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Guest Editorial

Does Environmental Pollution is Correlated with Clinical Profile of Aseptic Necrosis of Femoral Head in Children?: Special Reference with Heavy Metal Toxicity

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Aseptic necrosis of head of femur in children which is commonly known as Legg-Calve-Perthes Disease (LCPD) is the clinical manifestation of vascular compromise of femoral capital epiphysis having unknown etiology, primarily affecting children between 4 - 12 years of age. This happens when the lateral epiphyseal vessels which are the primary source vascular supply of the femoral capital epiphyseal region are involved [1]. The annual incidence of LCPD in children below 15 years of age ranges from 0.2 to 19.1 per 100,000 [2]. LCPD has usually an asymmetric presentation with only 15% of cases having bilateral involvement. Incidence of LCPD is 3 - 4 times more in boys than girls. The some of the known risk factors are: children exposed to maternal smoking, low birth weight neonates, low socioeconomic groups and children of white ethnicity [2-5]. The affected children are relatively short stature and have delayed osseous growth [6]. Exact pathogenetic mechanism of LCPD is still unknown and it may probably caused by a multifactorial etiology which still remains a question [7].

Moreover, among many children primary complaint is a painless limp [8,9]. According to literature [9,10], almost half of the cases of LCPD are diagnosed only in their advanced stages. Thus, it is not a surprise that a huge number of LCPD patients in their initial stages are missed due to which the actual incidence revealed in literature is probably just a tip of an iceberg. Till date despite having detailed characterization of clinical and radiological features of LCPD, its etiology still remains essentially unknown [10]. It may be thought that both environmental and genetic factors have a role to play in development as well as its progression of LCPD [11].

Initially, Walden-storm described the natural course of the LCDP into 4 stages: initial stage, fragmentation, healing and residual stage [9]. It was further modified and divided in 4 stages: sclerotic, fragmentation, healing and healed stages [10]. The radiologically the Perthes disease can be divided into 4 stages: early (stage of ischaemia), stage of fragmentation (vascular infiltration in the ischaemic section), reparative stage (stage of reossification) and healing stage.

Many of the previous studies reported that apoptosis of osteoblasts and osteoclasts is a strictly regulated process and plays vital role in physiological bone turnover and in the development of various pathological conditions in skeleton [14], but none of the studies have questioned the association of these mechanism with the etiopathogenesis of LCPD patients so far. Alteration in osteogenesis/bone remodelling is the one of the most important factor in the pathophysiology of LCPD, which leads to development of severe deformity in the affected hip and thus affecting the clinical course of the disease [15-17].

Now a day due to huge urbanization, heavy metals are one of the significant environmental pollutants that are inhaled / ingested by the human beings by mean of air or water pollution [19,20]. Heavy metals are generally referred to as those metals which possess a specific density of more than 5 g/cm^3. Although, these metals are quit essential to maintain various biochemical and physiological functions

in living organisms when in very low concentrations; but they become noxious when they exceed certain threshold concentrations [21]. Although it is acknowledged that heavy metals have many adverse health effects which last for a long period of time, heavy metal exposure continues in daily life activities and is increasing in many parts of the world.

As per Carmouche., *et a*l. (2005), lead (Pb) treated animal's shows a significant decrease in osteoprogenitor cell frequency. It has been observed that Pb exposure inhibits fracture healing and is associated with increased chondrogenesis, delay in cartilage mineralization, and a decrease in osteoprogenitor frequency [20]. Pb suppresses the Wnt/β-catenin signaling in fracture repair which may cause delayed endochondral ossification and conversation of cartilage tissue to bone. Pb effectively reduced the size of the mineralized callus at 7 and 14 days post-fracture. Decreased mineralized callus could result in increased instability and reduce functional strength during a critical phase of healing. In fact, Pb exposure has shown reduced bone mineral properties and bone strength in mice and rats [21,22].

It also has been seen that bone is one of the target organs for Cd toxicity [23,24]. The high concentrations of Cd (>10 μm) inhibit the process of vascularization by inhibiting vascular endothelial growth factor (VEGF) expression and disrupt the growth of blood vessels [25]. Various pathologies like osteopenia, osteoporosis, and/or osteomalacia leads to increased incidence of bone fractures belong to the main unfavorable health effects of chronic environmental and occupational exposure to Cd [21,26,27]. Several studies [28-32] revealed that Cd stimulates the differentiation and activity of osteoclasts, however inhibits osteoblast activity and differentiation. These effects cause an uncoupling of the normal balance between osteoblastogenesis and osteoclastiogenesis resulting in decreased bone mineral density and prone to fracture incidence, i.e. typical manifest symptoms of osteoporosis. The results obtained by Brzoska and Moniuszko-Jakoniuk [30] have shown that even low-level exposure to Cd disturbs bone metabolism and furthermore increased the urinary Ca excretion and subsequent skeletal demineralization, i.e. may accelerate bone loss and increase bone fragility [33,34]. The recent studies demonstrated the inhibitory effect of Cd on synthesis and/or releasing of endothelium derived vasoactive substances (e.g. nitric oxide – NO) [35-37]. The decrease of NO concentration in vessels of hypertensive rats also leads to increased superoxide anions as a result of Cd-induced oxidative stress [38]. On the other hand, exposure of endothelial cells to Cd significantly increased the secretion of vasoconstrictors (angiotensin-II and endothelin-I) [39]. Cd can also directly inhibit endothelial migration and tube formation. These aspects could supposed to contribute vascular (Haversian) canal constriction in the rats exposed to Cd [40]. It has been also observed that the manganese deficiency results in skeletal and postural defects in many species of animals, like shortening of limb bones and abnormal cartilage and bone matrix formation on rat model [41,42]. As per the above evidences, Pb as well as Cd toxicity may affect the fragmentation stage and healing stage affecting the final outcome of the head of femur in children affected with LCPD.

The course as well as prognosis of LCPD is difficult to predict. The prognosis of the disease depends on bone age at presentation, the sphericity and congruency of femoral head at skeletal maturity, height of the lateral pillar of the capital epiphysis at the presentation, and range of motion of hip joint [8]. In the clinical setup, many patients present in the later stage of disease, when there is already hinge abduction with poor range of movements of hip has developed. This condition may lead to degenerative arthritis during early adulthood in about half of these patients [18]. These findings in LCPD patients suggest that the immature articular cartilage undergoes active patho-physiological changes in response to aseptic ischaemia of LCPD.

In a recent study by the author, it has been observed that many of the heavy metals [As, Pb, Hg] were beyond their normal upper limit concentration in LCPD patients. Amongst them the Pb reached the maximum toxicity level in most of the LCPD patients that also showed positive correlation to with the clinico-radiological profile of LCPD categorized by lateral pillar classification. On the basis of this study observations, author drew an inference that due to huge urbanization and pollution, the heavy metal toxicity is on alarming phase and may be associated/correlated with clinico-radiological profile of LCPD in children.

Thus, we may conclude that although there are insufficient evidences that heavy metals contribute in the causation of ischemia of LCPD but the evidences do support the hypothesis that the heavy metal toxicity may affect the natural history of LCPD. The authors observe that more research is required to establish the association of heavy metal with the clinic-radiological profile of LCPD. This can help in opening new horizons in the diagnosis as well as management of LCPD.

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