Summary:
Diseases that present with asymmetric development of one of the extremities are unusual entities and are considered a diagnostic challenge for radiologists. Within these group of entities, we could find Proteus syndrome, Maffucci syndrome, Klippel-Trenaunay-Weber syndrome and lipomatous macrodystrophy. It is important to recognize radiological findings of the diseases that are characterized by gigantism in order to achieve an accurate diagnosis.

Key Words (MeSH)
Gigantism
Extremity
Proteus
Maffucci Syndrome
Klippel-Trenaunay-Weber

Introduction
There are diseases that cause overgrowth of an extremity or extremities, or parts of it, with the consequent asymmetry in the size of the extremities, and that do not constitute congenital malformations, but abnormalities that are developed during lifetime. Frequently we face the challenge of evaluating studies of patients with clear limb asymmetry, with excessive growth in some of their extremities, global or focal, associated with or without alteration in the morphology of soft tissues. Differential diagnosis is not broad, clinical history, physical examination and evaluation of comparative images are essential elements, in most cases it is possible to reach an adequate diagnosis.

Maffucci Syndrome
Maffucci syndrome is an unusual condition, not inherited (1). It is a congenital mesodermal dysplasia (2), characterized by multiple enchondroma associated with cavernous hemangiomas, lymphangiomas are less often found in the soft tissues (3,4).
Enchondromas are benign cartilaginous tumors that can occur in any bone but most commonly occur in phalanges and long bones (2). In 25% of cases, symptoms appear during childhood or during the first year of life, in 45% the beginning of symptoms occur before the age of 6 years, and in 78% before puberty (1). The bone and vascular lesions in the extremities are usually asymmetrical in distribution, with a unilateral compromise in 50% of patients. Hemangiomas are located in the subcutaneous tissue and are seen as bluish nodules, although there may also be visceral and mucous involvement. Bony lesions have a predilection for the tubular bones, with greater compromise in metacarpals and phalanges of hands. Enchondromas can also be found in the bones of the foot, tibia, fibula, radius and ulna. They might present with painless swelling or pathological fractures in 26% of cases (2,3). The prevalence of malignancy in the literature varies from 23% to 100%, where chondrosarcoma is the most common tumor, with an incidence of 51% in patients with Maffucci syndrome (5). Other malignancies (1) as fibrosarcoma, hemangioendothelioma, hemangiosarcoma or lymphangiosarcoma could be found. Maffucci syndrome is also associated with tumors in other organs such as CNS, gastrointestinal tract, pancreas and ovary (3,4). Radiographically, the abnormalities are more evident in the hands and feet (2), and appear as radiolucent lesions with well defined borders, with expansive remodeling of bone, cortical thinning and endosteal scalloping. In some cases it can be seen chondroid matrix mineralization in arcs and rings. These changes cause bone deformity. In the soft tissues are evident phleboliths and “popcorn” calcifications (1,3,6) (Figures. 1a, 1b).

Magnetic resonance imaging (MRI) is useful for diagnosis and location of deep hemangiomas (2,5,7). Maffucci syndrome treatment is largely symptomatic and patients should be followed periodically to detect malignant transformation. In some cases surgical management is indicated to correct the bone and soft tissue deformities especially if there is
functional impairment of the extremity or for cosmetic reasons (1.8).

Klippel-Trenaunay-Weber syndrome

Described by Klippel and Trenaunay in 1900, it is considered a rare entity characterized by combined capillary, vein and lymphatic malformations, and congenital hypertrophy of a lower extremity (9). It occurs in 1 in 20,000 live births, and there are no gender differences (10-13).

Parkes-Weber syndrome, which consists of varicose vein dilatation and multiple congenital arteriovenous fistulas with secondary outgrowth of the limb that occurs until epiphyseal closure is a similar condition.

Klippel-Trenaunay-Weber syndrome etiology is unclear. There are three origin theories. Staple and Bliznak propose damage to the sympathetic ganglion or the lateral intermediate tract dilatation leading to microscopic arteriovenous anastomoses, resulting in venous abnormalities (15). Servelle suggests that blockage of the venous flow secondary to deep venous abnormalities causes, venous hypertension and varicose dilatations. Baskerville suggests that due to a mesodermal defect abnormal vascular communications occur (9,10,16).

Venous malformations or varicose dilations occur in 72% of cases, and often the abnormal venous flow is caused by persistent embryonic veins, agenesis, hypoplasia, valvular incompetence, or aneurysms of deep veins, and they occur in the superficial, deep and perforator venous systems (2.17 to 19). These vascular malformations are slow flowing, because there are no arterial compromise, associated lymphatic compromise, turns the skin blue or purple (Figures. 2a, 2b) (13,20,21).

Hypertrophy of the extremity is due to the vascular malformations described and the increased volume of the soft tissues and bone, usually in an asymmetric configuration, it occurs in 95% of the cases.

Proteus Syndrome

It was described by Cohen and Hayden in the year of 1979. The name comes from
the Greek God Proteus who had the ability to change shape, and was proposed by Wiedemann in 1983 (3335). It is an entity of unknown cause, although it is believed that is caused by a somatic gene mutation, which has not been identified. It is a rare hamartomatous condition, characterized by a broad spectrum of malformations. Focal overgrowth of tissues derived from all three germ layers is found, it is a multisystemic disease with a great clinical diversity (3638).

In general, it is not apparent at birth, it develops in childhood and early adolescence after this time disease stabilizes. It has general and specific clinical diagnostic criteria.

General Clinical criterion:
• Random distribution in the body
• Progressive course of lesions
• Sporadic Occurrence.

Specific clinical criterion:
• Category A: Cerebriform connective tissue nevus (pathognomonic but uncommon) (35.39).
• Category B: Linear squamous cell nevus, disproportionate, asymmetric overgrowth (compromise of one or more limbs, skull and vertebrae) (Figure. 3a), specific tumors (bilateral ovarian cystadenoma and monomorphic adenoma before or during the second decade), hemimegalencephaly, splenomegaly and fatty infiltration of the parotid gland, usually, in the right side, rarely occur. Increased subcutaneous fat and muscle pseudohypertrophy on the affected side of face is observed (35.39).
• Category C: Adipose tissue compromise: Lipoma or regional absence of fat, vascular malformations, lung cysts and facial phenotype (may not be present: dolichocephaly, long face, mild ptosis, low nasal bridge, wide or inverted nostrils, mouth open at rest) (35.39).

Diagnosis is made if one of the signs of A category two of the B category or 3 three in the C category is present. (35.39). In plain films osteoporosis or hyperostosis is evident; macrodactyly (Figures. 3b, 3c) clinodactyly, polydactyly and syndactyly are occasionally found. In addition, malformed vertebral bodies and asymmetric cranial vault
thickening can be observed (35). Computed tomography (CT) and MRI shows diffuse asymmetric hypertrophy of soft tissues, muscle and adipose tissue (Figures.3d3f), sometimes associated with lymphatic, capillary and venous malformations, (35). Visceral compromise is less common than musculoskeletal and soft tissue abnormalities, splenomegaly, asymmetric megalencephaly white matter abnormalities and nephromegalia could occur. Cases of pulmonary embolism and pulmonary cystic changes has been described (34, 40, 41).

6 Lipomatous Macrodistrophy
This rare disease is characterized by overgrowth of all mesenchymal elements surrounding the toes or fingers, associated or not to macrodactyly (4244). It is a nonhereditary disease that can manifest in two ways: The first way of presentation is detectable from birth (static form), asymmetry of the fingers of the affected limb, which grows synchronously with the rest of the body is evident. (43). The second way of presentation (progressive form) is detected in older age patients) disproportionate and progressive growth of the affected part is found (45). Generally growth stops at puberty, the lateral aspect of the upper extremity is usually affected (finding described by Golding in 1960) and the medial aspect of the lower extremity (finding described by Feriz 1925) (43.46). It equally affects both genders unilaterally, lower limb compromise is predominant; second and third toes are more often involved (46). The etiology of this disease is unknown, it is suspected that alterations may be linked to changes in uteru with growth factor or fetal circulation changes. Another theory relates to lipomatous degeneration (46, 47). Histology shows proliferation of a fibrous network and fat that normally surrounds the bones, tendons, muscles and nerves, especially in the palmar or plantar aspect of the affected limb, resulting in extra deposit of bone material in the fingers, at the endosteum and peristium with subsequent overgrowth, this results in aesthetic deformity and
functional impairment. (47,48). Median and planter nerve compromise produce compression neuropathy. Plain radiography demonstrates focal macrodactyly secondary to increase in thickness and length of the metacarpals or metatarsals and their phalanges, as well as thickening of the soft tissues that surround them (Figures.4a, 4b) (44). It is common to find degenerative changes in juxta articular regions, probably by an alteration of the normal biomechanics of the limb, which leads to formation of osteophytes, subchondral cysts, joint space narrowing and subluxation, predominantly compromising the the ulnar aspect of (hands) or the lateral aspect of foot) (Figures. 4c, 4d). Soft tissues show normal fat tissue lucency (46,47). CT shows negative attenuation coefficients in tissues surrounding bony structures (44,49). Due to increased fibrofatty tissue on fat saturation sequences, MRI could confirm the lipid nature of the tissue surrounding the affected fingers, and at the same time, could evaluate the bone marrow infiltration of the phalanges, which shows high signal intensity in sequences with T1 and T2 information, and decreased signal intensity on STIR(short time inversion recovery) or FATSAT(fat saturation) sequences . Fibrous tissue has low signal intensity on all sequences (Figures.4e, 4f) (43,50).

Conclusion

Conditions that produce asymmetry in the growth of the extremities are rare entities associated with a variety of clinical and imaging findings, which allow differentiation between them. It is therefore important to recognize particular imaging findings of these group of diseases that are characterized by gigantism, to achieve an accurate diagnosis.

References

3. Zwenneke Flach H, Ginai AZ, Wolter Oosterhuis J. Best cases from the AFIP.


10
11


49. Aisen AM, Martel W, Braunstein EM, McMillin KI, Phillips WA, Kling TF. MRI and
CT evaluation of primary bone and soft tissue tumors. AJR. 1986;146(4):74956.


Figures

Figs. 1a, 1b. Maffucci syndrome. Radiographs of upper limbs in two patients. Maffucci syndrome, popcorn vascular calcifications are evident in the soft tissues. Enchondroma in the fourth and fifth finger in the first patient.

Figs. 2a, 2b. Klippel-Trenaunay-Weber syndrome. Clinical photographs of two patients, the lower limb edema, venous congestion and echymotic vascular markings on the skin. Figs. 2c, 2d. Klippel-Trenaunay-Weber syndrome. Radiography of the foot and right leg venography of a different patient, there is asymmetric enlargement of the first finger and absence of the deep venous system, with a large draining superficial vein. Figs. 2e, 2f, 2g. Klippel-Trenaunay-Weber syndrome. Venography, coronal and axial MR images of a patient with multiple serpintiginos tubular images corresponding to superficial venous dilatations.

14

Fig. 3a. Proteus Syndrome. Clinical photograph of a patient with Proteus syndrome, which shows exaggerated increase in size of the second finger of right hand. Figs. 3b, 3c. Radiographs of hands and feet of another patient who presented macrodactyly of the third finger and third toe of the right foot. Figures. 3d, 3e, 3f. Coronal gradient echo MR images, DP and 3D reconstruction in a patient with amputation of the fourth finger, macrodactyly and subluxation of the distal interphalangeal joint of the third finger, with ulceration of the dorsal region and a fluid collection due to repetitive trauma in that location.

Fig. 4a. Lipomatous Macrodistrophy. Radiographs of patient with macrodactyly, asymmetrical third and fourth fingers of the feet with prominence of the soft tissues. Fig. 4b. Lipomatous macrodistrrophy detected from birth affecting the first finger. Figs. 4 (cd).

Same patient. Significant degenerative changes in the distal interphalangeal
joints:
fusion of the fourth and fifth fingers, surgical absence of phalanges of the second and third fingers. (E) T1 MR images (same patient), shows signal intensity similar to subcutaneous fat in the tissues surrounding macrodactyly of the fourth and fifth toes. signal intensity of the bony structures is slightly lower than in normal bone. Fig. 4f. fat saturation sequence in the same patient, homogeneous decrease of signal intensity of bone marrow and soft tissues confirming its fatty nature.

Contact
Catalina Wilches
Carrera 51 No. 123A53,
apto. 304
Bogotá, Colombia

cwilches30@hotmail.com
Received for evaluation: September 12th, 2009
Accepted for publication: November 18th, 2009
Figs. 1a, 1b. Síndrome de Maffucci. Radiografías de miembros superiores en dos pacientes con síndrome de Maffucci, donde son evidentes las calcificaciones vasculares en forma de palomitas de maíz en los tejidos blandos. Encondromas en los dedos cuarto y quinto en el primer paciente.
Figs. 2a, 2b. Síndrome de Klippel-Trénaunay-Weber. Fotografías clínicas de dos pacientes, en las que se evidencia el edema por congestión venosa del miembro inferior, así como la presencia de marcas vasculares equimóticas en la piel.

Figs. 2c, 2d. Síndrome de Klippel-Trénaunay-Weber. Radiografía de pie y venografía de miembro inferior derecha de otro paciente, donde se observa tumefacción asimétrica de los tejidos blandos del primer dedo y anomalia del sistema venoso profundo, el cual es rodeado por una gran vena.
Fig. 2a, 2f, 2g. Síndrome de Klippel-Trenaunay-Weber. Víneografía e imágenes de RM en los planos coronal y axial, de un paciente con múltiples imágenes tubulares serpentiniformes que corresponden a dilataciones venosas superficiales.

Fig. 3a. Síndrome de Proteus. Fotografía clínica de un paciente con síndrome de Proteus, que demuestra incremento exagerado en el tamaño del segundo dedo de la mano derecha.

Fig. 3b, 3c. Radiografías de manos y pies de otro paciente, quien presenta macrosomia del tercer dedo de la mano y el pie derecho.
Fig. 3d, 3e, 3f. Imágenes coronales de RM en secuencias eco de gradiente, DP y reconstrucción 3D, en un paciente con amputación del cuarto dedo, macrodactilia del tercero y subluxación de la articulación interfalángica dorsal del mismo dedo, con ulceración de la región dorsal y colección líquida por trauma o separación en dicha localización.

Fig. 4a. Macrodistrofia lipomatosa. Radiografías de paciente con macrodistrofia lipomatosa, donde se evidencia macrodactilia asimétrica de los dedos tercero y cuarto de los pies, con prominencia de los tejidos blandos.

Fig. 4b. Macrodistrofia lipomatosa que afecta el primer dedo, lo cual es perceptible desde el nacimiento.
Figs. 4(c–d). El mismo paciente. Importantes cambios de tipo degenerativo en las articulaciones metacarpofalángicas distales: la fusión de los dedos cuarto y quinto, y la ausencia de falanges en los dedos segundo y octavo. (a) Resonancia magnética en secuencia con supresión T1 del mismo paciente, que muestra intensidad de señal similar a la de la grasa subcutánea, en los tejidos que rodean la macrodacilita de los dedos cuarto y quinto. Obsérvese que la intensidad de señal de las estructuras óseas es discretamente menor a la de las muesas normales.
Fig. 4f. Secuencia con saturación grasa en el mismo paciente, donde es posible evidenciar la disminución homogénea de la intensidad de señal de la médula ósea y de los tejidos blandos, lo cual confirma su naturaleza grasa.