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Evaluation of constitutional chromosome aberrations in hematologic disorders

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Abstract We have reviewed 4164 patients with various hematologic disorders cytogenetically studied in our laboratory during the last 25 years to analyze the frequency of constitutional chromosome aberrations (CCA) and to evaluate their association with hematologic malignancies. Our population of patients included 1133 pediatric patients and 3031 adults. Twenty-four (0.58%) cases showed CCA. They included four patients with Robertsonian translocations, one patient with a balanced translocation, two patients with sex chromosome abnormalities, and 17 cases with Down syndrome (DS). Nonsignificant differences among the frequency of patients with CCA from our hematologic series and those observed in the two largest combined surveys of livebirth published (0.65–0.84%) were found. The incidence of DS patients in our population (0.41%) was approximately three times higher than of that observed at birth (0.12–0.17%; $P<0.001$). The total incidence of constitutional chromosome abnormalities in the non-DS hematologic patients was 0.168% (7 of 4164) lower than of that observed in the newborn population (0.51–0.67%; $P<0.001$). Nonsignificant differences were found when the incidences of structural aberrations and sex chromosome anomalies were individually compared with the data of the overall population. Our results suggest that the presence of a CCA, other than DS, would not predispose patients to hematologic malignancies.

1. Introduction

Some constitutional chromosome abnormalities (CCA) determine an increased risk of malignancy, mainly familial tumors in children and young people. A few congenital structural chromosome alterations are known to predispose to neoplastic disorders: del(13)(q14) to retinoblastoma [1], del(11)(p13) to Wilms tumor [2], and t(3;8)(p14;q24) to renal cell carcinoma [3,4]. Furthermore, it is known that there is an increased risk of developing specific types of tumors in patients with different constitutional autosomal trisomies. The association of constitutional numeric chromosome anomalies with a higher risk of germ cell tumors, particularly mediastinal tumors, has been reported in Klinefelter syndrome (KS) and Down syndrome (DS) [5–8]. In addition, KS predisposes patients to breast tumors, DS to acute leukemias, and Turner syndrome to tumors of neural crest origin [9–11]. Other congenital chromosome aberrations such as Robertsonian or other reciprocal balanced translocations, and the karyotype XYY also have been found in patients with malignant diseases [12–16].

Multiple cytogenetic studies reveal that 0.60–0.92% of newborns have a major chromosomal abnormality [17–20]. Particularly, the general population incidence reported by Hsu [20] include two large combined series of livebirths in which the relevant incidences of all constitutional chromosome anomalies can be analyzed individually.

Conversely, the frequency of CCA in patients with hematologic disorders has not been entirely settled yet. There are only a few reports of large series with different results [21–23]. In the present article, we have reviewed 4,164 patients with different hematologic disorders cytogenetically studied in our laboratory during the last 25 years (1975–2000) to analyze the frequency of CCA and to evaluate their association with hematologic malignancies.

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2. Materials and methods

Bone marrow (BM) cells of 4164 patients with various hematologic diseases: acute leukemias (AL) (1890), myelodysplastic syndromes (MDS) (511), malignant lymphomas (ML) (587), and myeloproliferative disorders (MPD) (1,176) were processed for cytogenetic analysis by short-term cultures (24–48 h) in RPMI-1640 medium supplemented with 15% fetal calf serum. GTG-banding technique was used for chromosome identification. Karyotype abnormalities were described using the International System for Human Cytogenetic Nomenclature (ISCN, 1995) [24]. Patients with a single chromosome alteration compatible with life were studied in phytohemagglutinin-stimulated cultures (72 h) of peripheral blood lymphocytes (PBL) to establish the existence of a constitutional anomaly at diagnosis or during remission. Fluorescence in situ hybridization (FISH) using centromeric and whole chromosome painting probes was performed according to standard protocols.

Our population included 1133 (27.2%) pediatric patients (0–17 years of age) and 3031 adults (72.8%). Down syndrome was observed in 17 (0.41%) individuals. The sex ratio was 1.4:1 (male:female). The statistical analysis to compare both populations (hematologic vs. overall population) was performed with Fisher exact test. This comparison was performed taking into account the frequencies (0.65–0.84%) found in the two largest combined surveys (68,159 and 34,910 livebirths, respectively) reported by Hsu [20].

3. Results

Twenty-four of 4164 (0.58%) cases showed CCA. They included four patients with Robertsonian translocations (RT) (cases 1–4), one patient with a balanced translocation (case 5), two patients with sex chromosome abnormalities (cases 6 and 7), and 17 cases with DS (cases 8–24). Clinical and cytogenetic data are summarized in Table 1.

Cases 1 and 2 with MDS had a der(13;14)(q10;q10) and case 3 with a diagnosis of polycythemia vera (PV), an MPD, showed a der(14;21)(q10;q10). These cases did not show additional karyotypic aberrations. Case 4 presented MDS at first, with evolution to acute myeloblastic leukemia (AML), der(21;22)(q10;q10), and del(6)(q21) and a non-identified marker chromosome (mar) as acquired changes in the karyotype.

Case 5 with a diagnosis of CLL showed a balanced recip-

Table 1
Patients with hematologic diseases and constitutional chromosome aberrations

Patient no.	Sex/Age (years)	Hematologic disorder	Constitutional anomaly	Additional karyotypic change(s)
1	F/2.9	MDS	der(13;14)(q10;q10)	None
2	F/5	MDS	der(13;14)(q10;q10)	None
3	F/42	PV	der(14;21)(q10;q10)	None
4	M/60	AML	der(21;22)(q10;q10)	del(6)(q21),+mar
5	M/54	CLL	t(9;20)(p12;p12)	+12 (FISH)[a] +12,+22[b]
6	M/46	NHL	XXY[c]	None
7	F/62	NHL	XYY[c]	+22
8	F/17	ALL	+21	None
9	F/10	ALL	+21	None
10	F/14 days	ALL	+21	None
11	M/0.7	ALL	+21[c]	None
12	M/2	ALL	+21	Bq+,Dq+
13	F/17 days	ALL	+21	None
14	F/2	AL	inv(9)(p12q21),+21	None
15	F/3	MDS	+21[c]	None
16	F/10	MDS	+21	None
17	M/1.83	MDS	+21	del(6)(q26),del(8)(q11;q21),del(18)(p11)[a] idem, +3[b]
18	M/21	MDS	+21	None
19	F/11	MDS	+21	−9
20	M/3	MDS	+21[c]	del(17)(q21)
21	M/6	MDS	+21	None
22	M/1.5	MDS	+21	None
23	F/0.75	MDS	+21	None
24	F/0.92	MDS	+21	None

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; FISH, fluorescence in situ hybridization; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma; PV polycythaemia vera.

[a]First study.

[b]Second study.

[c]Mosaic karyotype.

rocal translocation t(9;20)(p12;p12), confirmed by FISH, with extra changes in the karyotype. The first study at diagnosis, showed a clone with trisomy 12 by FISH (12% of cells), and the second study, 1 year after treatment, showed a karyotype: 46,XY,t(9;20)(p12;p12)[19]/47,XY,t(9;20)(p12;p12),+22[4]. In addition, FISH study showed 5% of cells with trisomy 12.

Cases 6 and 7 with diagnosis of diffuse large B-cell lymphoma had mosaic karyotypes with sex chromosome anomalies. Case 6: BM cells: 46,XY[6]/47,XXY[15], and PBL: 46,XY[2]/47,XXY[8]; case 7: BM cells: 46,XY[2]/47,XYY[10]/47,XYY,+22[2] and PBL: 46,XY[4]/47,XYY[7].

Fourteen of the 17 DS patients (82.3%) had nonmosaic constitutional karyotypes with trisomy 21, a value only slightly lower than the 93–96% observed in the general DS population [25]. The remaining three cases presented mosaic karyotypes. Seven of 17 (41.2%) DS cases had acute leukemia (six acute lymphoblastic leukemia (ALL) and one AML) and 10 (58.8%) presented MDS. Additional structural and numeric changes in the karyotypes were observed in four patients (cases 13, 18, 20, 21): del(6)(q26), del(8)(q11q21), del(18)(p11), del(17)(q21),+3,−9.

Table 2 shows the frequencies of patients with CCA in our hematologic population and in the two largest combined surveys reported by Hsu [20]. Nonsignificant difference between the incidences of CCA patients (0.58%) of both our hematologic and the overall population (0.65–0.84%) [17,20] was found. Down syndrome patients represent 0.41% (17 of 4,164) of cases from this series. This incidence was approximately three times higher than of that observed at birth (0.12–0.17%; $P<0.001$). Conversely, the total incidence of constitutional chromosome abnormalities in the non-DS hematologic patients was 0.168% (7 of 4,164) lower than of that observed in the newborn population (0.51–0.67%; $P<0.001$) [17,20]. The incidence of balanced alterations was similar in both populations (hematologic and newborn) although, in hematologic patients, reciprocal translocations presented an incidence approximately four to six times lower than of that observed at birth; this differences was only significant with respect to the series reported by Nielsen and Wohlert [17] ($P<0.05$). Nonsignificant differences were found when the incidences of patients with sex chromosome anomalies were compared with the overall population.

4. Discussion

In an approach to know the incidence of constitutional chromosome alterations in the hematologic population, we reviewed 4,164 unselected patients with different hematologic disorders cytogenetically studied in our laboratory during the last 25 years. An incidence of CCA, similar to that seen in the overall population was found. Note that 70.8% of our patients with CCA had DS. Thus, when DS patients were excluded, our incidence of CCA was significantly lower than of that observed in non-DS newborn population [17,20]. Furthermore, when structural aberrations and sex chromosome anomalies were individually analyzed, no differences with the incidence in the general population were found. Thus, our data suggest no association between CCA and hematologic malignancies.

The literature reports two large series of unselected patients with hematologic disorders in which the frequency of CCA were evaluated. The first one, reported by Alimena et al. [21] with 1,400 patients, found 1.28% cases with CCA (55.5% with DS). The other one reported by Benítez et al. [22] included 5,500 patients (718 from their own laboratory and 4,782 from unselected series of the literature) showing an incidence of patients with CCA of 1.073% (49.1% with DS). The frequencies observed in both studies were approximately double of that observed in the newborn population, but in the report of Benítez et al. [22] this difference disappeared when DS patients were excluded (0.57% vs. 0.65%). Another series of patients with CCA and malignant hematologic disorders was reported by the Group Français de Cytogénétique Hématologique, their results being inconclusive [23]. In addition, when the incidences of each chromosome anomaly were individually analyzed, the frequencies of our series of hematologic patients were lower than of those reported by Benítez et al. [22], although both did not show significant differences with respect to the overall population.

According to the literature, our data support the idea that DS patients are at greater risk of developing acute leukemia (10–

Table 2
Frequency of chromosome alterations in our hematologic population and the two largest combined surveys reported by Hsu [20]

	No. of cases (%)		
Type of abnormality	Our population of 4,164 patients	Combined surveys of 68,159 liveborns [20]	Survey of 34,910 newborns [17]
Total abnormalities	24 (0.58)	442 (0.65)	294 (0.84)
Robertsonian translocations	4 (0.096)	62 (0.090)	43 (0.120)
Reciprocal translocations	1 (0.024)[a]	64 (0.093)	49 (0.140)
47,XXY	1 (0.024)	45 (0.045)	28 (0.157)
47,XYY	1 (0.024)	45 (0.103)	21 (0.120)
47,+21	17 (0.410)[b]	82 (0.120)	59 (0.169)

[a] Significant difference with respect to the Nielson and Wohlert's survey [17], $P<0.05$.
[b] Significant differences with respect to the overall population: $P<0.001$.

20-fold) than normal subjects of the same age [26–28]. Seven of 17 DS patients (41.2%) developed AL (six ALL) according to the 4:1 ratio of lymphoid to myeloid leukemia reported in the literature in DS individuals [26–28]. The remaining 10 DS patients had MDS (58.8%), probably related to the fact that most of them (63%) were younger than 4 years of age. It is known that AML is the most common form of leukemia in DS children younger than 4 years, being often of megakaryoblastic phenotype (M7), the most frequent and often preceded by MDS [29–31]. Different reports indicate, that AML and MDS in DS often show additional chromosomal abnormalities other than the constitutional trisomy 21, being those seen in acute nonlymphoid leukemias (ANLL) higher than in lymphoid forms [32–34]. Acquired chromosome aberrations were more frequent in our DS patients with MDS than those without MDS (36%). Chromosome aberrations specific for ANLL and those for ALL were absent in these DS subjects.

Note that trisomy 21, the most frequent trisomy observed as a constitutional chromosome abnormality, is also one of the most common primary, single acquired autosomal trisomies in hematologic disorders, more commonly associated with disease progression than diagnostic features [35].

Our cases with sex chromosome abnormalities showed a diagnosis of non-Hodgkin lymphoma (NHL), association that was rarely observed in the literature [26,36]. The relation between the appearance of leukemia and/or similar conditions and constitutional sex chromosome pathologies (numeric and structural anomalies) is not yet well defined, whereas a definitely increased incidence of epithelial tumors of the gonads has been well documented. Our results and previous reports [21,22] did not find differences with the overall population [17,20]. However, it is in agreement with the hypothesis of an incidental occurrence of hematologic disorders in these subjects [9,36,37]. Moreover, evidence of leukemic transformation has been found in cytogenetically normal cell lines of patients with mosaicism for sex chromosome anomalies suggests that an abnormal chromosome complement alone does not necessarily predispose to the neoplastic transformation [32].

Several case reports have described the simultaneous occurrence of carriers of constitutional balanced rearrangements and hematologic diseases [14–16,38–40]. In most of them, it could not be determined whether a real association exists or if they only represent random events. In our series of patients with CCA, four cases with Robertsonian translocations and only one patient with a reciprocal translocation were found: t(9;20)(p12;p12), which to our knowledge has not been reported yet in the literature. Our findings and previous data in the literature [21,22] did not show differences in the incidence of balanced alterations with the overall population [17,20], except when reciprocal translocations were compared with the data reported by Nielson and Wohlert [17]. Various reports suggest that CCA could affect genes that would be mutated during meiosis or somatic malignant transformation [38]. Thus, the chromosome rearrangements may not be sufficient for full neoplastic transformation and other acquired gene mutations may be necessary. This possibility could explain the penetrance of the disease in families with constitutional chromosome anomalies [16].

In conclusion, our data did not show significant difference in the incidence of individuals with CCA compared with the overall population, suggesting that the presence of constitutional chromosome aberrations other than DS would not predispose to hematologic malignancies.

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