NEUROPATHOLOGICAL CONFERENCE

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A 10-Year-Old Girl with Progressive Generalized Weakness

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CASE PRESENTATION

Dr. Harvey Sarnat: A.Y. was a 10-year-old Mexican girl who presented with a 7-year history of progressive weakness. She was the full-term product of an uncomplicated pregnancy and delivery, weighing 2850 grams at birth. Early developmental milestones were achieved at the expected rate until age three, when frequent falling was noted. Progressive weakness of her legs ensued, and at age nine years, A.Y. lost the ability to walk beyond a few steps, and shortly thereafter she could not stand without support. She had no seizures, visual disturbance, dysphagia, or incontinence. Previously an excellent student, her academic performance in school had deteriorated over the past year. She was not on any medications. Family history was negative for any known neurological or neuromuscular diseases. A.Y. was an only child. Both parents were alive and well; there was no history of consanguinity.

Physical exam revealed a slender young girl with curly hair, unlike other members of her family. Her mental status and occipitofrontal circumference was normal. She had slurred speech with dysarthria. There were no cutaneous lesions or dysmorphic features. General exam including the heart, lungs, and abdomen was normal. Her hearing, vision, and olfaction were intact. Ocular fundi were normal, and visual fields were full. Coarse phasic nystagmus was apparent on extreme lateral gaze, to the left more than to the right. Other cranial nerves including facial muscles, tongue, and palate were normal. Motor exam revealed increased tone in the right upper extremity and reduced tone in the lower limbs, with moderate degree of generalized muscle weakness throughout. Cavovarus contractures of both ankles, flexion contractures of the third and fourth digits of both hands, and distal muscle wasting were present. Deep tendon reflexes were absent, and bilateral Babinski signs were elicited. Sensory exam revealed mildly diminished vibratory and position senses distally, with normal pain, light tactile, and temperature perception. A.Y. had difficulty with finger-to-nose testing due to poor precision and mild intention tremor; rapid alternative movements of the hands were slow. She could not stand without support or initiate a step.

Preliminary investigations including blood count, electrolytes, liver enzymes, serum creatine kinase, very long chain fatty acids, serum arylsulfatase-A and -B were normal. An electroencephalogram was normal. Nerve conduction study confirmed a symmetrical axonal sensorimotor polyneuropathy, with absent peroneal motor and sural sensory responses. Electromyography exam showed a chronic neurogenic process, with polyphasic high amplitude motor units firing at an increased rate. Brain magnetic resonance imaging (MRI) study revealed areas of hyperintense T2 signals in the periventricular white matter, dentate nucleus, cerebellar white matter, and midbrain [Figure 1].

A diagnostic procedure was performed.

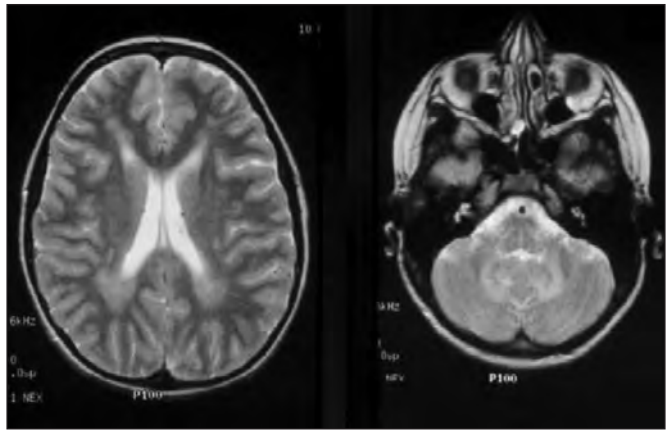

Figure 1: *Axial T2 brain magnetic resonance imaging studies: 1) left panel shows periventricular white matter changes; 2) right panel shows similar changes in deep white matter of the cerebellum and dentate nuclei.*

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Differential Diagnosis

Dr. Jean Mah: This 10-year-old Mexican girl had a progressive neurodegenerative disorder characterized by gait instability, increasing weakness, and recent cognitive decline. Her exam revealed signs of corticospinal tract dysfunction, peripheral neuropathy, and cerebellar ataxia. Disorders with progressive degeneration of the cerebellum with or without involvement of the spinal cord or the peripheral nerves are collectively known as the neurodegenerative ataxias (NDA).[1] Common presenting features of NDA include uncoordinated gait, limb, speech, and eye movements, with variable degrees of pyramidal and extrapyramidal features. Neurodegenerative ataxias are distinct from non-progressive congenital cerebellar ataxia, or acquired cerebellar disorders due to infection, demyelinating disease, stroke, neoplasm, toxins, or malabsorption. Most types of NDA are genetically mediated, thus obtaining a detailed family history is important. Even without a family history, patients with sporadic NDA may benefit from available genetic testing for autosomal dominant spinocerebellar ataxia.[2] In particular, spinocerebellar ataxia type 1, 2, 3, and 7 may present during childhood or early adolescence.[3] The incidence of NDA among children is presently unknown.

Differential diagnosis of autosomal recessive form of NDA should include: 1) primarily cerebellar atrophy, such as ataxia-telangiectasia; 2) spinocerebellar ataxia, with Freidreich ataxia as the prototypic disease; and 3) cerebellar atrophy with sensorimotor neuropathy, such as ataxia plus oculomotor apraxia or spinocerebellar ataxia plus neuropathy.[4,5] Among the lysosomal disorders, late-onset Tay-Sachs (LOTS) disease can also produce a NDA-like phenotype.[6] In contrast with infantile Tay-Sachs disease, affected individuals have no cherry red spots or seizures, and intelligence may initially be spared. Similar to our case, patients with LOTS may present with clumsiness, followed by dysarthria, dysmetria, progressive weakness, and subsequent loss of mobility. Additional features of LOTS may include neuropathy, motor neuron disease, dementia, or psychosis. The diagnosis is made by demonstrating reduced ß hexosaminidase-A activity in serum, leukocytes, or skin fibroblasts. Other metabolic disorders such as isolated vitamin E deficiency, abetalipoproteinemia, Refsum disease, cerebrotendinous xanthomatosis, maple syrup urine disease, Hartnup disease, biotinidase deficiency, and Wilson disease are amendable to nutritional supplement or dietary modification, so appropriate screening tests should be performed if clinically indicated.

Dr. Mah's Diagnosis: Neurodegenerative ataxia due to late-onset Tay-Sachs disease.

Pathological Discussion

Dr. Sarnat: The diagnostic procedures for this case involved an examination of the patient's hair and subsequently a sural nerve biopsy. Examination of the hair [Figure 2] under microscopy showed an abnormally twisted shaft (pili torti) due to defective keratin filament alignment.[7,8] The nerve biopsy revealed large axonal swellings and a reduction in the number of both myelinated and unmyelinated fibers [Figure 3 and 4]. Electron microscopy exam showed that the enlarged axons were comprised of tightly packed intermediate neurofilaments with reduction in the number of microtubules and axonal mitochondria. An additional pathognomonic feature in some giant axons was the presence of rough endoplasmic reticulum, which is never seen in normal axons [Figure 5]. These findings are characteristic of giant axonal neuropathy. Abnormalities are also found in endothelial cells, fibroblasts, Schwann cells, and melanocytes, because this disease not only results in a proliferation of neurofilaments in axons, but of many other types of intermediate filament proteins, including vimentin, cytokeratin and glial fibrillary acidic protein.[9,10] The involvement of multiple intermediate filament proteins distinguishes Giant axonal neuropathy (GAN) from other diseases specific for only one type of filament.

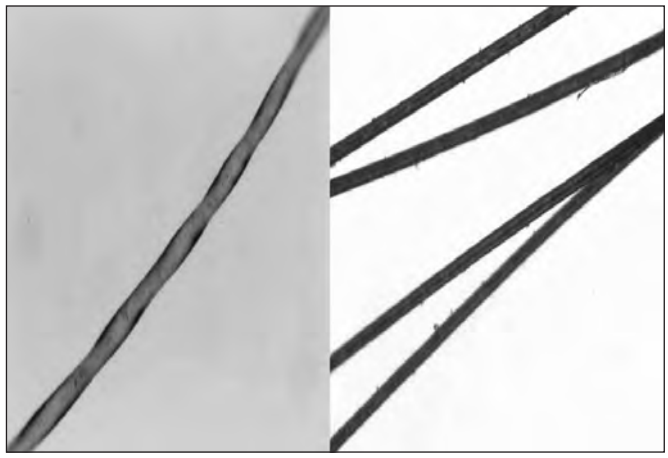

Figure 2: *Examination of the hair under microscopy: 1) left panel reveals an abnormally twisted shaft from this patient; 2) right panel shows strands of normal hair for comparison. Normal hair has a uniform diameter of the shaft without twisting. Straight hair is round in cross-section; curly (negroid) hair is oval shaped in cross-section, but the shaft remains uniform.*

Giant axonal neuropathy is an autosomal recessive neurodegenerative disorder that affects both the central and the peripheral nervous system. Berg et al[11] first described the accumulation of neurofilaments in a six-year-old girl with kinky hair, progressive weakness, and chronic polyneuropathy. Subsequently the gene for GAN was mapped to chromosome 16q24, and more than 30 different mutations have been identified.[12] The gene encodes a ubiquitously expressed novel protein called gigaxonin.[13] Gigaxonin is comprised of 597 amino acids arranged into two domains, including an amino-terminal BTB (Broad-Complex, Tramtrack, Bric a Brac) domain and a carboxy-terminal kelch repeat domain.[14] The exact function of gigaxonin is presently unknown, although other BTB/kelch proteins are implicated in the actin cytoskeletal network.[15,16] Binding of gigaxonin to microtubule-associated protein 1B enhances microtubule stability and enables axonal transport.[17] Mutations in the gigaxonin gene may result in abnormal phosphorylation of intermediate filaments, defective protease, defective neurofilament assembly, derangement in axonal transport, and/or damage to the Golgi apparatus.[13,18]

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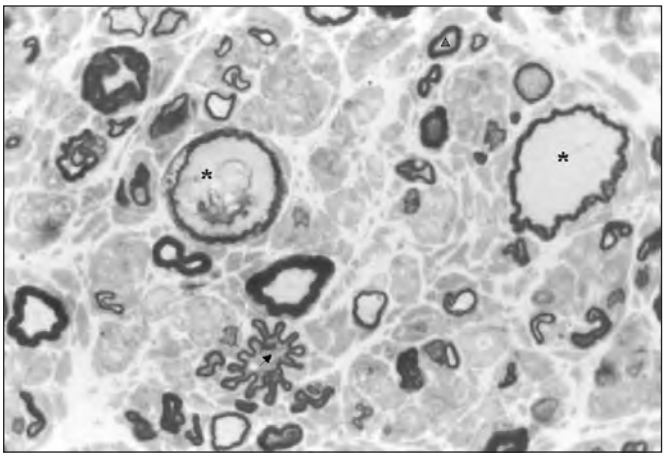

Figure 3: *Sural nerve biopsy, transverse section, shows reduction in number of large and small myelinated axons, and scattered giant axons (asterisks) with thin myelin sheaths and degenerative changes in the axoplasm in the one on the left. Another nerve fibre (arrow) has a highly crenated myelin sheath because this former giant axon has undergone involution of its excessive axoplasm due to degeneration, with collapse of the myelin sheath that is now redundant for the new smaller volume of axoplasm it encloses. A normal small myelinated nerve (arrowhead) is seen (toluidine blue stain, x 1000).*

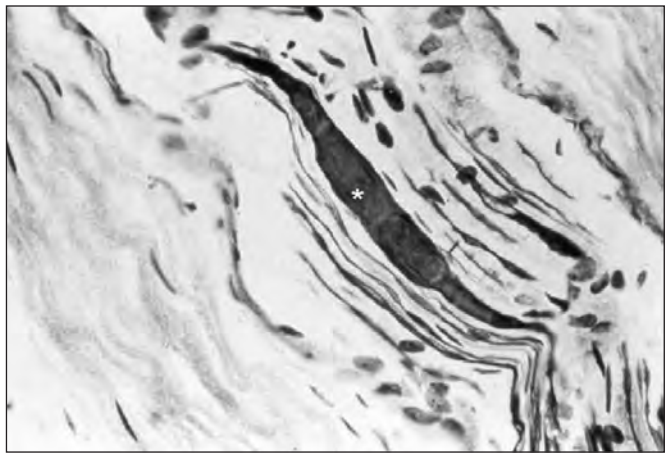

Figure 4: *Sural nerve biopsy, longitudinal section, shows a giant axon marked by an asterisk (Holmes silver impregnation, x 400).*

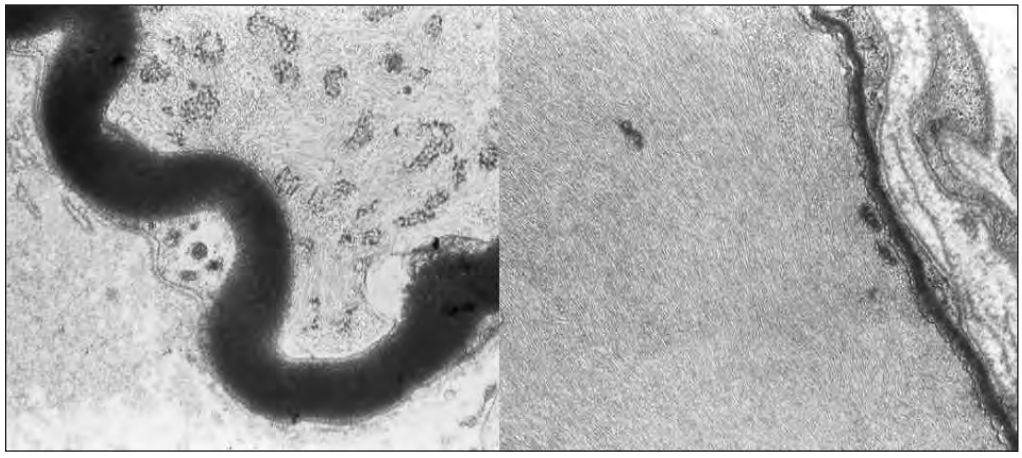

Figure 5: *Sural nerve biopsy, electron microscopy: 1) left panel shows proliferation of rough endoplasmic reticulum within axonplasm of giant axon. This organelle is not normally seen in axons and is characteristic for giant axonal neuropathy; 2) right panel shows a giant axon with a thin myelin sheath. The axoplasm is comprised almost entirely by a proliferation of neurofilaments with very few microtubules or mitochondria that normally are seen (uranyl acetate and lead citrate, x 12,500).*

Most individuals with GAN present during the first decade of life with tightly curled or "frizzy" hair, polyneuropathy, ataxia, and progressive weakness, leading to wheelchair dependency by the second or third decade of life. However, milder cases with normal hair and slower progression have also been described.[19,20] Lesions in the brain and spinal cord are responsible for the pyramidal and cerebellar signs. Others may have cranial neuropathy (especially the third and seventh cranial nerves), scoliosis, optic atrophy, epilepsy, mental retardation, and precocious puberty. The diagnosis of GAN is usually made by peripheral nerve biopsy.[21] Ancillary studies such as nerve conduction study show a mixed sensorimotor axonal polyneuropathy,[22,23] and EEG, evoked responses, or brain MRI may reveal subclinical central abnormalities.[24] Typical brain MRI changes include atrophy and demyelination involving the fronto-parieto-occipital periventricular white matter, brainstem, and cerebellum.

There is presently no cure for GAN, and only supportive therapies are available. Patients with GAN are at increased risk of anaesthetic complications, thus careful perioperative management is required.[25]

Final Diagnosis: Giant axonal neuropathy

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