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Hip fracture as the first manifestation of Cushing's Disease with genotype of Fabry's Disease

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Presentation of case

SLV is a woman of 35, who attended for a consultation for the first time in April 2008, having suffered a hip fracture.

Personal medical history: Arterial hypertension, with pre-eclampsia during her sole pregnancy which resulted in a cesarian section at 34 weeks, and at present controlled by medication.

Family medical history: Grandmother, father and sister with hypertension.

Start of the disease: The patient was found to be asymptomatic with adequate control of her arterial tension, until 17th November 2007, when, whilst going down the stairs carrying a load, the made a brisk movement of her right foot and noted a sensation of a "snap" in her right hip, without trauma and without falling over. She was seen the same day by a traumatologist who ordered an X-ray of her hip (Figure 1) on which no pathology was detected and from which the diagnosis of "torn muscle" was made, and for which he prescribed analgesics and rehabilitation, which the patient started to receive at a centre in this city.

The patient did not observe any improvement and attended the clinic again some days later. The rehabilitative doctor observed the existences of pain on the rotation, and limitations in the flexing, of the right hip, pain in when in the standing position, and the absence of contraction or haematomas. He requested a new X-ray of the pelvis (Figure 2) in which there were still no pathological signs, and he advised treatment with magnetotherapy, analgesics, pulsating ultrasound and by taking weight off the leg.

The patient continued to worsen, so an RMN of the hip was requested (Figure 3) in which was observed "bone oedema in the right femoral neck, with an oblique fracture without significant displacement of fragments (transcervical fracture, Pauwels type II), without changes in the morphology of either femoral heads". Treatment by resting the leg and with analgesics was prescribed. One month later the X-ray of the hip showed a radiological consolidation of the fracture with leg deformity, (Figure 4) for which was indicated a prgramme of rehabilitation, which included progressively increasing weight on the leg and hydrotherapy. For several months the patient followed the rehabilitative treatment, not observing any improvement in the pain. On the contrary, she noticed it worsening as soon she started putting weight on it.

In April 2008, the patient attended our Bone Metabolism Unit where a detailed clinical history was taken, which did not show any new details from those outlined earlier, the physical examination being normal (height: 157.5 cm. weight: 61 Kg. BMI: 24.7 Kg/m^2, arm span: 158 cm). We did not see the existence of the "buffalo hump", truncular obesity, wine-coloured stretchmarks, or any other characteristic signs of Cushing's Disease.

Figure 1. First X-ray of right hip, reported normal

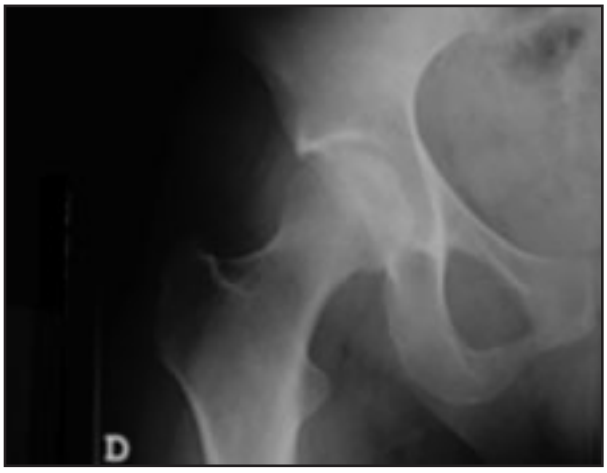


Figure 2. Second X-ray of right hip, also reported normal

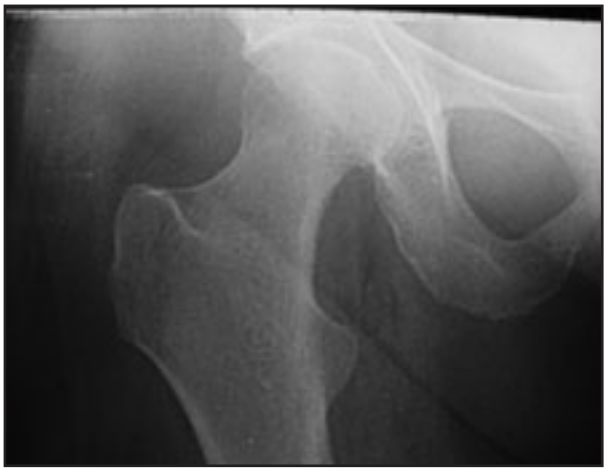
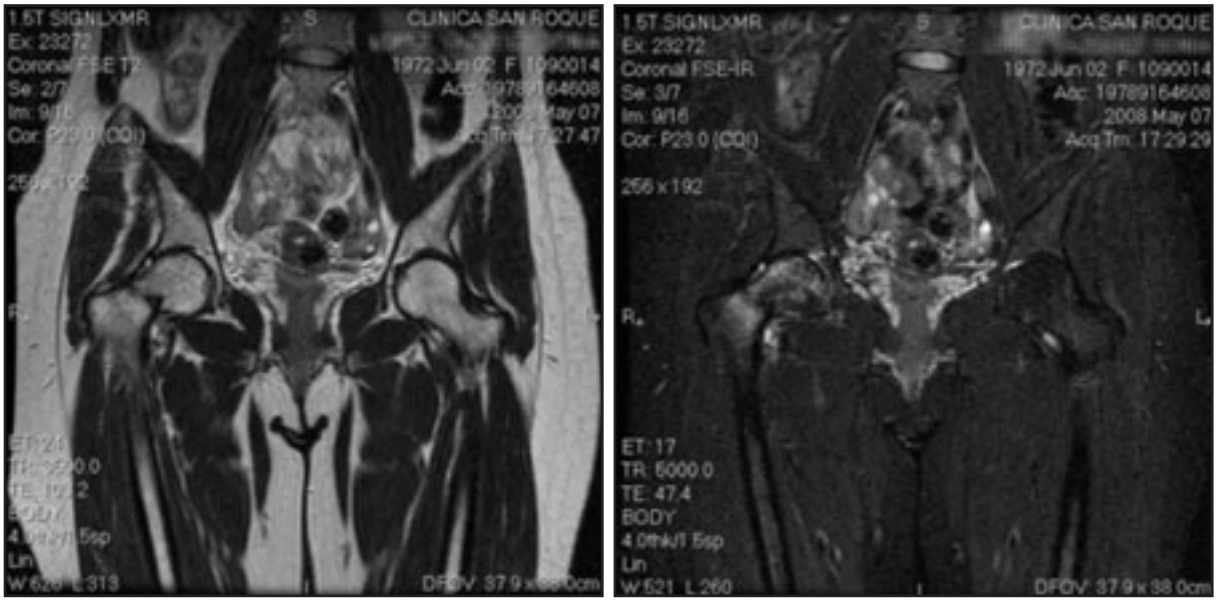


Figure 3. First RMN of hip, in which the oblique fracture is seen



A detailed analytical study was carried out, which was normal and which is shown in Table 1, a radiological study of the dorsal and lumbar spinal column, which did not show the existence of any vertebral fractures, and a bone densitometry in the lumbar spinal column and the proximal extremities of both femurs, and an estimation of the ultrasonographic parameters, also bilateral, whose values are shown in Table 2. Given the existence of pain when putting weight on the leg, and after almost a year of resting, a second opinion was requested from another traumatologist who, before the existence of the deformity in the femoral neck and the pain, suggested and carried out a surgical intervention, specifically a fixing, in situ, by means of an osteosynthesis with three cannulated screws by a minimum incision, to complete its consolidation. (Figure 5).

The patient began to put some weight on her leg with crutches and continued with aquatic physiotherapy. However, once she stopped using the crutches and started to put weight fully on her leg, the pain in the hip reappeared, a situation which lasted until December 2008, when pain in the lumbar region stated to appear – bilaterally, but more intense on the left side. A new RNM was carried out (Figure 6) which showed up the existence of a sacral fracture, on the left side. On this occasion there not been any trauma either. Some days later, pain in the right foot appeared and the gammagraphy carried out confirmed the existence of a fracture in the second right metatarsal. Both sacral and metatarsal fractures were diagnosed as "stress" fractures.

The patient was exhaustively re-evaluated and, among other complementary tests ordered, were a baseline cortisol test, and a suppression test with dexamethasone, as a genetic study to discount the possibility of diagnosing an illness of liposomal deposits. These results show the existence of

Figure 4. X-ray of hip. The consolidation with leg deformity is observed

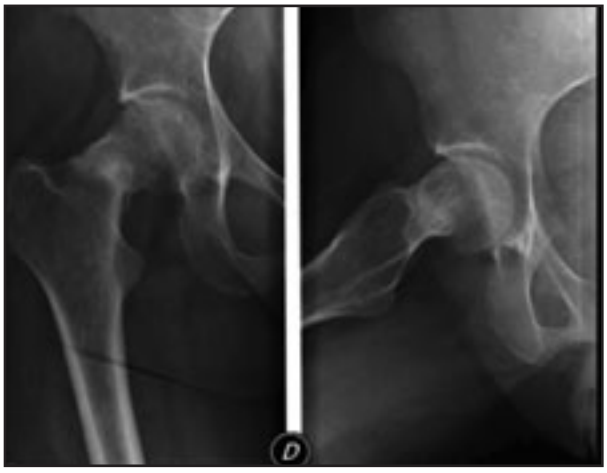


Figure 5. X-ray of hip after surgical intervention

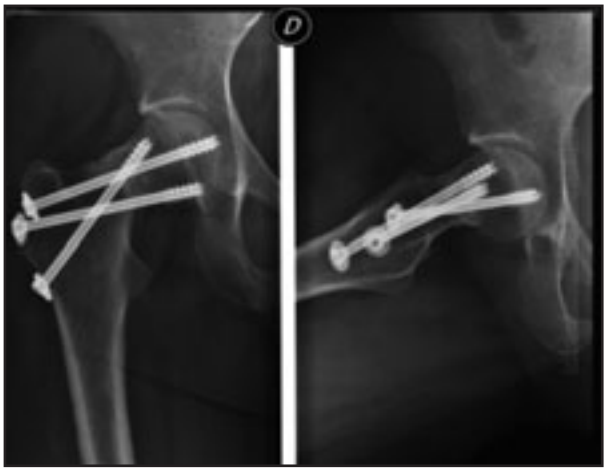
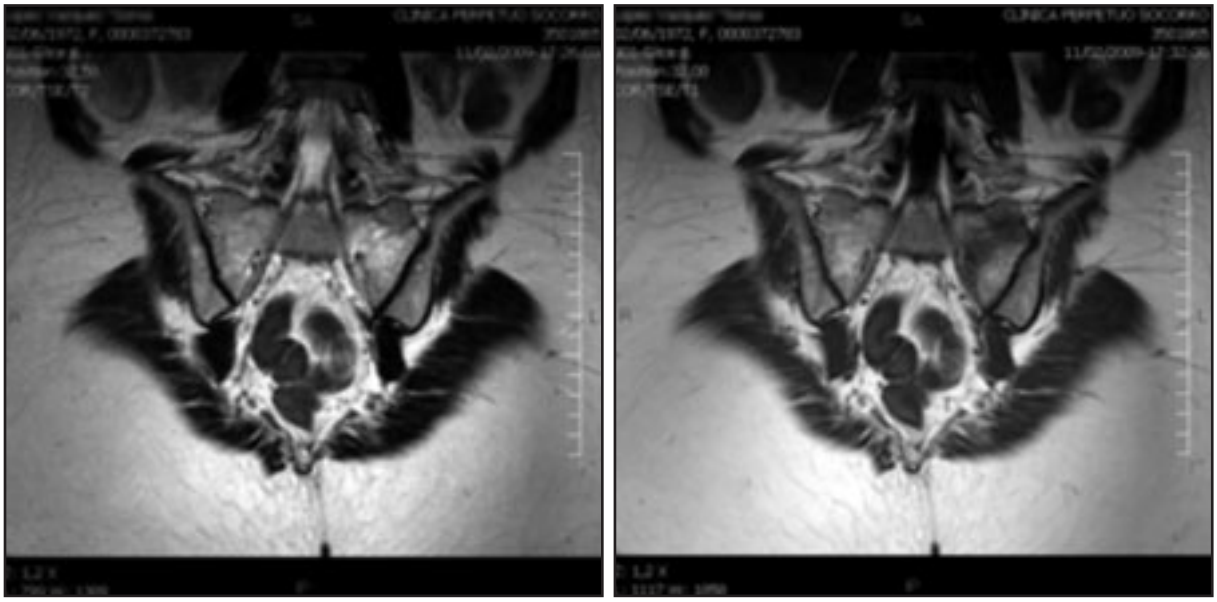


Figure 6. RNM of sacrum, in which is observed the existence of a new fracture



Cushing's Disease, confirming by RMN the existence of a hypophysary adenoma and a heterozygotic mutation in the GLA gene compatible with Fabry's Disease. Having completed the study the patient is on the waiting list for surgery.

Commentary

In this patient we were faced with two different clinical problems. In the first place, the appearance of a fracture of the femoral neck, as the first manifestation of Cushing's Disease, which on the other hand had not shown a single other clinical manifestation, save for arterial hypertension (well controlled by medication) without even being overweight (BMI: 24.7 Kg/m^2), and she was also a carrier of Fabry's Disease. The diagnosis of Cushing's Disease could only be made through an exhaustive search of secondary causes of osteoporosis, which did not even show clinical manifestations. Meanwhile, in addition to the fracture of the femoral neck the patient suffered two new fractures: one in the sacrum, the other in the fourth right metatarsal, which were initially considered to be "stress" fractures, the consequence of prolonged immobility the patient had suffered (more than one year), for treatment of the hip fracture.

The appearance of Cushing's disease in the form of various fractures, one of which being of the hip, in a young woman, has not been described until now in the literature we were able to consult. In itself, Cushing's Disease is an uncommon occurrence[1] and fractures can be a complication of this disease, but are usually late[2]. On the other hand, what calls ones attention as being atypical in this clinical case, is the practical absence of clinical manifestations of Cushing's, since the patient only showed HTA, which, what's more, was controlled with medication, in the context of a family with a wide history of HTA, her diagnosis being confirmed by the complementary test

Table 1. Some baseline data, related to bone mineral metabolism

Parameters (units)	Values
Calcium (mg/dL)	9.9
Phosphorus (mg/dL)	2.8
Total proteins (g/L)	7.4
PTH (pg/ML)	21.9
25-HCC (ng/mL)	18
PINP* (ng/mL)	16.5
Osteocalcin (ng/mL)	6
FATR** (UI/L)	2.4
Beta-crosslaps (ng/mL)	0.24
Urea (mg/dL)	26
Creatinine (mg/dL)	0.8
Na (U/L)	142
K (U/L)	4
Basal glucose (mg/dL)	93

* Amino-terminal procollagen type 1
** Tartrate-resistant acid phosphatase
All the values were within the limits of normality, with the exception of osteocalcin which was reduced (normal values between 11 and 43 ng/mL)

Table 2. Estimate of the bone mineral density in lumbar spinal column and both hips, and the ultrasonographic parameter in both heels

Anatomical location and (units)	Lower right member (fractured)	Lower left member
DXA		
Femoral neck (g/cm^2)	0.804	0.618
Tscore	-0.3	-2.0
Total in hip (g/cm^2)	0.653	0.710
Tscore	-2.4	-1.5
L2-L4 (g/cm^2)	0.888	
Tscore	-1.5	
Ultrasounds		
QUI	95.4	99.6
Tscore	-0.5	-0.2
BUA (dB/MgHz)	63.3	65.8
SOS (m/s)	1562.1	1572.6

carried out[3,4]. On the other hand, in the wide etiological search of the disease, we carried out a genetic study to confirm or deny diseases of storage, and obtained, to our surprise, a mutation in the same allele in heterozygocity for the GLA gene: heterozygote for the double mutation IVS4-16[a]>g; IVS6-22 c>t, also described as IVS+1704 a>g; IVS6+249 c>t[5], which indicated that the patient was a heterozygotic carrier of Fabry's disease with normal enzymatic activity (Alpha galactosidase in leukocytes: 61 nM/mgprot.h and Alpha galactosidase in blood: 20 nM/ mL.h).

Fabry's Disease, Anderso-Fabry or *angiokeratoma corporis diffusum*, is a hereditary disorder with the mutation of the alpha galactosidase A gene situated in the chromosome X (Xq 22.I). This mutation determines the storage of the neutral glycosphingolipids (globotriaosylceramide and galactosilceramides) in the lisosomes of the endothelial, perithelial and smooth muscle cells, with their accumulation in the blood. The incidence is of between 1/40,000 to 1/117,000 in the whole world[6], although in our environment it is one case for every 476,000 living persons (1:238,000 males)[7], and its distribution is pan-ethnic. Its clinical expressivity is usually more serious in males, although women carriers are not exempt from being affected[8]. The clinical spectrum is highly varied; from neutropathic pain, fever of unknown origin, intolerance to cold and hypohydrosis, corneal opacity, gastrointestinal affectation, angiokeratomas and tinnitus, to an affectation of the target organ with early cardiovascular disease, cerebrovascular accident, progressive renal failure to a terminal state, left ventricular hypertrophy and arrhythmia[9], without finding a single similarity with the clinical picture of our patient nor its sub-clinical detection through the complementary tests carried out. Manifestations less frequent are osteopenia and osteoporosis[10,11], with the description of an isolated case of avascular necrosis of the femoral head[12]. In this genetic study we found the same mutation in the mother and sister, with normal enzymatic activity in both. Neither had had fractures. There were no brothers.

We do not know to what extent Fabry's disease could have played a role in the appearance of these fractures or what may have been caused by co-existing Cushing's disease.

Secondly, the other clinical problem this patient had, was the delay in the diagnosis of the fracture of the femoral neck. The clinical data (young woman, previously healthy, minimum trauma), along with the fact that the first two X-rays did not detect the fracture, contributed to this happening unnoticed, and putting weight on a fractured neck produced a deformity of the leg, which finally required surgical treatment for its consolidation.

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