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Review

Neurological complications of Paget's disease of bone; a narrative overview

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Abstract

Paget's disease of bone (PDB) is an osteopathy that progressively affects one or multiple bones, often involving the neurological system. The disease can impact the spinal cord, cauda equina, brain, and cranial nerves due to their proximity to affected bones. The involvement of the cranial nerve may lead to vision, hearing or speech loss. Radiological identification includes features like hypertrophic bones and cortical thickening. Neurological symptoms such as headaches, dementia, cranial neuropathies, and spinal issues may arise, though many cases are asymptomatic and discovered incidentally. The skull is frequently involved, leading to abnormal bone growth. Neurological deficits are often caused by spinal hypertrophy, direct compression, or pathologic fractures. Diagnostic tools like magnetic resonance imaging (MRI), CT-myelography, and bone X-rays are essential for locating lesions and guiding treatment. Treatment varies based on the severity and progression of the neurologic deficit, with bisphosphonates commonly used for progressive or chronic cases.

Keywords: Paget's disease of bone, Polyostotic, Paget's disease, Cauda equine syndrome, Multiple cranial nerve palsies, Sphenoid bone

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Introduction

Paget's disease of bone (PDB) is a chronic metabolic osseous disease marked by increased osteoclast activity leading to excessive bone absorption and subsequent increased osteoblast activity resulting in disorganized bone formation (1). Osteoporosis and PDB are the first second most common metabolic osseous disorders. The skull, long bones of the limbs, pelvis, and spine are the most commonly affected bones (2). This disorder affects 1%–5% of those over 50, with a slight male predilection and the majority of patients being over 40 when the symptoms appear. Anglo-Saxon people, particularly in Europe, are particularly prone with a frequency of 3.7%. Vascular and fibrous tissue gradually replaces the bone marrow in the body, which lead to "enlarged, unusually curved, and misshapen" bones, as described by Sir James Paget in 1877 (3).

This disease is often an asymptomatic disease in at least 70% of cases, accidentally found on blood testing with an elevated alkaline phosphatase or radiological imaging showing abnormally thickened and or deformed bone. This disorder can cause long-term bone abnormalities, pathological fractures, and bone pain (4). The polyostotic form usually affects the pelvis, spine, femur, and head in order. The lumbar bones are impacted by half of all polyostotic involvement, followed by thoracic (45%) and cervical vertebra (14%) (5).

Neurological manifestations are heterogeneous resulting from the compressive effects of the abnormal bone overgrowth in the cranium and vertebral column and basilar invagination (6). Headache, cranial neuropathies resulting in impaired hearing, olfaction, vision and ocular movements, brainstem cerebellar symptoms and spinal cord compression syndrome together with cauda equina and or root involvement are amongst the spectrum of manifestations that can be seen in PDB.

Pathophysiology and causes

Primarily, PDB manifests through the formation of skeletal lesions resulting from increased and disorganized bone turnover. Initially, PDB is triggered by heightened osteoclastic activity, where osteoclasts become abnormally active, leading to an increase in both their size and number (2). This aberrant activity is often accompanied by the presence of inclusion bodies in the osteoclasts, which resemble viral particles, hinting at a potential viral component to the disease (7).

As osteoclasts break down bone at an accelerated

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Implication for health policy/practice/research/medical education

Paget's diseases of bone can have serious impacts on the skull and spine. These impacts cause a variety of neurological symptoms. The discourse of diagnosing and addressing the neurological complications of Paget's diseases of bone is discussed in this study.

rate, the body attempts to compensate with increased bone formation. However, this new bone is laid down haphazardly, resulting in a disorganized structure known as "mosaic bone", which comprises both woven and lamellar bone. Unfortunately, this mosaic bone is mechanically weak, making it more susceptible to fractures and deformities (1).

Research suggests that PDB is fundamentally a disease of the osteoclasts (1). Patients with PDB have osteoclast precursors that exhibit heightened sensitivity to bone-resorbing factors like receptor activator of NF-κB ligand (RANKL) and 1,25(OH)2 D vitamin (8). Moreover, increased levels of interleukin-6 (IL-6) further enhance osteoclastic activity (9). While osteoblasts, the cells responsible for new bone formation, are also increased in PDB-affected areas, their morphology appears regular and are not thought to be the disease's main cause (10).

Environmental factors have also been implicated in PDB (1). Studies in regions like Italy (11) and Spain (12) suggest an association between rural living, frequent contact with animals, and a higher risk of developing PDB, leading to the hypothesis that animals might carry infectious agents contributing to the disease. A viral infection, particularly involving paramyxoviruses like the canine distemper virus (13) and the measles virus (14), has been proposed as a possible trigger. Some studies have detected viral RNA in the osteoclasts of PDB patients, and experiments have shown that introducing viral genes into osteoclast precursors can induce changes similar to those seen in PDB (15). However, these findings remain controversial, as other studies have failed to detect viral presence in PDB patients, leaving the role of viruses in the disease unresolved (16).

PDB also has a notable genetic background, with many patients reporting a family history of the disease. The RANK/RANKL/OPG signaling pathway, which regulates osteoclast activity, is crucial in understanding the genetic basis of PDB (17). For instance, mutations in the OPG gene (TNFRSF11B) are linked to juvenile PDB, while activating mutations in the RANK gene (TNFRSF11A) are associated with other bone disorders but not with classical PDB (17). Several loci across different chromosomes have been identified as potential Paget's susceptibility genes, with mutations in the SQSTM1 gene being particularly significant. SQSTM1 mutations, which affect the p62 protein involved in osteoclast regulation, are found in a significant percentage of familial and sporadic PDB cases. However, the variability in mutation presence and disease expression suggests that these mutations predispose individuals to PDB rather than directly cause it (18).

Other genetic factors, such as mutations in the valosin-containing protein (VCP) gene, are linked to rare syndromes involving PDB, but these are not responsible for the common forms of the disease. Thus, PDB is a complex disorder influenced by both genetic predisposition and potential environmental triggers, with ongoing research aimed at fully elucidating its causes and mechanisms (19). Tables 1 and 2 summarize the genes and loci involved in the pathophysiology of PDB.

Clinical features

At least 70% of patients with Paget's disease are asymptomatic, and the condition can exist for many years without any symptoms. In symptomatic cases, the disease can affect the peripheral and central nervous system, mainly from the compressive effects of the abnormal bone overgrowth. A typical scenario leading to the diagnosis of Paget's disease could be common the combination of headache, bone pain and decreased hearing. It is uncertain how often the headaches occur in all patients (20). Previous research included 24 individuals with PDB symptoms; 7 of these patients had headaches in addition to the abnormalities in their skulls known as pagetoid alterations. The pain was characterized as intense, often occipital, and worsens when coughing, sneezing, or strains (21). In addition to occipital headache, ataxia,

Table 1. Genes' loci associated with PDB

Gene	Role in PDB
RANK (TNFRSF11A)	Encodes *RANK*, a receptor on osteoclast precursors. Activating mutations cause familial expansile osteolysis, expansile skeletal hyperphosphatasia, and early onset PDB. Not a common cause of classical PDB.
RANKL	Ligand that binds to RANK on osteoclast precursors to promote proliferation and differentiation of these cells.
OPG (TNFRSF11B)	Encodes osteoprotegerin, a fake receptor for RANKL to prevent it from attaching to RANK, and thus inhibiting the differentiation of osteoclasts. Inactivating mutations cause juvenile PDB (hereditary hyperphosphatasia). Common polymorphisms may be associated with PDB in women.
SQSTM1	Encodes p62, that regulates osteoclast cell cycle. Mutations in SQSTM1 are an important cause of PDB, with a higher frequency in familial PDB (28.8%) than in sporadic cases (6.1%). SQSTM1 mutations are associated with variable expressivity and incomplete penetrance of PDB.
VCP	Encodes valosin-containing protein. Mutations frontotemporal dementia and inclusion body myopathy, which are rare syndromes linked with PDB. This gene is not commonly responsible for familial or sporadic PDB.

Table 2. Genetic loci associated with PDB

Locus	Chromosome Location	Role in PDB
PDB1	Chromosome 6	Possible Paget's susceptibility locus.
PDB2	Chromosome 18q21	Possible Paget's susceptibility locus.
PDB3	Chromosome 5q35	Associated with SQSTM1 mutations, an important cause of PDB.
PDB4	Chromosome 5q31	Possible Paget's susceptibility locus.
PDB5	Chromosome 2p36	Possible Paget's susceptibility locus.
PDB6	Chromosome 10p13	Considered one of the strongest candidate genes for PDB.
PDB7	Chromosome 18q23	Possible role in lowering the onset age of PDB.

vertigo, tinnitus, dysphagia, dysarthria, and progressive indications of the cerebellum and corticospinal tract are among the symptoms and indicators (22).

Anatomical lowering of the softer base of the skull onto the upper cervical vertebrae in severe cases may result in cerebellum and brain stem compression (basilar invagination). Any odontoid protrusion greater than 6.5 mm above Chamberlain's line, which runs from the posterior end of the hard plate to the posterior lip of the foramen magnum, is referred to as basilar invagination. Compression of the cerebellum, lower cranial nerves, pyramidal tract, and upper cervical nerves may result, along with obstructive hydrocephalus. Acute tonsillar herniation and death are possible outcomes, depending on the severity. The neurologic condition typically progresses slowly over one to five years (23).

Obstruction of venous return and vertebrobasilar insufficiency may be caused by basilar impingement. Direct pressure on the cerebrum, along with hydrocephalus, are the two main causes of dementia. Progressive mental decline, fatigue, loss of memory, sluggish intellect, and stupor are present (24). The symptoms of basilar invagination-induced hydrocephalus include incontinence, apraxia of gait, and dementia. At its most severe, the patient's lack of motivation and lack of motor activity mimics akinetic mutism. Another name for this condition is hydrocephalic parkinsonism. The uncommon condition known as epilepsy is brought on by compression of the brain hemispheres (25).

All cranial nerves may be impacted by PDB of the skull; however, PDB most frequently afflicts the auditory and olfactory nerves. Smell loss may result from the cribriform plate complex PDB. The cranial nerve III may also be impacted at the optic foramen as a consequence of compression or compromised vasa nervorum circulation. Clinical manifestations include papilledema, angioid streaks, retinal hemorrhages, choroiditis, optic atrophy, and reduced vision or blindness (26). Papilledema might potentially be a sign of elevated intracranial pressure. As the oculomotor nerves (III, IV, and VI) cross the superior orbital fissure, aberrant pupillary movements and impaired eye movements (diplopia) may result. Rarely does concurrent exophthalmos cause the encroaching bone to directly impinge on the extraocular muscles (27). The trigeminal (V) nerve lesion causes numbness of the face and trigeminal neuralgia. Facial paresis or hemifacial spasm may be the outcome of facial nerve (VII) involvement. Of individuals with pagetoid abnormalities in the skull, 12%–50% become deaf (28). There are three types of hearing loss: mixed, conductive, or neuronal. It can be caused by direct cochlear invasion, direct pressure on the VIII nerve in the acoustic meatus, or involvement of the middle ear's bony ossicles and their fixation (29). The IX, X, XI, XII nerves as the lower cranial nerves may be affected by basilar invagination (30). Dysphonia, slurred speech, fasciculation, lingual, trapezius and neck muscles fatigue and atrophy, are among the symptoms. These individuals frequently have involvement of the brain stem and cerebellum (31).

Skull osteosarcoma affects less than one percent of people with PDB. It typically starts in mid-life following a protracted period of "benign" bone disease (32). There may be a short locally painful and partly fluctuating skull mass history, as well as fast neurological decline. Even with surgery and radiation treatment, the prognosis is poor. There have been reports of acute compression from epidural hematomas of the spine or skull, which is brought on by an increased risk of pathologic characteristics and increased blood flow to the bone. In many circumstances, the additional bleeding during surgery further worsens the prognosis (33).

In 10%–20% of people with Paget's disease, spinal stenosis develops; of them, half have neurologic impairment. There are several ways in which neurologic compromise can occur:

- The spinal cord, cauda equina, or radix nervi can be directly compressed by vertebrae affected by PDB.
- Joint fractures or subluxation.
- Hardening or bone formation in structures outside the dura mater.
- Redirection of the local blood flow to the highly vascularized bone affected by PDB.
- Due to the pressure exerted on blood vessels as they pass through the spaces between the vertebrae (34,35).

Back pain is seen in 11-43% of patients with Paget's disease affecting the spine (36,37). Distinguishing between osteoarthritis and PDB as the cause of pain can be difficult because osteoarthritis is so common in older

adults (38,39). Symptoms of myelopathy include spastic paralysis or weakness in the legs or all four limbs, a distinct sensory level, urinary urgency, frequency, incontinence, Lhermitte's phenomenon (a tingling or electric shock sensation in the arms or back when bending the neck), and quick deep tendon reflexes with upward-pointing toes. In cauda equina syndrome, symptoms can include weakness in the lower limbs, muscle atrophy, varying sensory loss often affecting multiple dermatomes, loss of deep tendon reflexes, low back pain radiating to the legs, pain that worsens with walking or extending the lower back, and relief with lumbar flexion (spinal claudication) (40). Figure 1 summarizes the key neurological findings of PDB.

Paraclinical findings

In individuals with neurologic problems, urine hydroxyproline and serum alkaline phosphatase amounts are often elevated. However, in thirty-one percent of individuals with spinal stenosis, alkaline phosphatase levels are normal. Calcium and phosphorus levels remain normal in PDB patients (41).

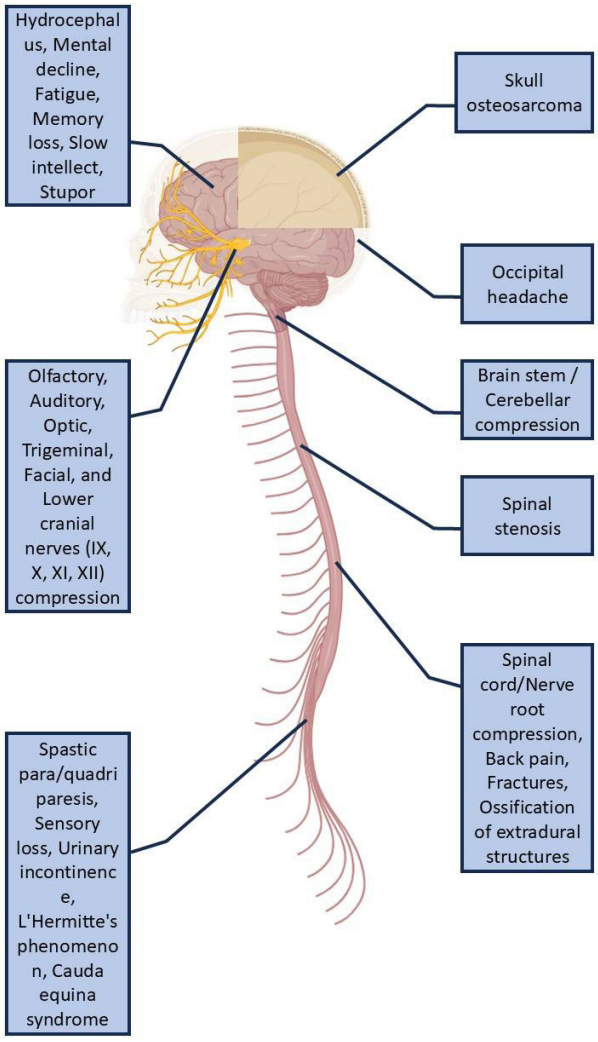

Figure 1. A summary of the key neurological findings of PDB.

CT imaging in Paget's disease reveals features that evolve as the disease progresses through its phases. In the early stages, osteolytic (lucent) areas are predominant, particularly in the skull, were large, well-defined lytic lesions known as osteoporosis circumscripta may be seen. These lesions are typically confined to the inner aspect of the outer table of the skull, while the inner table remains intact. Cervical cord involvement has been linked to an uncommon image that resembles an amyotrophic lateral sclerosis patient. As the disease progresses, the lytic areas are followed by a coarsening of trabeculae and bony enlargement, eventually leading to mixed lytic and sclerotic patterns, often referred to as a "cotton wool" appearance. Advanced stages of the disease may involve diploic widening, where both the inner and outer tables of the calvarium are affected, with a tendency for the inner table to be more extensively involved (42).

One of the pathognomonic signs in neurologic Paget's disease is the "Tam o' Shanter" sign, where platybasia and basilar invagination give the skull, a characteristic appearance resembling a tam o' shanter hat falling over the facial bones. In the spine, CT imaging reveals the "picture frame" sign, where the vertebral bodies exhibit cortical thickening and sclerosis encasing the vertebral margins, giving a rectangular or "picture frame" appearance. This, along with squaring of the vertebrae and vertical trabecular thickening, further defines the spinal involvement in Paget's disease (43).

Magnetic resonance imaging (MRI) findings in neurologic Paget's disease are variable, reflecting the different phases of the disease. The most common pattern observed is a signal intensity in the affected bone similar to that of fat, indicative of longstanding disease. A "speckled" appearance, characterized by relatively low T1 and high T2 signal alterations, corresponds to early mixed active disease where granulation tissue, hypervascularity, and edema are prevalent. In the late sclerotic stage, low signal intensity on both T1 and T2-weighted images suggests the presence of compact bone or fibrous tissue. Throughout the disease course, fatty marrow signal is generally preserved unless complications arise (42).

Bone scintigraphy, particularly using Tc-99m-MDP, is highly sensitive for detecting Paget's disease, although it lacks specificity. The modality is useful for defining the overall extent and distribution of the disease, showing markedly increased uptake in all phases. A distinct pattern observed in Paget's disease of the spine is the "Mickey Mouse" sign, where increased uptake in the vertebral body and posterior elements forms an inverted triangular pattern resembling the Mickey Mouse silhouette. Another distinctive sign is the "Lincoln sign," observed as diffuse mandibular uptake creating a bearded appearance (42).

Treatment

The place, cause, and severity of PDB will determine the treatment choice (44). Treatment with bisphosphonates is

advised for asymptomatic diseases of the spine or skull. Since they do not result in the mineralization problems associated with etidronate, one of the more recent bisphosphonates, such as pamidronate, alendronate, risedronate, or tiludronate, is advised in this situation (45). Initially, bisphosphonates should be used to address neurologic impairments that are chronic and gradually progressing (46).

Etidronate, IV pamidronate, and/or calcitonin have been demonstrated to have positive benefits in case reports and small patient series. When calcitonin or oral bisphosphonates are ineffective, intravenous bisphosphonates can be useful (47). It's critical to take adequate calcium and vitamin D supplements to prevent hypocalcemia, which is a side effect of bisphosphonate therapy (48). Even while pharmaceutical treatment is effective in treating certain disease-related problems, such as bone abnormalities and spinal cord compression, surgical treatments may still be necessary (49). It could be essential to do decompressive surgery if they don't react. To reduce bone bleeding and the need for surgery, rapidly progressing neurologic impairment should be treated simultaneously with medicinal therapy (calcitonin or IV bisphosphonates) (50).

Ventricular shunt insertion is necessary for obstructive hydrocephalus; as medical treatment is ineffective in treating it (51). There is a lack of research on how medicinal or surgical treatment affects cranial problems (51). Treatment with bisphosphonates has the potential to stabilize hearing loss (52). Etidronate and calcitonin together may be effective in treating memory loss and optic neuritis (53).

Carbamazepine has an effect on hemifacial spasm and trigeminal neuralgia (54,55). Surgical decompression may help facial nerve paresis and individuals with lower cranial neuropathies have previously been shown to benefit from suboccipital craniectomy and upper cervical laminectomy (56,57). Multiple degrees of involvement and vascular bone with problematic hemorrhage make surgical treatment of spinal illness challenging. They are less acceptable surgical candidates due to their advanced age (58,59).

Conclusion

Although rare, neurological symptoms of PDB can be serious. In patients with established PDB of the spine or skull, clinical neurologic evaluations must be carried out regularly by a qualified healthcare professional. Any afflicted patient should be evaluated for PDB as a potential cause of neurologic symptoms. Neurological symptoms involving the skull and spine may be present in PDB. When the disease is treated in its early stages, the prognosis is favorable. Neurological problems and bone abnormalities are associated with morbidity. Treatment with bisphosphonates was effective for the skeletal symptoms in this case, but it did not help the extra-skeletal abnormalities, such as hearing loss. normal levels do not rule out PDB as a possible source of peripheral or central neurologic complications, although raised levels of alkaline phosphatase enzyme are frequently observed in association with neurologic problems. Modern imaging techniques like MRIs and CT (computed tomography) scans have made it easier to assess neurologic signs in the setting of PDB. Therapy options include surgery, IV and oral bisphosphonates, calcitonin, and symptomatic therapy, depending on each patient's presentation.

Authors' contribution

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Visualization: Esma'il Akade.
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Writing–review and editing: Esma'il Akade.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Conflicts of interest

The authors declare that they have no conflicts of interest regarding this article.

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