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Osteoporosis in neurodegeneration

Per M. Roos [a,b,*]

[a] Department of Neurology, Division of Clinical Neurophysiology, Oslo University Hospital, Oslo, Norway
[b] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

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ABSTRACT

Osteoporosis affects bone microarchitecture and reduces bone mass. There are more than 200 million people with osteoporosis worldwide, and the prevalence is slowly increasing. The highest prevalences are found in Scandinavia and USA, also slowly increasing. A parallel increase in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, and multiple sclerosis has been noted since the middle of this century. Osteoporosis is more common in patients with each of these neurodegenerative conditions than in the general population. Several metals with neurotoxic properties accumulate in bone and can substitute for calcium in hydroxyapatite, the main mineral component of bone. Especially cadmium, but also lead, aluminum and arsenic affect bone mineral density negatively. Metals with neurotoxic properties have also been found in brain and cerebrospinal fluid from patients with Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, and multiple sclerosis, and markers for neurodegeneration such as amyloid beta peptide and amyloid precursor protein have been detected in bone tissue from patients with osteoporosis. A common mechanism contributing to the pathogenesis of both neurodegeneration and osteoporosis can be suspected. The hypothesis that neurodegenerative disorders are associated with osteoporosis is presented and discussed.

Introduction

Osteoporosis is a disorder of the skeletal system where bone microarchitecture is affected and bone mass reduced. By definition, osteoporosis is present when bone mineral density is measured as 2.5 standard deviations or more below the mean of the young adult reference range [1]. Osteoporosis affects more than 200 million individuals worldwide [2], and about 9 million osteoporotic fractures are noted each year [3]. A slow but steady increase in osteoporosis prevalence has been noted worldwide in the second half of this century with the highest rates found in Scandinavia [4,5] and USA. In recent years this increase seems to have reached a plateau in the western world while Asia shows a continuous rise.

Degenerative disorders in the nervous system include diagnostic entities such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). An increase in prevalence for these diagnoses has been noted in many countries [6–9] in recent decades. The causes of these disorders are unknown however, environmental toxic contributions to neurodegenerative disorders have long been suspected and toxicological knowledge seems necessary to disentangle the complicated interplay between organic molecules of the nervous system and inorganic exposures [10].

The increase in osteoporosis prevalence parallels the increase in neurodegenerative disorders in time, both showing a steady rise from about 1950. In AD, a decline has been possibly observed in recent years [9], but neurodegenerative disorders when considered together continue to increase in prevalence, as does the incidence of osteoporosis, with some regional variations.

The cause of osteoporosis is unknown. Several risk factors have been presented such as lack of physical activity, calcium or vitamin D deficiency, female sex, smoking, alcohol, steroid treatment or hypogonadism. Several metals with neurotoxic properties affect bone mineralization and the hypothesis that such metals concurrently affect the skeletal and the nervous system is presented in this short review.

Metals

Inorganic chemistry of osteoporosis

Calcium (Ca) and phosphorus (P) are present in the main mineral constituent of bone hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$. The nutrient artery of the bone and the periosteal arteries provide blood supply

* Corresponding author at: Nobels vag 6, Karolinska Institutet, 17177 Stockholm, Sweden.
E-mail address: per.roos@ki.se

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to the bone and allow for blood borne toxicants to interact with elements of hydroxyapatite. Several divalent metal ions such as manganese (Mn), lead (Pb), cadmium (Cd), copper (Cu), iron (Fe) or arsenic (As) can substitute for Ca in bone. The hydroxyl group can also be substituted for monovalent elements such as fluoride or bromide [2,11]. Environmental Cd exposure is associated with an increased loss of bone mineral density in both genders, leading to osteoporosis and increased risk of fractures, especially in elderly and in females [5,12]. Concentrations of Cd have increased in human bones in the 20th century, and is now about ten times above the pre-industrial bone Cd level [13]. In Cd exposed workers a dose-response relationship between cadmium exposure, measured as urinary Cd, and prevalence of osteoporosis has been noted [14].

Inorganic chemistry of neurodegeneration

Free Cu ions seem to contribute to AD pathogenesis, mediating aggregation and neurotoxicity of amyloid beta found in AD brains [15]. Exposure to Cu from drinking water and from other sources is a risk factor for AD development [16]. Metal distribution and redistribution seem to be affected in AD and especially Fe, Cu and zinc are involved in amyloid generation and brain deterioration in AD [17].

Accumulation of Fe has been noted in basal ganglia in PD [18] and neurodegeneration is associated with an increase in substantia nigra Fe concentrations, accompanied by decreased Cu and ceruloplasmin concentrations in substantia nigra and increased cerebrospinal (CSF) free Cu concentrations [18]. High affinity binding of Cu to N-terminal methionine residues of synuclein seems to promote aggregation and amyloid formation in PD [19].

In ALS twenty-two metals were measured in CSF from 17 patients and 10 controls. Significantly increased concentrations were found for Mn, Al, Cd, Co, Cu, Zn, Pb, V and U in CSF from ALS patients [20]. Manganese showed the most prominent differences between cases (median 5.67 mg/L) and controls (median 2.08 mg/L). CSF Mn concentrations were higher than plasma Mn concentrations (median 0.91 mg/L), suggesting Mn transport into the central nervous system [20]. Most of the metals detected in CSF are well known neurotoxicants. These data were presented at the 10th conference on Trace Elements in Health and Disease in Tokyo in 2013, held by the International Society for Trace Element Research in Humans (ISTERH). Other data [21] indicate specific Fe accumulation in deep cortical layers in ALS. Accumulations of Mn have also been noted in anterior parts of spinal cord transverse sections from patients with ALS, as well as increased concentrations of aluminum. Several metals with neurotoxic properties are related to ALS pathogenesis [22].

Multiple sclerosis is traditionally considered an inflammatory central demyelinating disorder however, recent data implicate neurodegeneration as the major cause of the irreversible neurological disability seen in MS patients [7]. Iron accumulation is an early event in MS [23]. Perivenular Fe deposits have been detected in MS brain plaque [24,25] and Fe is also found around the ventricular system in MS patients. A recent study has shown the presence of Fe in microglia and macrophages at chronically demyelinated brain lesion edges in MS, but not in the lesion center where myelin debris was found [26]. Increased urinary excretion of Fe and Al has also been noted in MS [27].

Barriers

Bone blood supply is provided by the nutrient artery system, where the inner two thirds of bone matrix are vascularized from arterioles via the Haversian system. Circulating elements may also reach bone matrix through the periosteal arterial system. Some 10% of cardiac output is received by the skeleton. Several metals with neurotoxic properties, such as Mn, bind to hydroxyapatite and bone is a compartment for accumulation and storage of metals [5,28] as is the brain [29]. In exposure experiments, bone Mn concentrations correlate to Mn concentrations in brain, choroid plexus and CSF in a linear manner [30]. An equilibrium exists between the bone metal pool and the CSF metal pool, separated by the blood–brain barrier (BBB) and the blood–CSF-barrier (BCSFB), where bone may serve as a sink/source for release of metals into the bloodstream.

Cerebrospinal fluid is one out of four major brain fluid compartments. The other compartments are the blood that perfuse brain cells and return through large vein sinuses to the heart, the interstitial fluid (ISF) that surrounds glial cells and neurons of the brain, and the intracellular fluid within those cells. There are no barriers between CSF and ISF and substances detected in the CSF are in equilibrium with the liquid compartment surrounding the nerve cells. However these two compartments are protected from the circulating blood by tightly connected endothelial cells in the blood vessels, constituting the BBB [31]. In addition to the well-studied BBB, a second barrier system, known as the BCSFB, anatomically represented by the choroid plexus (CP), separates the CSF from the systemic circulation. The lateral ventricles, the third and the fourth ventricle are harboring membranes of the CP and the CSF is secreted at a high rate through the large villous surface of the CP. Cerebrospinal fluid can be considered an ultra-filtrate of the blood.

Chemical protection of the brain and spinal cord depends on the integrity of these two barrier systems, the BBB and the BCSFB. CNS homeostasis is closely regulated by the BCSFB. Transport of metals across brain barrier systems has been investigated in detail and specific protein transporters for metals exist [29], some of them unidirectional allowing metals from the bloodstream to enter the CSF/ISF using inward directed transport mechanisms allowing for accumulation of metals inside of the barriers. The possibility of metals with neurotoxic properties to selectively injure the barrier structure themselves [32] must also be taken into consideration.

Osteoporosis in Parkinson's disease

Bone mineral density (BMD) seems to be lower in PD patients than in the general population, as reported in several studies [33]. Specifically, bone loss was significantly higher among men with PD than among men without the disease [34]. A dose-response relationship was found in women with PD where the more severely affected patients displayed the lowest bone mineral density values [35].

Osteoporosis in Alzheimer's disease

A large prospective Chinese study found that lower BMD and higher rates of bone loss were related to a higher risk of AD both in men and women, suggesting an intrinsic close relation between osteoporosis and AD [36]. Increased risk of dementia in patients with osteoporosis has also been shown [37]. Interestingly markers for neurodegeneration, such as amyloid beta peptide and phosphorylated tau have been detected in tissues outside of the central nervous system [38]. Recently amyloid beta peptide and amyloid precursor protein, the histopathological hallmarks of AD, were found in osteoporotic bone tissue expressed at higher levels in the cases with the lowest BMD, correlating in a linear fashion [39]. A common toxicant affecting both bone and brain can be suspected.

Osteoporosis in amyotrophic lateral sclerosis

Reports on osteoporosis in ALS are scarce. Bone mineral loss has been noted in ALS [40] and aberrant calcium metabolism and vertebral anomalies have been detected in a few ALS patients [41].