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SHORT COMMUNICATION

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No latent chromosome damage in oxygen-exposed premature neonates

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Abstract The possible effect of *in vivo* oxygen exposure on chromosomes was examined in lymphocyte cultures of 12 very-low-birthweight infants on the 1st, 8th, and 16th days of intensive care. No increase of cytogenetic anomalies was seen in untreated and bleomycin-treated cultures. The findings suggest that neonatal oxygen exposure is unlikely to cause latent chromosome damage.

Key words Neonatal intensive care · Oxygen toxicity · Chromosome instability

Introduction

In contrast to several *in vitro* and *in vivo* observations, in previous studies we found that very low birthweight (VLBW) in itself was not associated with an increased rate of chromosome breakage, and that routine neonatal intensive care did not cause chromosome damage (Méhes et al. 1984). Dobos et al. (1986), however, claimed that an increased chromosome instability may occur in premature infants ventilated with 70–80 vol.% oxygen for more than 7 days. Since the genotoxic effect of oxygen and its significance in neonatal care are still controversial, we made an attempt to reevaluate the possible therapy-induced latent chromosome instability in intensively treated VLBW premature neonates.

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Patients and methods

Twelve VLBW premature infants (seven girls, five boys) with a mean birthweight of 1130 g (range 880–1470 g) were examined. Each of them required some kind of mechanical ventilation. An oxygen concentration of more than 70 vol.% was given for 10 days or more in six cases, and for 3–9 days in the other six. Serial arterial pO_2 measurements revealed occasional severe hyperoxemia in three neonates, and significant undulation of blood oxygen tension was noted in most infants. Apart from administration of vitamin K, and occasionally of antibiotics and theophylline, no other drugs were given to the patients.

Lymphocyte cultures from each newborn were set up on admission (generally within 12 h after birth), on the 8th and on the 16th days of postnatal life. From the short-term (50 h) cultures, conventionally prepared slides were Giemsa stained without banding procedures. Parallel cultures were treated for the final 5 h with bleomycin in a final concentration of 30 μg/ml, as described by Tzancheva and Komitowski (1997). From both untreated and bleomycin-treated preparations, on each occasion 100 mitoses were analyzed for anomalies as follows: chromatid and chromosome breaks, other structural aberrations, pulverization, and premature centromere divisions (PCDs). Structural aberrations were expressed as aberrations per 100 cells, and pulverization and PCD as percentage of mitoses with these anomalies. PCD was defined as no centromeric connection between the two sister chromatids in at least 10 chromosomes of the same cell. In addition, the mean number of sister chromatid exchanges (SCEs) per cell was also determined from the untreated cultures only.

Lymphocyte cultures of six healthy infants served as controls. The slides were coded, and the examiners were not aware of the origin of the preparations.

Table 1 "Spontaneous" and bleomycin-induced cytogenetic anomalies in ventilated very-low-birthweight premature infants and in control infants[a]

	Premature infants						Controls ($n = 6$)
	Ventilated for 10 or more days ($n = 6$) Day of examination:			Ventilated for 3–9 days ($n = 6$) Day of examination:			
	1st	8th	16th	1st	8th	16th	
"Spontaneous"							
Chromatid break	0.17	0.17	0.17	0.17	0.33	0.17	0.17
Chromosome break	0.50	0.50	0.17	0.33	0.17	0.17	0.00
Other structural aberrations	0.00	0.00	0.17	0.00	0.17	0.00	0.00
SCE (±SD)	4.8 ± 2.1	5.2 ± 2.6	4.9 ± 1.9	5.3 ± 2.2	5.4 ± 1.8	5.0 ± 2.0	5.2 ± 2.1
Pulverisation	0.00	0.00	0.00	0.00	0.00	0.00	0.00
PCD	0.33	0.50	0.67	0.50	0.67	0.67	0.50
Bleomycin-induced							
Chromatid break	4.00	2.67	3.00	3.17	2.67	3.00	2.5
Chromosome break	0.00	0.33	0.17	0.17	0.33	0.17	0.33
Other sturctural aberrations	0.00	0.00	0.00	0.00	0.17	0.00	0.17
Pulverisation	0.83	1.33	1.00	1.17	2.17	2.00	2.17
PCD	2.67	2.17	1.83	2.33	2.00	1.83	2.33

The differences between the two groups of patients and controls are not significant in any comparison.
[a] Breaks and other structural aberrations are expressed as mean number per 100 mitoses: sister chromatid exchange (SCE) as the mean number per cell; pulverization and premature centromere division (PCD) as the percentage of cells with multiple pulverized chromosomes and with PCDs of more than 10 chromosomes, retrospectively

The one-tailed *t* test and *Fischer's exact* test were used for the statistical analysis.

Results

The karyotype of the infants examined proved to be normal in each case. Because no significant individual variation in the rate and distribution of cytogenetic aberrations was observed, only the cumulative results of the three groups are given in Table 1 (patients exposed to oxygen for 10 days or more, for 3–9 days, and controls).

As compared to controls, irrespective of oxygen exposure and medication, the prevalence of aberrations was not increased in the neonates under intensive therapy. Bleomycin treatment resulted in a higher frequency of anomalies in all the three groups; however, the differences between patients and controls were not statistically significant. No correlation between the rate of aberrations and duration of oxygen administration was found.

Discussion

The number of patients included in the present study was relatively small, but the patients were thoroughly investigated with several methods, including analysis of PCD, which may also be regarded as a sign of chromosome instability (Méhes and Bühler 1995). This was the first time that induced fragility was also investigated by means of bleomycin treatment. Although only short-term lymphocyte cultures were analyzed, possible chromosome damage in other tissues cannot be excluded, but no findings suggesting a preferential effect of oxygen or differences in DNA repair in various tissues have emerged so far.

The present findings confirm the assumption that VLBW *per se* is not associated with chromosome instability. Similarly, SCE was not increased in the 1st-day cultures of the infants. This is in accordance with the opinion of Hook (1986) that the occasionally recorded correlation of SCE with low birthweight may rather be due to some technical factor and/or difference in the populations of lymphocytes sampled. The premature infants in this study received only a few drugs in moderate doses; nevertheless, the analysis of medication is irrelevant since the frequency of cytogenetic anomalies did not increase during the course of intensive care and no differences between patients and controls have been found. This also means that oxygen exposure did not affect the chromosomes.

Since the results were in every respect unequivocally negative, we conclude that VLBW premature infants undergoing intensive care with a relatively vigorous oxygen exposure are not at an increased risk of latent therapy-induced chromosome damage.

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