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Melorheostosis: A Review Article

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Abstract

Melorheostosis is a benign sclerosing bone disease that affects the bone and adjacent soft tissue. Although the description of the disease was made nearly a century ago, many aspects of the condition are still unknown. This condition might be an incidental finding. Patients may present with pain that could be associated with deformities. The course is still unknown and various theories have been proposed in the literature. Diagnosis is normally made using X-rays and not all patients will have classical candle wax appearance. Recently, 'dumpling on a plate sign' for both MRI and CT scans for flat bones has been suggested. Biopsy may be done if the diagnosis is in doubt but there is no definitive histological feature. Association with other conditions is not unusual and multidisciplinary team approach should be considered. The femur seems to be associated with malignancy. The condition should be part of differential diagnosis for sclerotic bone conditions. Management is normally symptomatic relive either conservative or surgical.

Keywords: Melorheostosis; Leri disease; Sclerosing bone disease; Hyperostosis; LEMD3 gene

Introduction

There have been numerous medical advancements over the past century. In 1922 a description of melorheostosis was made by Leri and Joanny [1] yet many things about the condition are still unknown. However, the condition has been demonstrated to have been present during ancient times. Kelley [2] reported a case of a 25-year-old to 30-year-old Chilean female with melorheostosis that dated to between 4,000 BC and 5,000 BC. Canci et al. [3] reported the condition in a woman from the necropolis of Montescaglioso Belvedere that dated back to the 6th century BC. Melorheostosis is a rare, benign, sclerosing bone disease characterized by hyperostosis of the bone that resembles dripping or flowing candle wax [4]. The word derives from the Greek (melos = limb, rhein = to flow, and ostos = bone) [5]. The common synonym is Leri's disease. Other names include candle disease of the bone, osteosis eburnisans monomelica, eburnating osteitis, osteopathia hyperostotica congenita (unius membri) or hyperostotic osteopathy [6-8]. Patients may be asymptomatic or present with pain, swelling, deformities and joint stiffness [5]. There have been more than 400 publications on the disease, either as a case report or a mini-case series [9]. This manuscript will try to outline what has been done for those with the disease since the description of the condition by Leri and Joanny [1].

Incidence

The condition is rare, affecting fewer than a million globally. Forty to fifty percent of patients are diagnosed under the age of 20 years [7,10]. Most literature studies report an equal male to female distribution; however, a Mayo study found a high female involvement of 4:1 [5,11]. There are other case series studies showing high female involvement [12,13]. Dhillon et al. [5] reported 14 cases of foot and ankle while fewer than 10 craniofacial cases have been reported [13,14]. Although any bone can be affected, the most common bone affected is the lower limb [11,15]. The disease has a high affinity with the diaphyseal and epiphyseal bones. Only rarely does the disease affect the axial bones and joints [16,17]. The condition can be monostotic, polyostotic, monomelic or hemimelic with monomelic being the most common. Biaou et al. [18] reported a case of bilateral upper limb involvement. A person of any race can be affected [19] and while the disease has a slow progression in adults [20], in children its progression is rapid [21]. When melorheostosis occurs with other sclerosing bone dysplasia, the condition is termed overlap syndrome [22]. The most common sclerosing bone dysplasia that can occur with melorheostosis is osteopoikilosis, and osteopathia striata [23].

Pathogenesis

The cause and pathogenesis are still unknown although various hypotheses have been suggested. Some have also suggested that the condition may be associated with sclerotomes involvement. In

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Table 1: Radiographic variants of melorheostosis according to Freyschmidt [47].

Type	Description
1. Osteoma-like	Hyperostosis is located on either the outer or inner aspect of the affected bone
2. Osteopathia striata-like	Dense hyperostotic striations near the inner side of the cortex in two or more bones
3. Myositis ossificans-like	Ossifications in the soft tissues, which are more nodular in arrangement without any lamellar appearance to the ossification
4. Mixed	Combination of the above
5. Dripping wax appearance	Classic dripping wax appearance

1979 the sclerotomes theory was proposed by Murray and McCredie [24]. They suggested that the condition normally follows nerve segment distribution. This might be due to segmental nerve lesion due to infection, insult or injury to the neural crest during embryogenesis. The segmental nerve involvement closely resembles herpes zoster. Other authors also support the sclerotomes theory [25,26].

Fryns [27] proposed mosaicism as a cause of the condition. This is sporadic occurrence in the early postzygotic mutation of the mesenchyme that results in asymmetric involvement of skeletal structures, with concomitant vascular and hamartomatous changes in the overlying soft tissue.

Hellemans et al. [28] proposed that the condition might be due to a loss of function mutation in the LEMD3 gene (MAN 1). LEMD3 is a protein involved in bone morphorgenic protein and tumour growth factor- β signaling. The germline mutations of LEMD3 occur in patients with melorheostosis and osteopoikilosis or Buschke-Ollendorf Syndrome (BOS). However, LEMD3 mutations cannot be reproduced in patients with isolated melorheostosis.

Whyte et al. [29] reported KRAS mutation in the lymphatic malformation and hyperpigmented skin in a boy with polyostotic involvement. Half of the patients can have somatic heterozygous activating mutations in MAP2K1 that result in an increased proliferation of immature osteoblast [30]. Patients with positive MAP2K1 have the classic radiological "dripping candle" sign, as well as a high rate of joint involvement and a higher number of osteoblasts and osteoclasts [12,31]. Recently, Kang et al. [32] found that there were somatic SMAD3-activating mutations causing melorheostosis by up-regulating the TGF-β/SMAD pathway in four patients who were not related. Other types of pathogenesis included developmental, ischemic, telangiectatic, hypervascularity and infection [6,33].

Case Presentation

The condition can be an incidental finding due to its benign nature. Pain is the common presenting symptom in adults while children may present with deformities. Bone pain may be due to activation of pain receptors, increased osteoclastic bone resorption, raised intraosseous pressure, increased vascularity secondary to hyperostosis or soft tissue involvement around joints [34,35]. Other presentations include swelling, joint stiffness, muscle atrophy, soft tissue mass, myositis, subcutaneous fibrosis, scleroderma, hyperpigmentation, flexion contractures, and limb length discrepancy. Limb length discrepancy is due to early fusion of the growth plate. The involved bone can be longer or shorter [5,6,12,36]. There has also been a case of chronic patellar dislocation due to the disease [37]. Kingori et al. [38] reported an unusual presentation of increased temperature in a 56-year-old patient. The temperature was resolving on its own for most of the time, but it is not known if the high temperature was due to melorheostosis. About 77% of patients can have sensory deficit [12]. Nerve entrapment can also occur resulting in surgical intervention [39-42]. Spine involvement has been reported and the patient can present with scoliosis or severe myelopathy [43,44]. Vascular occlusion can occur. Ishibe et al. [45] reported occlusion of the dorsalis pedis artery.

Diagnosis

The diagnosis is made mainly through X-rays. Typical findings include undulating/flowing cortical hyperostosis (candle wax sign) along the cortex, patchy sclerosis or a linear endosteal hyperostosis. There can also be osteolysis radiology. The candle sign is the pathognomonic of the condition [4-6,46] (Figure 1). However, not all cases present in a classical manner. In children, the hyperostosis does not extend beyond the boundaries of the cortex while the external contours of the bone are usually undisturbed [36]. Freyschmidt [47] describes five radiological types (Table 1). The osteoma-like was common and myositis ossificans was the rare type. It is not unusual for the radiological types to occur together. Elsheikh et al. [48] reported a combination of classic and myositis ossificans in the shoulder.

Hematological and biochemistry parameters that include serum calcium, phosphorus, alkaline phosphatase, C-reactive protein, erythrocyte segmentation rate, alpha-fetoprotein, carinoembroyonic antigen, and carbohydrate antigen are within normal limits [49,50]. Kerkeni and Chapurlat [51] reported a case of high Fibroblast Growth Factor-23 (FGF-23) with normal serum phosphate. The association of high FGF-23 in the patient could not be determined [51].

The bone scan shows increased uptake in the distribution of the condition that might be due to increased bone metabolism or much greater bone mass in the affected area [35,52,53]. CT and MRI scans shows undulating hyperostosis along the cortex and encroachment of the medullary cavity. The other benefit of using MRI is evaluation of soft tissue masses that may be contiguous or adjacent to bony hyperostosis [54,55]. Recently, Chaudhary et al. [56] have added a 'dumpling on a plate sign' for both MRI and CT scans for flat bones.

Biopsy is normally not required to make the diagnosis, but it might be helpful if there is a doubt about the diagnosis [8]. There are no histological clear pathognomonic features of the condition. The findings normally include abnormal dense compact bone [5]. Fick et al. [57] in their case series reported that about 73.3% had dense cortical bone, 60% had woven bone and 66.7% had increased porosity. They concluded that patients might have similar histological features but the diagnosis is based on the clinical and radiological findings [57].

Differentials

Melorheostosis can resemble many conditions. Table 2 shows differentials of the condition [6,13,48,58,59] differentiating melorheostosis from other conditions requires careful assessment of the clinical, radiographic, histopathologic, and laboratory tests [13].

Table 2: Differentials of the condition.

Differential	Description
Osteoma	Has smooth outline, focal and size usually less than 1.5 cm
Caffey disease	Affects infants with lamellated periosteal reaction
Parosteal osteosarcoma	Tumour has cauliflower-like ossified mass and there can also be bone destruction
Osteopathia striata	Striations in melorheostosis are much larger, broader, and unilateral, unlike the genuine osteopathia striata
Osteopoikilosis	Osteopoikilosis has numerous round to ovoid white densities of similar size
Chronic osteomyelitis	The infection can cause destruction of the bone and the sequestrum can have a focal sclerosis
Synovial chondromatosis	Synovial chondromatosis has multiple intra-articular calcifications distributed throughout the affected joint
Osteochondroma	Cortex of the lesion appears to be attached to the cortex of underlying bone, and the medullary cavity of the lesion is continuous with the medullary cavity of the underling bone
Myositis ossificans	Usually a history of trauma accompanies myositis ossificans

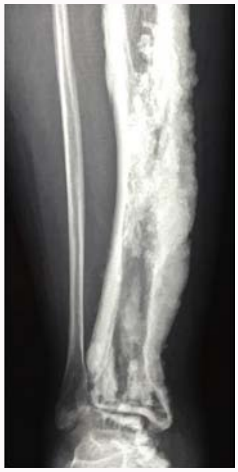

Figure 1: Showing candle sign.

Associated Conditions

Various systemic conditions can be found with the condition. Fryns [27] reported a follow-up case of a seventeen-year-old who was first examined when she was three years old. The patient had developed systemic arterial blood pressure and further investigations showed a small kidney on the side of the melorheostosis. Roger et al. [60] reported that the condition can be seen together with nephrotic syndrome, hyperpigmentation, and linear scleroderma, induration of subcutaneous tissue, capillary hemangioma, venous dilatation, arteriovenous aneurysms, vascular nevus, fibroma, fibrolipoma, and lipomatosis, retroperitoneal fibrosis.

Soft tissue tumors include demoid tumors [61] and multicentric fibromatosis [25] which are mostly found in the upper limbs. Benign osseous tumors include intrathecal lipoma, and fibrolipomatous lesions which in turn involve the axial bones [62,63]. Facial giant cell granuloma has been reported [13]. Lee and Sandferson [64] reported hypophosphatemic rickets in a 12-year-old boy. The femur is associated with malignancy. Malignant tumors include osteosarcomas [65,66] and malignant fibrous histiocytoma [67]. It is not known if the association of these malignant tumors was due to transformation or coincidental. Naik and Narang [33] reported a pathological neck of femur fracture in a known patient with prostate carcinoma. The patient's fracture healed quickly, however; his carcinoma disseminated in an unusual manner. Anthropologists excavating graves dating from prehistoric times observed the condition with Diffuse Idiopathic Skeletal Hyperostosis (DISH) [3].

Management

There is no definitive cure for the disease and due to various multiple organ involvement; the patient may need a multidisciplinary approach. Both conservative and surgical management are for relief of symptoms. Conservative management includes casting, bracing, physiotherapy, Non-steroidal Anti-Inflammatory Drugs (NSAIDs), bisphosphonates and rarely, nifedipine. After failed NSAIDs usage, the majority of patients do well on bisphosphonates. Commonly used bisphosphonates include pamidronate, alendronate and zoledronic acid [10,35,68,69]. The duration of bisphosphonates usage is not clear and not all patients respond well to them. Byberg et al. [70] reported a patient who responded to denosumab after not improving with zoledronic acid. Semble et al. [71] reported pain reduction with the usage of nifedipine but the patient developed side effects; the drug was stopped and the pain recurred. No drug has been shown to remove the condition. The literature search did not find usage of radiotherapy.

Surgical Technique

Surgical procedures include tendon lengthening, excision of fibrous and osseous tissue, fasciotomy, capsulotomy, osteotomies, spine decompression, nerve decompression, excision of hyperostosis, arthrodesis, amputation, replacement (arthroplasty) and limb lengthening procedures [21,34,35,72-74]. Soft tissue release in children has a higher number of failures that may result from repeated operations. Parents should be warned about failure rate and, if possible, the operation should be delayed until skeletal maturity. Core decompression has not shown to be of benefit [35]. Distraction osteogenesis (callotasis) has been shown to have good outcomes when treating limb length discrepancy [75]. Failure to apply the external fixation to a safe zone can result in multiple surgeries [76]. Foot deformities can improve with an external fixator [77]. Surgical intervention is for symptomatic relief.

Conclusion

Medicine has advanced, yet there are still much that has not been achieved for those suffering from melorheostosis since a century ago. Because the condition is rare, literature comprises mainly case reports or case series. The cause of the disease is still idiopathic. Sclerotomes involvement seems to be the common hypothesis theory. The diagnosis can be done with radiological images. There is no classification of the condition. Only radiological types have been identified. The condition should be considered in cases of bone sclerosis. The femur has a high rate of malignancy association. Management is still symptomatic relief and no drug has been found

to cure the disease.

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