A CASE OF DIFFUSE NEUROFIBROMATOsis INVOLVING THE CRANIAL, PERIPHERAL AND SYMPATHETIC NERVES, ACCOMPANIED BY TUMOR OF THE HYPOThALAMUS

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In 1860 Kölliker (1) described a disease which was chiefly characterized by multiple discrete tumors in the skin and subcutaneous tissues. In 1882 von Recklinghausen (2) established the relationship between these tumors and the peripheral nerves. He believed them to be neoplastic hyperplasias of the fibrous supportive tissue of the nerve trunks. He described the disease in its clinical aspects as it is recognized today.

Classically the disease presents multiple firm, movable, often protruding nodules in the epidermis or corium, which are frequently painful. The skin over them may be pigmented or there may be large, irregular, macular, chestnut-colored areas which may seem to have no relation to the tumor lesions. There may be concomitant multiple pigmented nevi. The tumors are usually benign but may undergo sarcomatous changes. Microscopically they usually present interlacing columns of fibers which tend to show hyalinization.

Since the original discussions an immense literature has grown up concerning the subject. The tumors may be large, poorly defined masses of nerve trunks in the subcutaneous tissue or viscera, these being called plexiform neurofibromas. Association has been described not only with nevi and macular pigmented areas, but with xanthomata, multiple lipomata, elephantiasis, and with tumors of sebaceous and sweat glands. The complexity is increased when diffuse or nodular involvements of the sympathetics are included. These tumors may apparently be limited to hyperplasias of the sympathetic system or be only a part of a more generalized involvement in which the sensory and motor peripheral nerves also participate. Tumors of the roots of the spinal nerves within the spinal canal are not uncommon. The cranial nerves, too, with the exception of the olfactory and optic, may support the same type of tumor growth seen in the peripheral nerves. Perhaps the most frequent of these is the cerebellopontine angle tumor or acoustic neuroma.

Until Verocay's (3) work these tumors were believed to be true fibromas associated with the sheaths of nerves. That author, however, demonstrated that at least some of the tumors consisted of a proliferation of the Schwann syncytium of the nerve axone. Recently Masson (4) has demonstrated rather conclusively by means of a silver stain technic that there is a relationship between the nevus cells of melanomas and this same syncytium. This helps to clarify the frequent concurrence of multiple pigmented macular areas in the skin that we have come to recognize as a part of the v. Recklinghausen syndrome.
Since the disease consists essentially of a neoplastic hyperplasia of one or more parts of the nerve or its supportive structure, there remain at most three possibilities as far as the peripheral nerve is concerned. The tumor must be a proliferation of the axone tissue, of the Schwann sheath, or of the fibrous connective tissue in relation to them, that is, the epineurium, perineurium, or endoneurium. Histologically those tumors which are shown to consist of hyperplasias of neurones are true neuromas, and strictly speaking do not belong in this classification. According to some writers the masses always consist of proliferations of the neurolemma cells. Any good stain, however, makes this conclusion extremely doubtful. Differential staining with Mallory’s connective-tissue stain and phosphotungstic acid seems to show that many of these tumors are made up almost entirely of connective tissue while others consist of hyperplasias of both elements in varying proportions. Since a considerable number of the sympathetic ganglion cells are provided with a medullary sheath, the same possibilities exist here.

In the central nervous system the axis cylinder and myelin are no longer ensheathed in neurolemma, but are enveloped by the neuroglia. The same is true of the optic “nerve.” Several cases of chiasmal tumor accompanying an otherwise typical v. Recklinghausen syndrome have been reported and at least three cases have been recorded in which autopsy proved the presence of associated brain tumors as well. Of these brain tumors, two have been diagnosed as spongioblastomas and the third as an unclassified glioma. An additional case has been found in the literature in which the presence of a brain tumor was suggested by clinical and x-ray evidence and a presumptive diagnosis of oligodendroglioma made.

No attempt can be made in this brief report to cover the enormous literature which has arisen regarding the fascinating problem of v. Recklinghausen’s syndrome in relation to several closely allied conditions. Just where the tuberous sclerosis of Bourneville and the angiomatosus cutaneous, retinal and brain lesions of Hippel-Lindau’s disease fit into this picture is hypothetical at best. Their hereditary aspects and the not infrequent association of epilepsy are phases of the problem which have been carefully gone into by other investigators. We refer particularly to the paper of Yakovlev and Guthrie (5), who emphasize the congenital nature of v. Recklinghausen’s disease as a manifestation of congenital malformation of the ectodermal tissues (nerve cells, glia, ependyma, choroid, cells of Schwann, sympathetic ganglia, and endings of cutaneous sensory nerves) accompanied by a hyperplasia or even a new growth of the mesodermal tissues, especially the connective tissue of the nerves and blood vessels. Gardner and Frazier (6) also call attention to the hereditary aspect of v. Recklinghausen’s disease in conjunction with acoustic nerve tumors, reviewing 33 cases and presenting, in addition, a familial study covering five generations with 217 individuals in which 38 instances of bilateral deafness occurred, followed in 15 by blindness.

We find three numbers of the Belgian journal of neurology and psychiatry (J. belge de neurologie et de psychiatrie) in 1933 (7) devoted to a symposium on tuberous sclerosis, von Recklinghausen’s disease, and closely associated conditions. Such men as van Bogaer, Van der Hoeve, Hartmann, Thienpont and others present in a series of brilliant papers the sum and substance of our
present knowledge of this extremely complex subject. Of the cases they report, only those of Hartmann (8) and van Bogaert (9) can be definitely included in this paper as essentially comparable to our case.

Nine cases collected from the literature are presented in tabular form for convenience. Of these cases, 7, definitely showing chiasmal tumors, were studied histologically, and in 5 instances the diagnosis of a glioma of one or another type was made. The other two tumors were classified as (1) an atypical meningioblastoma and (2) a neurofibroma (?) of the optic nerve.

Microscopic examination of the tumors of the hypothalamus and chiasm in the case to be reported here revealed gliomas, the former a bipolar spongioblastoma and the latter an astrocytoma. It would appear that the stimulus which causes tumor formation of the supportive tissue of the peripheral nerves also causes the analogous tissue of the brain and chiasm to become neoplastic. This idea was advanced by Verhoeff (15) in 1921.

Case Report

A two-year-old white American female child was admitted to Temple University Hospital on the service of Dr. Ralph M. Tyson with the following history. Three weeks previously she had had a severe attack of diarrhea lasting several days but without fever. Up to that time the mother felt that the child had been entirely normal. Following the intestinal upset, she lost her appetite and became progressively weaker, this weakness being most marked in her legs until it reached a point where she would not walk.

The day before admission she had a convulsive seizure lasting fifteen minutes and followed by a profound sleep. The mother had noticed a progressive drowsiness accompanying the weakness, and believed that there had been considerable weight loss in addition. Following the convulsion the child complained of pain in the back of her head and appeared very irritable.

The past history was essentially negative and the family history irrelevant.

The child was emaciated, with a prominent, lax abdomen. The head measured 51 cm. in circumference. Numerous pigmented and relatively hirsute oval lesions were present on the trunk and lower extremities. Examination of the eyes showed moderate right internal strabismus; the right pupil was wider than the left and the pupils failed to react appreciably to light or accommodation. Examination of the ears was unsatisfactory, but the child apparently did not hear much. Chest and abdominal examinations were essentially negative.

Neurologic examination showed moderate nuchal rigidity with pain on motion. The child lay in a flexed position on the side (usually right). Biceps, triceps and patellar reflexes were not elicited; questionable Kernig; positive bilateral Babinski; no ankle clonus.

The working diagnosis was: hydrocephalus, mental retardation, (?) congenital cerebral agenesis or post-encephalitic residue.

The results of laboratory examinations were as follows: Mantoux test: 1-1000 negative; red blood cells 5,140,000, hemoglobin 13 gm., white cells 9,900 (polymorphonuclears 82 per cent, lymphocytes 16 per cent, basophiles 2 per cent); spinal fluid, initial pressure 36 mm. Hg, chemistry essentially negative.

Ophthalmological consultation showed primary optic atrophy, probably post-infectious.

On neurologic consultation the differential diagnosis seemed to rest between: (1) Tay-Sachs or Schilder's disease; (2) a chronic inflammatory basilar lesion, infectious in origin; (3) a posterior fossa lesion, possibly a neoplasm. Encephalography was recommended to establish the type of hydrocephalus.

The encephalogram showed marked hydrocephalus with enlargement of the ventricles, and a dome-shaped soft-tissue opacity extending upwards between the lateral ventricles, obviously a midline lesion. The mid-line structures were not displaced. The sella turcica appeared large but not eroded. The findings could be explained on the basis of a Rathke's pouch tumor.
FIG. 1. Photomicrograph showing cell detail of hypothalamic tumor; predominance of bipolar type of spongioblasts with loose, fibrillar, edematous stroma. × 100

FIG. 2. Cross-sections of brain showing mid-line tumor producing obstructive hydrocephalus and distortion of ventricles

In lower view note appearance of optic chiasm and its relationship to the central tumor.

FIG. 3. Photomicrograph illustrating the proliferating bundles of fibrillary astrocytes with associated fibrous tissue septal hyperplasia

These cells appear somewhat hyperchromatic, but in other respects the picture is one merely of exaggerated gliosis. × 50

FIG. 4. Base of brain showing chiasmal astrocytosis, extraordinary bulbar nodulation of the optic nerves, and encroachment upon the other cranial nerves by the lesion
As a result of the x-ray findings the patient was transferred to the neurosurgical service of Dr. Temple Fay for operation. A transfrontal craniotomy was done. A large, solid tumor presented over the sella turcica and sphenoid ridge. The optic nerves were not identified. The lesion was deemed inoperable and tissue was taken for biopsy. Microscopically the sections showed a very diffuse fibrillary gliosis. No neoplasia was identified.

The child contracted pertussis and was transferred to the Municipal Contagious Hospital, where that disease ran an uneventful course. The neurological symptoms, however, showed steady progression and an osteomyelitis of the bone flap developed.

One month later the patient was brought back to the hospital. The bone flap was removed and the wound packed with iodoform gauze. Healing was satisfactory, but the child failed gradually, and died four months after the onset of symptoms.

Abstract of Autopsy Protocol: The body is emaciated; the head definitely of the hydrocephalic type. The operative wound appears healthy and to be covered with fresh granulation tissue. The pupils are unequal, the right measuring 6 mm.; the left 4 mm. The thorax is symmetrical. The abdomen is scaphoid. Over the abdomen and the thighs are many irregular macular, pigmented areas, chestnut in color and associated with marked fine hirsutism. No other external pathology of significance is noted.

On opening the peritoneal cavity one is struck by a diffuse and marked enlargement of all the lymph nodes of the mesentry. Both in the mesentry and mesocolon are several firm, glistening, bluish-white plaques of what resemble interwoven plexiform nerve tissue.

In the hilar notch of the spleen a similar mass of tissue is noted. From this mass four cords about 6 mm. each in diameter extend directly into the splenic pulp.

Aside from the pathology of the nervous system, no visceral lesions of any apparent importance are seen. The heart, lungs, liver, pancreas, kidneys, gastro-intestinal tract, and genitalia all are within normal limits. Even the adrenals show no change other than a moderate hypoplasia. They are small, firm, with well defined cortices and medullae. Together they weigh 4.8 gm.

On opening the calvarium and exposing the brain, the surface appears somewhat flattened, due to the hydrocephalus. No evidence of any inflammatory reaction is seen except around the margin of the decompression, and this appears free of infection. The under surface of the brain is remarkable in appearance on account of a fusiform, bulbous enlargement of the optic nerves and chiasm, which suggests a neoplastic process. Where these tumor-like masses come in contact with the cranial floor, the anterior part of the sella turcica and orbital foramina, there is marked pressure atrophy of the bony structures. The pituitary shows no gross abnormalities.

In addition to the enlargement of the optic nerves, all the cranial nerves are likewise increased in size. They appear larger than those of a normal adult (Fig. 4). On section of the optic tract, which is very firm, it appears to be entirely replaced by tumor tissue increasing the diameter to 2.1 cm. The white myelin structure of the nerve itself is completely replaced by a firm grayish, septate mass with a thickened capsule-like tissue surrounding it (Fig. 9).

When the brain is sectioned transversely there is seen a moderate hydrocephalic dilatation of the lateral ventricles. The ventral and lateral parts of the optic thalami are replaced by a mass that is partly continuous with the tumor of the chiasm (Fig. 2). In the more posterior part of the thalami the tumor is yellow and has a gelatinous structure. The tumor has occluded the third ventricle, thus causing hydrocephalus. The tuber cinereum is totally replaced by tumor.

The entire peripheral nervous system is also involved in a remarkable diffuse enlargement. The nerves of the brachial plexus are almost twice as large as those seen in the normal adult. The sciatic nerves each measure 0.7 cm. in diameter. The dorsal and lumbar spinal nerves look like thick white cords. There is a diffuse enlargement of the entire sympathetic nervous system, especially seen in the thoracic and abdominal sympathetic chains.

Histological Examination: The entire interest of the case centers in the nervous system. The study of the other tissues reveals very little of apparent significance, and only the few more outstanding findings are briefly indicated here.
FIG. 5. **Microtessar Photograph of One of the Mesenteric Plexiform Neurofibromatosis Plaques Seen in Relationship to the Wall of the Ileum**

Phosphotungstic acid-hematin stain showing the proliferation of all elements of the nerve, but especially of the sheath. × 12

**FIG. 6. High-power Photomicrograph (Phosphotungstic-acid Stain) of Field Shown in Figure 5, to Illustrate the Histologic Detail, Showing Neuronal as Well as Sheath Hyperplasia.** × 50

**FIG. 7. Section from Abdominal Sympathetic Nerve Trunk, Showing Particularly the Hyperplasia of the Schwann Cell Portion of the Nerve. Phosphotungstic-acid Stain.** × 50

**FIG. 8. Section from One Small Group of Fibers in the Sciatic Nerve**

Neurones appear normal in number but note the enormous amount of fibrosis present between the nerve bundles, which accounts for most of the increase in size of the peripheral nerve trunks. × 50
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Author</th>
<th>Sex and Age</th>
<th>Duration</th>
<th>Brain Tumor Location</th>
<th>Type</th>
<th>Optic Nerve or Chiasmal Involvement</th>
<th>Peripheral Nerve Involvement</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Martin and Cushing (10)</td>
<td>F. 20</td>
<td>Since childhood</td>
<td>None</td>
<td>Glioma</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Goldstein and Wexler (11)</td>
<td>F. 52</td>
<td>Over 30 yrs</td>
<td>None</td>
<td>Glioma</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Bueno and Llombart (12)</td>
<td>F. 6</td>
<td>2 yrs.</td>
<td>Rt. frontoparietal</td>
<td>? Oligodendroglioma</td>
<td>Atypical oligodendroglioma</td>
<td>Yes</td>
<td>X-ray diagnosis of brain tumor because of calcification</td>
</tr>
<tr>
<td>4</td>
<td>Hartmann (8)</td>
<td>F. 8</td>
<td>5½ yrs.</td>
<td>None</td>
<td>? Mixed type meningioblastoma</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Hartmann (8)</td>
<td>F. 27</td>
<td>3 yrs.</td>
<td>None</td>
<td>Neurofibroma of optic nerve</td>
<td>Yes</td>
<td>Acoustic nerve tumor, large nevus of scalp</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Hartmann (8)</td>
<td>M. 7</td>
<td>2 wks.</td>
<td>None</td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td>X-ray diagnosis</td>
</tr>
<tr>
<td>7</td>
<td>Shapland and Greenfield (13)</td>
<td>F. 22</td>
<td>11 mos.</td>
<td>Frontal lobe and medulla</td>
<td>Gliomat</td>
<td>Glioma</td>
<td>Yes</td>
<td>Multiple tumors of dura—psammomata</td>
</tr>
<tr>
<td>8</td>
<td>van Bogaert (9)</td>
<td>F. 31</td>
<td>7 yrs.</td>
<td>Cerebrum</td>
<td>Spongioblastoma</td>
<td>Encroaching on optic chiasm</td>
<td>Yes</td>
<td>Tuberous sclerosis; hypernephroma, left kidney</td>
</tr>
<tr>
<td>9</td>
<td>Fulton and Bailey (14)</td>
<td>F. 6</td>
<td>4 yrs.</td>
<td>Ant. 3rd ventricle</td>
<td>Spongioblastoma multiforme</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Aegerter and Smith</td>
<td>F. 2</td>
<td>3 wks.</td>
<td>Hypothalamus</td>
<td>Spongioblastoma</td>
<td>Astrocytosis</td>
<td>Yes</td>
<td>Also sympathetic nerve involvement</td>
</tr>
</tbody>
</table>
The myocardium shows an advanced toxic myocarditis with some fatty and hydropic degeneration, interstitial edema, and a Zenker-like hyalinitization of some of the muscle fibers. The right lower lobe of the lung shows many of the alveoli to be filled with macrophages which have ingested large quantities of fat droplets. What little cellular reaction accompanies this process is of a chronic rather than an acute nature, and probably represents the residue of the pertussis pneumonitis.

The spleen presents an essentially normal picture, but the histology of the lymph nodes is peculiar. The cells of the germinal centers present multiple vacuoles which are suggestive of a lipid infiltration or degeneration. Unfortunately no formalin-fixed material was saved so a fat stain could not be made.

In spite of the sympathetic origin of the adrenal medullae no changes could be found of a similar nature, and indeed both cortices and medullae appeared normal.

The histology may be summarized as representing an amazing generalized diffuse hyperplasia of the central, peripheral and sympathetic nervous systems.

In the peripheral system all three components of the nerve structure are involved. As evidence of an increase over normal of the axone tissue the fibrillar plaques in the mesentery are cited. These are in reality poorly defined nerve tumors. With differential stains the plaques are seen to consist of masses of interwoven peripheral nerve axones with proportionately normal Schwann sheaths and a massive increase in supportive connective tissue (Figs. 5-6). Their relation to the enlargement of the mesenteric lymph nodes and the distended lymph vessels is problematic.

The remarkable increase in the size of the peripheral system as demonstrated by the brachial and sciatic nerves appears to be due to the proliferation of fibrous connective tissues. The actual number of axones is apparently within normal limits. The perineural sheaths show extreme thickening with some increase in the endoneurium (Fig. 8).

The ganglia and trunks of the sympathetic plexuses show an increase in the ganglion cells and fibrils. The most striking characteristic of these sections, however, is the hyperplasia of the Schwann sheath. This hyperplasia appears to be responsible for the major part of the enlargement seen grossly (Fig. 7).

Sections through the tumor of the brain show many areas of degeneration. The cells of the tumor have a heterogeneous morphology (Fig. 1). For the most part the cells are rather large. The arrangement suggests no pattern. The nuclei are of varying sizes, more frequently oval than round, and tend to be hyperchromatic. With silver and phosphotungstic acid stains many of the cells are seen to be fusiform and bipolar, while others are pear-shaped and unipolar. There has been universal agreement among the pathologists studying these slides that the diagnosis is spongioblastoma, probably best classified as of the bipolar type.

**Fig. 9. Microtessar 48 mm. Photograph of Optic Chiasm, Showing the Uniform Glial Proliferation throughout the Entire Optic Tract**

Note the bundles of glial fibrils separated by coarse connective-tissue septa, and the thickening of the connective-tissue capsule around the entire nerve tract.
Sections from the optic chiasm and nerves show a homogeneous, uniform, diffuse overgrowth of adult fibrillary astrocytes. To call this overgrowth a neoplasm is hardly accurate, although there is replacement of the nerve tracts by glial tissue. The use of the term astrocytosis seems more justifiable here (Fig. 3).

Sections from other parts of the body show a diffuse hyperplasia of the terminal nerve fibrils. This is especially notable in the pericardium and corium of the skin. Here the increase in size appears to be largely due to the increase in the fibrous connective tissue of the sheath.

**Summary**

An unusual case of diffuse generalized neurofibromatosis in association with a semineoplastic glial proliferation of the optic chiasm and a central spongioblastoma of the hypothalamic area is reported. Degenerative lesions of this type involving the central, peripheral, and sympathetic nervous systems universally, appear to be most uncommon. A rather careful search of the literature reveals only about a dozen comparable cases. These are reviewed briefly. Speculation as to the nature of the process suggests some specific neuropathic growth-stimulating factor, which acts uniformly on the several component parts of the nervous system, but especially the various supportive cells including the glia, the endoneurium, the perineurium, and the epineurium. The nature of such an activator still remains completely obscure, but in line with the more recent work on cancerogenic agents, the possibility of its being some endogenous enzyme cannot fail to occur to one.

**Note:** We wish to acknowledge our indebtedness to the several members of the staff, especially Dr. Ralph M. Tyson, Dr. Temple Fay, Dr. W. Ivan Lillie and Dr. W. Edward Chamberlain for their cooperation in permitting us to present the clinical aspects of the case, and to Dr. Edwin S. Gault for his help in preparing the photomicrographs.

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