ACTA PEDIÁTRICA
Acta Pediatr Esp. 2006; 64(11): 562-564

Popliteal pterygium syndrome causing mutation in monochorionic twins

A. Pertierra, G. Sebastiani, M.D. Salvia[1], J. Figueras[1], A. Sánchez [2], X. Carbonell[1]
Departamento de Pediatría. Unidad Integrada Hospital Sant Joan de Déu-Clínic. Esplugues de Llobregat (Barcelona). [1]Departamento de Neonatología. Unidad Integrada Hospital Sant Joan de Déu-Clínic. [2]Departamento de Genética. Hospital Clínic. Barcelona. Spain

Abstract

Popliteal pterygium syndrome (PPS) is a rare disorder of genetic origin. In most cases, it has an autosomal dominant inheritance pattern, with incomplete penetrance and variable expressivity, although *de novo* mutations can exist. The clinical features are typical and they generally affect the ear, nose and throat (ENT) region and the lower extremities. The case reported here involves monochorionic twins with PPS whose relatives had no similar malformations. The genetic study showed a substitution in the gene that encodes interferon regulatory factor-6 (IRF6) (at position c.G251A) in one of the infants.

Keywords

Inheritance, popliteal pterygium syndrome, prenatal ultrasound, twins

Resumen

Título: Síndrome de pterigión poplíteo que produce mutación en gemelos monocoriales

El síndrome de pterigión poplíteo (SPP) es una enfermedad poco frecuente de origen genético. En la mayoría de los casos el patrón de herencia es autosómico dominante, con penetrancia incompleta y expresividad variable, aunque pueden presentarse mutaciones *de novo*. Los defectos son típicos y generalmente afectan al área de ORL y las extremidades inferiores. El caso clínico presenta unos gemelos monocoriales con SPP y sus familiares no presentaban malformaciones similares. El estudio genético mostró una sustitución en el gen que codifica el interferón regulador del factor 6 (IRF6) (posición c.G251A) en uno de los lactantes.

Palabras clave

Herencia, síndrome de pterigión poplíteo, ecografía prenatal, gemelos

Case report

The present case involves monochorionic diamniotic twins resulting from the first pregnancy of non-consanguineous parents with an unremarkable medical history. Cleft lip was diagnosed in one fetus during pregnancy and equinovarus foot was diagnosed in the other. Instrumental delivery took place at 37 weeks of gestation. The umbilical artery pH was normal and the result of the Apgar test was 9/10/10 in both neonates. No cardiopulmonary resuscitation was performed.

In the first twin, physical examination revealed:

- Normal anthropometric parameters (birth weight 2,630 g, length 47 cm, head circumference 32 cm).
- *Face:* Epicanthus, broad nasal root.
- *Ent:* Cleft lip and bilateral cleft palate. Lower lip pits. Intraoral fibrous bands between the jaws (syngnathia) that hindered mouth opening. Low set ears (figure 1).
- *Thorax:* Widely spaced nipples. BACK: Fibrous tracts in right scapula.
- *Genitals*: Clitoral hypertrophy and hypoplasia of the labia majora.
- *Lower limbs:* Fibrous tracts between the region of the ischial tuberosities and the heels (popliteal pterygium). Wide first interdigital space in both feet (figure 2).

- In the second twin, physical examination revealed:
- Normal anthropometric parameters (birth weight 2,240 g, length 45 cm, head circumference 31 cm)
- *Face*: Broad nasal root.
- *ORL:* Absence of uvula. Lower lip pits. Intraoral fibrous bands between the jaws (syngnathia) that hindered mouth opening.
- *Thorax:* Widely spaced nipples.
- *Genitals:* Clitoral hypertrophy and hypoplasia of the labia majora.
- *Lower limbs:* Fibrous tracts between the region of the ischial tuberosities and the heels (popliteal pterygium). Wide first interdigital space in both feet and pyramidal skinfold extending from the base to the tip of the toenails of both big toes. Equinovarus right foot, with syndactyly of 3rd, 4th and 5th toes and nail hypoplasia (figure 3).

Cerebral ultrasound, abdominal ultrasound, echocardiography and ophthalmologic evaluation were normal. Skeletal sur-

Date received: 23/08/06. Date accepted: 21/09/06.

Correspondence: A. Pertierra Cortada. Departament of Paediatrics. Hospital Universitario Sant Joan de Déu. Passeig de Sant Joan de Déu, 2. 08950 Esplugues de Llobregat (Barcelona). E-mail: apertierra@hsjdbcn.org

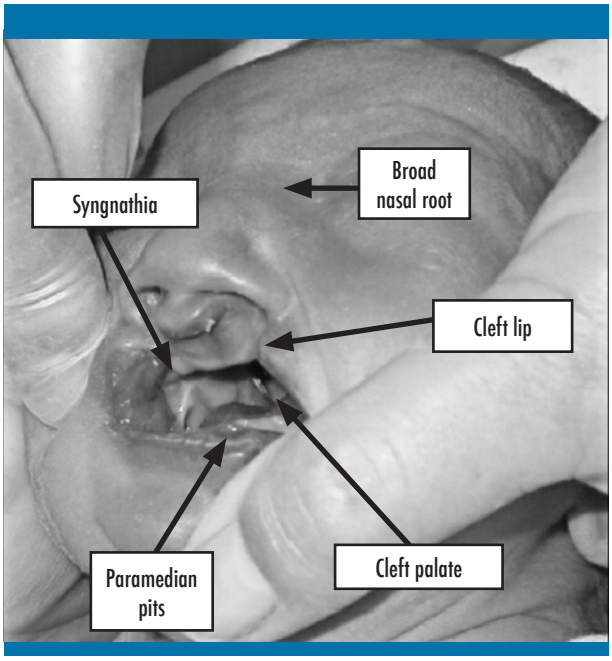

Figure 1. *ENT malformations. First twin*

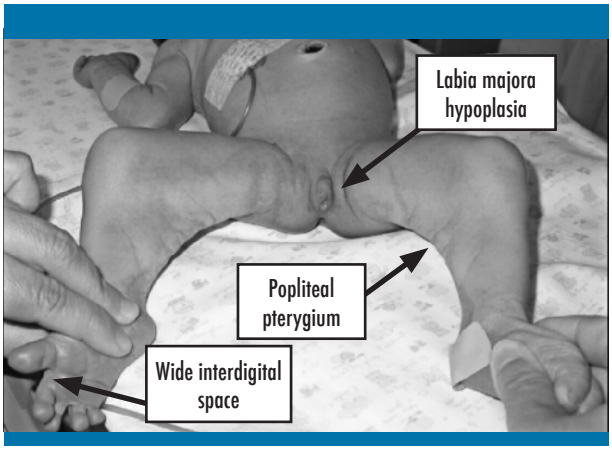

Figure 2. *Genital and lower limb malformations. First twin*

veys revealed maxillary hypoplasia in both neonates and short left tibia and equinovarus right foot in the second twin. Cranial scans showed maxillary hypoplasia in both, accompanied, in the first twin, by a bilateral cleft palate with cleft lip. Both karyotypes were normal (46 XX). The genetic study performed, in only one of the infants, showed a substitution in the gene that encodes interferon regulatory factor-6 (IRF6) (at position c.G251A), which produced an amino acid change (p.Arg84His).

During their hospital stay, the syngnathia was removed in both patients. A palatal prosthesis was implanted in the first twin. Splints were placed in lower extremities in both twins, and they were discharged to await further surgery.

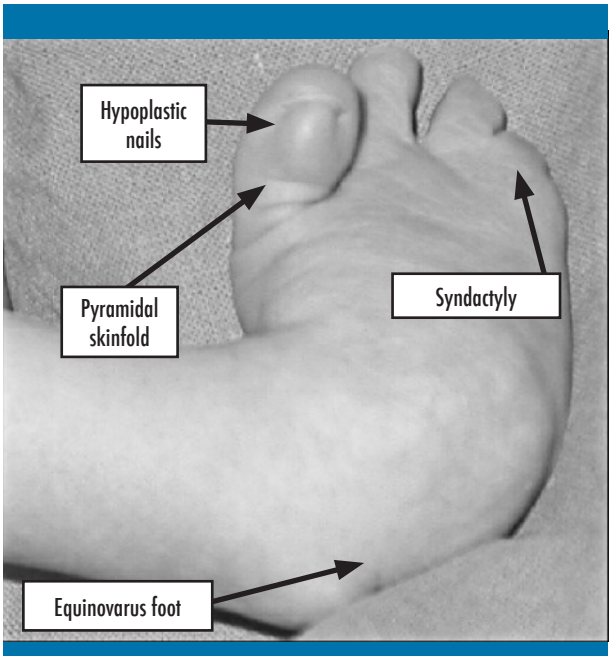

Figure 3. *Foot malformations. Second twin*

Discussion

The diagnosis of PPS is usually based on the clinical features alone, but it is well known that a nonsense mutation in the gene encoding IRF6 at chromosome 1q32-q41 has been implicated in the etiology of this syndrome. It seems to lead to an imbalance between mesodermal migration and ectodermic proliferation.[1-4] In our case, it was possible to demonstrate, on the basis of genetic evidence, the existence of an arginine-to-histidine missense mutation in the IRF6 gene using a direct sequencing method. The Arg84 residue is one of four residues that make critical contacts with the core sequence, GAAA, and it is essential for the DNA binding function of IRF6. In the literature, this mutation is reported to cause PPS.[1,2]

It has been proved that alterations in the same gene can develop the Van der Woude syndrome and that, due to this fact, they can be considered as allelic syndromes.[1-7] In Van der Woude syndrome, the orofacial anomalies are predominant and similar to the phenotypic features associated with PPS in that anatomical region, but alterations in other parts of the body are very rare. It is uncertain whether the extraoral manifestations are additional unassociated anomalies or infrequently expressed aspects of Van der Woude syndrome.[6,7] Autosomal dominant inheritance is generally suspected, but sporadic cases also exist, as seems to be that of our patients.[2,3,8] Moreover, it exhibits incomplete penetrance and variable expressivity and this may explain the phenotypic differences between our twins.[2,3,8] The approximate incidence is 1/300,000 live births. Since Trelat reported this syndrome for the first in 1869, fewer than one hundred cases have been documented.[3,4]

The most frequent signs are:[9]

- ENT region: Cleft lip/palate/uvula (these are present in most of the patients; 93% have cleft palate and 58%, cleft lip). Paramedian pits in lower lip (46%) that usually form canals.[4] In the labial mucosa, the fistula have bifurcated tracts, ending blindly under the skin. The pits are usually asymptomatic, but there can be continuous or intermittent salivary drainage.[6,7]
- Intraoral fibrous bands between the jaws (syngnathia, 40%) that secure them and impede mouth opening.[2] Frenulum is sometimes is present.
- Popliteal pterygium (58%): Fibrous tracts between the region of the ischial tuberosities and the heels, with a fibrous cord that runs along the free edge of the pterygium.[4] An intercrural pterygium is sometimes associated, producing genital distortion. Surgical resection of the pterygium, which reduces the mobility of the patient, is often necessary to relieve the resulting flexion deformity of the lower limb. The position and length of the popliteal artery and the peroneal nerve are a limiting factor in surgical correction of this deformity because they may be situated in the free edge of this fibrous tract.[3,8,10-12] Magnetic resonance (MR) imaging can provide useful information concerning the position of these structures and, therefore, prevent their damage and possible sequelae.[11] The MR image of a popliteal pterygium is that of a band of abnormal tissue extending from the ischium to the calcaneus. Signal characteristics of fibrous tissue often associated with anomalous muscle can be seen along portions of these tracts.
- Digital anomalies: Syndactyly predominantly of toes (50%; syndactyly of the fingers is rare).[2,4] The presence of a pyramidal skinfold extending from the base to the tip of the nails of the first toe is considered by some authors to be a pathognomonic sign, but it only appears in 33% of cases.[2,13] Equinovarus feet, valgus feet and crab clamp feet can be present. Nail anomalies (33%).[4]
- Genital anomalies (37%): Bifid scrotum and cryptorchidism are the rule in males and hypoplasia of the labia majora, vagina and/or uterus in females.[2,4]
- Skeletal anomalies (not very frequent): Bifid or absent patella, fusion of interphalangeal joints, tibial hypoplasia, posterior dislocation of fibula, spina bifida occulta, bifid ribs, scoliosis and lordosis.

The prognosis is good, although ambulation is usually difficult; the degree of this limitation varies greatly and can be important in nearly 30% of the patients.[9] PPS may be associated with visual problems because of eyelid malformations (ankyloblepharon) and speech problems because of limited mouth opening.[2,9] It is important to point out that mental development of these patients is strictly normal.[3,9] Genetic counseling should be provided for subsequent pregnancies and, although prenatal ultrasound may detect this syndrome, the diagnosis is difficult if there is no family history.

The interest of these cases lies in the documentation of a rare syndrome that had not previously been reported in twins with no family history of the physical anomalies characteristic of PPS. Genetic alteration was present in one of the infants (we assume that this alteration was present in the other infant too, although no genetic study was performed because they were monochorionic twins). This situation leads us to consider that the cause was a *de novo* mutation. It is important to point out the differences between the clinical features of the two children, a circumstance that supports the hypothesis of a variable expressivity. Therefore, it is important to remember this syndrome in cases of compatible congenital anomalies detected by prenatal ultrasound in twins, although there is no family history of malformations.

References

1. Kondo S, Schutte BC, Richardson RJ, et al. Mutations in IRF6 cause Van der Woude and popliteal pterygium syndromes. Nat Genet. 2002; 32: 285-289.
2. OMIM. On line Mendelian Inheritance in Man. Johns Hopkins University. http: //www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM.
3. Sasidharan CK, Ravi KV. Popliteal pterygium syndrome with unusual features. Indian J Pediatr. 2004; 71: 269-270.
4. Lees MM, Winter RM, Malcolm S, et al. Popliteal pterygium syndrome; a clinical study of three families and report of linkage to the Van der Woude syndrome locus on 1q32. J Med Gene. 1999; 36: 888-892.
5. Shotelersuk V, Srichomthong C, Yoshiura K, et al. A novel mutation, 1234del(C), of the IRF6 in a Thai family with Van der Woude syndrome. Int J Mol Med. 2003; 11: 505-507.
6. Rizos M, Spyropoulos MN. Van der Woude syndrome: a review. Cardinal signs, epidemiology, associated features, differential diagnosis, expressivity, genetic counselling and treatment. Eur J Orthod. 2004; 26: 17-24.
7. Conners GP. Van der Woude syndrome. Last update: 14 may 2003. http: //www.emedicine.com/ped/topic2753.htm
8. Oppenheim WL, Larson KR, Mc Nabb MB, et al. Popliteal pterygium syndrome: an orthopaedic perspective. J Pediatr Orthop 1990; 10: 58-64.
9. Cruz M, Bosh J. Síndromes con alteración destacada en extremidades: Síndrome del Pterigium Poplíteo. En: Atlas de síndromes pediátricos. Barcelona: Espaxs, 1998.
10. Parikh SN, Crawford AH, Do TT, Roy DR. Popliteal pterygium syndrome: implications for orthopaedic management. J Pediatr Orthop B. 2004; 13: 197-201.
11. Donnelly LF, Emery KH, Do TT. MR imaging of popliteal pterygium syndrome in pediatric patients. AJR Am J Roentgenol. 2002; 178: 1.281-1.284.
12. Maral T, Tuncali D, Ozgur F, et al. A case of popliteal pterygium treated along with nerve expansion. Plast Reconstr Surg. 1997; 100: 91-95.
13. Gorlin RJ, Cohen MM, Levin LS. Popliteal pterygium syndrome (facio-genito-popliteal syndrome). Syndromes of the Head and Neck. Oxford University Press, 1990; 629-631.