jcrpe-2018-0204.R2

Case report

Magnesium and anti-phosphate treatment with bisphosphonates for Generalised Arterial Calcification of Infancy: a case report

Running Head: Treatment of generalized arterial calcification of infancy

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What is already known on this topic?
Generalized arterial calcification of infancy (GACI) is a rare disease that is associated with a high mortality rate owing to the development of severe hypertension and cardiovascular complications. GACI can begin in utero during the third trimester, 50% of children with GACI present with well-developed large arterial calcifications within the first week of life. Although there is no definitive treatment, it is claimed that patients treated with bisphosphonates have better survival rates. In contrast, children not treated with bisphosphonates were also reported to have spontaneous regression of large arterial calcifications. Furthermore benefit has been shown from magnesium treatment in some experimental animal models.

What does this study add?
To date, there has been only a few experimental treatment for GACI patients other than bisphosphonates. The case presented here is of a patient who did not respond to bisphosphonates alone and then improved clinically after treatment with magnesium and anti-phosphate (calcium carbonate) with continued bisphosphonates therapy.

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08.08.2018
06.12.2018

Abstract
Generalized arterial calcification of infancy (GACI) is a rare autosomal- recessive disorder characterized by calcification of the internal elastic lamina, fibrotic myointimal proliferation of muscular arteries, and resultant arterial stenosis. Treatment with bisphosphonates has been proposed as a means of reducing arterial calcifications in GACI patients, although there is no formalized treatment approach. The case reported here is a patient with severe GACI diagnosed at 3 months of age who had no response to bisphosphonate treatment, but clinically improved after the initiation of magnesium and anti-phosphate (calcium carbonate) treatments. In patients unresponsive to bisphosphonate, magnesium and anti-phosphate treatment can be attempted.
Keywords: Generalized arterial calcification, infant, treatment, magnesium, etidronate

Introduction

Generalized arterial calcification of infancy (GACI) is a rare autosomal- recessive disorder characterized by calcification of the internal elastic lamina, fibrotic myointimal proliferation of muscular arteries, and resultant arterial stenosis (1, 2). An extravascular feature is that foci of periarticular calcification occur in many of the affected subjects. Depending on the severity and the local distribution of the calcific stenoses, affected patients can present with neonatal heart failure, arterial hypertension, and death within the first 6 months of life (3, 4). GACI is linked to mutations in the ectonucleotide pyrophosphatase/phosphodiesterase 1 (*ENPP1)* gene, which encodes for ectonucleotide pyrophosphatase/phosphodiesterase 1*(ENPP1).* This enzyme facilitates hydrolysis of ATP to AMP and inorganic pyrophosphate (PPi). PPi is a potent inhibitor of hydroxyapatite crystal deposition, while inorganic phosphate (Pi) serves as a pro-mineralization factor, and consequently, an appropriate ratio of PPi/Pi is required to prevent spontaneous calcium phosphate precipitation. In patients with GACI, deficiency of ENPP1 enzyme leads to reduced PPi/Pi and ectopic mineralization (5, 6, 7). In addition, *ENNP1* gene mutations

have been identified in some patients with pseudoxanthoma elasticum (PXE), another hereditary ectopic mineralization disorder. Most cases with PXE also harbor mutations in the *ABCC6* gene (8). Recent studies have demonstrated a considerable genotypic and phenotypic overlap between PXE and GACI (9).

There is no effective and formalized treatment approach for patients affected by GACI (6). After the original report by Meradji et al (10), first-generation bisphosphonates, which are synthetic analogues of PPi, have been widely used in an attempt to treat GACI patients. First-generation bisphosphanates have stronger effect in inhibiting formation and further growth of hydroxyapatite crystals compared to newer generation bisphosphonates (5, 11). However, a potential complication of bisphosphonates is severe skeletal toxicity associated with prolonged use in patients with GACI (6). In addition to the skeletal toxicity, bisphosphonate treated children also experienced persistent calcifications, which is an unwanted side effect of the treatment. Besides, some children not treated with bisphosphonates were reported to have spontaneous regression of large arterial calcifications (12-14). The lack of consensus and limited data about the efficacy of these compounds make it difficult to determine if bisphosphonates offer a safe and effective treatment for GACI.

Li Q et al (15) investigated the dual effects of bisphosphonates on ectopic skin and vascular soft tissue mineralization versus bone microarchitecture in a mouse model of GACI. Their results suggested that bisphosphonate treatment may be beneficial for preventing ectopic soft tissue mineralization while correcting decreased bone mineralization. Effects of etidronate and alendronate on ectopic calcifications in the *ENPP1* ^{asj} mice were assessed at three different concentrations (doses 1x, 5x, and 12 times greater than used for treatment of osteoporosis. It had been found that 5 times and 12 times greater doses of etidronate provided some benefit for calcifications of the kidney, heart, descending thoracic aorta, or the eye.

Albright et al (16) used the identical animal model to evaluate the efficacy of ENPP1 enzyme replacement therapy in GACI. In this report, the breeding pairs were placed on the 'acceleration diet' to mimic the in utero calcification induced by ENPP1 deficiency and death was used as a preclinical endpoint. The efficacy of the ENPP1-Fc in this more severe preclinical study was a complete suppression of all ectopic calcification, as well as elimination of mortality. The point is that it appears that the efficacy of bisphosphonates is quite limited compared with what can be achieved with other more rationale therapeutic interventions.

In a recent clinical trial of patients with PXE, the possibility of supplementing the diet with magnesium as a way of preventing mineralization was investigated (17). Kingman et al (8) showed the effects of dietary magnesium supplementation on ectopic mineralization in the vascular tissues in mice, a model for GACI which shares genotypic and phenotypic overlap with PXE. Furthermore Rutsch et al (4) reported that application of a phosphate poor diet or a phosphate binding agent would be of interest with respect to early intervention in GACI. However it was difficult to make a strong conclusion with retrospective small sized study that patients with GACI may benefit from anti-phosphate (calcium carbonate) treatment.

In this case report, we report a case of a 3-month-old boy diagnosed with severe GACI who was unresponsive to bisphosphonate therapy but recovered after magnesium and calcium carbonate treatment with continued bisphosphonates therapy.

Case Report

A 3-month old male infant with para-articular calcification was consulted to the paediatric endocrinology department. The patient history revealed referral to the neonatology clinic at 17th day because of arthritis in right hip which occurred in the first week of life. The infant was second child of a 39-year old healthy mother and a 37-year old healthy father, who were first degree cousins. He had been delivered by caesarean section at 38th weeks with a birthweight of 3680 gr. He also had a 3-year old healthy brother. Septic arthritis was suspected, however acute phase reactants and cultures were negative. Histopathologic investigation of a biopsy specimen obtained from right hip joint revealed severe calcification in the arterial walls with no evidence of inflammation. The weight was 4900 gr (-1.72 SDS) and the height was 58 cm (-1. 22 SDS). He had prominent ears. Systemic physical examination was normal except a swollen, painful and restricted right hip joint. Arterial blood pressure was measured 121/84 mmHg, which is high (>95th percentile) for a 3-month old boy. Echocardiography showed normal left ventricle wall and coronary arteria thickness. Odiologic and ophthalmologic assessments were normal. Routine biochemical tests were normal while plasma renin activity and aldosterone levels were above the normal reference (Table 1). Non-contrast abdomen computed tomography (CT) was performed. Diffuse narrowing of abdominal aorta, bilateral renal arteries and iliac arteries were observed (Figure **1A**). Soft tissue calcifications were observed in the paratracheal region at laryngeal level and around the hyoid bone (Figure **1B**). There were linear hyperdensities consistent with calcification in mesenteric artery and branches (Figure **1C**). Periarticular calcifications in right shoulder and right hip were observed (Figure **1D).** Baseline radiographic images revealed arterial calcifications of the brachial and radial arteries in left side and intra- and periarticular calcifications in left elbow and wrist joints as well (Figure **1E**). There was no evidence of calcification in arterial vessels of brain in cranial CT. As severe arterial calcification was determined in the histopathologic investigation, "generalised arterial calcification of infancy (GACI)" was considered and *ENPP1* gene analysis was performed. A previously identified homozygote (c.2677G>T p.E893*) (p.Glu893*) mutation was

determined in the *ENPP1* gene. The genetic analyses of parents had not been performed since the mutation was a previously reported one; however genetic counselling had been given.

Intravenous disodium pamidronate was administered as 3 doses (on days 0, 7, and 10) to the patient. At the fifth day of pamidronate treatment, oral etidronate was initiated at the dose of 10 mg/kg/day and was increased to 20 mg/kg/day after 3 days. At the 6th month of etidronate treatment, calcifications on direct radiographs and CT were persisting (Figure 2A, 2B, 2C) as well as intermittent swelling and restriction of joints. This suggested an inadequate response to biphosphonate treatment. Calcium carbonate treatment at the dose of 250 mg twice a day and magnesium oxide treatment 150 mg twice a day were started. Etidronate was reduced to a dose of 10 mg/kg/day at the same time. While calcium, phosphorus and other laboratory parameters were normal at baseline (table 1), serum phosphorus level was decreased following the anti-phosphate treatment as expected. After the initiation of calcium carbonate and magnesium treatments restriction and swelling of joints improved day by day. No adverse effects were experienced because of these treatments in the follow-up period. A marked decrease of calcifications was seen on radiographs which were performed at the sixth month. Calcium carbonate and magnesium treatments were continued while etidronate was reduced to the dose of 5 mg/kg/day.

CT and CT angiography was performed at the end of the first year of calcium carbonate and magnesium treatments. The calcifications previously observed in the abdominal artery and mesenteric arteries had disappeared, the narrowing of renal arteries had recovered and there was a significant reduction in calcifications in hip and shoulder joints (Figure 3A, 3B, 3C, 3D). There was a significant clinical improvement in joint functions and motor development as well. In the last examination of the patient at the age of 23th months, the weight was 10 kg (-1.93 SD), the height was 85 cm (-0.7 SD), arterial blood pressure measurements were normal, joint movements were comfortable, neuromotor development was improving. The etidronate treatment was stopped and magnesium treatment was continued. The course of treatment is shown in Figure 4, with the permission of his parents.

Discussion

A patient presented with arthritis at the 3rd month of life, diagnosed with GACI and treated with etidronate, magnesium and anti-phosphate. Approximately 50% of children with GACI present within the first week of life with large arterial calcifications which are reported to develop as early as the third trimester of pregnancy. The course of these children may be less favorable than children who present later (4). Although our patient was diagnosed with GACI at the 3rd month of life, clinical findings consistent with GACI were present during the first week of life.

Respiratory distress is one of the presenting features in more than 50% of cases, followed by feeding intolerance, poor weight gain, tachypnea, tachycardia, and cyanosis (4, 18, 19). The disease usually results in death in infancy due to progressive ischemic heart failure associated with coronary calcification. Survivors of GACI frequently present with periarticular calcifications rather than coronary calcification (4).

The treatment options in GACI are limited to the use of bisphosphonates, such as etidronate and pamidronate (18). Bisphosphonates are synthetic analogs of inorganic pyrophosphate, which block the conversion of calcium phosphate to hydroxyapatite and thus may reduce ectopic calcification (19). Etidronate, as a first-generation bisphosphonate, has been used most frequently at a dose of 5- 35 mg/kg/per day given orally (5). Etidronate has a stronger effect in inhibiting mineralization compared to the newer aminobisphosphonates and shows no adverse effect on growth (19). However, high-dose etidronate injections have been shown to induce vitamin D-resistant rickets in rats (20). Other nitrogen-containing bisphosphonates, which have been applied in case series of GACI patients, include intravenous pamidronate and oral risedronate (5, 21). In vitro studies have shown that bisphosphonates accumulate within vessel walls suggesting that these drugs may have a direct effect on calcification (6). As the starting treatment we administered three doses of iv pamidronate infusion, according to the reference reported by Edouard et al (6). Secondly, oral etidronate was added to the treatment.

It is difficult to evaluate if disease recovers spontaneously or with the effect of bisphosphonates. As long-term survival has also been reported in patients with no specific therapy, spontaneous resolution of calcification should be considered (12, 14). A retrospective study by Rutsch et al. reported that 17 of 55 patients affected by GACI were treated with bisphosphonates, namely etidronate, pamidronate, clodronate or risedronate. Survival rate of these treated patients was found to be 65%, while 69% of patients who were not treated with bisphosphonates had died in infancy (4). Rutsch et al. also claimed that children treated with bisphosphonates have a survival advantage, but this claim was based on observations in a retrospective study with a small sample size rather than a blinded clinical trial. In fact, the survival advantage suggested by Rutsch in this study was not statistically significant. More favorable outcomes of some children could be releated with less severe disease, who survive long enough to be transported to a medical center, evaluated, and treated with bisphosphonates. So, the perception that bisphosphonate therapy increases GACI survival has led to the adoption of bisphosphonates as the first-line treatment for GACI in Europe.

The persistence of calcifications, especially in periarticular regions leading to severe restriction and contractures, required the exploration of alternative therapeutic options. In the literature magnesium treatment was reported to be effective in *ENPP1* knockout mice. In a recent study, Kingman et al showed that elevated dietary magnesium

during pregnancy and postnatal life prevents ectopic mineralization in *ENPP1* ^{asj} mice, a model for generalized arterial calcification of infancy (8). Referring to this knowledge, oral magnesium oxide treatment at a dose of 150 mg twice a day was commenced.

The mechanism for the inhibition of ectopic mineralization by magnesium may involve direct interactions between magnesium and calcium ions in the mineralization process. Magnesium competes with calcium, reduces calcium-phosphate binding and forms magnesium phosphate complexes. These complexes, which are soluble, prevent the mineral deposition (8).

Higher phosphate levels are found in healthy newborns, probably due to low glomerular filtration rate and retention of phosphate (22). These higher levels may lead to an increased risk of arterial calcification in young patients with ENPP1 deficiency during the first few months of life, which could decline with age (6). PPi and Pi seem to have mutually antagonistic roles in tissue mineralization. Significantly, a phosphate-poor diet induces hypophosphatemia with markedly decreased artery calcification and periarticular calcifications. Furthermore, several mutations in the *ENPP1* gene result in the phenotype of autosomal recessive hypophosphatemic rickets (ARHR2) without any arterial calcifications (5, 23). Furthermore in some patients with generalised arterial calcification due to *ENPP1* mutations in infancy, hypophosphatemic rickets developed in the following years. Treating these patients with calcitriol and phosphorus leaded to the recurrence of calcifications. It had been experienced that hypophosphatemia is a protective factor against vascular calcification (24). Rutsch et al (4) found that both hypophosphatemia and hyperphosphaturia are related with GACI survival. The hypophosphatemia and hyperphosphaturia is linked to FGF23 elevation. FGF23 is a hormone which induces phosphate wasting in the urine. GACI patients with elevated FGF23 and low phosphate are expected to have reduced vascular calcifications. Therefore, phosphate wasting via FGF23 elevation may be an adaptive mechanism in GACI to accommodate the low plasma PPi by reducing plasma Pi in an attempt to preserve the Pi/PPi ratio. A consequence of the hyperphosphaturia is osteomalacia and rickets seen in ARHR2. This might be the possible mechanism connecting ARHR2 and GACI (25). Since arterial calcifications could be lethal in infancy, these observations reported in the literature encouraged the thought that creating a controlled hypophosphatemia could decrease mortality. The balance between bone demineralisation and arterial calcifications should be provided. In this patient, treatment with magnesium and calcium carbonate together, was started with the aim of lowering phosphate levels and keeping the magnesium levels within the upper limit. As shown in Table-1, there was a significant clinical improvement after the initiation of magnesium and calcium carbonate treatments. Joint movements had improved and hypertension had recovered. Marked reduction in calcifications was detected on direct radiographs and CT performed at the 12th month of treatment. No adverse-effects were observed during the treatment process.

The limitation of this study was that the lack of adequate experience in treating patients with GACI. Since recovery of calcifications in GACI occur in some of the survivors in the absence of any therapeutic intervention, it is difficult to conclude that the improvement is due to the treatment protocols. Because of inadequate knowledge about the process of disease, we hesitated to stop bisphosphonate treatment at the beginning of magnesium and calcium carbonate. Between the sixth and 12th months, patient also received etidronate at gradually reduced doses, together with other treatments. So, if any, effects of etidronate could also have contributed to the total effect.

Conclusion

In the current case, a sufficient clinical response was not obtained within 6 months of etidronate treatment. We thought that bisphosphonate treatment did not make a significant effect on the regression of calcifications. Although there is insufficient information in literature related to magnesium and calcium carbonate treatment, there are animal data showing that they could be effective. Since we observed a significant reduction in calcifications after the initiation of magnesium and calcium carbonate treatment, we could conclude that this treatment option can be considered as useful for GACI patients. Certainly, there is a need for further extensive studies on this subject.

Conflict of interest

The authors have no conflict of interests to declare.

Financial Disclosure: The authors declare that this study has received no financial support.

Authorship Contributions

Concept: FD, Design: FD, Data collection or processing: FD, SG, TÖ, BS, HK Analysis or interpretation: FD, SG, GSK, HK, SK, TÖ, Literature Search: FD, SG, TÖ, HK, GSK, Writing: FD, GSK, BS, HK, TÖ.

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Table 1: Laboratory and auxological findings of the patient under treatment

Age (months)	**At diagnosis 3 months**	**6 months**	**9 months**	**12 months**	**18 months**	**23 months**
Weight (SD)	-1.72	-2	-1.8	-1.66	-1.75	-1.93
Height (SD)		-0.95	-0.66	-0.53	-0.45	-0.7
Dose of etidronate (mg/kg/day)	20	20	10	5	5	-
Dose of Mg (mg/day)	-	-	300	300	300	300
Dose of anti-phosphate (mg/day)	-	-	375	375	-	-
Ca (mg/dL) (NL: 9-11. 5)	11.4	10.5	10.4	9.6	9.4	9.6
P (mg/dL) (NL: 4-6. 5)	5.5	5.9	4.5	3.2	3	3.2
Mg (mg/dL) (NL: 1. 7-2. 3)	1.9	1.8	2.2	2.3	2.6	2.5
ALP (U/L) (NL: <455)	226	185	261	255	231	156
PTH (pg/mL) (NL: 11-67)	49	18.1	25.3	51.6	50	51
25OHD3 (ng/mL) (NL>20)	38.9	31.1	33.9	-	20.8	17
Renin (ng/mL/h) (NL: 0. 3-1. 9)	18.5	15.8	3.6	-	2.05	-
Aldosterone (pg/mL) (NL: 10-160)	1243	489	133	207	21.6	-

SD: standart deviation, Mg: magnesium, Ca: calcium, P: phosphate, ALP: alkaline phosphatase, PTH: parathormone, 25OHD: 25- hydroxy vitamin D3, NL: normal level

Figure 1: At age 3 months, coronal non-contrast computed tomography (CT) of abdomen and chest, **1A**: Diffuse narrowing is seen in bilateral renal arteries, abdominal aorta and bilateral iliac arteries, **1B:** At the level of the larynx, soft tissue calcifications are observed in the paratracheal region and around the hyoid bone, **1C:** There are linear hyperdensities consistent with calcification in the mesenteric artery and branches, **1D:** Periarticular calcification in the right shoulder joint and in the right hip joint, **1E:** At age 3 months, on baseline radiograph; the left wrist shows arterial calcification of the brachial and radial arteries (thin arrow) and intra- and periarticular calcifications in left elbow and wrist joints (thick arrow).

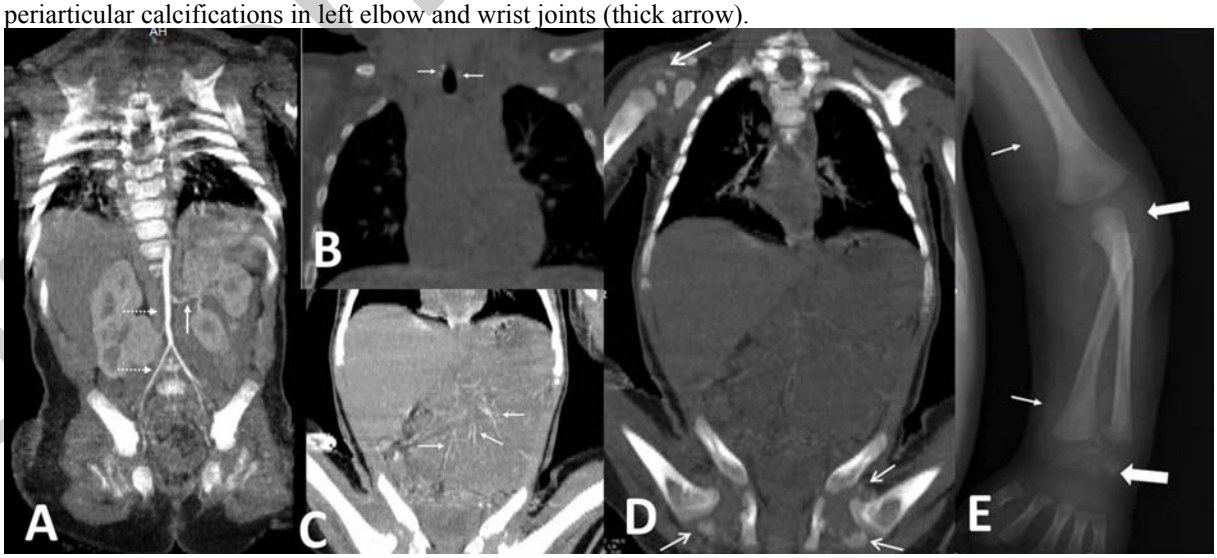

Figure 2: At age 9 months, radiograph before magnesium and anti-phosphate treatment **2A**: Radiograph shows progression of periarticular calcification in the right shoulder, elbow and wrist joint, **2B**: Coronal non-contrast

CT of abdomen demonstrates periarticular calcification in the right shoulder joint, and **2C**: shows periarticular calcification in right hip joint.

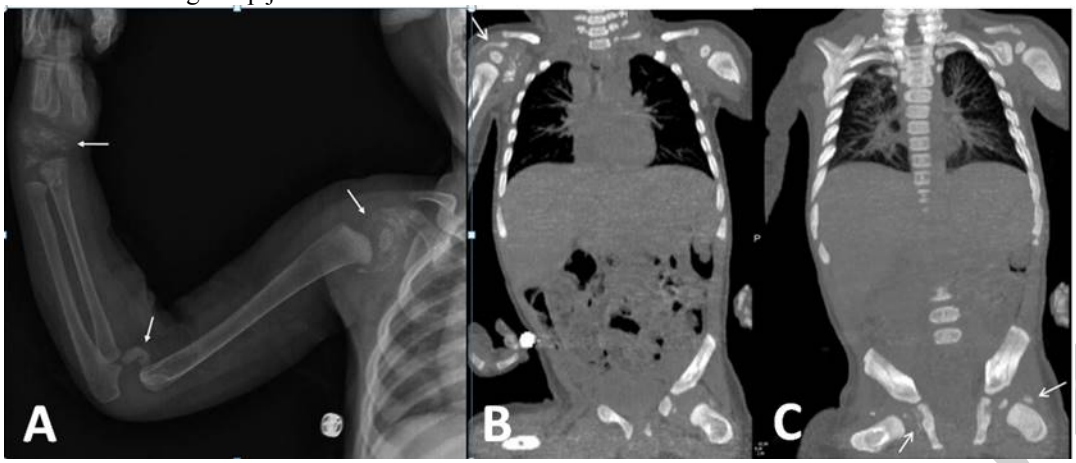

Figure 3: On CT angiography images and non-contrast CT of abdomen and chest after treatment with magnesium demonstrates: **3A**: Normal calibrations of abdominal aorta, bilateral internal and external iliac arteries, femoral artery, renal and mesenteric arteries, **3B**: At the level of the larynx, soft tissue calcifications are reduced in the paratracheal region and around the hyoid bone. **3C:** Wall calcifications in mesenteric arteries are not observed. **3D:** Periarticular calcification in the right shoulder joint and in the right hip joint are reduced.

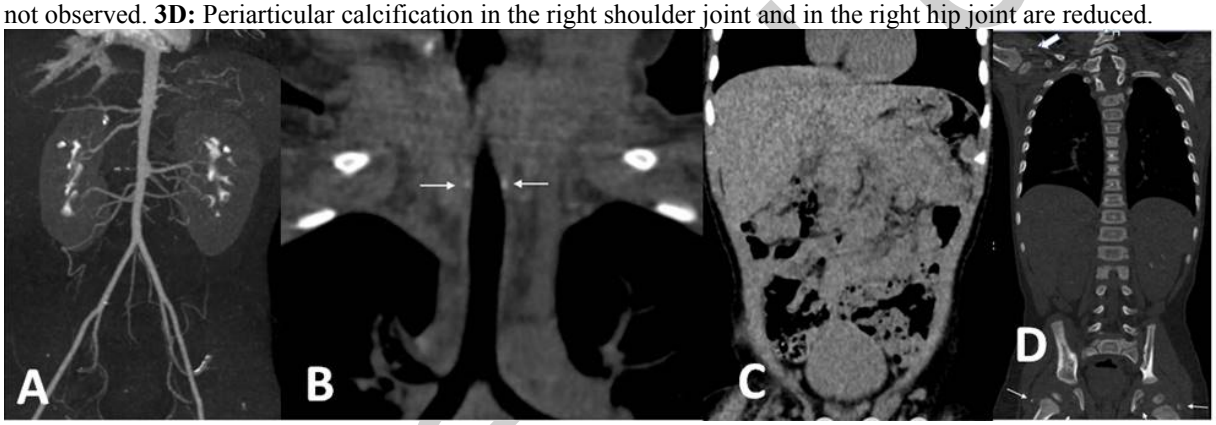

Figure 4: Time line chart of treatments received by the patient (*Mg: magnesium, ETD: etidronate, anti-P: anti-phosphate).*