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The association of neurofibromatosis 1 and spinal deformity with primary hyperparathyroidism and osteomalacia: might melatonin have a role?

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Abstract A 35-year-old woman with neurofibromatosis 1 and thoracic kyphoscoliosis had incomplete paraplegia. She had a history of hyperparathyroidism due to a parathyroid adenoma which had been excised 4 years previously. Plain radiographs of the spine revealed kyphoscoliosis from the third to sixth thoracic vertebrae. Kyphosis and scoliosis angles were 86° and 28°, respectively. Radiographs of the skull and hands showed radiological changes suggestive of hyperparathyroidism. Laboratory tests showed low-normal serum calcium, hypophosphatemia, elevated serum alkaline phosphatase, and low serum 25-hydroxyvitamin D. Retrospective review of the patient's laboratory data showed that she had osteomalacia at the time of diagnosis of primary hyperparathyroidism. The patient had been treated by anterior and posterior decompression and fusion with posterior instrumentation through a single posterior approach. The postoperative kyphosis and scoliosis angles were 30° and 12°, respectively. Neurological recovery and spinal fusion had been achieved. Osteomalacia responded well to vitamin D therapy. This is the first case of coexisting neurofibromatosis 1, primary hyperparathyroidism due to parathyroid adenoma and osteomalacia to be reported in the literature. The osteomalacia in this patient could be related to primary hyperparathyroidism, and not to neurofibromatosis 1. A drop in melatonin level after parathyroidectomy may have been the cause of spinal curvature progression in this patient.

Key words Neurofibromatosis · Scoliosis · Hyperparathyroidism · Osteomalacia · Melatonin

Introduction

To our knowledge, there have been only 13 documented reports of coexisting neurofibromatosis (NF) 1 and primary hyperparathyroidism (PHPT) in the literature, and only 1 of these patients had spinal deformity in the form of kyphoscoliosis.[7,10,15,22,23] However, none of these patients had, in addition, osteomalacia. Herein we report a case of NF1 coexisting with spinal deformity, PHPT, and osteomalacia and discuss this association and the roles that might be played by neurofibromin (the protein encoded by the *NF1* gene) and melatonin deficiency in the pathogenesis of spinal deformity in this patient.

Case report

A 35-year-old woman experienced back pain of gradual onset and progressive course in October 1996. In January 1997, she developed bilateral lower limb numbness and gait disturbance. She presented to our department for further evaluation in March 1997. On admission, her bladder and bowel functions were normal. Her mother and three siblings have cafè au lait spots, but complete medical evaluation was not possible.

In 1993, the patient had sought medical advice for muscle stiffness. At that time, investigations revealed that she had hypercalcemia. Serum calcium level was 12.5 mg/dl (normal range, 8.4 to 10.2 mg/dl); phosphorus, 2.1 mg/dl (normal range, 2.5–4.7 mg/dl); parathyroid hormone (PTH) level, 29800 pg/ml (normal range, 150 to 500 pg/ml); and serum alkaline phosphatase, 1489 U/l (normal range, 95–278 U/l). Electrophoresis revealed that 81% of alkaline phosphatase was of bone origin. Osteocalcin level was 78 ng/ml (normal range, 3.5–13.7 ng/ml). Urinary phosphorus ranged between 530 and 726 mg/day (normal range, 400 to 1300 mg/day) and urinary calcium ranged between 256 and 592.5 mg/day (normal range, 80–358 mg/day). Echography revealed a low-echoic mass of about 3.5-cm diameter compressing the inferior part of the thyroid gland on the right side. The patient had been diagnosed

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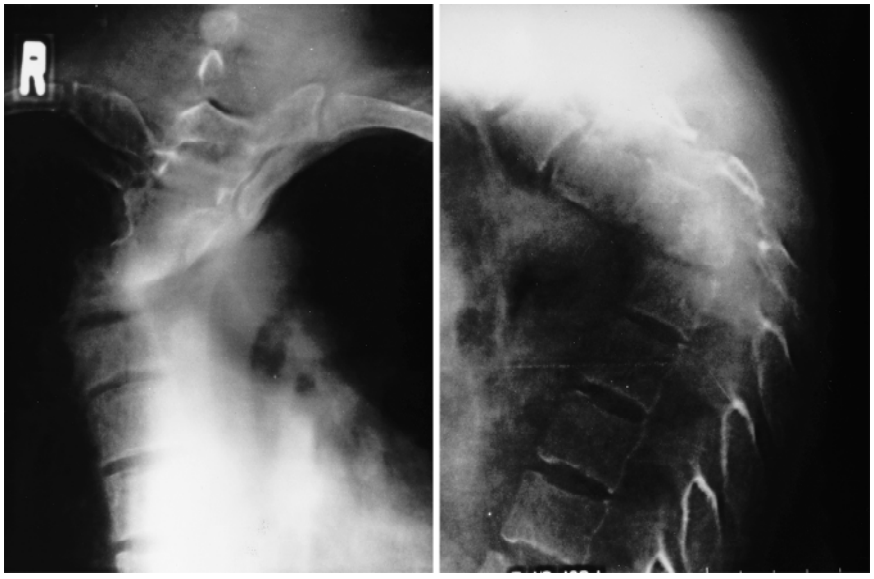

a b

Fig. 1a,b. Plain radiographs of the thoracic spine. **a** Anteroposterior view; **b** lateral view

as having PHPT, and surgical exploration in March 1993 revealed an adenoma in the right lower gland, which was excised and the diagnosis was confirmed by histopathology. Postoperatively, her serum calcium level ranged between 7.8 and 8.9 mg/dl, and serum phosphorus ranged between 1.5 and 2.6 mg/dl. Alkaline phosphatase remained high in most readings and ranged between 211 and 877 U/l.

On admission to our department, in March 1997, general examination showed eight cafè au lait spots, of more than 1.5-cm diameter, distributed on her body. She had multiple subcutaneous masses, one of which was biopsied and the histopathological picture was that of neurofibroma. Based on these data, she was diagnosed with NF 1 according to the criteria arising from the 1987 Consensus Development Conference of the National Institute of Health on Neurofibromatosis.[14]

Back examination revealed thoracic kyphoscoliosis. Neurological examination revealed bilateral hypesthesia in the lower extremities below the knees. The lower limbs showed hypertonia and hyperreflexia, with bilateral ankle clonus, although muscle powers were almost normal. Walking was almost impossible due to severe spasticity.

Plain radiographs of the spine (Fig. 1) revealed kyphoscoliosis from the third to sixth thoracic vertebrae. Kyphosis and scoliosis angles were 86° and 28°, respectively. Computed tomography (CT) myelography (Fig. 2) showed pediculo-lysis of the fifth thoracic vertebra and significant impingement on the spinal cord by the pedicle at that level. The spinal cord was extremely flattened anteriorly. Plain X-ray films of the hands (Fig. 3) showed overall loss of bone density in the phalanges of both hands, destruction of the midportions

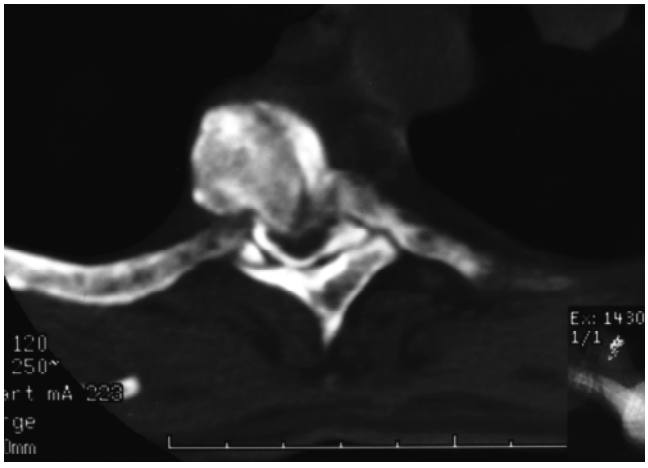

Fig. 2. Computed tomography myelography at the level of the fifth thoracic vertebra

of the distal phalanges, subperiosteal bone resorption of the phalanges with pathological striation of the phalangeal cortex, and healed fracture of the second metacarpal of the left hand. X-ray films of the skull (Fig. 4) showed granular decalcification with few radiolucent areas. These radiological changes are pathognomonic for hyperparathyroidism.[12]

Laboratory tests were performed at a different laboratory than 1993 investigations. Serum calcium, phosphorus, and alkaline phosphatase levels were 4.5 mEq/l (normal range, 4.3 to 5.2 mEq/l), 2.1 mg/dl (normal range, 2.2 to 4.4 mg/dl), and 637 IU/l (normal range, 108 to 324 IU/l), respectively. Serum sodium was 140 mEq/l (nor-mal range, 138–146 mEq/l); potassium, 4.3 mEq/l (normal range, 3.6–5.1 mEq/l); and chlorides,

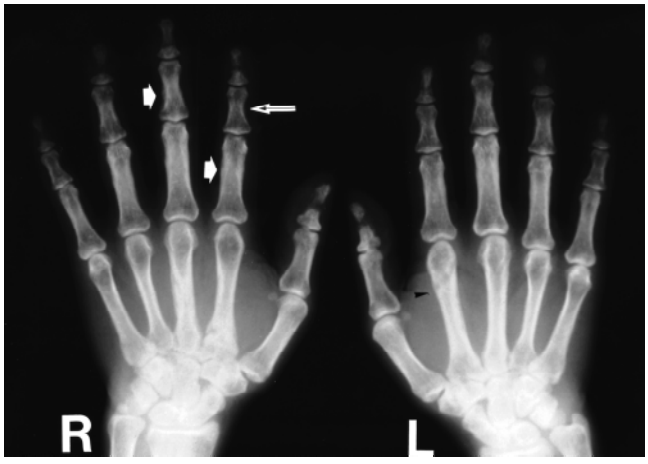

Fig. 3. Plain radiographs of bilateral hands (*R*, right; *L*, left) showed overall loss of bone density in the phalanges of both hands, destruction of the midportions of the distal phalanges, subperiosteal bone resorption of the phalanges (*thin arrow*) with pathological striation of the phalangeal cortex (*thick arrows*), and healed fracture of the second metacarpal of the left hand (*arrowhead*)

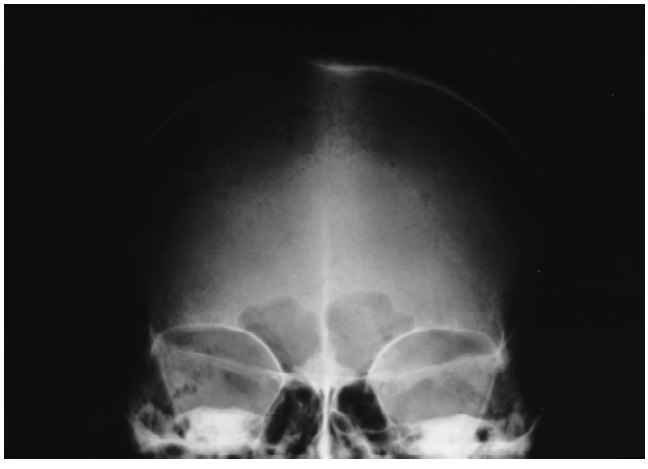

Fig. 4. Radiograph of the skull showed granular decalcification with few radiolucent areas

104 mEq/l (normal range, 99–108 mEq/l). Serum 25-OH vitamin D was 7 ng/ml (normal range, 12–62 ng/ml); 1,25 $(OH)_2$ vitamin D, 37.7 pg/ml (normal range, 27.5–68.7 pg/ml); 24,25 $(OH)_2$ vitamin D, 1.56 ng/ml (normal range 0.4–4.7 ng/ml); and intact PTH, 125 pg/ml (normal range, 12–60 pg/ml). Urinary calcium was 2.1 mEq/l (normal range, 2.6–12.4 mEq/l) and urinary phosphorus was 363 mg/day. Liver function test results were as follows: total billirubin, 0.5 mg/dl (normal range, 0.2 to 1.3 mg/dl); γ-guanosine triphosphate (GTP), 27 IU/l (normal range, 11 to 48 IU/l); aspartate aminotransferase (AST), 16 IU/l (normal range, 10 to 48 IU/l); alanine aminotransferase (ALT), 15 IU/l (normal range, 3 to 50 IU/l); lactic dehydrogenase (LDH), 204 IU/l (normal range, 120 to 214 IU/l); Zinc Sulfate turbidity test (ZTT), 13 Kunkel units (normal range, 4 to 14.5 Kunkel units); and thymol turbidity test (TTT), 9.3 Kunkel units (normal range, 0.6 to 9.4 Kunkel units). Serum total protein and albumin concentrations were 7.4 gm/dl (normal range, 6.3 to 7.9 gm/dl) and 4.4 gm/dl (normal range, 3.9 to 5.2 gm/dl), respectively. Levels of urea nitrogen and creatinine in the serum were 15 mg/dl (normal range, 7 to 22 mg/dl) and 0.4 mg/dl (normal range, 0.5 to 1.3 mg/dl), respectively.

The patient was treated by anterior and posterior decompression and fusion with posterior instrumentation through a single posterior approach. The postoperative kyphosis and scoliosis angles were 30° and 12°, respectively.

The patient could walk with a walker after 5 weeks and was able to walk unsupported after 3 months. 1α (OH) Vitamin D was prescribed at a dose of 0.25 μg twice daily, starting from May 1997. After 5 months the patient was free of neurological symptoms and signs, apart from slightly exaggerated left knee jerk, and had normal gait. After 15 months, X-rays of the thoracic spine showed solid radiographic fusion (Fig. 5). Plain radiographs of the hands and skull showed healing of the bone lesions of PHPT.

Discussion

To our knowledge, 13 cases of NF1 associated with PHPT have been reported in the literature.[7,10,15,22,23] The association of osteomalacia with NF1 has been documented only rarely; however, this association is more frequent than that of NF1 and PHPT. Konichi et al.[18] reviewed 35 cases of osteomalacia associated with NF 1; 1 of the patients had hypercalcaemic hyperparathyroidism due to clear-cell hyperplasia of the four parathyroid glands. Thus, it could not be verified whether the PHPT in that patient was primary or tertiary.[25] The association of NF1, PHPT due to parathyroid adenoma, and osteomalacia has not been previously reported. However, there are a few reports of PHPT associated with osteomalacia.[17] A question should be asked whether the osteomalacia in our patient was related to PHPT or to NF1. Patients with PHPT associated with osteomalacia are characterized by slightly elevated or even normal serum calcium levels, despite a high serum level of PTH, very high serum alkaline phosphatase, decreased serum phosphate level, normal or slightly increased urinary excretion of calcium, and low-normal or low serum 25 OH-vitamin D, while the 1,25 $(OH)_2$ level is almost normal.[17] Osteomalacia associated with NF1 is characterized by later onset in adulthood as a rule, renal phosphate loss with hypophosphataemia, multiple

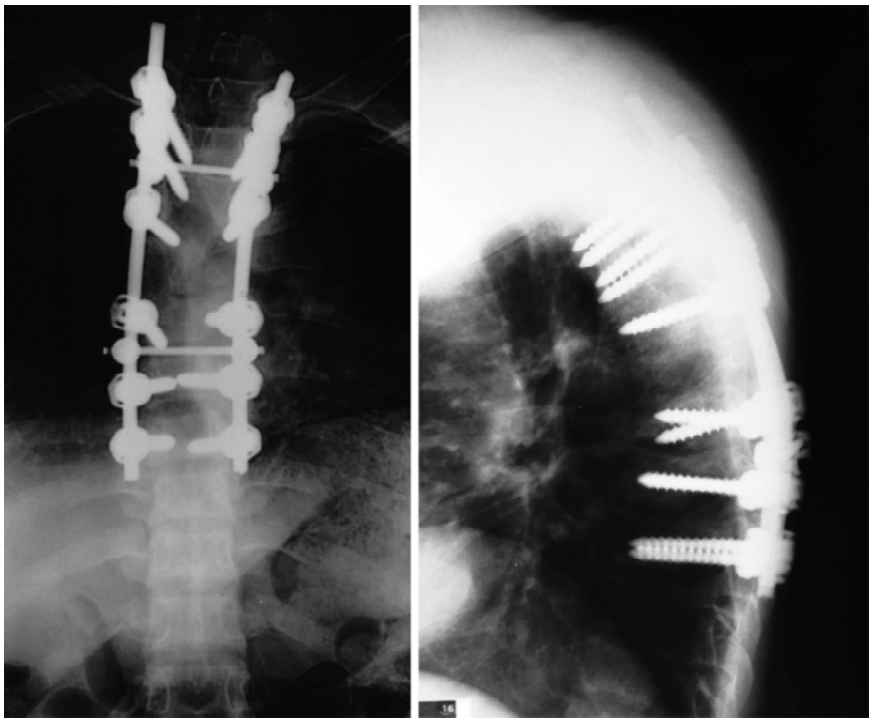

Fig. 5a,b. Plain radiographs of the thoracic spine 15 months after operation. **a** Anteroposterior view; **b** lateral view

pseudofractures in typical cases, and clinical response to treatment with clinical doses of vitamin D.[18] We could clearly relate the occurrence of osteomalacia in our patient to PHPT and not to NF1.

There are three theories that attempt to explain the association of a parathyroid adenoma and osteomalacia. The first is that vitamin D deficiency osteomalacia leads to compensatory hyperplasia of the parathyroid glands which progresses to autonomous adenoma formation in one gland. The second theory states that PHPT and osteomalacia coexist. The third theory states that longstanding PHPT leads to hypophosphatemia, which results in insufficient nucleation of mineral salts into bone. An additional factor could be added to these three explanations; that is, an increased requirement of vitamin D in patients with PHPT due to the increased renal conversion of 25 (OH) vitamin D to the active hormone 1,25 $(OH)_2$ vitamin D by the converting enzyme 25-(OH) vitamin D 1-α-hydroxylase.[17] Our patient was young, and longstanding PHPT would have been a remote possibility. So it seems that the second theory, in addition to relative vitamin D deficiency, could represent the etiology of this association in our patient.

Spinal deformities are the most common osseous defects associated with NF1, occurring in 10% to 77% of patients, and are generally classified into two basic categories: nondystrophic spinal deformity (NDSD) and dystrophic spinal deformity (DSD).[2,6,13,16] NDSD mimics idiopathic scoliosis (IS), while dystrophic changes such as vertebral scalloping and severe apical wedging and rotation are the hallmarks of DSD.[13] The etiologies of both types of spinal deformities in NF1 are still unknown. However, both types are well known for their progression potential.[1,9,13]

Osseous lesions in NF1, including dystrophic changes in the spine, are completely distinct from bone changes in osteomalacia.[18] The *NF 1* gene was found to encode a protein, called neurofibromin, that is ubiquitously expressed at some level in all tissues. It has been suggested that neurofibromin may play a role in the development of both neural crest cells and a variety of non-neural crest-derived tissues, and mutations in the *NF 1* gene result in loss of the functions of neurofibromin.[3,14] As NF1 could be associated with various bone abnormalities,[16] this may point to a role for neurofibromin in bone development. The absence of neurofibromin may represent the etiology of the dystrophic changes in the spine.[1] However, because the development of dystrophic changes in the spine does not always imply curvature progression,[11] it seems that other factor(s) may play a role in the spinal curvature progression.[1]

Machida et al.,[20] in a chicken model, found that pinealectomy on the third day after hatching caused scoliosis in 100%, of animals, and could be prevented in 80% by melatonin administration. They reported that the scoliosis developed in the pinealectomized chickens was identical to IS.[20] However, several authors have disputed this similarity. The vertebrae involved in the

curves in the chicken were wedged, whereas in the human the vertebrae remained unwedged.[24] In clinical practice, lower levels of melatonin have been detected only in patients with progressive IS, which implies that the melatonin deficiency may have a role in the progression rather than in the cause of IS.[21]

Melatonin deficiency could be proposed to be present in NF 1 due to the presence of pigmentation of the skin.[1,8] It is known that there is an inverse correlation between melatonin production and skin pigmentation: exposure to light, a potent inducer of melanin in the skin is the most powerful suppressor of melatonin production. Conversely, lack of exposure to light is a strong stimulus for melatonin production.[8] Campbell et al.[5] reported the occurrence of spinal malalignment greater than 15° in all 239 patients who had patterned pigmentation. The spinal deformities in their patients ranged from kyphoscoliosis (from mild to collapse), to long C curves, to four lateral curves. It seems that melatonin deficiency is a factor for progression of not only IS but also various other kinds of spinal malalignments, including both types of spinal deformities in NF1.[1] Supportive of this hypothesis is the finding that when either type of scoliosis is present in NF1, it seems to be consistently associated with café-au-lait spots on the skin.[6,26] It has also been reported that the scoliosis may have developed later in life than the café-au-lait spots on the skin.[6] This time gap might be the period during which melatonin deficiency might play its role in the progression of spinal deformity.[1]

In the 13 previously reported, cases of NF1 associated with PHPT, none of the patients were reported to have spinal deformity, except for that reported by Chakrabarti et al. (7.7%),[7,10,15,22,23] while 21 of 35 cases of osteomalacia associated with NF1 reviewed by Konichi et al.[18] had spinal deformities (60%). It has been proved previously that osteomalacia could not be considered as a cause of the spinal deformities in NF1.[16,18] However, calcium is essential for the stimulus-elicited secretion of melatonin.[19] Moreover, it seems that calcium affects the circadian rhythm of melatonin secretion from the pineal gland.[27] So, the low or low-normal calcium levels in patients with osteomalacia could be a factor for decreasing melatonin secretion or disturbing its circadian rhythm, thus causing spinal curvature progression. On the other hand, the chronic moderate PTH-dependent hypercalcemia in PHPT has been associated with a high melatonin level, which might halt spinal curvature progression. Three to four months after surgical treatment for PHPT and restoration of normal serum calcium levels, serum melatonin was found to be even lower than that in the control group.[4] It seems logical that the low or low-normal calcium levels in our patient after parathyroidectomy could have markedly decreased melatonin secretion. This could explain why the deformity in our patient progressed after parathyroidectomy and caused neurological compromise when she had overt osteomalacia.

Conclusion

This is the first documented case of coexisting NF1, PHPT, and osteomalacia to be reported in the literature. Osteomalacia in this patient was related to PHPT, and not to NF1. The role that might be played by melatonin in the pathogenesis of spinal deformities in NF1 is worthy of study.

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