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Generalized Giant Axonal Neuropathy

A Filament-Forming Disease of Neuronal, Endothelial, Glial, and Schwann Cells in a Patient without Kinky Hair

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Summary. The process of Giant Axonal Neuropathy (GAN) is not restricted to the peripheral nerves, but also involves the central nervous system. In a 25 year old man with normal hair, abundant axon swellings and spheroids were observed in the spinal cord, brain system, and cerebral cortex. The findings in the sural nerve have already been published by Boltshauser et al. (1977). Accumulations of filaments in the axons and in the perineural cells were accompanied by Rosenthal fibres. The ultrastructural pattern of GAN differs clearly from that of Neuroaxonal Dystrophies.

Key words: Giant axonal neuropathy – Neuroaxonal dystrophies – Kinky hair – Rosenthal fibres – Neurofilaments.

Introduction

Giant Axonal Neuropathy (GAN) is characterized clinically by a slowly progressive chronic polyneuropathy in children, morphologically by segmental enlargements of many axons of peripheral nerves. Electronmicroscopic examinations show closely-packed filaments in the swollen axonal segments. The first case was described by Asbury et al. (1972) (identical with Berg et al., 1972), followed by Carpenter et al. (1974), Ouvrier et al. (1974) (identical with Prineas et al., 1976), Igisu et al. (1975), Jedrejowska and Drac (1977) and Boltshauser et al. (1977). In these six cases the diagnosis was based on biopsies of the sural nerve. In view of the pathological EEGs in Berg's and his own case, Igisu et al. supposed that the process involves not only the peripheral nerves, but also the CNS. All described cases showed as a common feature remarkably kinky hair (inclusive the Japanese girl) with exception of these cases of Jedrzejowska and Drac and of Boltshauser et al. In this lastnamed Swiss child the diagnosis was made ultrastructurally in the sural nerve by Bischoff. We have now had the occasion to examine the CNS of the same case. For the first time our findings prove that GAN is a generalized disorder of the CNS.

Case Report

The *clinical aspects* and the report on the nerve biopsy examination are dealt with in detail by Boltshauser et al. Hans-Jacob C. (ES 254/76). 25 years old man. Normal family history. Uneventful pregnancy. Unsteady broad-based gait since his second year. He fell frequently and never managed to walk normally. He left the school at the age of 11 years because of his mental retardation. His motor performance deteriorated steadily and from the age of 10 years he became almost unable to walk. In his 12th year he developed a marked scoliosis. Right divergent squint. Nystagmus. Muscle tone reduced. No tendon reflexes elicited. Impaired position and vibration sense in arms and legs. Dysdiadochokinesis. The EEG showed some slowing of background activity. A pneumencephalogram demonstrated mildly enlarged lateral ventricles and a moderately enlarged fourth ventricle. IQ 56. The EMG disclosed a reduced interference pattern in the opponens pollicis and tibialis anterior muscles, but no spontaneous activity or fibrillation.

Sural nerve biopsy was performed in the patient at the age of 12 years. Bischoff described "in the enlarged axons appeared as a spindle-shaped focal distention of nonmyelinated and thinly myelinated nerve fibres in which an increased density of the axoplasm was apparent. By electron microscopy, the axonal swellings were found to be composed of densely packed 10 nm filamentous structures. At the border of the axon a rather well demarcated area of normally distributed neurofilaments, neurotubules, mitochondria and membranous organelles of the endoplasmatic reticulum was often preserved . . . Accumulation of 10 nm filaments was also present within the Schwann cell cytoplasm. In addition an increased density of filaments could be recognized in endothelial cells of endoneurial capillaries and in perineurial cells" (Boltshauser et al.).

Within 2 years the patient was almost paraplegic. Speech became dysarthric. Further intellectual deterioration occurred. At the age of 20 years impaired vision was noted with bilateral temporal pallor of the discs. Terminally the patient became bedridden and almost tetraplegic with extensive joint contractures.

Post Mortem Examination

Summary of autopsy performed 8 days after caecostomy (because of subileus and meteorism). Stress ulcer's below the pylorus. Diffuse, subacute peritonitis with severe intestinal adhesions. Paralytic ileus. Swollen splenic pulp. Diffuse fatty degeneration of liver parenchyma. Acute central necrosis of the liver cells. Pulmonary oedema. Dilatation of the heart. Interstitial renal oedema.

Neuropathological Findings

Material and Methods

Several paraffin embedded blocks of tissue were received from the frontal and occipital lobes, basal ganglia (putamen and caudate nucleus), pons medulla oblongata, and spinal cord, and also sections throughout three regions of skeletal muscle.Regrettably no tissue from one pallidum, substantia nigra and cerebellum were available.

For electronmicroscopic examinations selected portions of the formalin fixed spinal cord were postfixed in osmium tetroxide, dehydrated and embedded in araldite. Semithin and ultrathin sections were made with an LKB III ultramicrotome. The ultrathin sections were stained with uranyl acetate and lead citrate.

Results

The muscles showed the typical pattern of neurogenic atrophy. The myelinated as well as the unmyelinated nerve fibres within the muscles showed abundant areas with segmental enlargements of the axons (Fig. 1). These spheroids and the spindle-shaped or wormlike swollen areas were homogeneously stained pale green in Klüver Barrera, bluish in Mallory's trichrome, pink in haematoxylin-eosin and yellow in van Gieson preparations. They were PAS-negative, but argyrophilic.

Analogous lesions could be seen in *CNS:* The spinal cord revealed severe alterations throughout the whole cross-section, accentuated in the posterior tracts. Here, as in lesser degree in other parts of the spinal white matter, numerous spheroids of different sizes were observable (Fig. 2). The spinocerebellar tracts were demyelinated and had a spongiose appearance. The size of the spheroids here reached more than the two or three times that of an anterior horn cell. The spheroids did not always display a homogeneous structure but sometimes showed fine granularity or lamellation. Smaller axonal swellings were distributed in the anterior and posterior nerve roots. Within the anterior and posterior horns, the spheroids were only seldom located immediately adjacent to nerve cell perikarya. The nerve cells were slightly distended with central chromatolysis or with remarkable coarse clumps of chromatin (Fig. 3). They sometimes showed a dustlike distribution of chromatin. In a similar fashion, numerous spheroids were scattered throughout the pyramidal tracts, especially in the pons. Here all the tracts showed ubiquitous axonal swelling as, to a lesser extent, did the nuclei pontis (Fig. 4). Here, however, the ballooning of the axons was not as impressive as in the posterior funiculi. The corticospinal tracts of the pons revealed a spongiform

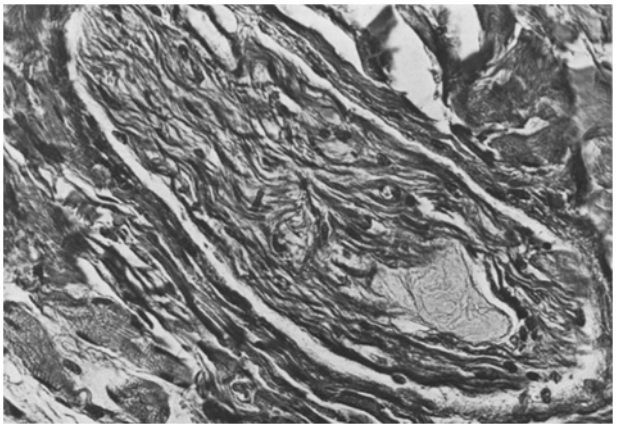

Fig. 1. Axon enlargements in small muscle nerve. Mallory trichrome

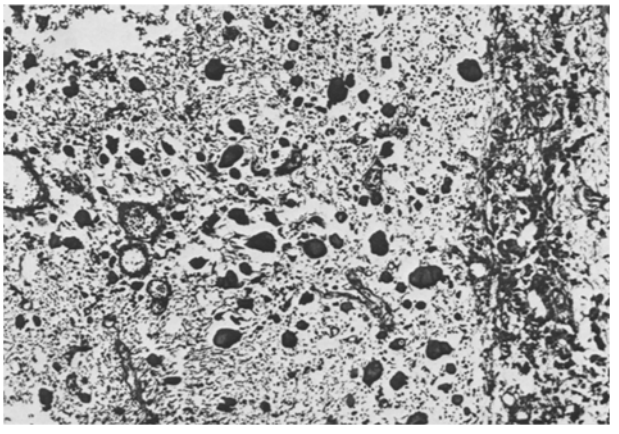

Fig. 2. Several spheroids in the spongiose posterior tracts. Klüver

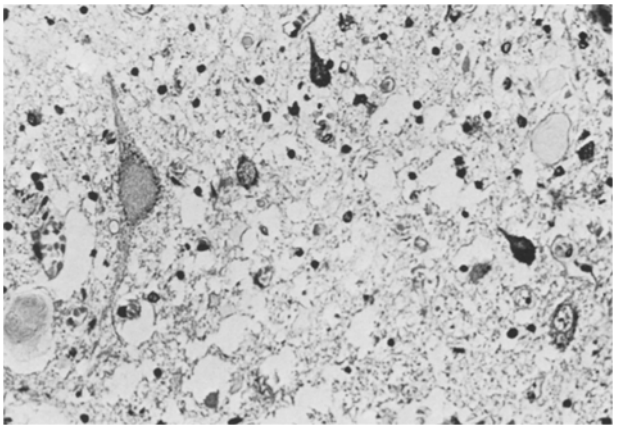

Fig. 3. Nerve cell with central chromatolysis. Many spheroids in the spongiose anterior horn. H.-E.

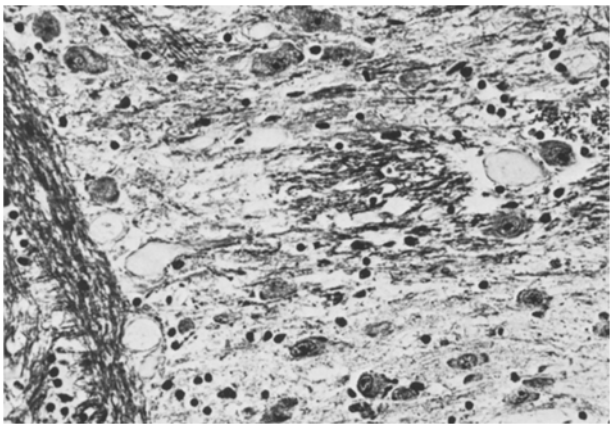

Fig. 4. Multiple swollen axons in the pons. Mallory trichrome

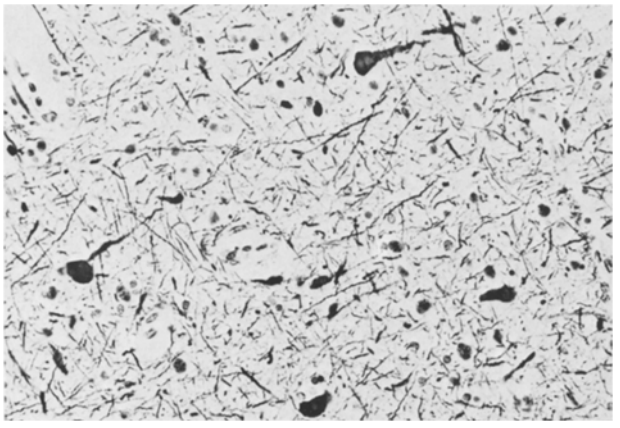

Fig. 5. Axon swellings in the frontal cortex. Bodian

alteration of small regions near the midline. In the putamen and caudate nucleus many small axonal swellings were also present. In the cortex their number was rather higher, but the size of the spheroids, as in the neostriatum, was smaller than in the spinal cord. Microglial reactions or astrocytosis were never found. The number of nerve cells in the cortex, as in the neostriatum, was not reduced and showed a normal picture. The cortex also showed numerous swollen axons (Fig. 5). No demyelination was apparent in the white matter of the cerebrum. We did not see abnormal pigmentation anywhere.

A pecular feature in the basal ganglia was the presence of abundant Rosenthal fibres connected with subependymal cells of the ventricular walls (Fig. 6). Some Rosenthal fibres were also seen in the pons and the spinal cord, mainly in a perivascular position. In the subependymal regions near the third ventricule many heterotopic ependymal cells were scattered between the glial tissue.

Under the electronmicroscope the enlarged axons were nearly entirely filled with bundles of fine 10 nm

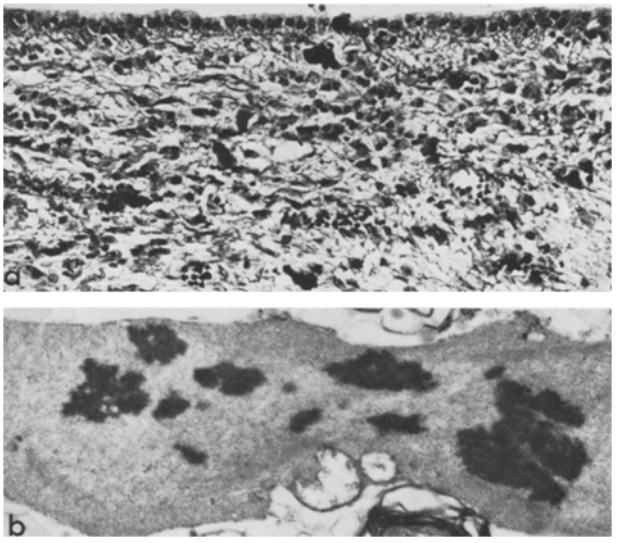

Fig. 6. a Ventricucle wall with abundant subependymal Rosenthal fibres. Mallory trichrome. **b** Rosenthal fibres in the white matter of the spinal cord. Electron micrograph, 4800:1

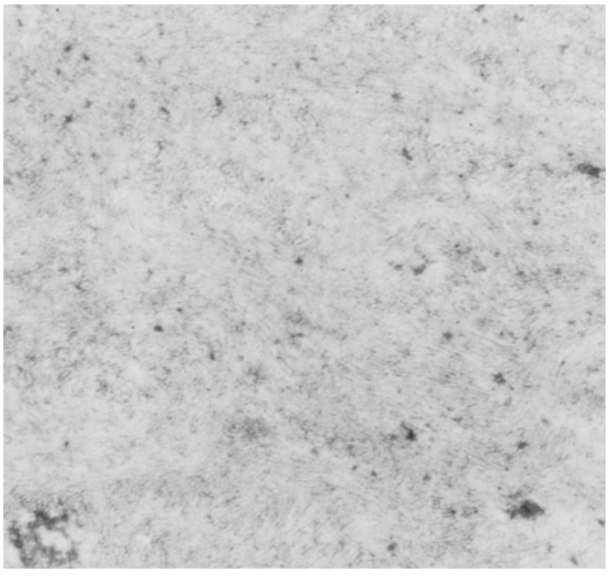

Fig. 7. Part of an axon enlargement filled by neurofilaments, 10 nm diameter, in bundles and incomplete whorls. Electron micrograph, 18000:1

filaments which were arranged in alternating directions; they often displayed incomplete whorl-like patterns (Fig. 7). No microtubules were seen, probably in consequence of the formalin fixation. Between the bundles of filaments, some accumulations of organelles were occasionally seen, as for example, membranous profiles of the endoplasmic reticulum and giant mitochondria (Fig. 8). Between them at places a dense material of fine granularity was present. The myelin sheaths of the enlarged axons showed dis-

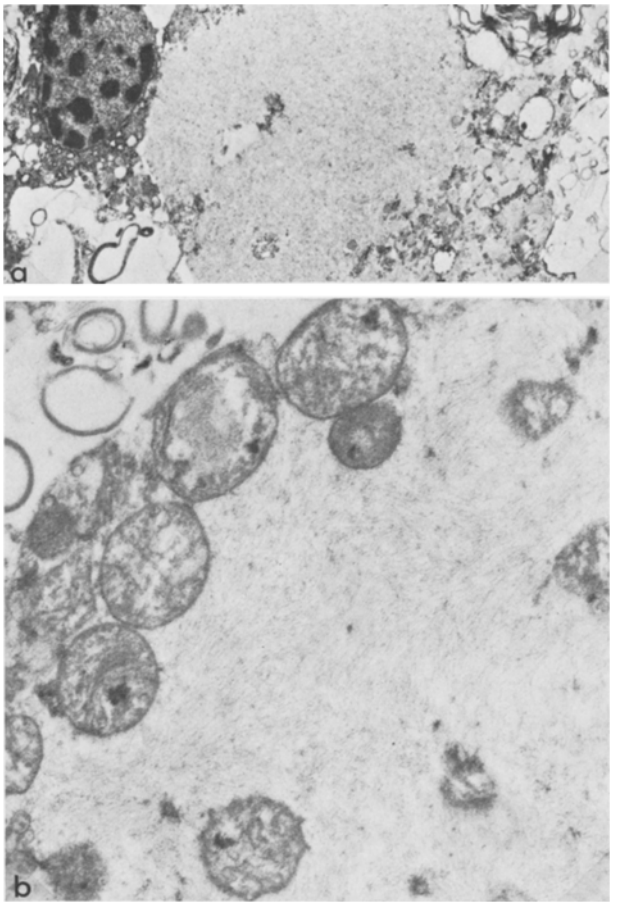

Fig. 8. a Enlarged axon filled with filaments, accompanied by an oligodendrocyte and at right by myelin debris. Electron micrograph, 4800:1. **b** Part of an axon enlargement containing, besides neurofilaments, rounded giant mitochondria with remnants of cristae, opaque material and dense osmiophilic inclusions. Electron micrograph, 25600:1

integration, with remnants of myelin seen at their edges. Other fibres demonstrated clear degenerative axonal lesions in the form of condensation of axoplasm and shrinkage of the axon accompanied by multifocal disruption of the myelin sheath. Most of myelinated fibres appeared normal. Normal oligodendrocytes were often seen in close contact with the enlarged axons. The walls of small vessels in the spinal cord were thickened by sheaths of densely packed bundles of collagen fibres surrounding the endothelial basement membranes. No filaments were seen in the endothelial cells. The perivascular fibrillary astrocytes and occasionally also interstitial astrocytic processes often contained a very dense material of irregular configuration and high osmiophilia which showed a granular fine structure at higher magnification. It was surrounded by astrocytic filaments. This material corresponded to the Rosenthal fibres seen by light microscopy.

Discussion

Our case was the subject of the previous report published by Boltshauser et al. (1977). All six published cases of GAN were diagnosed by sural nerve biopsy, which disclosed swellings of the axons, ultrastructurally composed of local accumulations of closely packed neurofilaments in myelinated and unmyelinated nerve fibres. Neurotubules, mitochondria and cisternae of the smooth endoplasmic reticulum were often absent in these enlargements, or were displaced to small peripheral areas near the axolemma. Prineas et al. (1976) first mentioned accumulations of filaments not only in the enlarged axons, but also in Schwann cells, endoneural fibroblasts and vascular endothelial cells. Whereas the diameter of the intraaxonal neurofilaments measured 10–12 nm, the diameter of these filaments amounts to 8–10 nm. Accumulations of such pathological filaments outside the axon were confirmed by Bischoff's examination of the sural nerve in our case. Boltshauser et al. therefore concluded "It does not seem possible to identify the axonal abnormality as an accumulation of *neuro*-filaments". These authors suggest a general abnormality of protein metabolism.

Already some clinical features have prompted previous propose that GAN is not only a disease of peripheral nerves, but a process involving the whole nervous system including the CNS. The reasons for this assumption were slight anomalies in the EEG (Berg et al.; Ouvrier et al.; Igisu et al.), pathological reflexes (Carpenter et al.; Prineas et al.), and other indications of cerebral lesions, as in our case (Boltshauser et al.). Morphological studies on the CNS, however, have not previously been reported.

Our case proves that the focal enlargement of axons and the accumulation of filaments is not restricted to the peripheral nerves. These filaments represent the main indication of a generalized process, accompanied by demyelination and a spongiose loosening of white matter in the posterior funiculi and in the brain stem. Focal enlargements of axons of peripheral nerves are known not only in GAN, but in Neuroaxonal Dystrophy (NAD) (Kamoshita et al., 1968; Berard-Badier et al., 1971; Sengel and Stoebner, 1972; Martin and Martin, 1972; Martin et al., 1972; Ametani, 1974; Shimono et al., 1976), and can be produced by many toxic agents, for example acrylamide, n-hexane, methyl-butyl-ketone (for review see Boltshauser, and new observations by Davenport et al., 1976; Rizzuto et al., 1977). Similar lesions were described in experimental neurolathyrism (Ule, 1961, 1962). The important criterion for the differentiation of GAN from the different types of NAD (Peiffer et al., 1976) is the ultrastructural pattern of the

swollen areas. Characteristic of the NAD are local accumulations of vesiculotubular structures (Gonatas et al., 1967; Sandbank et al., 1970; Hedley-Whyte et al., 1968; Martin et al., 1972; Peress and Kim, 1974), paracrystalline inclusions (Herman et al., 1969; Toga et al., 1970; Sandbank et al., 1970), and circular profiles of endoplasmic reticulum (Sandbank et al., 1970; Toga et al., 1970; Sengel and Stoebner, 1972; Liu et al., 1974). In NAD the spheroids are often found in a presynaptic position near the nerve cell perikarya, whereas this location is seldom found in GAN.

In addition to the dominant axonal neurofilamentous change in GAN, our case shows Rosenthal fibres as a sign of abnormal metabolism not only in the axons but also in astrocytes (Schlote, 1964). Rosenthal fibres are an unusual manifestation in NAD. We could find in the literature only one case with this glial transformation in a dystrophic axonal process. The description given by Ule (1972) resembles our observation in some respects, but differs in others. Contrary to the typical clinical picture of NAD, this 24 year old man developed slowly progressive muscle atrophy and paresis of the legs at the age of four. At about his tenth year speech difficulty appeared, unaccompanied by dementia or other symptoms of cerebral disturbance. Since his fourteenth year, the paresis also affected the arms. The patient died from alcoholic intoxication. The clinical diagnosis was pseudomyopathic spinal muscular atrophy (Kugelberg-Welander).

As in our case, Ule's case displayed neurogenic muscle atrophy and abundant axonal swellings in the peripheral nerves and in the CNS. Ule also described Rosenthal fibres near the ventricular wall and among the gray and white matter. Electron microscopy revealed predominantly filaments in the spheroids. His case nevertheless differs from ours by the lamellar configuration of the filaments resembling a moiré pattern. In spite of this difference, the morphological similarities with our case are very impressive. Ule imagined a dysmetabolic process involving proteins, evidenced by the combination of neuronal and glial lesions. The same conclusion was reached by Boltshauser et al., based on the abnormal increase of filamentous structures within the cytoplasm of neurons, Schwann cells and vascular endothelial cells. Filaments were lacking in the endothelial cells of spinal cord vascular walls, which seem to have less capability to react by productions of filaments in comparison to the endothelium of peripheral vessels. Nevertheless it would be more correct to designate this disease not as an axonal neuropathy but as a generalized disease of filament-forming cells in the nervous system, probably due to a disorder of protein metabolism.

Four of the six published cases of GAN were characterized by curly or kinky hair. Only the case of Jedrzejowska and Drac as our case have normal hair. The kinky hair in GAN should not be confused with Menkes Kinky Hair Disease with its different clinical and morphological pattern (spine-like sprouts from the Purkinje cell perikarya, excessive proliferation of Purkinje cell dendrites; Aguilar et al., 1966; Vagn-Hansen et al., 1973; Moellekaer, 1974; Kopp et al., 1975; Wray et al., 1976). Ultrastructurally however, Hirano et al. (1977) described accumulation of neurofilaments within axonal torpedos of Purkinje cells. Various disturbances in copper metabolism are the cause of Menkes disease. We still lack comparable biochemical a normalies in GAN.

The question remains open as to whether our case of GAN without hair anomalies but with pathological accumulations of filaments in axons and filament alterations in astrocytes can be considered as representative for the other cases of GAN characterized by kinky hair. Only further reports with examination of the central nervous system in GAN can answer this question.

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