Treatment and Outcome

The duration of hospitalization ranged from 7 to 32 (mean 16.5) days. All but one patient initially received parenteral acyclovir, 10 received antibiotics, and 6 received anticonvulsants. At discharge, 10 children had neurologic deficits. All 18 patients had at least one follow-up assessment, and 17 were available for the final follow-up 0.1 to 5.3 (mean 2.6; median 3.1) years after discharge. We failed to contact the family of a patient, but her last recorded data reported dramatic improvement 3 months after discharge. One patient required a nasogastric feeding tube for 2 months. Irritability and hyperactivity were reported in 13 children and fatigue and headaches in 15 children. At the final follow-up, 1.5 to 5.3 (median 4.0) years after discharge, five children still remained with mild to moderate deficits. Patient 1 presented with mild tremor, patient 5 with strabismus and right foot monoparesis, patient 9 with mild flexor hypertonia of the right hand, patient 13 with hyperactivity and speech difficulties, and patient 14 with hyperactivity. However, improvement was substantial, and physiotherapy and speech therapy were considered by parents as effective in all children. Among children initially treated with anticonvulsants, only one relapsed (patient 13) and was on carbamazepine 3.7 years after discharge.

Discussion

Recent progress in investigation has allowed for a better diagnosis of encephalitis, and brain biopsy is only rarely indicated nowadays.[2] However, given the great variety of both potential pathogens and noninfectious conditions with a similar presentation, acute encephalitis often lacks a definite diagnosis and is commonly underdiagnosed.[3,6–8] Large-scale studies have shown annual incidence rates of 7.3 hospitalizations per 100,000 population in the United States[7] and 10.5 cases per 100,000 children in Finland.[8] The findings of this study suggest a minimum of 2.6 cases per 100,000 children per year in Crete.

Etiology is characterized by considerable geographic variations.[3–9] In our series, encephalitis was attributed to a specific etiologic agent in 13 of 18 patients, a proportion comparable to recent studies.[3,6–9] However, etiology was based on blood and cerebrospinal fluid serology rather than on detection of the causative agent by culture or PCR, and this is a diagnostic limitation. Mumps, measles, and rubella virus–associated encephalitides were not noted, a finding clearly attributable to successful vaccination.[5,9] Arthropod-borne viral encephalitis is quite common in other areas of Europe[4,5] but was not documented in Crete. Encephalitis is commonly of viral origin[2–4,8]; however, bacteria were not rare in our area.

In our experience, early neuroimaging provided substantial help in diagnosis. MRI T_2-weighted and fluid-attenuated inversion recovery sequences were of higher diagnostic value than T_1-weighted sequences. The correlation between the evolution of MRI findings and the clinical progress in our series has also been noted in children with acute disseminated encephalomyelitis.[10] Therefore, the value of repeated MRI in patients with improvement is questionable.

No fatality was observed in this study; however, encephalitis was associated with considerable morbidity and occasionally guarded long-term outcome. Successful vaccination has eradicated mumps, measles, and rubella–associated encephalitides from the study area, and the same is expected for varicella-zoster virus in the near future. Our findings suggest that early imaging with MRI significantly facilitates diagnosis. Supportive measures, physiotherapy, and speech therapy were shown to be of considerable value.

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Giant Axonal Neuropathy: Diffusion-Weighted Imaging Features of the Brain

ABSTRACT

Giant axonal neuropathy is a rare autosomal recessive childhood disorder characterized by a peripheral neuropathy and features of central nervous system involvement. Magnetic resonance imaging (MRI) of an 11-year-old boy with giant axonal neuropathy revealed high signal intensity in the white matter of the cerebrum and cerebellum on T_2-weighted imaging. An apparent diffusion coefficient map revealed increased apparent diffusion coefficient values in the periventricular, deep, and cerebellar white matter, basal ganglia, and thalamus. Increased apparent diffusion coefficient values in distinct locations suggest increased mobility of water molecules in the brain of a patient with giant axonal neuropathy. This finding could indicate a myelin disorder such as demyelination. Diffusion-weighted imaging should be performed to reveal apparent diffusion

coefficient changes and determine brain involvement in patients with giant axonal neuropathy. (*J Child Neurol* 2006;21:912–915; DOI 10.2310/7010.2006.00211).

Giant axonal neuropathy is a rare, severe, autosomal recessive neurologic disease affecting both the peripheral and the central nervous systems. It was first described in 1972 by Asbury et al[1] and is characterized by a symmetric distal neuropathy, mental retardation, kinky hairs, and unique posture legs.[1–3] The gene for giant axonal neuropathy was mapped to chromosome 16q24. The course of the disease is severe, and patients die before the age of 30 years. Giant axonal neuropathy is characterized by axonal degeneration with mild or moderate demyelination.[4,5]

Previous neuroimaging studies reported involvement in the cerebral and cerebellar white matter and spinal cord and corpus callosum atrophy.[6–8] Diffusion-weighted imaging and apparent diffusion coefficient maps provide important information in evaluating the structure of tissues and intracranial lesions. Even subtle pathologic damage should disrupt the tissue architecture, increasing the mobility of water molecules and giving diffusion-weighted imaging the potential to detect structural changes that are inaccessible to conventional magnetic resonance imaging (MRI).[9] To our knowledge, the present diffusion-weighted imaging study is the first attempt to characterize apparent diffusion coefficient value alterations in the brain of a patient with giant axonal neuropathy.

Case

An 11-year-old boy, who was diagnosed as having giant axonal neuropathy at age 5 years with sural nerve biopsy, which demonstrated intra-axonal accumulation of neurofilaments, axonal swelling, and thinning in the myelin sheath, was admitted owing to an inability to walk. Our case has four siblings who are healthy. His father and mother are not consanguineous. His medical history revealed normal development up to age 3 years. After that time, he experienced difficulty in walking and mental deterioriation. He was wheelchair bound for the last year and was discontinued from primary school. His weight and height were below the 3rd percentile. He had curly hairs, dry skin, and mild palmar and plantar hyperkeratosis. A neurologic examination revealed bilateral pitosis, facial diplegia, weakness in the distal lower limbs, muscular atrophy, decreased deep tendon reflexes, bilateral positive Babinski reflexes, abnormal cerebellar tests, and absent tactile and vibration senses (Figure 1). He had skeletal abnormalities, including thoracic lordoscoliosis, drop feet, and bilateral pes equinovarus. Electromyography was concordant with sensorimotor polyneuropathy. Informed consent was obtained from the patient's parent. The MRI examination consisted of routine imaging and diffusion-weighted imaging. MRI was performed on a 1.5-Tesla system (Philips, Gyroscan Intera Master, Best, The Netherlands). T_1-weighted images (repetition time 560, echo time 15 milliseconds) were obtained in the axial and sagittal planes. T_2-weighted images (repetition time 4500, echo time 110 milliseconds) were obtained in the axial and coronal planes. For the diffusion-weighted imaging, a single-shot echo-planar pulse sequence (repetition time 4832 milliseconds, echo time 81 milliseconds, field of view 230 mm, matrix size 128 × 256, slice thickness 7 mm, interslice gap 1 mm) was used in the patient with two different b values (0 and 1000 second/mm^2). We calculated directionally averaged apparent diffusion coefficient values from an apparent diffusion coefficient map in circular or elliptical regions of interest drawn as the areas ranging between 50 and 100 mm^2. Six distinct locations (frontal, parieto-occipital, cerebellar, and deep white matter, thalamus, and basal ganglia) were selected for the analysis. Age-matched healthy children (n = 5) constituted the control group (9.6 ± 3.1 years old). The control group was recruited from our previous studies.

T_2-weighted images revealed high signal intensity in the periventricular, deep, and cerebellar white matter in our case. The apparent diffusion coefficient values obtained from periventricular (1086 and 1150 × 10^{-6} mm^2/second), deep (1084 × 10^{-6} mm^2/second), and cerebellar white matter (996 × 10^{-6} mm^2/second) were significantly increased in our case compared with the control subjects. Also, increased apparent diffusion coefficient values were evaluated in the normal-appearing basal ganglia (846 × 10^{-6} mm^2/second) and thalamus (910 × 10^{-6} mm^2/second) (Figures 2 and 3). Apparent diffusion coefficient values obtained from the patient and corresponding control group are presented in Table 1.

Discussion

Giant axonal neuropathy is a rare genetic, progressively fatal neurodegenerative disorder characterized by progressive sensorimotor neuropathy, central nervous system involvement that is evident in cerebellar and pyramidal signs, and mental retardation.[6,7,10]

Postmortem studies of central nervous system involvement have been performed in several patients.[4,11,12] Histopathologically, giant axonal swelling filled with neurofilaments on peripheral nerve biopsies, which reflects moderate axonal degeneration with mild or moderate demyelination, is a characteristic feature of this disease.[5,10,13] Giant axons are formed by intra-axonal accumulation of intermediate filaments leading to an increase in diameter and progressive thinning and loss of the myelin sheath.[14]

In neuroimaging studies, T_2-weighted MRI revealed diffuse high signal intensity, sparing subcortical U fibers, in the white matter of both the cerebrum and cerebellum and atrophy of the corpus callosum.[6–8] In our case, there was high signal intensity in the periventricular and

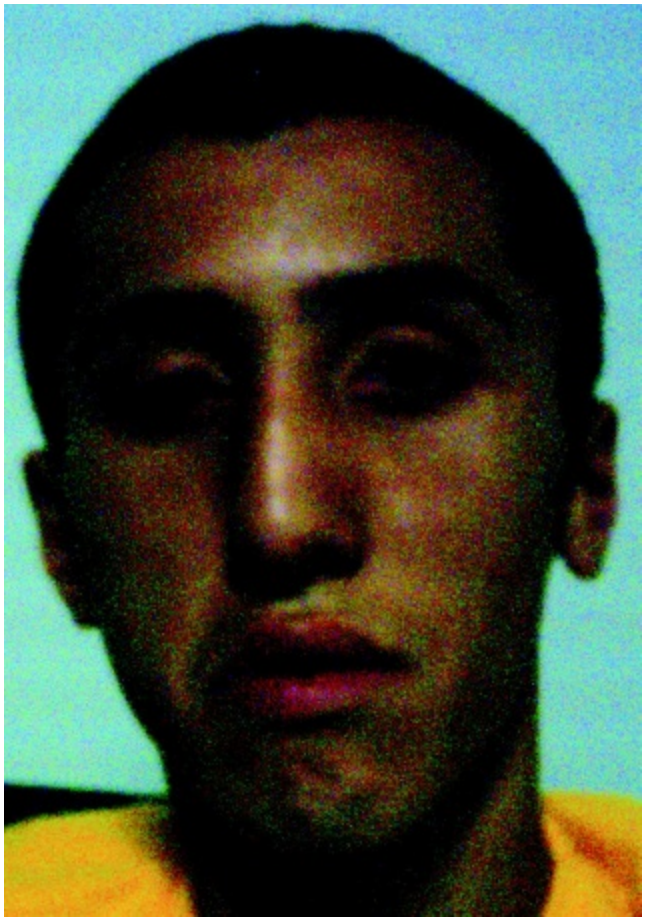

Figure 1. The face of an 11-year-old-boy with giant axonal neuropathy shows facial diplegia and bilateral pitosis.

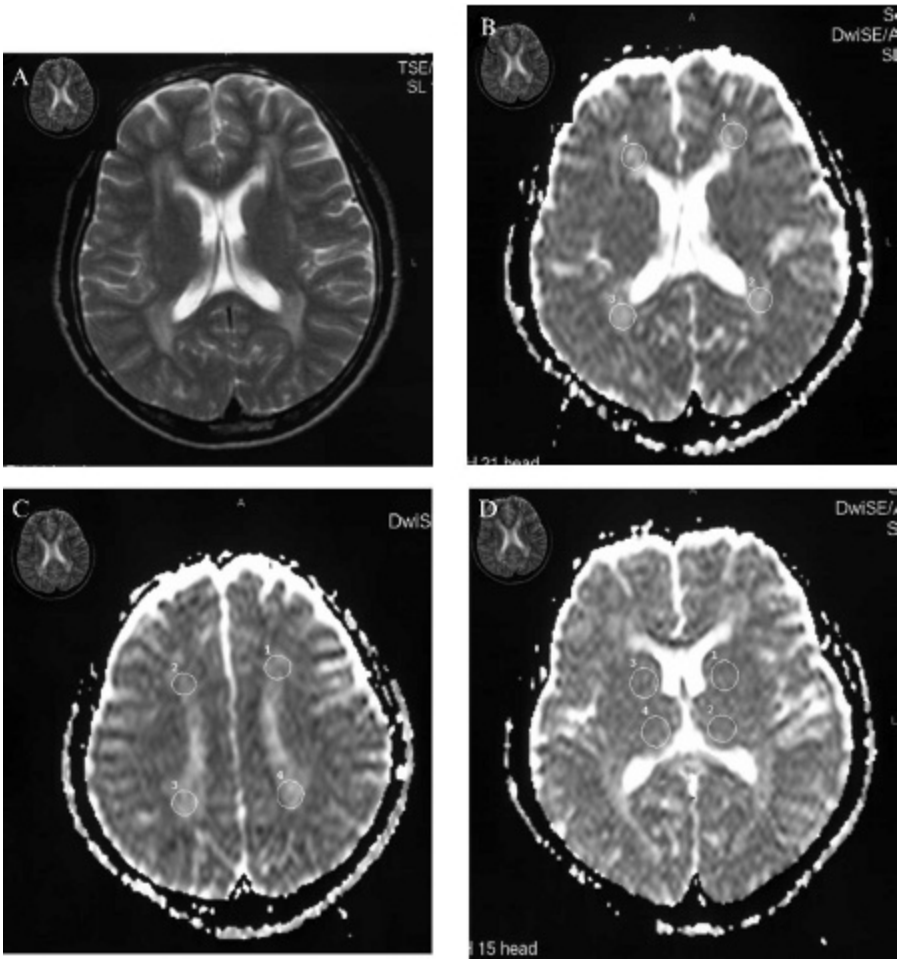

Figure 2. *A*, Axial T_2-weighted (repetition time 4500, echo time 110 milliseconds) images show high signal intensity in periventricular white matter. *B* and *C*, An apparent diffusion coefficient map reveals high signal intensity and apparent diffusion coefficient values in the frontal (1071 [1] and 1101 [4] $\times$ 10^{-6} mm^2/seconds), parieto-occipital white matter (1138 [2] and 1162 [3] $\times$ 10^{-6} mm^2/seconds), and deep white matter (1064 [1], 1076 [2], 1088 [3], and 1092 [4] $\times$ 10^{-6} mm^2/seconds). *D*, The apparent diffusion coefficient map shows high apparent diffusion coefficient values in the basal ganglia (814 [1] and 878 [3] $\times$ 10^{-6} mm^2/seconds) and thalamus (890 [2] and 930 [4] $\times$ 10^{-6} mm^2/seconds), although the signal intensity is normal.

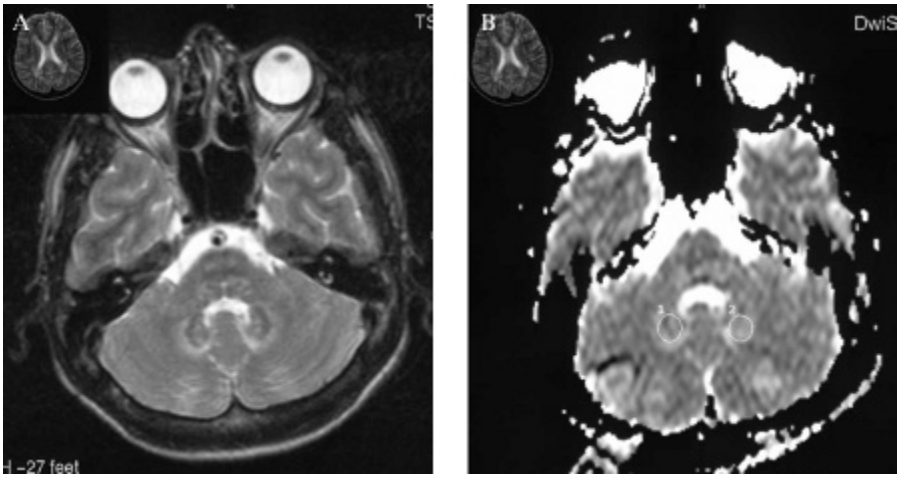

Figure 3. *A*, T_2-weighted (repetition time 4500, echo time 110 milliseconds) images show high signal intensity in the cerebellar white matter. *B*, An apparent diffusion coefficient map reveals high signal intensity and apparent diffusion coefficient values in the cerebellar white matter (976 [1] and 1016 [2] $\times$ 10^{-6} mm^2/seconds).

Table 1. Mean Apparent Diffusion Coefficient Values of Children With Giant Axonal Neuropathy

	Mean Apparent Diffusion Coefficient Values ($\times$ 10^{-6} mm^2/s)					
	FWM	*POWM*	*DWM*	*CWM*	*BG*	*Thalamus*
Case	1086	1150	1084	996	846	910
Control	786 $\pm$ 40	794 $\pm$ 30	780 $\pm$ 27	756 $\pm$ 33	723 $\pm$ 43	735 $\pm$ 40

BG = basal ganglia; CWM = cerebellar white matter; DWM = deep white matter; FWM = frontal white matter; POWM = parieto-occipital white matter.

cerebellar white matter on T_2-weighted images and in the centrum semiovale.

Diffusion-weighted imaging is dependent on the random motion of water molecules and offers an opportunity to evaluate the structural characteristics of tissues.[15] Diffusion of water molecules depends on tissue microstructure and microdynamics. It is particularly sensitive for the detection of acute ischemic stroke. It can also provide unique information on other cerebral disorders, including neoplasms, traumatic brain injury, demyelinating diseases, and prion diseases. The apparent diffusion coefficient reflects the structural properties of the cellular compartments and provides a rotationally invariant measurement of the total diffusion of water within a tissue.[16] In demyelinating disease, the loss of normal myelin structure and the axonal loss lead to an expansion of the extracellular space, which results in an increase in the apparent diffusion coefficient.[15,16] In our study, increased signal intensity and apparent diffusion coefficient values on an apparent diffusion coefficient map were revealed in the periventricular, deep, and cerebellar white matter. In our study, normal-appearing basal ganglia and thalamus on T_2-weighted images revealed high apparent diffusion coefficient values when compared with the control group. Caramia et al also showed diffusion changes in the normal-appearing brain parenchyma on T_2-weighted images with demyelination disease that is in accordance with our findings.[9] The higher apparent diffusion coefficient values in the patient with giant axonal neuropathy suggest that there is relatively high molecular motion in these locations compared with the normal brain parenchyma. These findings could indicate a myelin disorder such as demyelination.

Conclusion

Increased apparent diffusion coefficient values in distinct locations suggest increased mobility of water molecules in the brain of a patient with giant axonal neuropathy. It is probable that this vasogenic edema-like pattern corresponds to demyelination and axonal loss, which are among the reported histopathologic changes of giant axonal neuropathy. Therefore, diffusion-weighted imaging should be performed to reveal apparent diffusion coefficient changes and determine brain involvement in patients with giant axonal neuropathy.

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