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From Lysis to Hemolysis

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Abstract

Introduction: Sickle cell disease (SCD) is the most common genetic disease in the world. Vitamin D deficiency has been described in several patients with this disease. We report the case of a patient in whom osteomalacia revealed the disease. **Observation:** The patient was 35 years old, not an alcoholic, not exposed to toxic products, with a family history of sickle cell disease in her 4 brothers and sisters. She reports the appearance of diffuse bone pain but which predominates in the axial skeleton, the ribs and the rhizomelic zones having motivated several hospitalizations. These pains are recurrent with new attacks on the lumbar spine, and sacroiliac joints with intense pain. Paraclinical examinations revealed: normal long bone radiographs without bone lysis, a CT scan of the sacroiliac joints without any aspect of sacroiliitis, but revealing multiple vertebral condensing bone lesions in streaks, diffuse at the level of the iliac wings with osteolysis surrounded by non aggressive osteocondensation. Densitometry was normal, vitamin D deficiency was noted at 29 ng/mL with elevated alkaline phosphatase, normal concentrations of Calcemia and Phosphoremia respectively at 96 mg/L and 36 mg/L, contrasting with hyperparathyroidism with a blood level of parathyroid hormone elevated to twice the normal level at 104.4 pg/mL It should be noted that the patient had received per os vitamin D supplementation before coming to us. The diagnosis of osteomalacia secondary to vitamin D deficiency complicated by secondary hyperparathyroidism was retained. Given the family history, we looked for the existence of sickle cell disease which was finally confirmed on hemoglobin electrophoresis with an AS profile. **Conclusion:** The association between vitamin D deficiency and sickle cell disease is not uncommon, and is explained by the ethnic origin, race, skin color, genetics and physiological features of patients with this disease rather than the disease itself.

Keywords

Sickle Cell Disease, Vitamin D, Osteomalacia

1. Introduction

Sickle cell disease (SCD), also known as sickle cell anemia, is a real public health problem in Africa and the West Indies. It is the most common genetic disease in the world, affecting mainly black populations. It is due to an abnormality of the hemoglobin, a protein present inside red blood cells, which is used to transport oxygen from the lungs to all organs of the body. This hemoglobin abnormality results in sickle cell disease of the red blood cells.

Vitamin D deficiency is frequently found in people with sickle cell disease. Vitamin D is involved in the regulation of phospho-calcium metabolism. Insufficiency or deficiency of this vitamin has recently been described as aggravating bone health in patients with sickle cell disease [1]. Thus, we present an observation concerning a patient with a deficiency of this vitamin and a minor sickle cell syndrome.

2. Observation

This was a 35-year-old patient, residing in Dakar but originally from the northern part of Senegal in the city of Saint Louis. She has been divorced since 2015, has no children, and is non-alcoholic, with no toxic exposure or risky sexual behavior. Her socioeconomic level is considered low. She had no personal allergic, medical, or surgical history. At the family level, her mother had diabetes, her father had a stroke, and 4 brothers and sisters had sickle cell disease and were regularly monitored.

Since 2015, she reports the appearance of diffuse bone pain but predominantly in the axial skeleton, ribs and rhizomelic areas that have motivated several hospitalizations, particularly in Guéoul, but without a clear diagnosis. A long period of calm followed under self-medication with NSAIDs and analgesics. Then she came back to the clinic because of a recurrence and an increase in pain, this time affecting the lumbar spine and the sacroiliac joints with intense pain. The clinical examination revealed normal vital parameters, a normal appearance of the musculoskeletal system, and pale mucous membranes suggestive of anemia.

This clinical picture made us evoke the diagnoses of spondylarthritis, primary hyperparathyroidism, multiple myeloma, bone metastasis of a neo-primitive X, and osteomalacia. Paraclinical examinations revealed: normal long bone radiographs without bone lysis, a CT scan of the sacroiliac joints with no aspect of sacroiliitis, but revealing multiple vertebral condensing bone lesions in streaks, diffuse at the level of the iliac wings with osteolysis surrounded by non aggressive osteocondensation. Densitometry was normal, vitamin D deficiency was noted at 29 ng/mL (45 - 65 mg/L) with elevated alkaline phosphatase, normal concentrations of Calcemia and Phosphoremia respectively at 96 mg/L (90 - 105) and 36 mg/L (27 - 45), contrasting with hyperparathyroidism with a blood level of parathormone (PTHi) elevated to twice the normal at 104.4 pg/mL (10 - 60 pg/L). On the basis of the arguments, the diagnosis of osteomalacia secondary to Vitamin D deficiency complicated by secondary hyperparathyroidism was re-

tained. In view of the family history, the existence of sickle cell anemia was sought, which was finally confirmed on hemoglobin electrophoresis with an AS profile (Figure 1). The patient received appropriate oral vitamin D supplementation and all clinical pictures regressed.

3. Discussion

Vitamin D deficiency is one of the most common nutritional problems in people with sickle cell disease [1] [2] [3]. Some characteristics unique to sickle cell disease may contribute to this phenomenon, including decreased appetite [4] [5], an inability to absorb nutrients due to damage to the intestinal lining [6] [7], and a higher basal metabolic rate and greater nutritional requirements to maintain normal physiological function [8]-[16]. Vitamin D deficiency has been associated with bone health [17] [18], cardiovascular disease [19] [20] [21], asthma [22] [23] [24], nephropathy, and chronic pain, and individuals with sickle cell disease are susceptible to all of these complications [25] [26] [27] [28] [29]. Although the role of vitamin D deficiency as a contributing factor to these complications is unclear, vitamin D deficiency can be reliably and inexpensively treated, making it a preferred intervention to potentially improve health outcomes in individuals with this disease.

Studies suggest a high prevalence of vitamin D deficiency in people with sickle cell disease. This prevalence depends on the populations studied but does not appear to be higher than in the general population. The U.S. National Health and Nutrition Examination Survey shows an increasing trend over time in vitamin D levels in African Americans with sickle cell disease. While the prevalence

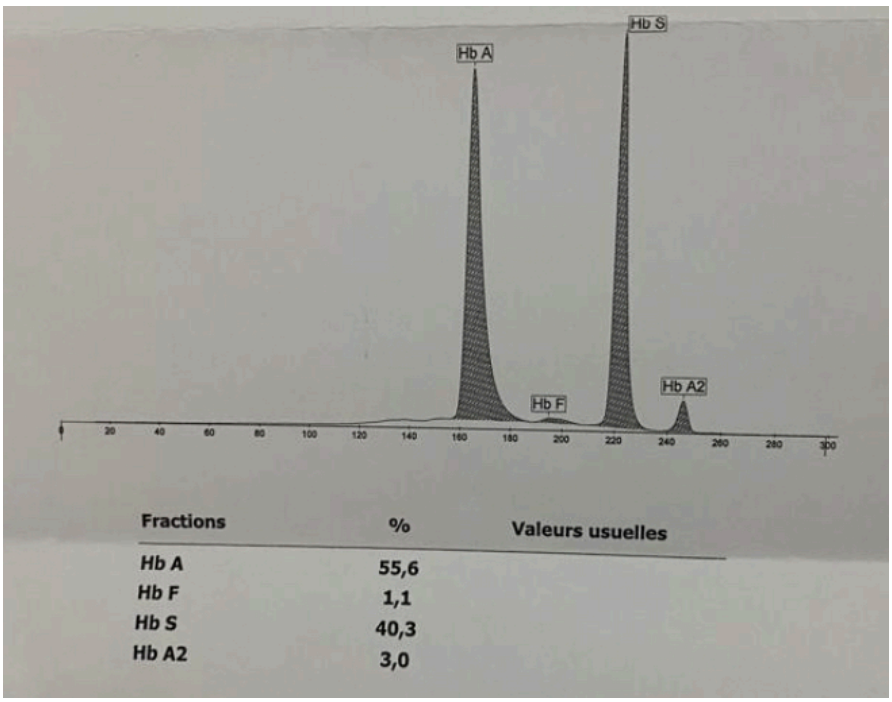

Figure 1. AS electrophoretic profile.

of normal levels (>30 ng/mL) was only 3% in 2001-2004, the prevalence of severe deficiency (<10 ng/mL) more than tripled between 1988 and 2014 from 9% to 29%. Furthermore, a more recent report from this survey of adult populations found that 81% of African Americans were deficient (<20 ng/mL), compared to 28% of Caucasians [30]. Four other studies of sickle cell disease [2] [17] [31] [32], were reviewed, only two [17] [31] found the prevalence of vitamin D deficiency comparable to that of adults in this survey 82% [17] and 84% [31]. Arlet *et al.* [2] and Goodman *et al.* [32] reported an extremely high prevalence of vitamin D levels < 30 ng/mL, 100% and 98% respectively. In addition, Arlet *et al.* [2] reported that 75% of adults with sickle cell disease in their Francaise study had vitamin D levels < 10 ng/mL and Goodman *et al.* [32] reported that 86% of their adult participants had levels < 10 ng/mL.

In our patient's case, this insufficient vitamin D level is noted despite evidence of previous supplementation, which suggests a more profound previous deficiency. It should also be noted that all the cases of sickle cell disease included in these studies are major syndromes and our patient has a minor syndrome. Furthermore, in sub-Saharan Africa, very few studies have been done on the vitamin status of this sub-population of sickle cell patients or even of the general population.

Many mechanisms have been proposed to explain the drastic differences between African Americans and Caucasians in the prevalence of vitamin D deficiency/insufficiency. Decreased vitamin D synthesis in the skin due to increased melanin [33] and dietary differences, particularly the avoidance of dairy products, have been suggested as causative factors as these are the two primary modes of acquiring vitamin D deficiency. It has been reported that 80% of African Americans have some degree of lactose intolerance compared to only 15% of Caucasian Americans, which may account for some of the difference in vitamin D deficiency/insufficiency between the groups [34]. A higher BMI in African Americans has also been implicated as a possible mechanism [35] since it has been shown that body fat acts as a storehouse for fat-soluble vitamin D and release of the stored vitamin from adipose tissue may be slow [36] [37]. It has also been suggested that racial differences in calcium absorption and metabolism may contribute to lower vitamin D levels in African Americans. African Americans absorb dietary sources of calcium more efficiently than Caucasians, and retain calcium better in the bones and kidneys, especially during growth. These observations suggest that African Americans may require less dietary calcium than Caucasians [38] and thus less vitamin D for calcium metabolism [30] [33]. Finally, African Americans may have lower levels of vitamin D-binding proteins than Caucasian Americans, likely due to racial differences in genetic polymorphisms of vitamin D-binding protein genotypes [39]. The clinical implications of this finding have been the subject of much debate [40], but imply that race is a key factor in the interpretation of vitamin D levels. Assessment of vitamin D binding protein may be useful in elucidating vitamin D bioavailability in individuals with sickle cell disease, but further research is needed to truly understand

the prevalence of vitamin D deficiency and insufficiency in this population.

In addition, the threshold of vitamin D should be considered, which would differ depending on whether the subject is black, Caucasian, or has a pathology such as sickle cell disease. In order to address the definition of "normal", Wright *et al.* [41] sought to determine an optimal vitamin D threshold in African Americans based on its association with intact parathyroid hormone (iPTH). The results of their study showed that the level at which PTHi was maximally suppressed was approximately 20 ng/mL in African Americans versus 30 ng/mL in Caucasians, indicating that a lower threshold for defining deficiency in African Americans may be warranted. These results are in agreement with two other studies that found that PTHi levels in African Americans stabilize around 20 ng/mL [30] [42]. The studies cited that argue for a lower threshold for vitamin D levels in African Americans included only healthy adults and excluded those with chronic kidney disease that is known to alter intact PTH levels and vitamin D metabolism. It is estimated that between 5% and 30% of individuals with sickle cell disease have reduced renal function [43] [44]. Decreased renal function, combined with reduced ability to properly absorb nutrients due to damage to the intestinal mucosa, can drastically affect serum vitamin D levels. This suggests that neither the threshold for Caucasians nor the suggested threshold for healthy African Americans is applicable to people with sickle cell disease. Further research is needed to identify optimal vitamin D levels in people with sickle cell disease.

4. Conclusion

Vitamin D deficiency is very frequent in African subjects living in temperate countries but we have very little data concerning its frequency in tropical environments. If this deficiency is added to sickle cell patients, it can lead to bone signs ranging from pain to fracture as in the case of our patient. In this context, cases of osteoporosis, osteomalacia, or even osteosclerosis have been described. The association of sickle cell disease and vitamin D deficiency is probably not explained by the genetic disease, but rather by the ethnic origin, skin color, and genetics of the patients with this disease.

Consent

Informed patient consent has been obtained.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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