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Parental Age in Retinoblastoma

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Summary. In a review of information on 444 patients with sporadic retinoblastoma, a correlation with increased fathers'age was demonstrated and no correlation with was found in the unilateral form. These data favor the hypothesis that the bilateral form is caused by a germinal mutation and the unilateral form is due to somatic mutations.

Zusammenfassung. In einer Übersicht über 444 Patienten mit sporadischem Retinoblastom wurde eine Erhöhung des väterlichen Alters demonstriert. Bei den einseitigen Fällen wurde eine solche Erhöhung jedoch nicht gefunden. Die Daten sprechen dafür, daß die doppelseitige Form durch Keimzell-Mutation verursacht ist, während die einseitige Form auf somatische Mutationen zurückgeht.

Introduction

The genetics of retinoblastoma is still a matter of dispute. Most authors consider the bilateral manifestation as an autosomal dominant trait with almost complete penetrance; many cases are sporadic and due to new mutations. In contrast, the mode of inheritance of the unilateral form is not clear: most of the cases are also sporadic, but are very seldom transmitted to the offspring. Some authors think that the unilateral form is a dominant trait with very incomplete penetrance; on the contrary, others think that unilateral retinoblastoma is not hereditary and is due to a somatic mutation.

The purpose of this study is to evaluate separately the unilateral and bilateral forms of sporadic retinoblastoma, mainly through the study of parental age: an elevated parental age can affect the rate of germinal mutation and not that of somatic mutation.

Material and Methods

A study of 1010 patients with retinoblastoma was made; almost all the cases were confirmed by pathological report. A complete family history was obtained in 504 cases, either by interviewing the families or by sending them a questionnaire.

444 apparently sporadic cases of retinoblastoma (289 unilateral, 155 bilateral) were found. These had no previous history of the disease.

To study the differences between the two groups of retinoblastoma, the following were determined:

percentage of offspring affected,

the mean parental age at the birth of these patients and the mean birth order (Tables 1 and 2).

In the evalution of this information, a comparison was made of the mean parental age and birth order of the two groups with the appropriate means computed from the French Vital Statistics for 1956 — which was the mean year of birth of our patients[1]

1 The maternal age is computed for all births, but the paternal age and the birth order

Table 1. Comparaison of Parental age and birth order for sporadic cases of bilateral retinoblastoma and the general population

	Mean paternal age	Mean maternal age	Mean birth order
Sporadic bilateral retinoblastoma	32.26 (SD = 7.12)	28.17 (SD = 5.36)	2.49 (SD = 1.61)
General population	31.05 (SD = 6.64)	27.64 (SD = 5.53)	2.68 (SD = 1.85)
Difference (significance)	1.21 ($p = 0.05$)	0.53 (N.S.)	—0.19

Table 2. Comparaison of parental age and birth order for sporadic cases of unilateral retinoblastoma and the general population

	Mean paternal age	Mean maternal age	Mean birth order
Sporadic unilateral retinoblastoma	30.90 (SD = 6.22)	27.73 (SD = 5.22)	2.30 (SD = 1.48)
General population	31.05 (SD = 6.64)	27.64 (SD = 5.53)	2.68 (SD = 1.85)
Difference (significance)	— 0.15	0.09 (N.S.)	— 0.38

Results

1. Incidence of Retinoblastoma among the Offspring of Sporadic Cases

a) Bilateral Retinoblastoma. 29 patients were 18 years of age or older; among them 8 had 9 children, 5 of whom were affected (3 with bilateral, 2 with unilateral retinoblastoma). The observed percentage of affected children (55.5%) does not differ from the expected value (50%) for dominant inheritance.

b) Unilateral Retinoblastoma. 102 patients were 18 years of age or older; 29 had 57 children, only one of them being affected. The observed percentage of affected individuals is 1.75%, which differs from any segregation ratio.

These data confirm that the two forms of retinoblastoma are very different in their mode of inheritance and probably also in their mechanism of occurrence.

2. Parental Age and Birth Order

The mean parental age and the mean birth order for the 289 unilateral and the 155 bilateral retinoblastoma were compared with the national average (Tables 1 and 2).

As outlined in Table 1 for the bilateral form, the elevation of paternal age is greater than that of maternal age, and only the former is significantly greater than the national mean. The mean birth order is not increased.

For the unilateral form, the mean paternal age and maternal age do not differ from the national average but the mean birth order does: it is much lower than the mean birth order of the general population. This difference is very likely due to the fact that the mean birth order found in the French statistics is overestimated.

The mean paternal age in the bilateral form is greater than that in the unilateral form: the difference of 1.36 years is significant ($p = 0.05$).

are computed only for children born to married women. Thus, the mean birth order of the general population is over-estimated because children of unmarried women are very often first born. As for paternal age, the bias — if it exists — must not be significant because these unknown fathers may be younger as well as older than the mean paternal age.

Discussion

This study shows no evidence of any parental age effect upon the occurrence of unilateral retinoblastoma, but found an elevated paternal age for the bilateral sporadic form of retinoblastoma.

Falls and Neel (1951) did not find any parental age effect, but their analysis did not separate the two forms of sporadic retinoblastoma.

Macklin (1960) found no parental age effect either in the unilateral or the bilateral form.

Matsunaga (1965) has shown that paternal age was raised significantly at the 5% level in 21 bilateral cases with sporadic retinoblastoma, the mean paternal age being 34.4 years in patients and 32.0 years in controls. No such increase was observed in 45 unilateral cases. No maternal age effect was seen in either bilateral or unilateral cases.

Fraser and Friedman (1967) presented information on the parental age of 37 cases of sporadic bilateral retinoblastoma: they found a difference of 1.9 years between the mean paternal age of the affected children and that of the general population. For the mothers, the difference was 2.3 years.

Tünte (1972) presented data on parental age in 17 bilateral and 51 unilateral isolated cases: he found that the mean paternal age of bilateral and unilateral cases exceeded the mean paternal age of controls by 2.0 years and 1.0 years respectively. Mean maternal age in unilateral cases was similar to the control value, whereas the average in bilateral cases was increased by 2.3 years.

The results of Fraser, Triedman, Tünte, and especially Matsunaga are in agreement with our data.

In terms of paternal age effect, the discrepancy between the two forms of sporadic retinoblastoma deserves consideration. This difference supports the hypothesis that the bilateral sporadic form is caused by a germinal mutation whereas the unilateral sporadic cases are due to somatic mutations. According to Vogel (1957), 50—100% of all bilateral sporadic cases are due to germinal mutations. Vogel (1967) states that all bilateral sporadic cases are due to germinal mutations. The same is stated by Knudson (1971). In the case of somatic mutation, no parental age effect is expected, but an elevated paternal age is thought to be a significant factor in the occurrence of new mutations in a number of inherited disorders. Penrose (1955) has discussed the causes of spontaneous mutation and the increased paternal age for new mutations. According to this theory, an effect of parental age may be expected in both parents if the mutagenic agent (irradiation) acts on both resting gamete-formingcells (oogenesis) and continually dividing gamete-formingcells (spermatogenesis), and this effect would be expected only in fathers if the mutation is due to a gene-copying error. In both cases, the mutant genes would accumulate in the stem cell pool and a linear increase of mutation rate with parental age may be expected (Cavalli-Sforza and Bodmer, 1971), for both parents in the first case, and for fathers only in the second case. The theoretical increase in mean age of parents of these fresh mutants compared with the population average can be calculated: it is $\frac{\text{var } x}{\bar{x}}$ where var x is the variance of parental age and $\bar{x}$ the mean parental age in the general population.

For the French population in 1956, the theoretical increase is 1.42 years for males and 1.10 years for females[2].

The increase of 1.42 years for the fathers is in agreement with our data; but we notice that in the other dominant mutations where a paternal age effect has been demonstrated, the difference is much higher than expected (Mørch, 1941; Penrose, 1957; Lynas, 1958; Blank, 1960; Tünte *et al.*, 1967; Murdoch *et al.*, 1970; Bouvet *et al.*, 1971); no explanation is known for this phenomenon.

On the other hand, an alternative explanation for the absence of a paternal age effect in sporadic unilateral retinoblastoma can be given: this form of the disease could also be caused by a germinal mutation with very low penetrance, the generation when the mutation occurred being consequently not known. However, this hypothesis supposes a penetrance of about 3%, which makes this assumption quite unlikely.

2 I.N.S.E.E.: Mouvement de la population.

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