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Articular ossification after malignant neurolepsis

A case of schizophrenia treated with phenothiazines

Following administration of phenothiazines for schizophrenia, a 25-year-old patient developed a malignant neuroleptic syndrome followed by bilateral periarticular ossification of the knees, with severely limited motion. Two years later, the patient regained useful motion after bilateral excision of the ossified tissue and intensive physiotherapy. No recurrence of ossification was observed 3 years after operation, and the patient has maintained almost normal motion.

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Introduction

Since the first description of heterotopic ossification following paraplegia (Dejerine & Ceillier 1918), other neural disorders resulting in periarticular bone formation have been identified. These are poliomyelitis, syringomyelia, myelitis, myelodysplasia, tabes dorsalis, tetanus, anoxic brain damage, stroke (Bayley 1979), head trauma, and prolonged coma (Roberts 1968).

We describe a case of bilateral periarticular ossification of the knees following a malignant neuroleptic state due to administration of phenothiazines.

Case report

A 25-year-old male professional driver was referred to our department in March 1983 with a 2-year history of severe limitation of motion in both knees. He was known to suffer from a hebephrenic type of schizophrenia since the age of 22 and had been frequently hospitalized in psychiatric institutions. During the last hospitalization in April 1981, he was treated with levomepromazine, 200 mg daily. After 36 hours of treatment, he developed malignant neuroleptic syndrome characterized by an acute psychotic state with audiovisual hallucinations, severe asthenia, fever, and diarrhea.

The drug administration was stopped and the patient received supportive therapy with gradual return to normal status within 10 days. However, during this period progressive rigidity developed, and a gradual limitation of motion with flexion contracture of both knees was observed. He now had physiotherapy, plaster splints, and forceful mobilization. Radiographs of the knees were normal, but 6 months later small zones of diffuse calcifications were seen around the knees. Alkaline phosphatase levels were elevated and began to normalize during the next year. No clinical improvement was achieved by conservative methods; rather, the rigidity of the knee joints became more and more pronounced.

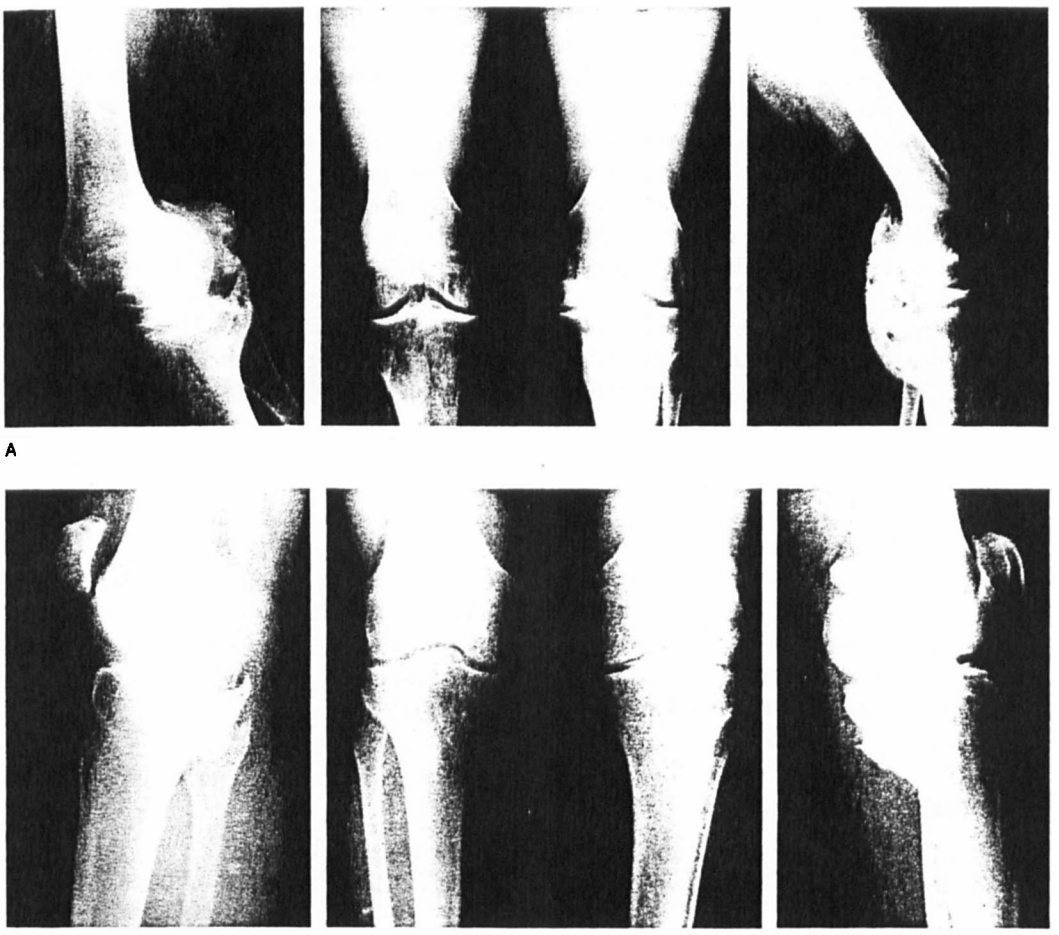
On admission 2 years later, he had a fixed flexion contracture of 30 degrees of his left knee and contracture of his right knee with flexion from 30 to 60 degrees. The patient walked without active propulsion by extension of his knees. Secondary bilateral pes equinus developed. All the other joints had a completely normal range of motion.

The radiographs (Figure 1) showed periarticular ossifications and bony bridges in the posterior and medial aspects of the knees. The laboratory findings, including alkaline phosphatase, were all within normal limits.

The ossified tissue was excised through a posterior approach, and capsulotomy and manipulation of both knees were performed. At the end of the operation the passive range of motion was 0–110 degrees in both knees. Bilateral percutaneous Achilles tendon lengthening was also performed with application of a below-knee plaster cast. The histologic examination of the excised tissue demonstrated trabeculae of well-formed and mature fibrous stroma and osteoid formation, which was consistent with heterotopic ossification.

Postoperatively, active and passive motions of the knees were encouraged with night splints alternately in flexion and extension. Strengthening of quadriceps and hamstrings followed.

At the last examination, 3 years after the operation, the patient had 0–110 degrees of motion of both knees, was able to put on his socks and shoes by himself, and could play football. Radiographically, the ossifications had not recurred.



A

B

Figure 1. A 25-year-old man with schizophrenia with malignant neuroleptic syndrome during treatment with levomepromazine. Periarticular ossifications developed in both knees.

A. Preoperative, 2 years after neurolepsis. Note the posteromedial ossification bridges.

B. Three years after excision of the ossified tissue. The extraarticular ossification behind the left femoral condyle is a small fragment that was unnoticed during surgery.

Discussion

To the best of our knowledge, no case of periarticular ossification of joints following neuroleptic malignant syndrome has been reported. Neuroleptic malignant syndrome is a rare and occasionally lethal condition occurring as an idiosyncratic response to major tranquilizers, such as butyrophenones and phenothiazines (Caroff 1980). The syndrome typically develops over 24–72 hours, with hyperthermia that usually is associated with muscle rigidity. Signs of autonomic dysfunction, such as tachycardia, labile arterial pressure, and sweating, may precede the onset of the hyperthermia (Editorial, 1984). Mortality, which has been estimated at 20–30 per cent (Caroff 1980), is most commonly due to respiratory failure. The pathogenesis of the neuroleptic malignant syndrome is unknown. An alteration of central neuroregulatory mechanisms was suggested as the cause (Editorial, *Lancet* 1984).

Heterotopic ossification following head or spinal trauma or as a complication of a neural disorder is a well-known condition. The incidence of heterotopic ossification in head-injured patients is in the range of 11 to 20 per cent (Garland

et al. 1980, Mendelson et al. 1975). In patients with paraplegia or quadriplegia, heterotopic ossification has been reported to occur in 20 per cent of patients (Wharton & Morgan 1970). The joint most frequently involved is the hip followed by the shoulder and elbow (Garland et al. 1980, Mendelson et al. 1975, Mietlants et al. 1975). The knee, which was affected in our patient, is rarely involved: viz., 0.3–8 per cent (Garland et al. 1980, Mendelson et al. 1975).

Several theories have been advanced to explain the development of periarticular extraosseous ossifications (Bayley 1979, Larson et al. 1981, Roberts et al. 1979), but none have been universally accepted. The factor that is common to all the etiologic conditions that lead to heterotopic ossification is the presence of a lesion of the central nervous system and a muscular or burn injury (Urist 1980). The administration of phenothiazines to our patient most probably caused a disturbance of the central nervous system.

The treatment of choice once the ossification restricts the joint motion is surgical excision of the ossified tissue after maturation to avoid recurrence (Morgan et al. 1973). There is no proof that physiotherapy affects the outcome of the condition (Sazbon et al. 1981). Maturity can be determined by radiographs, bone scans, and alkaline phosphatase testing. The levels of alkaline phosphatase are reported to be elevated during the active growing period and to return to normal values at maturation. Serial bone scans, with a tendency to decreased uptake, are valuable for determination of maturation. The radiographs have a limited role for determination of maturity, but serve to delineate the anatomic localization (Tibone et al. 1978). Despite the use of these parameters, the recurrence rate after excision of the calcified tissue in the hip is high when compared with the elbow (Garland et al. 1980, Roberts & Pankratz 1979). The reason for the recurrence of the heterotopic ossification of the hip and not of the elbow is unclear. We have not found any statement about the results following excision of the ossified tissue in knees.

References

Bayley, S. J. (1979) Funnybones: a review of the problem of heterotopic bone formation. *Orthop. Rev.* **8**, 113–120.

Caroff, S. N. (1980) The neuroleptic malignant syndrome. *J. Clin. Psychiatry* **41**, 79–83.

Dejerine, M. M. E. & Ceillier, A. (1918) Paraosteoarthropathies des paraplegiques par lesions medullaires (Etudes cliniques et radiographiques). *Ann. Med.* **5**, 497–535.

Editorial (1984) Neuroleptic malignant syndrome. *The Lancet* **i**, 545–546.

Garland, D. E., Blum, C. E. & Waters, R. L. (1980) Periarticular heterotopic ossification in head-injured adults. Incidence and location. *J. Bone & Joint Surg.* **62-A**, 1143–1146.

Larson, J. M., Michalski, J. P., Collacott, E. A., Eltorai, D., McCombs, C. C. & Madorsky, J. B. (1981) Increased prevalence of HLA- B27 in patients with ectopic ossification following traumatic spinal cord injury. *Rheumatol. Rahabil.* **20** , 193–197.

Mendelson, L., Grosswasser, Z., Najenson, T., Sandbank, U. & Solzi, P. (1975) Periarticular new bone formation in patients suffering from severe head injuries. *Scand. J. Rehab. Med.* **7**, 141–145.

Mietlants, H., Vanhove, E., de Neels, J. & Veys, E. (1975) Clinical survey of and pathogenic approach to para-articular ossifications in long-term coma. *Acta Orthop. Scand.* **46**, 190–198.

Morgan, T. H., Wharton, G. W. & Ellis, M. A. (1973) the treatment of ankylosis of the hip joint secondary to heterotopic ossification. *J. Bone Joint Surg.* **55-A**, 1304–1305.

Roberts, P. H. (1968) Heterotopic ossification complicating paralysis of intracranial origin. *J. Bone Joint Surg.* **50-B**, 70–77.

Roberts, J. B. & Pankratz, D. G. (1979) The surgical treatment of heterotopic ossification at the elbow following long-term coma. *J. Bone Joint Surg.* **61-A**, 760–763.

Sazbon, L., Najenson, T., Tartakovsky, M., Becker, E. & Grosswasser, Z. (1981) Widespread periarticular new-bone formation in long-term comatose patients. *J. Bone Joint Surg.* **63-B**, 120–125.

Tibone, J., Sakimura, I., Nickel, V. L. & Hsu, J. D. (1978) Heterotopic ossification around the hip in spinal cord injured patients. A long-term follow-up study. *J. Bone Joint Surg.* **60-A**, 769–775.

Urist, M. R. (1980) *Fundamental and clinical bone physiology*, pp. 369–393. J. B. Lippincott Co., Philadelphia.

Wharton, G. W. & Morgan, T. H. (1970) Ankylosis in the paralyzed patient. *J. Bone Joint Surg.* **55-A**, 105–112.