SHORT COMMUNICATION

"ATYPICAL FEMORAL FRACTURES" DURING BISPHOSPHONATE EXPOSURE IN ADULT HYPOPHOSPHATASIA

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We report a 55-year-old woman who suffered atypical subtrochanteric femoral fractures (ASFFs) after four years of exposure to alendronate and then zolendronate given for "osteoporosis" (Journal of Bone and Mineral Research, DOI: 10.1002/jbmr.1565 ePub: February 9, 2012). Before alendronate treatment, she had low bone mineral density. After several months of therapy, metatarsal stress fractures began. Bisphosphonate (BP) administration was stopped following the ASFFs, and the adult form of hypophosphatasia (HPP) was diagnosed from low serum alkaline phosphatase (ALP) activity, high endogenous levels of two natural substrates for the "tissue-nonspecific" isoenzyme of ALP (TNSALP), and a heterozygous mutation within the gene that encodes this enzyme. Her father and daughter had distinctly low serum ALP activity, but no medical history to suggest HPP. Experience with other HPP families showed that her mutation (Arg71His) with a second defective TNSALP allele can cause severe HPP in infancy, and when heterozygous can cause mild HPP featuring premature loss of deciduous teeth in children.

Since the skeletal disease of HPP results from extracellular accumulation of the TNSALP substrate inorganic pyrophosphate (PPi) and its inhibitory effect on mineralization, perhaps HPP patients or carriers will have adverse effects from BPs. BPs are analogues of PPi and can suppress bone turnover but also deactivate TNSALP. Our report is the first of BP exposure preceding ASFFs in adult HPP. To explore a potential role for TNSALP deactivation in ASFFs, mutation analysis of TNSALP should be studied in a cohort of these patients. Meanwhile, clinicians must suspect HPP when clinical or laboratory clues include premature loss of primary dentition, pseudofractures or recurrent poorly healing metatarsal stress fractures, a family history suggestive of HPP, or low serum ALP activity. If HPP is documented, BP treatment might be avoided. To establish the diagnosis of HPP, assays for two natural substrates for TNSALP and TNSALP mutation analysis are available in commercial laboratories. With positive findings, radiological or bone biopsy evidence of acquired osteomalacia would indicate the adult form of this inborn-error-of-metabolism.