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CASE REPORT

Hemihyperplasia-Multiple Lipomatosis syndrome (HHML) : a challenge in spinal care

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A 15-year-old girl developed a progressive paraparesis over a period of six months, secondary to spinal cord compression by a lipomatous mass and anomalies of the vertebral column. Clinically, a right hemihyperplasia affecting the trunk and lower limb was evident, as well as a right convex lumbar scoliosis. CT and MRI demonstrated severe spinal cord compression resulting from intraspinal lipomatosis, overgrowth of right facet joints (T8 to L5), and kyphoscoliosis. Surgical decompression was undertaken. A lumbar scoliosis of 48° was partially corrected by means of dual-rod instrumentation. The neurological deficit improved significantly, and ambulation was progressively restored. The patient carried the diagnosis of Proteus syndrome for several years, but re-evaluation of clinical features prompted the diagnosis of Hemihyperplasia Multiple Lipomatosis syndrome (HHML). This rare sporadic disorder is often confused with Proteus syndrome. As in Proteus syndrome, spinal cord compression in patients with HHML can result from lipomatous infiltration and/or significant spinal abnormalities including kyphoscoliosis and overgrowth. HHML and Proteus syndrome are discussed and compared with special emphasis on spinal and orthopaedic pathologies.

Keywords : Hemihyperplasia-Multiple Lipomatosis syndrome (HHML) ; vertebral anomalies ; scoliosis ; spine ; paraplegia ; Proteus syndrome.

INTRODUCTION

Hemihyperplasia-Multiple Lipomatosis syndrome (HHML) is a sporadic disorder delineated from the Proteus syndrome in 1998 by Biesecker *et al* (*3*). It is characterised by subcutaneous lipomatosis and an asymmetric overgrowth (hemihyperplasia) which is not as progressive and aggressive as in

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Proteus syndrome. Vascular malformations may occur (*3*). The aetiology of this rare disorder is unknown. Biesecker *et al* (*2*) stated that misdiagnosis of HHML and other asymmetric overgrowth syndromes such as Proteus syndrome is common, primarily because of confusion about the variability of Proteus syndrome. Diagnostic criteria for Proteus syndrome have been established to avoid a diagnostic dilemma (*2,16*).

There are only very few reports on patients with HHML (*3,6*).

CASE REPORT

A 15-year-old girl with supposed Proteus syndrome was admitted to the orthopaedic department because of progressive paraparesis since six months. She was unable to walk. Bowel and bladder function were disturbed since 6 weeks. According to the parents her motor development had been retarded, but her mental development had evolved normally. During her infancy several subcutaneous lipomatous tumours had been removed from the right side of the trunk. She had undergone right femoral shortening because of leg length discrepancy.

The patient was noted to have asymmetric overgrowth of soft tissues and bones. She had adipose overgrowth mainly of the right half of the trunk. Subcutaneous lipomatous masses extended into the right leg and foot. The overgrowth of the right foot was accompanied by thickening of the sole, but without the connective tissue naevus with cerebriform appearance so pathognomonic of Proteus syndrome. The right limb was longer (fig 1). Knee and hip contractures, and valgus knee malalignment were present on the right side. Paraparesis and sensory deficits were noted in both lower limbs. The left leg was spastic, and demonstrated hyperreflexia of the patellar and Achilles tendon reflexes, a non self-limiting patellar and ankle clonus, and a positive Babinski sign. On the right side, the patellar and Achilles tendon reflexes were absent. Both tonsils were enlarged.

Radiological examination showed a rigid right convex lumbar curve of 48°, a left convex thoracic curve of 32° and a localised kyphosis of 28° at T10-L2 (fig 2). Computed tomography (CT) (fig 3) and magnetic resonance imaging (MRI) (fig 4) revealed lipomatosis of the right anterior and posterior chest wall, infiltrating the erector spinae muscle and

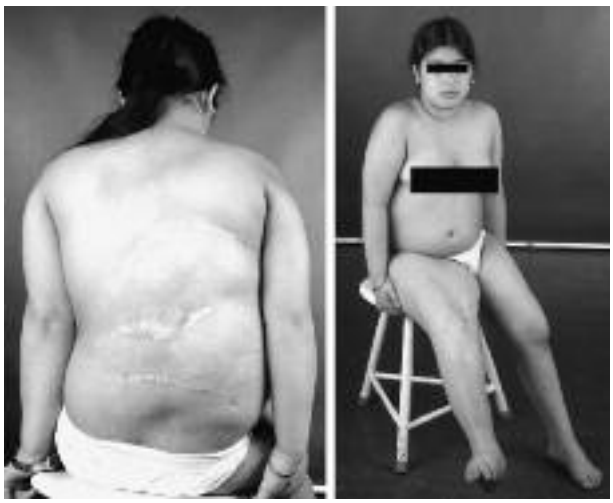

Fig. 1. — Preoperative clinical picture showing overgrowth of the right trunk.

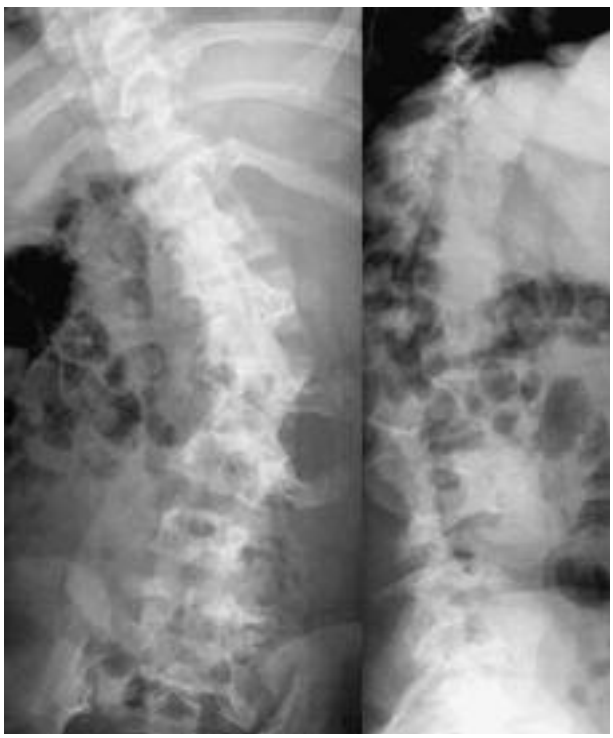

Fig. 2. — Preoperative anteroposterior and lateral radiographs demonstrating the lumbar scoliosis and the kyphosis T10-L2.

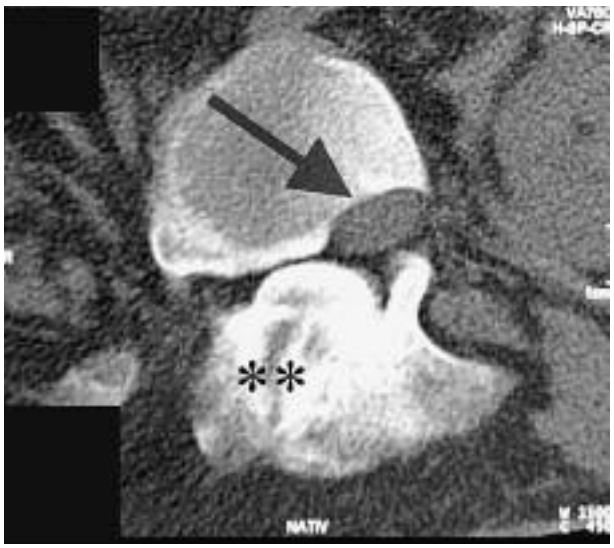

Fig. 3. — Axial computed tomography T12 : spinal cord (arrow) ; facet joint hypertrophy (**).

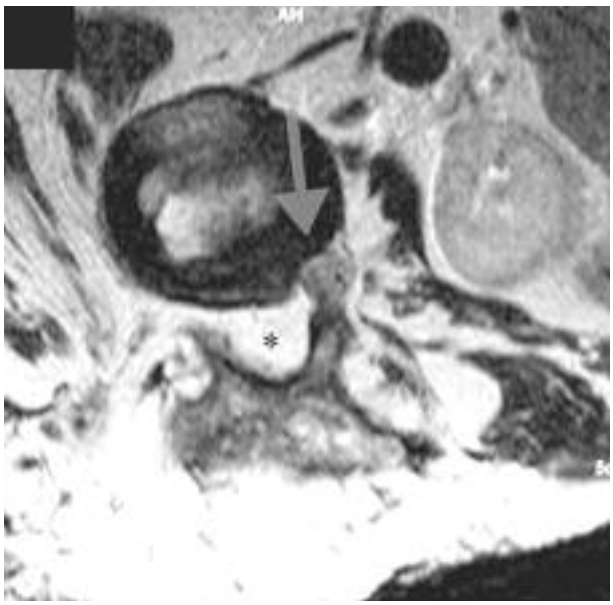

Fig. 4. — Axial MRI T12/L1 : lipomatosis filling the spinal canal (*) ; the spinal cord is shifted to the left (arrow).

reaching into the epidural space via the right neural foramina T8-L5. The lipomatosis also involved the right retroperitoneum and the pelvis minor. Spinal cord compression was demonstrated from T7 downwards, due to lipomatosis (fig 4) within the spinal canal, to overgrowth of the right-sided facet joints (fig 3) and to kyphoscoliosis (fig 2). Nephromegaly was noted by ultrasound.

The patient underwent surgical decompression T8-L5. This included laminectomy, excision of ligamenta flava, removal of fat tissue, and subtotal resection of the hypertrophic right-sided facet joints and pedicles ; the fat tissue did not infiltrate or damage the dura. The spinal deformity was partially corrected and instrumented via the same posterior approach, using a dual-rod system (Micomed Ortho, Schorndorf, Germany) from T7 to L5 ; allografts were added posterolaterally. Pedicle screws were only inserted at the levels T7, T8, L4, and L5 (fig 5) because of the dysplastic nature of the pedicles. An anterior approach was avoided because of the extensive right-sided retroperitoneal lipomatosis. Perioperatively the patient was treated with methylprednisolone according to the NASCIS-II protocol for neural protection *(4)*. The intraoperative blood loss was 5 litres, with an operation time of 7 hours. Histological examination of the soft tissue located in the spinal canal showed non-malignant mature adipose tissue.

The neurological deficit improved significantly within 24 hours, enabling the patient to move her legs. She developed pneumonia and a bilateral pleural effusion, which were successfully treated with antibiotics. The wound healing was significantly delayed and required revision surgery after 10 days. After three weeks the patient was able to walk a few steps by means of leg orthoses and rolling walkers. She was discharged after 7 weeks. Complete wound healing was seen after four months. Thanks to a strict rehabilitation program she was able to walk alone, without any assisting devices, at follow-up after three years.

During follow-up, the diagnosis of Proteus syndrome was rejected based on the established diagnostic criteria for Proteus syndrome (table I) *(1, 2,16)*. Although the patient fulfilled all the general criteria of Proteus syndrome (sporadic occurrence, mosaic pattern of the phenotype, and continued progression), she did not meet enough specific diagnostic criteria. In particular, she had only one

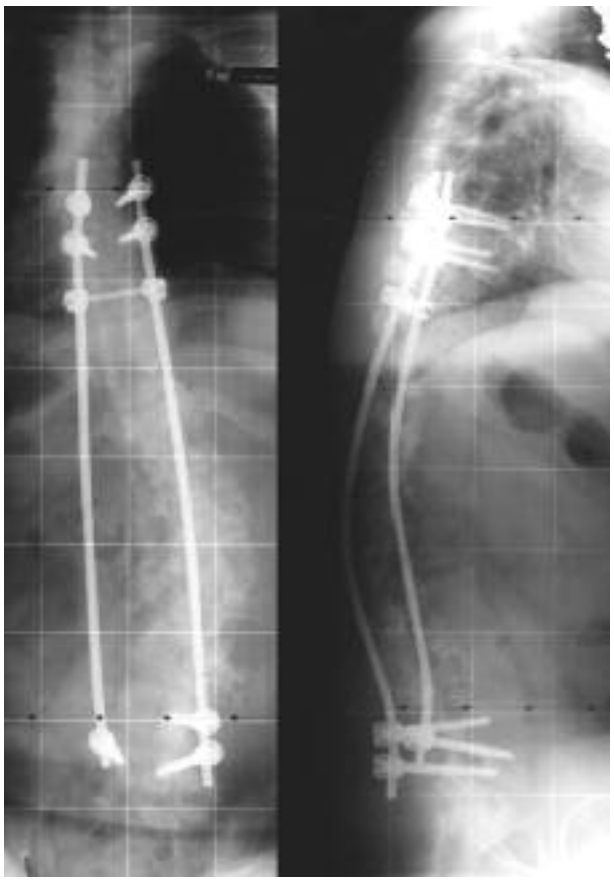

Fig. 5. — Postoperative anteroposterior and lateral radiographs.

criterion of category B (asymmetric overgrowth of limbs and vertebrae) and one criterion of category C (dysregulated adipose tissue). No other specific features of Proteus syndrome were present.

The best fitting diagnosis for the combination of hemihyperplasia and lipomatosis in the patient reported here appears to be HHML syndrome. Because the Cowden syndrome/Bannayan-Riley-Ruvalcaba syndrome is also characterised by multiple lipomas/lipomatosis a mutation analysis of the *PTEN* gene was performed. Direct genomic sequencing (DGS) of all nine *PTEN* exons including intron/exon boundaries failed to show a mutation.

DISCUSSION

The patient reported on here had impending paraplegia. Spinal cord compression resulted from facet joint overgrowth, kyphoscoliosis, and intraspinal lipomatosis.

Paraspinal or intraspinal soft-tissue masses (lipomas or angiolipomas), (asymmetrical) overgrowth of vertebral bony structures, particularly of the posterior elements, and kyphoscoliosis have been reported in patients with Proteus syndrome (*7,8,10-12,14,15,17,18*). The diagnosis in these patients is

Table I. — Proteus syndrome : diagnostic criteria (*1*)

General criteria : Mosaic distribution, sporadic occurrence, progressive course		
Specific criteria :		
Category A	Cerebriform connective tissue naevus	
Category B	1. 2. 3.	Linear epidermal naevus Asymmetric disproportionate overgrowth ; one ore more of : (a) limbs, (b) skull, (c) external auditory canal, (d) vertebrae, (e) viscera : spleen/thymus Specific tumours before 2nd decade of life ; one of : (a) bilateral ovarian cyst (b) adenomas or parotid zoomorphic adenoma
Category C	1. 2. 3. 4.	Dysregulated adipose tissue ; either one : (a) lipomas, (b) lipohypoplasia Vascular malformations ; one or more of : (a) capillary, (b) venous, (c) lymphatic Lung cysts Facial phenotype (long face, dolichocephalism, downslanted palpebral fissures, low nasal bridge, wide or anteverted nares, and open mouth at rest)
The diagnosis of Proteus syndrome requires all three general criteria as well as various specific criteria (either category A, or two criteria from category B, or three criteria from category C).		

in accordance with the recent criteria for Proteus syndrome (*1,2,16*). Progressive encroachment of the spinal canal has been reported (*7,12* (patient 1), *17*). The level of the spinal pathology was thoracic (*7,11,12,17,18*) or lumbar (*7*).

Although fulfilling the general criteria, such as mosaic distribution of lesions, sporadic occurrence, and progressive course, the patient reported here did not meet sufficient specific criteria of the Proteus syndrome (*1,2,16*).

Differential diagnosis for asymmetrical overgrowth and lipomatosis includes Cowden syndrome/Bannayan-Riley-Ruvalcaba syndrome, a multiple hamartous disorder. However, our patient did not demonstrate the main features of the Cowden syndrome/Bannayan-Riley-Ruvalcaba syndrome like mucocutaneous lesions and macrocephaly. Furthermore, a *PTEN* mutation, the molecular basis of Cowden syndrome/Bannayan-Riley-Ruvalcaba syndrome, could not be demonstrated.

The combination of hemihyperplasia and lipomatosis in this patient is suggestive of HHML syndrome. It is to note that since delineation of the HHML syndrome in 1998 no detailed reports on patients with HHML syndrome have been published (literature research based on MEDLINE 1998-2007) (*3*).

Although the case reported here cannot be seen as Proteus syndrome, the spinal lesions and lipomatous tumours that led to progressive spinal cord injury are not distinguishable from those in patients with Proteus syndrome.

Experiences with therapeutic interventions are reported in patients with Proteus syndrome (*7,8,10-12,15,17,18*). Decompression of the spinal cord requires a laminectomy (*11,12,17,18*) or even a combined anterior-posterior procedure (*11*). Debulking of tumours is recommended in cases with compression syndromes caused by tumours (*11,12,17,18*). There are only very few reports on instrumented corrective surgery of spinal deformities such as scoliosis or kyphoscolios in these patients (*4,17*). In case of resection of an angiolipoma a large amount of blood loss is to be expected (*11,12*). Resection may be facilitated by preoperative angiographic embolisation of the tumour (*10,12*). Chemotherapy, steroids, interferon, and radiotherapy have been tried in individual patients with angiolipomatosis, although without significant improvement (*10-12*).

Compression of the spinal canal in patients with HHML and Proteus syndrome should presumably be treated similarly, regardless of the diagnosis. All non-orthopaedic and non-cutaneous surgical interventions were compared in 81 patients with Proteus syndrome and 53 patients with other overgrowth syndromes (*9*). This was based on an extensive literature review, and on personal observations. The authors concluded that patients in the two groups should be treated in a similar manner. They emphasised the importance of a thorough preoperative assessment of otolaryngological and thoracic manifestations because tonsillar overgrowth and respiratory insufficiency are frequent problems. Anaesthesiologists should be informed of possible intubation difficulties, also in HHML (for instance, due to tonsillar overgrowth).

Vascular malformations, relative immobility, and surgical procedures predispose to deep venous thrombosis in patients with Proteus syndrome ; pulmonary embolism is one of the most common causes of death (*5,13*). Therefore, perioperative anticoagulant prophylaxis is strongly recommended. Cutaneous capillary malformations occur in some patients with HHML syndrome, but vascular malformations of deep veins have not been reported (*3*). For this reason, patients with HHML do not appear to be as susceptible to thrombosis (*1*).

The recurrence rate of lipomatous tumour growth in case of incomplete resection is high (*11,12,14*). In our case significant improvement of neurological condition and quality of life were obtained, but the follow-up period is only three years, and regular controls are necessary to detect a possible recurrence.

Wound healing was significantly delayed in our patient. This is consistent with wound healing problems seen in obese patients (*19*) and can be explained by the fact that adipose tissue is poorly vascularized.

CONCLUSION

The features of HHML syndrome partially overlap with those of Proteus syndrome. HHML and

Proteus syndrome are both asymmetric overgrowth syndromes with mosaic distribution of lesions, sporadic occurrence, and progressive course. The latter is more pronounced in Proteus syndrome, as HHML syndrome is relatively stable. Lipomatosis, the hallmark of HHML syndrome, is present in most but not all patients with Proteus syndrome. Vascular malformations, if present in patients with HHML syndrome, consist of capillary malformations and do not involve deep venous and lymphatic vessels, as they do in Proteus syndrome. The most important difference between the two conditions is that patients with HHML do not suffer from the aggressive overgrowth seen in Proteus syndrome and are not as susceptible to thrombosis (*1,3,6*). Patients with HHML syndrome are considered to be at elevated risk for Wilms' tumour and hepatoblastoma, and should be screened for those tumours (*1*).

Proteus syndrome and HHML syndrome can both lead to spinal stenosis with a progressive neurological deficit, due to bony overgrowth, lipomatosis and kyphoscoliosis. Surgical decompression and debulking may lead to significant neurological improvement. Spinal complications in patients with HHML and Proteus syndrome can be treated similarly.

Because of the diversity of the pathology a multidisciplinary approach to musculoskeletal pathologies is mandatory including the cooperation of anaesthesiologists, paediatricians, orthopaedic surgeons and geneticists.

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