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Morphological Investigations on Axonal Swellings and Spheroids in Various Human Diseases

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Summary. Axonal swellings and spheroids in various human diseases were studied by light and electron microscopy. 4 cases of infantile neuroaxonal dystrophy, 2 of degenerative diseases, 2 brain tumors and 3 of cerebrovascular disease were examined.

Ultrastructurally most spheroids in infantile neuroaxonal dystrophy consisted of interconnected tubules, stacked membranotubular profiles, alternating layered membranes and accumulations of neurofilaments. Combinations of these four constituents were seen only in infantile neuroaxonal dystrophy. "Torpedos" (fusiform swelling of the axon of a Purkinje cell) consisted exclusively of neurofilaments. Spheroids in case 6 (mental retardation) and 7 (atypical teratoma) consisted of interwoven skeins of neurofilaments and grouped mitochondria. Spheroids in case 8 (demyelination) and 9 (cerebrovascular disease) consisted of packed complex bodies and mitochondria. Spheroids in cases 10 and 11 (cerebrovascular disease) consisted of degenerating organelles only. The morphological differences between cases 9, 10 and 11 probably depends on the severity and timing of the cerebral injury.

Most spheroids show similar histological and histochemical properties, but ultrastructural study may give some clue to the origin of the bodies.

Keywords: Axonal swelling – Spheroid – Electron microscopy.

Introduction

The phenomenon of axonal swelling in the central and peripheral nervous systems is observed in a wide range of pathological conditions, including tumors (Reyes et al., 1976; Wolter, 1968), vascular lesions, degenerative and demyelinating processes (Sung and Stadlan, 1966; Schneck, 1966; Mruzek et al., 1975; Kamoshita et al., 1967), and systemic diseases suggesting generalized metabolic disorders (Terpan and Carest, 1972). The results of the development of discontinuous swellings are referred to as "Schollen" or "spheroids". By light microscopy these axonal bodies are said to be indistinguishable from one another.

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Axonal swellings in experimental animals have been classified on the basis of their ultrastructure into regenerative, reactive, degenerating and dystrophic types (Lampert, 1967). The fine structures of these bodies in human disease, however, appear to show some differences from those in Lampert's observations.

Although the fine structure of dystrophic axons has been suggested as a method of distinguishing dystrophic axonal changes from other reactions of neurones, it has been repeatedly argued that the changes seen are non-specific (Hager, 1966; Kolkmann and Rana, 1971).

The spheroids in dystrophic axons arise chiefly from the terminal axons and presynaptic endings (Sandbank et al., 1970) and at neuro-muscular junctions (Berard-Badier et al., 1971; Sengel and Stoebner, 1972; Martin and Martin, 1972). They may progress to involve proximal axons (Seitelberger, 1970). In infantile neuroaxonal dystrophy (INAD) the spheroids in the cerebral white matter probably consist of neurofilaments and neurotubules, which suggest that a secondary disturbance of axonal flow may be concerned with spheroid formation in this condition (Yagishita and Kimura, 1975).

The purpose of this study is to describe the histological, histochemical and ultrastructural properties of various kinds of axonal swellings and spheroids in human diseases and to speculate on the nature of the bodies.

Material and Methods

Ten autopsy cases and one biopsy case showing axonal swellings and/or spheroids were used for this study; 4 cases of INAD, 2 of degenerative diseases, 2 of brain tumor and 3 of cerebrovascular diseases. Observations were mainly made on the medulla oblongata in cases with INAD, although spheroids were widely distributed throughout the central nervous system.

Paraffin embedded sections were stained with hematoxylin and eosin (HE), phosphotungstic acid hematoxylin (PTAH), Azan-Mallory (AM), van Gieson, periodic acid Schiff (PAS), PAS after saliva digestion (S-PAS), Berlin blue, Sudan III, congo red, Nile blue, luxol fast blue (LFB), Bodian and Sudan black B.

For electron microscopic observation, the majority of specimens had been preserved in 10% commercial formalin for several months, the specimen of case 11 was from deparaffinized blocks.

Table 1.

Case No.	Age	Clinicopathological diagnosis	Fixation for EM.
1	7	Infantile neuroaxonal dystrophy	PM. Glu+Os
2	3	Infantile neuroaxonal dystrophy	PM. Glu+Os
3	7	Infantile neuroaxonal dystrophy	PM. Glu+Os
4	3	Infantile neuroaxonal dystrophy	Glu+Os
5	56	Kuru-like encephalopathy	PM. Glu+Os
6	20	Metabolic disease, unknown	PM. Glu+Os
7	48	Atypical teratoma, Pineal body	PM. F+Glu+Os
8	62	Brain tumor, metastatic	PM. F+Glu+Os
9	37	Massive cerebral hemorrhage	PM. F+Glu+Os
10	47	Brain softening	PM. P+Glu+Os
11	20	Metabolic disease, unknown	PM. F+Glu+Os

Abbrev. EM. Electron microscope, Glu. Glutaraldehyde, Os. Osmium tetroxide, PM. Postmortem, F. Formalin, P. Paraffinembedded tissue

Each small piece was fixed in 2.5% glutaraldehyde in phosphate buffer PH 7.4 and postfixed in 1% osmium tetroxide. After serial dehydration in graded alcohol, the tissues were embedded in Epon 812. Fixation methods and clinico-pathological diagnoses are shown in Table 1. Semi-thin sections were screened by light microscopy before thin sections were cut, mounted in copper grid, and stained with uranyl acetate for 30 min and lead citrate for 10 min. They were examined by Hitachi HU-12 electron microscope at 75 Kv.

Case Reports

Case 1,2 and *3* are typical cases of INAD (Clinico-pathological findings are reported elsewhere: Yagishta and Kimura, 1974, 1975). Death occured at the age of 7 years in case 1, at the age of 3 in case 2 and at the age of 3 in case 3.

Case 4 was a 3-year-old boy. His developmental milestones deteriorated gradually from the age of 12 months. Physical examination revealed horizontal nystagmus, optic atrophy and hypotonia of all limbs and a failure to follow moving objects. He regressed granually to a vegetative state. Routine laboratory findings and lysosomal enzyme analysis of leucocytes, including N-acetyl-βhexosaminidase, arylsulfatase A and B, β-glucosidase, β-galactosidase, β-glucuronidase, α-mannosidase and α-fucosidase gave results within normal ranges. Aminoacid and lipid analyses in urine showed a normal pattern.

Histology of the medulla oblongata of all 3 autopsy cases showed essentially similar findings; the medullary tegmentum was hypertrophic despite blurring of structural outline. The most striking findings was the presence of numerous oval or pleomorphic spheroids, measuring from several to over 200 μ. They were eosinophilic, homogeneous or granular, sometimes with vacuolation or clefts. Their shapes varied from a discrete round disk to an irregular oval, or sometimes to an ill-defined mass. Most spheroids seemed to have a deeply eosinophilic core (Fig. 1c). In addition, diffuse hyperplasia of astrocytes was evident. Some spheroids were surrounded so-called microglia, indicative of spheroidophagia. Their histochemical properties were essentially similar in all 3 cases. Histology of a biopsy of the sural nerve in case 4 revealed some loss of myelinated fibers and a slight increase of Schwann cell nuclei. There were no findings suggesting active myelin breakdown and no abnormalities in the perineural connective tissue. Occasinal axons showed a fusiform swelling.

Case 5 was a 56-year-old male. The patient developed gait disturbance and severe pain in the lower extremities at the age of 46 years. Subsequently dysarthria and marked truncal ataxia appeared. Six years later, apathy, bulbar palsy and convulsions were manifest. He died of subarachnoid hemorrhage in a decerebrate state. Neuropathology revealed a Kuru-like encephalopathy (Nakashima et al., 1976). Several torpedoes were seen in the granular cell layer of the cerebellum (Fig. 1j).

Case 6 was a 20-year-old female with a history of severe psycho-motor retardation since childhood. Neuropathology showed a diffuse degenerative process of the brain, and several torpedoes were found in association with mild Purkinje cell loss.

Case 7 was a 48-year-old male with atypical teratoma of the pineal who died six months after surgical treatment. Autopsy revealed evidence of widespread tumor dissemination on the wall of the lateral and third ventricles. Countless axonal swellings and spheroids were found around a small necrotic focus in the thalamus caused by tumor infiltration. The bodies were round or oval, but a few grossly irregular in shape, measuring about 30 to 100 μ. Most bodies were finely granular and ome had a smooth homogeneous appearance. Not infrequently an axis cylinder was directly connected to a spheroid. The majority of spheroids, however, lay free and unconnected. No definite nuclei were identified in any of these bodies. Moderate astrocytosis with mild astrogliosis was seen about the necrotic focus. Some fat-laden macrophages were found within or around the lesion.

In case 8, in addition to metastatic tumors, there were multiple discrete, frequently confluent foci of demyelination in the white matter of the brain stem. These foci consisted of areas of

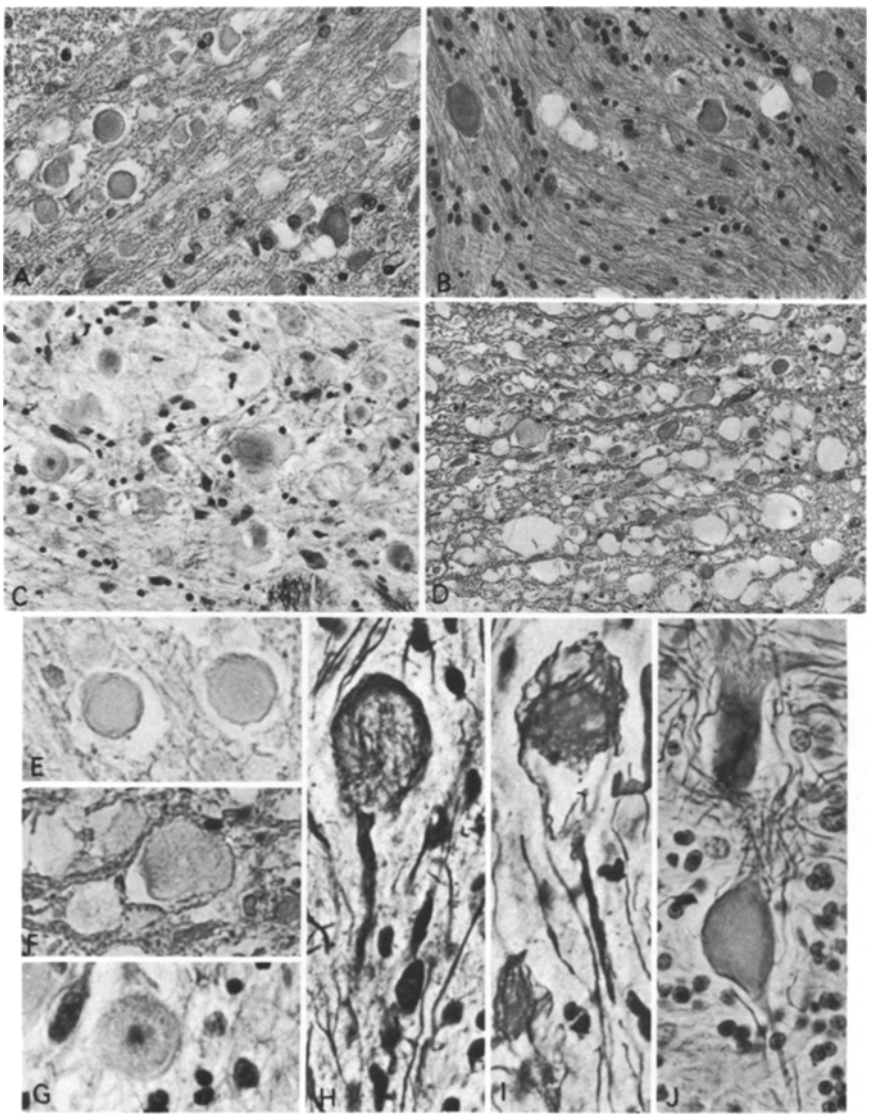

Fig. 1. A Many oval spheroid in the pons. Astrocytosis is seen. Case 8. H.E. ×200. **B** Three spheroids. Astrocytosis and many fat granule cells are present. Case 9. H.E. ×200. **C** Many spheroids in the gracile nucleus. Case 1. H.E. ×200. **D** Many spheroids in spongy area. Case 11. H.E. ×200. **E–I** Various prolile s of spheroids. E–G: H.E., H–I: Bodian ×400. **J** A torpedo in the granular layer of cerebellum. Bodian ×400

coagulative necrosis, unaccompanied by tissue breakdown and cavitation, and were characterized by severe and sometimes almost total loss of oligodendroglia. There was a diffuse infiltration of fat-laden macrophages and a reactive astrocytosis within or around some foci. Numerous pale eosinophilic axonal swellings or spheroids were seen both in and around these lesions (Fig. 1a), their nature was clearly confirmed by silver positivity in Bodian preparations. There was no inflammatory cell infiltration in the necrotic foci. Blood vessels were essentially normal. Clinically the patient was treated with irradiation and chemotherapy for cerebral metastases.

Table 2. Histochemistry of spheroids

Case No.	1, 2, 3	5, 6	7	8	9	10	11
HE	eosin	eosin	eosin	eosin	eosin	eosin	eosin
PTAH	−	−	−	−	−	−	−
AM	poly	poly	poly	poly	poly	blue	poly
van Gieson	yellow	yellow	yellow	yellow	yellow	yellow	yellow
Alcian Blue	−	?	−	−	−	−	−
PAS	++	+	+	+	++	+−	+−
Saliva-PAS	++	+	+	+	++	+−	+−
Berlin blue	−	−	−	−	−	−	−
Sudan III	−	−	?	−	−	−	−
Congo red	−	−	−	−	−	−	−
Nile blue	−	?	−	−	−	−	−
LFB	+−	−	−	−	−	−	−
Bodian	++	++	+	+	+	+~−	+~−

Eosino. Eosinophilic, Poly. polychromatic

Case 9 was a 37-year-old female with a longstanding left-sided hemiplegia who succumbed to recurrent cerebrovascular accidents. The necropsy disclosed several old apoplectic cysts walled by thick glial scar bilaterally in the basal ganglia. Many spheroid bodies were seen in the left internal capsule where moderate loss of nerve fibers with subsequent astrocytosis and scattered scavenger cells were also present. This finding was indicative of a relatively longstanding and progressive process. Some spheroids seemed to be connected with an axis cylinder, others were discontinuous with the axon. Some of the bodies had a deeply staining central core (Fig. 1b).

Case 10 showed an area of encephalomalacia. A few spheroids were seen but astrocytosis was less prominent than in the previous case and many scavenger cells were present in the lesion.

Case 11 showed many spheroids bilaterally distributed in the spongy areas of the columns of the spinal cord (Fig. 1d). No evidence of a reparative process nor "mobiler Abbau" (tissue destruction with reactive microgliosis and fat granule cell) were demonstrable, so the lesion was considered to be an agonal event secondary to circulatory disturbance.

The morphological features of the spheroids are illustrated in Figure 1, their histochemical properties are shown in Table 2.

Electron Microscopic Observations

Spheroids in INAD. Spheroids were plentiful in the tegmentum of the medulla oblongata. Most of them contained large numbers of smooth branching tubules, varying numbers of visicles and smooth membranes. The smooth tubules were about 200 Å to 400 Å in diameter and often showed cistern-like dilatation (Fig. 2a). A few mitochondria were entrapped within stacks of tubulomembranous structures. In addition to these profiles, some bodies had many myelin figures and aggregates of glycogen granules, the latter bordered by a single or multi-layered membrane or present within myelin figures (Fig. 2b). Some bodies were apparently enclosed by the myelin sheath, indicating their origin from myelinated axons (Fig. 2c). A few had watery or granular matrices with small aggregates of mitochondria in the periphery (Fig. 2d). Some axons were entirely filled by countless numbers of mitochondria (Fig. 2e). The tubulo-

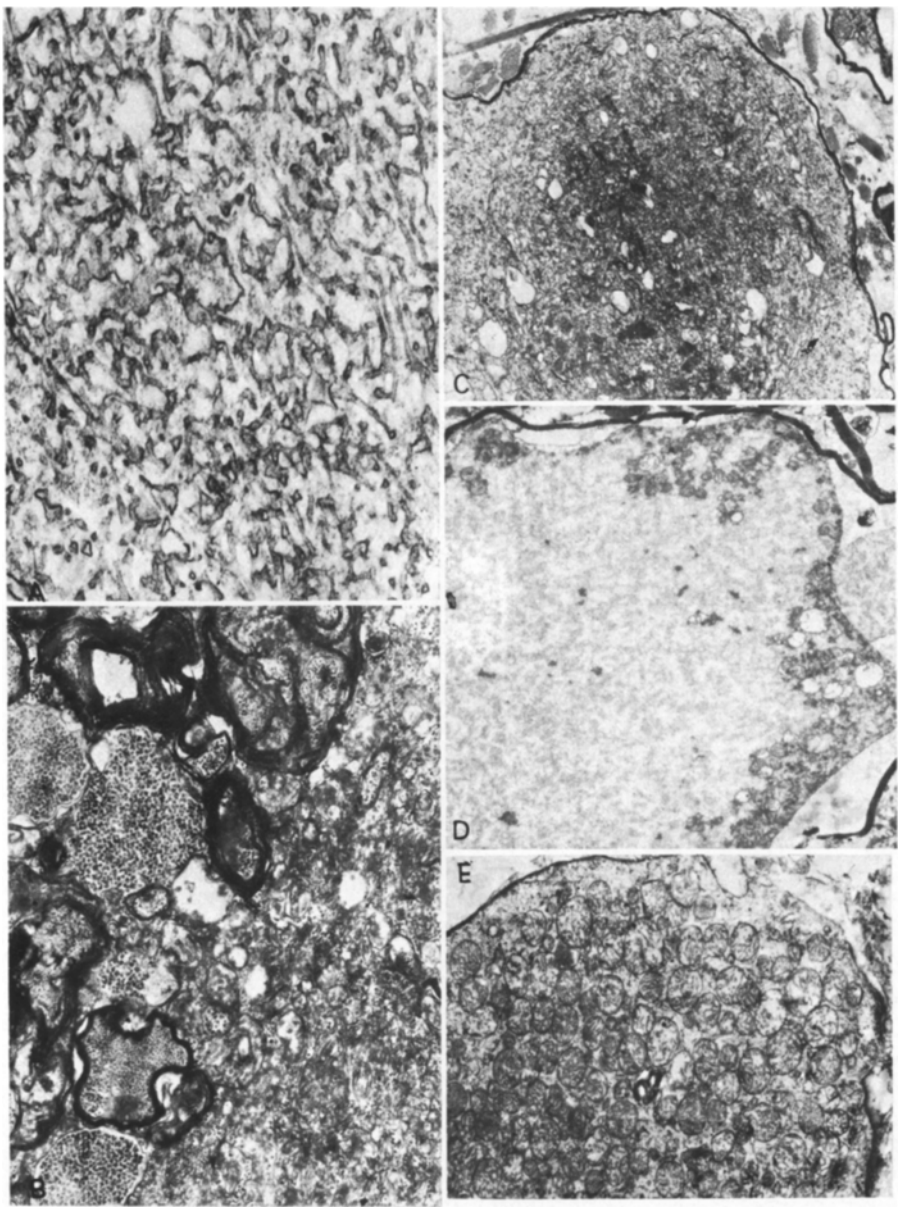

Fig. 2. **A** A spheroid consisting of interconnected tubules case 1. ×35,000. **B** Many myelin figures and glycogen granules in the left field and tubulo-membranous profiles in the right. Case 1. ×12,000. **C** Part of a spheroid in the thinly myelinated axon. Case 2. ×5,900. **D** A distended axon shows watery axoplasm with an aggregate of mitochondria at its periphery. Case 3. ×4,500. **E** An axon filled with mitochondria only. The myelin sheath (upper right) appears to be very thin. Case 3. ×5,900

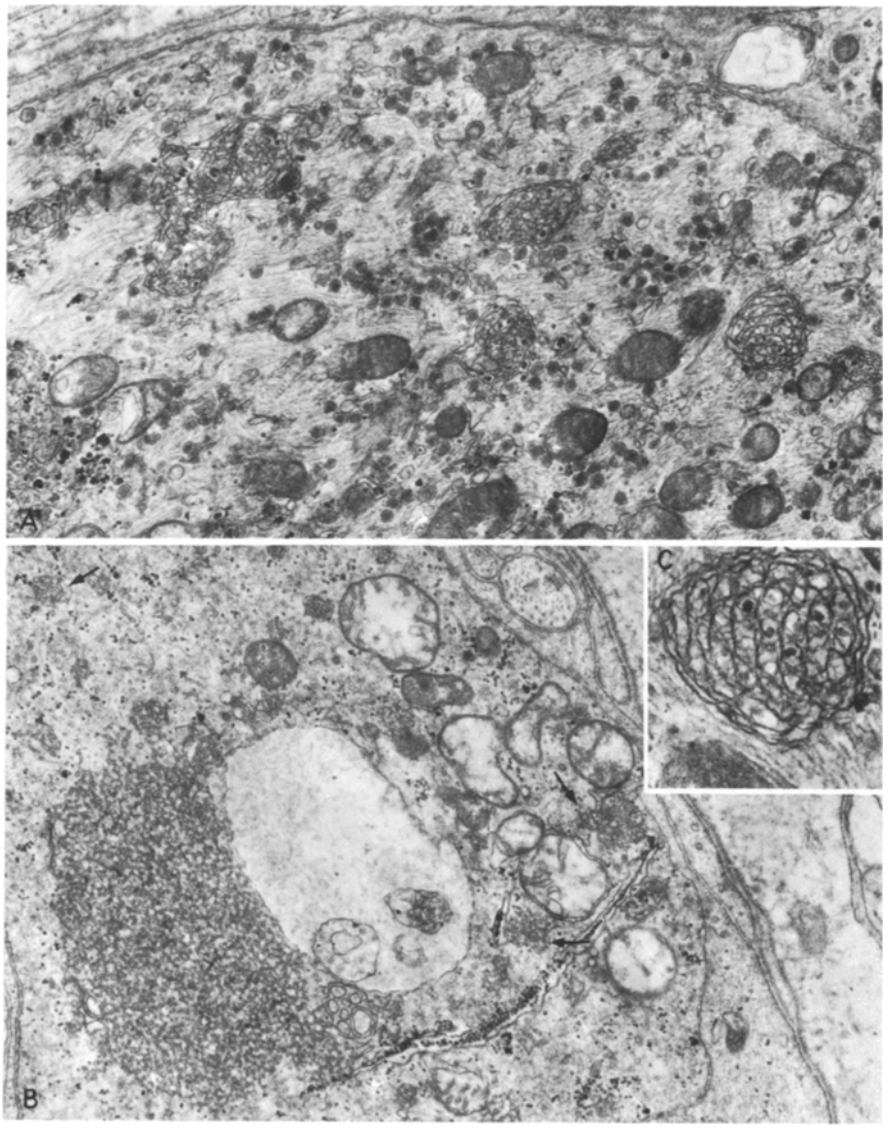

Fig. 3. A Diffuse proliferation of thin filaments and scattered small layered loops of membranes in a unmyelinated axon. Many dense core vesicles are also seen. Case 4. ×18,000. **B** Interconnected tubules are seen in a distended axon. They appear multicentric. Case 4. ×18,000 **C** Layered membranes seem to be closely related to filaments. Case 4. ×55,000

membranous structures were also present within the axon terminals, where aggregates of mitochondria and/or glycogen granules were scarcely seen.

Although the histology of the sural nerve in case 4 showed only few distended axons, accumulations of abnormal organelles in the axoplasm were easily seen with the electron microscope. Both myelinated and unmyelinated axons were affected. The abnormal structural components in the altered axon appeared

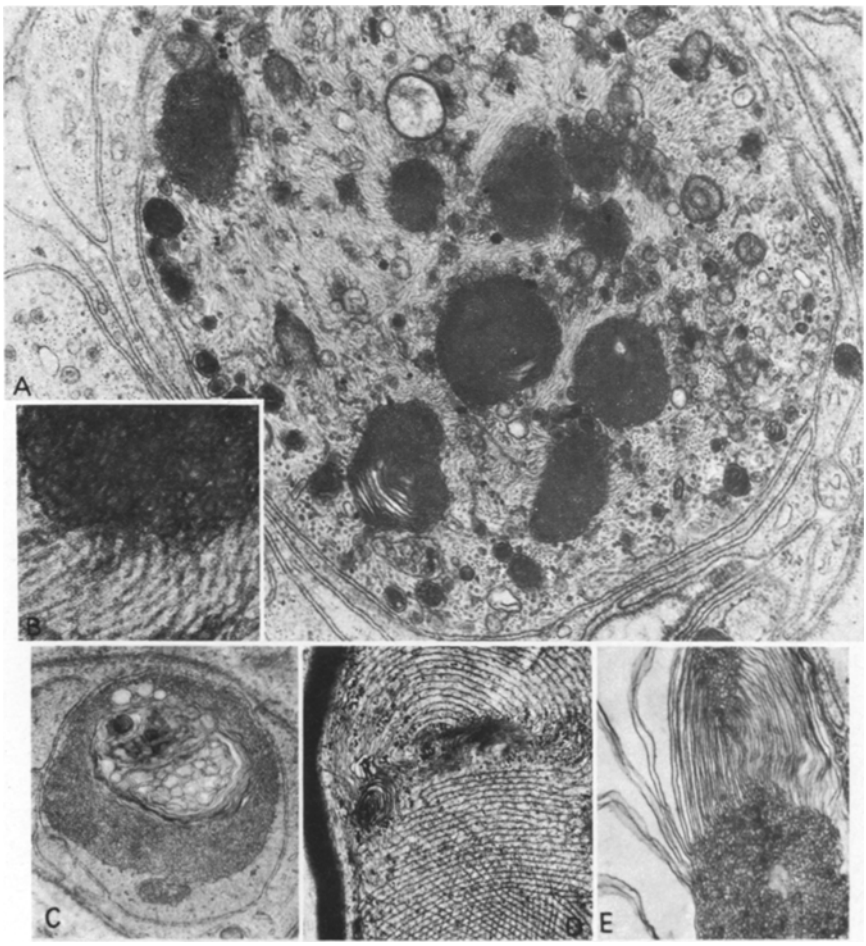

Fig. 4. A Diffuse proliferation of thin filaments and many tubulo-membranous bodies with clefts in a unmyelinated axons. Neurotubules are present only in the periphery. Case 4. ×22,000. **B** Tubulo-membranous profiles appear to be closely related to fibrils. Case 4. ×81,000. **C** Concentric membranes in the midzone of a spheroid. In the center many vacuoles are present. The outermost zone consists of tubulo-membranous structures. Case 4. ×14,000. **D** Alternating layered membranes arranged in a parallel array, being related to concentric membranes in the left field. Case 4. ×24,000. **E** Tubulomembranous profiles in the lower and layered membranes with elengated clefts in the upper fields. Both structures are closely related to each other. Case 4. ×23,000.

to have some minor differences from those seen in the central nervous system in INAD. They could be classified into four main types according to their appearance. Firstly, there were interconnected tubular profiles, the diameter of which was about 170 Å to 400 Å, which appeared multicentric in some distended axons (Fig. 3b). Secondly, membrano-tubular profiles were noted, sometimes arranged in a parallel array with elongated clefts (Fig. 4e) or with concentric lamellae (Fig. 4c). Thirdly, there were laterally layered membranes or whorl-like arrangements of layered loops which were regularly arranged

about 400 Å apart and were often curved (Fig. 4d). They presented a criss-cross appearance in some planes of sectioning. Some membranes showed spiral or more complex lamellae, with large amounts of glycogen granules in the center. Fourthly, there was a diffuse proliferation of 80 Å to 120 Å thick filaments arranged either at random or in bundles (Fig. 3a and 4a). These filaments seemed to be related to the membrano-tubular structures of type 2 (Fig. 4b) or the several layered membranes of type 3 (Fig. 3c). The tubular array of type 2 appeared to be a compact criss-cross arrangement of the filaments (Fig. 4a and 4b). The proportions of these four components varied greatly in any different diseased axon but they seemed to be closely related to each other.

The other conspicuous findings were the following; the presence of some axons showing watery axoplasm with scanty organelles, some membrane-bordered vacuoles, multivesicular bodies and dense core vesicles. Compact aggregates of glycogen granules and mitochondria were also seen. There were no tubular rings (Ametani, 1973).

The ultrastructure of the torpedoes in case 5 and 6 showed similar findings. They appeared as myelinated or unmyelinated spherical bodies, variable in size, mostly present within the granular cell layer, consisting of densely packed 100 Å filaments which were arranged irregularly or in bundles (Fig. 5b). A few mitochondria and dense bodies were seen among the fibrils. In addition, peculiar lamellate structures were seen in the torpedoes (Fig. 5a inset), which were thought to be characteristic of Purkinje cells. Some myelinated "balloons" were apparently connected to a unmyelinated segment, considered to be the initial segment of the axon of such a cell (Fig. 5a).

The ultrastructure of spheroids in case 7 and 8 showed essentially similar changes. The most prominent pathological abnormality was the occurrence of fibrillary accumulations and aggregations of complex bodies (Fig. 6a). The fibrils were composed of a short whorling and interlacing of fine filaments resembling neurofilaments; each filament was approximately 100 Å thick and showed local thickening with increased electron density occurring at irregular intervals. Lateral projections, seen in normal neurofilaments, were not clear. The amount of fibrillary material varied between bodies and even in different portions in the same bodies (Fig. 6B).

The majority of these complex bodies were round or oval and measured 0.1 to 0.9 microns across, occasionally being enclosed by double membranes. They were composed of an electron dense amorphous lamellar or granular material. Their morphology varied from body to body. They seemed to be closely related to degenerating mitochondria, in some there were focal collections of shrunken degenerative mitochondria and complex bodies simulating mitochondrial remnants and vacuoles (Fig. 6c). In still other bodies many sheets of double mitochondrial membranes were present. Although they were similar in structure to what have been called multivesicular bodies, it is more likely that they represent a transitory phase between these complex bodies and degenerating mitochondria.

Although most spheroids showed no connection with myelin sheaths, some were apparently surrounded by thin myelin sheaths or remnants of myelin.

The most impressive finding in the spheroids in case 9 was a marked accumu-

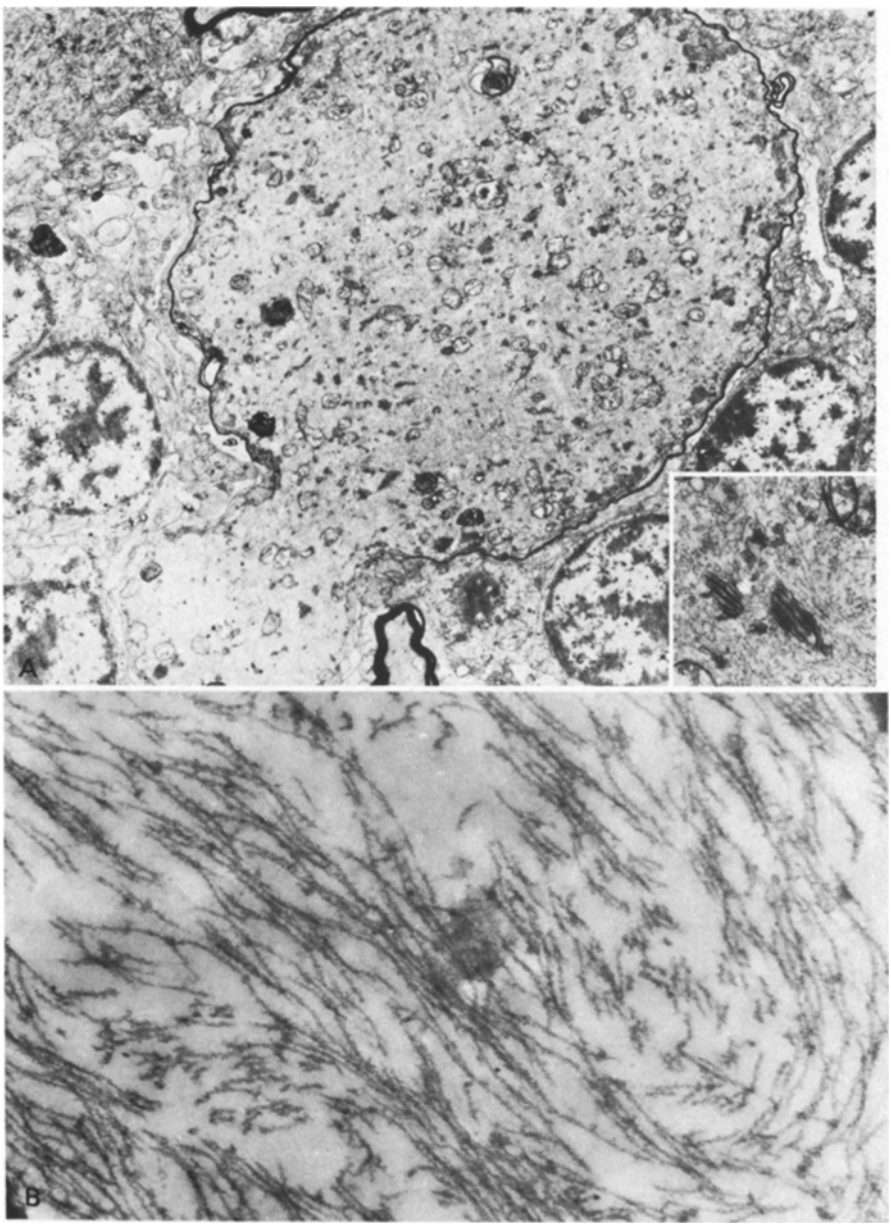

Fig. 5. A A torpedo in a myelinated axon of a Purkinje cell. These torpedos consist of accumulation of fine filaments and dense bodies, mitochondria and lamellar structures. One body is connected to a unmyelinated axon in the lower left field. Case 5. ×4,800. **B** Accumulations of 100 Å thick neurofilaments. They are arranged irregularly or in bundles. Case 6. ×46,000. Inset: Two lamellar structures. Case 5. ×50,000.

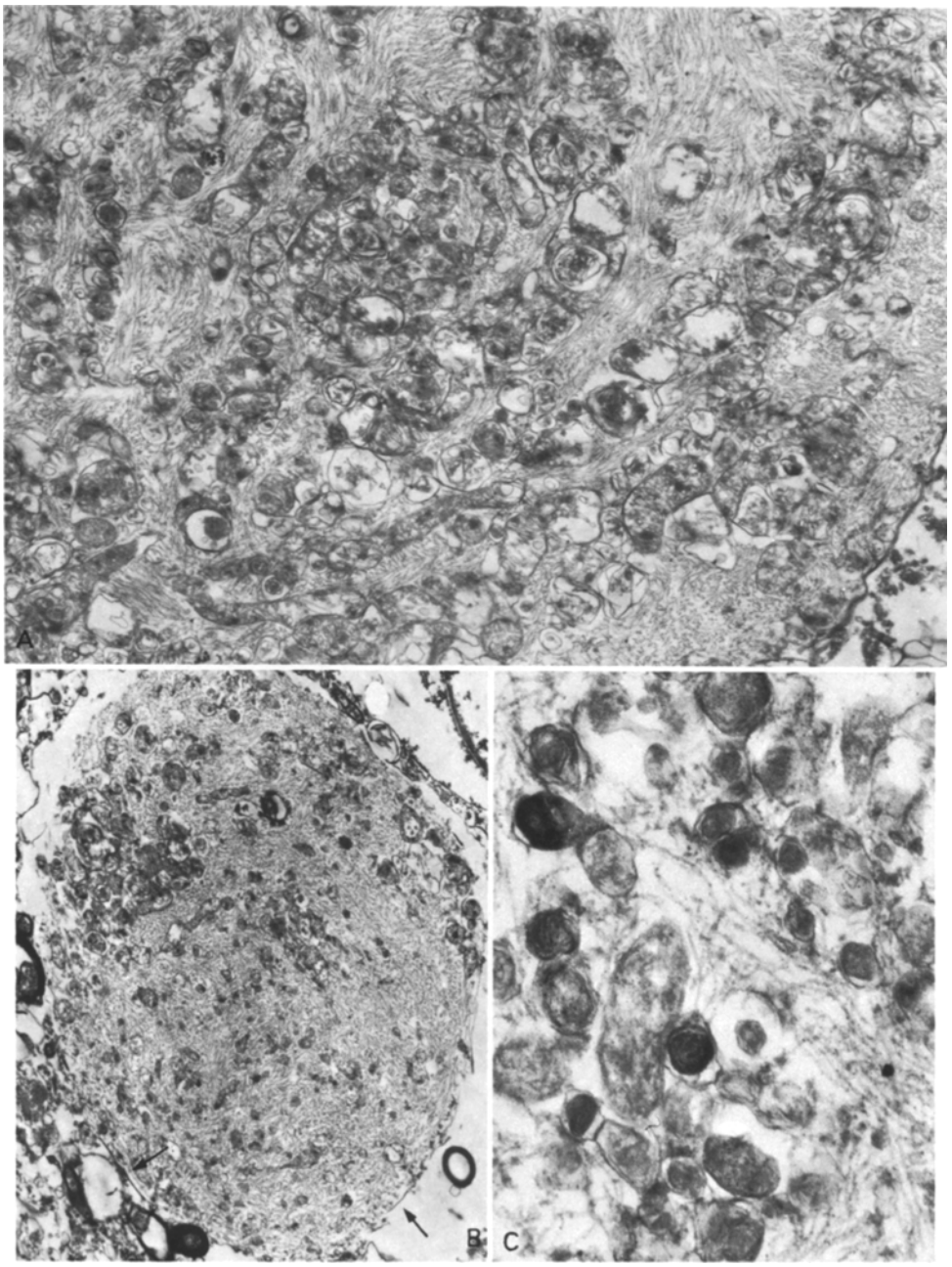

Fig. 6. A Part of a myelinated spheroid is filled with accumulations of neurofibrils and many interspersed complex bodies. The myelin sheath is very thin. Case 8, ×15,000. **B** An axon, surrounded by remnants of myelin sheath, is packed with fine filaments. In the upper left field many complex bodies are present, these scattered in the right lower field. Case 7. ×5,2000. **C** Various profiles of complex bodies. Case 8. ×52,000

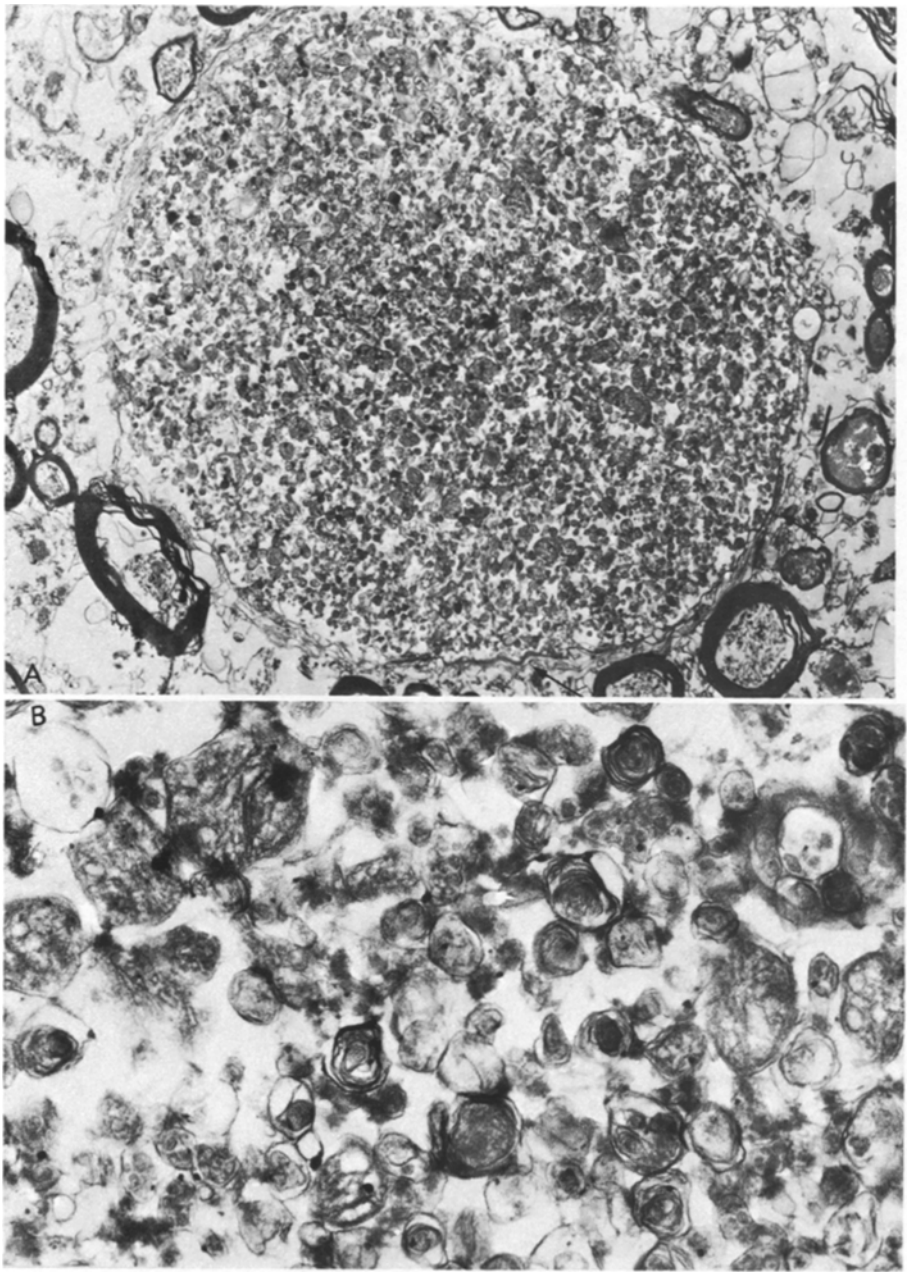

Fig. 7.A A spheroid consisting exclusively of complex dense bodies. The remnants of a myelin sheath are seen around the body (arrow). **B** Various profiles of complex bodies; many concentric bodies and multivesicular bodies. Two large bodies in the left upper field appear to be degenerating mitochondria. Case 9. A) × 5,000 B) × 34,000

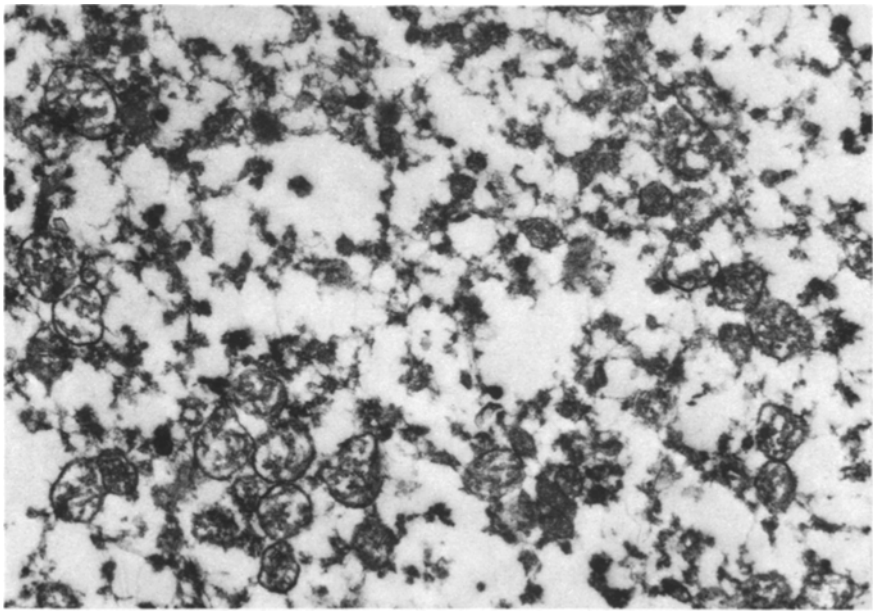

Fig. 8. Part of a spheroid body. Many degenerating mitochondria with dense granular matrix and floccular material are seen. Case 11. ×41,000

lation of closely approximated mitochondria and dense bodies in axoplasm (Fig. 7a). Many mitochondria contained amorphous dense bodies similar to those in autolysed or ishcemic tissue. The dense bodies were generally round or oval in shape and presented concentric laminations within their cores (Fig. 7b). It is noteworthy that neurofilaments did not participate in spheroid formation to any notable extent. The swollen segments were often enclosed by the remnants of a myelin sheath but some were devoid of it.

The spheroids in cases 10 and 11 showed granular disintegration of all organelles and massive floccular dense material (Fig. 8). The mitochondria were also degenerate, filamentous structures were rarely observed, and the bodies were not enclosed by myelin sheath. Nearly all normal-sized axons had lost their proper structure and were filled with amorphous floccular material only. They were also devoid of myelin.

In all the cases examined we found no twisted tubules (Lampert, 1971; straight tubules Roy, 1974) or tubular ring (Ametani, 1974)

Discussion

Under the light microscope, the spheroids in all the cases examined were seen as round, oval or pleomorphic axoplasmic masses of varying size, measuring several microns to over 200 μ. The profiles of these bodies represent focal swellings of axons (Fig. 1h–j). The histology of spheroids varies, to some extent,

from case to case, and in different bodies in the same case, so that it is difficult to distinguish bodies of a different nature from one another (as illustrated in Table 2). The best staining method for spheroids seems to be the Bodian stain, however some are poorly stained by this method, which may indicate a difference in the constituents of the bodies.

The spheroids in the INAD cases consist chiefly of interconnected tubules, stacked membrano-tubular profiles, alternating layered membranes, and accumulations of neurofilamentes. In addition, small numbers of myelin figures, mitochondria and glycogen granules are present. It seems likely that with the exception of the last mentioned changes these findings are pathogenic for INAD. A review of the ultrastructure of dystrophic axons in 19 cases of INAD reported in the literature favors this view. Abnormal mitochondrial and glycogen granules also participate in dystrophic process but are less significant. All of the other changes must be present however some of the others have been reported in amaurotic idiocy (Gonatas et al., 1965, 1968), olfactory esthesioneuroblastoma (Schochet et al., 1975; Berard et al., 1976) and Alzheimer's disease (Gonatas, 1967); The membrano-tubular structures are the most common and seem to be a cardinal feature in dystrophic axons. Alternating layered membranes are infrequently described in human INAD. Proliferation of neurofilaments is also a nonspecific change; it has been reported in various conditions such as motor neurone disease (Carpenter et al., 1968), toxic neuropathy (Rozzuto et al., 1977) and giant axonal neuropathy (Boltshauser et al., 1977; Prineas et al., 1977).

The proportions of the four principle components varies greatly in different axons. All four features seem to be closely related to each other, however, their relative differences appear to represent a chronological evolution of axonal changes. Hyperplasia of interconnected tubules or agranular endoplasmic reticulums might be considered to be the primary event in diseased axons and might evolve into membrano-tubular profiles. Figure 3 supports this view.

Torpedoes were composed ultrastructurally of accumulations of neurofilaments in the two cases examined. Mizushima et al. (1977) examined torpedoes formed after circulatory disturbance of the cerebellum and described their formation in the unmyelinated parts of Purkinje cell axons by an excessive proliferation of neurofilaments. However, this study showed that in some instances, torpedoes may also be formed in the myelinated axon (Fig. 5a).

The spheroids in both cases 7 and 8 consisted of interwoven skeins of neurofilaments and grouped mitochondria and were referred to as "filamentous". The common histopathological findings in both cases were the existence of moderate astrocytosis with partial astrogliosis and some fat-laden macrophages in or around the lesions with spheroids. In case 8 spheroids seem to develop in the area of demyelination and necrosis. These findings may indicate that the process is a relatively longstainding one, mildly destructive and also progressive.

The spheroid in case 9 consisted exclusively of complex bodies and they were called "complex body spheroids". The neuropathology revealed spheroid formation, moderate loss of nerve fibers with secondary astrocytosis and many scavenger cells in the affected areas, which indicated a relatively acute and progressive change. The destructive and "mobiler Abbau" processes were more marked in this case than in cases 7 and 8.

The "filamentous spheroid" has been described in chronic or subchronic diseases of the brain such as motor neuron disease (Carpenter, 1968; Ule, 1972), cardiomyopathy with target fibers (Liu and Gumbinas, 1974), and in experimental animals (Chou and Hartmann, 1965) and the "complex body spheroid" in more rapidly progressive diseases such as alcoholism with muscular weakness (Peress and Kim, 1974) and in experimental animals (Koenig, 1969, 1971). Their morphology in our cases (case 7 and 8) varies greatly from body to body in the same case and appears to indicate transitions between "filamentous spheroids" and "complex body spheroids". There is a noteworthy difference between the electron micrographic appearances of "Ghost cells" (Ule, 1961, 1962) and axonal swellings (Chou and Hartmann, 1965), both of which are induced experimentally by β-β-iminodipropionitrile (IDPN) in rats. The former contained more mitochondria and fewer neurofilaments than the latter; A possible reason for this difference might lie in the different method used to induce the lesions.

Axonal swellings of the Purkinje cells always consiste of neurofilaments in our experience and contain virtually no other organelles, in acute or chronic diseases (Scholte, 1971; Janota, 1973, 1974). This may be the characteristic response of this cell to certain injuries.

The spheroids in both cases 10 and 11 were present in lesions which showed no repair. It was therefore inferred that they might have been agonal induced by acute degeneration of axons secondary to circulatory disturbance.

In conclusion, apart from the spheroids in INAD, the spheroid bodies examined appear to have transitional features and nonspecific characteristics. This may reflect a nonspecific reaction of the axon to common and nonspecific noxious agents, and these bodies should not be grouped with dystrophic axons.

Ultrastructural study may give a valuable clue to the nature and morphogenesis of these lesions since most have similar histological and histochemical properties in different pathological conditions.

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References

Ametani, T.: Infantile neuroaxonal dystrophy: Light and electron microscopic observations of an autopsy case. Neuropädiat. **5**, 63–70 (1974)

Bérard-Badier, M., Gambarelli, D., Pinsard, N., Hassoun, J., Toga, M.: Infantile neuroaxonal dystrophy or Sietelberger's disease. 11. Peripheral nerve involvement: Electron microscopic study in one case. Acta neuropath. (Berl.) Suppl. **V**, 30–39 (1971)

Bérard-Badier, M., Toga, M., Gambarelli, D., Hassoun, J., Pellissier, J.F., Pinsard, N., Berard, R.: Infantile neuroaxonal dystrophy or Seitelberger's disease. IV. Autonomic nervous system involvement: Electron microscopic study in two siblings. Acta neuropath. (Berl.) **28**, 261–267 (1974)

Bérard, M., Tripier, M.F., Choux, R., Gambarelli, D., Grisoli, F., Toga, M.: Estérioneurocytome olfactif. Etude ultrastructurale d'un cas. Acta neuropath. (Berl.) **35**, 139–150 (1976)

Boltshauser, E., Bischoff, A., Isler, W.: Giant axonal neuropathy. Report of a case with normal hair. J. Neurol. Sci. **31**, 269–278 (1977)

Butzer, J.F., Schochet, S.S., Bell, W.E.: Infantile neuroaxonal dystrophy. An electron microscopic

study of a case; clinically resembling neuronal ceroid-lipofuscinosis. Acta neuropath. (Berl.) **31**, 35–43 (1975)

Carpenter, S.: Proximal axonal enlargement in motor neuron disease. Neurology **18**, 841–851 (1968)

Chou, S.M. and Hartmann, I.: Electron microscopy of focal neuroaxonal lesions produced by β-βiminodipropionitrile (IDPN) in rats. 1. The advanced lesions. Acta neuropath. (Berl.) **4**, 590–603 (1965)

Coster, W.D., Roels, H., van der Eecken, H.: Electron microscopical study of neuroaxonal dystrophy. Case report. Europ. Neurol. **5**, 65–83 (1971)

Gonatas, N.K., Goldensohn, E.S.: Unusual neocrotical presynaptic terminals in a patient with convulsions, mental retardation and cortical blindness: an electron microscopic study. J. Neuropath. exp. Neurol. **24**, 539–562 (1965)

Gonatas, N.K., Anderson, W., Evangelista, I.: The contribution of altered synapses in the senile plaque: An electron microscopic study in Alzheimer's dementia. J. Neuropath. exp. Neurol. **26**, 25–38 (1967)

Gonatas, N.K., Baird, H.W., Evangelista, I.: The fine structure of neocortical synapses in infantile idiocy. J. Neuropath. exp. Neurol. **27**, 39–49 (1968)

Gonatas, N.K., Evangelista, I., Walsh, G.O.: Axonic and synaptic changes in a case of psychomotor retardation: An electron microscopic study. J. Neuropath. exp. Neurol. **26**, 179–199 (1967)

Hager, H.: Regenerationsvorgänge am Neuron des zentralen Nervensystem. Verh. Dtsch. Ges. Pathol. **50**, 255–274 (1966)

Hedley-Whyte, E.T., Gilles, F.H., Uzmen, B.G.: Infantile neuroaxonal dystrophy. A disease characterized by altered terminal axons and synaptic endings. Neurology **18**, 891–906 (1968)

Herman, M.M., Huttenlocher, P.R., Bensch, K.G.: Electron microscopic observations in infantile neuroaxonal dystrophy. Report of a cortical biopsy and review of the recent literature. Arch. Neurol. **20**, 19–34 (1969)

Janota, I.: Pathological changes in the terminal parts of Purkyne cell axons in the dentate nucleus of the cerebellum. J. Neurol. Neurosurg. Psychiat. **36**, 596–603 (1973)

Janota, I.: Neurofibrillary change in the terminal parts of Purkyne cell axons in the dentate nucleus of the cerebellum following destructive cortical lesions in the cerebellar hemisphere in the cat. An electron microscopic study. J. Neurol. Sci. **22**, 367–373 (1974)

Jellinger, K.: Neuroaxonal dystrophy: Its natural history and related disorders. In: Progress in neuropathology. Vol. 111, pp 129–180 New York: Grune and Stratton. 1973

Kamoshita, S., Neustein, H.B., Landing, B.H.: Infantile neuroaxonal dystrophy with neonatal onset. Neuropathologic and electron microscopic observations. J. Neuropath. exp. Neurol. **27**, 300–322 (1968)

Koenig, H.: Experimental production of acute neuroaxonal dystrophy. J. Neuropath. exp. Neurol. **28**, 173–174 (1969)

Koenig, H.: Some observations on the experimental production of acute neuroaxonal and synaptosomal dystrophy. Acta neuropath. (Berl.) Suppl. **V**, 126–131 (1971)

Kolkmann, F.W., Rana, B.N.: Über die submikroskopische neuropathologie des experimentellen Vitamin E-Mangels der Ratte. Zentralbl. Allg. Path. **114**, 574 (1971)

Lampert, P.W.: A comparative electron microscopic study of reactive, degenerative, regenerating and dystrophic axons. J. Neuropath. exp. Neurol. **26**, 345–368 (1967)

Lampert, P.W.: Fine structural changes of neurites in Alzheimer's disease. Acta neuropath. (Berl.) Suppl. **V**, 49–53 (1971)

Liu, H.M., Gumbinas, M.: Axonal filamentous spheroid associated with cardiomyopathy with "targetoid fiber". I. Clinical, histological and electron microscopic studies. Neurology **24**, 547–554 (1974)

Martin, J.J., Martin, L.: Infantile neuroaxonal dystrophy. Ultrastructural study of the peripheral nerves and of the motor end-plates. Europ. J. Neurol. **8**, 239–250 (1972)

Mizushima, S., Oyanagi, S., Ishi, T.: an ultrastructural observation on torpedoes in the human degenerative cerebellum. J. Clin. Electron Microscopy. **31**, 672–673 (1976)

Nakashima, K., Makino, T., Kinoshita, J., Yagishita, S.: A peculiar case of panencephalopathy with widespread distribution of plaques, status spongiosus and demyelination. Adv. Neurol. Sci. **20**, 14–23 (1976)

Peress, N.S., Kim, B.H.: Profound muscle weakness associated with axis cylinder ballooning. Acta neuropath. (Berl.) **28**, 87–92 (1974)

Prineas, J.W., Ouvrier, R.S., Wright, R.G., Walsch, J.C.: Giant axonal neuropathy – A generalized disorder of cytoplasmic microfilament formation. J. Neuropath. exp. Neurol. **35**, 458–470 (1976)
Reyes, M.G., Chokroverty, S., Masdeu, J.: Thalamic neuroaxonal dystrophy and dementia in Hodgkin's disease. Neurology. **26**, 251–253 (1976)
Rizzuto, N., Terzian, J., Galiazzo-Rizzuto, S.: Toxic polyneuropathy in Italy due to leather cement poisoning in shoe industries. A light and electron microscopic study. J. Neurol. Sci. **31**, 343–354 (1977)
Roy, S., Datta, C.K., Hirano, A., Ghatak, N.R., Zimmermann, H.M.: Electron microscopic study of neurofibrillary tangles in Steel-Richardson-Olszeqski syndrome. Acta neuropath. (Berl.) **29**, 175–179 (1974)
Sandbank, U., Lerman, P., Geifman, A.: Infantile neuroaxonal dystrophy: Cortical axonic and presynaptic changes. Acta neuropath. (Berl.) **16**, 342–352 (1970)
Seitelberger, S.: Neuropathological conditions related to neuroaxonal dystrophy. Acta neuropath. (Berl.) Suppl. **V**, 17–29 (1973)
Schochet, S.S., Peters, B., O'Neal, J., McCormick, W.F.: Intracranial esthesioneuroblastoma. A light and electron microscopic study. Acta neuropath. (Berl.) **31**, 181–189 (1975)
Scholte, W.: How long can degenerating axons in the central nervous system produce reactive changes. An electron microscopic investigation. Acta neuropath. (Berl.) Suppl. **V**, 40–48 (1971)
Shimono, M., Ohta, M., Asada, M., Kuroiwa, Y.: Infantile neuroaxonal dystrophy. Ultrastructural study of peripheral nerve. Acta neuropath. (Berl.) **36**, 71–79 (1976)
Sengel, A., Stoebner, P.: Intérêt de la biopsie neuromusculaire dans le diagnostic de la dystrophie neuroaxonal infantile. Etude ultrastructurale de 3 cas dont 2 familiaux. Acta neuropath. (Berl.) **21**, 109–116 (1972)
Toga, M., Berard-Badier, M., Gambarelli, D.: La dystrophie neuroaxonale infantile ou maladie de Seitelberger. Acta neuropath. (Berl.) **15**, 327–350 (1970)
Terpan, K., Caresm, H.L.: Histopathology of the nervous system in carnosinase enzyme dificiency with mental retardation. Neurology **22**, 644–655 (1972)
Ule, G.: Zur Ultrastruktur der Ghost-Cells beim experimentellen Neurolathyrismus der Ratte. Zeitschr. Zellforsch. **55**, 130–142 (1962)
Ule, G.: Progressive neurogene Muskelatrophie bei neuroaxonaler Dystrophie mit Rosenthalschen Fasern. Acta neuropath. (Berl.) **21**, 332–339 (1972)
Wolter, J.R.: Axonal enlargements in the nerve fiber layer of the human retina. Amer. J. Ophthalmol. **65**, 1–12 (1968)
Yagishita, S., Kimura, S.: Infantile neuroaxonal dystrophy (Seitelberger's disease). Histological and electron microscopical study of two cases. Acta neuropath. (Berl.) **29**, 115–126 (1974)
Yagishita, S., Kimura, S.: Infantile neuroaxonal dystrophy (Seitelberger's disease). A light and ultrastructural study. Acta neuropath. (Berl.) **31**, 191–200 (1975)

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