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Co-Occurrence of Hemiscrotal Agenesis With Cutis Marmorata Telangiectatica Congenita and Hydronephrosis Affecting the Same Side of the Body

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To our knowledge, there are nine previous reports of patients with congenital scrotal agenesis (CSA), seven of which were bilateral, and unilateral in two, also named as hemiscrotal agenesis (HSA). Here, we report a male infant with the previously undescribed co-occurrence of HSA with cutis marmorata telangiectatica congenita (CMTC), and hydronephrosis due to vesicoureteral reflux, all of them on the left side. CMTC is a segmental vascular malformation usually attributed to mosaicism of a postzygotic mutation, whereas the mechanisms in the CSA involve a failure on the labioscrotal fold (LSF) development due to a localized 5α-reductase deficiency and/or androgen insensitivity. Since the skin with HSA was affected also by CMTC and by the fact that it exhibited lack of response to the topical testosterone treatment, all this suggests to us an androgen insensitivity mosaicism in our patient restricted to the left LSF, because skin with intact androgen receptors normally shows some type of response. Since CSA and/or HSA have been also seen in patients with PHACES, popitleal pterygium syndrome, or as part of a recently proposed familial entity with CSA (or agenesis of labia majora as its female counterpart), developmental delay, visual impairment, and moderate hearing loss, further reports could confirm this manifest genetic heterogeneity, highly evocative of somatic mosaicism in our patient.

Key words: mosaicism; congenital scrotal agenesis; cutis marmorata; hemiscrotal agenesis; hydronephrosis; vesicoureteral reflux; androgen insensitivity; 5α-reductase; didymosis

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INTRODUCTION

Congenital scrotal agenesis (CSA) is a rare malformation first described by Wright [1993], and to our knowledge, there are only nine reported patients with CSA, seven of which showed bilateral absence of scrotal reggae in the perineum between the penis and anus [Wright, 1993; Verga and Avolio, 1996; Montero et al., 2001; Janoff and Skoog, 2005; Mohan et al., 2006; Silay et al., 2013] and unilateral in two, also named as hemiscrotal agenesis (HSA) [Flum et al., 2012; Yilmaz et al., 2013]. All cases

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Yunis-Varón Syndrome Is Caused by Mutations in *FIG4*, Encoding a Phosphoinositide Phosphatase

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Yunis-Varón syndrome (YVS) is an autosomal-recessive disorder with cleidocranial dysplasia, digital anomalies, and severe neurological involvement. Enlarged vacuoles are found in neurons, muscle, and cartilage. By whole-exome sequencing, we identified frameshift and missense mutations of *FIG4* in affected individuals from three unrelated families. *FIG4* encodes a phosphoinositide phosphatase required for regulation of $PI(3,5)P_2$ levels, and thus endosomal trafficking and autophagy. In a functional assay, both missense substitutions failed to correct the vacuolar phenotype of *Fig4*-null mouse fibroblasts. Homozygous *Fig4*-null mice exhibit features of YVS, including neurodegeneration and enlarged vacuoles in neurons. We demonstrate that *Fig4*-null mice also have small skeletons with reduced trabecular bone volume and cortical thickness and that cultured osteoblasts accumulate large vacuoles. Our findings demonstrate that homozygosity or compound heterozygosity for null mutations of *FIG4* is responsible for YVS, the most severe known human phenotype caused by defective phosphoinositide metabolism. In contrast, in Charcot-Marie-Tooth disease type 4J (also caused by *FIG4* mutations), one of the *FIG4* alleles is hypomorphic and disease is limited to the peripheral nervous system. This genotype-phenotype correlation demonstrates that absence of FIG4 activity leads to central nervous system dysfunction and extensive skeletal anomalies. Our results describe a role for $PI(3,5)P_2$ signaling in skeletal development and maintenance.

Yunis and Varón first described the syndrome that bears their name in 1980, based on three Colombian families with a total of five affected children.[1] Since then, approximately 25 individuals with Yunis-Varón syndrome (YVS) (MIM 216340) have been described.[2–19] Frequent features include structural brain abnormalities, sparse and pale hair, and facial dysmorphisms. Skeletal abnormalities include wide fontanelles with calvarial dysostosis, aplasia or hypoplasia of the clavicles and phalanges in the hands and feet, and absence of thumbs and halluces. Pelvic bone dysplasia, absent sternal ossification centers, and fractures are also frequent.[17] Neuropathology shows extensive neuronal loss and diffuse atrophy affecting the cerebellar vermis, corpus callosum, basal ganglia, and frontal lobes. Vacuoles compatible with enlarged lysosomes are seen in neurons, muscle, cartilage, heart, and macrophages.[17] In the urine, multiple abnormal oligosaccharide bands appear, suggesting a dysfunction of lysosomal enzymes,[8,12] but no consistent storage material could be identified[12] and the enzyme activities of oligosaccharidases were normal.[8]

Six families affected by Yunis-Varón syndrome were included in this study. The clinical features of the eight affected individuals are summarized in Table 1. Pictures and radiographs of most affected individuals are available in previously published case reports.[5,7,8,18,20] The study was conducted according to the guidelines of the institutional review board of the Baylor College of Medicine and informed consent was obtained prior to collection of samples. The inclusion criterion was a high index of suspicion of Yunis-Varón syndrome by a clinical geneticist. Frequent features found in the individuals include sparse scalp hair, protruding eyes, low-set ears, a high arched palate, and micrognatia (Table 1). Skeletal features include wide fontanelles and calvarial dysostosis, digital hypoplasia, especially of the thumbs and halluces, pelvic dysplasia with hip dislocations, and absent or hypoplastic clavicles. Affected individuals were significantly hypotonic and presented global developmental delay and often feeding and swallowing difficulties. Central nervous system anomalies in individuals 1 and 2 consisted of frontal lobe atrophy with pachygyria and hypoplasia of the corpus callosum and cerebellar vermis. In individual 3, autopsy revealed an absent olfactory bulb and tract, an atypical ventricular hamartoma, and neuronal loss with vacuolation in layers

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RESEARCH LETTER

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Aplasia Cutis Congenita of the Scalp in a Female Infant With Anophthalmia/Microphthalmia–Esophageal Atresia Syndrome Negative for *SOX2* Mutation

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TO THE EDITOR:

The terms anophthalmia (AO) and microphthalmia (MO) describe the absence of an eye and the presence of a small eye within the orbit, respectively [Ragge et al., 2005]. The combination of AO/MO and esophageal atresia (EA) is a syndrome (AMEAS), also called as anophthalmia–esophageal–genital (AEG) syndrome [Shah et al., 1997], or microphthalmia syndromic 3 (OMIM #206900), consisting of an AO/MO, EA with or without tracheoesophageal fistula (TEF), and urogenital anomalies in males [Rogers, 1988; Shah et al., 1997]. Additionally, patients with AMEAS can also display anomalies at the central nervous system (CNS), craniofacial region, vertebras, and ribs, and on cardiovascular system [Arroyo et al., 1992]. Currently 23 patients with AMEAS have been reported [Schenk et al., 1976; Sassani and Yanoff, 1977; Rogers, 1988; Arroyo et al., 1992; Sandler et al., 1995; Ulman et al., 1996; Shah et al., 1997; Imaizumi et al., 1999; Menetrey et al., 2002; Messina et al., 2003; Bonneau et al., 2004; Petrackova et al., 2004; Bardakjian and Schneider, 2005; Hill et al., 2005; Morini et al., 2005; Kelberman et al., 2006; Williamson et al., 2006; Zenteno et al., 2006; Bakrania et al., 2007; Chassaing et al., 2007]. The heterozygous loss of function in the coding region of SRY (sex determining region Y)-box 2 gene (*SOX2*) has been previously identified in 10–15% of patients with bilateral AO/MO [Williamson et al., 2006]. Although AMEAS has been included as a different phenotypic expressions of the *SOX2* AO syndrome [Chassaing et al., 2007; FitzPatrick, 2009], its distinction as a separate entity seems to be appropriate because mutations or deletions on the *SOX2* gene are not present in all of the patients with AMEAS.

Aplasia cutis congenita (ACC) is an area with absent skin formation characterized by well-circumscribed, noninflammatory lesions, most commonly seen as a single lesion at the vertex of the scalp (OMIM %107600). There are more than 50 monogenic, chromosomal, and teratological disorders associated with ACC [Frieden, 1986]. We describe a female infant with severe AMEAS phenotype who also had ACC of the scalp, and who tested negative for mutation of the *SOX2* gene. We reviewed all previously reported patients with AMEAS but none had ACC. Thus, such a combination of ACC is proposed as a new cutaneous feature in AMEAS syndrome.

The proposita was the product of the second pregnancy of a healthy 18-year-old mother and a 25-year-old father. The family history did not reveal any malformations and there was no history of abortions, miscarriages, or consanguinity. During the first 2 months of pregnancy the mother smoked 1–5 cigarettes per day, but there was not history of exposure to drugs or other

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Confirmation of the macroblepharon, ectropion, hypertelorism, and macrostomia syndrome

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List of key features

Macroblepharon
Ectropion
Hypertelorism
Macrostomia
Corneal clouding

Case report

The proposita was born at term to a 32-year-old primigravid mother. The pregnancy was complicated with threatened abortion at the first month of gestation and by recurrent urinary tract infections, treated with ampicillin and amoxicillin in the second and third trimesters. There was no history of exposure to known teratogens. In terms of family history, the parents were nonconsanguineous, healthy, and have normal intelligence. A paternal uncle was born with a cleft lip and palate. The child was born at 37 weeks' gestation by cesarean section because of fetal distress. Birth weight was 2520 g (< 10th centile) and length was 49 cm (50th centile). Apgar scores were 8 and 9 at 1 and 5 min, respectively. At birth, macroblepharon, ectropion, and macrostomia were noticed (Fig. 1a). On physical examination at 4 months, her weight was 5600 g (ninth centile), length was 62 cm (25–50th centile), and occipitofrontal circumference was 39.7 cm (ninth centile). She had large fontanels, broad metopic suture, capillary hemangioma, mild synophrys, hypertrichosis of the eyebrows with lateral thickening, and increased density of the upper eyelid eyelashes more marked laterally. In addition, there were downslanting palpebral fissures, a broad nasal bridge, hypertelorism (inner canthal distance 3.3 cm, interpupillary distance 5.5 cm, both >97th centile), macroblepharon (palpebral fissures length 25 mm, >2 SD), upper and lower lid ectropion, posteriorly rotated ears, long and smooth philtrum, and macrostomia (intercommissural distance 38 mm, >2 SD) with a thin vermillion border to the upper lip. She initially showed a mild motor delay, but mental development was normal at the age of 4 years. On further follow-up, the lagophthalmos because of macroblepharon and ectropion produced corneal drying, chronic conjunctivitis, keratitis, and corneal clouding, apparent from the age of 2 months. She therefore underwent a lateral tarsorrhaphy at the age of 14 months. This was complicated by the formation of synechiae between the eyelids and a second corrective surgery was required at the age of 3 years (Fig. 1b).

Investigations

Echocardiogram and renal ultrasound were normal. A computed tomography scan of the brain showed no abnormality. Three-dimensional computed tomography scan of the craniofacial region showed large fontanels, broad metopic suture, and osseous hypertelorism (Fig. 1c). Cytogenetic analysis at the 550-band level showed a 46, XX karyotype.

Discussion

Verloes and Lesenfants (1997) reported a Belgian girl with normal growth and mental development and a previously undescribed pattern of defects that consisted of a round and flat face, hypertelorism, macroblepharon, ectropion, downslanting palpebral fissures, broad nasal base, anteverted nares, small, posteriorly rotated ears, long and smooth philtrum, a thin upper lip, macrostomia, and micrognathia. The authors considered that this pattern of defects corresponded to a new form of mandibulofacial dysostosis (MFD) with macroblepharon and macrostomia (OMIM 602562), thereby named as macroblepharon–macrostomia syndrome in the London Medical Databases (Winter and Baraitser, 2006). To the best of our knowledge, no other reports have since confirmed this syndrome. As our proposita showed the unusual combination of macroblepharon, ectropion, hypertelorism, and macrostomia (MEHM) in the presence of normal growth and intellectual development, it appears to confirm the existence of the MEHM syndrome or Verloes–Lesenfants syndrome. The patient of Verloes

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DYSGNATHIA COMPLEX SINE HOLOPROSENCEPHALY NOR SYNOTIA: A CASE REPORT AND DISCUSSION OF ITS NOSOLOGY

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Summary: *Dysgnathia complex sine holoprosencephaly nor synotia: a case report and discussion of its nosology:* A severe mandibular hypoplasia and microstomy with intraoral anomalies including hypoglossia, fused gums, persistence of buccopharyngeal membrane, and laryngeal hypoplasia were noted in a female newborn with the dysgnathia complex (DC). Additionally, our proposita also presented natal teeth as a probably new finding. These clinical manifestations overlapped with those of the fourth report of hypomandibular faciocranial syndrome (HFS) (31), and given that both lack for craniosynostosis (pathognomonic of HFS), we considered that both represent a subtype of DC proposed as DC sine holoprosencephaly nor synotia (DCSHS). Differential characteristics between the DCSHS, the HFS, and the DC with holoprosencephaly sine synotia are reviewed and additionally, we discussed some aspects about the nosology of the DC.

Key words: Mandibular hypoplasia – Microstomia – Hypoglossia – Gums fusion – Natal teeth – Polyhydramnios – Hypomandibular faciocranial dysostosis – Agnathia – Otocephaly – Dysgnathia spectrum – Synotia – Melotia.

INTRODUCTION

Dysgnathia is a malformative complex characterized by severe mandibular hypoplasia or agenesis (agnathia), microstomia or astomia, microglosia or aglossia, and a conspicuous ear anomaly (4, 11). Although the position of the ears has an indubitable diagnostic orientation in patients with the dysgnathia complex (DC), the use of the terms "otocephaly" or "synotia" does not seem always justified (13, 18), but are commonly used when the ears are displaced toward the midline (melotia) or fused in the position of the absent mandible (synotia), and this also has led to the use of terms such as "agnathia" or "agnathia-otocephaly", as synonyms for the "DC" (11). Patients with the DC may have other severe malformations such as hypoplasia of zygomatic arches, cleft lip and/or palate, choanal atresia and/or stenosis, fusion of mandible to maxilla (syngnathia), persistence of buccopharyngeal membrane, and other laryngo-tracheal anomalies (13, 18, 25,). In ad-

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ANGELMAN SYNDROME AND THYROID DYSFUNCTION

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Summary: *Angelman syndrome and thyroid dysfunction:* Angelman syndrome (AS) is a neurogenetic syndrome, has a prevalence of 1:10,000 to 1:40,000. Patients with AS have genetic alterations in maternal imprinting gene *UB3A* (15q11-q13) and molecular evaluations confirm the diagnosis. Our aim is to report a new case with AS and subclinical hypothyroidism (SCH) without goiter. Thyroid dysfunction has not been described as part of alterations in AS; the exact pathogenic mechanisms of SCH in patients with AS remains incompletely unknown.

Key-words: Hypothyroidism – Angelman syndrome.

INTRODUCTION

AS is a neurogenetic syndrome with severe mental retardation, has an estimated prevalence of 1:10,000 to 1:40,000 (4, 9). Clinically are characterized speech and developmental delay, seizures, abnormal electroencephalogram (EEG), singular behavior, stereotyped movements and characteristic facies (4, 6). Proposed genetic mechanisms of AS appearance are: 15q11.2-q13 deletion (60-75% of cases), *UBE3A* gene mutations (10-15%), uniparental disomy (2-5%), mutation/impronta center defect (2-5%), and (6, 4, 11) <1-2% of cases have structural chromosomal abnormalities in the karyotype (4, 11), and 10-15% of the cases remain without genetic cause (13). The diagnosis is clinical and complemented by molecular evaluation (6) with fluorescent *in situ* hybridization (FISH, detects 60-75%), DNA methylation (detects 78% of cases) (11).

The recurrence risk is approximately 1% for de *novo* mutations. The treatment is symptomatic, and may include anticonvulsants, physical and behavior therapy, with life expectancy near to normal (11), although the cognitive development prognosis is poor (6).

The primary hypothyroidism occurs in approximately 1/4,000 births, most of the infants are asymptomatic; thyroid-stimulating hormone (TSH) levels in serum are an extremely sensitive indicator of this pathology (10). Thyroid dysfunction has not been described as part of alterations in Angelman syndrome, however Paprocka *et al.* (9), reported three confirmed patients with classical deletion, who were diagnosed

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Agenesis of the vocal cords in a female infant with Robin sequence

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List of key features

Robin sequence
Cleft palate
Glossoptosis
Micrognathia
Laryngomalacia
Agenesis of the vocal cords
Pulmonary arterial hypertension

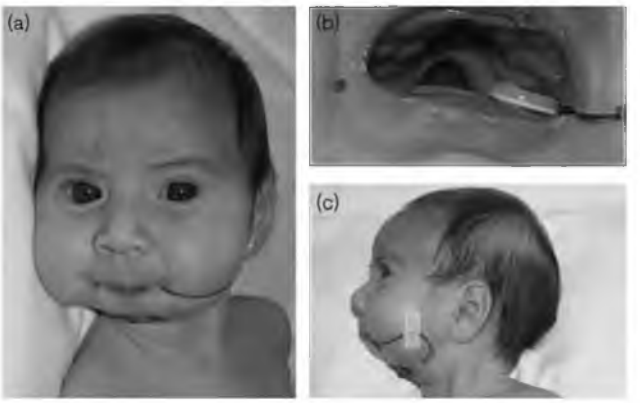
Clinical summary

The proposita, a female was the product of the third pregnancy of healthy parents aged 18 years (mother) and 21 years (father) at the time of birth. A threatened abortion at the third month of gestation was treated by rest and an unspecified drug. There was no history of exposure to teratogens and the family history was unremarkable. The baby was born by normal vaginal delivery weighing 3000 g. She cried spontaneously and gradually established respiration after birth. The Apgar scores were not available. During the first week of life, the mother noticed that she had feeding difficulty, respiratory problems, a weak and dysphonic cry and, a mild stridor. She was admitted to hospital when she was 11 days old with increased breathing difficulties. Chest radiograph showed an infiltrate consistent with aspiration pneumonia. Clinical examination at this age showed (Fig. 1), a weight of 2460 g (25th centile), length of 48 cm (10th centile), occipitofrontal circumference of 33.5 cm (25th centile), mild frontal hypertrichosis, slightly elongated philtrum, thin upper lip, small mouth glossoptosis, high palate with a posterior U-shaped cleft, and micrognathia.

Investigations

Ophthalmoscopic examination was normal. Radiographs of chest, spine, hands, and feet revealed no bony abnormality. Despite gastric tube feeding, the first month of her life was complicated due to abnormal sucking and swallowing, bronchial aspiration, and repeated pneumonia. Videofluoroscopic examination demonstrated that the oral, pharyngeal, and esophageal phases of swallowing were abnormal and showed tracheal aspiration with evidence of gastroesophageal reflux. As retrodisplacement of the tongue caused a functional upper airway obstruction, a glossopexy procedure was performed at 30 days of life but the stridor and the respiratory difficulties were not completely resolved. Fibreoptic laryngoscopy revealed a widely open larynx with marked edema, moderate salivary pooling, and an elongated omega-shaped epiglottis that prolapsed into the larynx during inspiration. The findings were consistent with the diagnosis of laryngomalacia. In addition, the vocal cords were absent and the arytenoid cartilages were not observed (Fig. 2). The procedure also confirmed laryngopharyngeal reflux but the proximal esophagus was considered endoscopically normal. Doppler

Fig. 1



General aspects of the proposita at the age of 1 month (a), note U-shaped cleft palate (b), and micrognathia (c).

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Short report

New ocular findings in two sisters with Yunis–Varón syndrome and literature review

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ABSTRACT

The Yunis–Varón syndrome (YVS) represents a rare autosomal recessive syndrome of easy recognition characterized by cleidocraneal dysplasia, absence of thumbs and halluces, distal aphalangia, ectodermal anomalies, and poor outcome. Here, we report two sisters with YVS who also had papillo-macular atrophic chorioretinopathy with "salt-and-pepper" appearance that could not be attributed to environmental or metabolic causes. Our best hypothesis is that the ocular findings in our two patients are part of the phenotypic manifestations of YVS. We suggest that an extensive ophthalmologic examination should be carried out in all children with YVS in order to define the frequency and nature of the ocular findings in these patients.

1. Introduction

In 1980 Yunis and Varón [17] reported five infants from three Colombian families who had cleidocranial dysplasia, absence of thumbs and halluces, distal aphalangia, ectodermal anomalies, and poor outcome. Three years later, Hughes and Partington [9] confirmed this pattern of anomalies and proposed the eponym of Yunis–Varón syndrome (YVS) for this rare autosomal recessive syndrome (OMIM #216340). Up to date, 23 patients with YVS from 18 families have been reported [1–6,8–17]. We describe two sisters with YVS which adds new ocular findings to the known features of this syndrome and review all previous reported cases for further clinical delineation of this entity.

2. Clinical reports

2.1. Patient 1

The *proposita* was the product of the third pregnancy of a healthy 22-year-old mother and a 25-year-old father who were third cousins and from Mexican origin. The first born child was healthy and the second pregnancy was spontaneously aborted. Pregnancy was uneventful with no exposure to toxic, traumatic, infectious agents or radiation. Vaginal delivery was at the 36th week of gestation. Apgar scores were 8 and 9 at 1 and 5 min, respectively. Birth weight was 2200 g (25th percentile), length 45 cm (25th percentile), and occipitofrontal circumference (OFC) 29 cm (<3rd percentile). Physical examination at 1 month (Fig. 1) showed general muscular hypotonia, irritability, high pitched cry, sparse scalp hair, large fontanelles, wide cranial sutures, sparse eyebrows and eyelashes, hypertelorism, protruding ears, hypoplastic ear lobes with cup-shaped right ear; anteverted nares, thin upper lip, narrow-arched palate, broad secondary alveolar ridge, labio-gingival retraction, micrognathia, loose nuchal skin, sloping shoulders, and heart murmur. The right thumb was virtually absent and had a hypoplastic nail, and the left was severely hypoplastic.

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CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Holoprosencephaly and Genitourinary Anomalies in Fetal Methotrexate Syndrome

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Prenatal exposure to methotrexate (MTX) in the first trimester may lead to fetal death, and surviving children have increased risks for cranial dysostosis, dysmorphic facies, skeletal malformations, limb defects, growth retardation, and, in some cases, developmental delay, a pattern of defects recognized as fetal MTX syndrome (FMS). We report on a male infant who, in addition to severe FMS, showed previously undescribed central nervous system (CNS) and genitourinary anomalies that contributed to the further delineation. The propositus was born to a G2, 20-year-old mother with an irregular menstrual history. The unplanned pregnancy was complicated by oral MTX treatment (5 mg/day) for suspected systemic lupus erythematosus for 14 days at the 5th week post-conception, as dated by the first trimester sonogram. In addition to the typical features of the FMS, our propositus exhibited congenital penile curvature, vesicoureteral reflux, hydronephrosis, and severe CNS anomalies including semilobar holoprosencephaly (HPE). A single previous report of lobar-type HPE in an infant with FMS led us to confirm that the HPE observed in the propositus is a feature attributable to MTX teratogenicity, although the exact mechanisms of the HPE production need to be further elucidated. Also, this case serves to highlight the presence of genitourinary anomalies in patients with FMS, a fact that requires intentional searches in future patients in order to confirm this as being characteristic of the entity.

Key words: aminopterin syndrome; penile curvature; vesicoureteral reflux; hydronephrosis; holoprosencephaly; cleft palate; hypospadias

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INTRODUCTION

Methotrexate (MTX), a methyl derivate of aminopterin, is a folic acid antagonist widely used as an antineoplastic agent, as well as in the treatment of several dermatological, rheumatologic, gynecological, and obstetric conditions, including the elective medical termination of pregnancy [Lloyd et al., 1999]. Prenatal exposure to MTX in the first trimester may lead to fetal death, and surviving children have increased risks for cranial dysostosis, cerebral anomalies, dysmorphic facies, skeletal malformations, limb defects, growth retardation, and, in some cases, developmental delay, a pattern of defects recognized as fetal MTX syndrome (FMS), or as aminopterin/MTX syndrome, however, aminopterin is no longer available [Del campo et al., 1999; Adam et al., 2003]. The critical period for the development of the FMS is thought to occur between 6 and 8 weeks after conception [Feldkamp and Carey, 1993;

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CHROMOSOME INSTABILITY IN A PATIENT WITH RECURRENT ABORTIONS

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Summary: *Chromosome instability in a patient with recurrent abortions:* Chromosomal aberrations are one of the recognized possible etiologic genetic causes of recurrent spontaneous abortions. Increased chromosome instability without constitutional chromosome abnormalities is uncommon in these couples. In this work we present a non consanguineous healthy couple with recurrent abortions without constitutional chromosome aberrations in which spontaneous and induced chromosome aberrations were observed in the female. Chromosome analysis was performed in the presence of different chromosome damage inductors such as gamma radiation, Uv light, and mitomycin-C. Alterations observed only in the female were: spontaneous and induced tetraradial chromosomes and increased chromosomal damage induced only by gamma radiation. Oral mucosa micronuclei were moderately increased in the female. Chromosome instability associated to abortion is proposed.

Key-words: Chromosome instability – Recurrent abortions.

INTRODUCTION

It is well known that around 50% of all early pregnancy losses are caused by chromosome abnormalities (11). Recurrent pregnancy loss or recurrent spontaneous abortions occur in 1 to 2 % of fertile women (6). The pathophysiological mechanism has not been well established. Among the recognized possible etiologic causes of abortion, genetic cause comprises single gene mutations, multifactorial inheritance, and chromosomal aberrations according to time of gestation (18). The importance of chromosome abnormalities in the occurrence of spontaneous abortions is well documented. Higher frequencies of balanced aberrations are found when compared to the general population (20). Couples with recurrent spontaneous abortions or infertility and without constitutional chromosome abnormalities may show increased chromosome instability (20-21). This can be manifested as a significantly greater number of single cell translocations (9), micronuclei (20), marker induced chromosomal aberrations (12-20), aphidicolin-induced common fragile sites (15), or spontaneous chromosome breakages (20-21). Non constitutional spontaneous or induced chromosome aberrations associated to genetic instability and abortion are infrequent. In this work we present a non consanguineous healthy couple without con-

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RESEARCH LETTER

AMERICAN JOURNAL OF medical genetics PART A

Further Clinical Delineation of Fine–Lubinsky Syndrome

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TO THE EDITOR:

In 1983, Fine and Lubinsky described a male infant who had congenital hydrocephalia due to aqueductal stenosis, an absence of the corpus callosum, brachycephaly without craniosynostosis, congenital body asymmetry, severe growth failure, and developmental delay. Aymé and Philip [1996] first coined the eponymous term Fine–Lubinsky syndrome (FLS) to refer to this pattern of defects, also classified as brachycephaly, deafness, cataract, microstomia, and mental retardation syndrome (BDCMMRS) [OMIM 601353]. Since the initial report, there have been five additional reported non-familial cases [Preus et al., 1984; Suthers et al., 1993; Aymé and Philip, 1996; Nakane et al., 2002; Schoner et al., 2008], and one family harboring an affected brother and sister [Holder et al., 2007]. Due to the reduced number of affected patients, a clinical delineation of FLS cannot currently be fully elucidated. We report on a male infant with a severe phenotype of FLS, and review all of the diagnostic criteria that can define this entity, as well as some aspects of its nosology.

The propositus was the product of the first uncomplicated pregnancy from non-consanguineous and healthy parents. Family data included three paternal uncles with mild mental retardation, and one maternal cousin with hydrocephaly. There was no prior history of exposure to teratogens. Delivery was carried out via cesarean in the 39th week of gestation. Apgar scores were 9 at 1 and 5′, respectively. The birth weight was 2,400 g (<3rd centile), the length was 48 cm (10th centile), and the infant had an occipitofrontal circumference (OFC) of 32 cm (10th centile). This infant experienced feeding difficulties as well as marked hypotonia. His mother observed that auditory responses to the environment were poor, and he also showed visual inattentiveness. Infantile spasms began at age 4 months. Clinical examination at 7 months showed (Fig. 1) a weight of 5,120 g (−4.2 SD), length of 79 cm (−1.3 SD), OFC of 42.5 cm (−1.2 SD), brachycephaly, posterior plagiocephaly, large anterior fontanel, round face, wide forehead; hypertelorism, midfacial hypoplasia, beaked nose, high-arched palate, micrognathia, asymmetric right-side chest, flexion contractures of proximal interphalangeal joints, adducted thumbs, long fingers, mild skin syndactyly on second to fifth digits, clinodactyly and absence of skin creases on distal interphalangeal joints of the fifth fingers, single

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Short report

Abnormal oral-pharyngeal swallowing as cause of morbidity and early death in Stüve-Wiedemann syndrome

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ABSTRACT

Stüve-Wiedemann syndrome (SWS) is an autosomal recessive bone dysplasia (OMIM #601559) characterized by bowing of long bones, camptodactyly, respiratory insufficiency, hyperthermic episodes, and neonatal death from hyperthermia or apnea. We describe two female siblings with SWS born from consanguineous Gypsy parents. For a further delineation of SWS, we report hypothyroidism and ectopic thyroid as part of its phenotypic spectrum. Molecular study in the leukemia inhibitory factor receptor (*LIFR*) gene (OMIM *151 443) demonstrated the presence of a mutation. We observed that in one of our patients, oropharyngeal disruption in the swallowing process caused repetitive aspiration pneumonias, life-threatening events, and finally death. We emphasize that these features represent dysautonomic manifestations of SWS, and are probably related to pharyngoesophageal dyskinesia due to abnormal autonomic control of the anterior rami of cervical roots C1–C5.

1. Introduction

Stüve-Wiedemann syndrome (SWS) is usually described as an autosomal recessive bone dysplasia (OMIM #601559) characterized by bowing of long bones, camptodactyly, respiratory insufficiency, hyperthermic episodes, and neonatal death caused by hyperthermia or apnea [1,4,9,13,15,17]. SWS is allelic to Schwartz-Jampel type 2 syndrome (SJS2) [4,17] and is recognized as an autonomic dysfunction syndrome [3,9]. Manifestations of bone dysplasia in SWS/SJS2 have been attributed to mutations in the leukemia inhibitory factor receptor (*LIFR*) gene located on 5p13.1 [7]. Recently, the ciliary neurotrophic factor receptor (*CNTFR*) gene (OMIM *118946) was identified as responsible for a couple of syndromes with autonomic nervous system dysfunction [8]. The SWS/SJS2 are included in the family of *CNTFR* pathway-related disorders, and show overlapping phenotypes with the Crisponi and cold-induced sweating syndromes [6]. We describe a pair of sisters with SWS born from consanguineous Gypsy parents, with emphasis on the clinical role of dysautonomia as a cause of morbidity leading to an early death in this disease. Additionally, we propose hypothyroidism and ectopic thyroid as new findings in the SWS phenotypic spectrum. Molecular studies in one of our patients demonstrated a mutation in the *LIFR* gene, which predicted a premature termination of protein translation.

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UMBILICAL CORD DISRUPTION SEQUENCE CAUSED BY LONG CORD IN TWO UNRELATED INFANTS WITH AMYOPLASIA

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□ *Encirclement of a fetal body part by the umbilical cord with or without vascular obstruction in either the umbilical cord or the encircled fetal part is considered an umbilical cord loop (UCL). Significant disruption of the encircled fetal parts is recognized as the umbilical cord disruption sequence (UCDS). UCL around fetal parts is an occasional anomaly in infants with amyoplasia. We report on 2 patients with amyoplasia and damage to the fetal limbs caused by UCDS and a long umbilical cord. Patient 1 showed two deep constrictions on the left lower limb caused by UCL with an intact skin and a mild mark of constriction on the left wrist. The umbilical cord in patient 2 produced 5 entanglements around the left thigh which resulted in a deep groove extending down to the femur and also showed an exposed fracture and gangrene of the entire lower limb with an unusual congenital paraumbilical "stoma" that corresponded to the afferent loops of a jejunal atresia. The UCDS in infants with amyoplasia has been associated with short umbilical cords, whereas in patients without congenital contractures, the UCDS or UCL has been related to long umbilical cords. Our observations of UCDS in patients with amyoplasia but with long umbilical cords suggest the influence of both pathogenic factors or the existence of additional mechanisms. Evidence in patient 2 may support a vascular pathogenesis.*

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Ataxia telangiectasia. Diagnóstico y seguimiento en una serie de cuatro casos

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Resumen

La ataxia telangiectasia (AT) es un síndrome de inestabilidad cromosómica, con herencia autosómica recesiva, causada por más de 500 mutaciones en el gen ATM, involucrado en la respuesta celular ante el daño al ADN. Su diagnóstico llega a ser difícil debido a la evolución de la enfermedad, su pobre conocimiento y limitado acceso a pruebas diagnósticas. La prueba de daño cromosómico inducido con radiación ionizante (RI) sigue siendo un método sensible para un diagnóstico temprano; este último es indispensable para un mejor manejo y asesoramiento genético. El presente trabajo muestra el diagnóstico y seguimiento de una serie de cuatro casos con AT

PALABRAS CLAVES: *Ataxia telangiectasia. Inestabilidad cromosómica. Daño cromosómico inducido por RI.*

Abstract

Ataxia telangiectasia (AT) is a chromosomal instability syndrome with autosomal recessive inheritance, it is caused by more than 500 mutations of the ATM *gene, which is involved in the cellular response to DNA damage. The diagnosis becomes difficult due to the evolution of the disease, their poor knowledge, and limited access to diagnostic tests. Chromosomal damage induced by ionizing radiation (IR) assay is still a sensitive method for early diagnosis, and it is essential for better management and genetic counseling. This paper shows diagnosis and follow-up in four cases with AT*

KEY WORDS: *Ataxia telangiectasia. Chromosomal instability RI-induced chromosomal damage.*

Introducción

Ataxia telangiectasia es una enfermedad autosómica recesiva, causada por mutaciones en el gen *ATM (ataxia telangiectasia mutated,* 11q22.3) (OMIM #208900), más de 500 mutaciones han sido descritas[1] y se caracteriza por inestabilidad cromosómica, hipersensibilidad a RI[1,2], inmunodeficiencia celular y humoral[3], y susceptibilidad a cáncer (40% de los casos, de tipo linforreticulares y/o epitelial)[4,5]. Clínicamente presenta neurodegeneración con marcha atáxica progresiva y otros desórdenes de movimiento; disartria, retardo mental, apraxia ocular, telangiectasias, inmunodeficiencia e infecciones frecuentes[4,6]; elevación de α-fetoproteína, hipersensibilidad cutánea a la luz, hipoplasia/ausencia de timo e infecciones recurrentes[3]. Actualmente no existe cura para esta enfermedad, por tanto el objetivo es realizar un diagnóstico temprano y mantener una

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Síndrome de Yunis-Varon

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Carta al editor:

Leí con interés el artículo publicado por Elizondo-Dueñaz, et al.[1] titulado: «Síndrome de Yunis-Varon», donde los autores presentan a un paciente masculino de 17 años con estatura baja, ojos prominentes, hipertelorismo, dedos deformados, problemas de pronunciación, hombros encogidos, prominencia del hueso frontal, orejas displásicas, hundimiento del puente nasal, de los márgenes infraorbitarios, ausencia de piezas dentarias, paladar ojival y micrognatia. Radiológicamente, demostraron múltiples dientes sin brotar, ausencia de piezas dentarias permanentes e hipoplasia clavicular. Sin embargo, de manera respetuosa, considero que los datos clinicorradiográficos anteriormente asentados por Elizondo-Dueñaz, et al.[1] no son suficientes para sustentar el diagnóstico de síndrome Yunis-Varon (SYV), sobre todo por la descripción que hacen de las extremidades de su paciente. El SYV es una displasia cleidocraneal plus (OMIM %216340), siendo el componente plus la ausencia de pulgares y primeros ortejos, afalangia distal, anomalías ectodérmicas y un reservado pronóstico de vida. El SYV fue descrito originalmente en Colombia y se conocen 25 pacientes publicados a nivel mundial[2]. En una revisión reciente[3], encontramos que el SYV tiene un componente esquelético sistémico obligado, ya que el 100% de los casos estudiados radiográficamente presentan ausencia o hipoplasia de falanges distales, tanto en manos como en pies, y en el 95% de ellos, hipoplasia severa o ausencia de los pulgares y/o primeros ortejos y, además, la afectación esquelética incluye la disostosis craneal y de clavículas, displasia de pelvis, junto a las anomalías acrales previamente mencionadas. El SYV también afecta frecuentemente al corazón y al sistema nervioso central, y se conocen solo pocos sobrevivientes a la infancia temprana, algunos de ellos con retraso psicomotor. Ya que el paciente publicado por Elizondo-Dueñaz, et al.[1] no presenta el componente plus característico del SYV, considero que el caso presentado corresponde más apropiadamente a una presentación típica de una displasia o disostosis cleidocraneal, entidad cuya etiología es autosómica dominante y cuyo pronóstico para la vida y la función son generalmente favorables, sobre todo si lo comparamos con el SYV, cuya herencia es autosómica recesiva y que tiene un muy diferente pronóstico y asesoramiento genético. Al día de hoy no se ha identificado el gen responsable del SYV, aunque seguramente será encontrado en un futuro próximo mediante técnicas actuales como el análisis de secuenciación exómica. Por el contrario, el gen RUNX2 ha sido recientemente identificado como responsable de la displasia cleidocraneal (OMIM #119600).

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CASE REPORTS

Apoyo nutricio intensivo en trillizas monocigóticas de nueve meses de edad con desnutrición grave discordantes para amioplasia de miembros superiores

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Objetivo. Reportar el caso de unas trillizas del sexo femenino con desnutrición proteínico-energética grave que caracteriza una velocidad de crecimiento y cambios en la composición corporal casi idénticos después de un apoyo nutricio intensivo de seis semanas. Descripción del caso clínico. El diagnóstico de cigocidad realizado mediante análisis de repeticiones cortas en tándem (STR), amplificadas mediante PCR-multiplex mostró que las trillizas provenían de un mismo huevo fertilizado (monocigóticas). Como hallazgo inusual se encontró que la segunda trilliza fue discordante para amioplasia con afectación principal de miembros superiores, lo apoya mayormente el que esta condición no está genéticamente determinada. Discusión. Se analiza la manera sorprendente de recuperación nutricia casi idéntica de una desnutrición proteínico-energética grave en el mismo periodo de tiempo y la presencia de amioplasia en la segunda trilliza.

Introducción

La amioplasia o artrogriposis múltiple congénita es una entidad de etiología multifactorial con ocurrencia usualmente esporádica y bajo riesgo de recurrencia, caracterizada por contracturas articulares congénitas múltiples y pérdida de masa muscular, aunque también se reconoce un subtipo con afectación principal de extremidades superiores [1]. La identificación de gemelos monocigóticos discordantes para amioplasia va en sustento de su carácter esporádico y multifactorial [1-5]. El presente reporte clínico agrega la ocurrencia inusual de discordancia para amioplasia pero en trillizas monocigóticas, lo que mayormente apoya la noción de que esta condición específica no está genéticamente determinada. Pocos estudios han informado acerca de la presencia de desnutrición proteínico-energética primaria (DPE) grave de manera simultánea en miembros de un grupo de trillizos. En un estudio solo un niño procedente de trillizos[6] presentaba desnutrición grave y en otro no se especifica claramente si los trillizos presentaban desnutrición al mismo tiempo[7]. Sin embargo, no encontramos algún estudio que mencione el periodo de recuperación nutricia o la gravedad de la desnutrición de un grupo de trillizos de manera simultánea. El proceso de recuperación de una DPE grave en lactantes difiere de la observada en niños mayores (preescolares y escolares), debido a que normalmente la velocidad de crecimiento es mayor y los cambios de composición corporal son más rápidos [8]. Sin embargo, no tenemos experiencia de qué tan similares pueden ser esos cambios en lactantes trillizas, considerando los cambios rápidos que ocurren en la composición corporal durante el segundo semestre de la vida.

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Palabras clave: *trillizas, desnutrición grave, amioplasia, artrogriposis múltiple congénita.*
Key words: *monozygotic triplets, severe malnutrition, amyoplasia, arthrogryposis multiplex congenital.*

Descripción del caso clínico

Informamos sobre unas trillizas producto de un segundo embarazo y concebidas de manera espontánea. Al momento de su nacimiento, la madre tenía 18 años y el padre 20 años, ambos son sanos y no consanguíneos. La madre presentó historia de tabaquismo con consumo de un cigarro por día y negó otras exposiciones a agentes teratógenos. La genealogía mostró historia familiar negativa para malformaciones y/o gemelaridad. El embarazo cursó con amenaza de aborto al cuarto mes, sin recibir tratamiento farmacológico. Posteriormente, presentó amenaza de parto pretérmino seguida de ruptura prematura de membranas y desarrollo de trabajo de parto prematuro que llevó al nacimiento

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National Prevalence and Trends of HIV Transmitted Drug Resistance in Mexico

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Abstract

Background: Transmitted drug resistance (TDR) remains an important concern for the management of HIV infection, especially in countries that have recently scaled-up antiretroviral treatment (ART) access.

Methodology/Principal Findings: We designed a study to assess HIV diversity and transmitted drug resistance (TDR) prevalence and trends in Mexico. 1655 ART-naïve patients from 12 Mexican states were enrolled from 2005 to 2010. TDR was assessed from plasma HIV *pol* sequences using Stanford scores and the WHO TDR surveillance mutation list. TDR prevalence fluctuations over back-projected dates of infection were tested. HIV subtype B was highly prevalent in Mexico (99.9%). TDR prevalence (Stanford score>15) in the country for the study period was 7.4% (95% CI, 6.2:8.8) and 6.8% (95% CI, 5.7:8.2) based on the WHO TDR surveillance mutation list. NRTI TDR was the highest (4.2%), followed by NNRTI (2.5%) and PI (1.7%) TDR. Increasing trends for NNRTI ($p = 0.0456$) and PI ($p = 0.0061$) major TDR mutations were observed at the national level. Clustering of viruses containing minor TDR mutations was observed with some apparent transmission pairs and geographical effects.

Conclusions: TDR prevalence in Mexico remains at the intermediate level and is slightly lower than that observed in industrialized countries. Whether regional variations in TDR trends are associated with differences in antiretroviral drug usage/ART efficacy or with local features of viral evolution remains to be further addressed.

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Introduction

Antiretroviral therapy (ART) has radically decreased HIV-associated morbidity and mortality in countries where broad access to antiretroviral (ARV) drugs has been achieved. However, a wider availability of ART has led to increasing transmission of HIV variants with reduced susceptibility to ARV drugs [1,2,3,4,5,6,7,8,9]. Transmitted drug resistance (TDR) can reduce the efficacy of first-line ARV therapy, as complete suppression of HIV may be compromised [10]. The presence of resistance mutations in isolates from ARV-drug-naïve patients remains an important concern for the management of HIV infection, especially in the setting of resource-limited countries that have recently scaled-up ART access. Nevertheless, most patients in this setting are starting ART on potent regimens, possibly delaying transmission of drug-resistant HIV strains as compared with high-income countries, where ART scale-up began with suboptimal and lower-potency regimes [11]. This hypothesis is supported by the observation of stabilizing or decreasing tendencies in TDR in some developed countries during the last few years, which could be reflecting the more recent broad use of high-potency ART regimes [1,12,13,14]. Ongoing TDR surveillance programs using comparable drug resistance definitions are necessary to guide worldwide efforts to improve treatment outcomes by supplying information to support education and prevention programs and promote the rational use of ARV drugs by clinicians and policy makers [11,15,16,17].

Efforts to provide broad access to ART in Mexico started in 2001 with a universal access program, but it was until 2004 that coverage for persons without insurance was initiated [18]. Currently, all individuals who approach the Mexican Health System have access to ART either through the traditional social insurance program or the popular insurance system, introduced widely in the population by 2006 [19]. According to data from the

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CASE REPORT

Adult intussusception secondary to an ileum hamartoma

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Abstract

Intussusception is a rare condition in the adult population. However, in contrast to its presentation in children, an identifiable etiology is found in the majority of cases. Clinical manifestations of adult intussusception are non-specific and patients may present with acute, intermittent or chronic symptoms, predominantly those of intestinal obstruction. A 27-year-old male patient with recurrent abdominal pain secondary to intussusception is herein reported. The clinical presentation and ultrasonographic findings led to the diagnosis. At laparotomy, an ileal hamartoma was found as the lead point of the intussusception. Surgical management and histopathologic studies are described. A recurrent intestinal obstruction and classic ultrasound findings may lead to the diagnosis of intussusception but surgical exploration remains essential. The principle of resection without reduction is well established.

Key words: Adult intussusception; Ileum hamartoma; Intestinal obstruction

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INTRODUCTION

Intussusception accounts for 1%-5% of all cases of intestinal obstruction in adults[1]. In the majority of adult patients, a cause is identified. However, clinical presentation is not specific, manifesting as chronic intestinal obstruction symptoms[2]. Although radiographic findings at abdominal ultrasonography and computed tomography may be indicative, a preoperative diagnosis is made less frequently in adult patients than in children[2,3].

CASE REPORT

A 27-year-old male patient presented at the emergency

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First Report of Staphylococcal Clinical Isolates in Mexico with Linezolid Resistance Caused by *cfr*: Evidence of *In Vivo cfr* Mobilization▽

An oxazolidinone resistance mechanism (Cfr) was recently described in human isolates of staphylococci (18). Cfr causes posttranscriptional methylation of the 23S rRNA (A2503), affecting drugs belonging to several antimicrobial classes (10). *cfr*-carrying isolates recovered from human clinical specimens are still rare (4, 6); however, cases were reported in the United States (12), Colombia (18), and Spain (15). Here, we report the first cases of human clinical infections caused by Cfr-producing *Staphylococcus* species in Mexico and demonstrate evidence of interspecies *cfr* mobilization.

Three linezolid-resistant (MIC, 32 μg/ml) Staphylococcal isolates were submitted to a central monitoring laboratory (JMI Laboratories) as part of the SENTRY Antimicrobial Surveillance Program in 2009. These strains were collected from hospitalized patients at the Hospital Civil de Guadalajara. *Staphylococcus cohnii* (10842A) was found in a blood culture (August 2009) from a 30-year-old man admitted with multiple trauma. *Staphylococcus epidermidis* (12898A) was also recovered in blood (October 2009) from a 50-year-old female with bacteremia who was admitted with a diagnosis of Guillain-Barre syndrome. Both isolates were cultured within 48 h after patients had developed clinical signs of sepsis (i.e., systemic inflammatory response syndrome [SIRS]). The third organism was an *S. epidermidis* isolate (5873X) cultured (October 2009) from abdominal fluid in a 36-year-old male presenting with multiple trauma.

Bacterial identification was confirmed by 16S rRNA sequencing (3). Isolates were tested for susceptibility by the reference broth microdilution method (1). MIC interpretations were performed based on Clinical and Laboratory Standards Institute criteria (2), except for retapamulin MIC values (19). Quality control strains included *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 (2). Isolates were screened for *cfr* and mutations in the 23S rRNA as described previously (12). L3- and L4-encoding genes were PCR amplified (13), amplicons were sequenced on both strands, and putative proteins were compared with those from linezolid-susceptible *S. epidermidis* ATCC 12228 and *S. cohnii* ATCC 29974. Pulsed-field gel electrophoresis (PFGE) and multilocus sequence typing were performed on *S. epidermidis* isolates (11, 14). After extraction (plasmid DNA minikit; Qiagen GmbH, Hilden, Germany), plasmid DNAs were digested (HindIII and XbaI), separated on a 1% agarose gel, and transferred onto a nylon membrane by Southern blotting (17). Membranes were hybridized using a *cfr*-specific probe (Roche Diagnostics GmbH, Mannheim, Germany).

Linezolid-resistant isolates had their identifications confirmed as *S. epidermidis* (isolates 12898A and 5873X) and *S. cohnii* (isolate 10842A). Isolates were oxacillin resistant (MIC, >2 μg/ml) and exhibited elevated MICs for linezolid (32 μg/ml), quinupristin-dalfopristin (1 to 4 μg/ml), retapamulin (≥8 μg/ml), chloramphenicol (16 to 32 μg/ml), and clindamycin (>64 μg/ml) (Table 1). Isolates were susceptible to tetracycline, tigecycline, daptomycin, and glycopeptides.

All strains were PCR positive for *cfr* and wild type for 23S rRNA and L4, except for *S. cohnii*, which showed L4 substitutions (Asn20Ser, Ala133Thr, and Val155Ile) (Table 2). L3 Ser158Tyr, Asp159Tyr, and Leu101Val mutations were noted in both *S. epidermidis* isolates, while Ser158Phe and Asp159Tyr were observed in *S. cohnii*. The L3 Leu101Val substitution was previously detected in a linezolid-susceptible clinical isolate (data on file, JMI Laboratories). However, Gly155 and Ala157 were previously implicated in disturbing linezolid binding (8, 9). Thus, due to the proximity of these amino acid substitutions to those found in this study, the L3 mutations coupled with *cfr* may act synergistically and possibly contribute to the elevated linezolid MIC results. An Asn158Ser mutation in L4 was previously noted in a linezolid-susceptible *S. epidermidis* strain (20). Therefore, since Val155Ile is close to Asn158 and the alterations found in L4 are not within a conserved region, they likely do not represent resistance mutations; however, additional experiments are needed.

The *S. epidermidis* isolates (12898A and 5873X) displayed

TABLE 1. Antimicrobial susceptibility profiles of *cfr*-carrying Staphylococcal isolates recovered from clinical specimens of hospitalized patients in Guadalajara, Mexico

Antimicrobial agent	MIC (μg/ml) (susceptibility category)[a]		
	S. cohnii 10842A	*S. epidermidis* 12898A	*S. epidermidis* 5873X
Linezolid	32 (R)	32 (R)	32 (R)
Quinupristin-dalfopristin	4 (R)	2 (I)	1 (S)
Retapamulin	>8 (R)	8 (R)	>8 (R)
Chloramphenicol	32 (R)	16 (I)	16 (I)
Clindamycin	>64 (R)	>64 (R)	>64 (R)
Tigecycline	0.06 (S)	0.12 (S)	0.25 (S)
Tetracycline	≤0.12 (S)	2 (S)	1 (S)
Doxycycline	≤0.12 (S)	0.5 (S)	1 (S)
Daptomycin	0.25 (S)	0.5 (S)	0.5 (S)
Vancomycin	1 (S)	2 (S)	2 (S)
Teicoplanin	≤2 (S)	8 (S)	8 (S)
Oxacillin	>2 (R)	>2 (R)	>2 (R)
Ciprofloxacin	>4 (R)	>4 (R)	>4 (R)
Erythromycin	>2 (R)	>2 (R)	>2 (R)
Gentamicin	>8 (R)	>8 (R)	>8 (R)
Trimethoprim-sulfamethoxazole	≤0.5 (S)	>2 (R)	>2 (R)

[a] MIC interpretive criteria were as published in CLSI M100-S20 (2). Retapamulin MIC results were interpreted according to parameters reported by Traczewski et al. (19). S, susceptible; I, intermediate; R, resistant.

TABLE 2. Molecular findings for *cfr*-carrying *Staphylococcus* isolates recovered from clinical specimens of hospitalized patients in Guadalajara, Mexico

Isolate	*cfr*	23S rRNA	Mutations in:	
			L3	L4
S. cohnii 10842A	Positive	WT[a]	Ser158Phe/Asp159Tyr	Asn20Ser/Ala133Thr/Val155Ile
S. epidermidis 12898A	Positive	WT	Ser158Tyr/Asp159Tyr/Leu101Val	WT
S. epidermidis 5873X	Positive	WT	Ser158Tyr/Asp159Tyr/Leu101Val	WT

[a] WT, wild type.

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PLoS one

Pilot, Randomized Study Assessing Safety, Tolerability and Efficacy of Simplified LPV/r Maintenance Therapy in HIV Patients on the 1st PI-Based Regimen

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Abstract

Objectives: To compare the efficacy and safety of an individualized treatment-simplification strategy consisting of switching from a highly-active anti-retroviral treatment (HAART) with a ritonavir-boosted protease inhibitor (PI/r) and 2 nucleoside reverse-transcriptase inhibitors (NRTIs) to lopinavir/ritonavir (LPV/r) monotherapy, with intensification by 2 NRTIs if necessary, to that of continuing their HAART.

Methods: This is a one-year, randomized, open-label, multi-center study in virologically-suppressed HIV-1-infected adults on their first PI/r-containing treatment, randomized to either LPV/r-monotherapy or continue their current treatment. Treatment efficacy was determined by plasma HIV-1 RNA viral load (VL), time-to-virologic rebound, patient-reported outcomes (PROs) and CD4+T-cell-count changes. Safety was assessed with the incidence of treatment-emergent adverse events (AE).

Results: Forty-one patients were randomized to LPV/r and 39 to continue their HAART. No statistically-significant differences between the two study groups in demographics and baseline characteristics were observed. At day-360, 71(39:LPV/r;32:HAART) patients completed treatment, while 9(2:LPV/r;7:HAART) discontinued. In a Last Observation Carried Forward Intent-to-Treat analysis, 40(98%) patients on LPV/r and 37(95%) on HAART had VL<200copies/mL (P = 0.61). Time-to-virologic rebound, changes in PROs, CD4+ T-cell-count and VL from baseline, also exhibited no statistically-significant between-group differences. Most frequent AEs were diarrhea (19%), headache (18%) and influenza (16%). Four (10%) patients on LPV/r were intensified with 2 NRTIs, all regaining virologic control. Eight serious AEs were reported by 5(2:LPV/r;3:HAART) patients.

Conclusion: At day-360, virologic efficacy and safety of LPV/r appears comparable to that of a PI+2NRTIs HAART. These results suggest that our individualized, simplified maintenance strategy with LPV/r-monotherapy and protocol-mandated NRTI re-introduction upon viral rebound, in virologically-suppressed patients merits further prospective long-term evaluation.

Trial Registration: ClinicalTrials.gov NCT00159224

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Introduction

The standard treatment approach in HIV-1 infection involves using a combination of at least three antiretroviral (ARV) drugs, designated highly active antiretroviral therapy (HAART) to fully suppress plasma HIV-1 RNA viral load (VL), in a sustainable fashion. Currently recommended first line antiretroviral regimens consist of two nucleoside (NRTI) or nucleotide (NtRTI) analog reverse transcriptase inhibitors and either a non-nucleoside reverse transcriptase inhibitor (NNRTI), an integrase strand transfer

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Diagnosis of latent tuberculosis infection among HIV discordant partners using interferon gamma release assays

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Abstract

Background: There is limited data on the effect of HIV status and CD4 counts on performance of Interferon-**g** Release assays (IGRAs) for diagnosis of latent tuberculosis infection (LTBI).

Methods: A cross sectional study was conducted to assess the prevalence of and risk factors for a positive diagnostic test for LTBI, using tuberculin skin test (TST) and IGRAs among HIV-discordant couples in Zambia.

Results: A total of 596 subjects (298 couples) were enrolled. Median CD4 count among HIV positive persons was 388 cells/μl, (range 51-1330). HIV negative persons were more likely than their HIV positive partner, to have a positive diagnostic test for LTBI with TST (203 vs 128), QFT (171 vs 109) and TSPOT (156 vs. 109). On multivariate analysis, HIV negative status was an independent predictor for a positive QFT (OR = 2.22, 95% CI 1.42- 3.46) and TSPOT (OR = 1.79, 95% CI 1.16-2.77). Among HIV positive subjects a CD4 count ≥ 388 cells/μl was associated with a positive TST (OR = 1.76 95% CI 1.10-2.82) and QFT (OR = 1.71 95% CI 1.06-2.77) but not TSPOT (OR = 1.20 95% CI 0.74-1.94).

Conclusions: Persons with HIV had significantly fewer positive diagnostic tests for LTBI with TST, QFT and TSPOT. Persons with a CD4 count < 388 cells/μl were less likely to have a positive TST or QFT, but not less likely to have a positive TSPOT. TSPOT may perform better than TST or QFT in HIV positive individuals.

Background

HIV and tuberculosis (TB) are the leading causes of death among adults due to an infectious disease worldwide. It is estimated that > 13 million people are co-infected with HIV and *Mycobacterium tuberculosis* [1]. The World Health Organization (WHO) estimates that there are approximately 9.3 million new cases of active TB and nearly 2 million deaths due to the disease worldwide each year [2,3]. Twenty-seven percent of TB cases and 31% of TB-related deaths occur in Africa, home to only 11% of the world's population [4].

HIV infection is the most important risk factor for progression from latent tuberculosis infection (LTBI) to active TB [5,6]. In patients with HIV and LTBI, the annual risk of progression to active TB is approximately 10% per year [7-9] compared to a lifetime risk of 5-10% in immunocompetent persons [7]. Diagnosis and treatment of LTBI is a major strategy for TB control and prevention in the US [7,10]. WHO has recommended the implementation of isoniazid preventive therapy for HIV-seropositive persons in an effort to prevent additional cases of TB, but this strategy has not yet been widely adopted in Africa [3].

For nearly a century, diagnosis of LTBI has relied on the tuberculin skin test (TST) which has several limitations including low specificity due to cross reaction with BCG vaccination and non-tuberculous mycobacteria (NTM) and low sensitivity in HIV infection. New diagnostic tests for tuberculosis are urgently needed to enhance global TB control [11,12].

Two Interferon-γ release assays (IGRAs) are now commercially available for the diagnosis of LTBI

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Granulomatous hypophysitis by *Mycobacterium gordonae* in a non HIV-infected patient

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Abstract

Lymphocytic or granulomatous hypophysitis is a rare entity with a difficult diagnosis. Our objective was to report a patient with non-tuberculous granulomatous hypophysitis. An HIV-negative 45-year old man with confusional state, subacute ophthalmoplegia, and clinical and laboratory findings of panhypopituitarism was seen in the emergency unit. A cranial MRI showed a sellar mass suggestive of hypophysitis. After an unsuccessful attempt with steroids and antituberculous drugs the patient died. *Post-mortem* histopathology revealed granulomatous lesions and restriction fragment length polymorphism analysis confirmed the presence of *Mycobacterium gordonae's* DNA. In conclusion, we should consider granulomatous hypophysitis in the differential diagnosis of non-secreting hypophyseal tumors. The etiology of a pituitary granuloma by a non-tuberculous mycobacteria is best reached by histopathological techniques and molecular assays. The optimal therapy is yet to be established.

Introduction

The pituitary region is susceptible to involvement by cystic, neoplastic, infectious and inflammatory processes.[1] Granulomatous hypophysitis (GH) is an inflammatory disorder characterized by the formation of granulomas frequently associated with tuberculosis, sarcoidosis, syphilis, and lymphocytic adenohypophysitis. This entity usually presents with systemic symptoms such as high fever and hormonal disturbances.[2]

We describe a *post-mortem* case of granulomatous hypophysitis secondary to infection caused by *Mycobacterium gordonae*. To our knowledge, only two other cases of GH caused by non-tuberculous mycobacteria infection (*Mycobacterium malmoense* and *Mycobacterium tokaiense*) in non-compromised hosts have been reported to date.[3,4]

Case Report

A 45-year-old man presented with a six-month history of weight loss, anorexia, vomiting, malaise and apathy. In the last month his condition worsened and headache, diplopia and left ptosis appeared. Neurological examination showed a person with slow mental processing, slow speech, affective flattening and left ophthalmoplegia (partial III cranial nerve palsy). No visual field disturbances, papilledema or meningeal signs were observed. General physical examination was unremarkable. Laboratory analyses only showed a low sodium blood level (114 mmol/L). A chest x-ray and a head CT scan were inconclusive and cerebrospinal fluid (CSF) was normal. After six days of hospitalization, fever, diarrhea and stupor appeared. A cranial MRI showed a sellar and parasellar heterogeneous mass, which in T1-weighted phase revealed a lesion with hypointense areas. In a T2-weighted phase this lesion was predominantly hyperintense with a hypointense center. After gadolinium administration, the lesion appeared heterogeneous with a parasellar extension toward the left cavernous sinus (Figure 1).

The measurement of plasma hypophysis hormones revealed a panhypopituitarism state. Based on the neuroimaging and hormonal findings, a presumptive diagnosis of hypophysitis was made. The patient was treated with steroid replacement, as well as with first- and second-line antituberculous drugs. Other laboratory studies were unremarkable, including serological tests for B and C hepatitis viruses, HIV, VDRL and *Brucella*, as well as erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies and rheumatoid factor.

Despite management, the patient died on day 11 of hospitilization. The autopsy showed

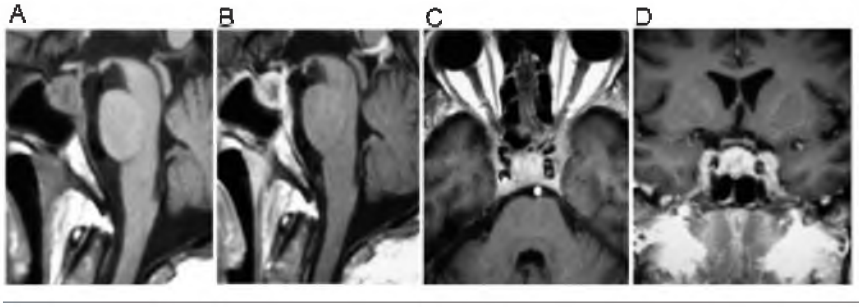

Figure 1. A cranial magnetic resonance imaging showed an intrasellar mass. (A) A sagittal T1-weighted image revealed a sellar lesion with hypointense areas. (B) A gadolinium-enhanced sagittal image showed an enhancing lesion with a hypointense center. Axial (C) and coronal (D) images demonstrated parasellar extension toward the left cavernous sinus.

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Key words: granuloma, hypophysis, non-tuberculous *Mycobacteria*, panhypopitituarism, pituitary gland.

Contributions: all authors have substantially contributed to the conception and design of the work and data analysis, take responsibility for the final version of the manuscript and approved it for publication.

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Roundtable on Urban Living Environment Research (RULER)

David Vlahov, Siddharth Raj Agarwal, Robert M. Buckley, Waleska Teixeira Caiaffa, Carlos F. Corvalan, Alex Chika Ezeh, Ruth Finkelstein, Sharon Friel, Trudy Harpham, Maharufa Hossain, Beatriz de Faria Leao, Gora Mboup, Mark R. Montgomery, Julie C. Netherland, Danielle C. Ompad, Amit Prasad, Andrew T. Quinn, Alexander Rothman, David E. Satterthwaite, Sally Stansfield, and Vanessa J. Watson

ABSTRACT *For 18 months in 2009–2010, the Rockefeller Foundation provided support to establish the Roundtable on Urban Living Environment Research (RULER). Composed of leading experts in population health measurement from a variety of disciplines, sectors, and continents, RULER met for the purpose of reviewing existing methods of measurement for urban health in the context of recent reports from UN agencies on health inequities in urban settings. The audience for this report was identified as international, national, and local governing bodies; civil society; and donor agencies. The goal of the report was to identify gaps in measurement that must be filled in order to assess and evaluate population health in urban settings, especially in informal settlements (or slums) in low- and middle-income countries. Care must be taken to integrate recommendations with existing platforms (e.g., Health Metrics Network, the Institute for Health Metrics and Evaluation) that could incorporate, mature, and sustain efforts to address these gaps and promote effective data for healthy urban management. RULER noted that these existing platforms focus primarily on health outcomes and systems, mainly at the national level. Although substantial reviews of health outcomes and health service measures had been conducted elsewhere, such reviews covered these in an aggregate and perhaps misleading way. For example, some spatial aspects of health inequities, such as those pointed to in the 2008 report from the WHO's Commission on the Social Determinants*

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NUTRITION JOURNAL

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Synbiotic therapy decreases microbial translocation and inflammation and improves immunological status in HIV-infected patients: a double-blind randomized controlled pilot trial

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Abstract

Background: HIV-infection results in damage and dysfunction of the gastrointestinal system. HIV enteropathy includes pronounced CD4+ T-cell loss, increased intestinal permeability, and microbial translocation that promotes systemic immune activation, which is implicated in disease progression. A synbiotic is the combination of probiotics and prebiotics that could improve gut barrier function. Our study goal was to determine whether the use of a synbiotic, probiotics or a prebiotic can recover immunological parameters in HIV-infected subjects through of a reduction of microbial translocation and pro-inflammatory cytokine production.

Methods: A randomized, double-blind controlled study was performed; twenty Antiretroviral treatment-naïve HIV-infected subjects were subgrouped and assigned to receive a synbiotic, probiotics, a prebiotic, or a placebo throughout 16 weeks.

Results: We had no reports of serious adverse-events. From baseline to week 16, the synbiotic group showed a reduction in bacterial DNA concentrations in plasma ($p = 0.048$). Moreover, the probiotic and synbiotic groups demonstrated a decrease in total bacterial load in feces ($p = 0.05$). The probiotic group exhibited a significant increment of beneficial bacteria load (such as *Bifidobacterium*; $p = 0.05$) and a decrease in harmful bacteria load (such as *Clostridium*; $p = 0.063$). In the synbiotic group, the CD4+ T-cells count increased (median: +102 cells/μL; $p = 0.05$) and the level of Interleukin 6 cytokine decreased significantly ($p = 0.016$).

Conclusions: Our study showed a significant increase in CD4+ T lymphocyte levels in the synbiotic group, which could delay the initiation of antiretroviral therapy and decrease costs in countries with limited resources.

Introduction

A huge Gastrointestinal (GI) pathology is observed in patients infected with HIV even during primary infection. Approximately 60% of total CD4+ T cells, reside in Gut-associated lymphoid tissue (GALT), and of all tissues, the latter is one of the most strongly affected during HIV infection [1]. In 1984, Kotler and collaborators described HIV enteropathy; subsequently, several studies have demonstrated HIV-associated damage to the GI tract [2-4].

Gastrointestinal damage in HIV infection and microbial translocation

Once HIV enters the mucosa of the gut, it finds a large pool of resting Ki67-CD4+ T cells; up to 60% of these cells are infected and are capable of produce the virus, constituting a dense network of cells in the intestinal mucosa, which is capable of spreading the infection to uninfected cells through cell-to-cell contact. This spread allows the maintenance of a continuous chain of viral transmission and forms part of a large reservoir that is

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Obstructing Gangliocytic Paraganglioma in the Third Portion of the Duodenum

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Key Words
Duodenal obstruction · Gangliocytic paraganglioma · Duodenal neoplasm

Abstract
Gangliocytic paragangliomas are infrequent tumors almost exclusively found in the second portion of the duodenum. An unusual case of a gangliocytic paraganglioma in the third portion of the duodenum with obstructive symptoms is herein reported. A 16-year-old male patient presented with epigastric pain, postprandial plenitude and reflux. A barium swallow failed to demonstrate abnormalities. Endoscopy showed a pedunculated submucosal tumor, originating at the third duodenal portion and causing partial obstruction. Biopsy was not performed due to the risk of bleeding. CT scan demonstrated a polypoid lesion. Through a transmesocolic approach and an anterior duodenotomy, resection of the tumor was performed. No lymph node or other organ affection was found. Histologic examination revealed a gangliocytic paraganglioma. Immunohistochemical examination was performed. Gangliocytic paragangliomas originating in the third or fourth portion of the duodenum, as in the present case, are extremely rare. Characteristic histologic features including epithelioid cells, spindle-shaped cells and ganglion-like cells were met. The majority of cases manifest with a similar benign behavior. Local resection of the tumor is recommended for these cases. An infrequent case of a gangliocytic paraganglioma located in the third portion of the duodenum, with a less common clinical presentation, is herein reported.

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KARGER

THE GLOBAL ROLE OF KIDNEY TRANSPLANTATION.

G. Garcia-Garcia, P. Harden,[1] and J. Chapman[2]

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Abstract

Go to:

Introduction

Kidney transplantation is acknowledged as a major advance of modern medicine which provides high-quality life years to patients with irreversible kidney failure (end-stage renal disease, ESRD) worldwide. What was an experimental, risky, and very limited treatment option 50 years ago is now a routine clinical practice in more than 80 countries. What was once limited to a few individuals in a small number of leading academic centers in high-income economies is now transforming lives as a routine procedure in most high- and middle-income countries, but can do much more. The largest numbers of transplants are performed in the USA, China, Brazil, and India, while the greatest population access to transplantation is in Austria, USA, Croatia, Norway, Portugal, and Spain. There are still many limitations in access to transplantation across the globe. World Kidney Day on 8 March 2012 will bring focus to the tremendous life-changing potential of kidney transplantation as a challenge to politicians, corporations, charitable organizations, and healthcare professionals. This commentary raises awareness of the progressive success of organ transplantation, highlighting concerns about restricted community access and human organ trafficking and commercialism, while also exploring the real potential for transforming kidney transplantation into the routine treatment option for ESRD across the world.

Go to:

Outcomes of Kidney Transplantation

The first successful organ transplantation is widely acknowledged to be a kidney transplant between identical twins performed in Boston on 23 Dec 1954, which heralded the start of a new era for patients with ESRD.[1] In the development years between 1965 and 1980, patient survival progressively improved toward 90% and graft survival rose from less than 50% at 1 year to at least 60% after a first deceased donor kidney transplant, based on immunosuppression with azathioprine and prednisolone. The introduction of cyclosporine in the mid-1980s was a major advancement, leading to 1-year survival rates of more than 90% and graft survival of 80%.[2] In the last 20 years, better understanding of the benefits of combined immunosuppressant drugs coupled with improved organ matching and preservation, as well as chemoprophylaxis of opportunistic infections, have all

Prediction of Retinopathy of Prematurity Using the Screening Algorithm WINROP in a Mexican Population of Preterm Infants

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Objective: To retrospectively validate the WINROP (weight, insulin-like growth factor I, neonatal, retinopathy of prematurity [ROP]) algorithm in identification of type 1 ROP in a Mexican population of preterm infants.

Methods: In infants admitted to the neonatal intensive care unit at Hospital Civil de Guadalajara from 2005 to 2010, weight measurements had been recorded once weekly for 192 very preterm infants (gestational age [GA] <32 weeks) and for 160 moderately preterm infants (GA ≥32 weeks). Repeated eye examinations had been performed and maximal ROP stage had been recorded. Data are part of a case-control database for severe ROP risk factors.

Results: Type 1 ROP was found in 51.0% of very preterm and 35.6% of moderately preterm infants. The WINROP algorithm correctly identified type 1 ROP in 84.7% of very preterm infants but in only 5.3% of moderately preterm infants. For infants with GA less than 32 weeks, the specificity was 26.6%, and for those with GA 32 weeks or more, it was 88.3%.

Conclusions: In this Mexican population of preterm infants, WINROP detected type 1 ROP early in 84.7% of very preterm infants and correctly identified 26.6% of infants who did not develop type 1 ROP. Uncertainties in dating of pregnancies and differences in postnatal conditions may be factors explaining the different outcomes of WINROP in this population.

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RETINOPATHY OF PREMATURITY (ROP) is a major cause of life-long blindness; its frequency is strongly associated with the quality of health care. In high-income countries, where many very immature babies survive, severe ROP affects the most immature, and screening and treatment programs make blindness rare. In middle-income countries, health care is good enough for survival of some extremely premature and more mature babies[1] but is insufficient in preventing ROP, leading to an increased prevalence of ROP in more mature babies; an epidemic of ROP-related blindness is presently seen in these countries. In the poorest parts of the world, where immature babies do not survive, ROP is not a problem.[2]

Current screening programs are based on gestational age (GA) and/or birth weight (BW) but, because of national differences in socioeconomic status and quality of care, different countries need different screening criteria.[2] The disadvantage of using GA for national screening criteria was recently shown in a study[3] from Rio de Janeiro. Two clinics with high survival rates had no infants with type 1 ROP whose GA was more than 32 weeks, while in 5 other clinics with poorer survival rates, infants with GA 35 weeks or less required screening.

In high-income countries that screen infants with GA less than 32 weeks, only 5% to 10% of the infants need treatment,[4] and many fragile babies who will never develop sight-threatening ROP undergo repeated painful and stressful eye examinations.[5]

Based on the finding of the association between poor early weight gain,[6] low serum insulin-like growth factor I, and ROP and in an attempt to refine ROP screening, the algorithm WINROP (weight, insulin-like growth factor I, neonatal, ROP) was developed and validation of its ability to predict severe ROP was performed.[7,8] Later, WINROP was found to function well using only weights,[9] allowing blood sampling and analyses to be omitted. Studies validating WINROP in 3 different populations with GA less than 32 weeks have been published. In one Swedish[9] and one US population,[10] sensitivity of 100% and specificity of 84.5% and 81.7%, respectively, were found, and in a Brazilian study,[11] sensitivity was 90.5% and specificity was 55.0%.

The aim of this study was to validate WINROP regarding its ability to predict

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ORIGINAL ARTICLE

Atypical forms of the osmotic demyelination syndrome

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Abstract Osmotic demyelination syndrome (ODS) is the damage over the central nervous system caused by several electrolytes, metabolic and toxic disorders. We aimed to describe cases of unusual forms of ODS. In a 9-year period, 25 consecutive patients with ODS (15 men; mean age 42 years) were registered in our referral institution, among them, four (16 %) with atypical neuroimaging findings were abstracted for this communication. None of them presented cardiorespiratory arrest, head trauma, seizures, neuromyelitis optica spectrum or contact with toxic chemicals. Case 1 was a 33-year-old alcoholic man without hypertension or electrolyte imbalance, who presented a classic central pontine myelinolysis (CPM) and a hemorrhage within the pons. Case 2 was a 34-year-old alcoholic man with hypoglycemia and hyponatremia who presented CPM and diffuse bihemispheric extrapontine myelinolysis (EPM) after correction of serum sodium. Case 3 was a 52-year-old woman with mild hypokalemia and hyponatremia (inadequately corrected), who presented a peduncular and cerebellar EPM. Case 4 was a 67-year-old woman who had a suicidal attempt with antidepressants and carbamazepine without impaired consciousness, who complicated with mild hyponatremia associated with a classical CPM and a spinal cord EPM. Case 2 died and the rest remained with variable neurological impairments at last follow-up visit. With modern neuroimaging, the so-called atypical forms of ODS may not be as rare as previously thought; however, they could have a more adverse outcome than the classical ODS.

Keywords Central pontine myelinolysis · Extrapontine myelinolysis · Neuroimaging · Osmotic demyelination · Osmotic myelinolysis

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Introduction

Osmotic demyelination syndrome (ODS) is the term that better describes the damage that over the central nervous system cause multiple electrolytes, metabolic and toxic disorders. Since the original description in 1959 by Adams et al. [1], and later in 1979 by Wright et al. [2], central pontine (CPM) and extrapontine myelinolysis (EPM), respectively, have been reported as the common forms of ODS. Rapid correction of hyponatremia was the first recognized risk factor, but it is currently known that ODS can occur even with an "adequate" correction of hyponatremia [3] and in the absence of serum sodium imbalances [4, 5]. Histopathologically, CPM is an axonal-sparing non-inflammatory degeneration of oligodendrocytes localized in the basis pontis [5]. The lesions are typically symmetrical and can spread to other anatomical areas such as cerebellum and supratentorial structures. This spread represents the main concept of EPM [4, 5].

ODS can be suspected on CT, but MRI is the technique of choice that suggests a premortem diagnosis of myelinolysis; lesions with hypointense signals are seen on T1 and they are hyperintense on T2-weighted MRI. Since ODS is not an inflammatory process, the lesions are classically non-enhancing after gadolinium administration [4, 6]. These neuroimaging characteristics correspond pretty well with those observed in autopsy investigations [4]. Thus,

Prediction of Retinopathy of Prematurity Using the Screening Algorithm WINROP in a Mexican Population of Preterm Infants

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Objective: To retrospectively validate the WINROP (weight, insulin-like growth factor I, neonatal, retinopathy of prematurity [ROP]) algorithm in identification of type 1 ROP in a Mexican population of preterm infants.

Methods: In infants admitted to the neonatal intensive care unit at Hospital Civil de Guadalajara from 2005 to 2010, weight measurements had been recorded once weekly for 192 very preterm infants (gestational age [GA] <32 weeks) and for 160 moderately preterm infants (GA ≥32 weeks). Repeated eye examinations had been performed and maximal ROP stage had been recorded. Data are part of a case-control database for severe ROP risk factors.

Results: Type 1 ROP was found in 51.0% of very preterm and 35.6% of moderately preterm infants. The WINROP algorithm correctly identified type 1 ROP in 84.7% of very preterm infants but in only 5.3% of moderately preterm infants. For infants with GA less than 32 weeks, the specificity was 26.6%, and for those with GA 32 weeks or more, it was 88.3%.

Conclusions: In this Mexican population of preterm infants, WINROP detected type 1 ROP early in 84.7% of very preterm infants and correctly identified 26.6% of infants who did not develop type 1 ROP. Uncertainties in dating of pregnancies and differences in postnatal conditions may be factors explaining the different outcomes of WINROP in this population.

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RETINOPATHY OF PREMATURITY (ROP) is a major cause of life-long blindness; its frequency is strongly associated with the quality of health care. In high-income countries, where many very immature babies survive, severe ROP affects the most immature, and screening and treatment programs make blindness rare. In middle-income countries, health care is good enough for survival of some extremely premature and more mature babies[1] but is insufficient in preventing ROP, leading to an increased prevalence of ROP in more mature babies; an epidemic of ROP-related blindness is presently seen in these countries. In the poorest parts of the world, where immature babies do not survive, ROP is not a problem.[2]

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The aim of this study was to validate WINROP regarding its ability to predict

Changes in MIC Within a Global Collection of *Acinetobacter baumannii* Collected as Part of the Tigecycline Evaluation and Surveillance Trial, 2004 to 2009

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ABSTRACT

Background: The Tigecycline Evaluation and Surveillance Trial (T.E.S.T.) began in 2004 to monitor global antimicrobial susceptibility to tigecycline and a range of comparator antimicrobials among gram-positive and gram-negative organisms.

Objective: The aim of this study was to report changes in MIC for tigecycline and other antimicrobial agents among 10,149 *Acinetobacter baumannii* isolates collected globally between 2004 and 2009.

Methods: MICs of 10,149 isolates were determined locally using Clinical Laboratory and Standards Institute (CLSI) methodologies. Antimicrobial susceptibility was ascertained according to CLSI interpretive criteria (no interpretive criteria have been approved for tigecycline against *Acinetobacter* spp).

Results: Increases in resistance were noted for most antimicrobial agents in all regions. Significant ($P < 0.05$) increases in percentage resistance were reported for all antimicrobial agents globally. The smallest changes in cumulative geometric mean MICs were reported for tigecycline (0.2 mg/L) and cefepime (3.5 mg/L). MIC_{90}s were at the top of their testing ranges for most agents against both multidrug-resistant (MDR) and non-MDR isolates; only tigecycline showed little change in MIC_{90} between MDR (2 mg/L) and non-MDR (1 mg/L) isolates. Resistance was higher among isolates from the intensive care unit (ICU) compared with non-ICU isolates.

Conclusion: These findings suggest that resistance is increasing among clinical isolates of *A baumannii* globally. Although resistance to tigecycline has been reported in the treatment of infections caused by *A baumannii*, it retains in vitro activity against this pathogen. (*Clin Ther.* 2012;34:101–112)

Key words: *Acinetobacter*, antimicrobial resistance, MIC creep, surveillance, tigecycline.

INTRODUCTION

Acinetobacter baumannii is an uncommon but important pathogen, as it is intrinsically resistant (any innate resistance mechanism[s]) to many antimicrobials, including penicillins, cephalosporins, and fluoroquinolones.[1] It is often associated with the intensive care unit (ICU), and *A baumannii* infections most frequently affect the respiratory tract of intubated patients.[2] The intrinsic resistance treatment choices are limited, with carbapenem resistance increasing as a result of the spread of β-lactamase–producing clones,[3] leaving agents such as colistin and polymyxin B as therapeutic options.[4,5]

Data presented in this study are taken from the Tigecycline Evaluation and Surveillance Trial (T.E.S.T.). T.E.S.T. began in 2004 to monitor antimicrobial susceptibility globally among a range of gram-positive and gram-negative organisms to a panel of antimicrobial agents. Tigecycline is licensed for use in the United States (complicated skin and skin structure infections, intraabdominal infections, and community-acquired bacterial pneumonia), Europe (complicated skin and skin structure and intraabdominal infections), and numerous other countries worldwide. However, tigecycline is not indicated for the treatment of infections caused by *Acinetobacter* spp.

Herein we examined the MIC profile of *A baumannii* collected globally between 2004 and 2009 utilizing traditional MIC categories (MIC_{50}, MIC_{90}) as well as geometric mean MICs. We also examined 2 important

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Cerebral Venous Thrombosis in a Mexican Multicenter Registry of Acute Cerebrovascular Disease: The RENAMEVASC Study

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Background: Cerebral venous thrombosis (CVT) is a rare form of cerebrovascular disease that is usually not mentioned in multicenter registries on all-type acute stroke. We aimed to describe the experience on hospitalized patients with CVT in a Mexican multicenter registry on acute cerebrovascular disease. *Methods:* CVT patients were selected from the RENAMEVASC registry, which was conducted between 2002 and 2004 in 25 Mexican hospitals. Risk factors, neuroimaging, and 30-day outcome as assessed by the modified Rankin scale (mRS) were analyzed. *Results:* Among 2000 all-type acute stroke patients, 59 (3%; 95% CI, 2.3-3.8%) had CVT (50 women; female:male ratio, 5:1; median age, 31 years). Puerperium (42%), contraceptive use (18%), and pregnancy (12%) were the main risk factors in women. In 67% of men, CVT was registered as idiopathic, but thrombophilia assessment was suboptimal. Longitudinal superior sinus was the most frequent thrombosis location (78%). Extensive (>5 cm) venous infarction occurred in 36% of patients. Only 81% of patients received anticoagulation since the acute phase, and 3% needed decompressive craniectomy. Mechanical ventilation (13.6%), pneumonia (10.2%) and systemic thromboembolism (8.5%) were the main in-hospital complications. The 30-day case fatality rate was 3% (2 patients; 95% CI, 0.23-12.2%). In a Cox proportional hazards model, only age <40 years was associated with a mRS score of 0 to 2 (functional independence; rate ratio, 3.46; 95% CI, 1.34-8.92). *Conclusions:* The relative frequency of CVT and the associated in-hospital complications were higher than in other registries. Thrombophilia assessment and acute treatment was suboptimal. Young age is the main determinant of a good short-term outcome. **Key Words:** Cerebral veins—cerebral venous thrombosis—cerebrovascular disease—cranial sinuses—outcome—stroke.

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Clinical Study

Differences in Salivary Flow Level, Xerostomia, and Flavor Alteration in Mexican HIV Patients Who Did or Did Not Receive Antiretroviral Therapy

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Introduction. Objective and subjective alterations related to salivary flow have been reported in patients infected with human immunodeficiency virus (HIV), and these alterations are associated with the introduction of antiretroviral therapy. The aim of the current study was to discern whether these alterations are disease induced or secondary to drug therapy. *Objective.* The objective was to determine the relationships between low salivary flow, xerostomia, and flavor alterations in HIV patients who did or did not receive antiretroviral therapy. *Materials and Methods.* In this cross-sectional study, HIV patients were divided into two groups based on whether they had received antiretroviral therapy. Those patients with a previous diagnosis of any salivary gland disease were excluded. A survey was used to assess subjective variables, and colorimetry and salivary flow rates were measured using the Schirmer global test. *Results.* A total of 293 patients were included. The therapy group showed a significantly lower average salivary flow than did the group without therapy, and we observed that the flow rate tended to decrease after one year of therapy. The results were not conclusive, despite significant differences in xerostomia and flavor alteration between the groups. *Conclusion.* The study results suggest that antiretroviral therapy can cause cumulative damage that affects the amount of salivary flow.

1. Introduction

Oral diseases related to human immunodeficiency virus (HIV) infection have been extensively described in the clearing house classification [1] and have since been used as indicators of this condition. Additionally, both objective and subjective alterations related to salivary flow (hyposalivation, xerostomia, and dysgeusia) have been reported in these patients but have not yet been completely linked to the advent of highly active antiretroviral therapy (HAART). It is difficult to discern whether these alterations are part of the course of the disease or therapeutic side effects; various studies, which can be divided into two theories, have been performed on this subject.

On the one hand, certain authors theorize that high levels of HIV RNA might reside in the lymph nodes that are enclosed within the parotid gland during embryonic development, thus directly infecting the salivary gland with HIV [2–6]. On the other hand, others suggest an indirect process in which increased CD8+ lymphocyte infiltration into these

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CASE REPORT Open Access

Intrathoracic intestinal diverticulum in a late presenting congenital bilateral diaphragmatic hernia: a case report

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Abstract

Introduction: Hernias comprise 3% of all defects of the diaphragm. Bilateral hernias are extremely rare and usually occur in children. Here we present a case report of a bilateral Morgagni-Larrey diaphragmatic hernia with an intrathoracic intestinal diverticulum and late presentation. To the best of our knowledge this is the first report of this type.

Case presentation: A 37-year-old Hispanic man was admitted to our emergency department with a 4-day history of obstipation, abdominal pain, distension, nausea, and vomiting. During the initial evaluation, chest and abdominal X-rays were performed, which revealed intestinal displacement into his right and left hemithorax. During laparotomy, a Morgagni-Larrey hernia with a sac was found. His small bowel with a large diverticulum, transverse colon, descending colon, and epiploic fat were herniated into his thorax. Tissues were returned to his abdominal cavity and the hernia defects were corrected with running non-absorbable sutures. He had no postoperative complications.

Conclusions: Bilateral congenital diaphragmatic hernias remain extremely rare. However, they should be considered in adult patients with intestinal obstruction even when respiratory symptoms are absent. This is the first description of a patient with a prolapsed intestinal diverticulum and bilateral diaphragmatic hernias.

Keywords: Bilateral congenital diaphragmatic hernia, Congenital diaphragmatic hernia, Late presenting diaphragmatic hernia, Morgagni-Larrey hernia

Introduction

Four types of diaphragmatic defects are documented. Bochdalek's hernias represent 90% of cases, and Morgagni's hernias comprise 2% to 3% [1]. In most cases, diaphragmatic hernias occur on the right side (10:1 ratio, right: left) [2]. When the defect is bilateral it is known as a Morgagni-Larrey type, which represents 0.12% of congenital diaphragmatic hernias [3]. This type of hernia is commonly diagnosed in pediatric patients, and late presentation is extremely rare [4]. Importantly, an intestinal diverticulum and bilateral herniation have never been reported together.

Case presentation

A 37-year-old Hispanic man who has human immunodeficiency virus was admitted to our emergency department with a 4-day history of obstipation, abdominal pain, distension, nausea, and vomiting. He did not report any episodes of shortness of breath, however, he reported transient tachycardia when lying on his right or left side. On physical examination, abdominal distension in his right upper quadrant was observed. Bowel peristalsis was noted during right chest auscultation. He complained of epigastric pain on palpation.

During the initial examination, chest and abdominal X-rays revealed intestinal displacement into his right and left hemithorax and air-fluid areas in both his abdomen and thorax (Figure 1). Computed tomography (CT) images revealed a large segment of small bowel herniating into his left hemithorax (Figure 2) and a portion of

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Original

Actualización de la Guía Mexicana para el Tratamiento Farmacológico de la Artritis Reumatoide del Colegio Mexicano de Reumatología

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Venous outflow obstruction and portopulmonary hypertension after orthotopic liver transplantation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 54
Final Diagnosis: Suprahepatic inferior vena cava anastomosis stricture
Symptoms: Ascites • fatigue • lower limb edema • hepatomegaly
Medication: —
Clinical Procedure: —
Specialty: Transplantology • Critical Care Medicine

Objective: Unusual clinical course

Background: Suprahepatic inferior vena cava anastomosis stricture is an unusual vascular complication after orthotopic liver transplantation with the "piggyback" technique. Clinical manifestations are dependent upon the severity of the stenosis. Portopulmonary hypertension after orthotopic liver transplantation is a complication that carries high mortality due to cardiopulmonary dysfunction. The pathogenesis of pulmonary vascular disorders after orthotopic liver transplantation remains uncertain.

Case Report: We report a case of acute right heart pressure overload after surgical correction of the suprahepatic inferior vena cava anastomotic stricture in a 54-year-old woman who had preexisting pulmonary arterial hypertension associated with portal hypertension after orthotopic liver transplantation. Twenty months posttransplantation, she developed fatigue and progressive ascites. On admission, the patient had hepatomegaly, ascites, and lower limb edema. Symptoms in the patient developed gradually over time.

Conclusions: Recurrent portal hypertension by vascular complications is a cause of pulmonary arterial hypertension after orthotopic liver transplantation. Clinical manifestations of suprahepatic inferior vena cava anastomotic stenosis are dependent upon their severity. Sildenafil is an effective drug for treatment of pulmonary arterial hypertension after portal hypertension by vascular complications.

Key words: liver transplantation • suprahepatic inferior vena cava • portopulmonary hypertension • pulmonary arterial hypertension • acute cor pulmonale

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Clinical Study

Effect of Abdominoplasty in the Lipid Profile of Patients with Dyslipidemia

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Introduction. Dyslipidemia like other chronic degenerative diseases is pandemic in Latin America and around the world. A lot of patients asking for body contouring surgery can be sick without knowing it. *Objective.* Observe the lipid profile of patients with dyslipidemia, before and three months after an abdominoplasty. *Methods.* Patients candidate to an abdominoplasty without morbid obesity were followed before and three months after the surgery. We compared the lipid profile, glucose, insulin, and HOMA (cardiovascular risk marker) before and three months after the surgery. We used Student's t test to compare the results. A P value less than 0.05 was considered as significant. *Results.* Twenty-six patients were observed before and after the surgery. At the third month, we found only statistical differences in LDL and triglyceride values (P 0.04 and P 0.03). The rest of metabolic values did not reach statistical significance. *Conclusion.* In this group of patients with dyslipidemia, at the third month, only LDL and triglyceride values reached statistical significances. There is no significant change in glucose, insulin, HOMA, cholesterol, VLDL, or HDL.

1. Introduction

Dyslipidemia is a silent pandemic affecting millions of people around the world. There is more than one factor predisposing this serious problem, where not only diet, exercise, and medications could solve it [1].

The truth is that a lot of people can be sick without knowing it. There is controversy of the possible benefit of liposuction or abdominoplasty in the metabolism of glucose or cholesterol. There are no reports about the effect of abdominoplasty in the metabolism of patients with dyslipidemia.

2. Objectives

Observe any possible change in the lipid profile, weight, cardiovascular risk markers (HOMA), glucose, or insulin of patients with dyslipidemia after an abdominoplasty.

3. Methods

A descriptive observational study was designed to follow up the lipid profile of patients with dyslipidemia candidates to a body contouring surgery as abdominoplasty. The research project was evaluated and approved by the ethics and research committee of the Antiguo Hospital Civil de Guadalajara (file number in the institution 112-11). The ethics and research committee evaluated all the research projects in the decentralized, academic, and public Antiguo Hospital Civil de Guadalajara. It follows the guidelines according to the Health Mexican Norm and the Helsinki ethical principles.

Abdominoplasty or lipoabdominoplasty is offered to women to improve the body images in case of severe skin laxity, excess fat, and flaccidity of the abdominal muscle [2, 3]. We did not operate patients with morbid obesity, where gastric bypass and other bariatric surgeries are suggested.

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CLINICAL RESEARCH

Evaluation of blood pressure measurements in first ambulatory neurological consultations: A missed part of the physical examination?

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KEYWORDS
Blood pressure;
Hypertension;
Medical practice;
Mexico;
Outpatient

Abstract
Objective: To obtain a blood pressure reading is mandatory during either the general or specialized physical examination. This study describes factors associated with the accomplishment of blood pressure measurement in the first neurological consultation.
Methods: We studied first ambulatory neurology consultations in a Mexican referral hospital. Demographic characteristics, diagnostic category of referral, final diagnosis and data on physical examination were collected to establish a logistic regression analysis in order to identify factors associated with the accomplishment of blood pressure measurement.
Results: Over 8 months 778 outpatients were studied. The most frequent diagnoses for first consultation were headache (26%), epilepsy (14%) and stroke (13%). Only in 39% ($n = 301$) of the outpatients blood pressure was registered, among them, 30% had normal blood pressure, 43% had 121–139/81–89 mmHg, 20% had 140–159/90–99 mmHg and 7% had ≥160/100 mmHg. The independent factors that favored the practice of BP determination in multivariable analysis were >65 years of age (odds ratio: 2.26; 95% confidence interval: 1.52–3.36) and headache complaint (odds ratio: 1.81, 95% confidence interval: 1.30–2.53). Notably, only 43% of patients with stroke had blood pressure registration, even when these stroke patients had blood pressure readings, they had higher blood pressure than with other diagnoses ($p < 0.05$).

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Acinetobacter baumannii Infections in a Tertiary Care Hospital in Mexico over the Past 13 Years

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Key Words
Resistance patterns · *Acinetobacter baumannii* · Antimicrobial susceptibility

Abstract
Background: *Acinetobacter baumannii* has evolved from an opportunistic pathogen into a common and persistent nosocomial bacterium capable of causing severe infections during endemic and epidemic periods. ***Methods:*** The study period extended from January 1999 to December 2011 and involved patients hospitalized at the Hospital Civil de Guadalajara, Fray Antonio Alcalde, Jalisco, Mexico. From each patient, a single isolate was obtained, and a total of 3,680 unique isolates were collected. Susceptibility tests were performed according to the guidelines of the Clinical and Laboratory Standards Institute. ***Results:*** *A. baumannii* has disseminated throughout the Hospital Civil de Guadalajara, Fray Antonio Alcalde, since 1999. *A. baumannii* isolates obtained from patients treated in the adult intensive care unit represent the majority of the isolates that have been collected. In addition, *A. baumannii* was isolated from the adult neurosurgical ward and the adult internal medicine ward, and these isolates were frequently obtained from secretions. A persistent decrease in the susceptibility of *A. baumannii* isolates to meropenem (92% in 1999 to 12% in 2011), imipenem and amikacin has been observed. ***Conclusions:*** *A. baumannii* became an endemic nosocomial pathogen during the study period at the Hospital Civil de Guadalajara, Fray Antonio Alcalde, and has exhibited a persistent decrease in susceptibility to all categories of antimicrobial agents over the past 13 years.

Introduction

Acinetobacter baumannii is a nosocomial pathogen found worldwide that is responsible for a diverse set of serious infections that include bacteremia, ventilator-associated pneumonia, postsurgical meningitis and skin and skin structure infections [1–3]. Moreover, *A. baumannii* has evolved from a nosocomial bacterium that primarily affects immunocompromised patients in hos-

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ETIO PATHOGENESIS OF AUTOIMMUNITY

Adverse events following immunization with vaccines containing adjuvants

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Published online: 11 April 2013

Abstract A traditional infectious disease vaccine is a preparation of live attenuated, inactivated or killed pathogen that stimulates immunity. Vaccine immunologic adjuvants are compounds incorporated into vaccines to enhance immunogenicity. Adjuvants have recently been implicated in the new syndrome named ASIA autoimmune/inflammatory syndrome induced by adjuvants. The objective describes the frequencies of post-vaccination clinical syndrome induced by adjuvants. We performed a cross-sectional study; adverse event following immunization was defined as any untoward medical occurrence that follows immunization 54 days prior to the event. Data on vaccinations and other risk factors were obtained from daily epidemiologic surveillance. Descriptive statistics were done using means and standard deviation, and odds ratio adjusted for potential confounding variables was calculated with SPSS 17 software. Forty-three out of 120 patients with moderate or severe manifestations following immunization were hospitalized from 2008 to 2011. All patients fulfilled at least 2 major and 1 minor criteria suggested by Shoenfeld and Agmon–Levin for ASIA diagnosis. The most frequent clinical findings were pyrexia 68 %, arthralgias 47 %, cutaneous disorders 33 %, muscle weakness 16 % and myalgias 14 %. Three patients had diagnosis of Guillain–Barre syndrome, one patient had Adult-Still's disease 3 days after vaccination. A total of 76 % of the events occurred in the first 3 days post-vaccination. Two patients with previous autoimmune disease showed severe adverse reactions with the reactivation of their illness. Minor local reactions were present in 49 % of patients. Vaccines containing adjuvants may be associated with an increased risk of autoimmune/inflammatory adverse events following immunization.

Keywords Adjuvant · Vaccines · Autoimmunity · Aluminum · Thiomersal · Syndrome

Introduction

Adjuvants have been used for decades to improve the immune response to vaccine antigens. Adjuvant is originated from the Latin word "adjuvare" which means "help" in English to enhance the immunologic responses when given together with antigens. The beginning of adjuvant was mineral oil which enhanced the immune response when it was given with inactivated *Salmonella typhimurium* [1]. Aluminum salt was used to precipitate diphtheria toxoid and increased level of antibody response was demonstrated when administered with alum-precipitated antigens. Since 1930, aluminum salt has been used as diphtheria-tetanus-acellular pertussis (DTaP) vaccine adjuvant. Many candidates were tested for adjuvant activity but only aluminum salt is allowed to use for human vaccines [2]. New adjuvant MF59, oil-in-water emulsion type, was developed for influenza vaccine for elderly (Fluad), and series of AS adjuvant are used for hepatitis B, pandemic flu and human papilloma virus vaccines. Oil-

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RETINAL DISORDERS

Early retinopathy of prematurity findings identified with fluorescein angiography

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Abstract
Background Fluorescein angiography has been fundamental for the understanding and description of vascular disorders affecting the retina and choroid. The aim of this report is to assess the early anatomic retinal changes visible with angiography, and their relation with the clinical findings of retinopathy of prematurity.

Methods Ten babies were included in the study, the initial examination being at 2 weeks after birth. Two cycles of tropicamide 0.8 % and phenylephrine 5 % eye drops were instilled into both eyes 30 min before examination. A RetCam II was used to obtain digital retinal images, after instilling topical anesthesia (tetracain 0.5 %) and using a contact gel. Fluorescein angiography was undertaken following administration of an intravenous bolus of 0.1 ml/kg saline fluorescein 10 % followed by a 3.0-ml isotonic saline flush, with the assistance of the neonatologist; the right and left eyes were imaged.
Results We observed that some of the vascular abnormalities described for threshold disease by Lepore were already present at the second week of life, preceding the diagnosis of threshold disease by 3–4 weeks in two cases. The main findings in our cases were arterio-venous shunts, surrounded by areas of capillary non-perfusion, rosary-bead-like hyperfluorescence, tortuosity and leakage from distal arterioles, none of which were detectable in the digital fundus pictures.
Conclusions Early ROP screening at the NICU that includes FA is a safe procedure, and gives the examiner details of vascular changes that are not detectable by indirect ophthalmoscopy, which could predict the progression to threshold disease, and provide an alert about the need of therapeutic interventions.

Keywords ROP RetCam · Fluorescein angiography · ROP screening · Tropicamide

Presentation at a conference This work was presented as a poster at the ARVO 2010 meeting.

The authors have full control of all primary data, and they agree to allow Graefe's Archive for Clinical and Experimental Ophthalmology to review their data if requested.

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Introduction

Fluorescein angiography (FA) has been fundamental to the understanding and description of vascular disorders

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ORIGINAL ARTICLE

Atypical forms of the osmotic demyelination syndrome

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Abstract Osmotic demyelination syndrome (ODS) is the damage over the central nervous system caused by several electrolytes, metabolic and toxic disorders. We aimed to describe cases of unusual forms of ODS. In a 9-year period, 25 consecutive patients with ODS (15 men; mean age 42 years) were registered in our referral institution, among them, four (16 %) with atypical neuroimaging findings were abstracted for this communication. None of them presented cardiorespiratory arrest, head trauma, seizures, neuromyelitis optica spectrum or contact with toxic chemicals. Case 1 was a 33-year-old alcoholic man without hypertension or electrolyte imbalance, who presented a classic central pontine myelinolysis (CPM) and a hemorrhage within the pons. Case 2 was a 34-year-old alcoholic man with hypoglycemia and hyponatremia who presented CPM and diffuse bihemispheric extrapontine myelinolysis (EPM) after correction of serum sodium. Case 3 was a 52-year-old woman with mild hypokalemia and hyponatremia (inadequately corrected), who presented a peduncular and cerebellar EPM. Case 4 was a 67-year-old woman who had a suicidal attempt with antidepressants and carbamazepine without impaired consciousness, who complicated with mild hyponatremia associated with a classical CPM and a spinal cord EPM. Case 2 died and the rest remained with variable neurological impairments at last follow-up visit. With modern neuroimaging, the so-called atypical forms of ODS may not be as rare as previously thought; however, they could have a more adverse outcome than the classical ODS.

Keywords Central pontine myelinolysis · Extrapontine myelinolysis · Neuroimaging · Osmotic demyelination · Osmotic myelinolysis

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Introduction

Osmotic demyelination syndrome (ODS) is the term that better describes the damage that over the central nervous system cause multiple electrolytes, metabolic and toxic disorders. Since the original description in 1959 by Adams et al. [1], and later in 1979 by Wright et al. [2], central pontine (CPM) and extrapontine myelinolysis (EPM), respectively, have been reported as the common forms of ODS. Rapid correction of hyponatremia was the first recognized risk factor, but it is currently known that ODS can occur even with an "adequate" correction of hyponatremia [3] and in the absence of serum sodium imbalances [4, 5]. Histopathologically, CPM is an axonal-sparing non-inflammatory degeneration of oligodendrocytes localized in the basis pontis [5]. The lesions are typically symmetrical and can spread to other anatomical areas such as cerebellum and supratentorial structures. This spread represents the main concept of EPM [4, 5].

ODS can be suspected on CT, but MRI is the technique of choice that suggests a premortem diagnosis of myelinolysis; lesions with hypointense signals are seen on T1 and they are hyperintense on T2-weighted MRI. Since ODS is not an inflammatory process, the lesions are classically non-enhancing after gadolinium administration [4, 6]. These neuroimaging characteristics correspond pretty well with those observed in autopsy investigations [4]. Thus,

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REVIEW

Alcoholism and liver disease in Mexico: Genetic and environmental factors

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Abstract

Alcoholism and cirrhosis, which are two of the most serious health problems worldwide, have a broad spectrum of clinical outcomes. Both diseases are influenced by genetic susceptibility and cultural traits that differ globally but are specific for each population. In contrast to other regions around the world, Mexicans present the highest drinking score and a high mortality rate for alcoholic liver disease with an intermediate category level of per capita alcohol consumption. Mexico has a unique history of alcohol consumption that is linked to profound anthropological and social aspects. The Mexican population has an admixture genome inherited from different races, Caucasian, Amerindian and African, with a heterogeneous distribution within the country. Thus, genes related to alcohol addiction, such as dopamine receptor D2 in the brain, or liver alcohol-metabolizing enzymes, such as alcohol dehydrogenase class I polypeptide B, cytochrome P450 2E1 and aldehyde dehydrogenase class 2, may vary from one individual to another. Furthermore, they may be inherited as risk or non-risk haplogroups that confer susceptibility or resistance either to alcohol addiction or abusive alcohol consumption and possibly liver disease. Thus, in this era of genomics, personalized medicine will benefit patients if it is directed according to individual or population-based data. Additional association studies will be required to establish novel strategies for the prevention, care and treatment of liver disease in Mexico and worldwide.

Key words: Alcohol; Genes; Alcoholism; Alcohol dependence; Alcohol addiction; Alcohol abuse; Alcoholic liver cirrhosis; Anthropology

Core tip: Alcoholism and liver disease are leading global health problems. However, the severity and outcome of liver disease appear to vary between individuals and populations. In the present review, we analyze the general scope of alcohol consumption and its relationship with the pattern of drinking score in different countries. We focus on the development of alcoholism in Mexico, which has a strong historical background, and emphasize the need to understand the genetic and environmental factors affecting each population or geographical region of the world.

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Bilateral tibial hemimelia type 1 (1a and 1b) with T9 and T10 hemivertebrae: a novel association

Bilateral tibial hemimelia tipo 1 (1a e 1b) com hemivértebras T9 e T10: uma nova associação

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KEY WORDS:
Femur.
Ectromelia.
Tibia.
Thoracic vertebrae.
X-rays.

PALAVRAS-CHAVE:
Femur.
Ectromelia.
Tíbia.
Vértebras torácicas.
Raios X.

ABSTRACT

CONTEXT: Congenital absence of the tibia is a rare anomaly with an incidence of one per 1,000,000 live births. It is mostly sporadic and can be identified as an isolated disorder or as part of malformation syndromes.

CASE REPORT: A male child, born to unaffected and non-consanguineous parents, presented with shortening of the legs and adduction of both feet. Physical examination at six months of age showed head circumference of 44.5 cm (75th percentile), length 60 cm (< 3rd percentile), weight 7,700 g (50th percentile), shortening of the left thigh and both legs with varus foot. There were no craniofacial dysmorphisms or chest, abdominal, genital or upper-extremity anomalies. Psychomotor development was normal. His workup, including renal and cranial ultrasonography, brainstem auditory evoked potential, and ophthalmological and cardiological examinations, was normal. X-rays showed bilateral absence of the tibia with intact fibulae, distally hypoplastic left femur, and normal right femur. In addition, spinal radiographs showed hemivertebrae at T9 and T10.

CONCLUSION: This novel association expands the spectrum of tibial hemimelia. Moreover, this observation highlights the usefulness of this inexpensive diagnostic method (X-rays) for characterizing the great clinical and radiological variability of tibial hemimelia.

RESUMO

CONTEXTO: Ausência congênita da tíbia é uma anomalia rara, com incidência em 1 por 1.000.000 de nascidos vivos, é principalmente esporádica e pode ser identificada como um distúrbio isolado ou como parte de síndromes de malformações.

RELATO DO CASO: Criança do sexo masculino, nascida de pais não afetados e não consanguíneos, apresentou-se com encurtamento das pernas e adução de ambos os pés. O exame físico realizado com seis meses de idade mostrou perímetro cefálico 44,5 cm (percentil 75), comprimento de 60 cm (percentil < 3), peso 7.700 g (percentil 50), encurtamento da coxa esquerda e as duas pernas com o pé varo bilateralhavia. Não houve dismorfismos craniofaciais, nem tórax, abdômen, genitais e anomalias das extremidades superiores. O desenvolvimento psicomotor foi normal. Os exames, incluindo ultrassonografia renal e da cabeça, potenciais auditivos evocados de tronco cerebral e exames oftalmológicos e cardiológicos, estavam normais. Raios-X revelou ausência bilateral da tíbia com fíbula intacta, hipoplasia distal do fêmur esquerdo e fêmur direito normal. Além disso, as radiografias de coluna mostraram hemivértebras em T9 e T10.

CONCLUSÃO: Esta associação nova expande o espectro de hemimelia tibial. Além disso, esta observação destaca a utilidade de tal método diagnóstico barato (raios-X), caracterizando a grande variabilidade clínica e radiológica de hemimelia tibial.

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The Global role of kidney transplantation

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ABSTRACT

World Kidney Day on March 8th 2012 provides a chance to reflect on the success of kidney transplantation as a therapy for end stage kidney disease that surpasses dialysis treatments both for the quality and quantity of life that it provides and for its cost effectiveness. Anything that is both cheaper and better, but is not actually the dominant therapy, must have other drawbacks that prevent replacement of all dialysis treatment by transplantation. The barriers to universal transplantation as the therapy for end stage kidney disease include the economic limitations which, in some countries place transplantation, appropriately, at a lower priority than public health fundamentals such as clean water, sanitation and vaccination. Even in high income countries the technical challenges of surgery and the consequences of immunosuppression restrict the number of suitable recipients, but the major finite restrictions on kidney transplantation rates are the shortage of donated organs and the limited medical, surgical and nursing workforces with the required expertise. These problems have solutions which involve the full range of societal, professional, governmental and political environments. World Kidney Day is a call to deliver transplantation therapy to the one million people a year who have a right to benefit.

Review

Implication for health policy/practice/research/medical education:
World Kidney Day on March 8th 2012 provides a chance to reflect on the success of kidney transplantation as a therapy for end stage kidney disease that surpasses dialysis treatments both for the quality and quantity of life that it provides and for its cost effectiveness.

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REVIEW

Alcoholism and liver disease in Mexico: Genetic and environmental factors

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Abstract

Alcoholism and cirrhosis, which are two of the most serious health problems worldwide, have a broad spectrum of clinical outcomes. Both diseases are influenced by genetic susceptibility and cultural traits that differ globally but are specific for each population. In contrast to other regions around the world, Mexicans present the highest drinking score and a high mortality rate for alcoholic liver disease with an intermediate category level of per capita alcohol consumption. Mexico has a unique history of alcohol consumption that is linked to profound anthropological and social aspects. The Mexican population has an admixture genome inherited from different races, Caucasian, Amerindian and African, with a heterogeneous distribution within the country. Thus, genes related to alcohol addiction, such as dopamine receptor D2 in the brain, or liver alcohol-metabolizing enzymes, such as alcohol dehydrogenase class I polypeptide B, cytochrome P450 2E1 and aldehyde dehydrogenase class 2, may vary from one individual to another. Furthermore, they may be inherited as risk or non-risk haplogroups that confer susceptibility or resistance either to alcohol addiction or abusive alcohol consumption and possibly liver disease. Thus, in this era of genomics, personalized medicine will benefit patients if it is directed according to individual or population-based data. Additional association studies will be required to establish novel strategies for the prevention, care and treatment of liver disease in Mexico and worldwide.

Key words: Alcohol; Genes; Alcoholism; Alcohol dependence; Alcohol addiction; Alcohol abuse; Alcoholic liver cirrhosis; Anthropology

Core tip: Alcoholism and liver disease are leading global health problems. However, the severity and outcome of liver disease appear to vary between individuals and populations. In the present review, we analyze the general scope of alcohol consumption and its relationship with the pattern of drinking score in different countries. We focus on the development of alcoholism in Mexico, which has a strong historical background, and emphasize the need to understand the genetic and environmental factors affecting each population or geographical region of the world.

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MINIREVIEWS

HBV endemicity in Mexico is associated with HBV genotypes H and G

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Abstract

Hepatitis B virus (HBV) genotypes have distinct genetic and geographic diversity and may be associated with specific clinical characteristics, progression, severity of disease and antiviral response. Herein, we provide an updated overview of the endemicity of HBV genotypes H and G in Mexico. HBV genotype H is predominant among the Mexican population, but not in Central America. Its geographic distribution is related to a typical endemicity among the Mexicans which is characterized by a low hepatitis B surface antigen seroprevalence, apparently due to a rapid resolution of the infection, low viral loads and a high prevalence of occult B infection. During chronic infections, genotype H is detected in mixtures with other HBV genotypes and associated with other co-morbidities, such as obesity, alcoholism and co-infection with hepatitis C virus or human immunodeficiency virus. Hepatocellular carcinoma prevalence is low. Thus, antiviral therapy may differ significantly from the standard guidelines established worldwide. The high prevalence of HBV genotype G in the Americas, especially among the Mexican population, raises new questions regarding its geographic origin that will require further investigation.

Key words: Hepatitis B virus genotypes; Hepatitis B virus genotype H; Hepatitis B virus genotype G; Molecular epidemiology; Mexico; Antiviral therapy; Severity of liver disease; Clinical outcome

Core tip: Molecular, clinical, geographical and ethnicity evidence are characteristics that define any hepatitis B virus (HBV) genotype. All of these features are there for HBV genotype H, which is most predominant in Mexico, but not in Central America. Likewise, HBV genotype G has unique molecular characteristics and a similar route of transmission among those infected with this viral genotype, but it lacks a geographic origin. To date, despite the high prevalence of HBV genotype G cases from the Americas, especially among Mexicans, the limited number of complete sequences hinders further investigation to establish a hypothesis of an Amerindian origin.

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INTRODUCTION

Definition of hepatitis B virus genotypes and their association with human liver disease

Hepatitis B virus (HBV) and humans share a close re-

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ORIGINAL

Variantes fenotípicas menores en pacientes con leucemia linfoblástica aguda del occidente de México

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Anormalidades fenotípicas;
Variantes comunes;
Anomalías menores;
Malformaciones;
Leucemia linfoblástica aguda;
Cáncer infantil;
Manchas café con leche

Resumen

Introducción: La leucemia linfoblástica aguda (LLA) se ha asociado a un exceso de variantes fenotípicas menores (VFM), que incluyen las variantes comunes y las anomalías menores, indicadoras de una fenogénesis alterada. El objetivo fue determinar la asociación entre VFM y LLA.

Pacientes y métodos: Estudio de casos y controles basado en hospital de 120 niños con LLA y 120 niños sanos como grupo control, emparejados por edad y sexo, atendidos en el Hospital Civil de Guadalajara Dr. Juan I. Menchaca (México). En ambos grupos, se realizaron 28 mediciones antropométricas y la búsqueda sistemática de un listado de 405 VFM mediante un examen físico minucioso. Se estimaron las *odds ratio* ajustadas (ORa) con sus variables intervinientes por regresión logística. El intervalo de confianza fue del 95% (IC del 95%).

Resultados: Los signos antropométricos asociados con LLA fueron: segmento superior largo (ORa = 2,19; IC del 95%, 1,01-4,76), mandíbula ancha (ORa = 2,62; IC del 95%, 1,29-5,30), pabellones estrechos (ORa = 6,22, IC95%: 2,60-14,85) y teletelia (ORa = 2,53; IC del 95%m 1,07-5,98). Las VFM hipoplasia mesofacial, frente ancha, nariz pequeña, columnela corta, pabellones estrechos, teletelia, línea Sídney, pie griego y manchas café con leche (MCL) tuvieron una frecuencia de 3 a 17 veces mayor en los niños con LLA. Por número, encontramos asociación a partir de ≥ 4 VFM (ORa = 2,14; IC del 95%, 1,25-3,66; p = 0,004).

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