Genetics inMedicine

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CORRESPONDENCE

Correspondence on "Prospective phenotyping of long-term survivors of generalized arterial calcification of infancy (GACI)" by Ferreira et al.

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Generalized arterial calcification of infancy (GACI) is a life threatening disease due to ENPP1 or ABCC6 deficiencies that present at birth or in the first few months of life as detailed described by Ferreira et al.[1] Overall survival of these patients has markedly improved over recent decades with the use of biphosphonates. While arterial calcifications resolved in a substantial proportion of patients, the development of rickets in ENPP1-GACI survivors appears to be universal.[1] Patients develop bone pain, bone deformities, and radiological signs of rickets. Moreover, the inverse relationship between serum phosphate and fibroblast growth factor 23 (FGF23) and the inappropriately normal 1,25-dihydroxyvitamin D levels suggest that the hypophosphatemia is FGF23 mediated. Eight of such patients received oral phosphate supplementation and/or active vitamin D sterols for the treatment of hypophosphatemia.[1]

Burosumab, a monoclonal antibody against FGF-23, has been found to improve phosphate homeostasis and radiological rickets lesions in *X-linked hypophosphatemic patients*.[2] Therefore, it has been suggested as a potential therapeutic strategy ENPP1 deficient hypophosphatemic patients.[3] However, more recently, Ferreira et al. raised a theoretical consideration that such therapy may lead to worsening of ectopic calcifications.[1] Thus, we report the first case documented in the literature of a GACI ENPP1 deficient treated with burosumab due to the development of hypophosphatemic rickets with subsequent worsening of vascular and valvular calcifications.

The patient is a 15-year-old male with GACI followed at our institution since birth when he presented with congestive heart failure and calcification of the valves, aorta, coronaries, pulmonary and abdominal vessels by echocardiogram. Genetic testing demonstrated ENPP1 variant (in exon 10 c.1046G>A, and in exon 17 c.1709A>G). Etidronate therapy was initiated as recommended[4] and by seven months of age only the aortic arch remained calcified (this resolved by two years of age). The only subsequent signs of calcification on echocardiogram over the next 12 years were two 2–3 mm calcified nodes on the aortic leaflets. The patient was followed regularly for monitoring for cardiac calcifications, coxa vara, and a history of avascular necrosis in the right hip as a toddler. At age 13, he developed hypophosphatemia and new genu varum deformity that required orthopedic correction, Therapy was initiated with calcitriol and phosphate supplementation. Radiological findings of the right leg were consistent with rickets. He underwent a hemilateral proximal right tibial hemiepiphysiodesis and an iliac crest bone biopsy. The biopsy demonstrated a mineralization defect in conjunction with an increase in nonmineralized bone. Features were consistent with osteomalacia and based on the patient's age, interpreted as rickets.

At age 14, due to persistent hypophosphatemia and elevated FGF23 levels (410 RU/ml), burosumab therapy (70 mg twice a month) was initiated; calcitriol and phosphate supplementation were discontinued.[2] During burosumab therapy, serum phosphate levels were overall within the normal range (see Fig. 1). Etidronate was discontinued after 8 months of burosumab therapy due to withdrawal from the market.

Prior to burosumab therapy, echocardiogram demonstrated the two stable calcified aortic nodes on the aortic valve and noted for the first time some limitation in movement of the right coronary leaflet of the aortic valve in a region of residual calcification without evidence of aortic stenosis or regurgitation. He also had his first coronary CT showing calcifications of the aortic valve leaflets and mitral annulus with no calcifications of the coronary arteries.

Four months after starting burosumab treatment a repeat echo was unchanged. However, 20 months after initiation of burosumab (and about one year after stopping etidronate), repeat echocardiogram demonstrated significant calcification of the right and noncoronary cusps of the aortic valve with mild aortic stenosis, extensive calcification of the left ventricular outflow tract with a 5 by 6 mm calcified nodule in the left ventricular outflow, and calcification of the posterior septum, inferior wall, and posterior medial papillary muscle of the left ventricle (see Fig. 1). Serum phosphate level was 3.1 mg/dl. Therapy with burosumab was discontinued and monthly pamidronate infusions were initiated.

Burosumab has been approved for the treatment of children with X-linked hypophosphatemia since 2018 due to its superior effect on patients' phosphate levels, radiographic findings of rickets, alkaline phosphatase levels, and growth.[2] A phase 2 trial of 52 children with X-linked hypophosphatemic rickets treated with burosumab for over a year did not demonstrate any myocardial changes on screening echocardiograms.[5] In a study of 28 adults receiving burosumab for X-linked hypophosphatemia, two subjects, one of whom also had hyperparathyroidism, had small increases in coronary artery or aortic valve calcifications scores from baseline but the calcifications were still classifiable as minimal–mild. There is also a reported case of a patient with hypophosphatemic rickets undergoing treatment with phosphate and calcitriol supplementation who developed cardiac calcifications, although this patient also had hyperparathyroidism, a known cause of cardiac calcifications.[6]

GACI patients with hypophosphatemic rickets and *ENPP1* variant have been safely treated with phosphate and calcitriol without worsening vascular calcifications.[7] In fact, our patient had been on calcitriol and phosphorus supplementation for about a year prior to initiation of burosumab without worsening of his calcifications. The cause of worsening vascular calcifications in our patient while receiving burosumab is unclear. Increase in serum phosphate levels may have contributed, since persistent hypophosphatemia has been suggested as a factor improving survival beyond the neonatal period.[4] On the other hand, Ferreira et al. suggested that FGF23 inhibition may lead to alkaline phosphatase upregulation, which may further decrease inorganic pyrophosphate levels, a potent inhibitor of hydroxyapatite formation and vascular calcification.[1] However, alkaline phosphatase levels were within the normal range. In summary, we believe that burosumab should not be used in GACI-ENPP1 deficient patients for the treatment of hypophosphatemia. ENNP1 enzyme replacement therapy may be a promising therapeutic strategy of such patients.[8]

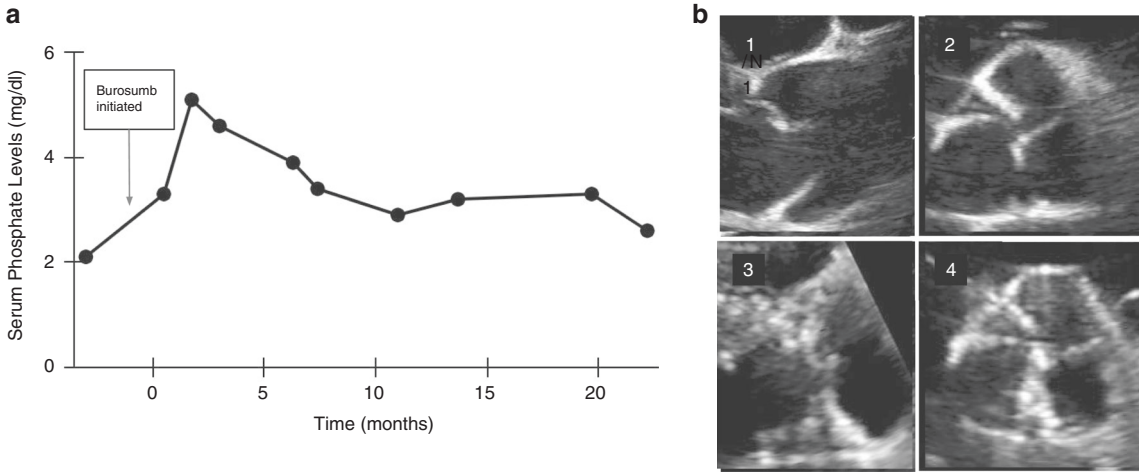

Fig. 1 Serum phosphate levels and echocardiogram changes during burosumab therapy. (**a**) Serum phosphate levels over time. Time "0" indicates when burosumab treatment was initiated. (**b**) (1,2) Long and short axis appearances of aortic valve at baseline. Aortic valve leaflets are thin and mobile; (3,4) long and short axis appearances of the aortic valves after burosumab treatment.

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COMPETING INTERESTS

The authors declare no competing interests

ADDITIONAL INFORMATION

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