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JUVENILE HYALINE FIBROMATOSIS IS AN AUTOSOMAL RECESSIVE GENETIC DISEASE. FOUR CASES REPORT

Aparicio-Rodríguez J Manuel

Genétics Hospital para el Niño Poblano, Estomatology, Benemérita Universidad Autónoma de Puebla

Hurtado-Hernández MdL

Cytogenetics, Hospital para el Niño Poblano

Barrientos-Pérez Margarita

Endocrinology, Hospital para el Niño Poblano

Chatelain-Mercado Sergio

Biotechnology, Universidad Autónoma Metropolitana, México

ABSTRACT

Juvenile hyaline fibromatosis (JHF) is considered a non frequent genetic, autosomic recessive; characterized by connective tissue disorder characterized by multiple subcutaneous nodules, gingival hypertrophy, osteolytic lesions, and joint deformities (contractures). As one of the main clinical symptoms, are multiple subcutaneous nodules, articular contractures, and gingival hypertrophy after 6 months of life. After one year old the subcutaneous nodules appears more frequently among teenagers a great variety of deformations are observed with movement limitations. 70 cases with JHC approximately are reported in the literature.

Keywords: Juvenile hyaline fibromatosis, Anal malformation, Gingival hypertrophy, Osteolitic lesions.

1. INTRODUCCION

The hyaline fibromatosis juvenile (FHJ) is a rare genetic disease of connective tissue, Aldred and Crawford (1987). It is characterized by multiple cutaneous nodules, hypertrophy, gingival, joint contractures and osteolitic injury Kaddoura and Mufarrij (1999); Schaller *et al.* (1997)Schaller M et al, 1997

FHJ is associated to genes that encodes the protein-2 morphogenesis (CMG2 or ANTXR2) located on the long arm of chromosome 4 (4q21.21) Rahman *et al.* (2002) **Figure 22** . FHJ has an autosomal recessive Mendelian Inheritance pattern. The official name of this gene is "anthrax toxin receptor 2." Mutations in the *ANTXR2* gene (also known as the *CMG2* gene) cause FHJ. The *ANTXR2* gene is therefore uncharged of producing a specific protein which is associated with the formation of small blood vessels (capillaries) Antaya *et al.* (2007);Dowling *et al.* (2007);Hanks *et*

al. (2003). It is believed that this particular ANTXR2 protein keeps the normal structure of basement membranes, which are tiny structures that separate and support cells in a great variety of tissues. The main clinical features of the disease are caused by the accumulation of a clear (hyaline) substance in different parts of the body. The nature of this substance is not clear, but its chemical composition is made up of a protein and sugar molecules. It is believed that mutations in the *ANTXR2* gene disrupt the formation of basement membranes, was the hyaline substance leaks through and alters various structure tissues body.

The FHJ was reported for the first time by Murray (1873) injury Kaddoura and Mufarrij (1999). with well-defined clinical manifestations, as mentioned before multiple cutaneous nodules, hypertrophy, gingival, joint contractures and osteolytic bone injury Kaddoura and Mufarrij (1999);Schaller *et al.* (1997);Aldred and Crawford (1987);Bedford *et al.* (1991);Breier *et al.* (1997).

It has been compared with Von Recklinghausen's disease (NF1) Vickochil (1993) and the congenital generalized fibromatosis (CGF). However clinically there are very notorious differences, the nodules begin in late childhood and adulthood, they are sliding, soft texture and is associated with milked coffee stains in NF1. The CGF is characterized by subcutaneous nodules of widespread distribution since new born Venencie *et al.* (1987) It has been also mentioned the importance in the differential diagnosis with infantile systemic hyalinosis syndrome (ISHS), characterized by the presence of papules on the face and perianal region as well as gingival hypertrophy. However contractures joint are not observed. Although at the skin histological level, there is abnormal hyaline deposit in dermis at fibroblasts and also biochemical changes in mucopolysaccharides are found in FHJ, whose etiologic factor is still under study in both cases Mancini *et al.* (1999).

It is also important to look at the Mendelian inheritance pattern, where FHJ has an autosomal recessive trait Katagiri *et al.* (1996);Haddad *et al.* (1997);Adamicov'a *et al.* (1998). Two varieties of FHJ have been described, with a different clinical evolution Campbell and Garrity (1991);Coffin and Dehner (1991). These clinical features are specifically associated to multiple cutaneous nodules, recurrent nodules in the parieto-occipital region and several nodules in the ears. Several nodules of different diameter were observed In the occipital area in the four patients in this study Figure 7. At the neck level several skin alterations by multiple neoformations at the occipital region, on the nape and a level of perinucal, giving an appearance of hyperkeratosis figures 8 and 9. Nodules in the craniofacial area and ears. It can also be seen recurrent nodules at the parieto-occipital region and several nodules in both ears figures 3 and 4 parietal area showed a relapsed nodule at the left ear region and in relation to gingival hypertrophy and severe gingival obstruction was observed. Figures 5 and 6. Joint deformities (contractures) and few movement was observed and all patients showed osteolytic lesions at both, upper and lower limbs, **figures 10 and 11** were nodulation in hand, feet and all the body is progressive and deforming **figures 20 and 21**. Alterations in the skin In the youngest patient starting by multiple nodule formations on face and neck specifically at nasal, perioral and neck region, (hyperkeratosis appearance) due to a serious scar lesion **figures 12 and 13.** Progressive contraction joint by radiographic studies identified osteopenia and severe limitation of mobility. However, all patients in this study have normal intelligence.

2. MATERIALS AND METHODS

XR studies were performed including computer tomography scan **(CTS)** of the skull. The final diagnosis of FHJ was confirmed with histopathology studies in all patients were hyaline deposition in the dermis was associated to, mesenchymal injury with a decrease in cellularity formed by fibroblastic cells with a high hyaline matrix.

karyotype in lymphocytes of peripheral blood of band G was also performed in all the patients with normal chromosome results 46 XY.

3. DISCUSSION

The etiological factor to develop FHJ has then been then associated to the anthrax toxin receptor 2 (ANTXR2) a gene also named CMG2 which is located on the long arm of the chromosome 4, Rahman *et al.* (2002) **Figure 22.** The specific protein derived from this gene, has a cellular basis for producing basement membranes malformations, this alters some tissues which are no able to separate and support the cell structure.

Patients with FHJ, as in this study, have multiple subcutaneous nodules mainly at craniofacial area, which growth slowly and are seen to be progressive causing skull deformities **Figures 16, 17, 18 and 19** , also observed at upper and lower limbs bones and joints **Figure 10, 11 and 21** . All four patients showed gingival hypertrophy, as reported Bedford *et al.* (1991) with a tumor like-type development in mouth **Figures 6, 3 and 13**. There are recurrent nodules in the parieto-occipital region and ears **Figures 1, 2, 3, 4, 5 and 6** with several recurrent nodules of different diameters at the occipital region level with presence of tumor masses, painful and ulcerated areas **Figures 5 and 7**. Hyperkeratosis at the base of the posterior region of the neck, observed in the younger patient approximate 0.2 x 0.2 mm size, **figures 8 and 9.**

The nodules size at the craniofacial area and ears vary approximately from 6 to 8 cm. Joint deformities (contractures) were observed with movement limitation for extension, due to tumor masses formations without bone damage **Figures 10 and 11** to severe damage **Figure 21,**, This bone malformation in hands and feet is progressive and deforming.

All four patients have multiple neo formations on face and neck, specifically at the nasal region, perioral and around the nose region. And one of the patients, at the perianal region neoformations were observed similar to those found at the nasal region.

AP and LAT X-rays apparently was normal with undamaged bones and normal cardiovascular structure **Figures 14 and 15**. A computer tomography scan (CTS) of the skull showed cortico-subcortical atrophy and the superficial growth tumor nodulation is observed at the parietal regions without invasion of bone tissue **figures 16, 17 and 18**, similar to the simple skull x-ray where it can be seen the nodulation at parietal regions without bone tissue invasion **figures 19**. Osteopenia was also diagnosed.

In relation to oral alterations, gingival hypertrophy was confirmed in most of the patients according to the classification of Schaller *et al.* (1997) gingival hypertrophy and small nodules at the base of the posterior region of the neck and the area perianal Schaller *et al.* (1997) are considered two important clinical parameters, which appears in the first month of life.

Surgical resection was held in one of the patients, in this study were two tumors at head level were resected, which improves the aesthetics and function of the patient, according to Kaddoura

and Mufarrij (1999);Nunziata *et al.* (1998) without any complication posterior to the surgery. Radiotherapy is no well accepted for these benign tumors and close monitoring of the behavior of these neoplasias Schmidt *et al.* (1999) should be performed. Surveillance is also important as well as the early diagnosis and early surgical treatment to offer the patient a better quality of life.

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FIGURE LEYENDS

Figures 1 and 2. Recurrent nodule, in the parieto-occipital region and several nodules in the ears can be seen.

Figures 3 and 4. Profile of the patient, is seen relapsing nodule, in the parieto-occipital region and several nodules in the pavilions headphone.

figures 5 and 6. Parietal area where recurrent nodule at the level of the parietal region, pinna and gingival hypertrophy is observed.

Figure 7. Occipital area where there are several recurrent nodules of different diameters at the level of the occipital region.

Figures 8 and 9. Occipital and area at the level of the neck showing alterations in the skin by neo multiple formations in the occipital region, in the nape of the neck and level perinucal, warty appearance with hyperkeratosis.

Figures 10 and 11. There is the beginning of nodulation in hands and feet what is progressive and deforming.

Figures 12 and 13. Alterations in the skin by neo multiple formations faces and neck specifically nasal, perioral region and neck, warty appearance with hyperkeratosis. There is a serious scar lesion.

Figures 14 and 15. AP and LAT apparently normal x-rays.

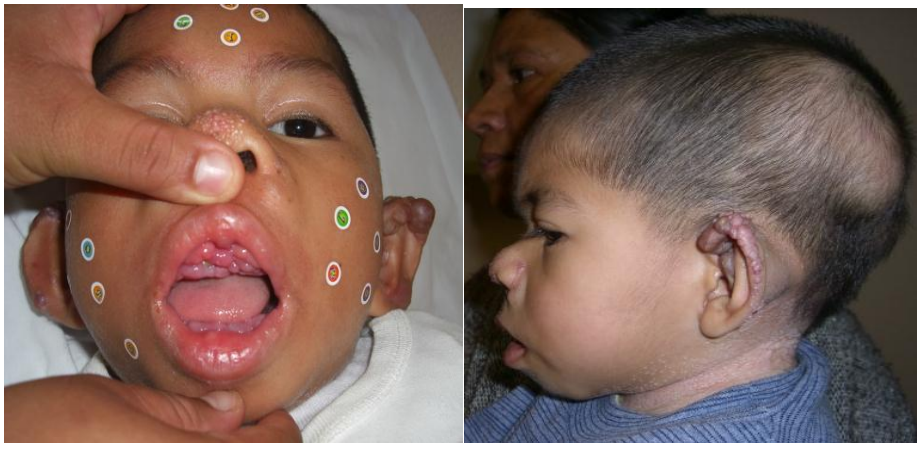
Figures 16 and 17. TAC of skull where cortico-subcortical atrophy is observed and the nodulation can be seen in parietal regions in four different times, without invasion of bone tissue.

Figures 18 and 19. It is a CT and plain X-ray of the skull where cortico-subcortical atrophy is observed, and the nodulation can be seen in parietal regions without invasion of bone tissue.

Figures 20 and 21 Recurrent nodule malformation and general body spread of several nodules is observed in this patient, and severe joint deformities (contractures) are observed with movement limitations.

Figure 22. The *ANTXR2* gene is located on the long (q) arm of chromosome 4 at position 21.21. More precisely, the *ANTXR2* gene is located from base pair 80,822,770 to base pair 80,994,476 on chromosome 4. Reference: http://ghr.nlm.nih.gov/gene/ANTXR2

Figures 1 y 2



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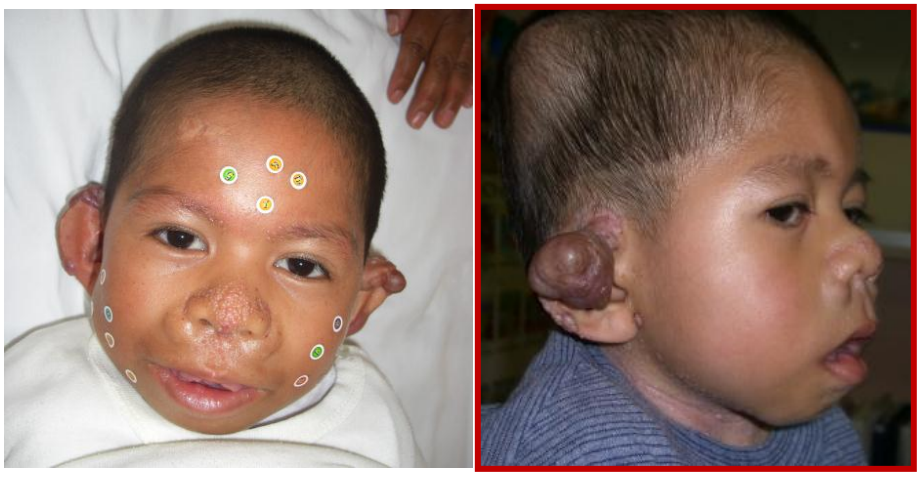

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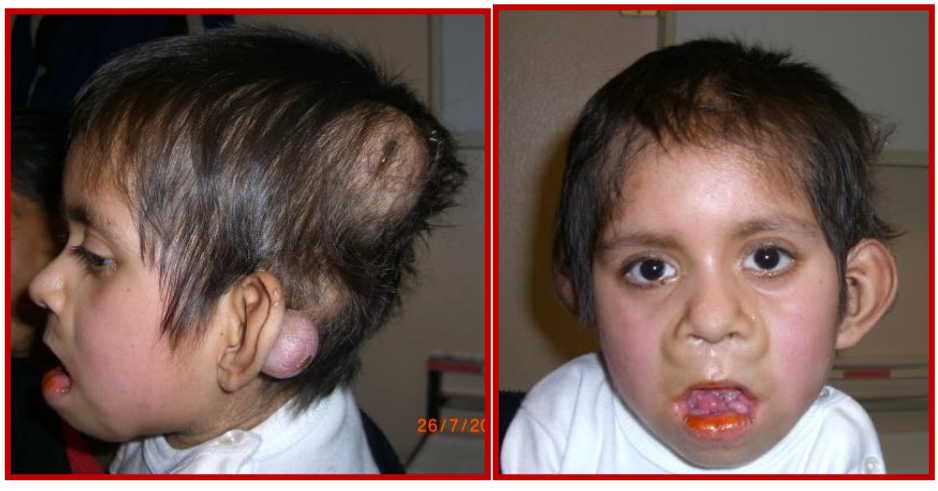

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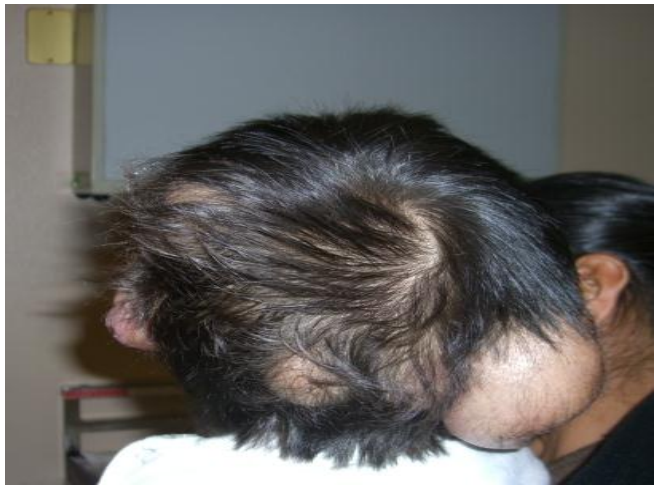

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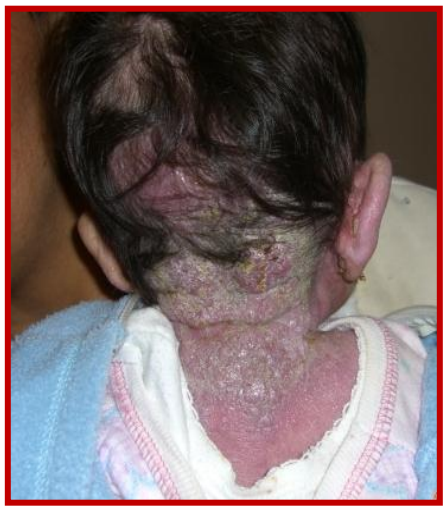

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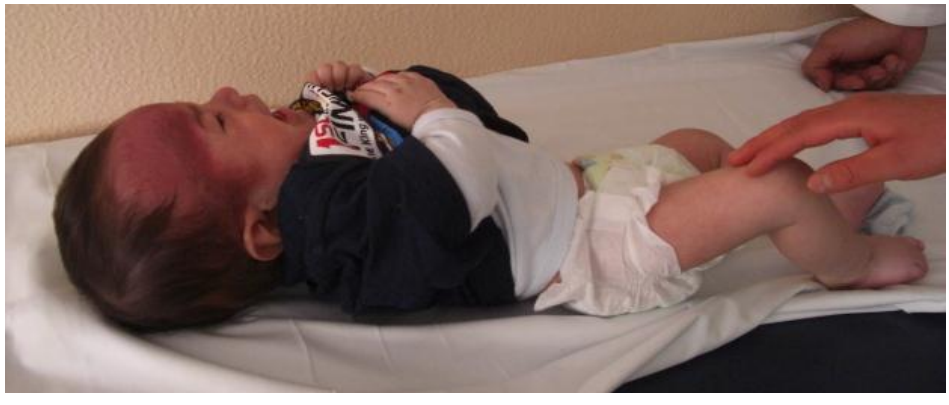

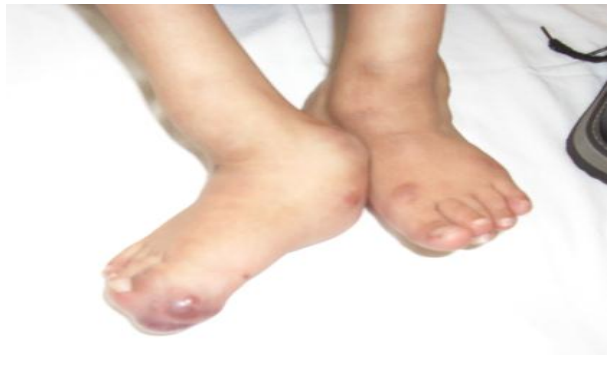

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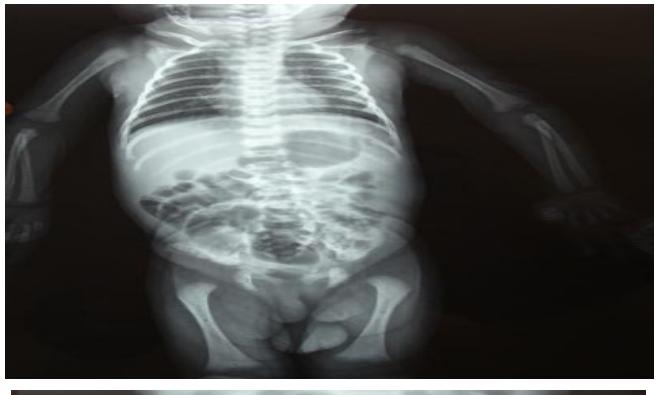

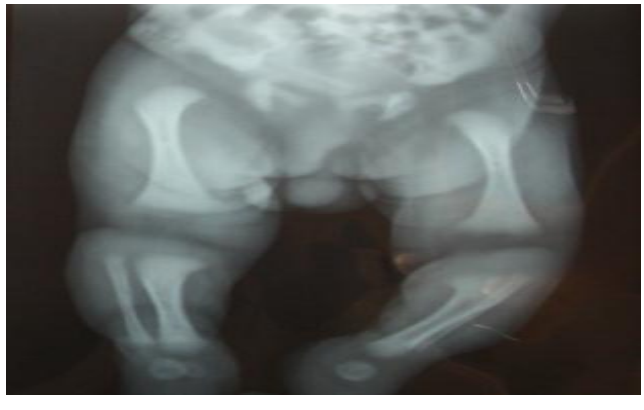

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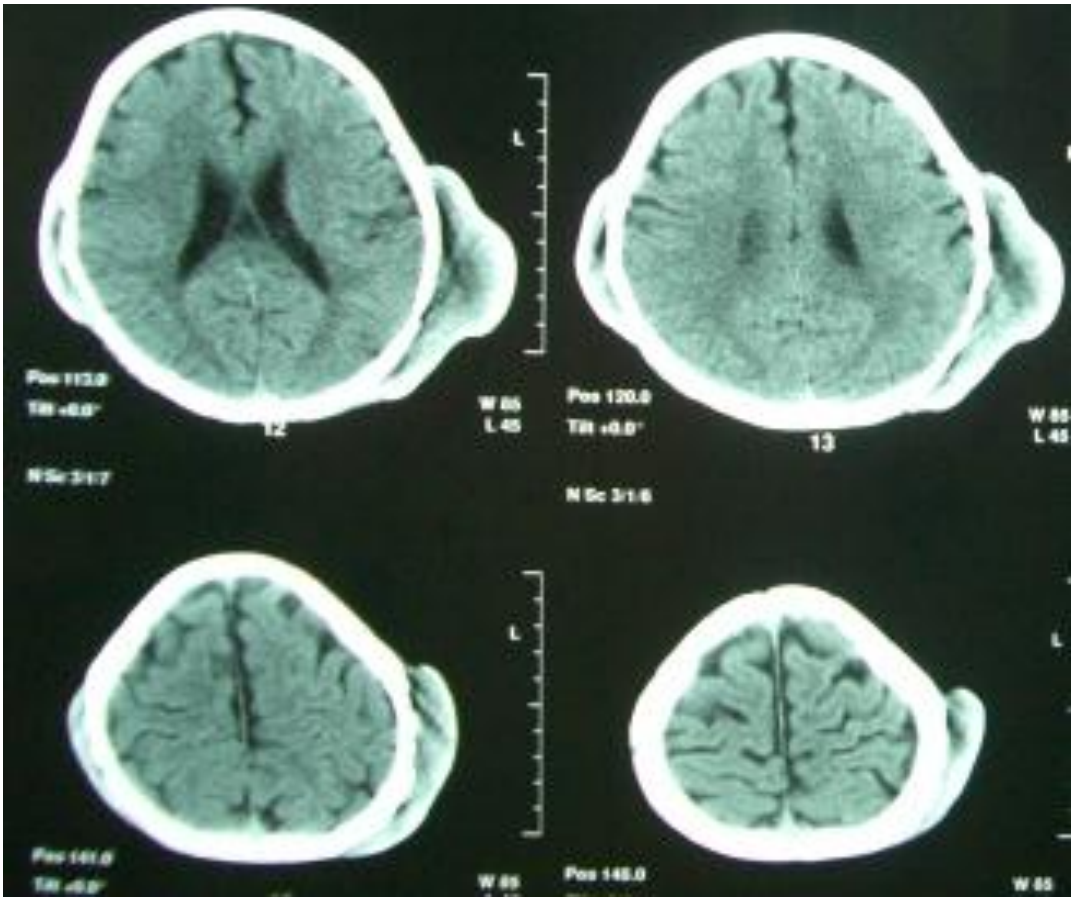

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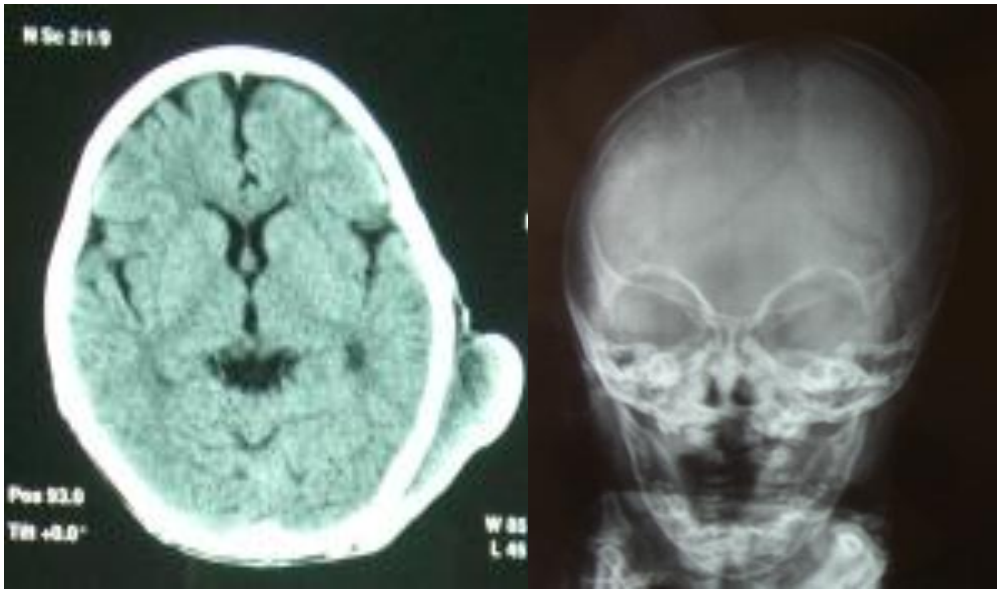

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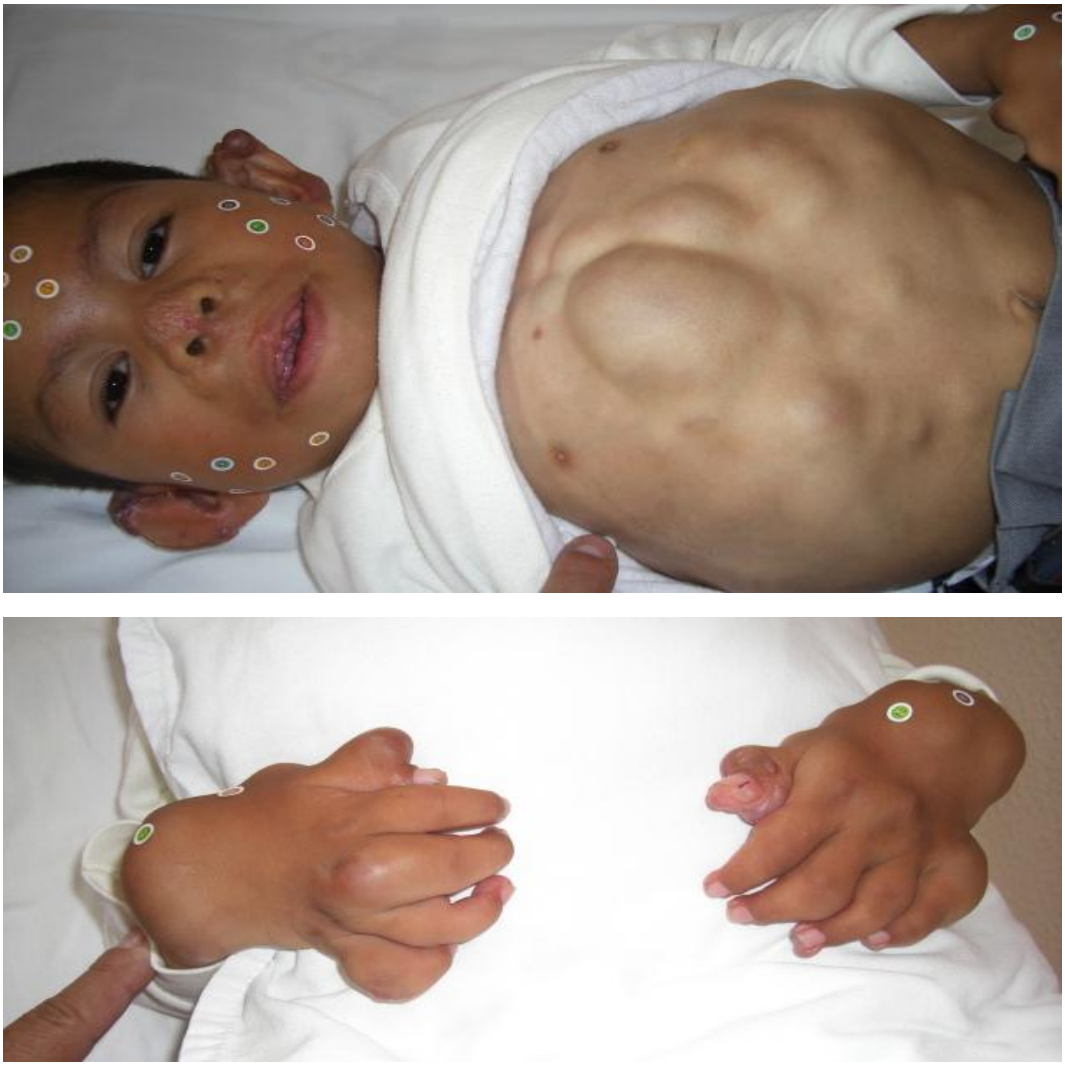

Figure 22.