

Bone Marrow Foot Oedema in Adolescents: The Role of Vitamin D

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Received: July 25, 2019

Revised: October 31, 2019

Accepted: November 1, 2019

Background: Bone marrow oedema (BMO) in children/adolescents is a rare clinical condition without an etiologic cause. It is associated with typical increased signal intensity on T2-weighted magnetic resonance images (MRI) and an increase in bone turnover in which vitamin D plays a pivotal role. No treatment guidelines for these young patients are to date available. **Methods:** We performed a retrospective study in a pediatric setting of 13 patients with diagnosis of primary BMO of the foot on the basis of clinical and radiological findings. Data collection included sex, age, patient history, symptoms at presentation, clinical examination, laboratory bone turnover markers, vitamin D levels, MRI, treatment, and outcome. **Results:** Vitamin D deficiency or insufficiency was found in 76.9% of cases. All patients were treated with adequate vitamin D daily intake, a short course of analgesic therapy, physical therapy, avoiding detrimental feet and ankle immobilization. All fully recovered in 3-month lag period. **Conclusions:** Our data highlight that environmental factors, such as underestimated articular or bone microtraumas, as well as joint hyper mobility, in a bone turnover milieu of vitamin D deficiency could be the cause of this clinical conditions. Adequate vitamin D supplementation, associated with physical and analgesic therapy, is crucial in the management of BMO.

Key Words: Bone marrow oedema · Child · Magnetic resonance imaging · Vitamin D

INTRODUCTION

Primary bone marrow oedema (BMO) is a rare clinical condition characterized by joint and bone extremity pain, out of proportion to the clinical findings, exacerbated by weight bearing, in the absence of a known etiologic cause.[1-5] These clinical symptoms are associated with typical increased signal intensity on T2-weighted magnetic resonance images (MRI), without evidence of focal specific signs of osteonecrosis, fracture, neoplasm, or infections.[1-4] This condition has been first described by Wilson et al.[6], who found ill-defined bone marrow hyperintensities on T2 weighted MRI in 3 patients with knee pain of no apparent cause. Since then, various terms have been used to describe this entity; in fact *transient osteoporosis*, *transient BMO syndrome*, and *migratory osteoporosis* have all been used interchangeably.[1,2] BMO could be a feature of other conditions (secondary BMO); among them trauma, inflammatory conditions (e.g., arthritis, enthesitis), infec-

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tious diseases (e.g., septic arthritis, osteomyelitis), ischaemic events (e.g., sickle cell disease, polycythaemia), neoplasm, degenerative disorders, neurologic disorders (e.g., Charcot arthropathy), metabolic/endocrine disease, and iatrogenic causes (e.g., drugs such calcineurin inhibitor or steroids, after radiotherapy or surgery).[1-3,5] Therefore, the diagnosis of primary BMO is made after the exclusion of these pathologies.[1-4,7]

The multiple names and the fact that primary BMO is diagnosis by exclusion, reflect the uncertainty about its aetiology.[1-3,8] It mostly affects middle-aged men (range, 30-60 years) and younger women (range, 20-40 years).[3] The most commonly affected sites are bone of the hip, knee, ankle and foot.[1,2] BMO is also rarely described in children/adolescents, even if the incidence is unknown.[1,4,7] It has been suggested that mechanical, vascular, inflammatory or metabolic trauma may initiate a chain of events resulting in increased intraosseous pressure, irritation of sensory nerves within the bone marrow, periosteum and periarticular structures. These lead to bone damage and BMO.[1-3] Clinically it manifests with pain, sometimes irritable joint or mild subcutaneous oedema of ankle or foot; but trophic or vasomotor changes are absent.[3] Pain usually improves within 3 to 9 months without treatment, although the course could be longer, up to 24 months.[2,9]

Treatment has mostly been reported in adult case series (corticosteroids, bisphosphonates, vasodilators, physiotherapy, reduction of weight-bearing, core decompression), but randomized controlled trials are lacking and no treatment guidelines for younger patients are available.[1-4,10,11] Recently, it has become evident that BMO is accompanied by an increase in bone turnover, in which vitamin D plays a pivotal role. Vitamin D deficiency and insufficiency negatively affect bone mineralization.[1,6,11-15] To date, limited information is available about vitamin D status in patients with BMO. Sprinchorn et al.[16] and Horas et al.[1] reported an association between hypovitaminosis D and BMO of the foot and ankle in small adult case series. No data are reported in cohorts of children and adolescents.

The purpose of this study is to investigate the incidence of hypovitaminosis D in a young aged population with primary BMO of the foot and the benefit of a vitamin D supplementation therapy.

METHODS

A retrospective study has been performed in a paediatric setting of 13 patients with persistent foot pain and MRI showing a picture compatible with bone oedema of the foot, referred to our Rheumatologic Paediatric Clinic in the period of 2015 to 2018. They are all misdiagnosed in other institutions as affected by algodystrophy or complex regional pain syndrome.

This study included patients with age ≤ 18 years, affected by primary BMO of the foot. The diagnosis of BMO was based on patient's medical history and clinical examination (sudden onset and persistent foot pain), and on the presence of ill-defined abnormal bone marrow hyperintensities on T2 weighted MRI. Exclusion criteria encompassed age > 18 years, MRI demonstrating other concomitant diagnosis affecting the bone (e.g., neoplasia, fractures, infections), the presence of other pathologies causing secondary BMO and patients lost during the follow up.

Data collection included sex, age, medical and surgical history, recent or remote trauma history, symptoms at presentation, clinical examination, laboratory bone turnover markers (if available), vitamin D levels, MRI, treatment and the outcome. Prevalence of hypovitaminosis D in this case series was evaluated.

Concerning vitamin D levels, to date there is no universally accepted classification of vitamin D deficiency and insufficiency according to the serum level of 25-hydroxy-vitamin D (25[OH]D). We used Endocrine Society Clinical Practice Guidelines defining vitamin D deficiency as 25(OH)D level of < 20 ng/mL (50 nmol/L), vitamin D insufficiency as 25(OH)D level between 20 and 30 ng/mL (50-75 nmol/L) and vitamin D sufficiency as 25(OH)D level ≥ 30 ng/mL (75 nmol/L).[13] Serum 25(OH)D was measured by a immunochemiluminescent assay (LIAISON[®], Diasorin; DiaSorin Ltd, Schiphol Rijk, The Netherlands).

This is a retrospective study, the investigations are based on preexisting clinical practice so ethical permission and informed consent are unnecessary. The study is performed following the Declaration of Helsinki and under the terms of relevant local legislation.

RESULTS

1. Clinical features of the 13 patients evaluated are reported in Table 1

Eleven/13 are female (male to female ratio 1:5.5). The

Table 1. Details of thirteen patients included in this study

Patient	Age (yr)/ Sex	Other pathologies	Joint hyper-mobility	History of trauma	Symptoms and clinical examination	MRI	Previous treatment	Vitamin D (ng/mL)	Treatment
1	9/F	No	No	Ankle strain	Pain of foot worsened by load	Astragalus and III and IV metatarsal algodystrophy	Foot immobilization and bisphosphonates	21	Vitamin D and calcium, paracetamol as needed, physical therapy
2	11/M	No	No	Recurrent microtraumas of feet	Pain of foot worsened by load, slight swelling of ankle	Foot algodystrophy	Foot immobilization	23	Vitamin D, vitamin C, physical therapy
3	10/F	Yes (JIA and uveitis)	Yes	Recurrent microtraumas of feet	Slight swelling and pain of foot worsened by load	Tarsus algodystrophy	Bisphosphonates	16	Prednisone, vitamin D
4	18/F	1 (JIA)	Yes	Trauma with ankle strain	Pain of foot worsened by load	Cuboid bone oedema	None	28	Prednisone, vitamin D
5	10/F	1 (JIA)	Yes	Ankle strain	Pain of foot worsened by load	Tarsus, cuneiform and navicular bone oedema	Bisphosphonates	26	Vitamin D
6	12/F	No	Yes	Ankle strain	Pain of foot worsened by load	Cuboid, navicular and cuneiform bone oedema	Foot immobilization	20	Vitamin D, vitamin C, paracetamol as needed, physical therapy
7	7/F	No	No	Trauma of the ankle	Pain of foot worsened by load, slight swelling of ankle	Foot bone oedema	None	31	Prednisone, vitamin D
8	11/F	No	Yes	Ankle strain	Pain of foot worsened by load	Cuboid and cuneiform bone oedema	None	33	Vitamin D
9	13/F	No	Yes	Recurrent microtraumas of feet	Pain of foot worsened by load	Foot bone oedema	Rest	27	Vitamin D, physical therapy
10	15/M	No	No	Recurrent microtraumas of feet	Pain of foot worsened by load	Talo and astragalus bone oedema	None	34	Vitamin D, ibuprofen as needed
11	11/F	No	Yes	Recurrent microtraumas of feet	Pain of foot worsened by load	Scaphoide, cuboid and cuneiform, II metatarsal bone oedema	Foot immobilization	28	Vitamin D, paracetamol as needed
12	14/F	No	Yes	Recurrent microtraumas of feet	Pain of foot worsened by load	II metatarsal bone oedema	Antiinflammatory therapy	10	Vitamin D, vitamin C, paracetamol as needed, physical therapy
13	12/F	No	Yes	Trauma of the ankle	Pain of foot worsened by load	Scaphoide, cuboid and cuneiform, II metatarsal bone oedema	Foot immobilization	24	Vitamin D, vitamin C, paracetamol as needed, physical therapy

F, female; M, male; JIA, juvenile idiopathic arthritis; MRI, magnetic resonance images.

mean age is 11.8 years (range, 7-18 years). All patients live near to Verona, in the Veneto region of northern Italy (latitude 45.26° N, longitude 19.59° E). Eleven/13 patients are Italians, 1/13 is Moroccan, 1/13 of Moroccan ethnicity was born and raised in Italy.

Three/13 had a previous diagnosis of juvenile idiopathic arthritis with positivity of antinuclear antibodies, but the disease was in complete remission at our evaluation. 10/13 were previously healthy.

In all cases history of minor ankle strain or recurrent microtraumas of feet prior to symptom onset had been reported after accurate interview. In particular, 7/13 patients reported an ankle strain or a major trauma; 6/13 had history of probable microtraumatism mainly due to sport activity.

In all cases the symptom at onset was pain. Clinical examination confirmed pain of foot and ankle, worsened by joint load. Two patients presented slight swelling of ankle or foot. No one presented hyperemia, heat, trophic or vasomotor change of the feet. Joint hypermobility was observed in 69.2% of cases.

The 77% of cases presented multiple lesions at MRI, while 23% of patients presented a single lesion. Five/13 patients were treated with foot immobilization before our evaluation. 3 patients were previously treated with bisphosphonates, without improvement.

Vitamin D deficiency or insufficiency was found in 10/13 cases (76.9%), deficiency in 3/13 patients (23.1%), insufficiency in 7/13 patients (53.8%). In 3/13 patients (23.1%) vitamin D was sufficient but at lower limits (range, 31-34 ng/mL). Medium 25(OH)D level is 24.7 ng/mL \pm 2.1 (range, 10-34 ng/mL). Inflammatory indices (leukocytes, reactive C protein, erythrocyte sedimentation rate) were normal in all cases. We have data on parathyroid hormone (PTH) status for 8 patients, it was high in 1 patient (44 pg/mL), normal in 7 patients, among them PTH was at the upper level of the normal range in 2 patients. Serum calcium levels, measured in 11/13 patients, were normal. Bone alkaline phosphatase had been measured in 6/13 patients, in all patients it was high (medium value of 136,5 μ g/L). Osteocalcin, measured in 3 patients, was high in 2 cases, normal in one patient. C-terminal telopeptide of type I collagen (CTX) had been measured in 3 patients and it was high in all patients (medium value of 2,3 ng/mL).

All patients were treated with adequate vitamin D daily intake (therapeutic dose and then maintenance dose, ac-

ording to current guidelines).[1,13,14] Pain relief was achieved with paracetamol, low dose ibuprofen, or a short course of oral prednisone. Rest from intense physical activity, physical exercises to promote the ability to move the foot and/or the ankle, avoiding detrimental feet and ankle immobilization were recommended. All children (100%) fully recovered in 3-month lag period.

DISCUSSION

Vitamin D deficiency or insufficiency is one of the most prevalent nutritional deficiency in the world and it has been estimated to affect more than 1 billion people globally.[1,13,14] In Europe almost 80% of adolescents have been found to have a hypovitaminosis D.[13,17] The prevalence of hypovitaminosis D in our case series is not so different from that of other studies.[18-22] Vitamin D and adequate calcium intake are crucial for bone health and for a balanced bone turnover. The 40% to 50% of skeletal mass is accumulated in childhood.[14] Vitamin D deficiency in childhood and adolescence is associated with suboptimal peak bone mass and lower bone mineral density, leading to insufficient bone mineralization and, as consequence, increased bone fragility and reduced self-repairing capacity of the bone tissue.[8,11,15] This causes not only osteoporosis, rickets, osteomalacia, but also aggravation of many orthopaedic and bone disease patterns, among them BMO.[11,13-15,23] Adolescence is a critical period because pubertal growth leads to a phase of accelerated bone turnover, which could predispose to bone microdamage even under physiological load.[8] Environmental factors, such as underestimated articular or bone microtraumas, as well as joint hyper mobility, typical of paediatric age, in a bone turnover milieu of hypovitaminosis D, could lead to the development of BMO.

BMO in pediatric age is uncommon, but it is an important cause of disability. It is often misdiagnosed as complex regional pain syndrome or algodystrophic syndrome manifestation.[7,24] To date there are few reports in literature about primary BMO in paediatric patients.[4,9,25-29] Like in adult, BMO lesions affect weight-bearing and thus load affected joints: more frequently foot and ankle,[4,6,9] but also acetabulum,[26] distal tibia and fibula,[4,25] femoral head,[27,29] knee and hip.[28] In the majority of these reports serum levels of vitamin D have not been analysed. Kröger et al.[4] reported normal vitamin D levels, with sli-

ghtly augmented bone turnover markers. Kaspiris et al.[9] reported association with vitamin D deficiency in a 12-year-old girl with primary BMO of the foot, like in our case. In these reports treatment is focused mostly on symptomatic relief, such as activity limitation, avoidance of weight bearing, protective boot application, analgesic drugs. In one case vasodilator treatment has been used,[26] but the possible side effects (e.g., headache, nausea, flushing), made this choice unlikely.[9] Only in one case a successful treatment with vitamin D administration, in order to correct hypovitaminosis D, has been reported.[9]

Our data are in accordance with the findings in the adult case series reported by Sprinchorn et al.[16] and Horas et al.[1]. They described a series of 9 and 31 middle aged patients with primary BMO; vitamin D deficiency or insufficiency had been detected in 90% of cases. In our case series hypovitaminosis D has been detected in 77% of cases, in the remaining 23% vitamin D was sufficient but at lower limits. Although serum calcium and PTH levels were in normal range except for one case, bone alkaline phosphatase and CTX (when available) were raised, reflecting an increased bone turnover.

Further studies are necessary to establish the precise role of vitamin D supplementation in the improvement of BMO in children as well as possible role of the association of medication (e.g., pharmacological therapy with vitamin D supplementation). Certainly our results highlight that adequate vitamin D supplementation, associated with physical and analgesic therapy, is crucial in the management of BMO. Paediatricians should be aware of the diagnosis and the management, in order to promptly begin an adequate treatment. All patients with primary BMO should be screened for bone metabolism disorders, especially vitamin D levels. [8] Delay in diagnosis, unnecessary diagnostic testing and procedures with incorrect or delayed treatment, lead to worsening the discomfort of the patients.

Furthermore, we underline the importance of supplementing vitamin D as recommended in the current guidelines,[1,13,14] in order to avoid its deficiency and prevent invalidating clinical complaints.

DECLARATIONS

Ethics approval and consent to participate

This study was conducted in accordance with the princi-

ples of the Declaration of Helsinki.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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