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INTEGRATED MANAGEMENT OF AN ADULT PATIENT WITH MUCOPOLYSACCHARIDOSIS TYPE IVA: A CASE REPORT WITH A SIX-YEAR FOLLOW-UP

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ABSTRACT

Mucopolysaccharidosis type IVA (MPS-IVA) is a rare lysosomal storage disease caused by N-acetylglucosamine-6-sulfate-sulfatase enzyme deficiency. MPS-IVA patients show severe extra-skeletal and skeletal manifestations, featured by bone pain and deformities, frailty fractures and early onset osteoporosis. The enzyme replacement therapy (ERT) with elosulfase-α stabilizes the MPS-IVA extra-skeletal manifestations but does not significantly improve MPS-IVA skeletal manifestations. We administered an integrated therapy to an MPS-IVA 41-year-old male patient, composed of zoledronic acid, cholecalciferol and a normocalcemic (calcium intake ≥1 g/day), hyposodic (sodium intake ≤5 g/day), and normocaloric diet (bone-diet), other than ERT. During the six-year follow-up, the patient did not develop any adverse events, obtaining an improvement of bone mineral density and quality of life. Given our results, we propose this integrated treatment (i.e. ERT, zoledronic acid, cholecalciferol, and bone diet) in the management of MPS-IVA adult patients.

KEYWORDS

Mucopolysaccharidosis IVA, zoledronic acid, cholecalciferol, enzyme replacement therapy, diet

LEARNING POINTS

- Mucopolysaccharidosis type IVA (MPS-IVA) is a genetic, rare, and degenerative spondylo-epiphyso-metaphyseal dysplasia characterized by extra-skeletal and skeletal manifestations. The latter impacts on MPS-IVA patient daily activities, and enzyme replacement therapy has a poor efficacy in improving skeletal involvement.
- The proposed integrated management with enzyme replacement therapy, zoledronic acid, cholecalciferol and bone diet improve both bone mineral density and the prognosis *quoad valetudinem* of our MPS-IVA patient.

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INTRODUCTION

Mucopolysaccharidosis type IVA (MPS-IVA) is a rare and degenerative spondylo-epiphyso-metaphyseal dysplasia included in Group 22 of genetic skeletal disorders[1,2], caused by N-acetylglucosamine -6-sulfate-sulfatase enzyme (*GALNS*) deficiency, and characterized by intracellular glycosaminoglycans (GAGs) accumulation[1]. The MPS-IVA first choice-treatment is enzyme replacement therapy (ERT), which improves or stabilizes the MPS-IVA extra-skeletal manifestations (in particular, cardio-pulmonary diseases), but does not significantly improve the MPS-IVA bone anomalies[1]. The latter is a critical and unsolved clinical problem, which negatively impacts the quality of life. We report a case of an MPS-IVA adult patient treated with ERT, zoledronic acid (ZA), cholecalciferol and bone diet, followed for six years.

CASE DESCRIPTION

In 2016, a 41-year-old Caucasian male patient affected by MPS-IVA (genotype *G47R/N407H*) referred to the Department of Clinical Medicine and Surgery of the Federico II University for systemic bone pain and significant deterioration of daily activities. He was born from unrelated parents and his brother had died of MPS-IVA. Since 2014, he was treated with ERT (elosulfase-α, at the dose of 2 mg/kg). On physical examination, he presented disproportionate short stature with short neck, prominent forehead, corneal opacities, large mandible, joint laxity, short and pectus carinatum, dorsal hyperkyphosis, lumbar hyperlordosis and bilateral genu valgum. At admission (T0), his height and weight were 1.16 m and 37 kg, respectively. The patient showed a poor functional capacity at a six-minute walking test (6MWT)[3], and high value of bone pain score (BPS) and medication pain score (MPS)[4]. A full skeleton X-ray came out a diffuse bone demineralization and bilateral femoral stapes *(Fig. 1)*. The bone mineral density (BMD), evaluated by dual energy X-ray absorptiometry (DXA) at lumbar spine, was reduced. We preferred to report BMD as DXA results, to avoid bias induced by anthropometric features and patient's skeletal alterations in case of evaluation of standard T-score and Z-score[5]. As reported in *Table 1*, at T0, our patient also showed a severe vitamin D deficiency (< 75 nmol/l).
Hypovitaminosis D was treated with cholecalciferol orally administered at the dosage of 50,000 UI (125 mcg) weekly

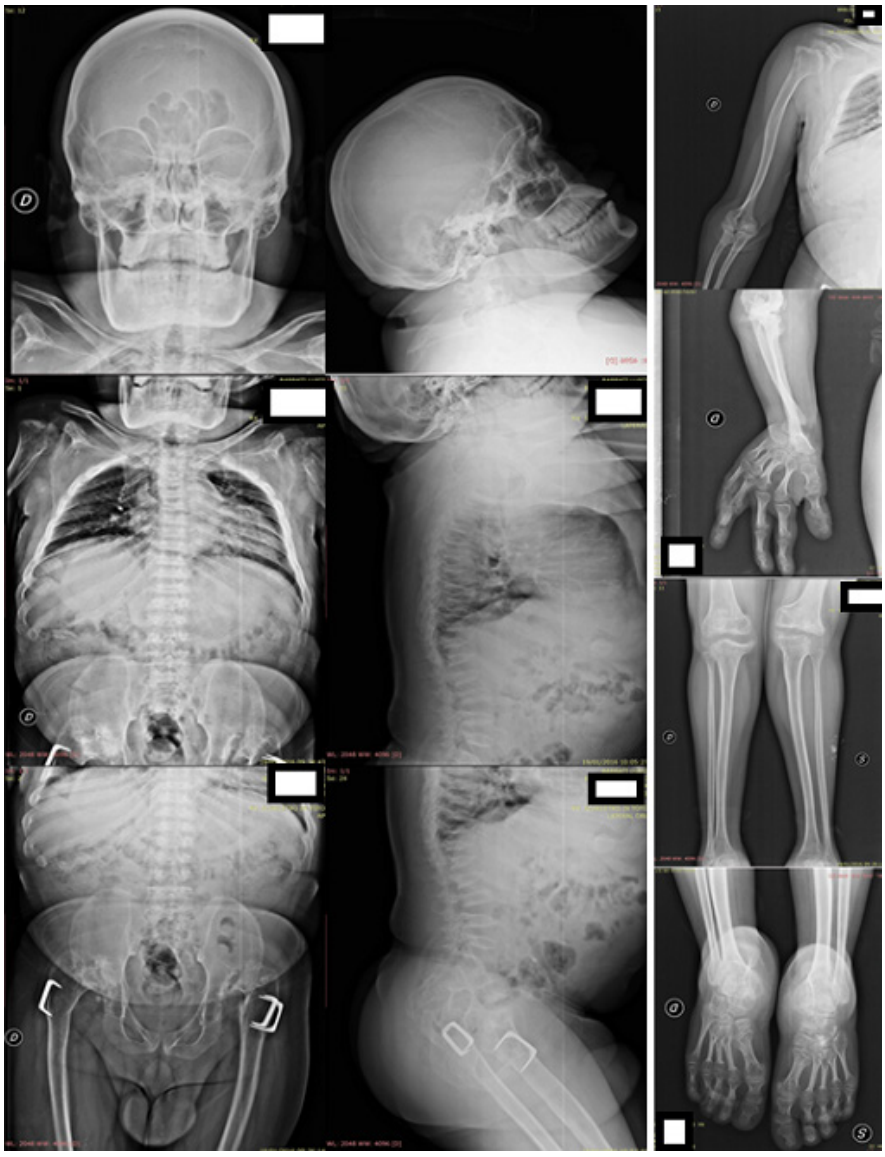

Figure 1. Full skeleton X-ray of Mucopolysaccharidosis type IVA patient

Follow-up time (months)	Ad	2	8	14	20	26	32	38	44	50	56	62	68	74	Reference values[a]
Bone pain score (BPS)	6	6	6	4	4	2	2	0	0	0	0	0	0	0	0
Medication pain score (MPS)	4	4	4	2	2	2	2	0	0	0	0	0	0	0	0
6-MWT (m)	<200	<200	<200	200	200	200	250	250	250	300	300	300	400	400	>600
Calcium[b] (mmol/l)	2.42	2.5	2.41	2.40	2.2	2.37	2.36	2.41	2.5	2.52	2.6	2.42	2.54	2.50	2.2 ± 0.4
Phosphate (mmol/l)	1.01	1.31	1.26	1.21	1.3	1.26	1.21	1.18	1.18	1.19	1.22	1.30	1.19	1.04	1.24 ± 0.20
Magnesium (mmol/l)	0.97	1.01	0.96	0.95	1	1.02	1	1	1.01	1.03	1.07	1.10	1.18	1.05	0.97 ± 0.10
Creatinine (µmol/l)	54.1	54	55.7	53	65	53.1	55	55.2	68.1	62.83	55.4	61.5	58.7	60.4	88.4 ± 8.84
25(OH)D (nmol/l)	16.25	83	83.2	95	94	80	91	87.5	105	101.25	80.5	91.2	89.7	79.0	79.8 ± 10.1
Lumbar spine BMD (g/cm^2)	0.547					0.645				0.749				0.76	-
ZA		INF		INF		INF		INF		INF		INF		INF	-
EKG	SR	SR	SR	SR	SR	SR	SR	SR	SR	SR	SR	SR	SR	SR	SR

(a) References values are expressed as mean ± standard deviation and are evaluated in eight 40-year-old healthy men, evaluated simultaneously to the MPS-IVA patient at the first in-hospital admission and enrolled among employers of the Federico II University in-law and non-genetically related relatives of MPS-IVA patient and a family reference panel.
(b) Total calcium corrected for albumin.
Abbreviations - Ad: in-hospital admission; 6MWT: six minutes walking test; 25(OH)D: 25 hydroxy-vitamin D; BMD: bone mineral density evaluated by dual energy X-ray absorptiometry; ZA: zoledronic acid; INF: intravenous infusion; EKG: electrocardiogram; SR: sinus rhythm.

Table 1. Clinical and biochemical parameters measured in the patient with Mucopolysaccharidosis type IVA at in-hospital admission and during the integrated treatment with enzyme replacement therapy (elosulfase-α, at the dose of 2 mg/kg), zoledronic acid (5 mg every year), cholecalciferol and normocalcic (calcium intake ≥1 g/day), hyposodic (sodium intake ≤5 g/day) and normocaloric diet.

for 8 weeks[6]. In combination with cholecalciferol treatment, we suggested a normocalcemic (calcium intake ≥1 g/day), hyposodic (sodium intake ≤ 5 g/day), and normocaloric diet (bone-diet)[7]. After vitamin D correction, a maintenance therapy was started at the dosage of 50,000 UI twice a month, to guaranteed vitamin D levels ≥75 nmol/l for the entire follow-up.

According to X-ray evidence and after correction of hypovitaminosis D, we prescribed an amino-bisphosphonate used for osteoporotic patients, zoledronic acid (ZA; 5 mg in 100 ml of 0.9 % saline solution intravenously infused for 15 minutes, followed by hydration with 0.9 % saline solution)[8]. One-week after the first ZA infusion, we assessed clinical, biochemical, and instrumental parameters, reported in *Table 1*, to exclude eventually adverse events (data not shown). We did not find significant differences between evaluated parameters compared to pre-treatment values. Furthermore, the patient did not mention acute phase symptoms (fever, arthralgia, and myalgia).

Considering these encouraging results, we scheduled i) a ZA infusion every 12 months (T14; T26; T38; T50; T54; T66), ii) an evaluation of clinical and biochemical parameters, *(Table 1)*, one week after each ZA infusion and every six months, and iii) the BMD evaluation every 24 months. We observed a progressive improvement of 6MWT, BPS, MPS and BMD *(Table 1)*. No additional frailty fractures, osteonecrosis of the jaw, electrolyte alterations or deterioration of renal function were observed during the six-year follow-up.

DISCUSSION

The proposed integrated management of skeletal anomalies using ZA, cholecalciferol and bone diet associated to ERT, was able to i) correct hypovitaminosis D and maintain vitamin D sufficiency during the 6-years follow-up; ii) improve the BMD, BPS, MPS and 6-MWT values, without additional bone complication and adverse events. Similar results have been observed in patients with Paget's disease of bone and in patients affected by Mucolipidosis II/III (*GNPTAB*- related) or Gaucher disease, both included in Group 22 of genetic skeletal disorders[2,9,10].

They may be linked to canonical and non-canonical (immunomodulatory) activities of ZA and cholecalciferol[5,11]. In the international literature, only one 11-year-old MPS-IVA patient was treated with neridronate, improving skeletal anomalies[12].

CONCLUSION

This is the first case report describing a satisfying and safe clinical response to an integrated treatment with ERT, cholecalciferol, bone diet and ZA in an MPS-IVA patient. Further intervention studies are necessary to confirm our interesting data results.

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