ABSTRACT

The majority of de novo structural chromosome aberrations in fetuses and newborns are considered being of cells of mammals for DNA damage during gametogenesis. 4617 chromosomal studies performed during 19 years (from 1992 to 2011), at Hospital Para El Niño Poblano in México, a total of 1596 patients showed positive for DNA aberrations. Among these studies population, 0.23% (11) chromosome translocations were observed. From this data, two male pediatric patients are described, with 1;4 and 6;9 chromosome translocations. Chromosome changes are classified as structural or numeric alterations respectively, and abnormal cell development has been associated with these two specific chromosomal translocations. The patients in this study were then analyzed and compared both hematological and compared to their clinical features.

Keywords: Chromosome, karyotype, leukemia, numeric and structural chromosome changes

INTRODUCTION

Chronic myeloid leukemia (CML) was reported in 1960 associated to the Philadelphia chromosome by Nowell and Hungerford and a large number of leukemias has been also associated with specific chromosomal translocations Trent et al. (1989). The development of new techniques enabled molecular biologists to isolate and characterize a number of genes involved in leukemias with reciprocal chromosome translocations and other various aberrations Table 1.
Due to the chromosome structure and important function, it has been considered vital for cell development and nuclei organization. Chromosomes also contain DNA-bound proteins, which serve to package the DNA and control its functions (Pereira et al., 1997; Sandman et al., 1998; Sandman and Reeve, 2000; Thanbichler et al., 2005). During evolution processes recombination has been considered for human being healthiness, Hinnebusch and Tilly (1993). If these structures begin through processes known as chromosomal instability and mutation, the cell may die or it may avoid apoptosis leading to initiation to cell malignization.

The preparation and study of karyotypes is part of cytogenetics in all kind of organisms. White (1973) this science has taking a very important part of human studies. One male patient in relation to chromosome 6 and its relation to leukemia with 6;9 translocation was studied Figures 1 A, B and C. It has been reported that translocations associated to chromosome 6 (Geraedts and Haak, 1976; Moormeier et al., 1991; Jonveaux et al., 1994; La Starza et al., 1998; Mohamed et al., 1998; Onodera et al., 1998; Wong, 2004) might be a part of the chromosome or the hole one (Chase et al., 1983; Bartalena et al., 1990; Uhrich et al., 1991; Brondum-Nielsen et al., 1993; Dellacasa et al., 1993).

Genetic counseling is considered a very important part of clinical genetics, due to the risk some healthy carrier parents might know, as balance translocation (6;9) associated to acute myeloid leukemia (Sandberg et al., 1983; Carroll et al., 1985; Schwartz et al., 1983; Rowley and Potter, 1976; Bemstein et al., 1989); young patients have been associated with leukemia and are considered very fragile. Where the translocation 6;9 is done, more studies must be performed as additional karyotypic studies were abnormalities may occur during progression of the disease (Carroll et al., 1985; Fonatsch et al., 1987; Pearson et al., 1985; Stejskalova et al., 1990)Fan et al., 1988; Levin et al., 1986; Horsman and Kalousek, 1987; Gold et al., 1983; Bemstein et al., 1989). Von Lindern et al., 1990 started studying the different genes at the main aberrations point among the chromosomes.

Chromosome 6 and participates in the balanced exchange (40kb) gene known as dek. Confirmed in 6;9 translocated patients located in one 9 kb intron, known as icb-6 (intron containing breakpoints). Differently, on chromosome 9 a 130kb DNA known as can gene or icb-9. Because of the translocation the 3’ part of the can gene is fused to the 5’ part of dek, resulting in a chimeric dek-can gene on the 6p- derivative, as reported by (Von Lindern et al., 1992). This specific gene is observed in an abnormal 5.5 kb-mRNA. The functions of the normal dek and can gene products are actually been studied.

In relation to chromosomes 1 and 2, a male adolescent Figure 2 A, with clinical, radiological and histopathological changes with cementoma Gigantiforme (CGnF) found associated for the first time to a reciprocal balanced translocation 46,XY,t(1;4) (q11q11) Figures 2 B, C and D. CGnF is a benign fibro-osseous tumor process, affecting the maxilla and the mandible. The fibro-osseous (LFO) injuryn
have in common that histopathological tissue is a replacement of the bone normal architecture by a tissue composed of collagen and fibroblasts fibers containing variable amounts of mineralized substance, which can have a bone cement-like appearance. These oral tumors, diagnosed by hystopathological studies as Cementoma Gigantiforme (are evaluated every 6 months by Oncology to avoid cellular metastasis) as mentioned before, associated to an unexpected translocation Figures 2 C and D, (Aparicio et al., 2002; Aparicio et al., 2006).

MATERIALS AND METHODS

From 4617 karyotypes performed at Hospital Para el Niño Poblano, Mexico in 19 years period of time, only 1596 patients (34.6%) showed chromosomal alterations, among the studies population, both 1;2, and 6;9 translocations were chosen to be studied during this period of time.

Both male patients, with chromosome translocation, were studied at the Department of Genetics in a multidisciplinary manner. DNA studies were performed by karyotyping all patients in this study by using GTG technique. By treating cell with colchicines the metaphase was arrested and then analyzed in order to support the clinical features. Hematological cells were then analyzed at the department of hematology. Cytogenetics study was conducted in lymphocytes of peripheral blood of the patient, mother and brother; chromosomes in metaphase with the conventional technique were obtained and analyzed with bands GTG Figures 1 C and 2 B.

To identify the involved centromeres, hybridization in situ was performed, with fluorescent (FISH) with alpha DNA probes satellite for the centromeres of the chromosome 1 and 4 (Vysis, USA) in red and green Figure 2 D.

Panoramic x-ray of jaws showed permanent dentition, with temporary upper central incisors. At the level of canines and premolars jaw on both sides, circumscribed, lesions with well-defined sclerotic borders, causing the divergence of the associated tooth roots. In the maxilla, on both sides, from molars area and continuing towards the anterior, in a close relationship of periodontal, presence of multiple masses lobed appearance, some of which occupy the maxillary sinuses. Another important radiographic finding is the presence in both jaws of multiple impacted teeth, in association with radiopaque mass. No abnormality was reported with imagining studies (RX).

DISCUSSION

Investigation into the human karyotype took many years to settle the most basic and major cause of genetic conditions in humans, such as Down syndrome, wish is considered to be one of the most frequent genetic aberrations on the diary clinical praxis. Since the beginning of genetics many questions have been developed as, the number of chromosomes inside a diploid human cell. Von Winiwarter (1912) reported 47 chromosomes in spermatogonia and 48 in oogonia, concluding an
XX/XO sex determination mechanism. Von Winiwarter (1912) and Painter (1922) was not certain whether the diploid number of man is 46 or 48, at first favoring 46. He revised his opinion later from 46 to 48, and he correctly insisted on humans having an XX/XY system, (Painter, 1923; Ford and Hamerton, 1956; Tjio and Levan, 1956). Considering the techniques of Von Winiwarter (1912) and Painter (1922), their results were quite remarkable. Hsu (1979) showed 48 chromosomes in chimpanzees that sheer with human being about 98.4% of the DNA. As mentioned before some carries parents are healthy during their life’s and will find any chromosomal abnormality until they give birth to a child with a chromosome disorder as observed in this study.

Chromosomal aberrations in this study were analyzed in relation to chromosomes 2 and 6, from 4617 karyotypes performed Figure 3 an 4, Table 2, (Aparicio et al., 2011). A large chromosome study was performed with malformed pediatric patients were chromosomal translocations, have some relation with cell development as oral tumors, diagnosed by hystopatological studies as Cementoma Gigantiforme (Aparicio et al., 2002; Aparicio et al., 2006). Abortions has also been associated to translocations as the case of a female patient with several abortion processes in her medical background with non crano-facial alterations with a chromosomal translocation t(2;18) (Aparicio et al., 2011), or craniofacial malformations due to translocations as the female patient diagnosed as Opitz G/B.B.B. syndrome with hypertelorism, unilateral cleft lip and palate and facial asymmetry had unexpected translocation between long arms of chromosomes 3 and 4, 46XX t(3q;4q). (Aparicio et al., 2011).

Nevertheless, one of the male patient in this study had specific clinical features; hypertelorism, sinofris, small nose and hypoplasia of nasal wings due to translocation from short arm of chromosome 6 to long arm of chromosome 9 t(6;9) Figure 1 A, B and C, which it has been associated to leukemia predisposition. Aparicio et al. (2006). Hematological studies were performed since translocation (6;9) is associated with a specific subtype of acute myeloid leukemia (AML). (Nowell and Hungerford, 1960; Gubler and Hoffman, 1983; Sandberg et al., 1983; von Lindern et al., 1989; Adriaansen et al., 1988; Heisterkamp et al., 1990; von Lindern et al., 1990; Kakizuka et al., 1991; Trent et al., 1989; Von Lindern et al., 1992; Pearson et al., 1985).

Previously, the hematological results have been reported as normal in this patient. However as mentioned before, it would be important to take in consideration that breakpoints on chromosome 9 are clustered in one of the introns of a large gene named Cain (can). cDNA probes derived from the 3’ part of can detect the presence of leukemia-specific 5.5-kb of DNA associated to bone marrow cells were patients with this kind of translocation has been reported on both 6 and 9 chromosomes.

A novel gene on chromosome 6 which was named dek observed by Von Lindern, in 1992 in one intron in relation to chromosomes aberrations. As a result the dek-can fusion gene, present in t(6;9) AML, encodes an invariable dek-can transcript (Von Lindern et al., 1992). Sequence analysis has
been reported as a chimeric DEK-CAN protein of 165 kDa. The predicted DEK and CAN proteins have molecular masses of 43 and 220 kDa, respectively, which has been associated to AML.

Cytogenetics abnormality have been reported in 12 cases of hematological disorders characterized by peripheral blood cytopenia and hypoplastic bone marrow; (Mecucci et al., 1986; Panani et al., 1980; Testa et al., 1985). Among these patients some had dysplastic transformation in the haemopoietic cells, some other did not taking in consideration that the pathogenesis of aplastic anaemia is considered heterogeneous. The real basis for this disease is associated to immunosuppressive therapy, it has been observed that damage of haemopoietic stem cell compartment is directly associated to clonal chromosomal abnormalities same as aplastic anaemia, which may be related to acute leukaemia as observed by Benedict in 1979.

Although acute myeloid leukemia (AML), is characterized by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells (Vardiman et al., 2002). Both patients in this study still with none clinical nor hematological symptoms yet, maybe because AML is considered to affect more to adults, and its incidence increases with age. Although the 1:2 translocated patient started to have solid cell development. The expected symptoms are caused by replacement of normal bone marrow with leukemic cells, which causes a drop in red blood cells, platelets, and normal white blood cells, including fatigue, shortness of breath, easy bruising and bleeding, and increased risk of infection. Several risk factors and other kind of chromosomal abnormalities have been identified, Le Beau et al., 1986. However there is still doubt whether acute leukemia development might become severe if no treatment is provided. Moreover, in relation to cytogenetics, Certain chromosome abnormalities have been associated with acute myelocytic leukemia Table 1, (Grimwade et al., 1998). as 15;17 translocation. About 50% of AML patients have normal cytogenetics; they fall into an intermediate risk group. A number of other cytogenetic abnormalities are known to associate with a poor prognosis and a high risk of relapse after treatment (Wheatley et al., 1999; Slovak et al., 2000; Byrd et al., 2002). An example is the male with 1:2 translocation found in this study and diagnosed with a Gigantiform cementoma which is a fibro-osseous tumoral lesion of jaws, a rare entity with sporadic or dominant autosomic inheritance. Until now, it has not been reported association of gigantiform cementoma and chromosomal abnormalities where the karyotype showed the existence of a de novo reciprocal chromosomal translocation between the long arms of chromosomes 1 and 4, Figures 2 B and C.

Therefore, chromosomal translocation 1:2 or 6:9, give rise to loss or DNA alterations which can lead to a variety of genetic disorders as it was found in both patients presented in his study. It is important whether these chromosomal aberrations can be diagnosed early for a better rehabilitation therapy and the best quality of life for the patient. Early intervention may be important in ensuring that affected children reach their potential and may be beneficial including special education and/or
other medical, social, and/or vocational services. Genetic counseling will also be of benefit for the families of affected patients.

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FIGURE LEYENDS

Figure 1. It can be seem a patient A. with sinofridia, telecanthus, B. plane face with small nose, and general facial hypoplasia. C. karyotype confirmed a 6 and 9 chromosomal translocation.
Figure 2. A. Male 15-year-old product, skull with tendency to the dolichocephalism, facies flat and antimongoloides palpebral commissures, broad forehead, ears flattened nasal bridge, elongated nose, Dysplastic, buccal commissure with deviation toward down. B.C. Cytogenetic bands GTG in the patient study resulted in 46, XY, t(1;4) (q11; q11). D. The study of FISH showed the adequate presence of centromeres in the derivatives 1 and 4 both the normal chromosomes
Figure 3. A large number of karyotypes were performed in Mexico, where only 34.6% had DNA aberrations.
Figure 4. 1596 patients with different kind of chromosomal aberrations were only 11 (0.23%) were diagnosed as translocations.
TABLES

Table 1. The first publication to address cytogenetics and prognosis was the MRC trial Grimwade in 1998.

Table 2. Different chromosomal alterations as translocations (0.23%) Were only one 1; 2 (0.02%) and one 6; 9 translocations (0.02%) were observed in 19 years at the Hospital para el Nino Poblano, Mexico.

Figure-1.
Figures-2.
Figure 3.

- 65.4%
- 34.6%

TOTAL NORMAL PATIENTS	PATIENTS WITH CHROMOSOMAL ALTERATIONS
Figure-4.

Total patients 1596

Translocations 11

CHROMOSOMAL ALTERATIONS IN 19 YEARS
(1596 PATIENTS)
(0.23%) 11 TRANSLOCATIONS

Table-1.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Abnormality</th>
<th>5-year survival</th>
<th>Relapse rate</th>
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<tr>
<td>Good</td>
<td>t(8;21), t(15;17), inv(16)</td>
<td>70%</td>
<td>33%</td>
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<tr>
<td>Intermediate</td>
<td>Normal, +8, +21, +22, del(7q), del(9q), Abnormal 11q23</td>
<td>48%</td>
<td>50%</td>
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<tr>
<td>Poor</td>
<td>-5, -7, del(5q), Abnormal 3q, Complex cytogenetics</td>
<td>15%</td>
<td>78%</td>
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Table-2.

<table>
<thead>
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<th>Chromosome aberration</th>
<th>(%) patients</th>
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<tbody>
<tr>
<td>Translocations</td>
<td>(34.6%)</td>
<td>11</td>
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</table>

1. Total Trisomies (33.6%) 1553
   A-Trisomy 21 (32.8%) 1511
   B-Various Trisomies: (0.90%) 42
   C. Trisomy 6 (0.02%) 1

2. Total Translocations (0.23%) 11
   A-Translocation 6;9 (0.02%) 1
   B-Translocation 1;4 (0.02%) 1

Total (karyotype studies in 19 years) (100%) 4617
Total normal karyotypes (65.4%) 3021
Total chromosome aberrations (34.6%) 1596