A focus on melorheostosis disease: a literature review and case report of femoral-acetabular impingement due to melorheostosis treated with surgical hip osteoplasty

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SUMMARY

Objective. Melorheostosis is a rare, non-hereditary, benign bone disease characterized by abnormal bone growth. Generally, melorheostosis develops during childhood or adolescence and progresses gradually over time. This disease represents a true challenge to the physician because of its variability due to location, extension of the affected bone, and involvement of associated soft tissue. Pain management, physical therapy, and surgery may be recommended, depending on the individual case. This review aims to get an overview of the latest evidence relating to epidemiology, clinical and radiographic characteristics, diagnosis, and possible therapeutic strategies for melorheostosis and describe our experience through a clinical case.

Methods. We designed a comprehensive literature search on melorheostosis in MEDLINE (via Pubmed) up to April 2023 and reviewed reports published in international journals.

Results. The purpose is to highlight the importance of a multidisciplinary approach in the management of a rare disease such as melorheostosis. We discuss the role of different physicians, including genetists, rheumatologists, physiatrists, physical therapists, and orthopedic surgeons, in providing accurate diagnoses and effective treatments.

We conducted a comprehensive review of the literature on the treatment of melorheostosis to support these findings. In addition, the article presents a case study of a patient suffering from melorheostosis, focusing on difficulties in reaching a correct diagnosis and attempts towards conservative and surgical interventions. The patient underwent hip arthroplasty, and the final result was an improvement in function and a reduction in pain.

Conclusions. Managing melorheostosis can be challenging, and there is no standardized treatment for this condition at the moment.

Key words: Melorheostosis, bone rare disease; orthopedic surgery, bisphosphonate therapy, musculoskeletal rehabilitation.

INTRODUCTION

Melorheostosis is a rare, non-hereditary, benign bone disease characterized by abnormal bone growth, typically involving the skeleton (1). Generally, melorheostosis appears during childhood or adolescence and progresses gradually over time (1, 2). The hallmark features of melorheostosis are the formations of dense bone areas described as having a “dripping candle wax” appearance, usually involving the long bones and potentially causing stiffness and pain (2-4). In some cases, the skin and soft tissues may be affected, which may lead to shininess, fibrosis, erythema, linear scleroderma, hyperpigmentation, edema, fibrosis, scleroderma-like changes, and joint contractures (1, 5). Other functional characteristic features of melorheostosis include muscle weakness, limited range of motion (ROM), and a reduced ability to use the affected limb (2, 3). Lery and Joanny first described this condition in a 39-year-old patient.
old woman in 1922 and reported finger deformations characterized by a slight spacing of the extremities of the index and middle fingers of the left hand (3). Historically, the clinical course of melorheostosis has been divided into two different phenotypes based on the number of bones affected over time: the monostotic form, which involves one bone, and the polyostotic form, which affects multiple bones (1-5). Treatment may involve pain management, physical therapy, and surgery to correct bone deformities (2-5). In this review, we focus on epidemiology, clinical and radiographic characteristics, diagnosis, and possible therapeutic strategies for melorheostosis, reporting our experience in a clinical case.

**METHODS**

We designed a comprehensive literature search on melorheostosis by examining reports published in international journals and searching for relevant articles in MEDLINE (via Pubmed) up to April 2023, using the search term “melorheostosis”. We followed the guidelines proposed for narrative review during our work (6), also looking for reference lists of relevant articles to find additional studies. A number of 493 articles, including observational studies, case reports, and case series, were assessed to summarize data about epidemiology, pathogenesis, diagnosis, management, and outcome in patients with melorheostosis.

**ETIOLOGY AND PATHOGENESIS**

Melorheostosis is an uncommon bone disease that affects bone growth (1-3). It is typically diagnosed during childhood or adolescence, although it can also appear later in life (5, 7-9). Melorheostosis occurs spontaneously as a result of somatic mutations in the genetic material of bone-forming cells, not being an inherited disease (7). Although not typically found in multiple members of the same family (9), rare cases of familial melorheostosis have been reported, suggesting that in some cases there may be a hereditary component to the disorder (9-11). The exact pathophysiological mechanism underlying melorheostosis is unknown (2). Over the years, several theories have been proposed to explain the development of melorheostosis, but none have been confirmed (10-12). There are currently two main types of scientific hypotheses (8-10). In 1979, Murray and McCredie correlated melorheostosis with sclerotomes, hypothesizing that melorheostosis may 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 (10). In 1995, Fryns introduced the concept of mosaicism as an explanation for the sporadic occurrence of dysplasia with an aberrant growth or development of cells, tissues, or organs (11). Fryns hypothesized that the asymmetric involvement of skeletal structures and the concomitant vascular and hamartomatous changes in the overlying soft tissues could be attributed to an early postzygotic mutation of the mesenchyme (11). This theory provides some interesting insights because the extent of involvement in dysplasia can vary greatly and because the incidence ratio in both sexes is the same since the mutation would occur randomly and early in development (11). Finally, recent reports have identified mutations in the mitogen-activated protein kinase kinase (MAP2K) gene that may be a potential cause of the disease. MAP2K1 is part of the MAPK/ERK signaling pathway and is involved in the control of cell growth and differentiation (12).

**CLINICAL FEATURE**

The clinical characteristics of the disease may depend on the location, the extension of bone involvement, and the possible associated soft tissue involvement (1-3, 7). This variability in clinical presentation represents a challenge for clinicians in their approach to this pathology (3-5). In fact, melorheostosis can be asymptomatic and discovered incidentally in imaging studies performed for other reasons (2, 5, 7). On the other hand, it can lead to significant disabil-
ity (1-5). In this context, abnormal ossifications frequently involve the soft tissues and extend to the joints, resulting in a limited ROM due to contracture and fibrosis (2, 5, 7-9). Soft tissue involvement can lead to pain, stiffness, and limited ROM in the affected joints, as well as possible complications involving the surrounding soft tissues, such as muscle weakness, contractures, and neuropathy (5).

The abnormal growth of bone tissue in melorheostosis could compress or trap nerves, leading to neuropathic symptoms such as numbness, tingling, and weakness in the affected areas (3-5, 7, 13). The severity of neuropathic symptoms can vary depending on the location and the extent of nerve involvement. The typical symptom in patients suffering from melorheostosis is pain, which is common with other pathologies, but this particular condition presents the following characteristics: it can vary in intensity and location, be dull or acute, and be described as a deep, throbbing pain or a burning sensation (5, 7-8). Pain may be localized or radiate to adjacent joints or soft tissues and may be intermittent or constant, exacerbated by climate or temperature changes (4, 5, 8). Melorheostosis can also affect the skin, causing various dermatological manifestations. The skin overlying the affected bone may thicken and have a rough or pebbly texture, a phenomenon known as dermal fibrosis (5, 7, 9, 14).

**MANAGEMENT**

The diagnosis of melorheostosis is mainly based on radiological findings, while histopathological examination and genetic testing have limited usefulness (15). Differentiating melorheostosis from other skeletal disorders can be difficult due to varying clinical presentations (7, 15). Therefore, radiographic imaging represents the cornerstone for the diagnosis of the disease (15). The radiographic appearance of melorheostosis is often described as a “dripping candle wax” appearance, characterized by linear hyperostosis and narrowing of the medullary canal (15). Moreover, Freyschmidt identified three additional radiological patterns: “osteoma-like” hyperostosis, characterized by hyperplasia limited to the internal surface of the bone along its longitudinal axis (15, 16). Additionally, these lesions may be more than 5 cm in diameter, involve multiple bones, and often have an eccentric location. In cases where only one bone is affected, additional manifestations such as circumscribed scleroderma or subcutaneous fibrosis above the lesion may be present; “striated osteopathy”, which presents as unilateral, elongated, and densely hyperostotic striations near the surface of the inner cortex in two or more bones; “myositis ossificans”, with unilateral involvement of two or more regions, accompanied or without intraosseous hyperostosis (5, 8, 15-17). Furthermore, second-tier tests can play an important role in the evaluation of melorheostosis and provide additional information about the disorder. Computed tomography (CT) provides detailed, three-dimensional images of the bones involved in melorheostosis.

This test can help evaluate the extent of bone lesions, their precise location, and the presence of complications such as compression of nerves or blood vessels (16). Specifically, CT scans can provide higher-resolution images than plain radiography, allowing visualization of bone sclerosis and spinal cord space reduction in greater detail (2, 4, 15-17). Magnetic resonance imaging (MRI) is particularly useful for evaluating the involvement of surrounding soft tissues, such as muscles, tendons, or nerve. On MRI, bone alterations associated with melorheostosis typically appear as areas of low signal intensity on both T1- and T2-weighted sequences (2, 4, 17). These regions do not show the typical high signal intensity observed in normal bone marrow (4). When a contrast agent, such as gadolinium, is administered, enhancement can be observed in the affected bone areas (18). In melorheostosis, Technetium-99 bone scans can detect increased uptake in the affected bones (18). This is attributed to the elevated blood flow and increased osteoblast activity within those areas, which helps confirm the diagnosis and assess the extent of the disease (18). Furthermore, there is a strong correlation between the distribution of the lesions
observed in scintigraphy and radiography (4, 18).

This characteristic finding helps to differentiate melorheostosis from other sclerosing bone dysplasias, such as osteopoikilosis and striated osteopathy since the latter conditions do not show scintigraphic abnormalities (4, 18).

Melorheostosis is a rare bone disease for which there is currently no cure (5, 7, 17). However, various treatment options are available to manage symptoms and improve the quality of life of people suffering from this disease (5, 8). Pain management, physical therapy, and surgery may be recommended depending on the individual case (5, 8, 19). Pain management is the primary goal of treatment for melorheostosis. Therapy with non-steroidal anti-inflammatory drugs such as ibuprofen and ketoprofen is suitable for mild to moderate pain (5, 7, 19, 20), while drugs such as opioids are recommended to manage severe pain. Nerve block and glucocorticoid injections can also represent valid alternative treatments for pain management (1, 5, 7-9). Physical therapy helps manage pain by improving mobility and flexibility (1, 2, 5, 8, 17). On this basis, physiatrists and physiotherapists can develop a rehabilitation protocol with a program based on specific exercises adapted to the patient’s needs and limitations (5, 17). This may include range-of-motion exercises, stretching, and strengthening exercises. Additionally, physical therapy can also improve balance and coordination, which can provide great benefits to patients suffering from melorheostosis (5, 7, 8, 17). Moreover, in some cases, surgery may be necessary, and the type of surgery needed strictly depends on the complications associated with the condition, the age of the patient, and also on his expectations (5, 7, 17).

Several surgical techniques are used to manage the complications of the disease. These options may include fibrous soft tissue excision, tendon lengthening, fasciotomy, capsulectomy, corrective osteotomies, Ilizarov correction, hyperostotic bone excision, implant arthroplasty, arthrodesis, and amputation (21). These procedures can be performed to restore function and reduce pain in patients presenting with symptoms who have failed conservative treatment or show a serious chronic condition (21). As regards hip surgery, one technique is to remove the affected bone, a procedure known as curettage (osteoplasty). However, this technique may not be suitable for all patients, as it can result in significant bone loss and may require a bone graft. Another technique is to use osteotomies, which involve cutting and repositioning the bone to improve alignment and reduce deformity (21, 22). Finally, several experimental treatments for melorheostosis are being studied, such as therapy with bisphosphonates or anti-sclerostin antibodies (23, 24). However, further research is needed to determine the efficacy and safety of addressing these new targets in the management of melorheostosis.

APPRAISAL OF THE LITERATURE

Smith et al. conducted a retrospective analysis of the medical records of patients diagnosed with melorheostosis at the Mayo Clinic between 2000 and 2021 (17). This comprehensive clinical review included 24 patients (11 females and 13 males) (17). The onset of symptoms ranged from childhood to middle age, with a mean age of 24.5 years. The duration of symptoms before diagnosis ranged from months to several decades, with an average duration of 9.9 years (17).

Pain was the predominant symptom reported by all patients, with 96% experiencing pain at the site of bone involvement (17). The severity of pain was variable, generally described as moderate to severe. Chronic pain management was necessary for 63% of patients, involving the use of long-term medication (17). The bones most commonly affected were the femur, tibia, and foot bones. Radiographic findings showed several bone changes, among which cortical thickening, hyperostosis, and a wavy appearance were the most frequent observations. Functional limitations were prevalent, affecting 83% of patients to some extent and interfering with daily activities such as...
walking, dressing, and combing hair. In some cases, the impact on function was severe enough to hinder employment and participation in recreational activities (17). Surgery has proven to be the most effective treatment for relieving pain and improving the functionality of the affected limb (17).

Approximately 46% of patients underwent surgical procedures, ranging from bone debridement to joint arthroplasty. The majority of patients who underwent surgery reported improvement in pain and function (17). Furthermore, Freyschmidt et al. described the clinical and radiological characteristics of melorheostosis in a large series of cases in the literature (16). The study enrolled 23 patients (13 males and 10 females). The age of onset of the symptoms ranged from childhood to middle age (7-69 years). The most common symptom was pain, reported by 18 patients, typically localized to the affected bone or joint and often aggravated by physical activity (16). Other symptoms included swelling in six cases, limited joint mobility in five cases, and deformity in four cases (16). In addition, melorheostosis was predominantly unilateral in 17 of 23 cases; in six cases, it was bilateral. The diagnosis was confirmed by radiography and CT, with a characteristic appearance described as “candle wax” or “dripping candle wax” in 19 of 23 cases (16). Some cases also showed signs of soft tissue involvement, such as muscle hypertrophy or atrophy (16). Biopsies were performed in ten cases and revealed increased bone density and thickening of the cortical bone. In some cases, fibrous tissue proliferation, vascular proliferation, or cartilage formation have been observed. Surgical excision of the affected bone or joint was performed in 11 cases, and most patients reported favorable outcomes. In all cases, physiotherapy and exercise were recommended to maintain joint mobility and prevent further bone deformities (16).

In 18 cases, painkillers were prescribed, among which non-steroidal anti-inflammatory drugs were the most commonly used. In some cases, other drugs such as opioids, corticosteroids, and bisphosphonates have also been used (16).

Gnoli et al. described 19 patients diagnosed with melorheostosis in a large Italian case series (25). The authors showed that 13 of 19 patients were female, and the age at diagnosis ranged from 6 to 63 years. The diagnosis was based on the radiological signs and typical clinical features. Specifically, persistent pain was reported by 15 out of 19 patients as the first clinical sign of the disease, while limitations to joint movement were reported in 8 out of 19. In general, melorheostosis involved the lower limbs in 13 of 18 patients, while hand involvement was reported in 4 of 19 patients (25). Based on the analysis of the available literature, it is evident that melorheostosis is a rare and complex bone hyperostosis disease that presents significant challenges in terms of diagnosis and treatment (2, 5, 8, 16, 25).

However, there is a paucity of reliable epidemiological data on melorheostosis, making it difficult to accurately estimate the true impact of the disease. This is mainly due to the lack of national disease registries and prospective databases, as well as the retrospective nature of most published studies. Furthermore, there is a noticeable lack of studies evaluating the direct and indirect healthcare costs associated with melorheostosis at the national level. The absence of such research limits our understanding of the economic impact and resource use associated with this condition. In conclusion, there are important unmet needs in the field of melorheostosis, particularly in terms of diagnosis and optimal management. There are currently no established guidelines for the management of melorheostosis; consequently, treatment decisions can be tailored to the severity of symptoms. Novel therapeutic possibilities highlight the need for further research and consensus development in this area.

CASE REPORT

This case report concerns a 19-year-old male who presented to our outpatient department for hip pain since the beginning of 2020 after a day of downhill skiing. As the pain persisted and worsened following the restrictions due to the global COVID-19
pandemic, he underwent a hip X-ray. On physical examination, hip ROM was reduced to 1/3. Based on clinical and radiographic characteristics (Figure 1), this patient was diagnosed with melorheostosis. Blood markers of bone resorption and turnover were normal.

In July 2020, a biopsy was performed to exclude the possible oncological nature of the lesions. The result showed trabecular and medullary bone tissue with aspects of necrosis and sclerosis, and qualified specialists in rare diseases subsequently (March 2021) confirmed the diagnosis of melorheostosis.

The primary therapeutic indication for this patient was neridronate infusions (1 infusion every 3 months) for a year (for a total of 4 infusions per year) and the initiation of physical therapy.

One year later (April 2022), the patient was re-examined in our outpatient clinic and the physical examination revealed that the treatment achieved only minimal relief of symptoms. The patient exhibited rather significant progressive hip joint limitations, elective hypotrophy of the quadriceps femoris, and lameness, while radiographs showed an increased antero-lateral casting. The patient underwent both a CT scan and an MRI to determine the extent of joint involvement (Figures 2 and 3).

Hip osteoplasty was proposed and performed in September 2022. The differences between the preoperative and postoperative radiographs can be seen in Figure 4.

In Figure 4, areas of irregular cortical hyperostosis, a characteristic sign of melorheostosis, are visible. Figure 4a shows the deformation of the left acetabular cup, with areas of sclerosis and subchondral bone resorption. Intra-articular calcified bodies are markedly evident. After surgery, a restored anatomical structure of the acetabular cup, which allows better joint motility, can be observed (Figure 4b).

At the orthopedic visit 40 days after surgery (November 2022), the patient showed increased hip flexion (up to 100°) and adduction (30°), with remission of pain. He exhibited a control hip X-ray exam (Figure 5).

During the orthopedic examination two months after surgery (December 2022), the patient reported weight-bearing pain when walking, despite the anti-inflammatory therapy. Clinically, ROM in flexion 0-90°, in abduction and rotations reduced to only a few degrees were observed.

The orthopedist decided to perform an ultrasound-guided infiltration of the left hip with betamethasone and lidocaine to reduce the painful symptoms and manage the disease conservatively. Furthermore, indications were given to continue physical therapy for mobility and muscle strengthening.

At the 3-month orthopedic follow-up visit

Figure 1 - X-ray showing cortical irregular hyperostosis, a characteristic sign of melorheostosis.
A focus on melorheostosis disease

(October 2023), the patient underwent an MRI, which provided the following findings: diffuse edematous imbibition with segmental distribution affecting the head and neck of the femur, with concomitant abundant coxofemoral joint effusion, and synovial hyperplasia. MRI signs of osteonecrosis of the femoral head were not detectable.

The patient reported only a partial and temporary benefit with cortisone-based infiltrative therapy (approximately 10-15 days). Clinical examination showed that the patient had lost the acquired ROM in flexion and abduction with a sub-ankylotic hip. Indications were given to continue physical therapy for joint release without limitation of ROM in all planes of motion and to recover deambulation without walking aids. A further course of neridronate infusions was prescribed.

The 5-month follow-up MRI scans (March 2023) showed a reduction in bone edema but an increase in the synovial inflammatory component. Therefore, an additional infiltration was performed under ultrasound

**Figure 2** - Pre-operative computed tomography scan shows signs of cortical irregular hyperostosis and acetabular deformation.

**Figure 3** - Magnetic resonance imaging details of left acetabular cup before surgery (coronal STIR sequence).

**Figure 4** - Radiographs of the hip before (a) and after (b) surgery.
guidance in addition to the extracapsular release of betamethasone and lidocaine to alleviate the painful symptoms and manage the increased synovial inflammatory component.

At the 6-month follow-up (April 2023), the patient still exhibited limited hip ROM and pain despite previous treatments, with impaired quality of life. Therefore, hip replacement surgery was proposed.

**DISCUSSION**

In this article, we aim to underline the importance of multidisciplinary team care in the management of rare diseases such as melorheostosis. This management is essential for a correct initial diagnosis, through biopsy and support from genetists, and further rehabilitation following surgery (5, 7, 22). The contribution of rheumatologists is important in the management of conservative pharmacological treatment. Likewise, both physiatrists and physiotherapists are important with regard to rehabilitation treatments aimed at maintaining muscle lengths and avoiding retractions and worsening of symptoms (8).

The role of the orthopedic surgeon is fundamental, as he follows the patient over the years, monitoring the evolution of the pathology and defining the surgical indication based on the affected joint segment and the clinical examination, without neglecting age and expectations (21, 22).

In our literature search about melorheostosis, variable treatment options, ranging from conservative to surgical, have been reported. Some authors have recommended symptomatic treatment, such as the use of painkillers, manipulation, serial casting, and bisphosphonate infusion (7, 8, 11, 23, 24, 26, 27). The latter is used for symptomatic control in melorheostosis associated with increased bone turnover (23, 24). Additionally, several surgical treatment options are available, but a high rate of symptom recurrence has been reported in cases involving only surgical soft-tissue resection and in cases of hyperostotic bone excision (22).

In our patient, we experienced a diagnostic delay of more than a year after the biopsy, despite the orthopedist’s clinical suspicion. According to the evidence reported in the literature, a conservative approach was first attempted through the infusion of neridronate following the rheumatologist’s instructions, unfortunately with unsatisfactory results. The rationale behind the choice was to use a highly bioavailable drug from the bisphosphonate class that could be effective on the excess deposit of bone tissue underlying this pathology. In the case of our patient, the affected joint was the hip, a joint subjected daily to considerable static and, above all, dynamic loads for walking. A decisive treatment of the painful symptoms was therefore neces-

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**Figure 5** - Hip radiographs one month after osteoplasty (November 2022).
necessary, also to avoid more serious consequences such as joint ankylosis resulting from kinesophobia.

After the failure of the pharmacological and conservative rehabilitation treatment, the orthopedic team decided to attempt a minimally invasive surgical approach given the young age of the patient. Therefore, an acetabular osteoplasty was carried out, trying to remove the bone glues that protruded from the acetabular cavity and were causing our patient’s painful symptoms. Although the surgery initially seemed to give good results with reasonable pain control and good hip articulation, at the check-up carried out a month after the operation, after a few months, an MRI showed an increase in bone edema and synovial hyperplasia, causing a recurrence of the painful symptoms and worsening the joint ROM obtained initially.

At that point, a further conservative approach by using local infiltrations of corticosteroid and a new cycle of neridronate was attempted, trying to control bone edema and increased synovial inflammation seen on MRI. There is no data about neridronate infusion efficacy in melorheostosis because it is still a rare and unknown condition with a lack of literature. On the other hand, neridronate is effective in the case of bone marrow edema (26, 27). The patient was therefore a candidate for hip arthroplasty surgery given the poor therapeutic response to treatment with neridronate.

Several studies show that joint replacement surgery remains the decisive intervention in this type of patient, even if it is an approach that is proposed later in life and not in the case of young patients. However, our patient had been suffering from chronic pain and joint stiffness for 3 years, which had led to a marked deterioration in his quality of life. The prosthetic replacement surgery restores the correct femoro-acetabular interface, improving function and reducing painful symptoms. Although further follow-up is needed to monitor patients after this type of surgery, we believe that total hip replacement may be considered a treatment option for patients with pain and contracture that do not respond to conservative treatment.

CONCLUSIONS

Melorheostosis is a rare and benign bone disease characterized by abnormal bone growth, which can be diagnosed using X-rays, CT scans, and MRIs. The radiological features of melorheostosis, such as the typical “candle wax appearance” of the bones and irregular bone surfaces, are described in detail. Once diagnosed, patients require a comprehensive, personalized treatment strategy involving consultations with both surgical and non-surgical physicians. Treatment options available for managing melorheostosis include anti-inflammatory drugs, physical therapy, and surgical interventions such as the removal of excess bone. However, management of this condition can be difficult, and there is no standardized treatment approach. Further research is needed to understand the genetic and developmental factors underlying melorheostosis, as it may provide valuable insights into aspects of bone physiology and pathophysiology that are currently not fully addressed. In conclusion, this study offers important insights into the diagnosis and management of melorheostosis, emphasizing the need for continued research to better comprehend its underlying mechanisms and develop more effective treatment approaches.

Contributions
MR, AC, NR, SS, contributed equally to the conception and design of the review. All authors made substantial contributions to the conception or design of the work, the acquisition and interpretation of data. All authors contributed to the critical review and revision of the manuscript and approved the final version. All the authors agreed to be accountable for all aspects of the work. contributed. All authors drafted and revised the manuscript. All authors read and approved the final manuscript.

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