LOSS OF THE SEX CHROMOSOME IN HUMAN NEOPLASIAS OF THE NERVOUS SYSTEM

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ABSTRACT

Thirty-eight tumors (five grade I-II astrocytomas, three grade III astrocytomas, four glioblastomas, one oligodendroglioma, four ependymomas, one pineocytoma, three medulloblastomas, four acoustic nerve neurinomas, one intraspinal neurinoma, one neurofibroma, 10 meningiomas, and one craniopharyngioma) and three benign lesions of the nervous system were evaluated cytogenetically after *in vitro* culture. Sex chromosome loss was detected in 56% of the cases (-X in 13 of the 25 female patients and -Y in nine of the 16 male patients). The objective of the present report was to study the role of this abnormality in cells of the nervous system.

INTRODUCTION

Specific and non-random chromosome abnormalities are frequently associated with different types of human neoplasias. Some chromosome regions are preferentially involved in structural rearrangements and the possible effects of these rearrangements in the process of carcinogenesis have been extensively discussed. Gain or loss of whole chromosomes has also been commonly reported in some types of tumors (see references in Mitelman, 1991).

Clonal numerical chromosome aberrations can occur as single alterations and probably represent primary abnormalities; however, they frequently appear as additional or secondary alterations which do not directly affect the establishment of a tumor but are related to neoplastic progression (Friedlander *et al.*, 1984; Heim and Mitelman, 1986).

Human tumors of the nervous system are usually aneuploid and heterogeneous and therefore are more difficult to analyse (Sandberg, 1990). The most frequent types of anomalies are losses or gains of whole chromosomes, loss of specific chromosome regions by deletions or unbalanced translocations (Bigner *et al.*, 1990).

A controversial topic in the cytogenetics of human tumors of the nervous system is the significance of the loss of sex chromosomes. There are many cases of tumors of the nervous system which present clonal and consistent losses of sex chromosomes, especially gliomas (Yamada *et al.*, 1980; Bigner *et al.*, 1984, 1986, 1988, 1990; Rey *et al.*, 1987a,b; Jenkins *et al.*, 1989; Ransom *et al.*, 1992; Thiel *et al.*, 1992), and meningiomas (Mark, 1977; Zankl and Zang, 1980; Yamada *et al.*, 1980; Zang, 1982; Al Saadi *et al.*, 1987; Rey *et al.*, 1988; Casalone *et al.*, 1990; Logan *et al.*, 1990), suggesting a relevant role of these chromosomes in the initiation or progression of these tumors. Heim *et al.* (1989) reported the loss of sex chromosomes and trisomy 7 in short-term cultures of non-neoplastic brain tissue and suggested that these changes may reflect normal *in vivo* mosaicism and therefore should not be considered to be specific events associated with neoplasias. Arnoldus *et al.* (1991a) analysed normal brain tissue collected from six autopsies and their results did not confirm those reported by Heim *et al.* (1989), suggesting that trisomy 7 and the loss of sex chromosomes detected by the latter authors may reflect *in vitro* artifacts occurring during short-term culture.

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We report here the incidence of sex chromosome loss in 38 tumors and in three benign lesions of the nervous system.

MATERIAL AND METHODS

Thirty-eight tumors (five grade I-II astrocytomas, three grade III astrocytomas, four glioblastomas, one oligodendroglioma, four ependymomas, one pineocytoma, three medulloblastomas, four acoustic nerve neurinomas, one intraspinal neurinoma, one neurofibroma, 10 meningiomas, and one craniopharyngioma) and three benign expansive lesions of the nervous system were analyzed cytogenetically after short- to medium-term *in vitro* culture (three to 20 days). Twenty-five patients were females and 16 were males, ranging in age from three to 75 years. All cases represented primary lesions of the nervous system and the patients were not submitted to chemotherapy or radiotherapy before surgery. The tumors and lesions were classified morphologically according to the World Health Organization brain tumor classification (Zülch, 1979).

Fresh tumor tissue samples collected under sterile conditions were processed promptly. The fragments were first sectioned and then dissociated enzymatically with a 0.4 or a 0.8% collagenase solution (type IV) (SIGMA) and transferred to culture flasks containing HAM F-10 medium (SIGMA) supplemented with 20% fetal calf serum, vitamins (DIFCO) and antibiotics. The cultures were maintained at 37°C and fed twice a week. Culture time was adjusted individually for each case depending on mitotic activity. For cytogenetic analysis, cells in the exponential growth phase were first treated with 0.0016% colchicine for at least six hours. Hypotonic 0.075M KCl was used for 30 minutes and methanol:acetic acid (3:1) was used as a fixative. Chromosome studies were made of primary cultures only. Slides were subjected to GTG banding (Scheres, 1972). The International Standard for Human Cytogenetic Nomenclature (ISCN, 1991) was used for karyotypic description.

RESULTS

Table I presents the histopathological findings related to 38 primary tumors (cases 1 - 38) and to three benign lesions (cases 39 - 41) of the nervous system.

Normal karyotypes were observed at varying frequencies in 33 cases. Loss of sex chromosomes was observed in 56% of cases (-X in 13 of the 25 female patients and -Y in nine of the 16 male patients). Only two of the 25 female patients presented cells with a 45,X,-X karyotype (cases 5 and 22), while 12 presented chromosome X monosomy as a clonal chromosome abnormality

Table I - Clinical and histological data about 38 primary tumors and three benign lesions of the nervous system.

Case no.	Age/Sex	Histopathological diagnostic
01	06/F	Grade I astrocytoma, NOS
02	13/M	Grade I sub ependymal giant cell astrocytoma
03	08/M	Grade II mixed oligoastrocytoma
04	06/M	Grade II astrocytoma, NOS
05	33/F	Grade II gemistocytic astrocytoma
06	61/M	Grade III astrocytoma, NOS
07	55/F	Grade III gemistocytic astrocytoma
08	56/M	Grade III anaplastic astrocytoma
09	51/M	Glioblastoma multiforme
10	31/M	Glioblastoma with sarcomatous component
11	22/F	Glioblastoma multiforme
12	75/F	Glioblastoma multiforme
13	06/F	Oligodendroglioma
14	38/M	Grade I ependymoma
15	03/M	Grade II ependymoma
16	36/M	Grade III ependymoma
17	05/F	Grade IV ependymoma
18	29/F	Pineocytoma
19	31/M	Medulloblastoma
20	06/F	Medulloblastoma
21	15/F	Medulloblastoma
22	50/F	Acoustic neurinoma
23	41/F	Acoustic neurinoma
24	31/F	Acoustic neurinoma
25	44/F	Acoustic neurinoma
26	50/F	Intra spinal neurinoma
27	44/M	Neurofibroma
28	45/M	Sarcomatous meningioma
29	65/F	Meningoendotheliomatous meningioma
30	60/F	Meningoendotheliomatous meningioma
31	62/F	Meningoendotheliomatous meningioma
32	46/F	Fibroblastic meningioma
33	64/M	Fibroblastic meningioma
34	49/M	Transitional meningioma
35	69/F	Transitional meningioma
36	66/F	Transitional meningioma
37	38/F	Psammomatous meningioma
38	07/F	Craniopharyngioma
39	29/M	Cerebral abscess
40	12/F	Benign lesion, NOS
41	36/F	Benign lesion, NOS

NOS - Not otherwise specified.

associated with other numerical and/or clonal structural aberrations (cases 5, 7, 11, 13, 17, 18, 20, 25, 31, 32, 35, and 40). Five of the 17 male patients showed cell lines in which loss of chromosome Y was the only alteration

observed, and in eight cases this loss was associated with other chromosome abnormalities (Table II). There were also random (non-clonal) losses of sex chromosomes.

Table II - Summary of chromosome analysis, including number of cells with normal karyotypes and number of cells with loss of sex chromosome.

Case no.	No. of GTG-banded cells	Normal karyotype	45,X,-X/ 45,X,-Y	-X/-Y with other abnormalities
01	20	4	-	-
02	32	-	-	-
03	32	7	-	-
04	23	6	-	-
05	33	1	-X [2]	-X [6]
06	30	2	-Y [4]	-Y [9]
07	24	4	-	-X [4]
08	24	4	-Y [2]	-Y [7]
09	14	1	-Y [3]	-Y [9]
10	22	2	-	-X [3]
11	23	-	-	-X [12]
12	44	4	-	-
13	21	-	-	-X [3]
14	31	3	-	-Y [5]
15	31	6	-	-
16	34	4	-	-Y [6]
17	30	5	-	-X [5]
18	30	9	-	-X [3]
19	15	-	-	-
20	23	3	-	-X [3]
21	29	-	-	-
22	28	11	-X [1]	-
23	32	12	-	-
24	17	10	-	-
25	32	3	-	-X [5]
26	22	-	-	-
27	16	2	-Y [2]	-
28	26	1	-	-Y [4]
29	16	5	-	-
30	26	3	-	-
31	23	10	-	-X [4]
32	14	1	-	-X [4]
33	15	-	-Y [2]	-Y [10]
34	27	-	-	-Y [4]
35	36	12	-	-X [5]
36	23	2	-	-
37	25	5	-	-
38	19	11	-	-
39	21	7	-	-
40	30	7	-	-X [7]
41	16	2	-	-

Structural alterations in chromosome X were also observed in some cases. The der(X)del(X)(p21)del(X)(q26) (24% of the cells) and del(X)(p21) (20% of the cells) were observed in case 17 (grade IV ependymoma); der(X)del(X)(p21)del(X)(q24) was the major chromosome alteration observed in 46% of the cells of case 30 (meningoendotheliomatous meningioma) with GTG banding, and inv(X)(q11.2 p22.3) was detected in two of 16 cells analyzed from case 41 (benign lesion).

Figure 1 (A and B) shows GTG banding karyotypes from a grade II gemistocytic astrocytoma. A cell with a 45,XX,-X, del(1)(p34.3) karyotype and a derived clone with additional abnormalities such as monossomy of chromosome 3 and ins(4;2) (q31;q24q32) were observed in this case. Figures 2 and 3 show the Y chromosome loss in cells with structural and/or numerical changes of chromosome 22 in meningiomas.

DISCUSSION

Loss of sex chromosomes has been described in a variety of benign and malignant neoplasias. Of the total number of human tumors catalogued after a cytogenetic study (Mitelman, 1991), approximately 4.8% involve tumors of the nervous system. In general, the total frequency of loss of a sex chromosome is less than 20% in this group of tumors and the significance of this event is still unknown.

Available data show that astrocytomas, especially when malignant (Yamada et al., 1980; Bigner et al., 1984, 1986, 1988, 1990; Rey et al., 1987a,b; Jenkins et al., 1989; Thiel et al., 1992) and meningiomas (Mark, 1977; Zankl and Zang, 1980; Yamada et al., 1980; Zang, 1982; Al Saadi et al., 1987; Rey et al., 1988; Casartelli et al., 1989; Casalone et al., 1990; Logan et al., 1990) present loss of chromosome Y twice as frequently as they do monosomy of chromosome X. Bigner et al. (1986) considered the loss of the sex chromosome to be a primary event in the pathogenesis of gliomas.

The loss of sex chromosomes has been recently described in short-term cultures of brain tissue located 2-6 cm outside the tumor front in 11 patients, seven of whom had a malignant glioma (Heim et al., 1989). These data suggested that these alterations derive from normal cells, and that they may reflect a normal organic mosaicism in vivo. Similar results were obtained by Elfving et al. (1990) in a study of normal cells from patients with renal carcinomas, and by Lee et al. (1987) in a study of non-neoplastic tissue from the lung of patients with carcinoma of the lung.

Limon et al. (1990) suggested that normal renal cells tend to lose one sex chromosome and to acquire an additional copy of chromosome 7. This tendency seems to be retained by renal carcinoma cells since changes such as
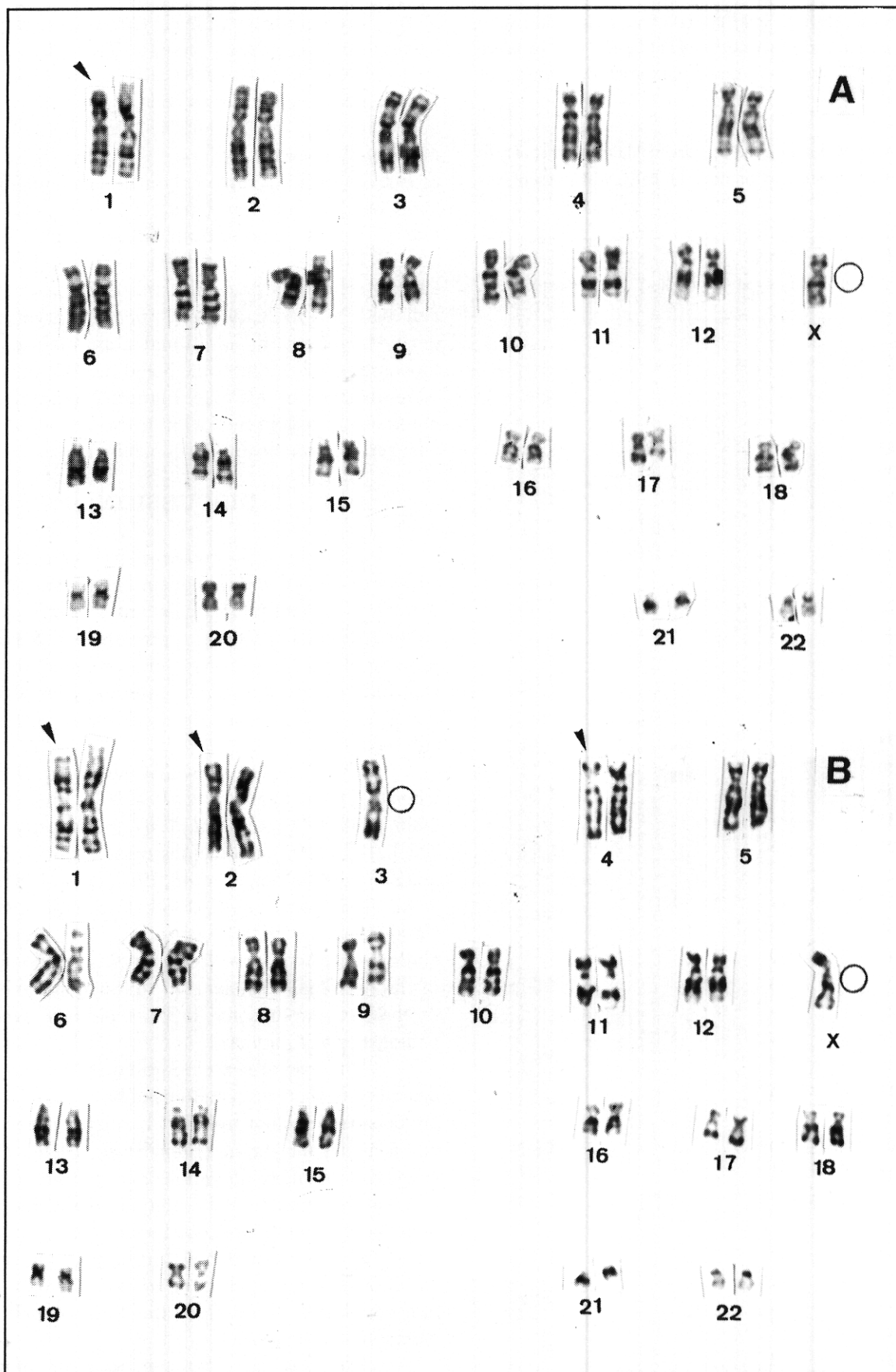
Figure 1 - GTG banded karyotypes from a grade II gemistocytic astrocytoma (case no. 05): A - Cell with a 45,XX,-X, del(1)(p34.3) karyotype; B - 45,XX,-X, del(1)(p34.3), -3, ins(4;2)(q31;q24q32). The arrows indicate structurally abnormal chromosomes.
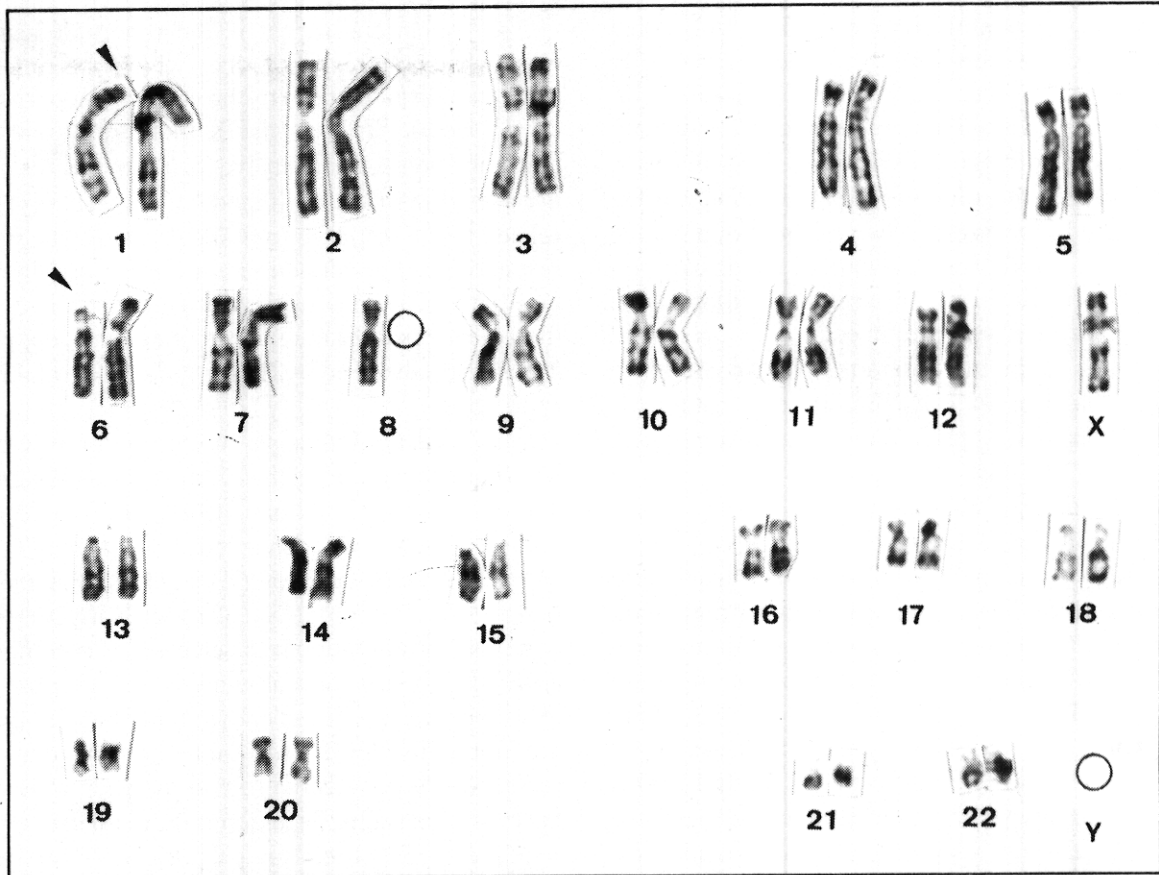
Figure 2 - The sarcomatous meningioma (case no. 28) with the karyotype: 44,XY,-Y,del(1)(p32), dic(6;22)(p12;q13),-8.
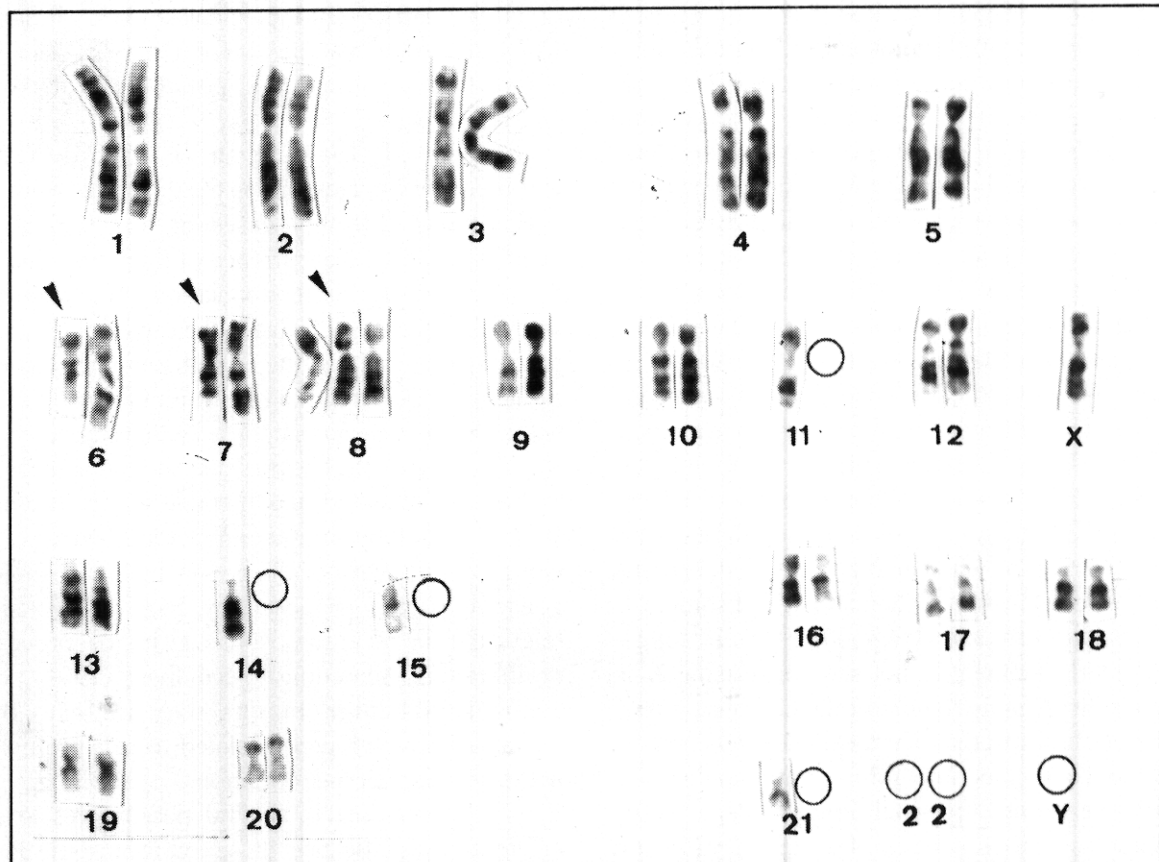

Figure 3 - Cell with a 39,XY,-Y,-6,dic(6;22)(q11;p11.2), del(7)(q31), +8,-11,-14,-15,-21,-22,-22 karyotype from a transitional meningioma (case no. 34).

+7 and -X/-Y have been rarely detected in lines with clonal structural abnormalities considered to be pathogenetically important, especially those involving 3p. Lindström *et al.* (1991), in a study of 88 brain tumors, selected 40 malignant gliomas of astrocytic origin in which the loss of a sex chromosome was the most frequent alteration and was the only abnormality in 38 cases. In two of these tumors, the clonal loss of sex chromosomes was detected as part of a clone which also contained structural abnormalities, and in six cases the loss of a sex chromosome was present in secondary clones as the only abnormality. According to these authors, the loss of sex chromosomes cannot be considered as a specific tumoral alteration of malignant gliomas.

Approximately half of our cases presented sex chromosomal loss in cell lines which had other karyotypic alterations, also of the clonal type. The highest frequencies of sex chromosome loss were observed in malignant gliomas (cases 6, 8, 9, and 11) and in one meningioma (case 33), a fact generally coinciding with data in the literature (Yamada *et al.*, 1980; Bigner *et al.*, 1984, 1986, 1988, 1990; Rey *et al.*, 1987a,b; Jenkins *et al.*, 1989; Casalone *et al.*, 1990; Logan *et al.*, 1990; Thiel *et al.*, 1992). In 13 cases with complex karyotypes the loss of chromosome X or chromosome Y occurred at considerably low frequences, though clonal, possibly indicating that this event was random.

Heim *et al.* (1989) and Arnoldus *et al.* (1991a) suggested that the loss of chromosome X and trisomy 7 may be due to chromosome aneuploidy in the normal brains of older men or may be the result of cell culture techniques. Arnoldus *et al.* (1991b) performed interphase cytogenetic analysis on 11 uncultured glioma specimens and found trisomy 7 in two and loss of Y in one. Ransom *et al.* (1992), in a cytogenetic and molecular study of 10 tumors, found that -Y and +7 were present in tumor tissue. This offers additional evidence that in some cases these abnormalities are not artifacts of methodology.

There are reports of a loss of chromosome Y, probably associated with an aging process in bone marrow cells of healthy older men, but not in the blood lymphocytes of the same subjects. Thus, loss of chromosome Y may be a normal aging phenomenon of hematopoietic cells, although the question of whether it has any pathogenetic and/or prognostic relevance in hematologic disorders is still controversial (Pierre and Hoagland, 1972). It is noteworthy that elderly women do not show a missing X in bone marrow cells. Among tumors of the nervous system, the loss of sex chromosomes has been reported both in tumors commonly detected in children and young people, such as primitive neuroectodermal tumors (Biegel *et al.*, 1989) and gliomas with a low grade of malignancy (Griffin *et al.*, 1988, 1992), as well as in tumors commonly detected in adults, such as glioblastomas and meningiomas.

A curious aspect is the report of loss of Y in established cultures of a kidney which was removed from a 69-year old patient due to chronic pyelonephritis (Elfving *et al.*, 1990). We detected X monosomy and structural rearrangements in expansive non-tumoral lesions of the nervous system (cases 40 and 41, respectively), probably related to the response to tissue damage. The presence of sex chromosome alterations in tumors and in expansive non-tumoral lesions of the nervous system suggests that these abnormalities are not tumor specific, supporting the hypothesis advanced by Heim *et al.* (1989) and Lindström *et al.* (1991).

Structural changes in chromosome X have been less frequently reported than X monosomy in tumors of the nervous system (Mitelman, 1991). In case 17 (grade IV ependymoma), we observed deletions der(X)del(X) (p21)del(X)(q26) and del(X)(p21). In the meningioma (case 30), der(X)del(X)(p21)del(X)(q24) the major chromosome alteration was detected. According to Bigner *et al.* (1990) structural alterations of chromosome X are relatively frequent in ependymomas but the breakpoints are not consistent. This fact suggests that if the X chromosome plays some role in the neoplastic process in nervous tissue cells, its action is more related to the loss of a suppressor function than to a position effect. James *et al.* (1990) reported a case of ependymoma which presented loss of heterozygosity for loci in chromosome X. Logan *et al.* (1990) carried out molecular studies on meningiomas which suggested that the loss of Y may be associated with a growth suppressor gene possibly involved in tumor progression.

The difference in the incidence of sex chromosome changes among the different tumor types and even among different cases of histologically similar neoplasias, and the occurrence of these changes in normal tissue cells, probably in association with an aging process and with benign lesions (as in the case of the inflammatory process) suggests that the loss of sex chromosomes is not exclusively associated with a tumoral process. This does not necessarily mean that these changes do not act in some way on cell growth. The presence of other genes in addition to those which determine the male sex in chromosome Y, such as the colony stimulating factor (Gearing *et al.*, 1989; Gough *et al.*, 1990) or the gene which may predispose to gonadoblastoma proposed by Page (1987) suggests a relevant role of chromosome Y in the process of cell proliferation. According to Sandberg (1991), karyotypic changes in benign tumors may indicate that these alterations involve genes related to cell proliferation but not to malignant transformation.

In conclusion, several possibilities exist for the origin and significance of sex chromosome loss. When observed as a solitary anomaly, a non-tumoral origin seems to be the most widely-accepted interpretation. Our results

suggest that the anomaly is present in the tumor cells of several types of tumors of the nervous system, however, further comparative, cytogenetic and molecular studies on normal and tumoral cells from histopatologically similar tissues and in a variety of organs are needed to elucidate the significance of sex chromosome loss in human cells.

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RESUMO

Trinta e oito tumores (5 astrocitomas graus I, II, 3 astrocitomas grau III, 4 glioblastomas, 1 oligodendroglioma, 4 ependimomas, 1 pineocitoma, 3 meduloblastomas, 4 neurinomas de acústico, 1 neurinoma intra raquídeo, 1 neurofibroma, 10 meningeomas e 1 craniofaringeoma) e três lesões benignas do sistema nervoso foram avaliadas citogeneticamente após cultivo *in vitro*. A perda de cromossomos sexuais foi uma anormalidade verificada em 56% dos casos (-X em 13 das 25 pacientes do sexo feminino e -Y em 9 dos 16 pacientes do sexo masculino). Este relato tem como objetivo discutir o papel desta anormalidade nas células do sistema nervoso.

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