

Bisphosphonate therapy for painless fracture: Change of HSAN 1 clinical course with bisphosphonate and Vitamin D therapy

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Abstract

Hereditary Sensory and Autonomic Neuropathies comprise a set of 5 rare neurologic conditions, little known to radiologists as the neurologic and skin abnormalities precede the radiographic changes by months or even years. We report a Caucasian patient with a clinical history of HSAN, most consistent with subtype 1, whose progressive, destructive bone changes of the foot were not only controlled but to a degree reversed by the administration of bisphosphonates (Alendronate) and vitamin D (Colecalciferol). The authors believe that combined bisphosphonate and vitamin D therapy is the treatment of choice for progressive bony changes in HSAN1. This therapy may be beneficial in other neuropathic osteoarthropathies and possibly osteolytic bone disorders.

Keywords: Fracture, Hereditary Sensory Neuropathy, Thevenard Disease, Acropathia Ulceromutilans Familiaris, Bisphosphonate, Vitamin D

Introduction

Hereditary Sensory and Autonomic Neuropathies comprise a set of related genetic disorders sharing overlapping clinical descriptions¹. In particular, type 1 [HSAN1, Acropathia ulceromutilans familiaris², Thevenard syndrome³] is an axonal form of hereditary motor and sensory neuropathy distinguished by prominent early sensory loss and later positive sensory phenomena including dysesthesia and characteristic shooting pains predominantly affecting the lower extremities distally, presenting with callus formation and ulceration of soles of the feet. Loss of sensation can lead to painless injuries, which, if unrecognized, result in slow wound healing and subsequent osteomyelitis requiring

distal amputations. The term hereditary sensory neuropathy (HSN) was first used by Hicks in 1922 to describe a family with associated spontaneous shooting pains and deafness⁴. The insidious onset of HSAN1 is in the second or later decades of life. The disease is inherited as an autosomal dominant trait⁵⁻⁸. Positional cloning has identified mutations in genes SPTLC1 and SPTLC2, encoding the two subunits of serine palmitoyltransferase (SPT). SPT catalyzes the pyridoxal phosphate-dependent condensation of L-serine and palmitoyl-coenzyme A, the initial step in the de novo synthesis of sphingolipids⁹. Full gene sequence analysis of SPTLC1, the only gene known to be associated with HSAN1A¹⁰, is available on a clinical basis and may be indicated for families with HSAN1A known to be linked to chromosome 9 but in whom sequencing of exons 5 and 6 does not reveal a mutation. HSAN type II, primarily caused by mutations in an alternatively spliced exon of the WNK1 gene, closely resembles the type I form of disease, but typically has earlier onset and more severe symptomology including more typical involvement of the upper limb extremities^{11,12}.

We report a Caucasian patient (Czech family/parents) with a noteworthy clinical and radiographic course of the disease that was successfully influenced by administration of Alendronate (bisphosphonate) and Colecalciferol (Vitamin D3). Initially the patient did not receive any surgical treatment.

The authors have no conflict of interest.

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Figure 1A (3.7.04). Radiograph of the left foot taken 3 weeks after injury. Fractures at the distal end of 2-4 metatarsals with minor displacement.



Figure 1B (20.9.04). Radiograph of the left foot taken 3.5 months after injury. Periosteal reaction along the 2nd and 3rd metatarsals. Treatment with Alendronate 70 mg per week and Colecalciferol 1000 IU every day was commenced.

Case Report

The patient was a 34 year old man of presumptive Caucasian ethnicity, who sustained a twisting injury to his left ankle. Prior to this injury he enjoyed good health and had no symptoms relating to his left ankle and forefoot. Subsequent to the injury he experienced a “strange, non-painful feeling” in the left foot, with progressive swelling and discoloration evident on the dorsal aspect of the foot. Radiographs of the left foot taken 3 weeks after injury documented fractures of the 2-4th metatarsal necks (Figure 1A - 3.7.04).

Three months after injury there was no evidence of fracture healing. A periosteal reaction was present along the 2nd and 3rd metatarsals and the lateral aspect of the 1st metatarsal. The latter showed also some destructive changes at the base (Figure 1B - 20.9.04). The patient was referred to the Ambulant Centre for Defects of Locomotor Apparatus in Prague, Czech Republic, for further investigations.

The clinical presentation and history of disease in the patient suggest a genetic form of HSAN, particularly HSAN1. It was not possible to obtain material for a direct molecular confirmation of the underlying genetic defect, thus HSANII remains a potential alternative diagnosis. A recent large study of HSAN among English patients suggests that there are additional genes to be discovered as well for this disorder (Davidson, J Neurol 2012 Epub).



Figure 1C (20.9.04). Photo of the left foot taken 3.5 months after injury. The foot is swollen. The dorsum is red with prominent vascular pattern.

On examination the dorsum of the left foot was swollen and erythematous with prominent blood vessels (Figure 1C - 22.9.04). The right foot was normal. On the soles of the feet

	Baseline	5 months	4 yrs.	6 yrs.	7 yrs.
CRP (mg/l) (0.0-5.0)	6.7	<3.0	5.0	3.8	4.2
Chol (mmol/l) (3.9-5.2)	6.5	6.3	7.2	5.8	6.8
tALP (μ kat/l) (0.60-3.00)	1.77	1.43	0.80	0.77	0.85
bALP (μ kat/l) (0.26-0.53)	0.58	0.39	0.24	0.16	0.12
OC (μ g/l) (3.1-13.7)	7.2	1.5	3.2	2.9	4.6
U-DPD (nmol/mmol creatinine) (2.3-5.4)	3.2	5.8			
CTX (ng/ml) (0.142-0.522)			0.140	0.143	0.123
vit. D (nmol/l) (23.5-131.0)			67.4	62.9	39.6
PTH (pg/ml) (15.0-68.3)			40.2	57.1	48.7

Note:

CRP - C-reactive protein

Chol - Cholesterol

tALP - total alkaline phosphatase

bALP - bone alkaline phosphatase

OC - osteocalcine

U-DPD - urine deoxypyridinoline

CTX - carboxyl-terminal telopeptide of collagen type I

vit. D - 25-hydroxyvitamin D

PTH - parathormone

Table 1. Development of the lab values and bone markers: baseline and follow-up during administration of Alendronate (70 mg per week, after 5 months the dosage of Alendronate was increased to 70 mg three times per week, in the 5th year the dosage of Alendronate was again decreased to 70 mg per week, five years after the commencement of Alendronate it was replaced by Acidum ibandronicum 150 mg per month) and Colecalciferol 1000 IU per day.

there was loss of pain and thermal sensation, but preservation of touch and pressure sensations. There was hyperaesthesia of the dorsum of both feet. The tendon reflexes were normal and there was no atrophy of the calf muscles. The musculoskeletal examination was otherwise unremarkable. The patient was overweight - his height was 170 cm and his weight 88 kg.

Biochemical tests showed normal spinal fluid and urine examinations. The serum CRP was increased to 6.7 mg/l (normal 0.0-5.0 mg/l) and the serum cholesterol level was slightly elevated at 6.48 mmol/l (normal 3.9-5.2). Serum bone formation markers were in the normal range (total alkaline phosphatase 1.77 μ kat/l - norm 0.6 - 3.0 μ kat/l, bone alkaline phosphatase 0.58 μ kat/l - norm 0.25-0.53, osteocalcine 7.2 μ g/l - norm 3.1-13.7). Markers of bone resorption in urine were normal (deoxypyridinoline 3.2 nmol/mmol creatinine - norm 2.3-5.4). Densitometry of the lumbar spine and femora was normal. Electromyography of the lower and upper extremities was consistent with HSAN1.

A similar clinical presentation, consistent with HSAN 1, was observed in the patient's younger sister at the age of 22 years. Her disease had a typical course of severe, neglected HSAN with ulceration of the soles of both feet followed by cellulitis, osteomyelitis and amputation below the knee of the left leg at the age of 26 years, and a right below knee amputation six years later. Radiographs of the sister left foot before amputation documented osteolysis of the metatarsal heads in an apparently random fashion, loss of phalanges and periosteal reaction at the distal end of the left tibia and fibula. (Figures 2A & B - 2.12.96). Similarly HSAN potentially type 1 was di-

agnosed in the mother of the two affected siblings, at the age of 30 years. She died of colonic carcinoma aged 43 years.

On the basis of our experience with the severe course of the patient's younger sister, we decided to begin treatment of the presented patient with Alendronate 70 mg per week and Colecalciferol 1000 IU every day. The treatment was commenced 3 months after the onset of the metatarsal fractures and continued for a year. A calcium rich diet was prescribed.

Biochemical tests after 5 months of medical therapy showed a low level of bone formation markers: osteocalcine in serum 1.5 μ g/l (normal 3.1-13.7 μ g/l), total alkaline phosphatase 1.43 μ kat/l - norm 0.6-3.0 μ kat/l, bone alkaline phosphatase 0.39 μ kat/l - norm 0.25-0.53 and a higher level of bone resorption marker deoxypyridinoline in urine 5.8 nmol/mmol creatinine (normal 2.3-5.4 mmol). CRP was at normal value and cholesterol was still slightly elevated (Table 1).

The dorsum of the left foot was warm and swollen. There was erythema and increased sweating with a prominent vascular pattern (Figure 1D - 8.7.05). He walked with a limp. Active flexion of the big toe was impaired, but movements of the 2nd to 5th toes were not restricted. Radiographs taken a year after injury showed characteristic neuropathic joint and bone disease (Charcot's arthropathy) involving the tarso-metatarsal joints. (Figure 1E - 8.7.05).

Because of absence of clinical improvement and progress of the radiographic findings the dosage of Alendronate was increased to 70 mg three times per week and continued for next 3 years. The dose of Colecalciferol was unchanged. Radiographs taken after 2 years after injury and one year after in-



Figure 1D (8.7.05). Photo of the left foot taken 1 year after injury. Progression of clinical changes. The left foot is red, swollen and deformed.

tensive treatment showed little change (Figure 1F - 1.6.06).

At the end of the 4th year of combined Alendronate - Colecalciferol treatment (3 years of intensive treatment) there was a significant decrease in bone turnover. Osteoresorption marker CTX (carboxyl-terminal telopeptide of collagen type I) was below the normal range (0.140 ng/ml - norm 0.142-0.522). Osteoformation markers were also below normal range (osteocalcine 3.2 µg/l - norm 3.1-13.7, bone alkaline phosphatase 0.24 µkat/l - norm 0.26-0.53), 25-hydroxyvitamin D was 57.4 nmol/l - norm 23.5-131.0, parathormone 40.2 1 pg/ml - norm 15.0-68.3) (Table 1).

Therefore in the 5th year of therapy the dosage of Alendronate was decreased to 70 mg per week. The Colecalciferol dosage was unchanged. Radiographs of the left foot taken in Jan 09 (Figure 1G - 21.1.09) showed decreased osteosclerosis. Radiographs 11 months later showed significant remodelling at the proximal end of 1st- 4th metatarsals and distal tarsal bones (Figure 1I - 2.12.09). Five years after the commencement of Alendronate treatment it was replaced by Acidum ibandronicum 150 mg per month.

The patient is now progressing well. He limps slightly on the left leg due to dysfunction of flexor hallucis longus. Clinically the foot has improved significantly. The skin of foot is of normal appearance (Figure 1J - 21.10.10). The patient complains of paraesthesia in the foot. There is insensitivity to pain and touch, but temperature sensation is normal. Medical imaging with 3D CT scan reconstruction (Figure 1H - 21.9.09) and radiography (Figure 1K - 27.10.10) demonstrate the result of the Alendronate-Colecalciferol therapy. Biochemical tests performed 6 years after the commencement of combined bisphosphonate-vitamin D therapy, showed bone turnover to be



Figure 1E (8.7.05). Radiographs taken a year after injury (6.5 months treatment with Alendronate 70 mg per week) showed neuropathic osteoarthropathy. Rapid progress of the disease. Extensive sclerosis of the metatarsals and adjacent tarsal bones. Deformity of the 1st and 2nd metatarsals. Small, loose bony fragments are present at the proximal end of the first metatarsal.



Figure 1F (1.6.06). Radiographs taken after 2 years after injury and one year after intensive treatment (dosage of Alendronate was 70 mg three times per week). Little change since last examination. Note irregularity of the tarsometatarsal joint.



Figure 1G (21.1.09). Radiographs taken 4 years and 5 months after injury showed decreased osteosclerosis. Dosage of Alendronate was decreased to 70 mg per week.



Figure 1H (29.1.09). 3D CT scan reconstruction taken 4 years and 5 months after injury demonstrates deformity of the 1-3 metatarsals. Note small bony fragments involving the tarso-metatarsal joint.



Figure 1I (2.12.09). Radiographs taken 5 years and 4 months after injury showed marked decrease of osteosclerosis and significant remodelling at the proximal end of 1st-4th metatarsals and distal tarsal bones. Alendronate treatment was replaced by Acidum ibandronicum 150 mg per month.



Figure 1J (27.10.10). Photo of the left foot taken 6 years and 4 months after injury. Treatment of Acidum ibandronicum 150 mg per month. The left foot is swollen, slightly deformed but the skin is of normal colour and texture.



Figure 1K (27.10.10). Radiograph taken 6 years and 4 months after injury demonstrates decreased density and a delicate trabecular pattern of all the bones.

at the lower limit of normal (as bone formation markers /total alkaline phosphatase and osteocalcine/ as bone resorption marker/CTX/) (Table 1).

The last biochemical tests were performed 7 years after the commencement of combined bisphosphonate-vitamin D therapy. There was a significant decrease in bone turnover (Table 1 and radiographs in Figures 1B, E, K).

Based on the significant radio-clinical improvement of the foot and decrease in bone turnover, therapy was then terminated. The patient was encouraged to take daily Colecalciferol 1000 IU.

Discussion

The natural history of HSAN1 in untreated or under-treated patients typically includes repetitive injury to the feet, leading to indolent ulceration of the soles, recurrent cellulitis and chronic osteomyelitis. Resorption of bone and formation of sequestra as a consequence of the osteomyelitis may result in bone and joint deformities and loss of toes (Figure 2A). However before ulceration develops, loss of sensation in the feet and subjective sensory disturbances associated with leg muscle atrophy, abnormal gait, sprained ankles are the earliest, often not recognized, signs of the disease. In none of the 44 patients of a large family affected by HSAN1 did a bone fracture precede the development of ulcerations⁵⁻⁸. Our patient did not notice any signs of the dis-

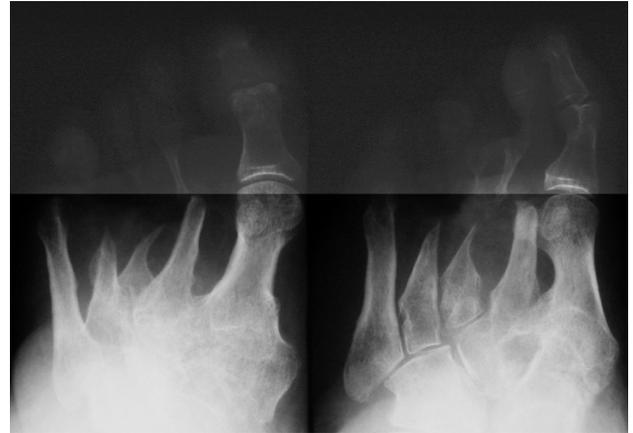


Figure 2A (12.1.96). Osteolysis of the metatarsal heads in an apparently random fashion, partial loss of phalanges of the left foot - sister of proband.

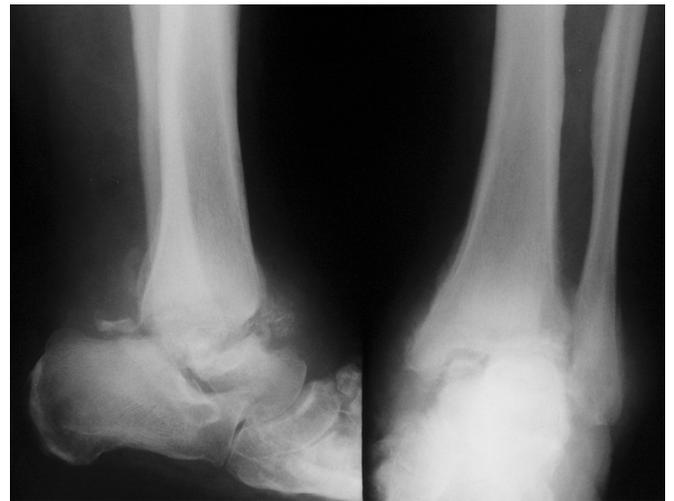


Figure 2B (12.1.96). Periosteal reaction of the distal end of the left tibia and fibula, partial loss of talus – sister of the proband.

ease until he twisted his ankle and forefoot. He did not feel any pain at the time of injury but a “strange, non-painful feeling in the foot” developed a short time later. He sought medical advice 3 weeks after the injury because of progressive swelling and discoloration of the dorsum of the foot. The latter was probably the result of damage to sympathetic vaso-constrictor nerve fibers by accumulation of specific molecules (two atypical deoxysphingoid bases 1-deoxy-sphinganine and 1-deoxymethyl-sphinganine) which are “toxic for sensory neurons”⁹.

Radio-clinical examination and experience with the typical course of severe neuropathy of the patient’s sister was sufficient to establish the diagnosis in the proband. Molecular genetic testing for all the possible candidate genes for both

HSAN1 (multiple subtypes) and HSAN2, and sural nerve biopsy were unfortunately not possible for confirmation.

Hereditary neuropathies are common neurological conditions characterized by progressive loss of motor and/or sensory function. The differential diagnosis of HSAN1 includes other types of HSAN syndrome, in particular HSAN2. The latter is an autosomal recessive mutilating acropathy with onset of symptoms in infancy or childhood. It affects both lower and upper extremities^{1,2,8-10}. HSAN types 3-5 as well as other sensory neuropathies such as syringomyelia, tabes and mononeuropathies are unlikely to cause confusion for clinicians familiar with HSAN1^{5-7,13,14,16}. Among the many causes of hereditary neuropathies are dominant mutations in either of two subunits of serine palmitoyltransferase, long chain base subunit 1 (SPTLC1) and subunit 2 (SPTLC2), which cause hereditary sensory and autonomic neuropathy type 1 (HSAN1). By incorporating L-alanine in place of L-serine, the mutant HSAN1 - associated serine palmitoyltransferase generates deoxysphingolipids, which are thought to be neurotoxic¹⁷.

The usual radiographic consequences in HSAN1 are atrophic changes resulting from peripheral neuropathy. They entail resorption of metatarsal heads in an apparently random fashion which leads to a spindle-shaped appearance of the ends of the metatarsal bones, ankylosis or dislocation of the metatarso-phalangeal and interphalangeal joints, loss of digits and a periosteal reaction involving the distal tibia and fibula⁸.

In our patient radiographs performed 3 weeks after the sprained left ankle documented fractures of 2-4 metatarsals without periosteal reaction. Uncharacteristic for HSAN1 is the development of Charcot's arthropathy. This is thought to be attributable to the changed course of the disease due to Alendronate-Colecalciferol therapy.

We previously observed positive results of Alendronate treatment in a patient with familial expansile osteolysis (MIM 167250)¹⁸ that belongs to extremely rare heritable disorders of the RANK/RANKL/OPG pathway. The pathogenesis of this bone disorder is excessive RANK effect (mutations in TNFRSF11A)¹⁹. This wheelchair patient three months after commencement of Alendronate treatment (70 mg per week) and Colecalciferol (1000 IU every day) observed striking relieve of the upper and lower limb pains. Two years later multilevel corrective osteotomy of the left shank was carried out with excellent long term result and she is able to walk with crutches up to the present time. X-rays proved total but late remodelling of osteotomies (it lasted 2 years). At present, no osteolysis around intramedullary nail, no new expansion and bend of other long bones, cortical thinning, and fractures were detected.

In the patient we decided for Alendronate treatment according to our experience mentioned above and on the basis of unsuccessful symptomatic treatment of proband's sister who suffered from a typical course of severe HSAN1 with ulceration of the soles followed by cellulitis and osteomyelitis. Radiographs of the sister left foot before amputation documented osteolysis of the metatarsal heads, loss of phalanges and periosteal reaction at the distal end of the left tibia and fibula. (Figures 2A & B - 2.12.96).

The replacement of Alendronate by Acidum ibandronicum 150 mg per month was carried out five years after the commencement of treatment from these reasons: Bone markers showed a significant decrease in bone turnover and we furthermore wanted to keep low bone turnover. It was known that acidum ibandronicum (IBN) is a bisphosphonate with weaker binding to bone mineral than Alendronate and intermittent usage can facilitate cyclic remodelling of bone. The study of Binkley et al. in 2009²⁰ explored the between-dose profile of changes in serum CTX-I and found that the median relative change in serum CTX-I levels fluctuated with a monthly pattern. Specifically, the greatest reduction in serum CTX-I concentration occurred just after ibandronate dosing and then decreased to a minimum level just before the next dose. The retrospective cohort study VIBE (The Evaluation of Ibandronate Efficacy) in 2009²¹ found that patients treated with oral monthly ibandronate or weekly bisphosphonates (alendronate and risedronate) had similar, low risks of hip fracture, nonvertebral fracture and any clinical fracture. Ibandronate patients had a significantly lower relative risk of vertebral fracture than weekly BP patients. Further studies (e.g. the MOBILE, the DIVA LTE)²² and histomorphometric analysis of transiliac bone biopsies^{22,23} that demonstrated normal micro-structure of newly formed bone with normal mineralization and reduced remodelling, encouraged our decision to use Acidum ibandronicum 150 mg per month.

The observed healing and remodelling of the affected forefoot bones can be explained by the complementary action of Alendronate and Colecalciferol. Bisphosphonates reduce osteoclast metabolism by inducing apoptosis and inhibiting enzymes of the mevalonate pathway²⁴. Vitamin D 3 decreases osteoclastogenesis by decreasing the pool of osteoclast precursors in the bone marrow, and exhibits a certain degree of anabolic action²⁵. Signalling via the Vitamin D receptor tends to stabilize and normalize bone turnover through anti-resorptive and anabolic mechanisms. The authors presume the long-term combined bisphosphonate and vitamin D therapy equilibrated bone turnover and averted osteolysis of the metatarsal heads and loss of phalanges.

Garofalo et al. in 2011²⁶ published a perspective paper where showed that oral L-serine reverses the accumulation of deoxysphingolipids in humans with HSAN1 and in a transgenic mouse model.

Conclusion

A case of HSAN, type 1, with an unusual clinical course and distinctive radiographic features is reported. Painless metatarsal fractures were indicative of an underlying neuropathy. The patient's family history allowed an early diagnosis of HSAN1 and that is why the medicament therapy was indicated. The authors believe the course of the disorder in this case was changed by immediately instituted bisphosphonate and vitamin D therapy that equilibrate bone turnover. To our knowledge this is the first clinical study documenting the use of bisphosphonates in the treatment of bone complications in

HSAN1 or other acroosteolysis conditions (e.g. Hajdu-Cheney syndrome²⁹) and/or non-infectious inflammatory bone diseases (like chronic recurrent multifocal osteomyelitis³⁰), although oral L-serine was reported to reduce the severity of neuropathy in a mouse model of HSAN1²⁶. Our results suggest a rational candidate therapy for this devastating condition. Combined bisphosphonate and vitamin D therapy may be useful in the comprehensive treatment of other bony disorders characterised by osteolysis and osteoporosis^{18,19,27,28}.

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