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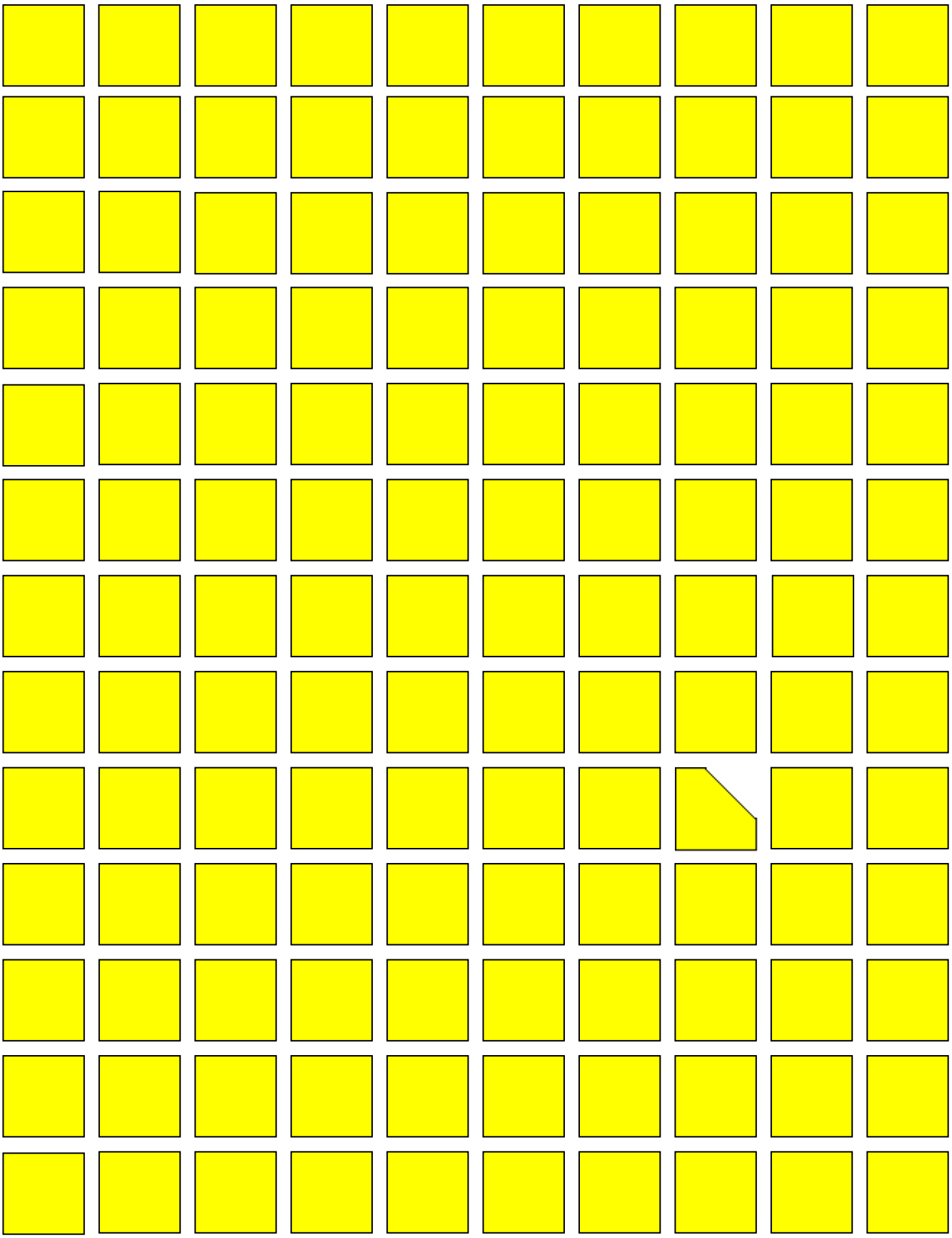

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D O C U M E N T O F I N A L

XLVI REUNION ANUAL DEL ESTUDIO COLABORATIVO LATINOAMERICANO DE MALFORMACIONES CONGENITAS

BÚZIOS/RJ

02 a 07 de noviembre de 2014

Versión Electrónica

Junio 2014

Rio deJaneiro

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HOS= **Klin**: genética clínica; **Koo**: Coordenação, **Kon**: Convidado; resto: código eclamc do hospital.

AGRADECIMIENTOS

Gracias a las instituciones:

CAPES: PAEP - Processo nº 23038.005950/2014-11

CNPq: ARC - Processo nº 440742/2014-5

Laboratório de Epidemiologia de Malformações Congênitas: POM/2014

INCT - INAGEMP
Instituto Nacional de Genética Médica Populacional
Processo 573993/2008-4

RAE46-2014
46th REUNIÃO ANUAL DO ECLAMC
2-7 DE NOVEMBRO DE 2014
BUZIOS, RJ
Assunto Central: REDES de REDES e OSTEO.CONDRO.DISPLASIAS

Domingo 2

15:00-20:00 Chegadas
21:00-22:00 Jantar e apresentações

2a Feira 3

08:00-08:30 Conferência-1: Rede de Redes-Introdução (Eduardo E Castilla)
08:00-10:30 Oficina-1: Redes, Visão Preliminar (Juan A Gilli)
11:00-12:00 Revisão da Teoria das Redes, Parte-1: (Gilli e Castilla)
12:00-13:00 Conferência-2: Displasias Esqueléticas: Patogênesis e classificação (Denise Cavalcanti)
15:00-18:30 Consultório: Casos OCD (Osteo-Condro-Displasias) 1 a 12 (D.Cavalcanti)

3ª Feira 4

08:00-08:30 Conferência-3: Diagnóstico y Manejo Neonatal de Malformaciones (Julio Nazer-Herrera)
08:30-10:30 Consultório: Casos de Osteo-Condro-Displasias 13 a 20 (D.Cavalcanti)
11:00-12:00 Consultório: Casos Interessantes 1 a 4 (F Vargas)
12:00-13:00 Conferência-4: What Patients Have Taught Me (J Clayton-Smith)
15:00-16:00 Consultório: Casos Interessantes 5 a 8 (F Vargas)
16:30-18:30 Consultório: Casos Interessantes 9 a 16 (F Vargas)
22:00-23:00 Assembleia das Associações ECLAMC

4a Feira 5

08:00-08:30 Conferência-5: Espectro de la Fetopatia Alcohólica (M del Campo)
08:30-10:30 Oficina-2: Redes, Visão Depurada (Juan A Gilli)
11:00-12:30 Revisão da Teoria das Redes, Parte-2: (Gilli e Castilla)
12:30-13:00 Conferência-6: Le Coesinopatie: Geni E Sindromi Correlate (G Scarano)
15:00-20:00 Tarde livre

5ª Feira 6

08:00-08:30 Conferência-7 : ATLAS-ECLAMC de Malformações (I Zarante)
08:30-10:30 Oficina-3: Assuntos Operacionais do ECLAMC: discussão aberta
11:00-12:00 Oficina-4: Integração das Redes, Teoria e Prática (E Castilla e JA Gilli)
12:00-13:00 Conferência-8: Next Generation Sequence in Osteo-Chondro-Dysplasias (Pablo Lapunzina)
15:00-16:00 Conferência-9: Displasias esqueléticas e fissuras (Antônio Richieri-Costa)
16:30-17:30 Conferência-10: Os Tempos na Vigilância de Defeitos Congênitos (Eduardo E Castilla)
17:30-18:30 Conferência de Encerramento: Gordos e Cilios (José Carlos Cabral de Almeida)

6a Feira 7

07:00-08:00 Café da manhã
10:00 Ônibus para o Rio de Janeiro

CASOS CLÍNICOS

No	Médico	País	Resumo	OBS
01	Luís Madeira	BRA	Waardenburg	
02	Juan Llerena Jr	BRA	Hypophosphatasia	OCD
03	Horacio Aiello	ARG	Sirenomelia	
04	Raquel Toja Couto	BRA	MMIH Syndrome	
05	Juan Llerena Jr	BRA	Del22q11.2/dup22q11.2	
06	Gloria Porras Hurtado	COL	Smith-Magenis (?)	
07	Jair Tenorio	SPA	Laurin-Sandrow	
08	Luiza Mariath	BRA	Bowed femorae	OCD
09	Mariana Aracena	CHI	Spondylo-carpal-tarsal synostosis	OCD
10	Mariana Aracena	CHI	Stuve-Wiedemann	OCD
11	Guilherme Oliveira	BRA	Opsismodysplasia	OCD
12	Guilherme Oliveira	BRA	Achondrogenesis II	OCD
13	Aurora Canessa	CHI	Limb-body-wall	
14	Cecília Mellado	CHI	OAV spectrum	
15	Mariana Aracena	CHI	SED congênita	OCD
16	Rosa Pardo	CHI	Chondromatosis	OCD
17	Teresa Aravena	CHI	Microphthalmia and...(?)	
18	Teresa Aravena	CHI	Hisrchprung and	OCD
19	Cecília Mellado	CHI	Paternal UPD14 (?)	OCD
20	Teresa Aravena	CHI	Cutaneous somatic mosaicism	
21	Mariana Aracena	CHI	ASD + polyd + larynx	
22	Fernando Vargas	BRA	Mesomelic dysplasia (?)	OCD
23	Silvia Castillo	CHI	Hand-foot-genital syndrome	
24	Braulio Jatar	VEN	Bartsocas-Papas	
25	Braulio Jatar	VEN	Bartsocas-Papas	
26	Braulio Jatar	VEN	Bartsocas-Papas	
27	Mª Teresa Sanseverino	BRA	Skeletal dysplasia	OCD

Case 1 - A05 – Madeira → WAARDENBURG

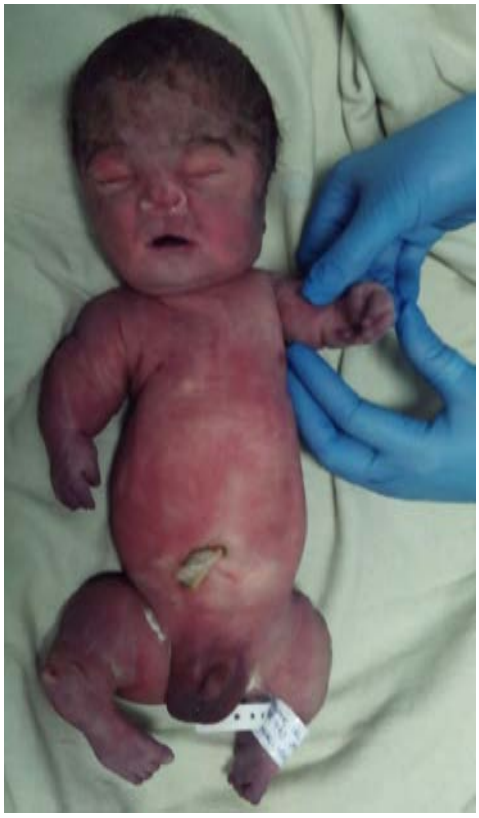
DOB: 28.1.2014. Male newborn, product of first pregnancy of a young and non consanguineous couple. No reports of malformation in the family. Born at term, weight 3210g, length 53cm, head circumference 40cm, Apgar 9/9. Findings at birth: macrocephaly, area of poliosis in the frontal region, stridor, and tumor on the back of the head. CT scan: macrocrania; Dandy-Walker malformation; meningoencephalocele; agenesis of corpus callosum. Laryngoscopy: malacia in the epiglottis. Karyotype: 46, XY. Fundoscopy, echocardiography and abdominal ultrasound: normal. Audiometry (BERA): severe hearing loss on the right and moderate on the left ear. 2nd day of life surgery for correction of meningoencefolocele; 2nd month of life was placed ventriculoperitoneal shunt. Evolved with global growth and developmental delay, isochoric and photo reactive pupils with impaired ocular motility, generalized hypotonia with grade 3 muscle strength and increased reflexes. At 7 months had seizures, easily controlled with phenobarbital. Currently at 8 months, polyosis is fading but maintains the global deficit of development.
Impression: malformation of CNS, polyosis and congenital deafness, suggesting Waardenburg like syndrome plus CNS malformation.

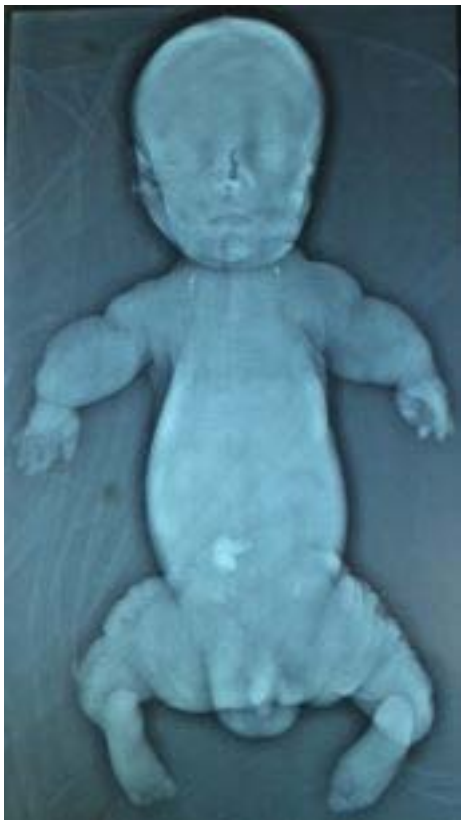
Se aceptó el diagnóstico de síndrome de Waardenburg (PAX3) propuesto. Como diagnóstico diferencial se mencionó al síndrome de Walker-Warburg por presentar encefalocele.

Case 2 – Llerena → HYPOPHOSPHATASIA

DOB: 13.10.2014. Newborn 33 weeks of gestational age, weight 1,750g. Product of the second pregnancy of consanguineous couple (first cousins); mother 25 years old; father 32 years old. The first conception also had a skeletal dysplasia which eventually was given the diagnosis of tanatophoric dysplasia. No other reports of malformation in the family. Prenatal Ultrasonography showed significant shortening of the long bones associated with reduced thoracic diameter suggesting skeletal dysplasia with a lethal prognosis. Cloverleaf skull deformity.

Impression: hypophosphatasia (?)



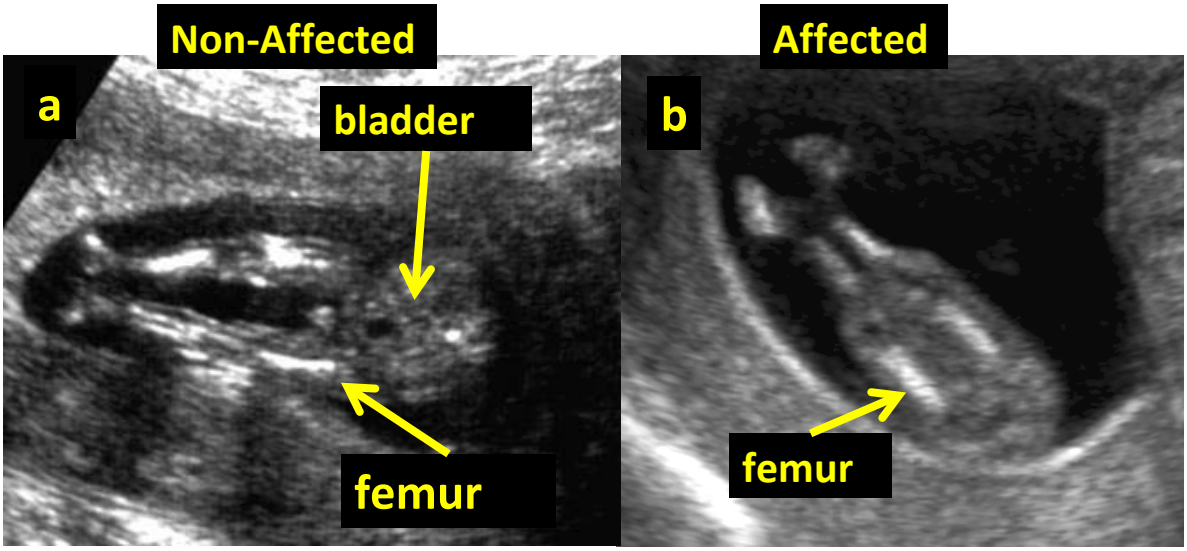


Se aceptó el diagnóstico propuesto de hipofosfatasia (ALPL). Por ser una entidad muy rara, se mencionó la necesidad de conocer los apellidos de los padres y el lugar de origen de los abuelos.

Case 3 - H. Aiello → Sirenomelia

A 37 year-old pregnant woman, G3P2, was referred to our Unit from Monte Grande (Bs.As.) at 12 week gestation in order to perform a 1st trimester screening for chromosome anomalies. It was a non-consanguineous couple with 2 sons. The patient was healthy without medical antecedents and did not take any medication. Her husband has hypoplastic right kidney and one the sons has a right duplex collecting system. Prenatal diagnosis: Transabdominal sonography revealed a fetus with CRL of 55 mm (12w+0d). Nuchal translucency (1.5 mm) was within normal limits. The lower limbs appeared to be fused in a single leg. Furthermore, the fetal bladder was not visible, kidneys were difficult to assess, and the cord had a single umbilical artery. A chorionic villus sampling was performed and showed a normal male karyotype 46,XY. At the next visit at 16 weeks the amniotic fluid was absent. At 18 weeks intrauterine fetal death was detected by ultrasound. Necropsy: The stillborn had Potter's face, fused lower limbs, absence of external genitalia, and absence of anus. Postmortem radiography showed sacral agenesis, and fused lower extremities with paired femurs, tibias, and fibulae. Two feet were evident and the fusion appeared to affect only soft tissues (Sirenomelia type I). Visceral malformations included bilateral lung hypoplasia, ventricular septal defect, blinded rectum, left renal agenesis with hypoplastic right kidney, rudimentary bladder, urethral agenesis, and two vessel cord. Previous cases of sirenomelia at our Unit included 3 fetuses with prenatal ultrasound scans during 2nd and 3rd trimester. All of them have male karyotypes and due to severe oligohydramnios, diagnosis of sirenomelia was performed after birth.

Impression: sirenomelia diagnosed in a 12 week pregnancy. Father with unilateral kidney hypoplasia.



Diagnóstico prenatal de sirenomelia y antecedentes familiares de malformaciones renales. A pesar de que la mayoría de los casos son esporádicos, se mencionó que hay reportes de recurrencia en la literatura, también de componentes Vater en familiares de casos con sirenomelia. Además, se comentó la necesidad del monitoreo ecográfico desde el primer trimestre de la gestación, ya que más tarde el an/oligoamnios en general impide el diagnóstico.

Case 4 – Raquel → MMIH SYNDROME

DOB: 7.2.14. Newborn, 33 weeks of gestational age, BW 4,000g. Product of the fifth pregnancy of non-consanguineous couple; mother 32 years old; father 46 years old. No reports of malformations in the family. Prenatal ultrasound: severe adramnia, intrauterine growth restriction, mild ascites, and anechoic image with regular contours in the fetal abdomen compatible with megacystis. Fetal karyotype: 46,XY, inv(9) (p12;q13). Necropsy: Male with Potter facies, pulmonary hypoplasia, microcolon, very large bladder, renal hypoplasia on the right side, clubfeet, dilated distal ureters, imperforate anus, rectal atresia finishing in the bladder wall, abdominal testicles.

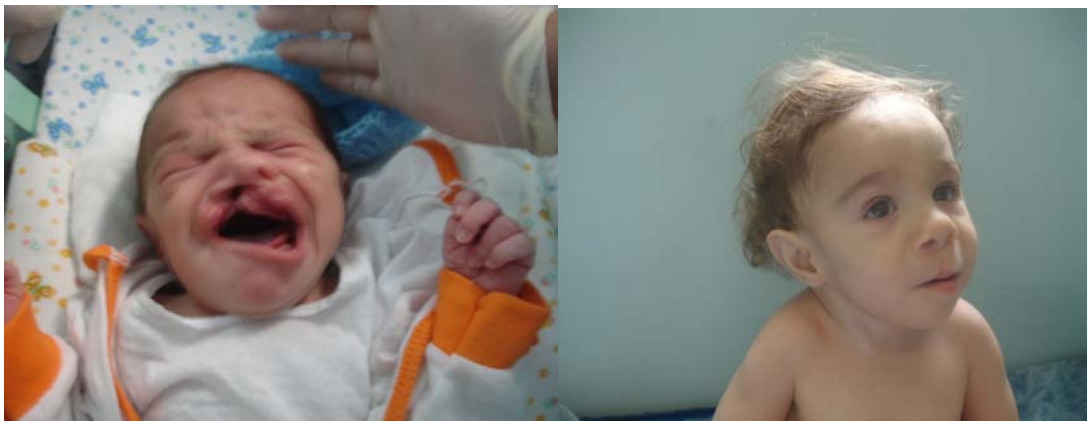
Impression: Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome (MMIH)

Los datos clínicos y de autopsia (macroscópicos) eran compatibles con el diagnóstico propuesto – Megacystis-microcolon-intestinal hypoperistalsis. Se sugirió realizar histología para confirmar las anomalías del músculo liso (vacuolización y degeneración) y estudiar al gen (ACTG2). Los heterocigotas pueden tener colon irritable.

Case 5 – A05 – J. Llerena → del22q11.2/dup22q11.2

DOB: 19.3.2010. Male, non-consanguineous parents (Gesta I; Para I, father 32, mother 28). BW 2,420 g, small for gestational age. Prenatal ultrasound: left labial cleft, left kidney agenesis and single umbilical artery. At birth, presence of left asymmetric crying face was obvious; complete left labial and palate cleft; congenital cardiopathy (ASD, VSD, pulmonary hypertension), and a balanic hypospadia was present. Left kydney agenesis was confirmed. Clinical follow-up at 17 months of age revealed a young boy with weight and length below 3rd centile; no developmental delay was noted; and no obvious dysmorphies were present. Karyotype: 46,XY.ish TUPLE1x2. This case was presented and discussed at RAE43 and no diagnosis was proposed at the time. Molecular cytogenetic follow up of the case revealed an abnormal MLPA result with at least 17kb duplication of PRODH3+ gene (exons 1 & 3) within the 22q11.2 region. Cases of del 22q11.2 and dup22q11.2 have been reported in the literature sharing some common clinical features described in the VeloCardioFacial syndrome/phenotype. As a consequence of genomic abnormal recombination involving one of the 4 rich low copy repeats (LCR) blocks within the 22q11.2 region different derivative chromosomes (regions) can be expected. In due time, CGH-array will confirm these results.

Impression: del 22q11.2 / dup22q11.2.

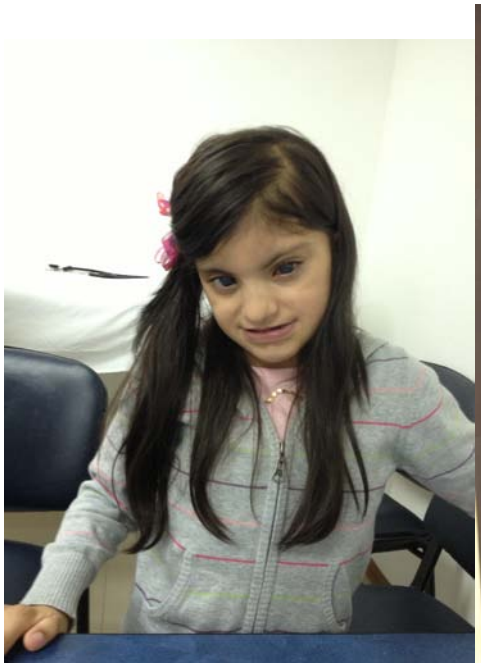


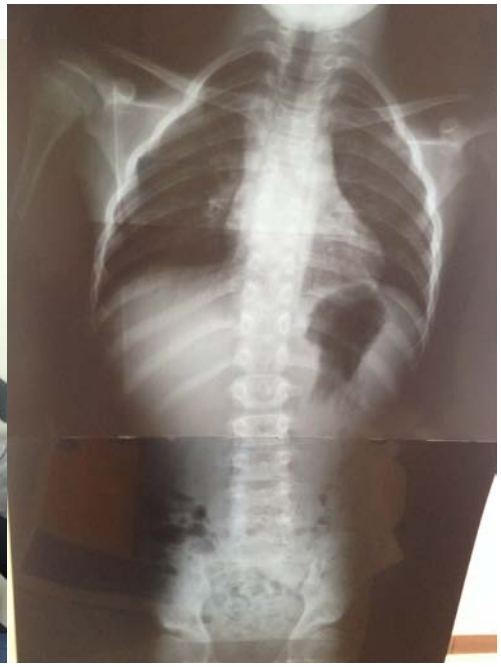
Este caso se había presentado en la RAE 43. Ahora se agregó el diagnóstico: duplicación 22q11.2. Se discutió si la asimetría facial se debía a un defecto del músculo depresor de la boca o a una parálisis del séptimo par craneal. Las cejas altas son un signo orientador de duplicación 22q. Se recomendó realizar MLPA y no FISH para evitar perder entre un 8 y un 10% de los casos positivos.

Case 6 – Hurtado → SMITH-MAGENIS (?)

Female patient, 10 years old, polyhydramnios. At birth: bilateral congenital glaucoma, cleft palate, absence of phalanges in hands, hipoplasia of thenar and hypothenar regions. Hypotonia, hypernasal voice, left torticollis. Flat feet. Radiographs show scoliosis, increased acetabular angle, bilateral coxa valga. Brain MR: Dandy-Walker anomaly, colpocephaly. Echocardiogram: supravalvular pulmonary stenosis, mild tricuspidinsufficiency. Pelvic ultrasound: vesicoureteral reflux, hydronephrosis right kidney, bilateral duplication of renal pelvis, uterus and ovaries not visualized. Bilateral hipoacusia. Ophthalmology: strabismus, bilateral glaucoma, Haab`s estriae in the cornea, corrected with Ahmed. Child developed hyperactive behaviour, treated with risperidone and methylphenidate. Karyotype 46,XX.

Impression: Smith-Magenis (?), Pitt-Roger-Danks (?)

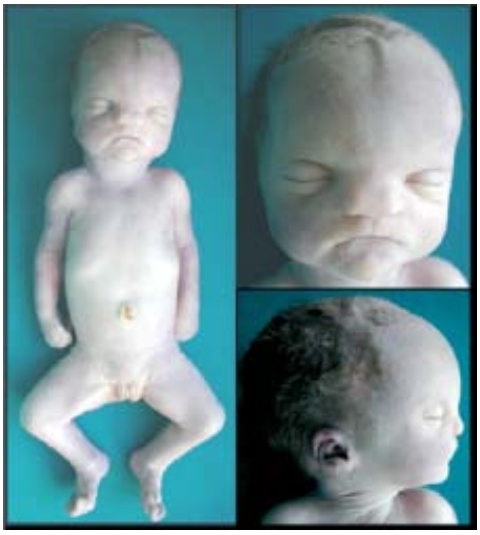


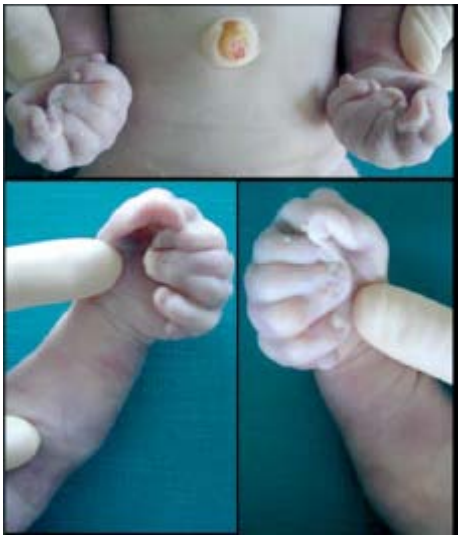


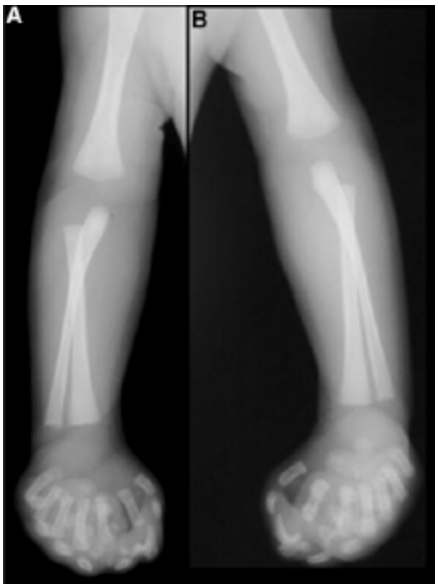
Sin diagnóstico. Tiene cariotipo 46,XX normal pero se mencionó que tiene aspecto de anomalía cromosómica y se sugirió realizar array y descartar 4p- y deleción en 6p25.

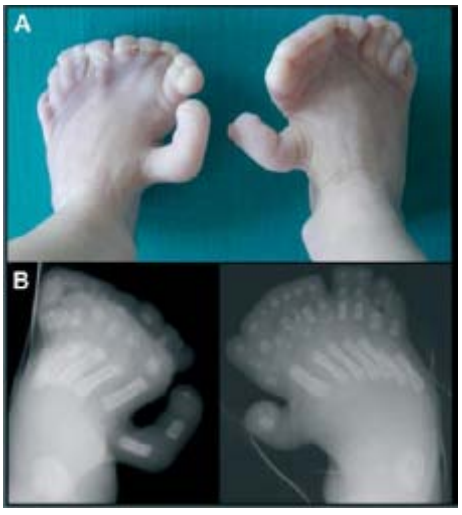
Case 7 – J. Tenorio Castaño → LAURIN-SANDROW

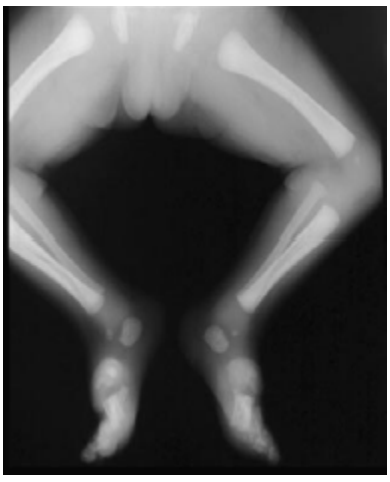
We report a patient with clinical features of Laurin-Sandrow Syndrome (OMIM #135750). These features include hypertelorism, flat nose with grooved collumella, “V” shaded mouth with thin lips, 7 well-recognized and fused digits and 1 additional postaxial bilateral appendix on each hand. The right and left feet had 12 and 11 toes respectively, the 4 external ones were recognizable, and the rest were fused in a uniform mass but with independent nails. Karyotype was normal 46XX and no other molecular screening was performed in 5 years. After that, cGH-array and SNP-array were performed in order to detect the molecular defect in the patient and we found a deletion that either encompasses a candidate gene for the syndrome or changes the initial clinical diagnosis.
Impression: Laurin-Sandrow syndrome.









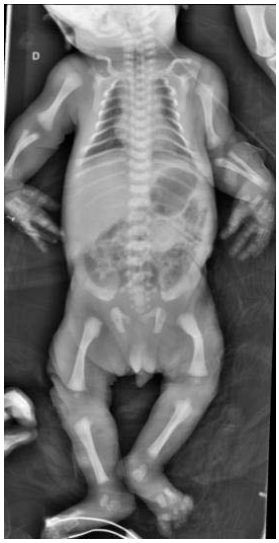


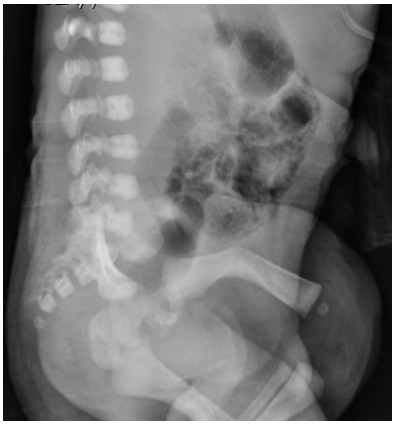
Se descartó el síndrome de Laurin Sandrow propuesto por la polidactilia que en este paciente no es en espejo, tipica del SLS. Se detectó una deleción del gen GLI3 y se sugirió como diagnóstico probable al síndrome de Greig.

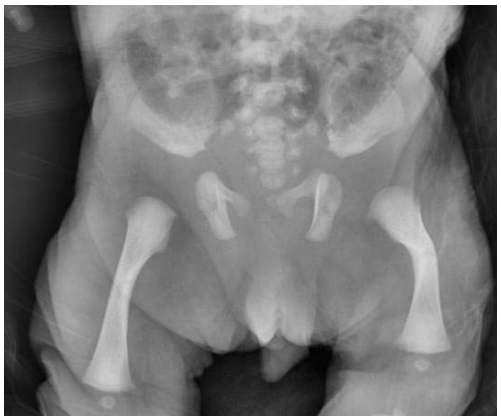
Case 8 – L. M. Mariath → BOWED FEMORAE

DOB: 14.6.2014. Male, delivered by C-section, at 35+5 weeks gestation, with a BW 2,870g; BL 46 cm. The patient is the 4th child of a 31 y-o mother, non-consanguineous parents. Family history negative for birth defects. No prenatal infections, exposure to drugs during pregnancy. The first radiological investigation, performed shortly after birth, indicated the presence of bowed femur and humerus, bell shaped thorax, double ossification centers in the body of the calcaneus, and brachycephaly (figures 1-5). The initial analysis did not indicate a conclusive diagnosis. Three months after the birth, the patient was evaluated at outpatient clinic. At physical examination (with 3 mo of age) the baby presented: weight 4.7 kg (p5), length 55 cm (p3); HC: 39 cm (between -2 SD and p50). The main characteristics observed were dysmorphic appearance with arched eyebrows, frontal plane; excess skin in eyelids; micrognatia; ryzomelia of 4 limbs; bowed femurs with joint restriction; hands with few palmar creases, joint restriction; narrow chest with right accessory nipple; sacral dimple; male genitalia, bilaterally palpable testes, penis chordee. He was submitted to another radiological exam, which pointed some different characteristics than the first radiographic test (figures 6-12). The new results indicated short middle phalanx of fifth finger in both hands, angulation of the left femur and no other apparent alteration in the long bones. The calcaneus presented no abnormality and the vertebral column did not present any alteration. A specific radiological exam to evaluate the thoracic, lumbar and sacral spine will be performed to discard any modification. The thorax presented the typical configuration. A mild cranial asymmetry and brachycephaly, supposedly postural, were observed. The karyotype test indicated a normal chromosomal composition (46,XY).

Impression: Bowed femorae, final diagnosis (?).





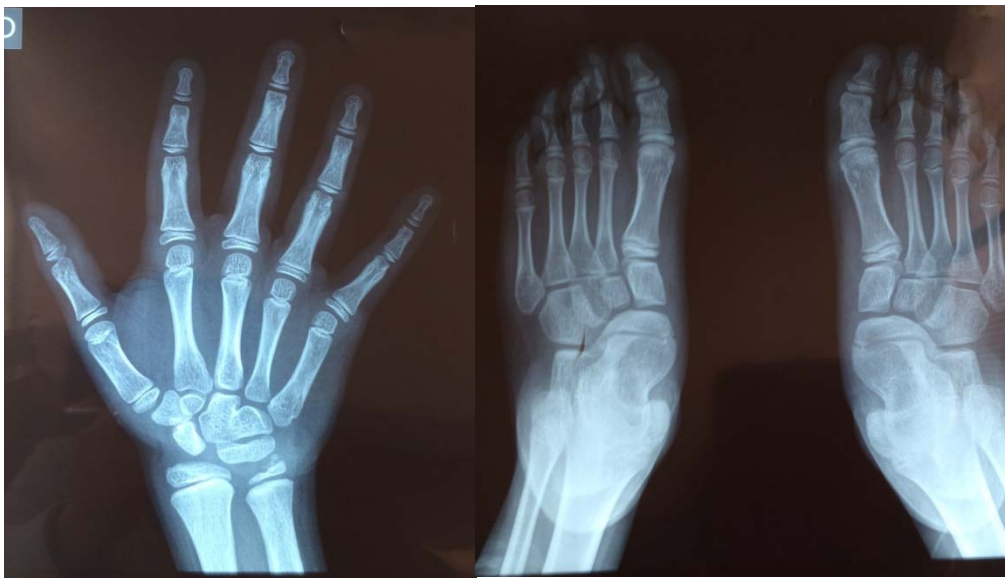


La opinión fue que se trataría más de un caso sindrómico que de una displasia esquelética y la propuesta fue descartar un mosaico (en piel y también en saliva) por las manchas de piel y las mamilas supernumerarias (frecuentes en casos de mosaicismo). También se propuso el diagnóstico de síndrome de Frank-ter Haar.

Case 9 – M. Aracena → SPONDYLO-CARPAL-TARSAL SYNOSTOSIS

Proband 10 y.o., referred for short stature and scoliosis, is the third son of 30 y.o. mother (height 1,48 m), 40 y.o. father (height 1,78 m), non-consanguineous. C-section, large for gestacional age, BW 4,220 g, BL 52 cm. Mild developmental delay. Gorwth delay more evidente alter 1 year. Physicial exam at age 10: weight 26.2 kg (P10), height 116 cm (P), HC 54.5 cm (P90). Face similar to mother, relative macrocephaly, ocular hypertelorism, limited prono-supination of elbows, scoliosis,, short fingers, flat feet. Spine CT spinal dysraphism T6, T8, T9, and partial fusion of T6-T7. Spine MRI: scoliosis, spinal dysraphism. Hands and feet X-ray: fusion of capitate and hamate, bilateral; malformed radial epiphysis.

Impression: spondylo-carpal-tarsal synostosis.

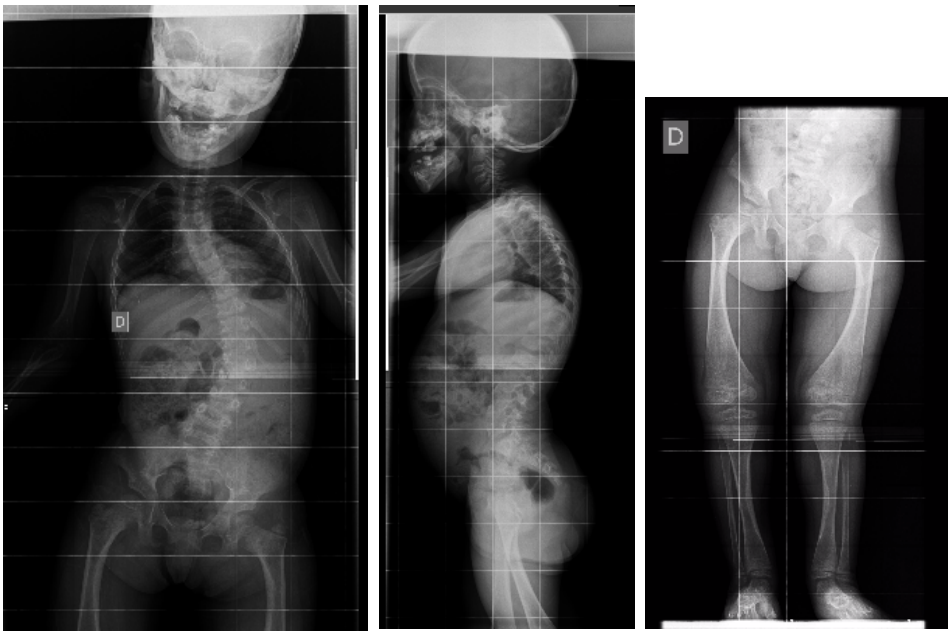


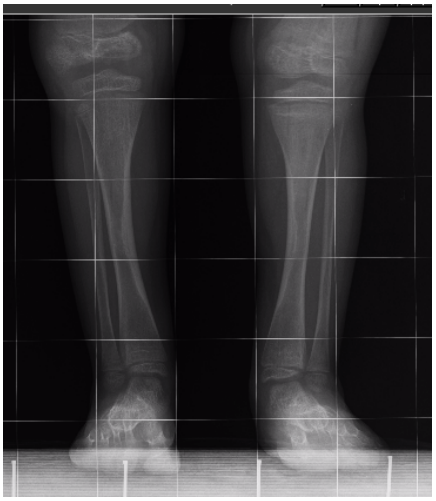
Diagnóstico: síndrome espóndilo-carpo-tarsal, entidad etiológicamente heterogénea. En las formas dominantes hay mutaciones en el gen NOG y en las recesivas en el de la filamina B. Se resaltó que las anomalías de columna no son defectos de segmentación y se mencionó como fenocopia al síndrome de alcohol fetal.

Case 10 – M. Aracena → STUVE-WIEDEMANN

First daughter of consanguineous parents. She is now 5 years old. Prenatal ultrasound showed long bones <p5. BW: 3140g, BL: 46cm, CC:33.3cm. Physical examination showed a normocephalic newborn, with rhizomelic shortening of the limbs, slightly bowed legs. She had a round face with low nasal bridge, high palate, short neck, and overlapping fingers. Skeletal survey showed mild osteopenia, irregular metaphysis, shortening and bowing of femur and tibia. Dr. Andrea Superti-Furga suggested Stuve-Wiedemann syndrome. Molecular study confirmed a *LIFR* mutation present at the homozygote state. She had prominent autonomic manifestations during her first year of life, including temperature instability, tongue with no fungiform papillae, oropharyngeal incoordination, decreased body sweating and cold induced sweating in the upper lips. She had frequent crisis of abdominal pain that have improved with Gabapentin. She has developed severe spine deformities and has had recurrent infections.

Impression: Stuve-Wiedemann syndrome



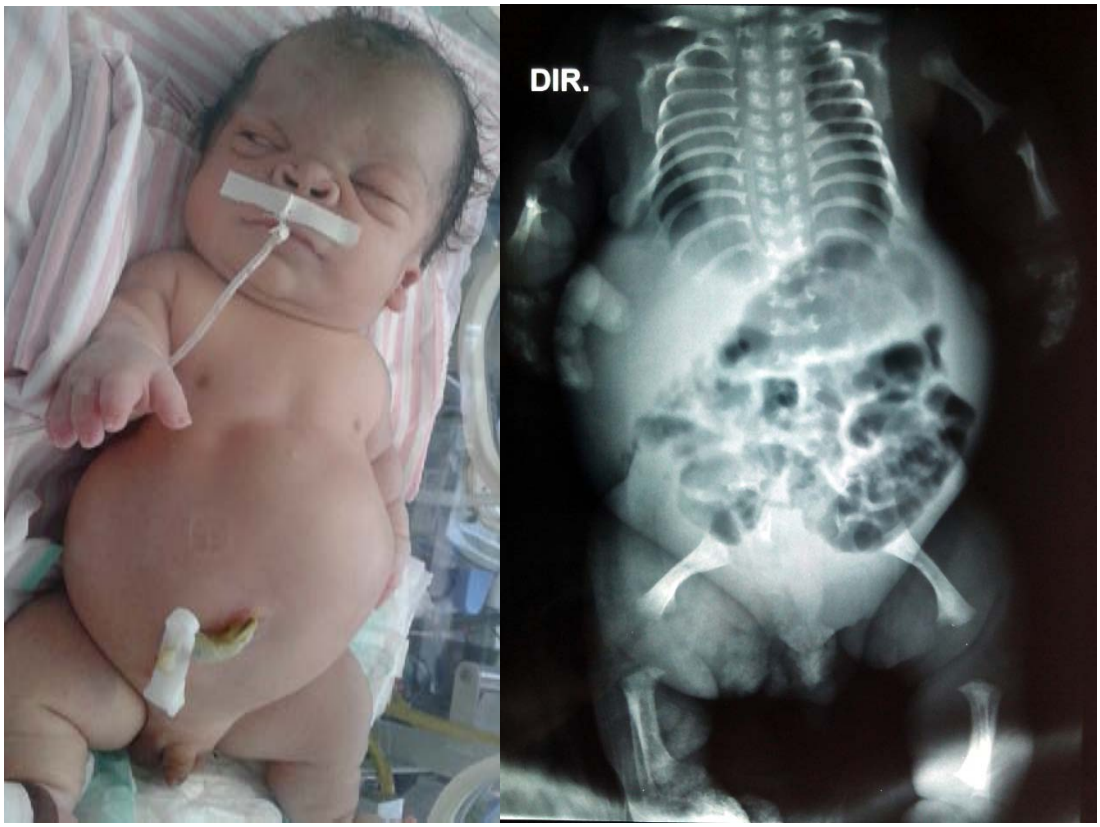


Diagnóstico: síndrome de Stüve-Wiedemann con estudio molecular confirmatorio.

Case 11 – Guilherme → OPSISMODYSPLASIA

DOB: 22.5.2014. First newborn of IAL, male, parents with consanguinity, weight 2530g (5th percentile), gestational age 38w+2d (term), progressing with respiratory failure culminating in death by 9th day. Report of gestational ultrasound: 36w + 2d (on 25/04/2014) similar to 32s 6d + (on 04/01/14). Pronounced shortening of all long bones, from micromelic type; apparently narrow chest, skull with changes of form and polidaminia. Placenta of pregnancy in the 3rd quarter with diffuse and important circulatory disorder characterized by chorioangiomatosis associated with villous edema. Amnio hyperplasia; presence of small peripheral basal infarction (nonspecific), cord with three vessels, with only mild hyperplasia chorion amnion. On examination: Broad forehead, micrognathia, saddle nose, anteverted nares, grooves bilateral at the nasal tip, short trunk and limbs, short neck, low set ears, short broad hands fingers, broad thumb and toes. Radiologic exam: some platyspondyly, deficient ossification in the cervical-thoracic vertebrae and the sacral, pubic and ischia bones? Discordant ossification phalanges delay?

Impression: Opsismodysplasia

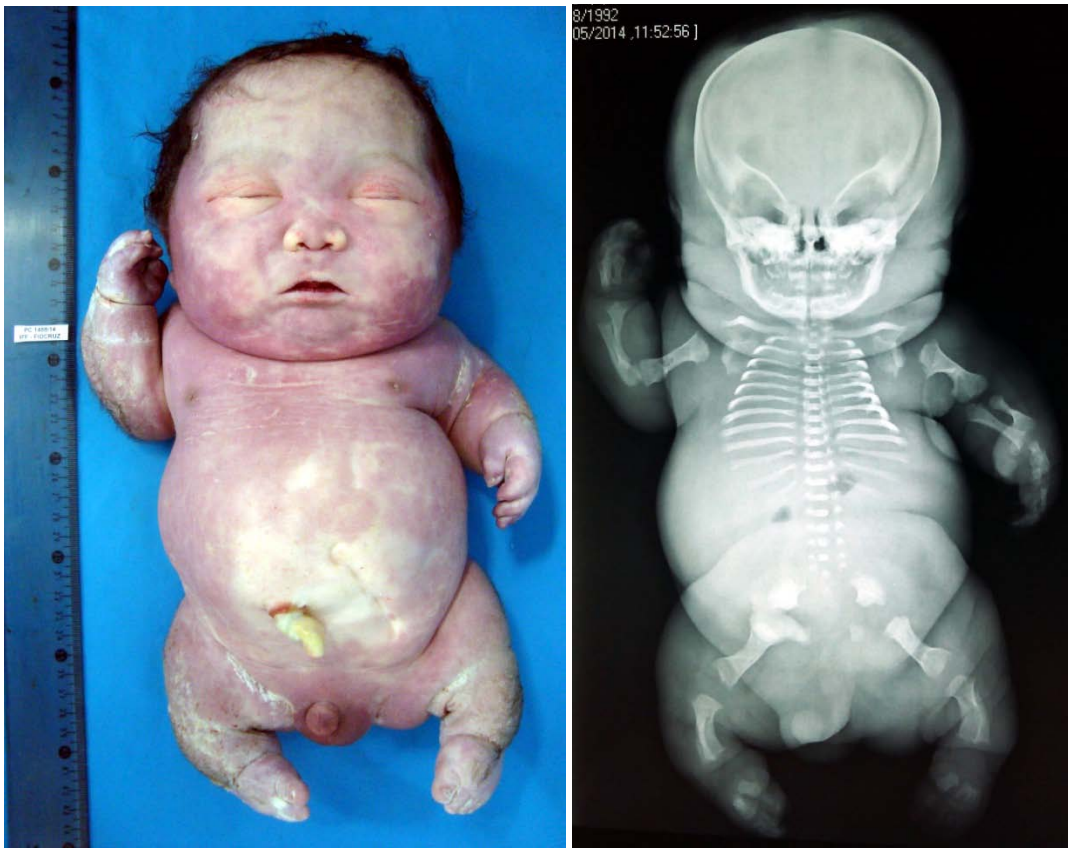


Se aceptó el diagnóstico de opsismodisplasia (mutación en INPPL1) en base a la radiografía, a pesar de que no se ven las manos ni los pies con sus característicos huesos muy cortos.

Case 12 – Guilherme → ACHONDROGENESIS II

DOB: 29.5.2014. Male, 3rd son of couple having no consanguinity, unplanned pregnancy evidenced in the 5th month, refers short episodes of small amount metrorrhagia until the 5th month. Gestational US: marked shortening of the long bones with micromelic type; narrow chest with short ribs, cardiothoracic and chest / abdomen ratio greatly diminished; polidraminia and complex malformation of vertebral column. Born with Apgar 02/02/02, G.A. 39wk, weight 3770g (75th percentile), length 43cm (<5th percentile), CP=42cm (>90th percentile), umbilical vessels unchanged, developed respiratory insufficiency, and died one hour after birth. On examination: increased head circumference, arched palate, forked tongue, redundant nuchal skin, short limbs, mitral systolic murmur 3+/6, abdominal distention with a palpable mass in the left iliac fossa, liver palpable 5cm below the right costal margin and cryptorchidism. Radiologic exam was conducted for whole body: presenting micromelic short limbs, narrow chest short ribs, platyspondyly, and pelvis with suggestive iliac bone hatchet.

Impression: Achondrogenesis II



Se aceptó el diagnóstico de acondrogenesis tipo II en base a las características típicas de la radiografia. El paladar hendido es muy frecuente.

Case 13 – Canessa → LIMB-BODY-WALL

Five unrelated children born in 2014 in Cauquenes, Chile (population 40,245) with congenital malformations.

Case 1. DOB 14.5.2014. Dx: multiple congenital anomalies

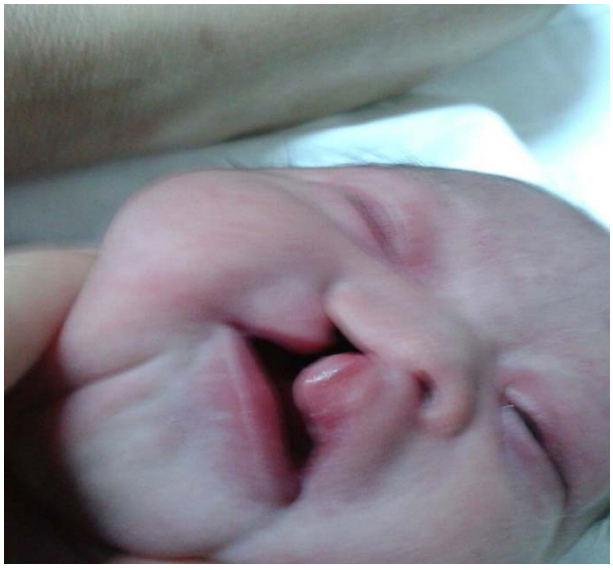
Case 2. DOB 1.8.2014. Dx: limb-body-wall complex

Case 3. DOB 5.8.2014. Dx: spina bifida

Case 4. DOB 14.8.2014. Dx: cleft lip / palate

Case 5. DOB 19.8.2014. Dx: multiple congenital anomalies


case 2


case 4

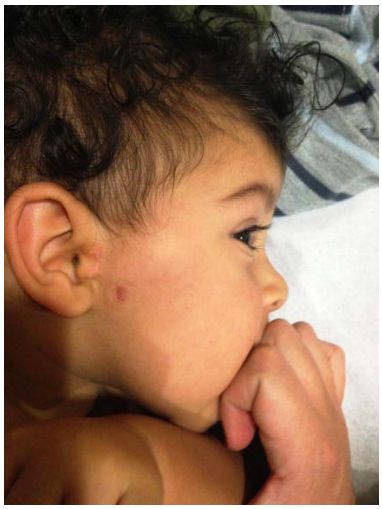
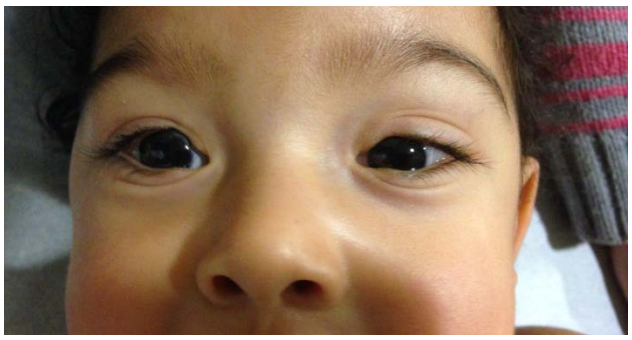
El motivo de la presentación de 3 casos con anomalías diversas fue la preocupación de la gente en los hospitales por el aparente aumento de la cantidad de nacimientos de malformados. Sin embargo los defectos en las fotografías no pudieron ser adecuadamente identificadas y se concluyó que no permitía el análisis del supuesto aumento.

Case 14 – C. Mellado → OAV SPECTRUM

DOB:8.4.2013 (no ECLAMC). Proband is the second child of young, healthy unrelated couple; he was born by C-Section at the 39th week of an uncomplicated gestation. BW 2850 g, BL 49 cm HC 35 cm. At birth bilateral preauricular tags were noticed, at 2 months old he was diagnosed with bilateral palpebral coloboma, left eye iris synechiae, and astigmatism. OAV spectrum was suspected at that time and was sent to genetics. At 1 year 3 months old evaluation psychomotor milestones were mildly delayed, weight was 9.9 k (35th centile, -0.38 SD) length 76.5 (14th centile, -1.06 SD), head C. 46 (26th centile, -0.62 SD). The bilateral preauricular tags were removed; he has bilateral coloboma of the upper lids. No other anomalies are described. Echocardiogram, cerebral and abdominal renal ultrasound, spine X-rays, brainstem auditory evoked potential were normal. Karyotype 46,XY. MRI showed a paramedian skull base cyst.

Impression: OAV spectrum with a paramedian skull base cyst.



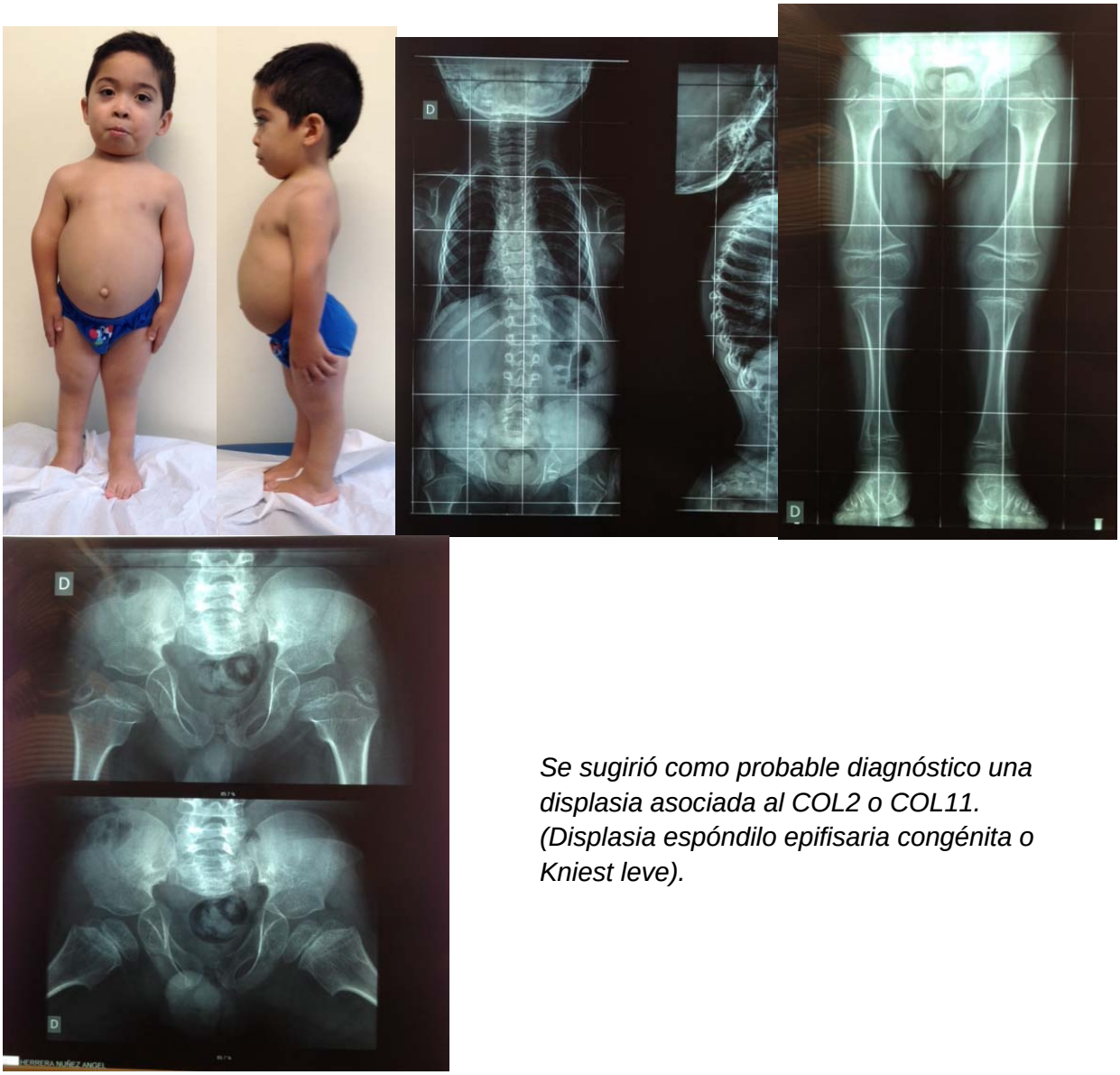



Colobomas de párpado superior bilateral, apéndices preauriculares y un quiste en la base del cráneo. Impresión diagnóstica: OAV. Se sugirió buscar mutaciones de los genes asociados al síndrome de Treacher-Collins y de los spliceosomas.

Caso 15 - M. Aracena → SED CONGENITA

Male, 6 years old, referred because of skeletal dysplasia, is the first child of a young non-consanguineous couple. Prenatal ultrasound at 6 month pregnancy: shortening of long bones, club feet. Born through C-section at 39+4 wk, BW 3,100 g; BL 39 cm. Several hospitalizations for bronchitis; high grade myopia, adequate psychomotor development. Molecular study for chondroplasia: negative. Physical exam: weight 13 kg; height 87 cm; HC 53 cm; relative macrocephay; flat midface; low, broad nasal bridge; anteverted nares; short neck and thorax; prominent abdomen; normal male genitalia; symmetric shortening of four limbs, with prominent elbows and knees; brachydactyly; lumbar hyperlordosis.

Impression: Congenital Spondylo-Epiphyseal Dysplasia (SED congenita).

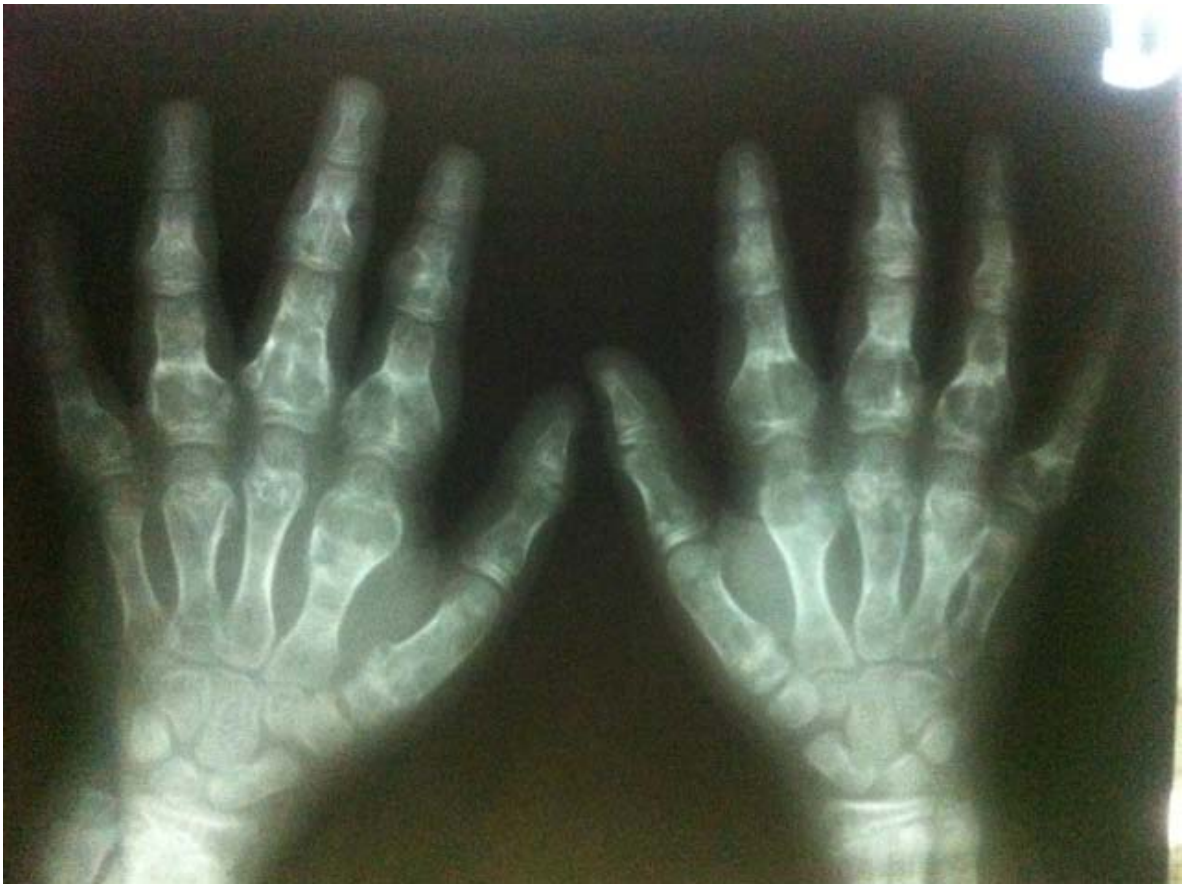


Se sugirió como probable diagnóstico una displasia asociada al COL2 o COL11. (Displasia espóndilo epifisaria congénita o Kniest leve).

Case 16 – Rosa Pardo → CHONDROMATOSIS

The patient is a boy. He is 12 years-old. His mother is young and healthy. Consanguinity: negative. Father`s data are not available. He has a healthy brother. He has seen followed by orthopedics since 4 years, because osseous anomalies in his fingers (cystic), and a fracture on his right femur at 5 years-old associated to a fail. Currently his finger lesions have increased, X-rays suggest osteoporosis and his doctor suspects about a genetically condition. Clinical evaluation: Height: 141, 3 cm weight 39,7Kg cc: 55 cm. Tanner 2. Broad metacarpo-phalangeal and interphalangic joints, hypoplastic of 4^{th} and 5^{th} right toes, with short metatarsals.

Impression: chondromatosis

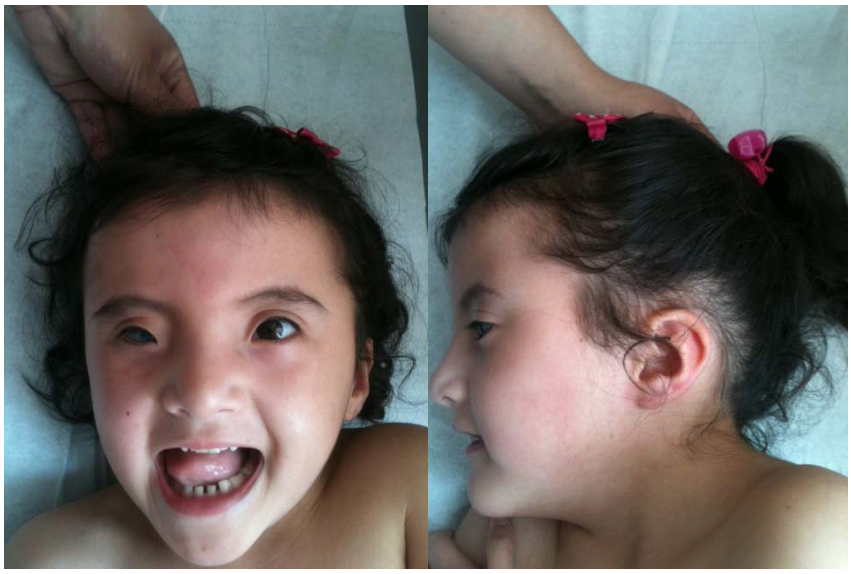


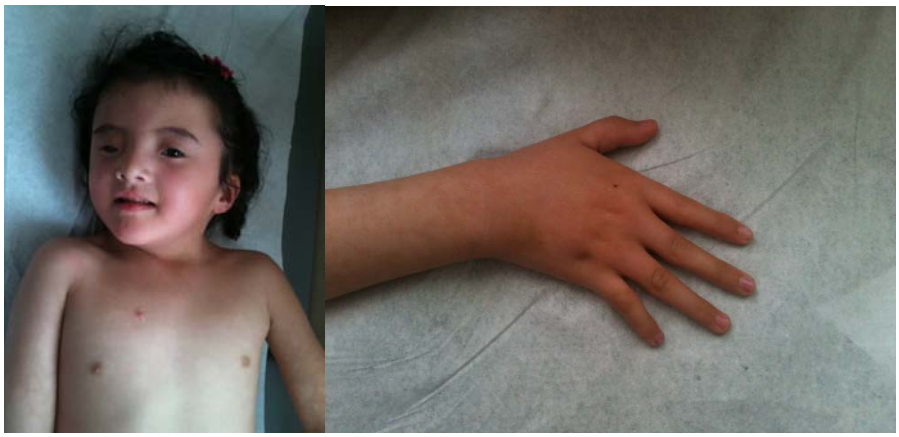
Encondromatosis con las típicas lesiones de manos que tienden a reducirse con la edad.

Case 17 – T. Aravena → MICROPHTHALMIA AND… (?)

This female patient was born to young nonconsanguineous and health parents at 39 weeks gestation by cesarean. The family history is unremarkable. The mother of patient had no past medical history of drug use or use of medications. The pregnancy was uncomplicated. Four sonograms were performed and at 26 weeks of gestation microphthalmia was diagnosed. At birth, his weight was 3270 gr, length 49 cm, head circumference 39 cm and APGAR of 8 and 9. On physical examination at 4 years, she presents weight: 18.200 kg (P75), height: 103.5 cm (P75), head circumference: 54 cm (P97). She has a macrocephaly, mild facial asymmetry, left microphthalmia and left retinal coloboma, hypertelorism, broad nose, asymmetrical ears. Ulnar deviation of the hands, camptodactyly of 5th fingers, palmar transverse groove. Bilateral valgus foot and scoliosis. She developed psychomotor developmental retardation and an episode of febrile seizure at 18 months. Exams: MRI brain: dilatation of cerebral ventricles and cranial asymmetry. Echocardiography: normal. The karyotype was normal 46, XX. mCGH: normal.

Impression: microphthalmia, large ventricles, cranial asymmetry . Final diagnosis (?)



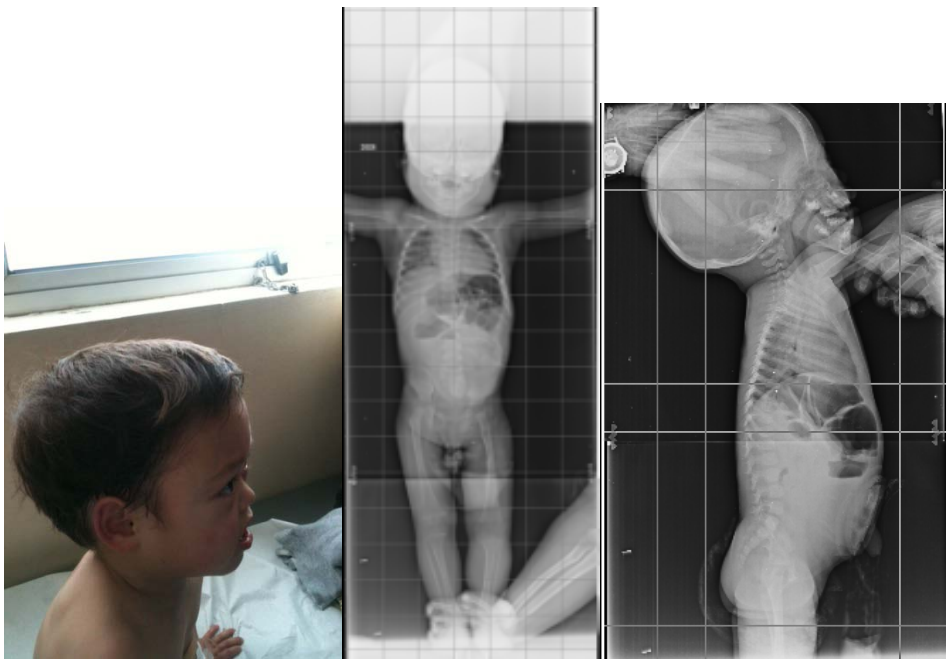


Sin diagnóstico. Por la asimetría se sugirió buscar mosaicismo.

Case 18 – T. Aravena → HISRCHPRUNG AND… skeletal dysplasia (?)

DOB: 29.8.2010. The patient is a male child born to healthy non-consanguineous parents. Parents' heights are 185 cm for the father and 162 cm for the mother. First child of healthy parents and youth. No family history of importance. The pregnancy was uncomplicated and prenatal sonograms were normal. He was born at 37 weeks of gestation. Birth weight was 2760 gr, birth length was 45 cm (p95), cranial perimeter 34 cm and Apgar: 9-9. He evolves with persistent constipation. Ileostomy is performed for intestinal obstruction at one month old, with biopsy confirmed Hirschsprung's disease. The patient had multiple hospitalizations the first years of life by recurrent infections. Blood count, complement studies and profile immunoglobulin were normal. At 11 months, during hospitalization for abdominal sepsis, he presents a deep vein thrombosis of femoral vein; he is treated with anticoagulants for 6 months. During hospitalization hypothyroidism was diagnosed. Additionally, he presents a short stature and central hypotonia. Psychomotor development: head control 9 months, seated 14 months, up 2 years 9 months, first words from 2 years, not form sentences. On physical examination at 4 years, he presents weight: 11.610 kg (P75), height: 84 cm (P75), head circumference: 54 cm (P97). He has macrocephaly, flattened facie, high forehead, low nasal bridge, epicanthal folds, small nose, micrognathia. Thin neck. Symmetric thorax with no murmurs. Abdomen with colostomy. Normal genitalia. Predominantly rhizomelic short limbs, small hands and feet. Central hypotonia. Exams: Abdominal Ultrasound: normal. Urethrocystography: normal. Brain CT: nonspecific cerebral atrophy, enlarged lateral ventricles, metopic and sagittal craniosynostosis. EEG: normal. IGF1: 1.6 Normal. Echocardiography: normal. Karyotyping was normal. Study of mucopolysaccharides in urine: normal. Molecular Studio of hypochondroplasia (FGFR3 gene): without mutations. Eye fundus examination: normal.

Diagnosis: skeletal dysplasia (?).

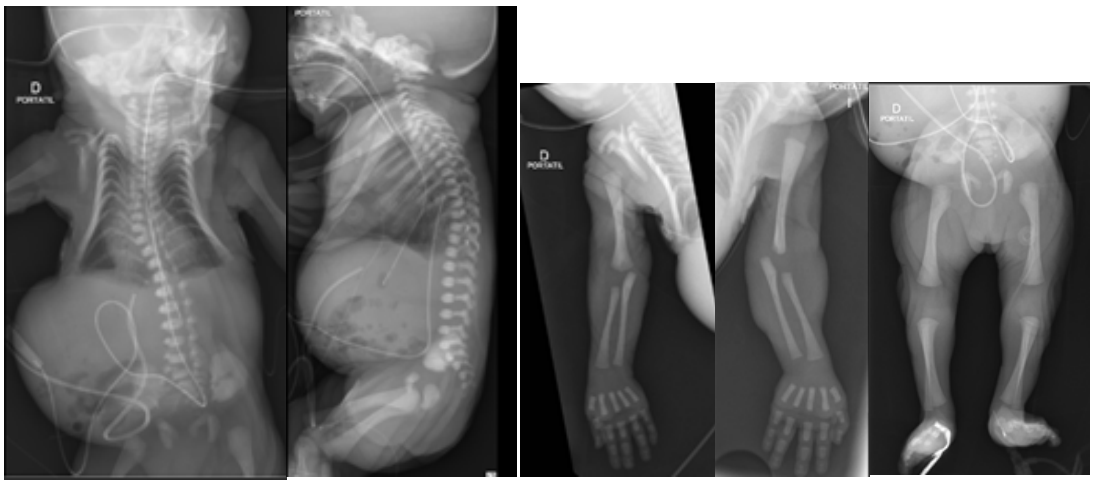


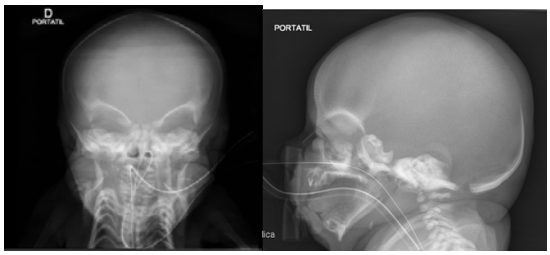
Paracía más un caso sindrómico que una displasia esquelética. Se sugirio hacer array.

Case 19 – C. Mellado → PATERNAL UPD14 (?)

DOB:100814. DZ was a newborn girl with an extremely narrow chest. She was the 4th child of healthy non-consanguineous parents with 3 unaffected older children. During pregnancy prenatal US showed increased nuchal translucency, short long bones, edema, and polyhydramnios. Prenatal karyotype was normal 46,XX. She was born at 30 weeks by C-section due to a premature labor (BW 2005 g LW 40 cm HC 31); she presented a narrowed chest.with respiratory failure. On physical examination she showed facial dysmorphic features, redundant nuchal and neck skin, microretrognathia, short and narrow chest, prominent abdomen with a thin abdominal wall, apparently proportionate limbs with long digits, no other anomalies were detected on hands and feet. Echocardiogram showed PDA and small ASD. Encephalic and abdominal US were normal. This case was presented online at the Skeldys group, a paternal UPD14 was suggested by the X-rays and phenotypic findings; array with SNPs is pending.

Impression: paternal UPD14 (?)



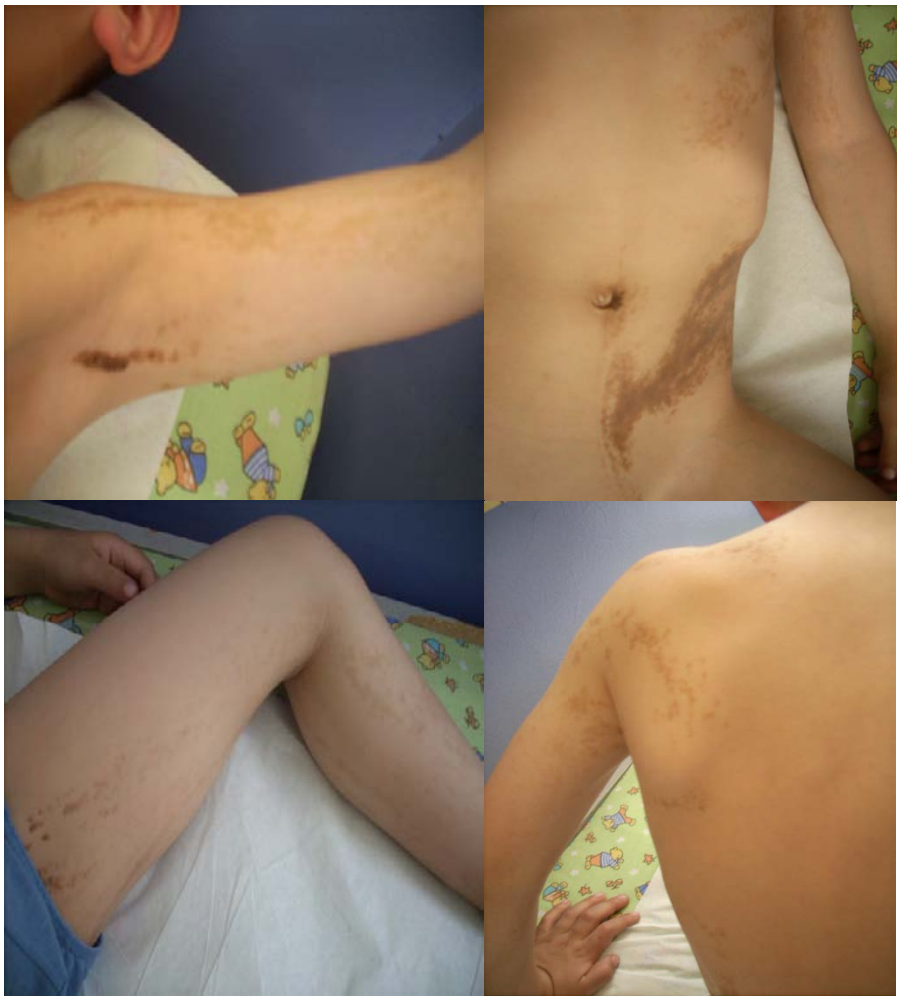


El paciente tenía la deformación típica del tórax – coat-hanger-, de la disomía uniparental del 14. Se sugirió estudiar microsatélites o metilación del cromosoma 14.

Case 20 – T. Aravena → CUTANEOUS SOMATIC MOSAICISM

Male child born to healthy non-consanguineous parents and family history unremarkable. The pregnancy was uncomplicated and prenatal sonograms were normal. He was born at 38 weeks of gestation. Birth weight was 3470 (p90), birth length was 53 cm (p95) and Apgar: 9-9. Exams: Blood and skin karyotypes were normal (46,XY). Cerebral MRI was normal. He has a history of anemia treated with iron and folic acid from 8 months to 4 years and varus foot with templates from 4 years. From newborn spot on left chest, he was assessed at 6 months of life for dermatology: lineal epidermal nevus in left hemithorax. The psychomotor development was normal, except for language delay. He said his first words after two years; with speech therapy since age 2 and attended language school from 3 years. This year he is in kindergarten, only with some dyslalias, he has a good performance. He has an attention deficit hyperactivity disorder and sleep onset insomnia. On physical examination at 5 years, he presents weight: 19.800 kg (P65), height: 113.5 cm (P75), head circumference: 51.5 cm (P50). He has a normal skull, epicanthic folds, low nasal bridge, simple and prominent ears, and normal palate. Genu Valgum feet. He has brown hyperkeratotic macules distributed in a linear pattern of Blaschko lines and unilateral segmental fashion on the left thorax, arm, abdomen and leg.

Impression: cutaneous somatic mosaicism?

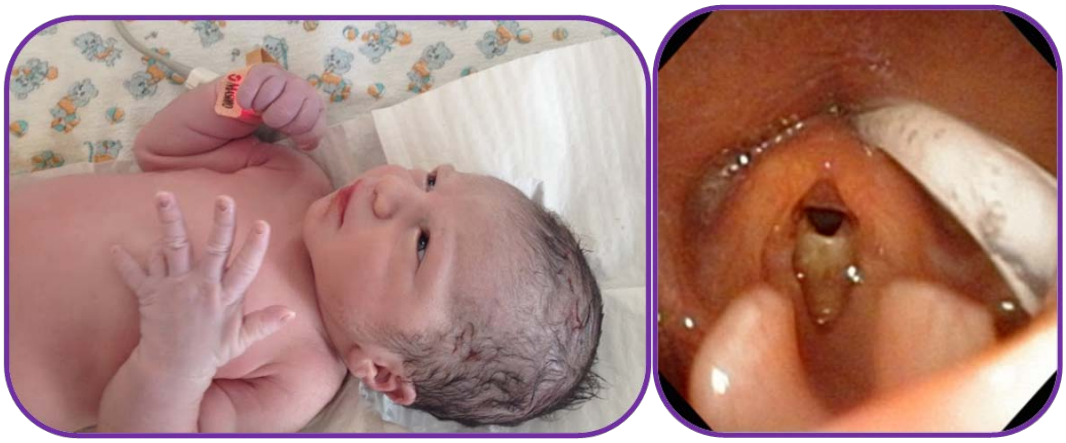


Se sugirió mosaicismo por las lesiones de piel.

Case 21 – M. Aracena → ASD + POLYD + LARYNX

DOB: 7.5.2014, Second child, healthy, non consanguineous parents. Prenatal diagnosis of congenital heart defect. Term pregnancy, adequate for gestacional age. BW 3,340 g; BL 51 cm; HC 35 cm. Physical examination: Very weak cry at at birth. Postaxial polydactyly of both hands and feet. No dysmorphic features. Vigorous suck, breast feeding. On day 9: respiratory distress, rapidly progressive. Traqueostomy: laryngeal web with out subglotic stenosis. Good post-surgery evolution. Cardiac surgery planned for age 5 moths. Echocardiogram: large atrial septal defect, small interventricular defect. Laryngoscopy: anterior glottic laryngeal web occluding 75% of the airway. Karyotype in amniotic fluid: 46,XY. FISH chr 22: no deletion. Karyo Array: no abnormality.

Impression: new syndrome (?)

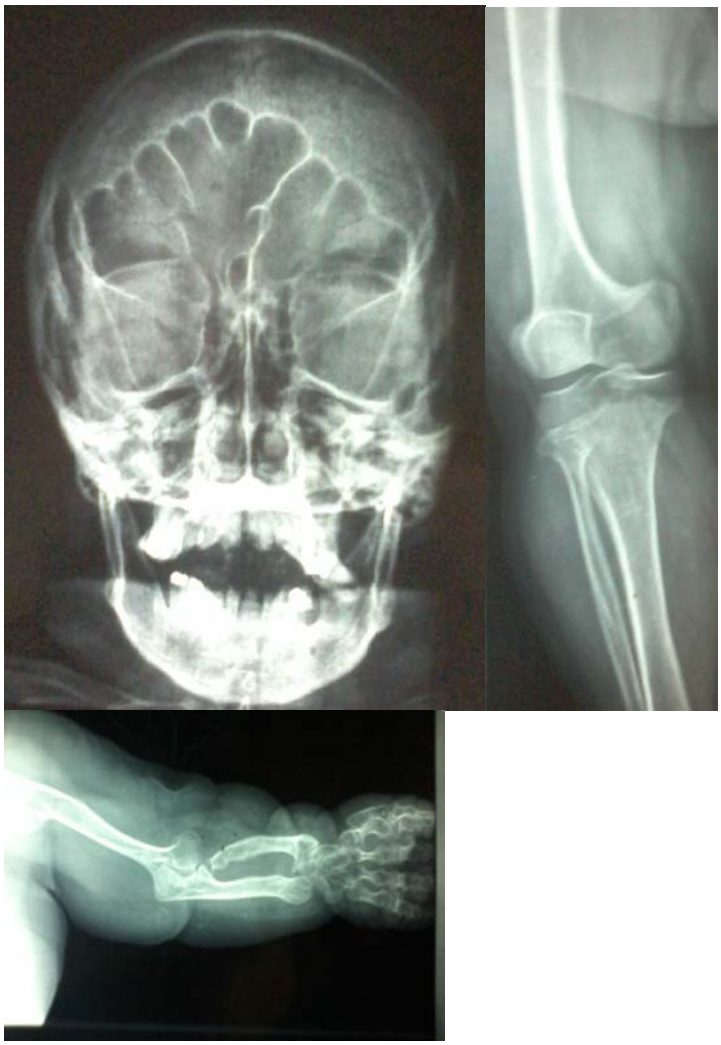


Se sugirió el síndrome de Pallister-Hall (mutación en GLI2 o GLI3). Polidactilia postaxial tipo A es más frecuentemente sindrómico, especialmente si es de los 4 miembros. Buscar hamartomas cerebrales.

Case 22 – Vargas → MESOMELIC DYSPLASIA (?)

Proband was referred for evaluation at age 64 because of thyroid cancer associated with skeletal dysplasia. The parents are consanguineous, had normal height, and the proband has a similarly affected sister. Medullary thyroid cancer was diagnosed in the proband at age 63. She also has situs inversus totalis, and had a unilateral nephrectomy performed at age 26. Her height is 102 cm, mesomelic shortening. Thin hair, slightly sparse, normal nails. Radiographs show acromesomelic shortening, enlarged metaphyses of humeri and femora, large pneumatization of frontal sinuses.

Impression: acromesomelic dysplasia (?); McKusick mesomelic dysplasia (?) with medullary thyroid cancer and situs inversus totalis (?)



Si sugirió el diagnóstico de displasia acromesomélica tipo Maroteaux, con mutación en el NPR2. Por el situs inversus también se opinó que pueden ser 2 entidades, por ejemplo una mutación en el PKD2 (poliquistosis renal y situs inversus).

Case 23 – Castillo → HAND-FOOT-GENITAL SYNDRME

First child of healthy, non-consanguineous parents. No known contact with teratogenic agents. The pregnancy was unplanned and controlled, she underwent 4 “normal” ultrasounds. A normal delivery at 39+5 weeks gestation gave birth to a male newborn with weight 3,260g and height 48cm and head circumference of 34cm. Dg: hypospadias and digital anomalies. Surgery for hypospadias at 11 months, and for syndactyly at 12 months.Vesicoureteral reflux at left kidney and recurrent urinary tract infections. Normal psychomotor development, academic success at school. After her second now planned pregnancy, the mother gave birth to a healthy girl, who is 6 years old.

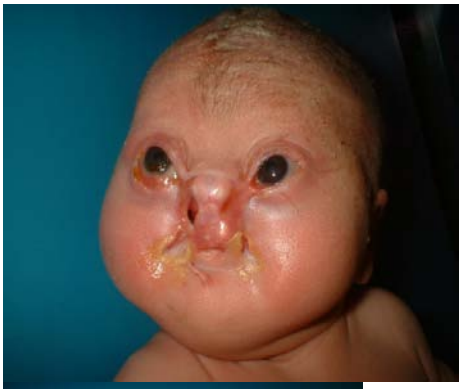
Impression: Hand-Foot-Genital syndrome

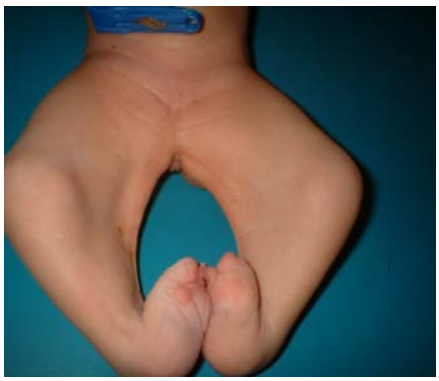
Se aceptó como diagnóstico más probable el síndrome hand-foot-genital.

Case 24 – Jatar Senior → BARTSOCAS-PAPAS

Female newborn, first pregnancy, parents are third degree cousins from Dabajuro, Venezuela. Gestational age 39 weeks. Seven prenatal appointments, seven ultrasounds performed, all reported as normal. C-section, cephalic presentation. BW 2,700 g. Adequate for gestational age. physical exam: cleft from medial side of eye until upper lip. Lips are partially by fibrous bands. Absence of nose, presence of two orifices on the nasal region. Absence of eye lashes and eyebrows. Absence of fingers in both hands, presence of tiny nails. Bilateral popliteal pterigium. Hypoplasia of toes in both feet, syndactyly 1-2. Constriction ring in right foot. Female genitalia. Karyotype: 46,XX. Autopsy: conotruncal defect.

Impression: Bartsocas-Papas syndrome



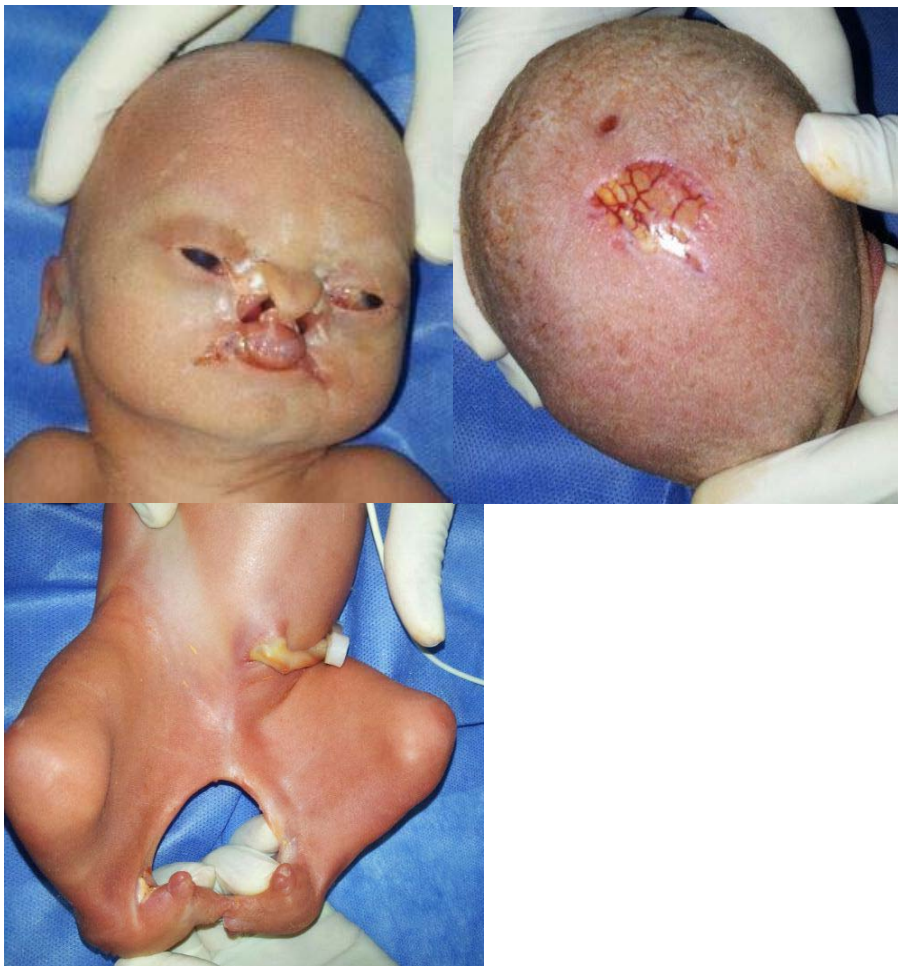


Bartsocas Papas (3 casos: 24, 25, 26). 2 hermanos de padres primos en tercer grado y 1 de otra familia de padres primos hermanos. Probable consanguinidad lejana entre las 2 familias. Se sugirió realizar estudio molecular.

Case 25 – Jatar Senior → BARTSOCAS-PAPAS

Female newborn. First pregnancy, parents are first degree cousins, from Dabajuro, Venezuela. Pregnancy 37 weeks, 4 prenatal appointments (from 12th through 37th week), four ultrasounds performed. C-section, BW 1,300 g, small for gestational age. Physical exam: bilateral facial cleft of palate, lip, nose, until eye globes. Absence of scalp hair, aplasia cutis in right pariteo-occipital region. Absence of nose, paramedical orifices in nasal region, upper and lower lips partially fused by fibrous bands. Corneal opacity in left eye. Severely hypoplastics fingers in both hands, tiny nails. Bilateral popliteal pterigium. Severe hypoplasia and syndactyly of toes in both feet.

Impression: Bartsocas-Papas syndrome

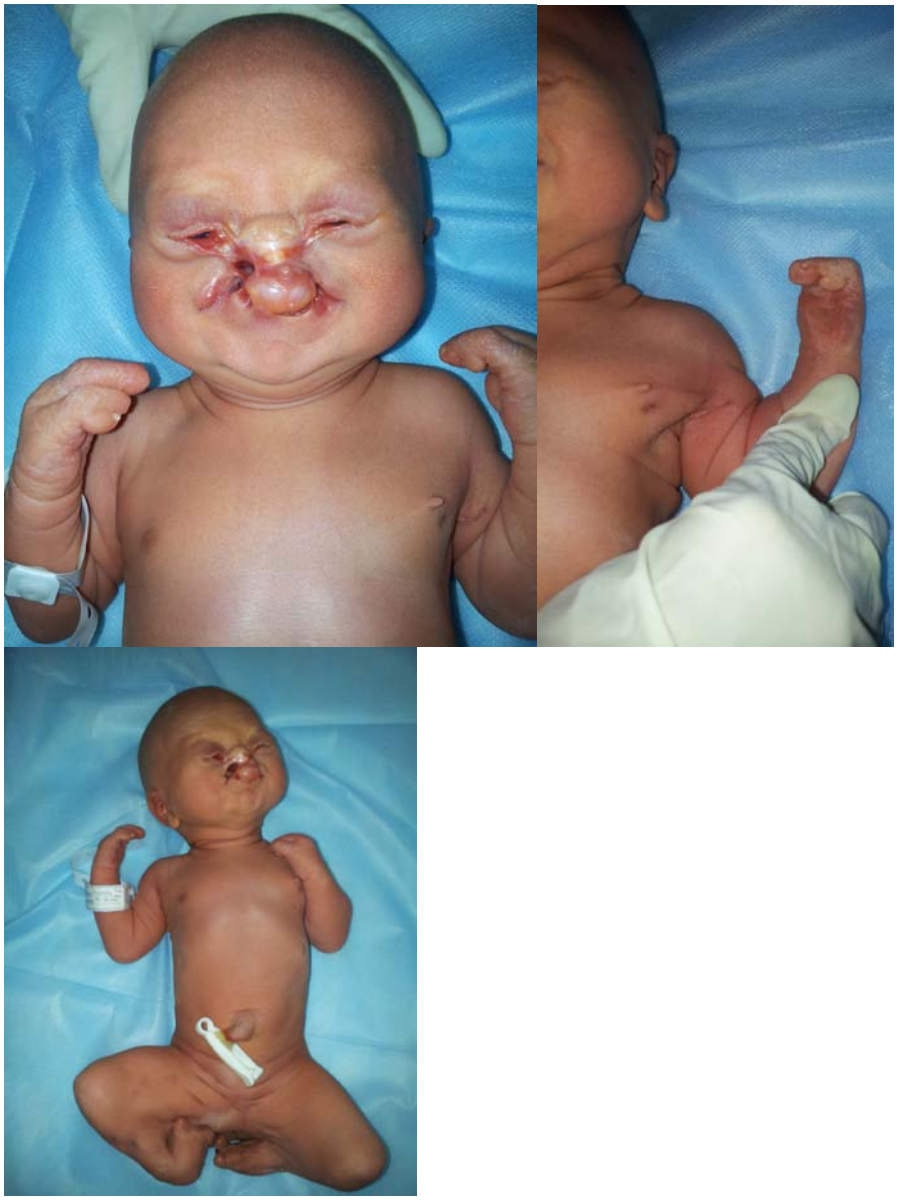


Bartsocas Papas (3 casos: 24, 25, 26). 2 hermanos de padres primos en tercer grado y 1 de otra familia de padres primos hermanos. Probable consanguinidad lejana entre las 2 familias. Se sugirió realizar estudio molecular.

Case 26 – Jatar Senior → BARTSOCAS-PAPAS

Male newborn, sixth pregnancy, consanguineous parents (cousins) from Dabajuro, Venezuela. Pregnancy 37 weeks. Nine prenatal appointments (8th through 36th week), 9 ultrasounds performed, all reported as normal. C-section, cephalic presentation, BW 2,300 g, adequate for gestational age. Physical exam: bilateral facial cleft extending from lower lids to upper lips. Mouth partially fused by fibrous bands. Nasal hypoplasia, paramedical orifices in nasal region. Absence of eyelashes, eyebrows, and scalp hair. Hyperteloric, asymmetric nipples. Skin appendage (supernumerary nipple ?) under left nipple and axillary region. Severe hypoplasia of fingers, tiny mails. Popliteum pterigium. Severe hypoplasia and syndactyly of toes in both feet. Male genitalia, micropenis. Karyotype 46,XY.

Impression: Bartsocas-Papas syndrome.

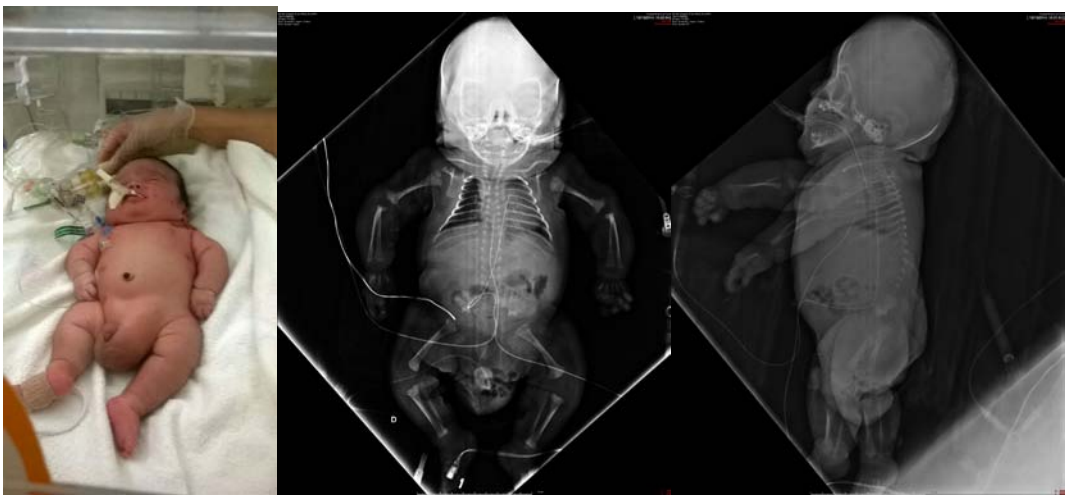


Bartsocas Papas (3 casos: 24, 25, 26). 2 hermanos de padres primos en tercer grado y 1 de otra familia de padres primos hermanos. Probable consanguinidad lejana entre las 2 familias. Se sugirió realizar estudio molecular.

Case 27 – Sanseverino → Skeletal dysplasia

DOB: 10.10.2014. He is the second child of a non-consanguineous healthy couple. The pregnancy was uneventful except for the fetal abnormalities on ultrasound: US 19 wks – abnormal lumbar spine (initial suspicion of a NTD; short long bones; club feet; US 31 wks – subcutaneous edema; same finds. He was born by a C-section. BW 2,670 g; BL 38 cm; OFC 34 cm. Gestational age 38 wks. He was immediately transferred to NICU and he is on mechanical ventilation up to now. At physical examination the baby presents: dwarfism, micromelic appearance; large head; edema; face with up slanting palpebral fissures, flat nasal bridge, anteverted nostrils; normal palate; short thorax; distended abdomen; inguinal herniation; short limbs; short hands and feet. X-rays attached –under ossification of spine; thin ribs and thin long bones; under ossification of pubis; short long bones.

Impression: ?



Displasia esquelética probablemente del grupo de las platispondilias letales. Se sugirió evaluar metabolismo de calcio y fósforo. Probablemente autosómico recesivo.