PLEXIFORM NEUROFIBROMA is a subject which presents many very interesting problems which have been discussed only sporadically in the literature. The most striking finding in the start of a search for a concise presentation of the disease is the difficulty in uncovering an apt description of either gross or microscopic picture. We have collected here a brief resume of the clinical and pathologic problem with a report of 11 cases treated at the Children's Hospital of Philadelphia.

Thomson in 1900 wrote the most complete review of the problem and classified plexiform neurofibroma as one of the most interesting types of neurofibroma. It is but one of the manifestations of diffuse neurofibromatosis or von Recklinghausen's disease, being given the descriptive name because of the characteristic gross appearance of this benign tumor wherever it appears.

Typically, the growth is in the distribution of one or more contiguous, usually sensory, nerves or of a plexus of nerves, and it often appears at birth or soon afterward. The skin over superficial masses may be normal, discolored brown, or thickened and hairy as well as pigmented. The sensation on palpation is unmistakable, being described as feeling like a bag full of worms, a tangle of spaghetti or grains of boiled tapioca on a string. The disease may also appear as a diffuse thickening of a single nerve trunk without the nodular sensation. The patient's or parents' attention is aroused because of deformity and almost never because of pain or discomfort. The tumor may appear as a sharply localized and relatively small mass or as a diffuse and sometimes quite large growth. Seldom is there any detectable neurologic deficit. Most patients who present with this problem have obvious cafe-au-lait patches over the surface of the body, these having been noted at birth or shortly after and almost always before the appearance of the plexiform tumor.

The distribution of the growths is quite wide, although a majority of them first appear about the head and neck (41 of 58 in the study by Thomson, 6 of 11 in the present series). In one of its more favorite sites, the periorbital area, the growth may cause marked deformity of the eye, either pushing it out of position or covering it with a grossly distorted eyelid. Nevertheless, the optic nerve is not destroyed and careful reconstructive surgery can restore normal vision. It is important in this regard to know of the propensity for this process to appear in one location and then to crop up in an entirely different area, probably a manifestation of multiple foci of disease.

Major concern centers about this particular tumor because of its relentless progression along the distribution of a nerve, especially about the head and neck, following it through the tiniest foramen and thence invading the skull and leading to compression of adjacent cranial nerves or brain substance. This occurs in similar fashion in the spine passing through the vertebral foramina to cause compression of the cord. For this reason it is important to try to remove the mass completely as soon as possible in order to stall the process, even though we know it may involve some other...
focus at a later date. Except for this phenomenon, our approach would be to correct only the deformity.

At operation the tumor appears very much as it was described on palpation, with masses or strands of smooth, shining nerves which are easily separated from each other. They vary in size from that of an adult finger down to the most attenuated fiber and are typically not cylindrical but present nodular, fusiform or beaded swellings. The tissue has a soft, gelatinous consistency without elasticity so that it is very easily torn and hence lost. It is important to follow the tiniest tendrils out to the end in order to eradicate the tumor.

The histologic picture is similar to that of generalized neurofibromatosis with overgrowth of endoneurium surrounding or separating individual nerve fibers. Whether this is a proliferation only of connective tissue elements or also of the sheath cells of Schwann is unknown. The large amount of edema causes a lattice-like appearance with axis cylinders persisting with displacement or dissociation but very rarely with degeneration or disappearance.

In the past 9½ years we have seen 11 patients with various manifestations of this problem. The youngest patient was 8 months old when first seen, the oldest, 9 years. There were five girls and six boys, and one child was a Negro, all the rest being white. Each presented because of a mass except one which was detected on roentgenographic examination of the chest. Three of the children had complained of slight discomfort on palpation of the mass. Six of the tumors appeared first about the head and neck, two were on the thoracic wall, one was in the posterior mediastinum with extension into the neck, one appeared in the lumbar area near the midline and one presented in the rectovaginal septum. None of the children presented with any abnormality of the neurologic examination, and seven of them had typical cafe-au-lait spots, often noted soon after birth and before the mass of tumor appeared.

Five patients had primary resection of the entire presenting mass and have shown no evidence of further disease in follow-up examinations up to 3 years later. The most revealing material we have, however, is in the study of the other six children. Two of them had excision of what was believed to be all of the tumor, one after two previous operative procedures elsewhere. One boy has slowly developed another focus of similar appearance adjacent to the original and excision of this is planned for the near future. The other had to have another excision 9 months after the operation performed by us, and there has been no recurrence in 4 years since then. One 9-year-old girl, who was found to have plexiform neurofibroma arising in the rectovaginal septum with extension into the right adnexa, had biopsy only and has been followed for 2 years during which time she has done well except for persistence of difficulty controlling the rectal sphincter, which had been present previously.

The other three present the most complex situations. We shall give summaries of the disease in two. The third has had excision of three foci of tumor to the present: in May, 1955, excision of a mass posterior to the left ear with extension up to the carotid foramen; in October, 1957, excision of the left peroneal nerve, which was diffusely involved from the ankle to the knee; and in October, 1958, excision of another plexiform mass in the right side of the neck.

CASE REPORTS

Case 1

HISTORY AND PHYSICAL FINDINGS: C.J., an 8-month-old white boy, was first seen in January, 1949, with a grossly swollen, discolored left eyelid which had been present and had slowly grown since birth causing some proptosis of the eye. The only other abnormal finding was scattered cafe-au-lait spots.

ROENTGENOGRAPHIC AND OPERATIVE FINDINGS: Roentgenograms showed erosion of the lower border of the left orbit and of the superior portion of the maxilla and the sphenoid bone. A biopsy showed this to be plexiform neurofibroma, and wide excision was carried out re-
moving the zygoma, a large part of the temporal bone and segments of the sphenoid and maxilla. Recovery from this massive procedure was uneventful and he did well for about 18 months. Slow recurrence of the swelling of the left orbital area was noted then, and in February, 1951, a recurrent mass of plexiform neurofibroma was excised including much of the sphenoid bone and carrying the dissection to the point where tumor was removed from the dura. It was felt certain that all of the growth had not been excised but that to do more would cause irreparable damage to the brain. One small cerebrospinal fluid fistula in the wound had to be closed, but in every other way he had a smooth recovery.

**COURSE:** Normal development continued with little change in the left periorbital area and with definite vision in the left eye. In November, 1952, two small nodules were noted at the left ankle, and a plexiform neurofibroma involving the posterior tibial nerve was excised only partially because of proximal extension. As he was followed over the subsequent years, there was no other change in condition except for the slow development of a mass in the left popliteal space. Exposure of this in April, 1957, demonstrated diffuse involvement of the sciatic and popliteal nerves with plexiform neurofibroma, proven by biopsy. It was felt that radical resection was not indicated, in large measure because of the minimal neurologic deficit. The boy has been seen at regular intervals since then and has continued to do well with no serious problems with regard to either eye or leg.
Fig. 2. Nerve bundle, demonstrating marked involvement of one axis cylinder with normal or slightly involved cylinders in close approximation to it.

Fig. 3. Specimen shown in Figure 2; a normal nerve fiber is in the center with the periphery of the involved fiber to the left.
PLEXIFORM NEUROFIBROMA

Case 1

History and Physical Findings: A patient presented with a mass in the right posterior mediastinum, which was excised. The growth shown in the neck was excised, but it was felt that some remained in the left mediastinum and could not be removed. The most distal part of tissue excised, however, showed thymus, and for that reason further surgery was not attempted. She was followed closely with roentgenograms of the chest, and no further evidence of tumor appeared. But in November, 1956, a nodule appeared on the right eyelid and when this was excised it proved to be plexiform neurofibroma with myxomatous degeneration. She continued otherwise healthy until December, 1957, when suggestive nodules were palpated in the right posterior cervical region. In January, 1958, a wide dissection was carried out removing a large number of typical tumor tentacles from the posterior occipital area and both posterior cervical triangles. The tumor was again plexiform neurofibroma. Over the years there has been an increase in the number of cafe-au-lait spots and the right Horner's syndrome, incident to the first operation, has persisted, but there has been no significant change in the 9 months since the last operation.

Since the presentation of this paper, another patient with this same lesion has been treated at the Children's Hospital of Philadelphia. She is an 8-year-old white girl who had been known to have a soft mass over the lumbosacral region since birth. This had become tender after a blow 3 months before, but no other symptoms had been noted. Examination revealed a soft midline mass measuring 7 by 8 cm over the lumbosacral area and also a large rectal mass lying on the right side. Neurologic examination was normal. Cafe-au-lait spots had been noted since birth. Roentgenograms showed no bony abnormality except...
large sacral foramina, pressure on the rectum by an extrinsic mass and, by myelography, a mass lesion in the spinal canal at L-5 pushing from the right. Abdominal exploration showed an extensive, typical plexiform neurofibroma, grossly and microscopically extending up and down in the retroperitoneal area. Biopsy only was carried out. Twelve days later, laminectomy was performed from L-4 to S-2 with excision of an intra- and extra-dural mass, which was also plexiform neurofibroma. She has recovered well from operation and is now at home and asymptomatic.

DISCUSSION

In a review of the general pathology of neurofibromatosis, we should mention several facets of the problem with particular regard to plexiform neurofibroma. The age of onset is probably very early, although the tumor may not make itself manifest until later in life. Appearance after the age of puberty is exceptional. The influence of heredity is frequently mentioned and certainly is noted on occasion, but there is no very clear relation. Seven of 56 patients studied by Thomson had a positive family history as did 2 of the 11 patients in the present series.

Simultaneous defects of developmental origin appear surprisingly often. There is said to be 20 times more mental retardation associated with this disease than would normally be expected. Other congenital anomalies have been noted also, particularly in the development of the genital organs. There does not seem to be any relation between sex or race and this disease. The influence of external factors in causation has never been clearly delineated, although it has been found in von Recklinghausen’s disease that more cutaneous nodules appear in locations where friction or pressure is common.

The origin of this tumor is unknown. Neurofibromatosis is said to appear in one of every 2,000 people in the general population and no causative agents have been found. It is apparently a form of giantism of the connective tissue elements of the peripheral nervous system. This type of tumor has been noted in lower animals on occasion.

Is plexiform neurofibroma a premalignant growth? Some writers have said that the tumors are prone to malignant change in 8 to 12% of cases. One group reported 16% malignancy but not because of surgery. Stout, who has done some of the definitive studies of nerve tumors, feels that they can occasionally undergo malignant degeneration. The general impression is that when malignant change is noted it has appeared as a separate phenomenon and not in a previously innocuous mass. With plexiform neurofibroma we do not see the finding common in generalized von Recklinghausen’s disease of great increase in activity of lesions or appearance of new lesions after surgery or injury to one focus of tumor. Skin which may be widely involved with tumor may be used in plastic repair with cosmetic success and no fear of trouble when a plexiform tumor has been partially excised. Davis and his group do not hesitate to operate repeatedly in the same area if the activity of that focus requires it for cosmetic or functional purposes.

One thesis has been advanced that local overgrowth of the tumor leads to breakdown of its circulation and then to degeneration and malignant change.

The prognosis for a child with plexiform neurofibroma is difficult to gauge. Since we know that it tends to appear in other places even though it may have been eradicated in one focus, we often feel that the treatment of this disease is in the way of being a delaying action to hold off the inevitable. Nonetheless, there are certainly patients who have had the tumor completely excised in one area and have had no recurrence over long follow-up periods.

SUMMARY

Plexiform neurofibroma is a relatively uncommon manifestation of diffuse neurofibromatosis and is characterized by its unique gross appearance. Because of its tendency to involve peripheral nerves centripetally it must be vigorously treated surgically to
prevent damage to vital areas, notably the brain and spinal cord, although the tumor is basically benign.

We have presented our experience with 11 children who had this disease, demonstrating that despite the propensity for the growth to crop up in several areas it can be eradicated locally, and the patient may have no further trouble for a long time.

We believe that resectable lesions should be removed even though this may require repeated operations over a period of several years.

**Acknowledgment**

We wish to express our thanks to Dr. Twining F. Campbell, Jr., who as a medical student did the initial studies of these cases. Also to Dr. William C. Yakovac, Pathologist of the Children’s Hospital, who helped in clarifying a confusing picture and in reviewing the pathologic sections for us.

**REFERENCES**

# EXPERIENCES WITH THE MANAGEMENT OF PLEXIFORM NEUROFIBROMA

Charles L. Minor and C. Everett Koop

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