HEREDOPATHIA ATACTICA POLYNEURITIFORMIS

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A familial syndrome was described by Sigvald Refsum of Norway, under this title, as a new contribution to the literature on hereditary recessive diseases of the nervous system. He classified the clinical features at first as heredoataxia hemeralopica polyneuritiformis. However, being unable to prove anatomically and pathologically its relationship to the familial heredo-ataxias (Friedreich or Pierre Marie) with known variations, he introduced it under a new clinical name, heredopathia atactica polyneuritiformis. Eight-hundred fourteen bibliographic (for the most part indirectly bearing on the subject) references are analyzed in his monograph.

Refsum's five cases, ranging in ages from 25 to 41 years, occurred in two genealogically well documented, unrelated families in Norway. The consanguineous marriages (first cousins) supported the speculation of an hereditary transmission. All cases presented nyctalopia, restriction of the visual fields, nystagmus, symmetrical polyneuritic-like pareses, predominantly peroneal amyotrophy with reflex and sensory disturbances, and incoordination in walking with vague cerebellar signs. In addition, three patients of one family had retinitis pigmentosa, two had miosis and bilateral deafness. In three, the cerebrospinal fluid showed an increase in the total protein from 100 to 165 mg. per cent; three demonstrated myocardial involvement. None of the patients presented pyramidal or extra-pyramidal signs, speech disorders, or obvious psychopathology.

Reviewing our cases of cerebellar or spinocerebellar degeneration, of amyotrophies, and of retinitis pigmentosa alone or associated with congenital deafmutism, Refsum's syndrome was encountered only in an incomplete form. The following case documents such a complex clinical syndrome.

CASE REPORT

History. (B. A.) aged 25 years, was admitted to the Wisconsin General Hospital in 1935 because of slowly progressing night blindness since the age of 18 years. The family history was not contributory; there were no familial similarities nor abnormalities in parents and four brothers. The parents of the patients were first cousins and Jewish.

The patient was of asthenic constitution and normal intelligence. He had small irregular pupils, slight nystagmus, advanced retinitis pigmentosa, markedly constricted visual fields (studies to correlate the nyctalopia with retinitis pigmentosa were unsuccessful), intention tremors, and hyporeflexia with absent abdominal reflexes. There were also developmental abnormalities in both hands and feet with an overgrowth of the second toe and exostosis of the sternum.

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The patient subsequently visited the Mayo Clinic three times. Resumés of the three admissions to the Clinic were provided by Dr. Henry Woltman.

Findings in 1936: "anosmia, bilaterally reduced hearing, questionable left Achilles tendon reflex, slightly ataxic gait with action tremors bilaterally; thread-like retinal arteries, retinitis pigmentosa with concentric contraction of the visual fields, anomalous bony development of hands and feet. Clinical classification: Laurence-Moon-Biedl syndrome."

Findings in 1938: "Had developed marked weakness of both lower extremities particularly below the knees, patellar reflexes reduced bilaterally; Achilles reflexes absent, appreciation of movements of the joints was impaired, fundi and ears unchanged. Clinical impression: Primary cerebral degeneration, mixed syndrome."

Findings in 1939: "very small pupils with diminished light reaction, total deafness on the left, reduced hearing on the right; labyrinths normal; marked weakness in lower extremities; impairment of vibratory sense, ataxia and steppage gait and greatly reduced tendon reflexes. The atrophy in the lower extremities had progressed. Blood cholesterol, cholesterol esters, lecithin, fatty acids and total lipoids were within normal range. Diagnosis: Marked atrophy in the lower extremities and peripheral neuritis."

The patient was seen in September 1947 by us, when he complained of wasting and weakness of the legs, vague pains in the legs, especially thighs, inability to walk without support, bilateral deafness and progressive failing of vision. The family history revealed that a nephew, three years of age, had "purposeless movements of the hands and severe impairment in balancing and walking; he is a bright child." The patient, now aged 37 years, stated that since the age of 14 and 15 he was clumsy in sports, stumbled often and walked with a steppage gait when tired. He had been a good student and mixer, graduated with honors from high school, and attended a business college. He adjusted himself to his physical disabilities by attending the school for the handicapped, studied Braille and prepared himself for the activities and a vocation of a blind person. He reads a great deal, is cheerful, has many friends and gives a good chronologically well organized history. At the age of 18, without progressive impairment or pain in the legs, he noticed night blindness and funnel-shaped vision. The reduced hearing, left greater than right, had progressed since 1936 resulting in bilateral deafness. During the past years he had had dull pains in his thighs, but no subjective sensory changes. Muscular atrophies of his legs, first observed in 1938, slowly progressed over a period of ten years with increasing static equilibratory difficulties. Since 1947 he has been very dyspnoic. He has had scarlet fever in childhood; otherwise gives a normal history until the age of 14 years.

Examination. The patient was described as short and well nourished. His falsetto-like voice was associated with grunting dysarthria. The skin was without ichthyotic, neurofibrotic or xanthomatous alterations; nowhere were there gout-like (cholesterinlipoides) tendon swellings. The cyanotic, edematous feet were not of the *pes cavus* type. Nowhere was there enlargement of the nerve trunks, nor was there tenderness on pressure over nerves; the joints were free of involvement. The fifth fingers revealed congenital shortening and overdevelopment of their metacarpal and middle phalanges. The 3rd, 4th, and 5th metatarsals presented bilateral congenital shortening with overgrowth and elongation of the second toe in its metatarsal and all phalanges (not neuritic bony atrophy). There was no kyphoscoliosis, no congenital fusion of the vertebrae. Nystagmus was present in recumbent position only; there was extreme miosis without suggestion of Horner's syndrome. Neither pupil reacted to light or in convergence; they could not be dilated by mydriatics; attempts to dilate them resulted in glaucomatous attacks. The visual fields showed severe concentric contraction. Bilateral pigment degeneration of the retina and very attenuated retinal arteries were present. There was complete anosmia and bilateral nerve deafness without vestibular impairment. Audiograms showed: right, 100% deafness, left, 80% to 90% deafness. The blood pressure was 136 systolic 90 diastolic, peripheral pulses were 80 to 124 per minute; an electrocardiogram was normal. Urogenital-rectal functions and tests were normal. Muscle power, sensory status, and deep reflexee were normal in his arms and trunk. Pronounced muscle atrophy with functional disability increasing distally

to paralysis was present in the lower extremities including the pelvic girdle. The peroneal, tibialis, and foot muscles, right more than left, were firmer than the calf muscles, but not painful. The adductor and hamstring groups were less impaired. The iliopsoas were of good strength bilaterally. There were no fasciculations nor fibrillations. Station was unsteady and required support. Walking was attempted with the aid of crutches and with forward hip swinging of the legs. The deep reflexes in the lower extremities were absent. There were no abnormal reflexes. Sensations of touch, pain, and temperature were preserved, but proprioceptive sense was greatly impaired. Handwriting was disturbed due to fatigue tremors. Truncal incoordination, faulty pointing with marked leg ataxia were present.

The laboratory findings were negative except for a total protein of 185 mg per cent in the cerebro spinal fluid, and the colloidal gold curve was 0012322100. Biopsy of the right superficial peroneal nerve disclosed a firm and hypertrophic nerve. Biopsy of the long peroneal muscle showed atrophic, reddish muscle substance. Electrical studies were not conclusive; there was no reaction of degeneration.

Course. Throughout the thirteen days of hospitalization he was markedly dyspnoic and confused. Increased labored respiration (no signs of infection) with a thready pulse, profuse diaphoresis, progressive cyanosis, marked abdominal distension suggested cardiovascular collapse.

Medullary vagal crisis was considered; an endotracheal tube was inserted and supportive medication given, but without benefit.

Necropsy findings

(Autopsy was performed three and one-half hours after death.)

Lungs. There are many small areas of ecchymosis present on the posterior surfaces of lower portion of the upper and lower lobes of both lungs. A moderate amount of pulmonary edema and bronchiolitis is also present. The trachea and bronchi are filled with a small amount of blood-tinged frothy fluid.

Heart. There is moderate vacuolation and basophilic degeneration of muscle fibers.

Aorta. Several small yellow plaques are found in the intima near the coronary ostia.

Liver. Extensive fatty degeneration is present.

Kidneys. Numerous fat globules are noted in the tubular epithelium; there are also a few albuminous casts.

Testicles. Incomplete spermatogenesis.

Pituitary. Small chromophobe adenoma.

Muscle (gastrocnemius, iliopsoas, diaphragm and rectus abdominis). All appear atrophic with reduction in size of the individual fibers, but with preservation of cross striations (fig. 1). A patchy increase in connective tissue and a minimal amount of adipose tissue are present between muscle bundles.

Bone Marrow. Normal.

Brain. It weighs 1360 grams. There is some thickening of the pia arachnoid over both frontal lobes; the pacchionian granulations are more conspicuous than usual. There is definite thickening of the optic nerves and chiasm. There is a relative increase of white as compared to the grey substance, with normal basal ganglia and a normal cerebellum, pons, and medulla oblongata.

The spinal cord is very firm throughout. The cut sections reveal a yellowish discoloration of the anterior horns which appear to be reduced in size.

Peripheral nerves (peroneal, lumbosacral plexus, intercostals, sympathetics and vagus). These appear to be edematous and somewhat larger than normal.

Microscopic observations

Cerebrum. The pia-arachnoid is thickened throughout and the smaller arteries contain an increase in intimal tissue. In some areas there is swelling and prominence of nerve fibers with occasional satellitosis. Very many amyloid bodies are present, particularly in the

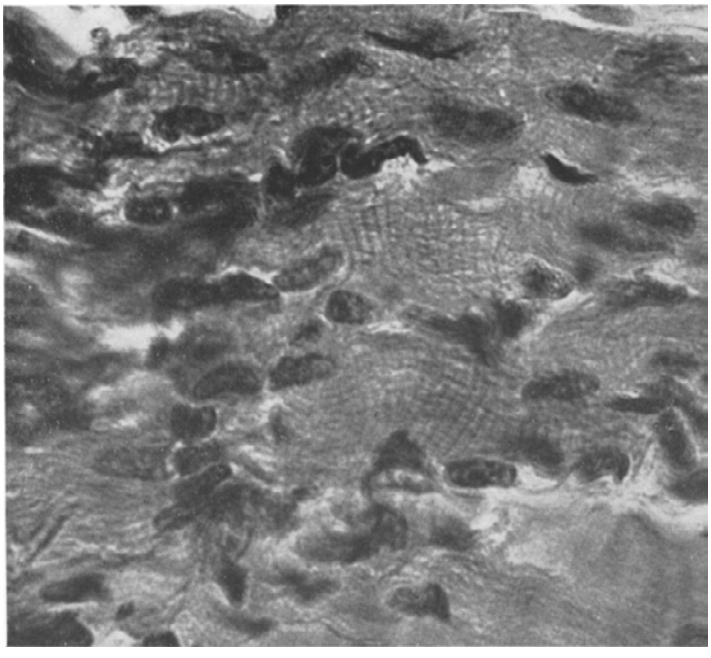


FIG. 1. Longitudinal section of gastrocnemius muscle illustrating microfibers with increase in the number of nuclei. Cross striations are still present. Hematoxylin and Eosin stain, × 900.

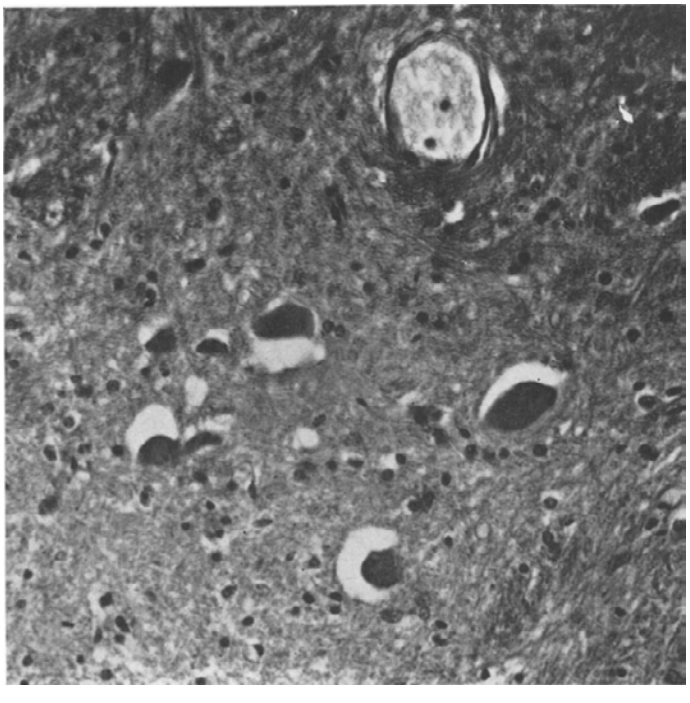


FIG. 2. Vagal nucleus showing paucity of cells and chromatolysis of those remaining. Hematoxylin and Eosin stain, × 200.

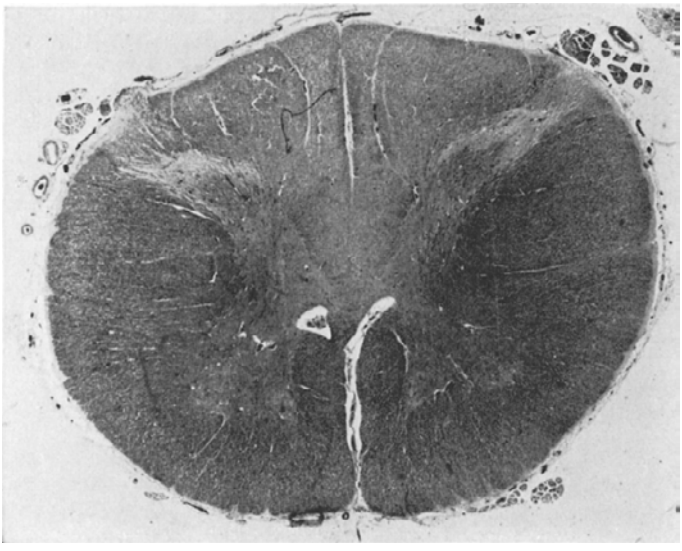
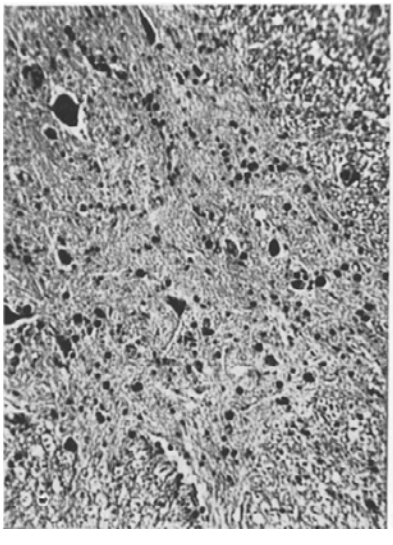


FIG. 3. Lumbar segment of the spinal cord, showing moderate demyelination of the posterior columns. Geist's myelin sheath stain of the spinal cord, × 10.



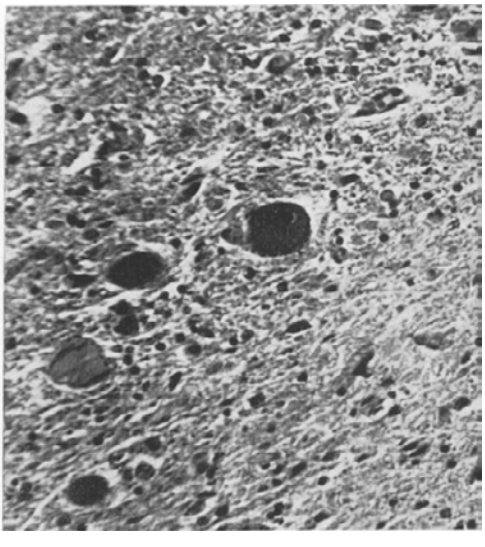


FIG. 4. FIG. 5.

FIG. 4. Section of anterior horn, showing a paucity of anterior horn cells and chromatolysis of remaining cells. Hematoxylin and Eosin stain, × 80.

FIG. 5. Higher magnification of field in Figure 4, showing swelling of nerve cells with displacement of nuclei. Hematoxylin and Eosin stain, × 200.

outer molecular layer. There is a scattered increase of oligodendroglia cells. Some nerve cells show pyknosis. Perivascular loss of substance in the form of mild demyelination is present.

Thalamus. Congestion with many amyloid bodies, especially near the ventricular lining.

Cerebellum. The meningeal arteries are congested in the thickened leptomeninges. Again, many amyloid bodies are observed throughout the outer molecular layer and white mat-

ter. Some of the Purkinje cells show pyknosis and shrinkage of their cytoplasm. In the dentate nuclei there are many nerve cells containing a yellow pigment in their cytoplasm, and eccentric nuclei.

Pons and Peduncles. The blood vessels are congested. Many amyloid bodies are seen in the periphery of the peduncles about the fourth ventricle. The ganglion cells show degenerative changes, mainly pyknosis.

Medulla oblongata. Many amyloid bodies are present in the floor of the fourth ventricle and in the periphery of the brain stem. The nerve cells of the vagal nuclei show degenerative changes and a decrease in number (fig. 2).

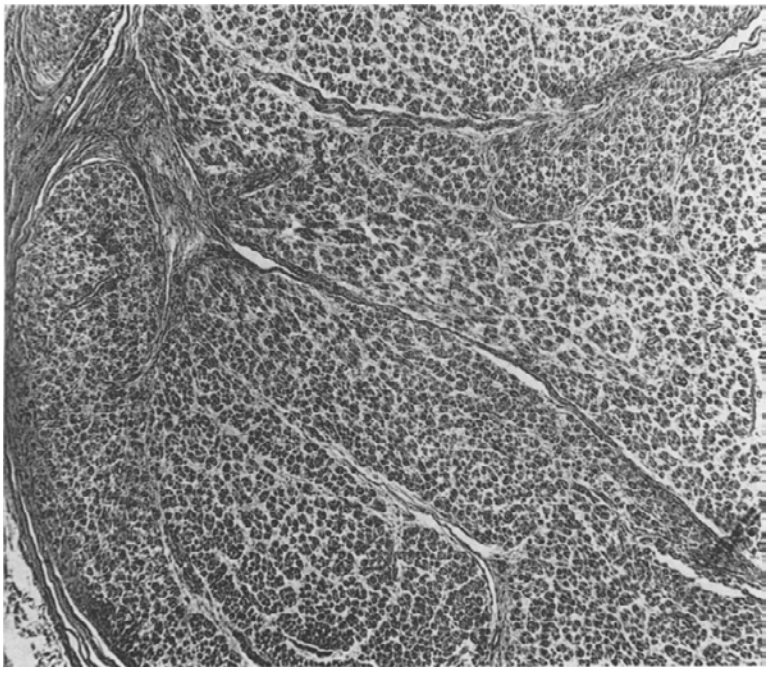


FIG. 6. Cross section of sympathetic nerve, showing separation of individual nerve fibers and increase in thickness of the perineurium and endoneurium. Crossman's trichrome stain, × 40.

Olfactory Nerve. There is increased gliosis at the periphery and infiltration with amyloid bodies.

Optic Nerve and Chiasm. The surrounding leptomeninges are thickened and hyaline in character. There is a heavy infiltration of these structures by amyloid bodies. The endoneurial tissue is increased in amount, and coarse.

Eye (Examined by Dr. P. Duehr).* The retina showed advanced atrophy, all layers being abnormally thin. The ganglion cell layer, inner molecular layer, and outer molecular layers were all represented by a smaller number of cells than is usually seen. The rods and cones have entirely disappeared. The pigment epithelium of the retina is atrophic, and there is almost no pigment present in this layer. Bruch's membrane is degenerated and cannot be seen in many areas. The choroid, sclera and optic nerve appear normal. Diagnosis: Retinitis pigmentosa.

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8th Nerve. Infiltration by amyloid bodies.

Petrous Bone (Examined by Dr. T. H. Bast of the Anatomy Department, University of Wisconsin). The following observations were made: (1) Organ of Corti is not well preserved; (2) There is an area of swelling and loss of definition in the nerve to the lateral and superior canal ampulla; (3) A bony otosclerotic patch with fatty bone marrow in fissular region replacing, in part, a residual cartilage; (4) Base of the bony spiral lamina is largely degenerated where it joins the modialus. There is a marked increase in pigment cells in this region; (5) The spiral ligament has lost its tendinous character and appears reticular.

Vagus Nerve. Contains a large number of amyloid bodies and shows patchy increase of fibrous tissue and of the glial elements.

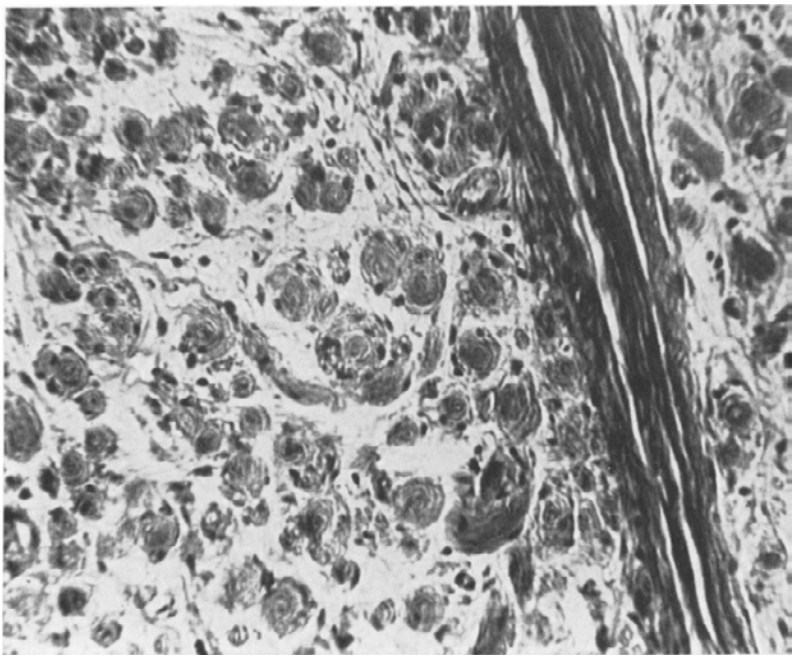

FIG. 7. The myelin has been replaced by concentrically layered connective tissue (onion skin effect). The myxomatous appearance of the endoneurial tissue is seen in this section. Crossman's trichrome stain, × 175.

Spinal Cord. There is moderate demyelination of the posterior funiculi and in the region of the posterior horns (fig. 3). The number of anterior horn cells is definitely reduced, with the remaining cells showing chromatolysis or pyknosis and condensation (figs. 4, 5). Similar changes were noted in the posterior horn cells. The white matter, especially at the periphery, is infiltrated by many amyloid bodies. The anterior and posterior nerve roots show fragmentary demyelination and a marked proliferation of connective tissue of the same character as in the peripheral nerves. The blood vessels of the spinal cord exhibit hyalinization and an increased eosinophilic affinity of their walls.

Peripheral and Autonomic Nerves (peroneal, lumbosacral, plexus, intercostal and sympathetic). The changes in these structures differ only in the degree of involvement. The perineurium and endoneurium are thickened, and some nerve bundles at the periphery contain a homogenous eosinophilic staining material, probably serous fluid. Individual nerve fibers have disappeared, and were replaced by concentric layering connective tissue in onion

bulb fashion (figs. 6, 7). The axons have completely disappeared in some fibers, while other fibers contain several fibrils (fig. 8). Toluidine blue preparations reveal an increase in metachromatic material between the separated fibers. Upon incubation of the tissues with hyaluronidase, the metachromatic substances decreased almost to the point of disappearance. Many mast cells are present between the nerve bundles. All blood vessels about the nerves reveal an intimal hyperplasia.

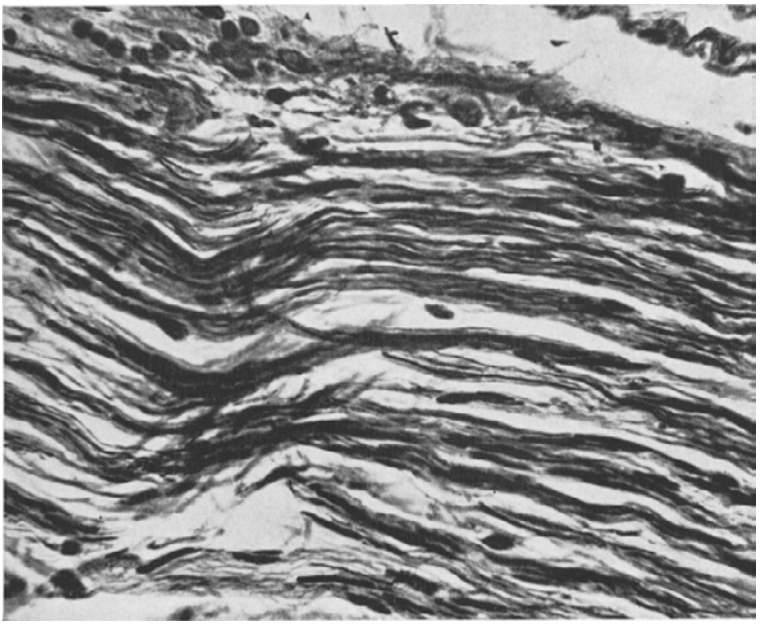

FIG. 8. Longitudinal section of sciatic nerve, showing nerve fibrils coursing through the connective tissue which has replaced the myelin of the individual fibers. Van Gieson and Bodian stain, × 350.

Comment. From a pathologic standpoint, this case belongs in the group of interstitial hypertrophic neuritides. The changes in the peripheral nerves, the demyelination of the posterior columns, and the degeneration of the motor cells are consistent with such a diagnosis. The primary changes in this disease are not known but have been presumed to affect the vascular tree (2). The earliest significant alteration observed is an accumulation of fluid between the nerve fibers; later the nerve becomes myxomatous. At this time proliferation of the Schwann cells becomes evident, and finally there is a connective tissue proliferation with the formation of reticular tissue about the nerve fibers. This is apparently the mechanism of the "onion skin-like" formation.

Some authors have claimed a pathognomonic value for this lesion. However, it has been shown that it may occur in the other peripheral neuropathies such as neuromuscular atrophy (2), Von Recklinghausen's disease (2, 5, 6), multiple sclerosis (2, 3), and recurrent polyneuritis (6).

It would seem from the evidence presented that the mucoid substance responsible for the myxomatous appearance is hyaluronic acid or a related substance.

This is of interest since the acid mucopolysaccharides may participate in the formation of collagenous tissue.

Secondary to the connective tissue changes there is a degeneration of the nerve axons and a slowly progressive demyelination which begins distally and progresses proximally. It is felt that this is due to newly formed collagenous tissue enveloping and impinging upon nerve structures.

Subsequent to the nerve lesions the posterior columns of the spinal cord undergo demyelination which is most marked in the lumbosacral region. Degeneration and loss of motor cells in the ventral horns also occur relatively late in the disease process.

DISCUSSION

The multiplicity of clinical findings leads to much speculation in an effort to fit them into some form of heredo-degenerative disorder. Night-day blindness with advanced retinitis pigmentosa and deafness are known manifestations of hereditary disorders, when associated with other signs and symptoms of the central nervous system disturbance. They are most frequently grouped with various grades of mental deficiency. Dysdactylism, retinitis pigmentosa and muscular atrophy or dystrophy remind one, even in the absence of mental deficiency and adiposogenital dystrophy, of an abortive Laurence-Moon-Bardet-Biedl syndrome. The vast literature on familial amaurotic idiocy includes extensive studies of the juvenile form of Spielmeyer, of Vogt-Stock and the adult form of Mayou-Batten and that of Kufs (8). Kuf's type of amaurotic idiocy occurs in the third decade and is associated with retinitis pigmentosa, neurogenic deafness, cerebellar ataxia of the Marie type and organic dementia. However, the clinical investigation eliminated diffuse Schaffer-Spielmeyer ganglion cell pathology, and therefore gangliocellular heredo-degeneration was rejected. Spielmeyer, Hassin (9), Josephy, Weil and others agree, that if no Schaffer-Spielmeyer process occurs in the ganglion cells, a different nosological classification should be considered. Globus (10, 11) states: "Schaffer's ganglion cell process is and remains the common connecting link among cases belonging to the large group of amaurotic idiocy." We are aware that hereditary diseases can be expressed in complex phenotypic manifestations, and that the later the onset of familial amaurotic idiocy occurs, the more atypical may be its clinical course and its symptoms.

To the question whether our patient belongs to the heredoataxias, the answer is no. Retinitis pigmentosa and deafness (Barrett, Devic, Lenoble-Aubineau, Clauss) were considered; Sjogren and Grinker reported neural muscular dystrophy and neuritic progressive atrophy with heredoataxias. Kinnier-Wilson believes, however, that peroneal atrophy is another disease form with which some Friedreich's ataxia cases are associated or into which heredoataxias may merge. Rombalt and Riley reported interesting abortive types of Friedreich's disease within three generations with spontaneous arrest. An analysis of progressive neurospinal amyotrophy—the Charcot-Marie-Tooth type—finds no counterpart with clinical complications as in our case. Nevertheless, malformations and

symptoms of heredito-degenerative disease are not uncommon in the elderly cases of stationary progressive muscular dystrophy especially in those starting as Erb's juvenile types. These cases present hereditary ataxia, familial spastic paralyses, congenital muscle defects, bony alterations with shortening of fingers especially thumbs or exostoses with deaf-mutism.

Progressive hypertrophic polyneuropathy has similarities with the neurospinal forms of amyotrophy and may resemble clinically Friedreich's ataxia. The increase of interstitial tissue with De Bruyn-Stern's plasmatic swelling in the peripheral nerves is not as characteristic as the lamellar hypertrophy of the sheaths of Schwann, therefore clinically palpable hypertrophic nerve trunks (neuromegalia peripherica progressiva of Tarassewitch and Michejew) are not essential. Furthermore, the onset does not have to begin in "de l'enfance" nor is familial occurrence necessary. Déjerine-Sottas, Boveri, Schaller-Hoffmann, De Bruyn-Sterna, Dwidenkow, Wolf-Rubinowitz-Burchell (12) (three cases) and Krücke, to name only a few contributors to be topic of hypertrophic neuritis, reported pupillary changes with various degrees of light reaction, nystagmus, scanning speech, intention tremors, slowly developing limb paralysis of the atrophic type, with or without diminution of sensibility, ataxia with other variations. The age of onset is under or after 21 years, the duration of the phasic development and its rapidity determine the clinical stage and the degree of neuropathology. It is a rare disease; Schaller described his first case in 1912, and only after 23 years could he describe with Newmann a second case.

Our case presents many features of Refsum's syndrome. Clinically we placed the case, however, into the complex disease of progressive interstitial polyneuropathy.

CONCLUSION

A case is described of Refsum's Heredopathia atactica polyneuritiformis. It is clinically a complicated syndrome of familial progressive interstitial hypertrophic polyneuritis of the Déjerine-Sottas variety. Its ultimate cause, whether endogenous or exogenous, hormonal or neural, is unknown. Many combination types of heredo familial diseases are clinically, pathologically and genetically recorded in the literature.

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