised form March 12, 2003. Accepted for publication March 23, 2003.

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Previous neuroimaging studies[8-10] on GAN have reported involvement in cerebral and cerebellar white matter and the spinal cord, as well as corpus callosum atrophy. Magnetic resonance spectroscopy (MRS) imaging provides additional independent information compared to conventional magnetic resonance imaging (MRI); it may prove useful in improving the accuracy of these imaging modalities. But to the best of our knowledge, there is no published report of MRS findings on GAN in the literature. MRS was performed in this case to determine the relationship between the severity of metabolite changes in central nervous system involvement areas (i.e., white matter) demonstrated by routine MRI and the neurological findings caused by these changes and also to find out whether the reported histopathological findings show concordance with the MRS findings or not.

Case Presentation

An 11-year-old boy, who had been diagnosed as having GAN at age 5 by a sural nerve biopsy that demonstrated the intra-axonal accumulation of NFs, axonal swelling, and thinning of the myelin sheath, was admitted because of an inability to walk. His medical history revealed normal development up to age 3. After that time, the boy had experienced difficulty walking and mental deterioration. At the time of admission, he had been wheelchair bound for 1 year. His weight and height were below the third percentile. He had curly hair, dry skin, and mild palmar and plantar hyperkeratosis. A neurological examination revealed bilateral pitosis, facial diplegia, weakness in the distal lower limbs, muscular atrophy, decreased deep tendon reflexes, a bilateral positive Babinsky reflex, abnormal cerebellar tests, and absent tactile and vibration senses. The boy had skeletal abnormalities, including thoracic lordoscoliosis, drop feet, and bilateral pes equinovarus. Electromyography was concordant with sensory-motor polyneuropathy. MRI and MRS were performed on a 1.5-T system (Philips, Gyroscan Intera, Best, the Netherlands). Axial and sagittal T1-weighted images (TR = 560 ms, TE = 15 ms) and axial and coronal T2-weighted images (TR = 4530 ms, TE = 100 ms) were obtained. Single-voxel proton MRS was performed using the point-resolved spectroscopy sequence (PRESS) (TR = 2000 ms, TE = 31 ms). Voxel sizes of $15 \times 15 \times 15$ mm were used. Voxels were placed in the frontal white matter (FWM) and parietal white matter (PWM). Short-TE PRESS (31 ms) was chosen as the primary pulse sequence because of the increased signal/noise ratio of short TE and the visualization of additional compounds seen by short TE (myoinositol [MI]). After automatic shimming and gradient tuning, a water suppression with water-selective excitation pulse

Table 1. Metabolite Ratios of White Matter in the Patient With Giant Axonal Neuropathy and the Control Group

Metabolite Ratio	Patient's FWM	Patient's PWM	Control Group's FWM (n = 5)	Control Group's PWM (n = 5)
NAA/Cr	1.96	1.80	1.82 ± 0.27	1.79 ± 0.12
Cho/Cr	1.25	1.66	0.72 ± 0.18	0.68 ± 0.14
MI/Cr	1.16	1.37	0.67 ± 0.15	0.66 ± 0.12

FWM = frontal white matter, PWM = parietal white matter, NAA = *N*-acetylaspartate, Cr = creatine, Cho = choline, MI = myoinositol.

was interactively optimized on the display console. Analysis of the spectra was performed with the manufacturer-supplied spectroscopy software package of the MR system (MMR 5461 1 H spectroscopy 1.5-T package, MR VMS software, Digital Corporation). Spectral postprocessing, including 4K zero filling, gaussian line broadening (3 Hz), Fourier transformation, and manual phase correction, was performed. Resonances were assigned as follows: *N*-acetylaspartate (NAA) = 2.0 ppm, creatine and phosphocreatine (Cr) = 3.02 ppm, choline (Cho) = 3.2 ppm, and MI = 3.56 ppm. Peak area metabolite ratios (NAA/Cr, Cho/Cr, and MI/Cr) were calculated. A group of 5 age-matched healthy children constituted the control group for MRS. MRI showed diffuse hyperintensities in cerebral and cerebellar white matter on T2-weighted images (Figs 1A and 1B). Increased Cho/Cr and MI/Cr and normal NAA/Cr ratios were detected in both the FWM and the PWM of our patient compared to the healthy control group. MRS metabolite ratios obtained from the patient and the corresponding control group are presented in Table 1.

Discussion

GAN is a rare, genetic, progressively fatal neurodegenerative disorder characterized by progressive sensory motor neuropathy, central nervous system involvement that is evident from cerebellar and pyramidal signs, and mental retardation.[8,9]

Histopathologically, giant axonal swelling filled with NFs on peripheral nerve biopsies, which reflects moderate axonal degeneration with mild or moderate demyelination, is a characteristic feature of this disease.[3,7,11] In an autopsy study,[12,13] it was reported that the pathological process involved all brain structures and the spinal cord.

In neuroimaging studies of GAN patients, computed tomography and MRI reveal diffuse cerebral and cerebellar white matter disease and atrophy of the corpus callosum.[8-10] In classical GAN cases, white matter abnormalities are characterized by diffuse demyelination, which sometimes involves the cerebellum.[9] Our patient also showed diffuse hyperintensity in cerebral and cerebellar white matter on T2-weighted images.

MRS could reveal the biochemical bases of various disease processes by providing information on neuronal and axonal viability, cellular energetics, and cellular membrane status. It gives information that could indicate demyelination, neuronal dysfunction, and gliosis.[14] Cr plays an important role in cellular energy metabolism. It is more concentrated in glia than in neurons. Except in trauma, stroke, tumors, and Cr deficiency syndromes, Cr levels tend to remain relatively unchanged. Therefore, Cr is often used as a putative internal standard against

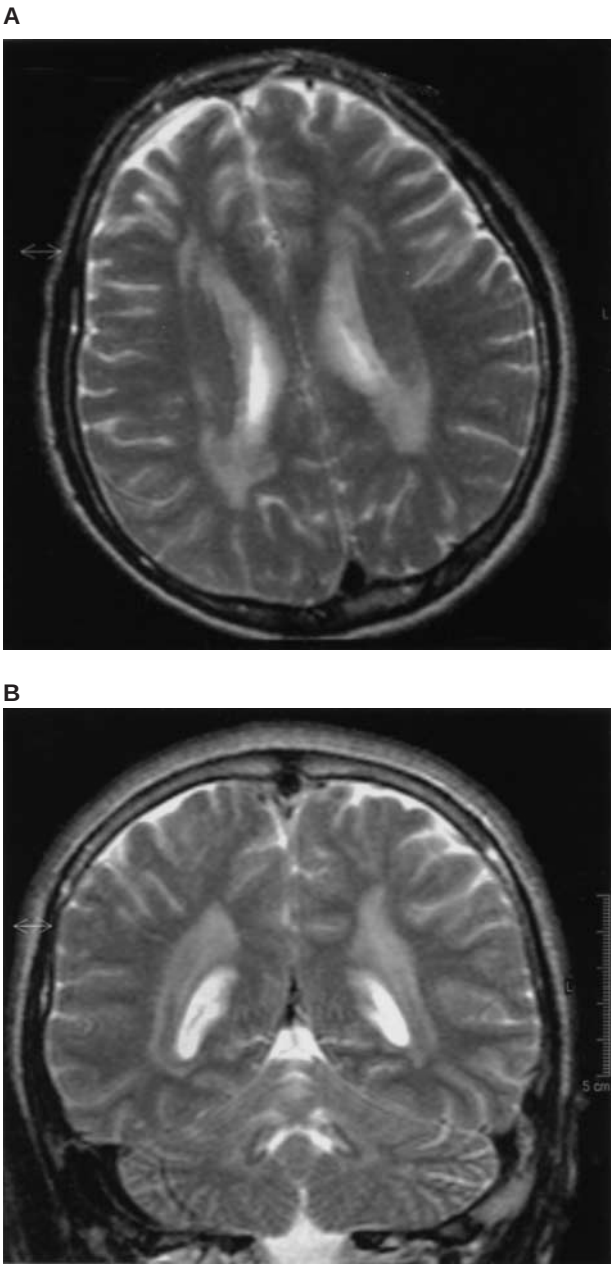

Fig 1. (A) Axial T2-weighted (TR = 4530 ms, TE = 100 ms) image shows diffuse hyperintense lesions in white matter. (B) These lesions are more prominent in posterior parietal white matter on coronal T2-weighted image (TR = 4530 ms, TE = 100 ms), which also shows similar lesions in cerebellar white matter.

which the other metabolites can be compared.[14] In cases with disruptions of Cr concentration, a reference voxel in a visually normal region with similar gray and white matter composition can be sampled and compared with the voxel in the affected pathology. This is usually achieved by comparing the contralateral hemisphere. However, this was not possible for our patient because of the diffuse nature of GAN. Therefore, we used the same white matter location of an age-matched and sex-matched healthy control group for comparison. NAA is the most sensitive central nervous system metabolite. The NAA/Cr ratio in our patient was found to be normal when compared to that of

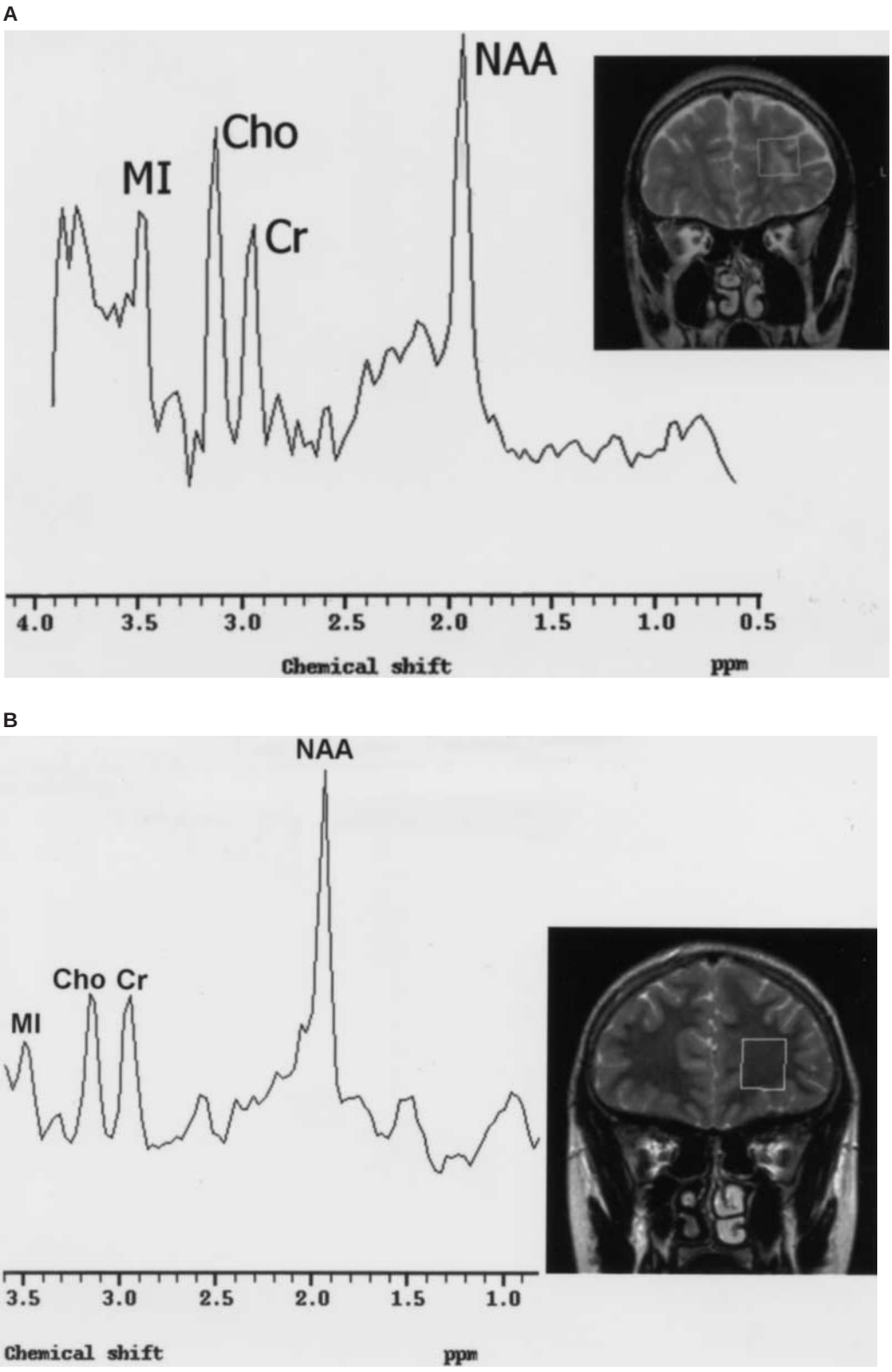

Fig 2. (A) Magnetic resonance spectrum (point-resolved spectroscopy sequence [PRESS]; TR = 2000 ms, TE = 31 ms) obtained from patient's frontal white matter shows increased choline (Cho)/creatine (Cr) and myoinositol (MI)/Cr and normal *N*-acetylaspartate (NAA)/Cr ratios. (B) Corresponding magnetic resonance spectrum (PRESS; TR = 2000 ms, TE = 31 ms) obtained from a healthy control's similar location shows normal metabolite peaks.

the control group. This could indicate the absence of neuroaxonal loss.

Cho is a structural component of all cell membranes, and it is regarded as a marker of membrane stability. Major components

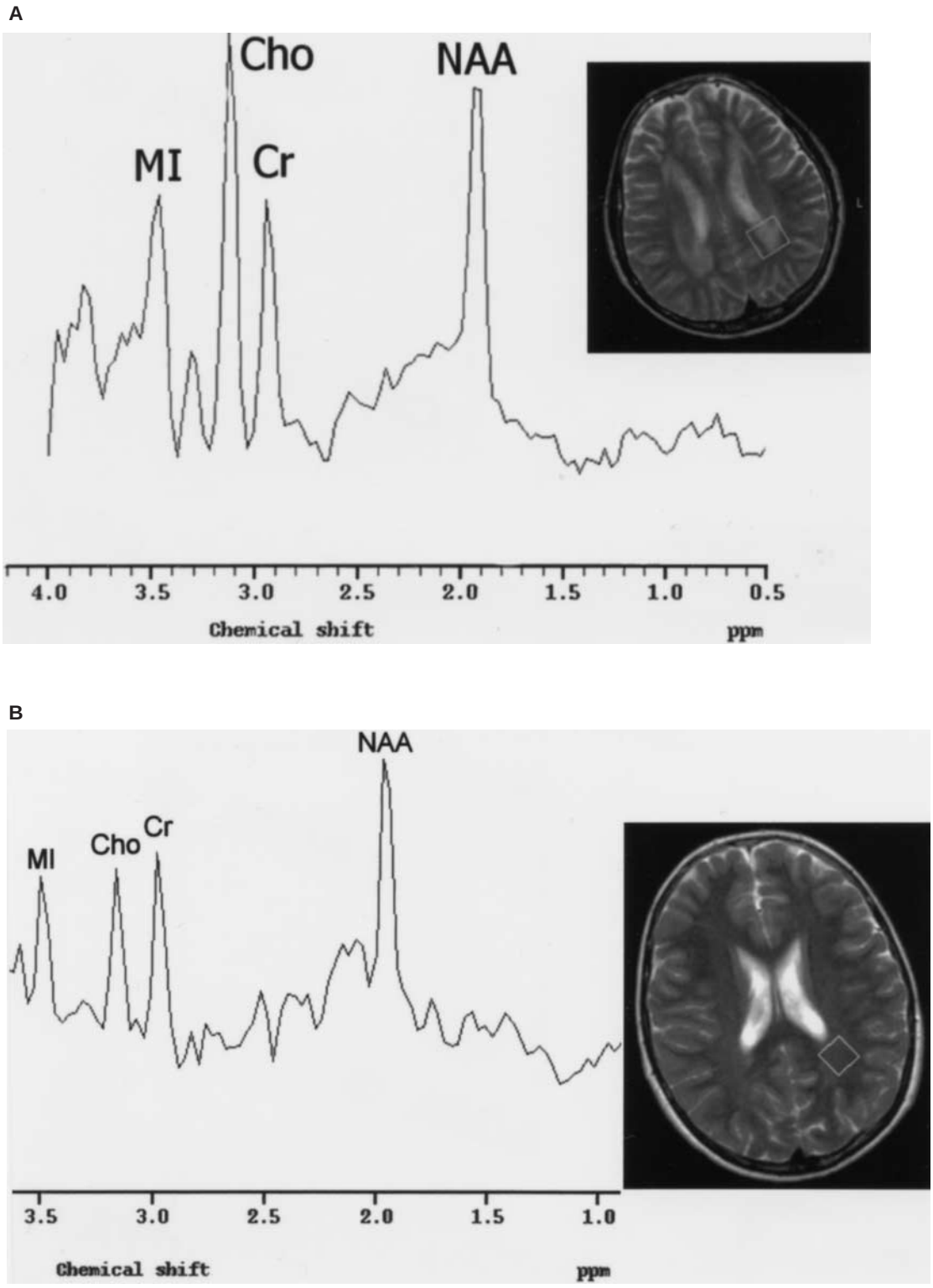

Fig 3. (A) Magnetic resonance spectrum (point-resolved spectroscopy sequence [PRESS]; TR = 2000 ms, TE = 31 ms) obtained from patient's posterior parietal white matter shows significantly increased choline (Cho)/creatine (Cr) and myoinositol (MI)/Cr, and normal *N*-acetylaspartate (NAA)/Cr ratios. (B) Corresponding magnetic resonance spectrum (PRESS; TR = 2000 ms, TE = 31 ms) obtained from a healthy control's similar location shows normal metabolite peaks.

of the Cho resonance are choline-containing compounds with small molecular weights, such as phosphorylcholine and glycerophosphorylcholine, that form a pool involved in membrane synthesis and degradation. The increase in the Cho/Cr ratio might point to an inability to properly incorporate Cho-containing molecules into myelin. In conditions such as the loss or disruption of normal myelin, the availability of Cho increases.[14,15] Thus, an increase in the Cho/Cr ratio could indi-

cate demyelination. MI may be related to intracellular sodium content and glial activation. Increased Cho and MI levels may correspond to glial proliferation.[15] Cho/Cr and MI/Cr ratios in our case were found to be significantly higher in frontal and parietal white matter compared to the control group (Figs 2A and 2B). The significant increases in the Cho/Cr and MI/Cr ratios, in both the FWM and the PWM, could be an indication of demyelination and glial proliferation, which were prominent in posterior parietal white matter (Figs 3A and 3B).

It has been reported that the clinical degree of peripheral and central nervous system involvement in GAN could be different.[5,7] A relationship between the severity of symptoms and neuroaxonal loss has also been reported. In contrast to Malandrini et al,[7] the finding of severe clinical symptoms without MRS evidence of central neuroaxonal damage in our patient might indicate that clinical severity could be related to demyelination rather than neuroaxonal damage in some patients with GAN.

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