Von Recklinghausen's Disease

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Von Recklinghausen's disease or multiple neurofibromatosis is a rare syndrome characterized by abnormal cutaneous pigmentation, numerous skin tumors and multiple tumors of the spinal or cranial nerves. Although the syndrome was previously described by Smith in 1849, this pleomorphic variety of disorders is usually associated with the name of von Recklinghausen who, in 1882, described the disorder in great detail.1,2

Materials and Methods

One hundred and ten patients with von Recklinghausen's disease were seen and followed over the years at the Memorial Hospital for Cancer and Allied Diseases and the James Ewing Hospital in New York. An additional 10 patients seen at the University of Illinois Hospitals in Chicago provided tissue specimens for histologic, histochemical and ultrastructural studies. These 10 patients are not included in the description of the end results of treatment.

General Features

INCIDENCE

In this study the incidence of the disease was roughly equal in both sexes (56 men and 54 women). The preponderance of male patients reported by other authors has not been seen in our series.3,4

The patients when first seen ranged in age from immediately after birth to 50 years. The majority, however, were seen before the age of 30.

Ten of 110 patients (9 percent) were blacks, which reflects the equal frequency of von Recklinghausen's disease in both races. Multiple neurofibromatosis is observed in all races and in every part of the world.

Crowe et al. at the University of Michigan estimated that neurofibromatosis appeared once in every 2,500-3,000 live births.5

GENETIC FACTORS

Crowe and his colleagues concluded that approximately 50 percent of the people with neurofibromatosis have affected relatives and that the distribution of cases is consistent with the hypothesis of a dominant gene.6 They further proposed that sporadic or isolated cases are the result of mutation to this gene.

In this series, 53 of the patients (48.2 percent) had approximately 183

174
affected relatives. In five families the disease was traced in four generations, and in two of these families, all affected individuals were treated.

ENDOCRINOLOGIC ASPECTS
Although we were not primarily interested in detailed endocrinologic studies in these patients, a number of apparent endocrine abnormalities were found. Six male and four female patients were significantly retarded somatically and sexually.

It is not immediately apparent whether this type of retardation is a nonspecific manifestation of a disease which may encroach upon the normal functioning of every part of the body, or whether it is a reflection of a more specific endocrine disorder.

Enlargement of the thyroid gland was observed in five patients (4.5 percent); none of these patients had hyperthyroidism.

An association of neurofibromatosis with chromaffin tumors of the adrenal has been reported and the incidence of neurofibromatosis in pheochromocytoma patients apparently varies between 5 to 23 percent.6-7 Hume suggested a four percent overall incidence of neurofibromatosis in patients with pheochromocytoma,6 but only one patient in our study had pheochromocytoma.

MENTAL STATUS
It is generally recognized that patients with von Recklinghausen's disease have some degree of mental retardation.6 Borberg obtained a median intelligence quotient between 85-90 in his patients; however, imbecility or idiocy was rare.6

Clinical Aspects of von Recklinghausen's Disease
Clinical aspects of neurofibromatosis in general have attracted little attention because diagnosis of a fully developed case is simple. It is important, however, to consider the initial symptoms of this entity in order to have a clear understanding of the natural history of multiple neurofibromatosis. For the sake of clarity, the presenting complaints were classified into the following three categories: (1) cosmetic symptoms of neurofibromatosis (patient unaware of disease); (2) complaint related to other diseases, such as asthma, etc.; (3) and complaints of related conditions such as an associated deformity or an accompanying tumor.

Analysis of the presenting complaints shows that 20 of 110 patients (18 percent) were unaware of any underlying disease and sought medical opinion for purely cosmetic reasons. Twenty-five patients were first seen by their physician for unrelated rea-
sons like asthma, flu, etc. Sixty-five patients (59 percent) were first seen because of conditions associated with von Recklinghausen's disease. Of these, 42 had a family history of neurofibromatosis.

CAFE-AU-LAIT SPOTS OR MACULAR PIGMENTATION

Crowe et al. investigated the genetic and clinical significance of these macular pigmentations, and from their studies, they concluded that cafe-au-lait spots are pathognomonic findings of generalized neurofibromatosis. These authors suggested that any person with more than 6 cafe-au-lait spots which exceed more than 1.5 cm. in diameter must be presumed to have neurofibromatosis even in the absence of a positive family history. We agree with this hypothesis as we have seen a number of patients in whom the only early evidence of neurofibromatosis was macular pigmentations and who did not develop cutaneous tumors until later in life.

CUTANEOUS AND SUBCUTANEOUS TUMOR

These tumors varied in size from a few millimeters to about 20 cm. in diameter and were scattered all over the body. In our series, no tumors were seen at birth, the majority of them initially appeared during puberty; however, patients were seen with tumors as early as 6 months of age and as late as 18 years of age. By the fourth decade cutaneous and subcutaneous tumors involve most of the body. (Figs. 1 and 2.)

NATURAL HISTORY OF VON RECKLINGHAUSEN'S DISEASE

When patients with von Recklinghausen's disease are followed through several decades, involvement of different organ systems and neoplasm formation are frequently observed. In order to obtain accurate information about the history and prognosis of neurofibromatosis, the patients were arbitrarily divided into the following five age groups, and the evolution of the disease in these groups is described.
INITIAL DIAGNOSIS OF VON RECKLINGHAUSEN'S DISEASE

| Age         | Patients |
|-------------|----------|
|             | Number   | Percent |
| At birth    | 26       | 23.6    |
| 1 month to 5 years | 34 | 31.0    |
| 6 to 15 years | 26       | 24.0    |
| 16 to 25 years | 15       | 13.6    |
| Over 25 years | 9        | 7.8     |
| All ages    | 110      | 100.0   |

Patients in Whom von Recklinghausen's Disease Was Diagnosed at Birth. Twenty-six patients (23.6 percent) were born with the stigmata of von Recklinghausen's disease. Of these, four were born with giant bathing trunk nevus. (Fig. 3.)

Five of the 26 patients (19 percent) developed brain lesions before the age of 12 and all 5 succumbed either to the tumor or its complications, within 8 years of diagnosis. The earliest diagnosis was within two years of birth and the latest within eight years.

Fourteen of the twenty-six patients (54 percent) developed symptomatic osseous deformities within 15 to 25 years. The commonest type of deformity was kyphoscoliosis. The usual vertebral anomaly is a low thoracic kyphoscoliosis, the cause of which is not yet clearly known. (Figs. 4 and 5).

Peripheral nerve tumors constitute one of the major neoplastic complications of this disease. Sixty-nine percent of the children born with neurofibromatosis developed 1 or more benign schwannomata by the age of 20, and 19 percent developed malignant schwannoma by 40 years of age. Benign schwannomata can be distributed...
all over the body and can sometimes produce considerable local deformity for which surgery is required. (Figs. 6-9.)

Patients in Whom von Recklinghausen's Disease Was First Diagnosed Between the Ages of One Month to Five Years. There were 34 patients (31 percent) in this group. Forty-four percent of these patients developed osseous complications, the majority of which involved the vertebral column. Only occasional instances of long bone involvement were noted. Osseous complications appeared from 8 to 30 years after diagnosis of neurofibromatosis and no approximate age of the appearance of vertebral involvement can be determined.

Four of the 34 patients (12 percent) showed associated brain involvement and the patients with brain tumors succumbed to their disease before the age of 15. The incidence of benign or malignant peripheral nerve tumors was similar to the previously described group of patients.

Three of the 34 patients (8.8 percent) were treated for cancer apparently related to von Recklinghausen's disease. Two of them had melanoma and one had thyroid cancer.

Patients in Whom von Recklinghausen's Disease Was First Diagnosed Between the Ages of 6 to 15 Years. In this group of 26 patients (24 percent) the osseous complications were mainly confined to the vertebral axis. However, two patients had symptoms due to pressure erosion of the long bones (one complained of pain at the upper
end of the arm and one had pain near the greater trochanter of the right femur.

Three patients (11.5 percent) had involvement of the central nervous system, all with involvement of the spinal cord alone. The cord was secondarily involved due to progression of the disease along the spinal roots.

Peripheral nerve tumors occurred with the same frequency as in the other two age groups. The benign variety was more common in younger and the malignant variety in older age groups.

Three of the 26 patients (11.5 percent) developed other types of malignant tumors, 2 melanomas and 1 carcinoma of the breast.

Patients in Whom von Recklinghausen’s Disease Was First Diagnosed Between the Ages of 16 and 25 Years. Seven of the fifteen patients (13.6 percent) in this group showed vertebral anomalies, and five of these seven were initially seen for kyphoscoliosis and large subcutaneous tumors.

One of the 15 patients had paraplegia due to spinal cord involvement. Myelogram showed compression at D10 to D12 level. On exploration, neurofibromata was found infiltrating the cord and the spinal roots. The patient ultimately developed quadriplegia and died of intercurrent infection.

Benign schwannomas were frequently the presenting symptom in this group of patients and the stigmata of the disease was noted during the
clinical examination. Eight (53 percent) in this group developed malignant schwannoma within 5 to 8 years of clinical diagnosis of von Recklinghausen's disease. Four patients developed other types of cancer: two were treated for thyroid cancer, one for melanoma and one for breast cancer.

**Patients in Whom von Recklinghausen's Disease Was First Diagnosed After Age 25.** There were nine patients in this group. (Fig. 10.) Four of them showed involvement of the vertebral column, and all four were first seen because of kyphosis or kyphoscoliosis. One patient had additional involvement of the gastrointestinal tract. (Fig. 11.)

![Fig. 11. Multiple neurofibroma in the colon.](image1)

![Fig. 12. A cut section of a malignant schwannoma.](image2)

The incidence of malignant schwannoma in this age group is quite high. Three of nine patients were primarily seen for a malignant nerve tumor, including a retroperitoneal malignant schwannoma. (Fig. 12.) It should be emphasized that the tumors in these three patients were presenting symptoms and were not found through regular follow-up of previously diagnosed neurofibromatosis.

Two patients developed non-neurogenic malignant tumors. One had carcinoma of the breast, the other had lung cancer.

**Prognostic Factors Affecting Patients With von Recklinghausen's Disease**

The ultimate outcome of von Recklinghausen's disease is dependent on the involvement of various organ systems or specific types of somatic tissues. In this series, 47.1 percent of the patients had osseous involvement. The major site was the vertebral column, resulting in a number of vertebral deformities. (Table 1.) Because of this type of deformity, pulmonary function was severely impaired in a number of patients, which resulted in a restricted life. Pressure effects of benign or malignant nerve tumors on long bones were observed in five percent of our patients. The usual symptoms were pain and tenderness, which did not, however, incapacitate any of these people.

The age of initial diagnosis apparently did not influence either the type of bony involvement, or the degree of incapacitation. The degree and severity
of deformity is a function of time, and we know of no way by which a prediction as to the degree of bony involvement can be made in patients with von Recklinghausen's disease.

Central nervous system involvement was characterized by tumors of the brain, or involvement of the spinal cord through extension along the spinal roots. In our series, 12 percent of the patients had involvement of the central nervous system. Of the nine symptoms appeared between the ages of 20 and 25.

Our study suggests that brain involvement in multiple neurofibromatosis is due to a separate neoplasm. The clinical symptoms are usually manifested before the age of 10 and the majority of patients die before reaching adulthood. The spinal cord involvement, in contrast, is due to direct extension of the nerve tumors and it usually takes between 20 and 25 years before the cord is actually involved.

Symptomatic benign peripheral nerve tumors were seen in 65 (59 percent) of the patients. (Table 1.) The tumors were either pure schwannoma or occasional neurofibroma or mixed histological types, and were commonly seen before the patients were 30 years old. The tumor mass was usually the initial symptom. (Table 2.) The management of benign schwannoma in these patients is similar in principle to that described for solitary benign

| Types of Associated Complication          | Number of Patients* | Percent |
|-------------------------------------------|---------------------|---------|
| Osseous system involvement                | 52                  | 47.2    |
| Central nervous system involvement        | 13                  | 12.0    |
| Gastrointestinal tract involvement        | 12                  | 11.0    |
| Vascular lesions involvement              | 4                   | 3.6     |
| Benign schwannomata                       | 65                  | 59.0    |
| Malignant schwannomata                    | 32                  | 29.0    |
| Other types of cancer                     | 16                  | 14.5    |
| Miscellaneous cancer                      | 5                   | 4.5     |

*Often same patient had more than one system involved.

patients (eight percent) with tumors of the brain, seven were dead at the time of this report (autopsy was performed on four of these patients). All the patients with brain tumors had clinically recognizable symptoms before the age of 10. (Table 2.)

Four patients had definite clinical evidence of spinal cord involvement leading to paraplegia or quadriplegia. In our group, only those patients in whom multiple neurofibromatosis was observed after six years of age developed spinal cord involvement, and the
Seventy-five percent of benign schwannomata occurred before the age of 19 and 15 percent between 20 and 29 years. Therefore, to avoid needless radical surgery, it is suggested that nerve tumors in young patients with von Recklinghausen's disease should be considered benign, unless adequate proof of malignancy is obtained.

The overall incidence of malignant schwannomata in this series was 29 percent. This probably represents the true incidence of peripheral nerve malignancy in von Recklinghausen's disease. Twenty-seven of 32 patients were over 30 years of age. (Table 2.) Of 18 followed to 50 years of age, 9 were treated for malignant schwannoma. Therefore, it seems likely that if a patient with von Recklinghausen's disease survives for 50 years or longer his chances of developing a malignant nerve tumor are extremely high.

Although a relationship between the tumors of the sympathochromaffin system and von Recklinghausen's disease has been reported by several authors, we have not observed an increased incidence of tumors of sympathochromaffin system in our patients with neurofibromatosis. It is not, therefore, possible from our material to estimate the influence of such tumors on prognosis in these patients.

**TABLE 2 – ASSOCIATED NEUROGENIC TUMORS**

| A. Related to Central Nervous System | Number of Patients | Percent | Age Commonly Seen          |
|-------------------------------------|-------------------|---------|-----------------------------|
| Cerebral tumors                     | 9                 | 8.0     | Before 10 years             |
| Spinal cord lesions                 | 4                 | 3.6     | 20-30 years                 |

| B. Related to Peripheral Nerves     | Number of Cases   | Percent | Age Commonly Seen          |
|-------------------------------------|-------------------|---------|-----------------------------|
| Benign                              | 65                | 59.0    | 0-19 years (75 percent)    |
|                                     |                   |         | 20-29 years (15 percent)   |
| Malignant                           | 32                | 29.0    | 30 or above                 |

Sixteen of the patients (14.5 percent) in our series developed second primary tumors, but it is difficult to assess whether this particularly high incidence of second primary cancer is purely coincidental or related to the underlying multiple neurofibromatosis.

It has also been difficult to gauge the effect of underlying multiple neurofibromatosis on the prognosis of co-existing cancer. However, our results (e.g., all of the breast cancer patients in our series died within five years of the initial diagnosis of breast cancer) have led us to conclude that underlying multiple neurofibromatosis does have an adverse effect on the prognosis in cancer patients and we believe that a larger study will establish this point.
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