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Anemia in Vitamin D Deficiency Rickets

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Abstract

The relation between rickets and anemia was known as Von Jacks anemia since 1937. The association between anemia and rickets was reported from UK, but we confirmed this in Saudi Arabia. In this communication, we are reviewing the subject and the association of hemolytic congenital anemias with ricket is discussed, together with Celiac disease. A rare finding of myelofibrosis with rickets was reported from many centers but its pathogenesis is not yet that clear, suggestions include a role of vitamin D in proliferation of stem cells. The aim of this presentation is to stress on that when diagnosing rickets, anemia must be thought of with its many varieties, but iron deficiency is the commonest.

Keywords: Rickets; Anemia; Malabsorption; Vitamin D deficiency

Introduction

The association between hypochromic anemia and rickets as part of a study of vitamin D deficiency rickets, in Almadinah was recently reported [1]. On reviewing the literature, it was found that the first report of anemia in rickets by Williams in 1929 [2]. A syndrome was identified that affected 16 Indian infants roughly 3 months old, who were carried in the villages in the Canadian Arctic. The infants presented with a clinical picture that included hepatitis, hemolytic anemia, rickets and respiratory distress, a combination that resembled a syndrome first described in malnourished infants known as Von Jaksch and Luzet Syndrome. The anemia associated with rickets might be due to a combined deficiency or part of generalized malnutrition or due to an occult role of the vitamin in the metamorphosis of the blood cells. Otherwise, both anemia and rickets might be circumstantially appearing together without having a direct common cause which is unlikely. In addition, vitamin D is said to play a part in cell proliferation which might cause anemia in vitamin D deficiency, myelofibrosis being an example. This review is a trial to study this association of anemia and rickets to clarify the factors leading to these combined devastating diseases with the objective to elucidate their combined pathogenesis if any, with the objective of their eradication.

Diachronic Aspects of Rickets and Anemia

The first reported example of this association of rickets and anemia by Pearce Williams: [1] A female, with bow legs and paler diagnosed as severe rickets with anemia. She was placed on irradiated milk. There was irregular fever during the first month. Her hematological findings and general health improved. Another case reported in 1933: a girl, aged 9 months, was very anemic, the wrists enlarged, and there was a moderate degree of genu vulgum. X-ray examination of wrists and knees revealed active rickets [3]. Blood tests revealed -Hb. 33%; Serum phosphorus was low. 27 mg%; serum calcium 8-6 mg%; urea 30 mg%; X-ray examination of the wrists before and after the institution of vitamin D therapy revealed definite advanced healing. These data show evidence of healing of rickets with vitamin D metabolite as well as improvement of anemia. These examples have shown the gravity of the affiliation between the deficiency of iron and vitamin D in that day and age.

The anemias associated with rickets in addition to the hypochromic iron deficiency which has been described recently [1], there is vitamin D deficiency associated with hemolytic inherited anemias also, anemia found in celiac disease and B12 related anemia in addition to myelofibrosis which is a very rare association with rickets. Each of these animals will be discussed in this review.

Anemia Associated with Rickets in Celiac Disease

It was in 1939 that Crowley reported iron resistant anemia and latent rickets in school children. Seven years later Konstam reported a case of steatorrhea with tetany, osteomalacia and macrocytic anemia due celiac disease [4]. The association of osteomalacia and anemia was then reported in a 56 years' lady with dwarfism [5]. There was a response to treatment of vitamin D and iron [6]. Baloweska, recently reported, a case of a 6-year-old male child with a delay in physical and psychomotor development with rickets, severe anemia and bloody diarrhea, that was diagnosed as celiac disease and ulcerative colitis, although the coexistence of both disorders is extremely rare in childhood [7]. However, ulcerative colitis were seen in celiac children on restrictive gluten-free diet with persistent diarrhea or bleeding from lower gastrointestinal tract. Al-Sharafi reported a 13-year-old female child with rickets lasting for seven years, causing multiple bone deformities leaving the child crippled with bowing of both of her arms. The patient was also found to have growth failure, anemia and on further work-up, she was found to have celiac disease. Celiac disease should be bearded in mind as a cause of rickets in patients not responding to the usual forms of treatment or when linked up with other manifestations of malabsorption [8]. Celiac disease was also reported from Pakistan in children with chronic diarrhea, failure to thrive, pallor, abdominal distention and iron deficiency anemia were common presenting features, with antibodies strongly positive in most of the cases. All children showed substantial improvement in clinical characteristics and the reduction in antibody titers after six-month trial of gluten free diet [9]. Celiac disease still might show with diverse

features, as an endocrine disrupter as well as having varied presentations, including short stature, delayed puberty, anemia and rickets. Interestingly celiac disease may not have any GI symptoms, making the diagnosis yet, more obscure. In addition, there is a significant incidence of celiac disease with hypothyroidism and type-1 DM, making screening for it, being important in these diseases [10]. Childhood diseases such as rickets, have re-emerged in recent years with high prevalence of associated iron deficiency anemia has increased, particularly among Asian migrant populations in the UK [11]. Further a student from Russia among orphanage resident infants have shown, frequent diagnoses of the children having rickets in 21%, fetal alcohol syndrome in 10%, and anemia in 6%, stressing on the high prevalence of rickets and anemia [12]. Cases reported from Tunisia with osteomalacia presenting in three women, all were diagnosed as celiac disease (CD). Direct inquiry revealed an important weight loss and a history of diarrhea in two of them, with a 15-year history of anemia. Laboratory tests showed severe anemia in the three cases. Reduced calcium was found in two instances, and corrected calcium was found in one. Radiological examination showed a fracture in two cases. The diagnosis of osteomalacia was made by clinical, biochemical and radiological characteristics [13]. The anemia in celiac disease, although is due to malabsorption of iron, a recent study suggests celiac disease is increasingly being recognized as presenting with atypical presentation like short stature, failure to thrive, unexplained anemia, rickets, abdominal distension and abdominal pain, where the classical malabsorption features are not dominant. [14]. The CD is likely to be missed as in these present three young girls with ages 18, 19, 23 years at presentation, who were hospitalized as intractable seizures and found to have low serum calcium, with features of rickets/osteomalacia and anemia. This prompted to consider malabsorption of the CD which was confirmed by serologic tests, IgA transglutaminase and IgG anti gliadin antibodies and biopsy of the duodenum. In these patient's gluten, free diet not only provided drug free control of seizures, but also helped in correction of other features of hypocalcemia and anemia as the other symptoms were corrected by gluten free diet and vitamin D and Calcium, No doubt anemia associated with celiac disease as well as rickets are due to malabsorption, which is a major feature of celiac disease, yet they can be a presenting feature without obvious features of malabsorption [15]. These associations of rickets or osteomalacia with celiac disease are due to the malabsorption of calcium despite having normal vitamin D levels. In some cases of mild celiac disease, rickets and osteomalacia in adults might be the presenting feature. The association of anemia with a vitamin D deficiency needs to be examined to clarify the role malabsorption which might not be obvious in most cases, but no doubt malabsorption per se can lead to both diseases by impairing absorption of calcium and iron, without being a florid malabsorption syndrome.

Iron Deficiency Anemia in Rickets

The association between iron deficiency anemia in infants with vitamin D deficiency (VDD) rickets was first reported by Williams [1] but it was Grundulis in 1986 [16] who reported the combined deficiency of iron and vitamin D deficiency rickets as a major problem among Asian immigrants in the UK. Then Lawson and Lawson studied this combined deficiency among the Asian three communities in the UK. They reported first, the iron status and, [17] hemoglobin and ferritin values were analyzed in 1057 children, aged 2 years, of Asian parents living in England. (Children who had thalassemia trait or a current/recent infection were excluded). 29% of Pakistani, 25% of Bangladeshi, and 20% of Indian children had hemoglobin <110.0 g/l. The recent national diet and nutrition survey of preschool children found a prevalence of 12% of 2-year-old with hemoglobin <110.0 g/l. Taking vitamin or iron supplements was positively associated with iron status in one or more of the three groups. About vitamin D [18], 618 had a blood sample analyzed, plasma vitamin D values were lower in the three groups of Asian children than values reported for children of a similar age in the National Diet and Nutrition Survey. Between one third and a half of youngsters with low hemoglobin also had lower plasma vitamin D values; at that place was a substantial connection between failure to select a vitamin supplement, Chapati consumption and low vitamin D values. They reasoned that it is peculiarly important that pre-school Asian children receive a vitamin D supplement and children with low hemoglobin values should be screened for vitamin D insufficiency. These studies have beyond doubt stressed, the gravitational force of the combined vitamin D and iron status and the need to confirm the presence of a sort of a common factor playing a role of this almost twin deficiency. As part of our study, of children with rickets attending Almadina Children's Hospital, iron deficiency anemia was found to be 47% [1]. All were breastfed a situation in which, the iron content of breast milk is low as the mothers were also found to be vitamin D deficient. Nowadays, with the epidemic of vitamin D deficiency becoming a worldwide problem mainly in oil producing countries, it is likely to increase the prevalence of iron deficiency anemia. This high incidence of hypochromic anemia among rachitic children who are mostly breastfed but lucky, are throwing a normal protein calorie nutritional status, as seen in most rachitic children in a recent report of ours [19]. It has shown that the anemia is not part of generalized protein calorie malnutrition as most of these rachitic children were found to be well nourished on the breast even after being weaned. In Australia, Low 25-hydroxyvitamin D (25-OHD) levels (<50 nmol/l) occurred in 87% of children, and VDD (25-OHD <25 nmol/l) in 44%. Risk factors included age <5 years, female gender, increased indoor time in Australia, and decreased daylight exposure in winter and spring seasons. Anemia (20%), vitamin A deficiency (20%) and iron deficiency (19%) were also identified [20]. In another study from Northern India, anemia was present in 66% of 25 [OH] D deficient subjects compared with 35% in vitamin D sufficient individuals ($p<0.0001$). The association of breastfeeding and development of VDD was also important ($p<0.05$). Serum levels of 25 [OH] D were found lower in females if the analysis was performed in the winter/spring seasons [21]. In Korea, in breast fed infants below 24 months of age, the prevalence of iron and vitamin D deficiency was higher in breastfed children. There was also a significant association between iron and 25 [OH] D levels in infants. Since all breastfed babies should get vitamin D supplementation, there should also be concerned about a concurrent iron deficiency [22]. In another study from Korea results demonstrated that VDD has a high prevalence in children with iron deficiency anemia (IDA). Primary care physicians should be concerned about the possibility of VDD in children with IDA and should supplement them with vitamin D as well as iron [23]. These findings of iron deficiency and vitamin D deficiency among breastfed infants from different parts of the world are indications of the deficiency of both iron and vitamin D in the breastfeeding mothers as well. This finding is strong evidence supporting the importance of supplementing the mothers during pregnancy, as well as their infants during breastfeeding and beyond. Rickets start intrauterine accordingly considered occult congenital rickets and likely to be missed [24]. Iron and vitamin D deficiency has become a twin deficiency that strongly needs antenatal and post-natal combined prevention using iron and vitamin D supplementation during pregnancy and beyond.

Vitamin D Deficiency Associated with Inherited Hemolytic Anemia

The association between sickle cell anemia and spherocytosis with vitamin D deficiency

As vitamin D deficiency is common we are reviewing relation with inherited anemias, starting with sickle cell anemia and spherocytosis. Nolan, et al. [25] reviewed the related literature which is summarized by, stating that vitamin D deficiency has emerged as a public health problem in recent years and patients with sickle cell disease (SCD) reported to suffer a high prevalence of vitamin D insufficiency. The authors' objectives were to sum up the definitions of vitamin D inadequacy and insufficiency reported in the literature, and to limit the prevalence and magnitude of each in patients with SCD through a systematic review conducted per PRISMA guidelines. They state that, the definitions of deficiency and insufficiency varied greatly across the studies, making direct comparisons difficult. They provided evidence suggesting that suboptimal vitamin D levels are extremely prevalent among cases with SCD, far more than in comparable non-SCD patients or matched control populations. Defining deficiency as vitamin D <20 ng/ml, prevalence estimates in SCD populations ranged from 56.4 % to 96.4 %, but when compared with results from the population-based National Health and Nutrition Examination Survey, however the general African American population appeared to have a similarly high prevalence of vitamin D deficiency. African American patients with and without SCD were having higher levels of vitamin D deficiency than that of Caucasians. What remains to be learned in their survey is whether there are adverse health effects for patients with SCD because of concurrent vitamin D insufficiency. The osteoclast activity is pronounced to be increased in patients with sickle cell disease. This could ponder the result of inflammation in such patients. The relationship between osteoclast activity and higher tricuspid regurgitation velocity could also reveal important mechanistic pathways for further works. These studies could specifically focus on the function of macrophage monocyte activation in the pulmonary and bone complications of sickle cell disease [25]. About management Wykes, et al. [26] in a recent study revealed that, vitamin D deficiency is very common in the SCA and can be effectively corrected with high-dose intramuscular ergocalciferol or 4 days of high-dose oral cholecalciferol. They suggested that prospective, randomized studies are required to evaluate the clinical value of vitamin D supplementation. Patients with homozygous sickle cell anemia were more frequently and more severely affected by impaired bone health than patients with hereditary spherocytosis [26].

About spherocytosis only one study compared bone metabolism [27]. On comparing Spherocytosis and sickle cell anemia, serum levels of 25-OH vitamin D in patients with Hb SS were approximately half of those in patients with spherocytosis. Severe vitamin D deficiency (<10 ng/ml) was not detected in children with spherocytosis compared to 80% of the patients with Hb SS. Hyperparathyroidism was observed in 22% of patients with Hb SS, while it was found only in 14% of patients with spherocytosis. Osteocalcin levels differed significantly between patients with sickle cell disease, spherocytosis and healthy controls. Patients with sickle cell disease displayed the lowest levels of osteocalcin (45.6 ± 17.6 ng/ml), which were significantly lower than those observed in healthy controls and in patients with spherocytosis. Frequent back pain and knee pain after exercise can be suggestive of impaired bone health. The authors proposed to see whether self-reported bone pain and biochemical parameters of bone metabolism were associated in this cohort of patients, they also found that, patients who reported bone pain displayed significantly lower levels of 25 OH-vitamin D. They too found that recurring knee pain was linked to higher serum alkaline phosphatase levels in patients with hemolytic anemia. They indicated that it is also feasible that severe hemolysis may be responsible for the more pronounced impairment of bone health in patients with sickle cell disease. Patients with sickle cell disease display more severe alterations of bone health than patients with spherocytosis. Thus, the pathogenesis and severity of hemolysis may be a decisive component in influencing the phenotype of bone pathology in these hemolytic anemias.

Thalassemia and vitamin D

Soliman, et al. [28] reviewed the effect of vitamin D deficiency (VDD) on thalassemic children and adolescents verifying that many factors can compromise the adaptation process to VDD including: IGF-I deficiency, hypoparathyroidism due to iron deposition in the parathyroid gland, delayed puberty and hypogonadism, decreased bone mass and decreased synthesis of 25-OH-D due to hepatic siderosis. They emphasized on that several fields have reported a higher risk of VDD due to genetic and ethno-cultural elements; in addition to dark skin or concealing clothing that may lead to limited sun exposure. Decreased outdoor activities in thalassemic patients can also compromise cutaneous synthesis of vitamin D. A blunting of PTH response to VDD and a combination of hypovitaminosis D and hypoparathyroidism has been reported in many thalassemic patients. Further, they found that histopathology shows that in sub optimal blood-transfused thalassemic with iron overload, osteopenia was primarily caused by focal osteomalacia as well as a decreased bone formation. Densitometric and histo-morphometric studies indicated impairment of both trabecular as well as cortical bones in those hemochromatosis patients. Field reports from USA and India is recording, the high incidence of vitamin D deficiency among thalassemic patients. Further, they stressed on the pathophysiology of vitamin D deficiency among thalassemic patients and suggested a management plan to hepatic siderosis. With thalassemic patient's symptoms of VDD are commonly confounded with the symptoms of anemia and side effects of chelation therapy, including: joint and back pain, muscle weakness and osteopenia/osteoporosis. Nevertheless, improvement of back and joint pains and increased tolerability for walking and exercise has been reported in thalassemic adolescents after treatment with vitamin D. Even in adequately treated thalassemic patients, some radiological abnormalities of the long bones and vertebrae appear like those described in rickets, especially after long-term chelation therapy. Besides the iron overload associated with hyper transfusion programs of thalassemia and its injurious effect on the heart was strained. In summation to that the deleterious effect vitamin D deficiency increases the prospects of developing cardiomyopathy associated with vitamin D deficiency which have recently been surveyed [29] and reported in a six-month-old with cardiomyopathy showing good recovery on cardio tonic, calcium and vitamin D medications [30]. We postulate from this that the cardiomyopathy associated with hypocalcemia and vitamin D deficiency, might be aggravated by the iron overload in tissues. Vitamin D deficiency with 25 OH-vitamin D serum levels below 20 ng/ml was a common finding [80.5%] in this cohort. Bone pain was present in 31% of patients.

Mishra, et al. [31] surveyed the field in a comprehensive communication, stating that the array of diagnostic work-up for pyrexia of unknown origin (PUO) generally involves searching for endocrine etiologies, and hemolytic anemia and others, like Evans

syndrome and paroxysmal nocturnal hemoglobinuria (PNH). They also consider a role of low vitamin D and calcium in the hemolytic anemia. They state that lower levels of calcium and phosphorus at presentation prompted them to check for vitamin D levels, which were found to be very depressed, although it was prevailing in epidemic proportions all over India. Consequently, they found that, subclinical vitamin D insufficiency is extremely prevalent in both urban and rural settings, and across all socioeconomic and geographic strata as was seen in their patients. They postulated a role of this hypovitaminosis D-induced hypophosphatemia, in contributing to the severity of hemolysis as an effect of hypophosphatemia causing hemolysis which is well recognized. However, the levels of serum phosphorus may sometimes be normal or even spuriously increased in cases of severe hemolysis due to leakage of phosphorus from the RBCs. The concurrent presence of such deficiencies should be looked for and corrected for timely recovery. We did not find another evidence to hold up a relation of hemolysis to anemia associated with rickets.

Megaloblastic Anemia and Vitamin D Deficiency

Megaloblastic anemia is commonly associated with insufficiency of vitamin B12 and folic acid. The latter might be more likely during pregnancy. Vitamin B12 deficiency anemia is a condition in which the body does not have enough healthy red blood cells, due to deficiency of vitamin B12 which is needed to make red blood cells. Anemias caused by a lack of vitamin B12 or a lack of folate conform the two types of megaloblastic anemia. In this communication, the relation between vitamin D and. Megaloblastic anemia is discussed. Bailey, et al. [32] reviewed the risk of osteoporosis and bone fractures that increases with age. Several other factors are also related to bone disease, including gender, calcium and vitamin D. B-vitamins (folate, B12, and B6) are also emerging dietary factors related to bone health, both individually and through their action on influencing total plasma homocysteine concentrations (tHcy). In populations without folic acid fortification, the totality of evidence suggests that elevated tHcy has a small but significant association with bone fracture risk and bone quality, but not with bone mineral density (BMD) or bone turnover biomarkers. Very little supportive evidence exists for a direct role of folate on either BMD or fracture risk; however, the data available are quite limited. Meta-analyses and some cross-sectional and cohort studies suggest a small but significant role of vitamin B12 status on risk of fracture but not on BMD. The mechanism by which Hcy and B12 may influence bone health is not well characterized but may be through modulation of collagen cross-linking or through altering osteoclasts or osteoblasts. Much more data are needed-particularly the role that each vitamin directly has on bone or whether the vitamins only exert their effect though tHcy concentrations. Nevertheless, consistent findings across different populations with different study designs suggest a role for tHcy and B12 in reducing fracture risk. A report on the case of an infant who was hospitalized because of failure to thrive, megaloblastic anemia, and delayed psychomotor development. He was 10 months old and had been exclusively breastfed by his vegan mother. Investigations showed vitamin B [12] deficiency with hemocytopenia and pervasive developmental disorders as well as vitamin K and vitamin D deficiencies. The infant's mother presented the same deficiencies. Introduction of vitamin supplementation normalized the biological disorders, and the infant showed weight gain and neurological improvement. This case highlights that a vegan diet during pregnancy followed by exclusive breastfeeding can induce nutritional deficiencies in the newborn, with clinical consequences. Detecting mother and child vitamin deficiencies and preventing them is essential [33].

Myelofibrosis and Vitamin D Deficiency

The association between myelofibrosis and rickets and hypocalcemia, which is the earliest manifestation of rickets, was first reported by Coopersburg in 1966 [34]. I reviewed this association and highlighted that it is uncommon but dangerous. The myeloproliferative disorders comprise several clonal hematologic diseases that are thought to arise from a transformation in hematopoietic stem cells. The main clinical features of these diseases are the overproduction of mature, functional blood cells and a longer clinical course. It is actualized in all with bone marrow biopsy, showing reticulin deposition. In a recent review [35] I found that all cases of hypocalcemic myelofibrosis reported in infants are less than fifteen months of age, varying from 5 to 10 months with a mean age of 6.5 months. They presented with pallor and found to have hepato-splenomegaly. Since the first report, eleven cases were reported. Male sex was dominant except female twins Hemoglobin ranged from 3 to 9.7 mg% with a mean level of 6.7 mg%. Platelets and white blood cell levels were depressed after all. Dry bone marrow aspiration was suggestive and is considered diagnostic of myelofibrosis. All cases responded to vitamin D and calcium therapy with frank evidence of healing of rickets, but the blood parameters specially leucopenia persisted in some leading them to succumb to infection at a later age, although hemoglobin recovery was upheld.

The pathogenesis of Myelofibrosis in association with Rickets

The hallmark of MF is increased reticulin staining. The fibrous network observed in MF is collagenous and contains fibronectin; the reticulin (silver or Gomori) stain reacts with a protein that is intimately linked with type III collagen and is generally thought to be a form of procollagen. Fibrosis of the bone marrow presumably reflects overgrowth of the normal marrow matrix. Matrix homeostasis results from a correspondence between its deposition and its removal. The late is defined by several growth factors, most notably platelet-derived growth factor (PDGF), whereas the latter presumably reflects the activity of collagenase-expressing monocytes, macrophages, and granulocytes. The diseases associated with MF can be classed per whether the basic defect is matrix overproduction, under-resorption, or both. The last of these is typified by vitamin D deficiency because 1,25 [OH] 2D3, the active metabolite of vitamin D3 inhibits the proliferation of megakaryocytes and encourages monocyte/macrophage differentiation. This procedure seems to need certain specific ingredients that need to be identified and may be this is what is producing only very few cases of rickets proceed to show this complication which is uncommon [35].

Conclusion

The role of vitamin D in pathogenesis of anemia is still an open field of study, although this association historically is reported since 1929.The association of iron deficiency anemia with rickets was recognized among the Asian immigrants and it is common among breastfed babies. Anemia associated with rickets in celiac disease is due to malabsorption of iron and present as hypochromic anemia with good response as the malabsorption is corrected. Myelofibrosis associated with rickets although it is not as common, however it is dangerous. It is suggested to look for anemia in rickets bearing in mind

it is commonly iron deficiency that will react to treatment when iron is given together with vitamin D, but other more serious cases must be looked for especially if there is a short initial response. Myelofibrosis is a rare association that needs further studies to elucidate the mechanisms causing it. The relation with megaloblastic anemia is still an open issue for studies.

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