Acute myeloid leukaemia associated to chromosome 6: Clinical and phenotypical implications in two pediatric patients with chromosome trisomy and translocation


1Department of Genetics, Hospital para el Niño Poblano, Puebla, Mexico.
2Department of Cytogenetics, Hospital para el Niño Poblano, Puebla, Mexico.
3Department of Urology, Hospital para el Niño Poblano, Puebla, Mexico.
4Department of Physical Therapy, Hospital para el Niño Poblano, Puebla, Mexico.
5Department of Oncohematology, Hospital para el Niño Poblano, Puebla, Mexico.
6Department of Estomatología, Benemérita Universidad Autónoma de Puebla, México.
7Department of Biotechnology, Universidad Autónoma Metropolitana, Mexico City, Mexico.

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Chromosome aberrations are considered alterations in the chromosome number or structure. They are mainly considered due to gametogenesis inborn error or during the zygote first cellular divisions. Among 4617 chromosomal studies performed during 19 years (from 1992 to 2011), at Hospital Para El Niño Poblano in México, 34.6% (1596 patients) had chromosomal alterations. Among these study populations, a male and a female pediatric patient were described, with 6;9 translocation and trisomy of chromosome 6, where chromosome changes are classified as structural or numeric alterations respectively, and a number of leukemias has been associated with specific chromosomal translocations. Both cases were described in this study analyzing their hematological, clinical features, medical treatments and prognosis.

Key words: Chromosome, karyotype, leukemia, numeric and structural chromosome changes.

INTRODUCTION

Since the report in 1960 of the Philadelphia chromosome in relation to chronic myeloid leukemia (CML) by Nowell and Hungerford, a large number of leukemias has been associated with specific chromosomal translocations (Nowell and Hungerford, 1960; 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, trisomies and other various aberrations Table 2.

A chromosome is an organized structure of DNA and protein found inside cells. It is a single piece of coiled DNA with many genes, regulatory elements and other nucleotide sequences. Chromosomes also contain DNA-bound proteins, which serve to package the DNA and control its functions (Thanbichler et al., 2005; Sandman et al., 1998; Sandman and Reeve, 2000; Pereira et al., 1997). Chromosomes are in different organisms. The DNA molecule may be circular or linear, and can be composed of 100,000 to 10,000,000,000 nucleotides in a long chain (Paux et al., 2008). Normally, eukaryotic cells (White, 1973) have large linear chromosomes, and prokaryotic cells (Thanbichler and Shapiro, 2006; Nakabachi et al., 2006; Pradella et al., 2002) have smaller circular chromosomes.

Chromosome recombination plays a vital role in evolution and genetic diversity (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
malignation.

Human's chromosomes are divided into two known
types: autosomes and sex chromosomes. Certain genetic
traits are linked to a person's sex, and are passed on
through the sex chromosomes. The autosomes contain
all the genetic hereditary information. Both chromosome
types act in the same way during cell division. Human
cells have 23 pairs of large linear nuclear chromosomes.
The karyotype is the characteristic chromosome
complement of eukaryote organisms (White, 1973), the
preparation and study of karyotypes is part of a science
called cytogenetics.

Two patients in relation to chromosome 6 and its
relation to leukemia were studied, a female with trisomy 6
(Figure 1A, B and C) and a male patient with a 6;9
translocation (Figures 2A, B and C).

In relation to Chromosome 6, total (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 et al., 2004) and partial (Dellacasa et al.,
1993; Brondum-Nielsen et al., 1993; Uhrich et al., 1991;
Bartalena et al., 1990; Chase et al., 1983) trisomy 6q is
an extremely rare chromosomal disorder. Associated
symptoms may vary depending on the case. However, in
this study, a total trisomy is reported where slow physical
development (growth retardation), mental retardation, no
malformations of the skull and facial (craniofacial) region
with short, webbed neck, joint contractures were
observed, and normal hematological results.

Partial Trisomy 6q, all or a portion of the end (distal)
region of the long arm (q) of chromosome 6, is due to
duplication portion at various points (that is, breakpoints)
and the range and severity of associated symptoms may depend on the specific length (Turleau and de Grouchy, 1981; Schmid et al., 1979) or total duplication of the entire chromosome, as in this study.

In most reported cases, chromosome 6, partial trisomy 6 has resulted from a balanced chromosomal rearrangement in one of the parents (Chase et al., 1983), usually of maternal origin. However, paternal chromosomal rearrangements are rare and such a chromosomal rearrangement may be associated with an increased risk of abnormal chromosomal development in one of the parents. There have also been cases in which

Figure 2. Male patient: (A) with hypertelorism, sinofris; (B) small nose, hypoplasia of nasal wings. (C) Karyotype revealed a chromosomal translocation from short arm of chromosome 6 to long arm of chromosome 9 t(6;9).
Chromosome 6, partial Trisomy 6, has appeared to result from spontaneous (de novo) changes very early in embryonic development (Bartalena et al., 1990; Neu et al., 1981). In such de novo cases, the parents of the affected child usually have normal chromosomes and a relatively low risk of having another child with the chromosomal abnormality.

Chromosomal analysis and genetic counseling are often recommended for parents of an affected child to help confirm or exclude the presence of a balanced translocation or other chromosomal rearrangement.

In relation to complete trisomy 6 as the patient in this study, it has been associated to acute myeloid leukemia (AML) and myelodysplastic syndrome (Benedict et al., 1979; Panani et al., 1980; Testa et al., 1985; Mecucci et al., 1986).

Three out of four AML patients with trisomy 6 in one series showed AML-M1 morphology and expression of stem cell antigen CD34 on the leukemic blasts, suggesting that trisomy 6 may be associated with a different form of AML. Nevertheless, other reported cases have no hematological problems yet; however, she will be studied frequently to search for AML as the case in this study.

In relation to 6;9 translocation, a specific subgroup of acute myeloid leukemia (AML), a t(6;9) (p23;q34), has been widely reported (Rowley and Potter, 1976; Schwartz et al., 1983; Sandberg et al., 1983; Carroll et al., 1985; Bemstein et al., 1989). Patients with this type of leukemia are usually quite young and their prognosis is poor. Blast cells are mostly classified as French-American- British (FAB)-M2 or M4 (90%) and in a minority as M1 (10%). At the beginning of diagnosis, the t(6;9) is usually the sole cytogenetic aberration. Additional karyotypic abnormalities may occur during progression of the disease (Carroll et al., 1985; Bemstein et al., 1989; Pearson et al., 1985; Horsman and Kalousek, 1987; Heim et al., 1986; Gold et al., 1983; Fan et al., 1988; Fonatsch et al., 1987; Levin et al., 1986; Stejskalova et al., 1990). Recently, the genes located at the chromosomal breakpoints of this translocation were isolated and characterized (von Lindern et al., 1990).

The gene on chromosome 6 that participates in the reciprocal exchange is a 40 kb gene known as dek. Southern blot analysis of four patients with t(6;9) indicated that breakpoints are located in one intron of 9 kb, which is called (intron containing breakpoints on chromosome 6 or icb-6). The can gene on chromosome 9 is more than 130 kb in length. Here, breakpoints occur in one intron of 7.5 kb (icb-9) that is located in the middle of the gene.

The can gene is transcribed into a 6.6-kb mRNA. 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 (von Lindern et al., 1992).

This chimeric gene is transcribed into an aberrant 5.5 kb-mRNA. The functions of the normal dek and can gene products are as yet unknown and it is equally unclear in which way the hybrid product may be involved in leukemogenesis.

**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, a 6;9 translocation and a 6 trisomy were observed during this period of time (Figure 3).

A male and a female patient, both with chromosome trisomy and translocation reciprocally, were studied at the Department of
Chromosomal alterations in 19 years, show shows 1596 patients (33.6%) with different aberrations. From these, 1553 (33.6%) were trisomies and 11 (0.23%) translocations.

**DISCUSSION**

Chromosomal aberrations are disruptions in the normal chromosomal structures of a cell and are a major cause of genetic conditions in humans, known as genetic disease which might have or not an inheritance pattern, such as Down syndrome, considered as the more frequent chromosomal trisomy. Investigation into the human karyotype took many years to settle the most basic question. How many chromosomes does a normal diploid human cell contain? In 1912, von Winiwarter reported 47 chromosomes in spermatogonia and 48 in oogonia, concluding an XX/XY sex determination mechanism (Von Winiwarter, 1912). Painter (1922) was not certain whether the diploid number of man is 46 or 48, at first he favored 46. He revised his opinion later from 46 to 48, and he correctly insisted on humans having an XX/XY system (Painter, 1923; Tjio and Levan, 1956; Ford and Hamerton, 1956). Considering the techniques of Von Winiwarter (1912) and Painter (1922), their results were quite remarkable. Hsu in 1979 showed that chimpanzees (the closest living relatives to modern humans) have 48 chromosomes. Some chromosome abnormalities do not cause disease in carriers, such as translocations, or chromosomal inversions, although they may lead to a higher chance of birthing a child with a chromosome disorder as was found in both patients in this study.

Chromosomal aberrations in this study were analyzed in chromosome 6 from 4617 karyotypes performed from 1992 to 2011 (Aparicio et al., 2011), only 33.6% (1553 patients) have chromosomal trisomies (Figure 4). From these 33.6% trisomic population, 32.8% (1511 patients) were diagnosed as Down syndrome (trisomy 21) and 0.90% has other kind of trisomies (Table 1).

Finally, a diversity of pediatric patients with phenotypical malformations was evaluated during 19 years at the Department of Genetics. In relation to chromosomal translocations, it has been associated to oral tumors, diagnosed by histopathological 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 cranio-facial alterations with a chromosomal translocation t(2;18) 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, the patient in this study, a male patient with hypertelorism, sinofris, small nose and hypoplasia of nasal wings, was also analyzed with a translocation from short arm of chromosome 6 to long arm of chromosome 9 t(6;9) (Figure 2A, B, 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; Trent et al., 1989; von Lindern et al., 1992; Adriaansen et al., 1988; Gubler and Hoffman, 1983; Heisterkamp et al., 1990; Kakizuka et al., 1991; Pearson et al., 1985; Sandberg et al., 1983; von Lindern et al., 1990; von Lindern et al., 1989). Previously, the hematological results have been reported as normal. It was found 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 transcript in bone marrow cells from t(6;9) AML patients. cDNA cloning of this mRNA revealed that it is a fusion of sequences encoded on chromosome 6 and 3’ can.

A novel gene on chromosome 6 which was named dek has been isolated (von Lindern et al., 1992). In dek, the t(6;9) breakpoints also occur in one intron. 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.

From a total of 4617 karyotypes (100%) performed in this study (Aparicio et al., 2011), 33.6% (1553 patients) (Table 1 and Figure 4) were diagnosed as chromosomal trisomy, were 32.8% (1511 patients) diagnosed as Down syndrome (trisomy 21) (Aparicio et al., 2009). Moreover, 0.90% with different trisomies (Table 1), as the case of the female patient in this study with a complete trisomy 6 (Figure 1C), without any phenotypical malformations nor cranio-facial dimorphism (Figure 1A and B), taking in consideration that trisomy 6 is an extremely rare chromosomal disorder and has been associated to aplastic anaemia (Geraedts and Haak, 1976).

Cytogenetics abnormality has been reported in 12 cases of hematological disorders characterized by peripheral blood cytopenia and hypoplastic bone marrow (Panani et al., 1980; Testa et al., 1985; Mecucci, 1986). Among the 12 cases, eight cases showed dysplastic change in the haemopoietic cells, whereas four did not. The pathogenesis of aplastic anaemia is heterogeneous. While an immunological basis for this disorder is established based on response to immunosuppressive therapy, there is also evidence for clonal nature resulting from damage to the haemopoietic stem cell compartment. Indeed, clonal chromosomal abnormalities are reported in otherwise typical aplastic anaemia. Furthermore, aplastic anaemia evolving into acute leukaemia is well documented (Benedict et al., 1979).

Rare instances of trisomy 6 may be encountered in childhood acute mixed lineage leukaemia, lymphoblastic transformation of chronic myeloid leukemia, and chronic myeloproliferative disorder.

Trisomy 6 may define a distinctive subtype of aplastic anaemia with mild dysplastic changes (Geraedts and Haak, 1976; Moormeier et al., 1991; Jonveaux et al., 1994; La Starza et al., 1998; Mohamed, 1998; Onodera et al., 1998; Wong, 2004), poor response to steroids and ATG therapy, and propensity for AML transformation. More cases need to be collected to substantiate this contention.

Partial trisomy 6, however, may be variable. The disorder is characterized by growth delays before and

<table>
<thead>
<tr>
<th>Chromosome aberration</th>
<th>Patients</th>
<th>(%)</th>
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<tbody>
<tr>
<td>Trisomies</td>
<td>A-Trisomy 21</td>
<td>1511</td>
</tr>
<tr>
<td></td>
<td>B-Various Trisomies:</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>C. Trisomy 6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total Trisomies</td>
<td>1553</td>
</tr>
<tr>
<td>Translocations</td>
<td>A-Translocation 6:9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Total Translocations</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Total (karyotype studies in 19 years)</td>
<td>4617</td>
</tr>
<tr>
<td></td>
<td>Total normal karyotypes</td>
<td>3021</td>
</tr>
<tr>
<td></td>
<td>Total chromosome aberrations</td>
<td>1596</td>
</tr>
</tbody>
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Table 2. The first publication to address cytogenetics and prognosis was the MRC trial (Grimwade, 1998).

<table>
<thead>
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<th>Risk category</th>
<th>Abnormality</th>
<th>5-year survival (%)</th>
<th>Relapse rate (%)</th>
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</thead>
<tbody>
<tr>
<td>Good</td>
<td>t(8;21), t(15;17), inv(16)</td>
<td>70</td>
<td>33</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Normal, +8, +21, +22, del(7q), del(9q), abnormal 11q23, all other structural or numerical changes</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>Poor</td>
<td>-5, -7, del(5q), abnormal 3q, complex cytogenetics</td>
<td>15</td>
<td>78</td>
</tr>
</tbody>
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after birth, severe to profound mental retardation, a delay in the acquisition of skills requiring coordination of muscular and mental activity (psychomotor retardation), with malformations of the skull and facial (craniofacial) region as microcephaly, ocular hypertelorism, micrognathia and cleft palate, musculoskeletal abnormalities, and/or additional physical features. Chromosome 6, partial Trisomy 6q, is an extremely rare chromosomal disorder that appears to affect males and females equally (Dellacasa et al., 1993; Brondum-Nielsen et al., 1993; Uhrich et al., 1991; Bartalena et al., 1990; Chase et al., 1983).

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 are still with neither clinical nor hematological symptoms yet, maybe because AML is considered to affect more to adults, and its incidence increases with age. 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. But the specific cause is not clear. As an acute leukemia, AML progresses rapidly and is typically fatal within weeks or months if left untreated. Moreover, in relation to cytogenetics, certain chromosome abnormalities have been associated with acute myelocytic leukemia (Table 2) (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).

Chromosomal trisomy or translocation 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 this 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. Special services that may be beneficial include special education and/or other medical, social, and/or vocational services. Genetic counseling will also be of benefit for the families of affected individuals. Other treatment for this disorder is symptomatic and supportive.

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REFERENCES


