

Clinical Progression of Giant-Axonal Neuropathy over a Twelve Year Period

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ABSTRACT: *Giant-axonal neuropathy (GAN), a chronic peripheral neuropathy with associated Central Nervous System dysfunction and tight curly hair, is described in a 17-year-old girl. Biopsies of this girl's muscle and nerve are characteristic of this condition. Her clinical course over a 12 year period characterizes a disease of a slowly progressive nature.*

RÉSUMÉ: *Nous décrivons une axo-neuropathie géante (une neuropathie périphérique chronique avec dysfonction associée du SNC et, des cheveux frisés) chez une fille de 17 ans. Les biopsies musculaires et nerveuses furent caractéristiques. L'évolution de sa maladie sur une période de 12 ans démontre la nature progressive lente de cette entité.*

INTRODUCTION

Giant-axonal neuropathy (GAN) was first described by Asbury et al (1972). Their findings included tight curly hair, peripheral neuropathy, ataxia, isolated triphasic and giant potentials on electromyography (EMG), absence of evoked responses in the peroneal and posterior tibial nerves on nerve-conduction studies and abnormal findings on nerve biopsy. Other cases with similar findings have been reported (Berg et al, 1972; Carpenter et al, 1973 and 1974; Ouvrier et al, 1974; Igisu et al, 1975; Koch et al, 1977; Gambarelli et al, 1977; Watters et al, 1978; Mizuno et al, 1979; Jones et al, 1979; Larbrisseau et al, 1979 and Takebe et al, 1979). In this paper we describe the progression of this disease in a 17-year-old girl who has been followed for 12 years.

CASE REPORT

This girl presented to The Hospital for Sick Children, Toronto, at 4.5 years of age because of frequent falling. She had been the product of a normal pregnancy and was the only child of unrelated parents. Her development had appeared normal until she began falling nine months before her hospital admission.

The child had remarkably curly, wiry hair unlike that of her parents. Examination showed mild wasting around the buttocks, weakness of the flexors and extensors of the knees and absence of deep tendon reflexes in the lower extremities. There was no evidence of distal weakness or muscle wasting. Electroencephalography (EEG), nerve-conduction studies and serum enzymes and cerebrospinal-fluid (CSF) investigations were normal. However, a muscle biopsy indicated neurogenic atrophy. Peripheral neuropathy of unknown type was diagnosed.

By 7 years of age, the patient was ataxic, and proprioception and pinprick perception were depressed below the knees. Creatine kinase, CSF protein, brain scan, and pneumoencephalography were all

normal. However, an EEG now showed bursts of 4 Hz. slow wave activity in the post-central regions, more marked on the right, and the EMG showed isolated triphasic potentials and giant potentials consistent with chronic denervation in the legs. Motor nerve conduction velocities were normal in the ulnar nerves but no response was obtained from peroneal and posterior tibial nerve stimulation.

At 8.5 years of age, scoliosis and precocious puberty (breasts at Tanner stage 4 and pubic hair at Tanner stage 3-4) became apparent. Bone age at this stage was 10 years. Levels of FSH and LH were normal as were thyroid studies.

Harrington rod instrumentation with fusion was performed when she was 9 years old. Biopsy of the left sural nerve showed GAN. Symptoms and signs of neurogenic bladder developed shortly afterwards and by 11 years of age the patient had fecal incontinence; rectal manometry at that time showed no external sphincter reflex. At 15 years, detailed psychological testing demonstrated excellent preservation of verbal and cognitive skills but some loss of visual perception.

At age 17, the girl is ambulatory with the help of a wheeled walker but spends about half of each day in a wheelchair. She can feed herself but needs help with dressing and toileting. She has nystagmus on lateral and vertical gaze and slightly slurred speech but very good head control and a full range of motion in her neck.

Her arms are wasted distally and the lumbrical and thenar muscles are severely weakened. There are fixed flexion contractures of the proximal interphalangeal joints. Passive motion in the hips is normal but she cannot flex her hips or lift her legs against gravity. There is very little activity in the dorsiflexors, plantar flexors, invertors and evertors of her feet (grade I power on the Medical Research Council scale). Muscle bulk is decreased, especially in the distal lower extremities.

Muscle tone is generally decreased, most markedly in the lower limbs. She has bilateral dysmetria and lower-limb reflexes are absent. Deep tendon reflexes in the upper limbs can barely be elicited. Sensa-

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tion in her arms is normal for pinprick and touch and she has proprioceptive sensation in her wrists but not her fingers. All sensory modalities in the lower limbs are decreased in a stocking distribution; vibration sensation is perceived only on the forehead and sternum. Computerized tomography of the head was normal.

PATHOLOGY

A biopsy of quadriceps muscle was fixed in Bouin's solution and embedded in paraffin for hematoxylin and eosin, Masson's trichrome and phosphotungstic acid-hematoxylin stains. Another segment of muscle was fixed in phosphate-buffered 2% glutaraldehyde, postfixed in phosphate-buffered 1% osmium tetroxide and embedded in Epon-Araldite. One micron sections were also cut and stained with toluidine blue. Sections 600 Å thick stained with uranyl acetate and lead citrate were examined with a Philips 201 electron microscope.

Cross and longitudinal sections of the sural-nerve biopsies were fixed in formalin, embedded in paraffin and stained with hematoxylin and eosin, Luxol fast blue, Masson's trichrome, Bielschowsky's and osmium tetroxide stains. Teased-fiber preparations were obtained by staining with phosphate-buffered 2% osmium tetroxide and immersion in 66% glycerin in water. Another segment of nerve was fixed for electron microscopy and processed according to the method described for muscle.

The muscle biopsy taken at 6 years of age showed groups of small angulated fibers consistent with neurogenic atrophy. Electron microscopy showed no degeneration of muscle fibers. Excessive fine filaments had accumulated in axons of myelinated fibers of intramuscular nerves, in fibroblasts and in endothelial cells of some arteries.

The first sural-nerve biopsy, taken at 9 years of age, showed enlarged axons scattered throughout all nerve fascicles. Electron microscopy was not performed.

In the second sural-nerve biopsy (at age 14 years) the most striking finding was severe reduction of large myelinated fibers. There was axonal swelling (Fig. 1) but no onion-bulb formation.

Teased-fiber preparations showed marked fusiform axonal dilation.

Electron microscopy showed that the axonal swellings (with and without myelin sheaths) were filled with tightly-packed, neurofilaments (approx. 7.6 ± 0.9 nm in diameter) (Fig. 2A) as in other reported cases (Asbury et al, 1972; Ouvrier et al, 1974; Igisu et al, 1975; Koch et al, 1977 and Mizuno et al, 1979). Some fascicles of filaments streamed together in parallel rows and others were arranged in whorls. At high power, the filaments appeared connected to oval-shaped bodies consisting of random-sized, electron-opaque particles (Fig. 2B). Clusters of filaments were seen in the cytoplasm of Schwann cells, fibroblasts and perineural and endothelial cells but not in smooth muscle cells enclosing arterioles. Most axonal swellings also contained small clusters of neurotubules and mitochondria in the periphery of the axoplasm. Vesicles about 70 to 90 nm in diameter with an electron-opaque core, together with multivesicular bodies, were frequently present in axonal swellings. Some giant axons without myelin sheaths were surrounded by two or more Schwann cells.

Macrophages were present in the endoneurial space but not within the

basal lamina of the Schwann cells. Occasionally there were mast cells in endoneurial and epineurial spaces. Filaments did not proliferate in either macrophages or mast cells.

COMMENT

Excluding patients who do not have curly, wiry hair (Boltshauser et al, 1979; Jedrzejowska et al., 1977; and Peiffer et al., 1977) this girl is the oldest reported patient with GAN and has been followed for the longest period of time. Despite the girl's relatively advanced age, the nerve pathology is similar to that in the other reported cases.

The clinical presentation of our patient (precocious puberty, nystagmus, slurred speech and abnormal EEG) suggests that GAN is a generalized condition with a slowly progressive course. Consistent with this, Jones et al., (1979) described similar pathologic changes including demyelination and Rosenthal fibres throughout the white matter of brain and spinal-cord at autopsy. Neither electroretinography nor visual evoked potentials were studied in this patient (Kirkham 1980). The precocious puberty was not associated with increased FSH or LH,

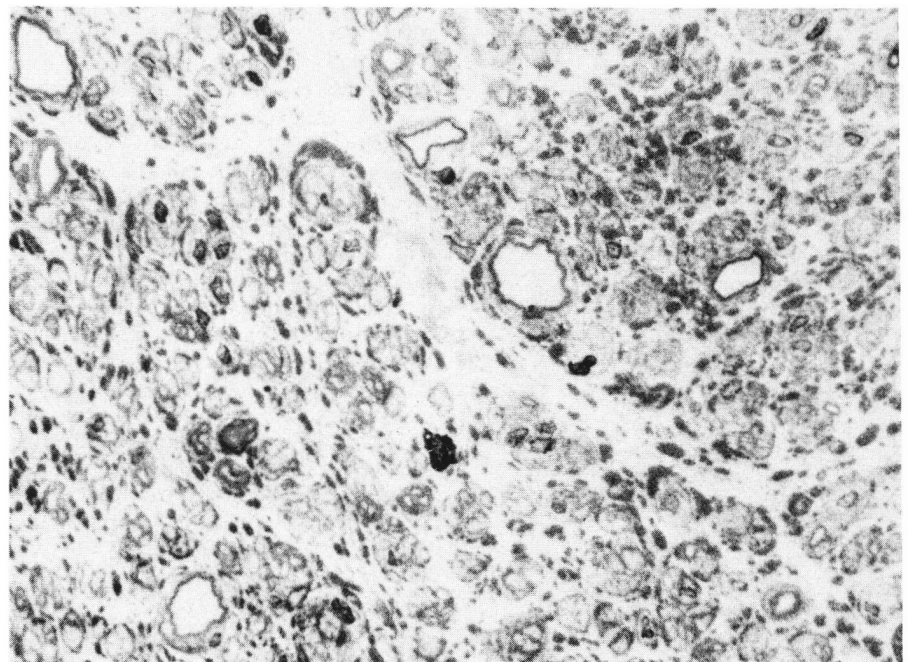


Figure 1 — Transverse section of sural nerve stained with toluidine blue showing single, large fibers and greatly reduced numbers of myelinated fibers, x 500.

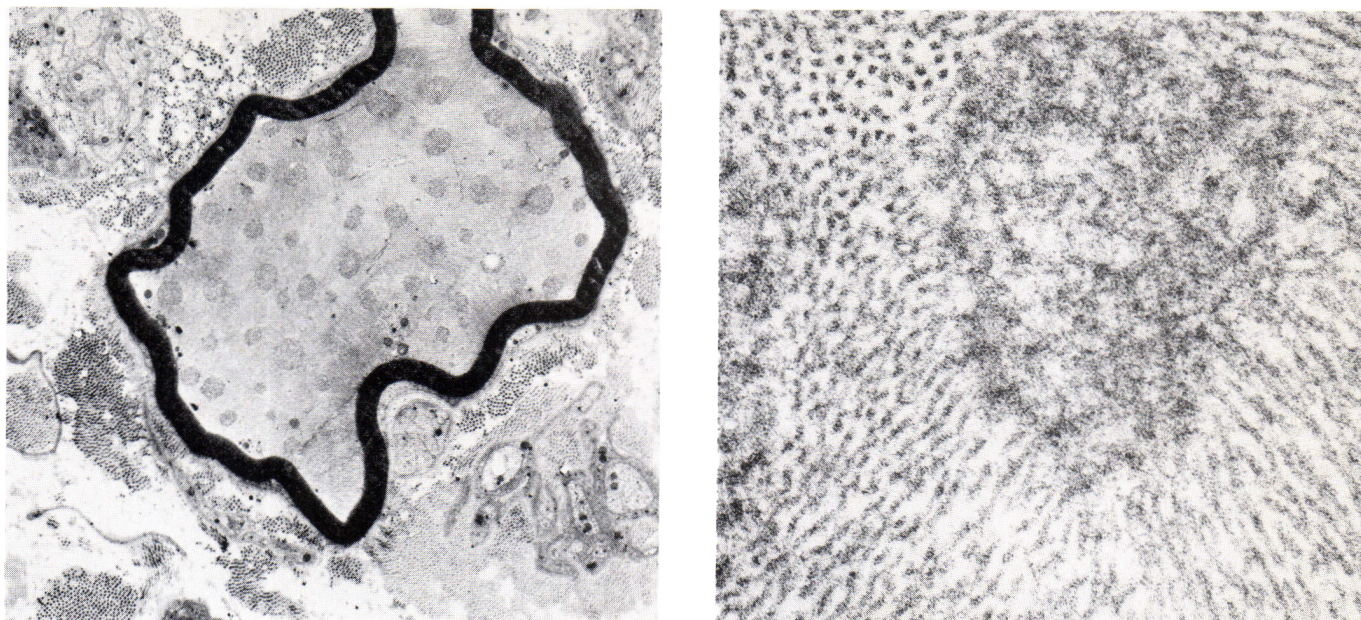


Figure 2—(A) Transverse section of axon containing filaments, x 5,000. (B) Unorganized electron-opaque body with apparent continuity with filaments, x 118,000.

although Takeba et al (1979) did find abnormal hormonal levels in one of two siblings with GAN.

The accumulation of intermediate size filaments in peripheral nerve, and fibroblasts and endothelial cells of muscle supports the hypothesis of Prineas et al, (1976) that GAN is a cytoplasmic filamentous disorder.

The disease appears to be inherited in an autosomal recessive pattern. In three cases parental consanguinity was reported (Ouvrier et al, 1974; Igisu et al, 1975; Gambarelli et al, 1977) and in one other there were affected siblings (Jones et al, 1979).

The diagnosis of GAN should be considered in any child with features of peripheral neuropathy who also has tightly curled hair and central nervous system dysfunction. Nerve biopsy is necessary to confirm the diagnosis.

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