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Paget's disease

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ABSTRACT

Paget's disease of bone is a much uncommon, chronic bone disorder that occurs in only about one percent of people in the United States and slightly more often in the gender of men than in women (three to two). Paget's disease of the bone, also termed as osteitisdeformans, is a chronic disorder that disrupts the normal bone reframing process, causing bones to become enlarged, weakened, and prone to fractures. The condition is specifically characterized by excessive bone breakdown followed by the disorganized bone regrowth, paving to bone deformities and also potential complications.

KEYWORDS: *Paget's disease, osteitisdeformans, bone reframing, process, fractures, bone breakdown.*

INTRODUCTION

Individuals with the Paget's disease experience rapid isolated bone repair, which causes a variety of the symptoms from softer bones to enlarged bone growth, typically involving one or more bones of the pelvis, the low back (spine), hips, thighs, head (skull) and arms. This can lead to problems such as the bending, breaking, pinched nerves, arthritis and reduced hearing. Medical therapies have been proven effective in reducing the frequency of pain, fractures and arthritis that may be caused by this condition.

If one has Paget's disease you may not have any symptoms at all. It's not unusual for Paget's to be diagnosed by chance when one has an x-ray or blood test for a completely different reason (Daroszewska et al., 2005).

If one does have symptoms, pain is the most common problem, and it's usually felt in the bone itself or in the joints near the affected bones. There are many possible causes of the bone pain in people with the Paget's disease, including (Reddy et al., 1995).

- elevated blood flow – this often causes the affected parts of your body to feel slightly warmer to the touch, especially if the bones is close to your skin
- the nerve fibres surrounding the bone becoming stretched as a result of bone enlargement or bending
- osteoarthritis (a common complication of the Paget's disease), which often causes pain in the joints near the affected bones
- Enlarged bone pressing on nerves, causing pain in the back, neck and legs.

Causes

One doesn't yet know exactly what causes Paget's disease but the following factors may play a part:

- Genetic factors – About 10–15 in every 100 people with the Paget's disease have relatives who also have the condition. In these cases the conditions can be passed on from one generation to the next. But often there's no family history of the conditions.
- Lifestyle factors – There's some evidences that poor diet or a bone injury early in life may act as triggers for the later developments of Paget's in people who also have genetic risk factors.
- Another theory is that the Paget's disease may be linked to a viral infection early in life, but some experts dispute this (Singer, 1999).

ETIOPATHOGENESIS

Currently, the causes of the PDB are unclear. Evidence indicates both genetic and also environmental influences. Several rare genetic bone disorders with the clinical, radiological, and also histological features in common with the classic form of PDB have been described. These are the familial expansile osteolysis (FEO), expansile skeletal hyperphosphatasia (ESH),the idiopathic hyperphosphatasia, also known as juvenile PDB, early onset PDB and a ramified syndrome characterized by inclusion body myopathy, early onset PDB and the fronto-temporal dementia (IBMPFD)(Reddy,2006) .FEO is related to PDB, but occurs in the younger patients and the skeletal involvement is more severe; this condition is linked to activating mutations in the gene encoding the receptors activator of the nuclear factor kB

(RANK) on chromosome 18q . Juvenile PDB is characterized by the wide-spread lytic osseous involvement and it is caused by homozygous deletion of the gene on chromosomes 8q24.2that encodes osteoprotegerin (OPG). The existence of a sporadic and a familial forms of PDB have been described, the latter recognizing an autosomal dominant inheritance with the incomplete penetrance.PDB has initially been accounted a slow paramyxo viral infections process after the early descriptions of nucleocapsid-like structures in the nuclei and cytoplasm of pagetic osteoclast by the electron microscopy (Mills et al.,1976). Further studies confirmed that these inclusions cross-react with antibodies against the measles virus (MV) and also the respiratory syncytial virus (RSV) nucleocapsid antigens. Some authors have also identified the presence of the MV mRNA sequences in up to 90%of osteoclasts and other mononuclear cells in the pageticspecimens. It has to be noted that paramyxoviralnucleocapsid antigens were also detected in the osteoclast of patients affected by osteopetrosis, the pycnodisostosis, and otosclerosis (Whyte, 2006)

Several open questions remain about the roles of MV in the etiopathogenesis of PDB. First of all, the MV infections predominantly occur worldwide in children rather than in adults, while the PDB is usually diagnosed in elderly people. Moreover, osteoclasts are formed by the fusion of the postmitotic precursors and so are not self-renewing cells. This means that some others cell types serve as a specific reservoir for MV; regarding this topic, it can be argued that the pluripotenthematopoietic stem cells may be the initial target for para-myxovirus infections in patient with PDB .Researchers have demonstrated that other hematopoietic lineages from the subjects with PDB, including erythroid precursors and the multipotent myeloid precursors, also express MV nucleocapsid transcripts (Daroszewska et al., 2006).

GENE LEVEL ANALYSIS

Taken together, these data supports the hypothesis of a viral etiology of the PDB, anyway an infectious virus has never been isolated; furthermore any study has yet demonstrated that a virus is the cause of the PDB. In familial forms of the PDB, several potential susceptibility loci have been identified. The Wrst locus (PDB1) was identified in the year 1977 on the basis of a candidate gene linkage study but has not been later confirmed. The remaining loci specifically (PDB2-7) were identified by genome-wide sequences .PDB3 is primarily involved in the PDB; in particular, seques to some 1 (SQSTM1) represents the initial gene for which a role in Paget’s disease of bone has been established. This geneconsists of around

2,870 nucleotides grouped into eight exonsspanning 17kb genomic sequences .The SQSTM1 is ubiquitously expressed in human tissues and encodes precisely 440 amino acids p62 protein, divided into three domains: a cysteine-rich domain, involved in the protein–protein or DNA–protein interactions, and two highly conserved PEST motifs, allied with ubiquitin-binding domain (UBA-domain). The exact function of the p62 protein is not fully understood, but it probably plays a role in the NF-kB transcription activations pathway, which participates in the osteoclast regulation (Sofaer et al.,1983).Probably, the pathogenetic mechanism specifically involves a defective ubiquitination leading to the accumulation of the sequesto-some 1/p62 protein and then to overstimulation of the NF-kB pathway. According to that, the viral particles present in a bone in a genetically predisposed individual pave to an irreversible change in osteoclastogenesis. To date, 14 mutations affecting the UBA-domains ofSQSTM1 have been identiWed in patients with PDB. The most recurrent of the delineated mutations is P392L, present in 23% of familial cases of PDB and in 8% of the apparently sporadic cases. Other mutations have been described, but it appears that they are less important than the P392L. It has to be mentioned that some polymorphisms in the TNFRSF11A gene on chromosome the 18q22.1,which encodes RANK, have been found to increase the risks of PDB .Both genetic and viral hypothesis, however, do not answer the question how the PDB is a focal disease. Anyway, also bones not clinically affected by the disease that appear to show increased bone remodeling; this behaviour has been delineated to secondary hyperparathyroidism, but only 20-20.5%of the patients have elevated parathyroid hormone levels. Other systemic factors also seem quietly implicated in the pathogenesis of PDB and can be useful markers for monitoring the disease activity. In fact, it has been demonstrated that in the pagetic patients there are enhanced levels of IL-6, RANKL, M-CSF and endothelin-1(Morales-Piga et al., 1995).

Paget’s osteoclasts also seem to precisely produce higher levels ofIL-6 receptors than normal osteoclast and this appears to initiate an autocrine–paracrine loop that can copious osteoclast formation and increase the osteoclast precursor pool. In fact, it has been demonstrated and assessed that the number of earlyosteoclast precursors in bone marrow aspirates from patients with PDB are significantly aggrandized compared to normal (Kanis,1988)

PATHOPHYSIOLOGY

Paget's disease is a disorder of the bone that evolves through various stages of activity followed by a quiescent phase. Initially the disease is mainly characterized by an intense wave of osteoclastic activity with resorption of normal bone by the giant multinucleated cells, this osteolytic front precisely progress approximately 1cm yearly. Subsequently, an osteoblastic response paves to an excessive and disorganized new bone formation. The aberrant bony tissue resembles woven bone with the increased vascularity and a pronounced connective tissue reaction (Cundy, 2006). The combination of the osteoclastic and osteoblastic activity accounts for marked elevation of the osseous turnover rate .Hypervascularity of the pagetic bone and the cutaneousva so dilatation lead to an increase in regional blood Xow, manifested clinically as a rise in the skin temperature .After a variable period of time, osteoclastic activity may decrease, although there occurs the deposition of abnormal bone and some of the immature woven bone may be replaced by the normal-appearing lamellar bone. The histological landmark of pagetic bone is represented by a mosaicpatterns of irregular cement lines joining areas of lamellarbones. The new bones are ivory-hard and heavier than normal because of their incapacity to form haversian systems or to the center about blood vessels .The vertebral column has five segments and in the L1-L2 portion is conusmedullaris (S. Sreeremya, 2018b). Other major bone disease is Collagen Induced Arthritis (Dr. S. Sreeremya, 2019a) and Idiopathic Scoliosis (S. Sreeremya, 2018a). An effective treatment for adjusting and arranging the vertebral column is chiropractic science (Dr.S.Sreeremya, 2024a). There are different dynamics to disease (Dr. S. Sreeremya, 2024b).

Osteoblastic activity may eventually decline too and the diseases become quiescent; in this stage, the sclerotic bone is observed and there is no evidence of resorption and increased cellular activity. Anyway, the delineated changes are not invariable; in polyostotic disease, in fact, different stages of the disease may be identified in different skeletal regions (Poor et al., 2006) (Fig-1).

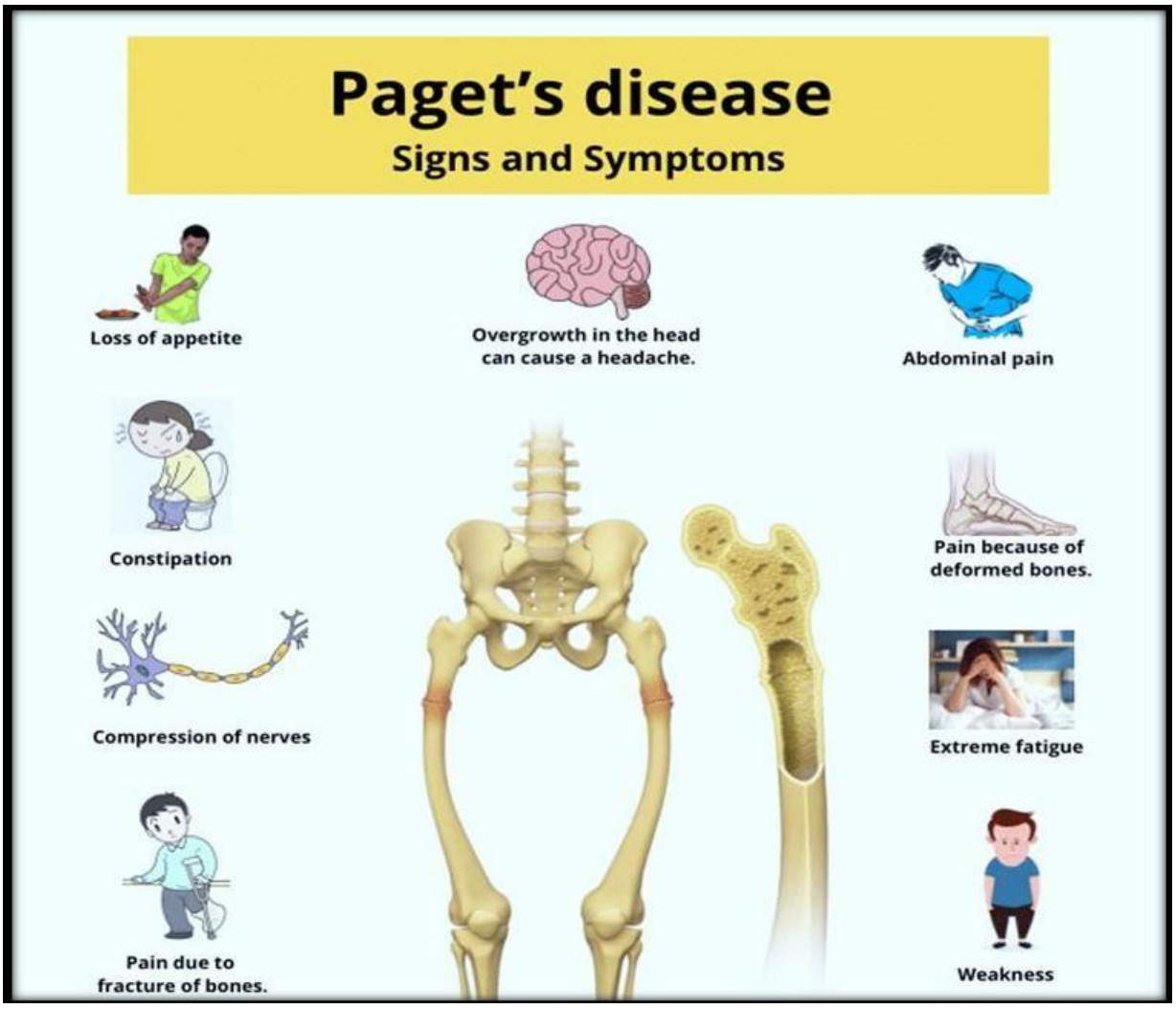

Figure: 1

CLINICAL FEATURES

In the majority of the cases, PDB is asymptomatic. When symptomatic (about 30% of patients), the presenting manifestations is a deep, aching bone pain, that persist through-out the day and at rest, seeming worst at night. Typically, the conditions may involve just one bone (monostotic) or few bones (polyostotic) , in the latter cases producing a richer clinical picture . Affected bones are precisely involved right away with no new involvement during the evolution. PDB may virtually affect every bone in the skeleton system, but the sites more often implicated are, in order of frequency, the pelvis and sacrum (>60%), the spine (50%), the thigh bones and skull (40%), tibias, humeri, and clavicles (20%). Hands, feet, and the facial bones are rarely affected (Gennari et al., 2007).

Pain is often allied with bone deformities such asbending of long bones, enlargement of the skull, and with elevated skin temperature facing a Vected bones. Pageticbone is brittle and may fracture even spontaneously, particularly the femur, tibia(leg), the humerus, and the forearm; these acute fractures, typically transverses, can mend rapidly, although malunion is not uncommon. Chronic, fractures may also occur along convex surfaces of long bones and are frequently asymptomatic, but when painful may specifically represent a harbinger for a complete fracture. Fissure fractures represent a unique feature of the PDB and have to be distinguished from fractures occurring in hyperparathyroidism and the osteomalacia (Takata et al., 2006).

In long bones, especially in the limbs, the deformities may induce secondary osteoarthritis. In facial bones, the deformitiesmay create difficulties for artificial dentures and tooth extractions. Neurologic complications may also result from skull involvement. The most frequent are hearing loss and the cranial nerves palsies, when the base of the skull is affected there may be the platybasia, the basilar invagination, basilarimpression, and vertebrobasilar insufficiency .The Spine involvement may be responsible for “vascularsteals”, causing pain, dysesthesias or the paralysis (Shadada et al.,2006).

CONCLUSION

This paper encompasses the clinical manifestations, signs and symptoms, pathology of Paget’s disease. The gene level assessment of patient’s body having Paget’s disease is understood. The seques to some 1 (SQSTM1) represents the initial gene for which has a pivotal role in Paget’s disease of bone has been established. This geneconsists of around 2,870 nucleotides grouped into eight exons which has the coding or information containg sites, spanning 17kb genomic sequences. The SQSTM1 is ubiquitously expressed in the human tissues and also encodes precisely 440 amino acids p62 proteins.

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