Aberraciones cromosómicas en un hospital pediátrico de tercer nivel. Anillos de los cromosomas 13 y 18

Chromosome abnormality in a pediatric tertiary hospital. Ring Chromosomes 13 and 18

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RESUMEN

La alteración autosómica debido a la formación de un anillo, es una aberración rara de cualquier cromosoma 13 y 18 que está relacionada con las malformaciones fenotípicas, problemas neurológicos y anormalidades genitales.

Se presenta el caso clínico de polimalformado con cráneo treboliformedismorfias con convulsiones tempranas y malformaciones genitales con micropene. Entre las alteraciones cromosómicos, el anillo de herencia autosómica del cromosoma 13 y 18 no son frecuentes, las alteraciones fenotipicas en este estudio son en relación a las malformaciones craneofaciales, genitales y neurológicas.

Palabras clave. cromosoma 13 cromosoma 18, cromosoma del anillo, cariotipo, mosaisismo, malformaciones.

Abstract

The autosomic alteration due to a ring formation is a rare aberration of either chromosome 13 and18 which is in relation with phenotipic malformations, neurologic problems and genital abnormalities.

It is the clinic case of polimalformado with skull treboliformedismorfias with early seizures, and genital malformations with micropenis. Among the chromosomal alterations, the autosomal ring of chromosome 13 and 18 are not frequent, the

phenotypic alterations in this study are in relation to Craniofacial, genital, and neurological malformations.

Key Words: chromosome 13, chromosome 18, chromosome ring, karyotype, mosaicism, malformations.

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Introduction

Considering that the mutations or chromosomal aberrations are known to be alterations in the structure or number of chromosomes. They are considered mainly due to gametogenesis inborn error (meiosis) or during the Zygote first cell division. All these alterations might be observed during metaphase from the cellular cycle, where DNA loses are seen due to DNA repair processes deficiency o total absence, among others. 4617 chromosomal studies were performed at Hospital Para El Nino Poblano (Pediatric Hospital) in Mexico (from 1992 to 2011) were 34.6% (1596 patients) showed different chromosomal alterations and only two patients showed ring chromosome aberrations. These chromosome changes are classified as structural alterations. Both pediatric patients with these genetic diseases are described in this study analyzing their clinical characteristics, medical or surgical treatments according to the phenotypic alterations.

Chromosomes contain DNA-bound proteins, which serve to package the DNA and control its functions Thanbichler and Shapiro (2006); (Pereira et al., 1997; Sandman and Reeve, 2000). Chromosomes are different according to a variety of organisms. The DNA molecule may be circular or linear, and can be composed of 100,000 to 10,000,000,000 Paux et al. (2008) nucleotides in a long chain. Normally, eukaryotic cells (cells with nuclei) White (1973) have large linear chromosomes and prokaryotic cells (cells without defined nuclei) Thanbichler and Shapiro (2006); Nakabachi et al. (2006); Pradella et al. (2002), have smaller circular chromosomes. Also, cells may contain more than one type of chromosome. Regarding the number of chromosomal alterations pairs 13 and 18,

monosomies, tetrasomies, deletions, translocations and training in the ring chromosome material losses and phenotypic characteristics variables like 1, 2, 3, 4 have been described as malformations retardation, hypotonia and mental craniofacial and varies depending on the degree (R Vivarelli et al., 1992, MJ McGinniss et al, 1993, Khalifa m et al.1996).

Within monosomy of chromosome 18, there are two variants: Monosomy 18p and 18q; While 70 patients with 18p chromosomal disorder has been observed in both monosomies, there are mental retardation, skeletal and connective rounded walls abnormalities. Although 50 patients reported with monosomy 18q, there craniofacial abnormalities such as microcephaly and undershot, and vertebral abnormalities.

Altered Ring chromosome 18 (r18) Figure 4, however, is a rare genetic and the condition is less severe than that presented monosomy 18, although some clinical alterations in both syndromes. It has been observed hypotonia (90%), microcephaly (75-90%), epicanto present more than two thirds and hypertelorism, ocular disorders such as strabismus (50%), ptosis, nystagmus, partial aniridia and microphthalmia; malformations of the ear structures, low-set ears, low oral commissure, microglossia and micrognathia. Furthermore, neurobehavioral disorders such as autism (JP Fryns and Kleczkowska, 1992), epilepsy and Arthrogryposis multiplex congenita (E Sheridan et al, 1994). Some other clinical manifestations that have emerged are: skeletal abnormalities of the lower and upper extremities (Andersen UM, 1992), fifth finger clinodactyly and overlapping toes. They have been observed abnormalities of the genitalia. The reduction of clinical disorders can be the result of a chromosomal abnormality in the patient mosaic as in this study. Other associated findings that have been documented are renal and cardiovascular disorders, hemiatrophy body with skin hyperpigmentation and Hypomelanosis in patients with mosaic r18 (Bocian E. et al., 1993); growth hormone deficiency (Meloni A. et al., 1994) by a neurosecretory dysfunction (Aritaki S. et al., 1996, Eiben B, et al., 1992) and hypothyroidism and hypoparathyroidism. More than 70 cases have affected r18 described in the literature, Fukushima in 1984 observed an association between the ring and autoimmune thyroiditis. There have been midline defects ranging from a palate incomplete closure to serious holoprosencephaly (E Sheridan et al, 1994). The legacy of

ring chromosome 18 is rare, with particular chromosomal novo ring formations, the most frequent. Some authors mention that the cancellation occurs in 18p 11 and 18q23.

Relative to chromosome 13, Figures 1, 2 have been published more than 60 cases, which lack the long arm of chromosome D and chromosome of this group has been replaced by a ring. Although these cases may represent heterogeneity, there is evidence to suggest that the affected chromosome is number 13. The average survival is variable for cases 39 months and 89 months 13q 13r cases.

The loss of the long arm of one chromosome in group D, was described initially in a patient with growth failure who presented from prenatal age. Subsequently, they described more than 50 cases and partial chromosome loss has been regarded as the number 13. The phenotype varies, but the pattern of malformations allows the suspicion of this disorder. There has been a phenotype, where missing part of the short arm and part of the long arm of chromosome 13. The following features have been observed in patients 13q-; Central, short and redundant neck (TC Hsu 1979), nervous system all patients had mental and somatic retardation, many have been hypotonic (Huret 2000), microcephaly (with a tendency to hydrocephalus, trigonocephaly, Aprosencephaly, arrinencefalia (LM Kelman, 2004) and holoprosencephaly (Huret et al 2000). agenesis of the corpus callosum (Guala A et al. 1997) and alopecia. Although the degree of mental deterioration has been variable, most patients have severe mental retardation. Other defects as microphthalmia, coloboma of the iris and optic nerve dysplasia hypertelorism, epicanthal folds, ptosis and apparent telecanthus. prominent nasal bridge. Cleft palate, micrognathia, a high palate has been reported in several cases of 13q syndrome.

Have discussed the phenotypic changes associated with different degrees of removal and hypoplasia of the thumb were missing in 70% of cases with 13q-about and less than 30% of the cases was also noted 13r, fifth finger clinodactyly, talipes, Simian creases, synostosis of the fourth and fifth metacarpals and equinovarus. Pigmentation changes. Congenital cardiovascular anomalies (ventricular septal defect or aortic malformation) have been described around 50% of both groups.

Within musculoskeletal abnormalities they reported bilateral hip dislocation, inguinal hernia and coxa valga. Genitourinary anomalies are represented by hypospadias, cryptorchidism, cleft hypoplastic scrotum or penis, small pelvic kidney (Sparkes 1967) and anal atresia; kidney abnormalities and pelvic rhabdomyosarcoma (CG Woods et al. 1994). Unilateral or bilateral retinoblastoma has been documented in over half of the cases 13q - was more pronounced (Taylor et al 1970.) As well as in several patients with ring chromosome 13 (Grace et al., 1971).

Compaction results of duplicates during mitosis and meiosis in the classic structure of four arms called chromosomes. Chromosomal recombination plays a vital role in the evolution and genetic diversity, Hinnebusch and Tilly, 1993. If these structures begin through processes known as mutation and chromosomal instability, the cell may die, or can avoid apoptosis lead to cancer initiation.

MATERIALS AND METHODS

Chromosome studies (karyotype) which performs for all patients in this study using GTG bands. 4617 karyotypes were performed at the Hospital For Children Poblano, Mexico in 19 years time (from 1992-2011) Figures 5.6. However, only 1596 patients (34.6%) showed chromosomal alterations, including the pediatric population studies were analyzed with various genetic diseases. For patients r18 karyotype was performed, 80 metaphases were analyzed using two cell lines, of which 12 metaphases showed normal XY formula 46 and 68 remaining metaphase chromosome ring 18 chromosome formula 46, XY / 46, XY, r (18) Figure 4.

For patient r13 Figure 1, the karyotype, 100 metaphases were analyzed with two cell lines, of which 20 metaphases showed a man regular formula 46 XY and 80 metaphases remaining ring chromosome 18 with chromosome formula 46, XY / 46, XY, r (18). The karyotype of the mother, in 100 metaphases, also located two cell lines, of which 90 metaphases showed a normal female formula 46, XX and 10 remaining 18 metaphase chromosome ring 46 chromosome formula XX / 46, XX, r (18). However the father filed between 100 metaphases normal chromosome formula, 46 XY.

Different studies for patients both r18 and r13 were performed; hormonal determinations (17-OH-progesterone, dehidroepiandros-cations and serum cortisol) and pelvic ultrasound. Also at the request of Urology echocardiogram bladder and pelvis because of the association of these chromosomal anomalies with renal impairment was performed.

DISCUSIÓN

Chromosomal aberrations are changes in the normal structure of chromosomes of a cell and are a major cause of genetic diseases in humans beings known as genetic disease that may have or not a pattern of inheritance, r13 and r18 syndromes are rare and clinically They have similar patterns. Most of these patients were registered with cranial disorders and mental retardation or microcephaly skull treboliforme as in this study. In approximately 50% of patients with this anomaly Cromosomic, a history of low birth weight data is not observed in this work. However facial alterations are represented by hypertelorism, epicanthal low-set ears and in some cases has been observed.

The molecular mechanism of carcinogenesis, in the stomach is directly related to a loss of genetic, coupled with impaired heterozygosity on chromosome 18 (Ttahara, et al., 1993) and myeloid disorders in patients with structural malformations formations and ring chromosome 7 18.Es conceivable that there is a significant causal relationship between genetic imbalance and the possibility of developing this type of tumor. The loss of the long arm of chromosome 13 q-14 band was the specific region, implicated as a cause in this particular case for retinoblastoma. Chromosome studies would be useful in patients with retinoblastoma with mental retardation and growth, as well as other abnormalities mentioned above.

Approximately 70 patients affected with r18 and r13, as in this study (Figures) are connected with similar clinical manifestations skeletal abnormalities in the lower extremities (Andersen, 1992), neurological disorders such as autism (Frynsjp and Kleczkowska a., 1992), epilepsy, multiple congenital arthrogryposis and neurological disorders, body hemiatrophy with skin hyperpigmentation and Hypomelanosis (Bocian E., et al. 1993) in patients with mosaic r18, deficiency of growth hormone hypothalamic

origin was not confirmed in this study (Meloni A., et al., 1994) by a neurosecretory dysfunction (Aritaki S. et al., 1996). The decrease in abnormal genitals of one fifth of the patients were reported. The difference in this study could be due to the result of a chromosomal abnormality in 13 or 18 mosaicism.

Hemiatrofia body with skin hyperpigmentation hypomelanosis (Bocian e. Et al., 1993) in patients with mosaic r18, due to hypothalamic hormone deficiency (Meloni A. et al., 1994) by a neurosecretory dysfunction (Aritaki S . et al., 1996, Eiben B, et al., 1992). As hypothyroidism and hypoparathyroidism, r18 over seventy cases described affected by Fukushima in 1984. There is also an association between the ring and autoimmune thyroiditis, cleft palate (Gorlinr. J., 1971).

Alteration in both ring chromosomes 13 and 18 registered in mothers with healthy carriers mosaicism 46XX / 46XX r (18) and children of r (13) with multiple phenotypic abnormalities as in this study (figures), when compared with mothers reported a single cell line (Frynsjp, et al., 1992). The midline defects were observed from an incomplete closure of the palate to serious holoprosencephaly (E Sheridan et al, 1994).

An investigation of the gene defect on chromosome 13 and 18 was conducted using specific markers in comparative studies. With regard to genetic counseling in prenatal diagnosis possible early detection of both r13 or r18. Studies of amniocentesis already described in the first trimester of pregnancy (Beiben et al, 1992), subsequently confirming malformations in the fetus autopsy study (FJ., Et al., 1996).

It reported trisomies injury, duplication or rings 13 and 18, related to mental retardation, hypotonia and craniofacial malformations that varies with the degree of suppression or type of trisomy (Vivarelli, R. et al., 1992, MJ et al, 1993 Mcginnisskhalifa, M et al., 1996).

This paper reports the case of two male patients 13 18 respectively ring syndrome, treated in a pediatric hospital, which presents some typical clinical abnormalities of this chromosomal disorder as mentioned above; It is interesting to compare both 13 and 18 ring with trisomy 13 and 18 as both chromosome aberrations have specific clinical conditions.

Both trisomies, and Edwards and Patau syndromes are rarely found among pediatric patients. Both share similar symptoms and syndromes share some clinical manifestations such as r13 and r18 chromosomal aberrations. Figure 16, B and C show a female patient with trisomy 13 or Patau syndrome hypoplastic, face bilateral cleft lip and palate and craniofacial dimorphism, absent or malformed, especially nose, bending the fingers of both hands. Trisomy 13 is the least common of the trisomiesautosomal after Down syndrome (trisomy 21) and Edwards syndrome (trisomy 18). The extra copy of chromosome 13 Patau syndrome causes severe neurological and heart defects that make survival difficult for newborns. In connection with Edwards syndrome in a male patient hirsutism, microcephaly, synophrys, hypoplasia of the jaw also flex the fingers of both hands, which karyotype revealed trisomy 18, Figure 21, B, C and D. It was observed

As mentioned ring alterations in this study of both chromosomes 13 and 18 ring aberrations; Figure 15, B and C shows a female patient with bilateral cleft lip and palate and craniofacial dimorphism hipertelorismo characterized by progressive deformity of the spine malformation hemivertebra and ring chromosome 13 (Aparicio et al., 2000) and are different clinical features of a male patient with ring chromosome 18 aberration general hipertelorismo hypoplasia and hypotonia, ambiguous genitalia and small hands with special finger flexion Figure 22B and C. Aparicio et al., 1998.

Some mutations are neutral and have little or no effect. However, other chromosomal aberrations, change the patient's life and has a great role in evolution. Therefore, international organizations and institutions such as the Vega Institute presents data for manual annotation of the human genome. The entry shown in this version of Vega is a datafreeze taken from 2008-2011 and gene structures, presented in Table 2.

An abnormal number of chromosomes or chromosome sets, aneuploidy, can be fatal or lead to genetic disorders Huret et al .. 2000. some major chromosomal abnormalities in this study can be seen in Table 1 and Figures 5 and 6 . genetic counseling was offered to the carrier in this study, carrying these chromosomal rearrangements. The gain or loss of DNA in the chromosomes can lead to a variety of genetic disorders as found in this study.

It is important early and accurate diagnosis of these chromosomal aberrations, for an early treatment, better genetic counseling and a better quality of life.

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FIGURE LEYENDS

Figure 1 A. Female patient with bilateral cleft lip and palate and cranio-facial dimorphism and hypertelorism B. characterized by progressive deformity of spine with hemivertebrae. C. karyotype revealed a 13 chromosome ring malformation.

Figure 2 A. Female patient with Patau syndrome with hypoplasic face, bilateral cleft lip and palate and cranio-facial dimorphism, absent or malformed nose B. especial flexion of the fingers on both hands C. karyotype revealed a 13 chromosome trisomy.

Figure 3 A. Male patient with hirsutism, microcephaly, sinofris and general hypoplasia B. hypoplasia of the jaw C. especial flexion of the fingers on both hands D. Karyotype reveals an 18 trisomy.

Figure 4 A. Male patient with general hypoplasia and hipotonía, ambiguos genital and hypertelorism B. Small hands with especial flexion of the fingers C. karyotype reveal an 18 ring chromosome aberration.

Figure 5. 4617 karyotypes were performed from 1992 to 2011, where 1596 patients (34.6%) showed chromosomal alterations.

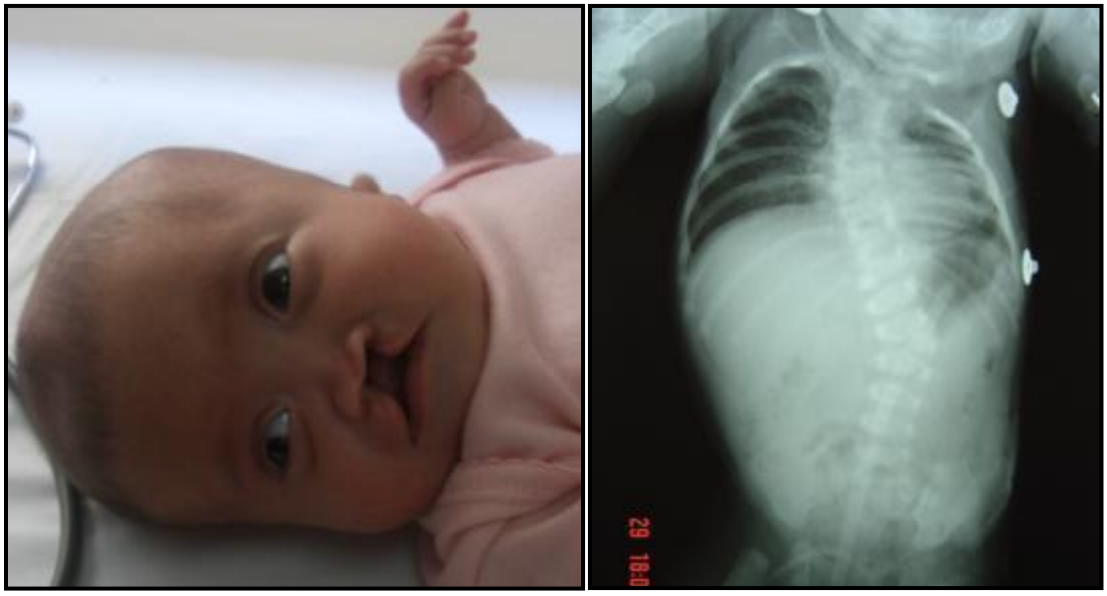
Figure 6. Chromosomal alterations in 19 years, shows 1596 patients (34.6%) with different aberrations. From these, 1553 (33.6%) were trisomy.

TABLES

Table 1. Different chromosomal alteration in 19 years at the Hospital Para el Nino Poblano, Mexico.

Table 2. Sequencing (http://www.ncbi.nlm.nih.gov/genome/seq/of the human genome

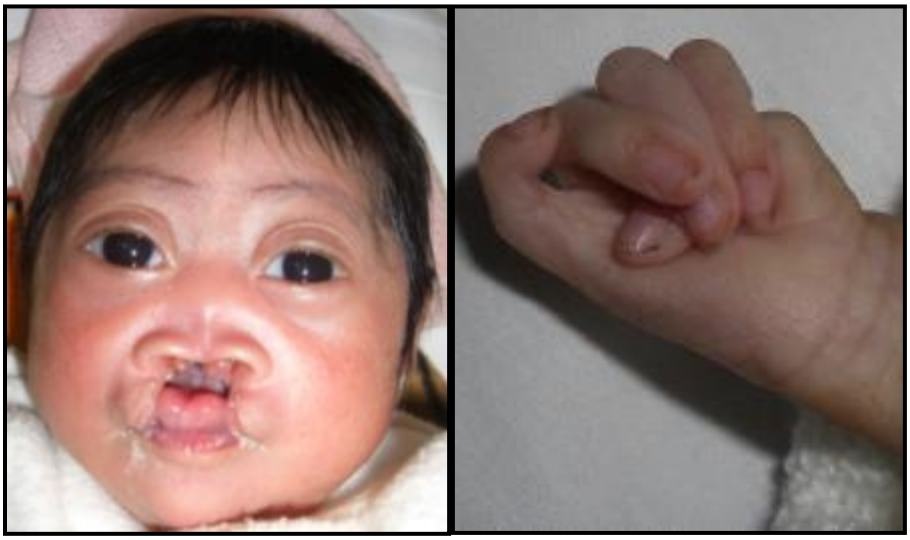
has provided a great deal of information about each of the chromosomes. This table is compiling statistics for the chromosomes, based on the Sanger Institute's human genome information in the Vertebrate Genome Annotation (VEGA) database.Vega.sanger.ad.uk,2008-2011



A **B**

C

Figura 1



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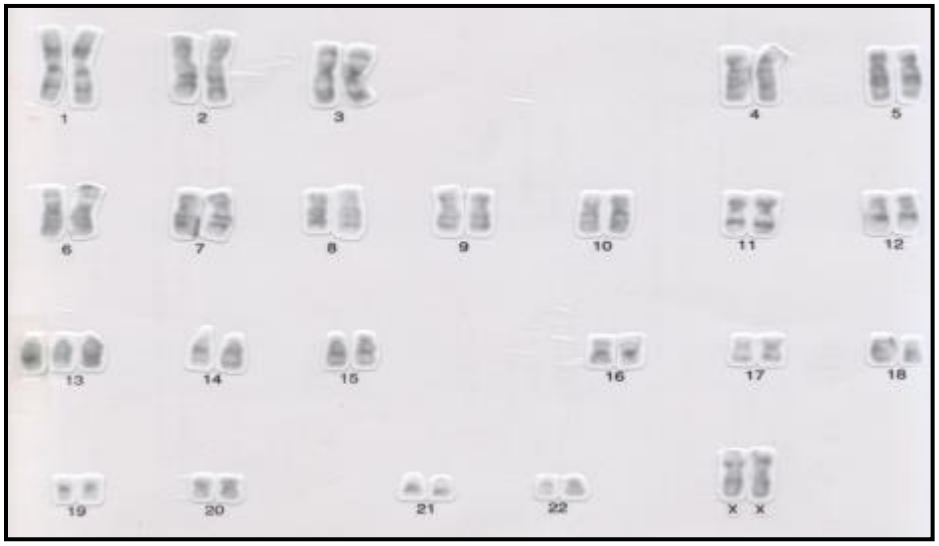
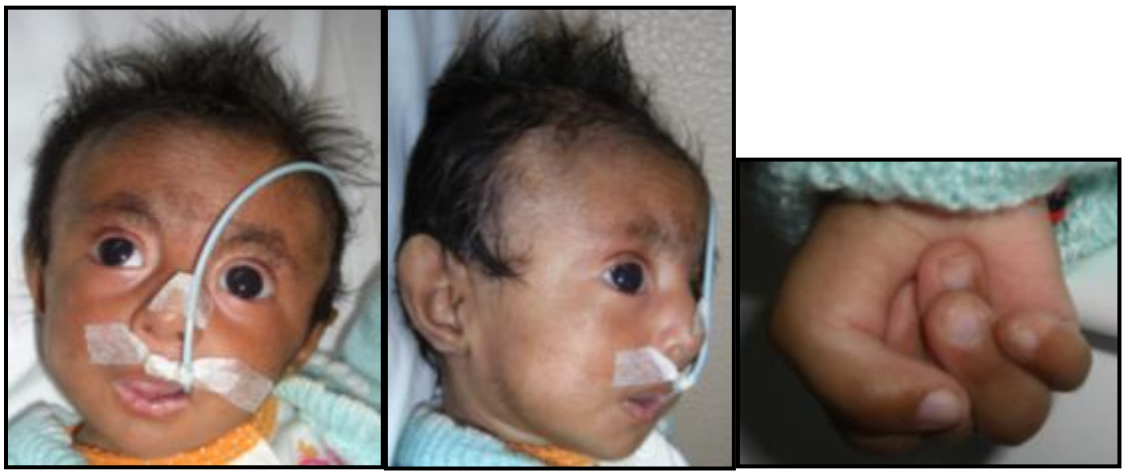
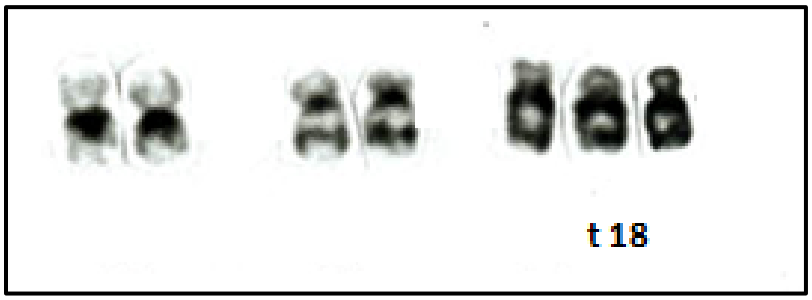


C

Figura 2

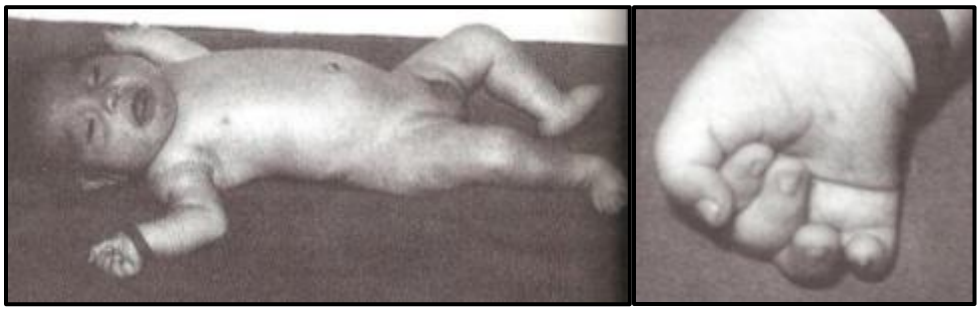


A **B** **C**

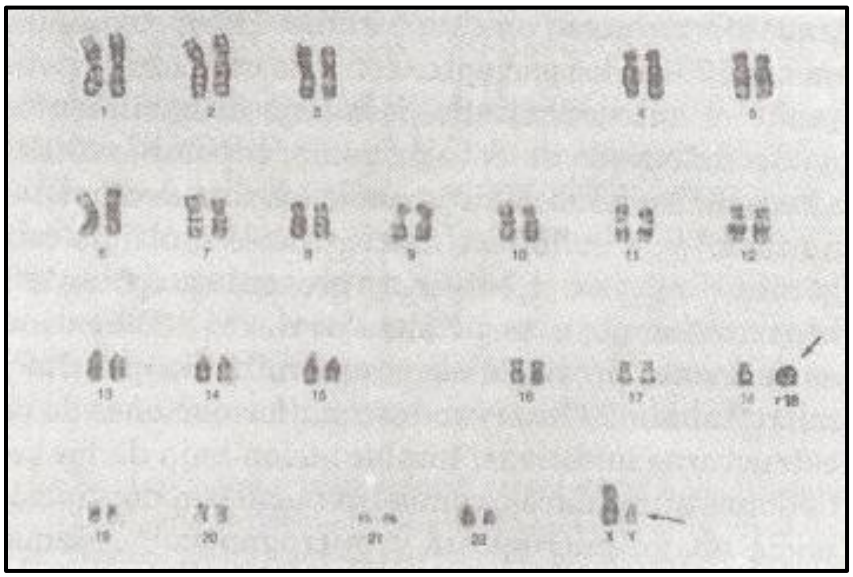


D

Figura 3



A **B**



C

Figure 4

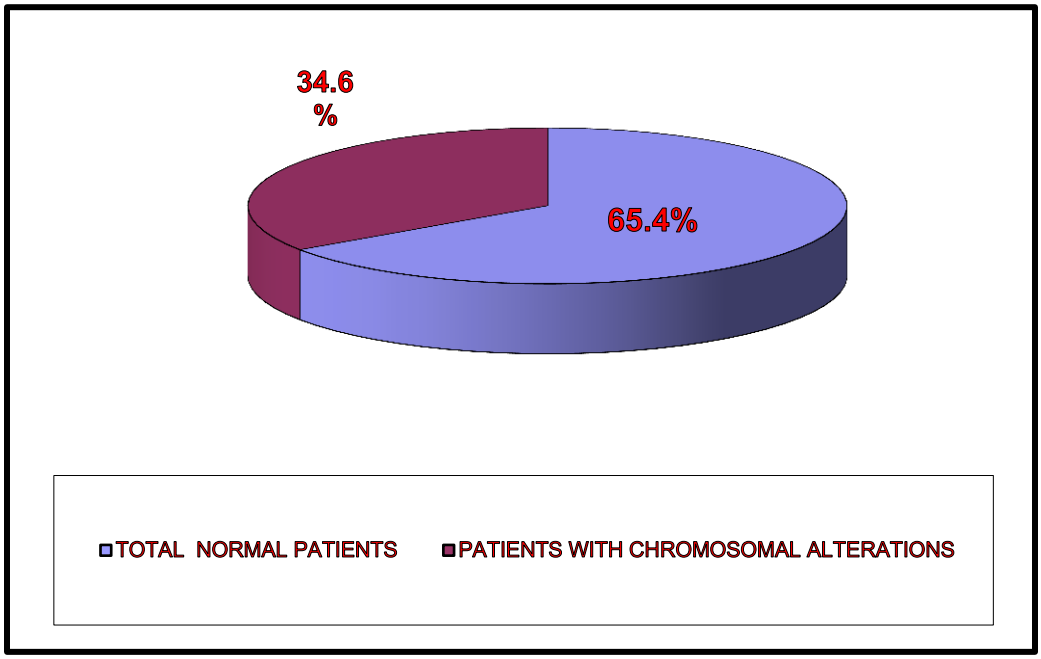

34.6 %
65.4%
TOTAL NORMAL PATIENTS
PATIENTS WITH CHROMOSOMAL ALTERATIONS

Figura 5.

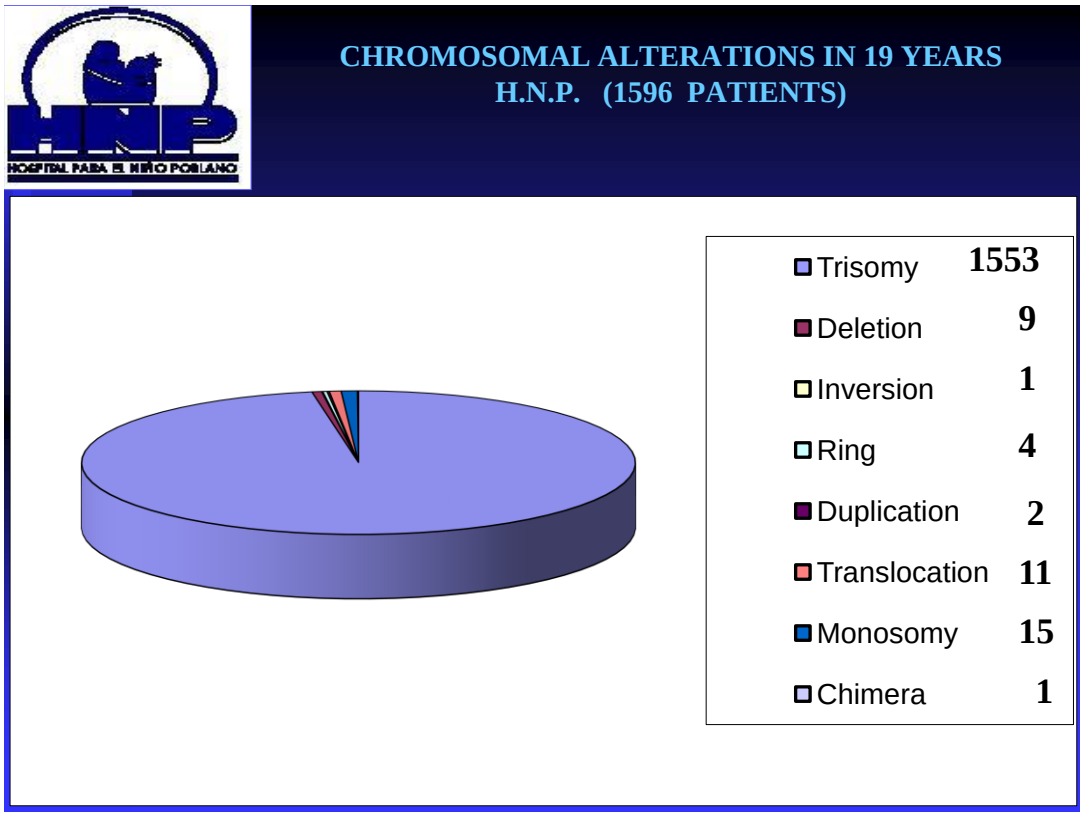


Figura 6.

TABLE 1

Chromosomalaberration(%)patients	
1. Trisomy1553	
2.Deletions(chromosomes 4,6,9)6 Otherdeletions	3
3. Invertion1	
4. Ring	4
5. Duplication	2
6. Translocation	11
7. Monosomy	15
8. Chimera	1

Chromosomalaberrations(34.6%) 1596		
Total Trisomies33.6%) 1553		
A-Trisomy 21	**(32.8%)1511**	
1. T 21		1127
2. T21;14		260
3. T21;21		43
4. Mosaicism81		
B-VariousTrisomies:	**(0.90%)42**	
Differentchromosomalaberrations:		**(0.93%) 43**
Total (karyotype studies in 19 years)(100%) 4617		
Total normal karyotypes(65.4%) 3021		
Total chromosomalaberrations(34.6%)1596		

Table 2.

Chromosome	Genes	Total bases	Sequenced bases
1	4,220	247,199,719	224,999,719
2	1,491	242,751,149	237,712,649
3	1,550	199,446,827	194,704,827
4	446	191,263,063	187,297,063
5	609	180,837,866	177,702,766
6	2,281	170,896,993	167,273,993

7	2,135	158,821,424	154,952,424
8	1,106	146,274,826	142,612,826
9	1,920	140,442,298	120,312,298
10	1,793	135,374,737	131,624,737
11	379	134,452,384	131,130,853
12	1,430	132,289,534	130,303,534
13	924	114,127,980	95,559,980
14	1,347	106,360,585	88,290,585
15	921	100,338,915	81,341,915
16	909	88,822,254	78,884,754
17	1,672	78,654,742	77,800,220
18	519	76,117,153	74,656,155
19	1,555	63,806,651	55,785,651
20	1,008	62,435,965	59,505,254
21	578	46,944,323	34,171,998
22	1,092	49,528,953	34,893,953
X (sex chromosome)	1,846	154,913,754	151,058,754
Y (sex chromosome)	454	57,741,652	25,121,652
Total	**32,185**	**3,079,843,747**	**2,857,698,560**