

Melorheostosis and a review of the literature in China

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Summary Melorheostosis is an uncommon, non-genetic, non-developmental, sclerosing dysplasia of bone and adjacent soft tissues, with deformity of the extremity, pain, limb stiffness and limitation of motion. The characteristic radiographic appearance consists of irregular hyperostotic changes of the cortex resembling melted wax dripping down the side of a candle. In this review, clinical characteristics of Melorheostosis are discussed and reports in the Chinese literature are summarized.

Keywords: Melorheostosis, sclerosing bone dysplasia, developmental anomalies, bone sclerosis, China

1. Introduction

Melorheostosis is a rare, non-hereditary, benign, sclerosing mesodermal dysplasia which affects the skeleton and adjacent soft tissues (1-3). It got this name because of the characteristic periosteal hyperostosis along the cortex of long bones which looks similar to the flowing or dripping of candle wax (originated from Greek, melos = limb, rhein = to flow, ostos = bone) (4-6). Melorheostosis is also known by other synonyms such as candle disease of the bone, and osteosis eburnisans monomelica (7,8). Until now, there have been about 400 cases reported in the English literature (9).

In 1922 Melorheostosis was first described by Leri and Joanny, and was also called Leri's disease or syndrome thereafter (10). This condition may affect only one bone (monostotic form, representing a forme fruste of the disorder), one limb (monomelic form), or multiple bones (polyostotic form). Although a benign dysplasia, the osseous changes can cause morbidity. Skin and subcutaneous tissue involvement can result in fibrosis and joint contractures leading to deformity and limb-length discrepancy (3,11-13).

The aim of this study is to summarize the classical features of this disease and review the literature reported

in China, to enrich our knowledge of melorheostosis and provide information in the Chinese population, which we believe will enhance understanding of this anomaly and improve the accuracy of diagnosis and efficacy of treatment.

2. Search strategy

The electronic database of Chinese Medicine, Wanfang Data, was searched using the keyword "melorheostosis" to identify all literature published in peer-reviewed Chinese journals since January 1990. The full text was reviewed and clinically related data extracted, summarized and discussed. Cases from the same authors were examined to avoid repetition.

3. Etiology and pathogenesis

The etiology of melorheostosis remains unknown. There have been various theories proposed to explain the pathogenesis of this disease such as a developmental disorder theory (14), ischemic theory (15), telangiectatic theory (16), and infective theory (17). Currently, there are two major hypotheses in existence. In 1979, Murray and McCredie (18) correlated melorheostosis with sclerotomes, hypothesizing that melorheostosis might be the result of a segmental sensory lesion due to a specific infection, insult, or injury to segments of the neural crest during embryogenesis, which partially explains the peculiar monomelic involvement of melorheostosis. In 1995, Fryns (19) proposed mosaicism to explain the sporadic occurrence of dysplasia which suggests

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that the asymmetric involvement of skeletal structures and concomitant vascular and hamartomatous changes in the overlying soft tissues result from an early post-zygotic mutation of the mesenchyme which explains why the extent of involvement is so variable and why the incidence ratio in both genders is equal.

4. Histopathology

As has been reported by various researchers, microscopic examination of cortical specimens from melorheostosis patients reveals nonspecific periosteal bone formation with thickened trabeculae and fibrotic changes in the marrow spaces (1-3). These bones consist mostly of primary haversian systems and are largely obliterated by the deposition of sclerotic, irregular, and thickened lamellae, particularly on the periosteal surface (4,6,20).

Islands of cartilage have been described in periarticular lesions with evidence of endochondral bone formation in addition to intramembranous bone formation within the peri-joint cellular fibrous tissue (4). Osteoblastic activity along the margins of osteons is common, while osteoclastic activity is never a prominent feature although occasionally noted (20).

5. Clinical Presentation

Onset of melorheostosis is usually insidious. The symptoms, which include pain, limb stiffness, limitation of motion in the joints, and deformity of the involved extremity, usually do not manifest until late childhood or early adolescence and tend to progress into adult life (1-4). The disease usually exhibits a chronic course with periods of exacerbation and arrest. Progression of melorheostosis can be rapid in childhood but often slower in adulthood, during which joint stiffness and pain are the predominant symptoms (6-8,10,12,21-26). Because the abnormal ossifications frequently involve soft tissues and extend into the joints, the latter often exhibit a restricted range of motion as the result of contracture and fibrosis. Other deformities are also common, including flexion contractures of the hips and knees, varus or valgus deformities of the feet, and overlapping toes (27-29). Joint ankylosis may be present as a result of heterotopic bone formation and soft-tissue calcification (30,31). Laboratory findings for serum calcium, phosphorus, and alkaline phosphatase levels have been reported to be within normal limits (1-3,6).

6. PrP^C: a novel therapeutic target for AD

Flowing cortical hyperostosis along one side of the shaft of the long bone resembling "melting wax flowing down the side of a candle" is the characteristic radiographic appearance of melorheostosis (2-4,28,31-34). The

areas of dense hyperostosis have a linear, segmental distribution and tend to extend distally from one bone to the next, ultimately involving the bones of one or more digits. The classic presentation is not always seen in all patients and there are other patterns well described by Freyschmidt (6). These include: *i*) osteoma-like appearance with hyperostosis located either on the outer or inner aspect of the affected bone (the most common pattern in his study); *ii*) osteopathia striata-like pattern, which shows long and dense hyperostotic striations near the inner side of the cortex in two or more bones. Occasionally, melorheostosis may be mistaken for osteopathia striata, but the striations in melorheostosis are much larger, broader and unilateral, unlike the genuine osteopathia striata; *iii*) myositis ossificans-like ossifications in soft tissues, which are more nodular in arrangement without any lamellar appearance to the ossification. In later stages of the disease, endosteal hyperostosis may be seen, and this can partially or completely obliterate the medullary cavity. Bony overgrowth, particularly around the hip, may simulate osteochondroma.

7. Diagnosis and differentiation diagnosis

The polystotic form of melorheostosis, due to its characteristic appearance on conventional radiography, can be readily distinguished from other lesions (35,36). However, monostotic lesions can have varied appearances, and should be differentiated from myositis ossificans, osteochondroma, osteoid osteoma and parosteal osteosarcoma (37,38). In myositis ossificans the ossification is more significant at the periphery than at the center, and a radiolucent cleft can be seen between the lesion and the cortex. Mature myositis ossificans usually shows no uptake or only minimal activity on scintigraphy. In osteoid osteoma, unlike melorheostosis, the surface of the lesion is usually smooth rather than wavy, and a confident diagnosis can be made when the nidus is observed on cross-section imaging. In osteochondroma, the cortex of the lesion is continuous with the cortex of the parent bone and there is also continuity of the medullary cavity, which are its characteristic features, while in melorheostosis, the lesion typically has paraosteal or endosteal involvement. In parosteal osteosarcoma, the major sign to differentiate it from melorheostosis is bone destruction. Radionuclide bone scintigraphy can also help with intense uptake and increased activity in the medullary cavity.

8. Treatment

Various conservative or surgical methods have been practiced in treating the pain and deformities associated with melorheostosis. Conservative therapies include oral medications such as bisphosphonates, NSAIDs, and

nifedipine. Other nonsurgical treatments have also been used such as physical therapy, manipulations, serial casting, braces, and nerve block, but unfortunately most of these methods are ineffective. Surgical procedures consist of soft-tissue procedures such as tendon lengthening, excision of fibrous and osseous tissue, fasciotomy, capsulotomy, osteotomies, excision of hyperostoses, arthrodesis, contralateral epiphysiodesis, and amputation (1-6,39-41). When treating limb deformities associated with surgical treatments in melorheostosis patients, recurrences are common.

9. Chinese literature review and discussion

As a result of the Chinese literature review, 104 papers were retrieved from the database since January 1990, among which 95 were case reports and 9 case series studies. The total number of Melorheostosis cases reported in these last 23 years in China is 223. The male/female ratio in these cases was 115/108. The age at which the cases were diagnosed ranges from 3 to 72. Though the etiology of Melorheostosis remains unknown, research indicates that women and men are affected equally by the disorder, and it usually presents after early childhood. As was reported in the English literature, Melorheostosis occurs at about 0.9 cases per million population and is a very uncommon disease (9). But unfortunately, we failed to find any study that investigated the incidence of melorheostosis in the Chinese population.

Melorheostosis's onset is often insidious. In our study, 14 patients out of 223 (6.28%) were found accidentally. 3 of which were diagnosed by routine physical examination, and the other 11 by regular imaging because of trauma in the ipsilateral limb. The most common complaints of the symptomatic patients in our study were limb pain, joint stiffness, limitation of joint motion, and later on deformity.

The distribution of the lesion is mostly segmental and unilateral (hemimelic). It may affect only one bone (monostotic), one limb (monomelic) or multiple bones (polyostotic), which in our study, were 3.14%, 78.53% and 18.33% respectively. In cases with multiple adjacent bones affected, the lesions tend to be in a sclerotomal distribution, and the lower extremity is more frequently involved than the upper extremity. The long tubular bones are most commonly affected although the disease may involve any of the short bones of the hand and foot. Melorheostosis can also have rare features such as spinal involvement, para-articular soft-tissue masses and intra-articular extensions. In our cases, 2 patients were found with lumbar spine involvement, but with no neurogenic symptoms (26,42). The co-occurrence of melorheostosis with osteopoikilosis was presented in 3 cases (43,44).

The spectrum of diseases might be very different between countries and cultures. As rare as melorheostosis

is, there are still clues leading to a correct diagnosis of uncommon cases. We hoped to provide evidence that might not be easily accessed by non-Chinese physicians and share our experience with foreign doctors with this review.

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