NEUROFIBROMATOSIS, GIGANTISM AND SUBPERIOSTEAL HAEMATOMA

Report of Two Children with Extensive Subperiosteal Bone Formation

L. KULLMANN, BUDAPEST, HUNGARY, and H. W. WOUTERS, ROTTERDAM, NETHERLANDS

Many authors have described the skeletal manifestations of neurofibromatosis. Holt and Wright (1948), Moore (1957), Hunt and Pugh (1961) and Besirsky (1970) have suggested different classifications of the disease. The pathology has been described by Masson (1932), Lichtenstein (1949), Stout (1949), Schmincke (1956) and Gruner (1960).

We have observed two patients with manifestations of remarkable similarity. The abnormalities of the skin, the gigantism with elephantiasis of a limb and other findings were not so exceptional, but the formation of a subperiosteal haematoma and new bone, which have also been found, have been mentioned in only a few publications.

CASE REPORTS

Case 1—A boy, born in September 1959, had a family history of dysraphism. His mother and a paternal aunt had café-au-lait spots, and a cousin had meningomyelocele. Soon after birth the boy was admitted to hospital with paresis of the left leg. In the first year three operations were performed. At the first, specimens of tumours originating from the extradural nerves were taken for histological examination. At the second these tumours were partially

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**Fig. 1**

Case 1. Figure 1—Silent fracture of the left tibia without displacement. Note the elevation of periosteum and the extensive callus formation. **Fig. 2**—Swelling of the thigh, gigantism and soft-tissue tumour of the foot. Left side.
excised, and at the third a thickened nerve of the sympathetic chain was removed by block dissection. Histology confirmed the diagnosis of neurofibromatosis.

In January 1961 the patient was examined by one of us for the first time. Café-au-lait spots, scars of operations and on the left side paresis of the quadriceps with hypertrophy of the leg were noted. There was also a contracture of the left hip in flexion, lateral rotation and abduction, and of the left knee in valgus and flexion. Sensibility was not severely disturbed. Slight scoliosis was noted.

At the age of six years an increase of the scoliosis with scalloping of the vertebral bodies was evident. Gigantism of the left leg had increased. There was coxa valga and the shaft of the femur was curved. In 1969 at the age of ten the left lower limb was 13 centimetres longer than the right. During epiphysiodosis at the distal end of the longer femur a fibrous mass was found replacing the quadriceps. The underlying bone was very soft and was red. Biopsy revealed fragments of viable lamellar bone and a partly haemopoietic, partly necrotic bone marrow containing a small piece of rather dense fibrous tissue.

In February 1970 the patient reported a slightly painful swelling of the thigh which had increased gradually for five days. He did not feel unwell, but there was pyrexia of 39 degrees Celsius. On examination a large fluctuant swelling was found over the front of the femur. There was a slightly painful swelling of the lower leg and one enlarged inguinal lymph node was felt. The patient seemed in good general health but the erythrocyte sedimentation rate was raised at 80 and later 100 millimetres in the first hour. Radiographs revealed a fracture of the left tibia without displacement, and with callus formation (Fig. 1).

A week later a hard swelling was observed anterior to the left femur (Fig. 2), and radiographs disclosed new bone formation around an enormous subperiosteal cavity (Fig. 3). Three weeks later the situation was unchanged.

Investigations of the serum calcium, inorganic phosphate, serum proteins, vitamin C content, and liver function tests and extensive blood coagulation investigations were all normal. Operation—In June 1970 the wide lateral longitudinal scar was excised in a bloodless field. The distal growth plate of the femur was exposed and seemed to be ossified. The distal part of the tumour was freed. The vastus lateralis was fibrotic, and no red muscle tissue was seen. All the tissues appeared very vascular. The smooth, friable bony shell of the tumour was opened: its inner surface was covered by a gelatinous, fibrous material. The cavity contained dark serous fluid. The bare femoral surface appeared necrotic. A large part of the wall of the haematoma was removed, but some of it was left behind because of danger of causing a fracture. Partial excision of the hypertrophic plantar fatty tissue and epiphysiodesis at the proximal ends of the tibia and fibula were also done. Recovery was uneventful, but very slow.
Investigations showed a raised level of adenosine triphosphate in the erythrocytes (1·90 umol/ml RBC), but the other investigations including blood coagulation values were normal. Histology—Under a pigmented epidermis a fibrous, non-encapsulated tumour was found in the cutis and subcutis. The tumour was more cellular than the subcutaneous connective tissue. Its fibres were thinner, more wavy and less eosinophilic than the collagen fibres of the subcutaneous tissue.
There were many abnormal thickened nerves in the tumour mass (Fig. 4). With Van Gieson stain the fibres of the neurofibromatous tissue were coloured slightly pink or yellow. Microscopically the fibrous tissue which was found replacing the vastus lateralis had mainly ovoid nuclei, without a special arrangement of the cells and fibres. No muscle fibres were found but a few structures resembling Meissner tactile corpuscles were seen (Fig. 5).

In the deeper layers this fibrous tissue was looser and more vascularised. At this level the arrangement of the fibres was nearly parallel with some nuclei arranged in rows, but without formation of Verocay bodies. No separate periosteum could be distinguished. Osteoblasts covered fibrous bone trabeculae. A 1–10 millimetre thick osseous layer contained a highly vascularised tissue between the trabeculae. This interlamellar tissue contained osteoclasts and giant cells. The material, which was loosely attached to the interior surface of the bony shell, was completely necrotic, and so was the surface of the femoral cortex.

The plantar lipoma was divided by fibrous septa similar to those observed in a subcutaneous neurofibroma.

The cartilage of the distal tibial and fibular growth plate was active, without neurofibromatous changes.

With toluidine blue staining many mast cells were visible in the fibrous part of the neurofibromatous tissue. No mast cells were found inside the encapsulated structures such as the abnormal nerves, the Meissnerian corpuscles and other structures. The chromosomai pattern was normal.

Case 2—This patient, a boy born in January 1958, was described in this Journal by Smithuis in 1969. He had been seen at the age of three on account of enlargement of the left lower leg, and an enormous mass of subperiosteal new bone had been removed from the left tibia. There was no family history of neurofibromatosis.

In March 1970, a day after a slight injury, the left leg started to swell gradually. There was no pain. The general condition was good. A week later the boy was admitted to the Wilhelmina Children's Hospital, Utrecht. As the swelling was still enlarging a compressive bandage was applied. The erythrocyte sedimentation rate was 77 millimetres in the first hour. Other investigations including blood count, coagulation studies, liver function tests, serum iron, calcium and phosphorus, and alkaline phosphatase were normal. We found him to be covered with café-au-lait spots. There was slight webbing of the fingers, hypertelorismus, slight epicantus, and on the right side pes cavus was noticed. On the left side there was a more pronounced deformity of the foot with a soft swelling of the sole suggestive of a lipoma. The left lower leg was increased in length by 4 centimetres, and an enormous fusiform swelling with fluctuation and hyperthermia was present. The maximal circumference of the right leg was 30 centimetres, and of the left leg 38 centimetres (Fig. 6). The vessels were not dilated and no vascular bruit was present. There was no pyrexia. One enlarged inguinal lymph node was found on examination.

The power of the calf muscle was 0, of the extensors and flexors of the toes and of the anterior tibial and peroneal muscles 2 and of the thigh muscles 5. Sensibility was normal.

Radiographic examination revealed bone formation in the wall of a huge cavity around the left tibia (Figs. 7 and 8).

Operation—In April 1970 the haematoma was punctured and dark blood was aspirated. The lateral longitudinal, abnormally wide, soft scar was excised. The wall of the haematoma presented itself directly under the subcutaneous tissue. It had a vitreous aspect and was rather thickened. The wall was incised. Approximately one litre of dark blood was removed, which even at the end of the operation did not show signs of coagulation. The wall of the cavity consisted of fibrous tissue and soft bone, which were loosely connected. The tibial cortex seemed to be bare and had a coarse appearance. Anteriorly, in a region of irregular aspect, presumably the site of a former biopsy, bone was chiselled away. From the medullary
canal a yellowish friable material was removed. After removal of the bony wall of the haematoma, the gelatinous fibrous covering sheath was too large and was only partly excised. A greenish looking mass was also excised, probably representing parts of necrotic soleus muscle.

The course after operation was uneventful although because of slow healing the stitches—as in Case 1—were left in for three weeks.

The gas analysis both from the haematoma and from the venous blood showed normal values. Repeated investigations of blood coagulation and vitamin C content of the serum were normal.

The adenosine triphosphate level in the erythrocytes (in June 1970) was raised in this case too (1·90 umol/ml RBC).

Histology—Greyish, and partly greenish, fibrous tissue replaced the muscles of the leg. Microscopically it consisted of fibrous tissue with oedematous, myxomatous changes in some places, without a specific pattern of fibres, and nuclei. The nuclei were elongated or oval. Some of the cells appeared to be star-shaped. In one area only, a few muscle fibres were found showing different degrees of degeneration. Around the blood vessels particularly the fibrous tissue appeared to be more cellular and contained some nerve structures, structures like Meissner bodies and longitudinal wavy structures of Schwann cell origin (Fig. 9).

A thickened, fibrous periosteum covered a newly formed fibrous cancellous bone layer, with an average diameter of 1 millimetre. A very vascular fibrous tissue with giant cells and osteoblasts filled the spaces between the trabeculae (Fig. 10). The internal wall of the cavity of the haematoma consisted of fibrous tissue which in places had an organised contact with the haematoma. Van Gieson and toluidine blue staining gave results similar to those seen in Case 1.

The lamellar cortical bone showed partial necrosis at the site of the biopsy. The bone marrow was partly necrotic. It contained cells with a vacuolated cytoplasm and large round nuclei, resembling Gaucher cells, but without a positive periodic acid-Schiff reaction. The chromosomal pattern was normal.

DISCUSSION

Both patients showed gigantism with elephantiasis of one of the lower limbs—two rather characteristic phenomena in neurofibromatosis.

The cause of both the gigantism and the elephantiasis is unknown. Some authors (Holt and Wright 1948; Göbbelet, Löhr, Magnus and Sailer 1969) have suggested vascular dysplasia, while others (Inglis 1950a and b, Gruner 1960, Hunt and Pugh 1961) consider basic changes which they mention as neurogenic factors, mesodermal dysplasia or congenital developmental disturbance, as causative.
The third interesting phenomenon is the looseness and mobility of the skin, an anomaly which was observed by Stout (1949) and Fairbank (1950). The skin seems flabby and inelastic, as in the Ehlers-Danlos syndrome.

In this respect it is of interest that in our two cases healing of the wounds was unquestionably delayed, an observation which was not found in the literature. Also, the pre-existing scars were unusually wide. Neurofibromatous tissue had replaced the normal subcutis, and in this abnormal subcutaneous tissue no normal formation of collagen fibres could be seen. This might explain both the abnormally slow wound healing and the width of the scars.

The fourth interesting finding in our patients was the absence of striated muscles in the areas examined. A greyish, soft-tissue mass occupied the space between the skin and the bone. In this tissue mass in Case 2 only a few muscle fibres were found and in Case 1 none was found. McCarroll (1956) and Guilleminet, Creyssel, de Mourgues and Fischer (1970) made similar observations in a giant limb. Hudson and Cox (1956) stated that the neurofibromatous tissue had infiltrated and separated the striated muscle fibres. In Case 2 some muscle fibres were surrounded by a fibrous mass, most of which had a normal appearance, but some parts showed signs of degeneration, suggesting a slow invasive process. In Case 1 no fibres of the quadriceps were detected microscopically, but the interpretation of this observation was obscured by preceding operations on the lumbar plexus.

In another patient suffering from neurofibromatosis with orbital dysplasia we observed infiltration of the temporal muscles by neurofibromatous tissue. Similar observations were made by Heuer and Bell (1931) and by Hruban, Evans and Humphreys (1960). Stout (1949), Crowe, Schull and Neel (1956) and Gruner (1960) found a great number of mast cells in...
neurofibromatous tissues. We also observed many mast cells, but only within the fibrous masses surrounding the encapsulated neurogenic structures.

Perhaps the most interesting is the sixth observation of huge subperiosteal haematoma which developed in Case 1 on the femur, and in Case 2 on the tibia. In neurofibromatosis little attention has been paid to haemorrhage. In 1939 Jones and Hart reported a case of a twenty-three-year-old female who was suffering from gigantism with elephantiasis of her left hindquarter in whom voluminous bleeding in the neurofibromatous subcutaneous tissue occurred in the lumbar region. These authors collected from the literature seven other cases of bleeding in neurofibromatous soft tissue.
Recently Naunton and Hemenway (1960) and Turner, Kelly and Payne (1963) described similar cases of their ten patients; three died of haemorrhage without evidence of malignancy. Soon after the development of a haematoma, three more died of a malignant tumour; in two cases the tumour had developed at the site of the bleeding.

Kleitsch, Kehne and Gutch (1951) described gastro-intestinal haemorrhage due to neurofibromatosis. Guilleminet and colleagues (1970) described a subperiosteal haematoma of the femur on which one month earlier an operation had been performed.

In neurofibromatosis vascular changes such as angiomata, aneurysms and other pathological changes of the walls of the vessels have been described by Moore (1957), Hruban and colleagues (1960), Cambier (1962) and Halpern and Curranino (1965).

According to most authors haemorrhage in neurofibromatosis might be due to these vascular changes. We wonder if there may be a relationship between the gigantism, the looseness of the diseased tissue and the occurrence and size of the haemorrhage. We assume that in our two patients, in whom subperiosteal haemorrhage occurred in a limb with looseness of the soft tissues, the connection between periosteum and the underlying bone was abnormally loose. Lack of resistance of the periosteal sheath may be responsible for overgrowth (Crilly 1970). In Case 1 this theory is strengthened by the observation that a silent fracture without displacement occurring in the tibia of the affected leg, produced very extensive elevation of the periosteum with extensive local callus formation.

Moreover, the fact that subperiosteal haemorrhage seems to occur predominantly in children in whom normally the periosteal sheath is less adherent to the underlying bone than in adults, supports this idea. Brooks and Lehman (1924), Friedman (1944) and Hensley (1953) each described one patient with neurofibromatosis, gigantism and local extracortical bony proliferation.

We agree with Hensley, who presumes that the latter was the result of subperiosteal haemorrhage. Miller (1953) described an eleven-year-old boy with an 18-centimetre long subperiosteal haematoma and bone formation at the left tibia. Gigantism was not mentioned. The diagnosis of neurofibromatosis was based on histology.

Another observation we made in both cases was the elevated ATP level of the red blood cells, a finding which will be discussed elsewhere.

SUMMARY

Two cases of neurofibromatosis with gigantism of a lower limb complicated by subperiosteal bleeding, and exuberant subperiosteal bone formation are reported. Both patients were young boys. Five similar cases were found in the literature.

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REFERENCES


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