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Anticipation phenomenon in familial adenomatous polyposis: an analysis of its origin

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Abstract

AIM To analyze the origin of the anticipation phenomenon, which means earlier death in successive generation in familial adenomatous polyposis.

METHODS The study subjects were 2161 **patients with familial adenomatous polyposis and their** 7465 **first-degree relatives who were members of 750 families registered at our Polyposis Registry. The ages at death and cumulative mortality rates in the parent, the proband, and the child generations were compared for both all subjects and the patients alone.**

RESULTS In the patients over 5 **years of age, the mean age at death was** 50.9 **years for the parent,** 42.3 **years for the proband, and** 33.3 **years for the child generations, respectively(*P* <**0.001**). The deceased rates in the three generations were** 90.7%, 51.3% **and** 23.1% **of the patients, respectively, and this difference was the main cause of the anticipation measured by parent-child paring method. The cumulative mortality rates for all subjects failed to show anticipation, however the cumulative mortality rates for the patients showed the anticipation. The anticipation phenomenon was shown by any parent-child pairing methods for the deceased patients. Other important causes of the anticipation were different proportion of causes of death between generations (*P*<**0.001**), and a low proportion of detected or deceased patients (*P*<0.001) in the child generation.**

CONCLUSION Anticipation in familial adenomatous polyposis may be caused by parent-child paring methods as well as several intergenerational biases.

INTRODUCTION

The earlier onset of a hereditary disorder in successive generations, often with increased severity or early death, is known as anticipation [1,2]. Despite the development of medical care over generations, this phenomenon is commonly encountered in human dominant type hereditary disorders including familial adenomatous polyposis (FAP) clinically. The anticipation was evaluated by Penrose[1] in myotonic dystrophy and by Veale[2] in FAP using parent-child pairs. They attributed the apparent anticipation to ascertainment biases and the general variability in age of onset in the parent-child pairs. They assumed that the modifying allelic gene might be the cause of the lack of the parent-child correlation. Of these two conditions, the cause of the anticipation in myotonic dystrophy was proved to expand trinucleotide repeats in the causative gene[3-9].

However, a mutation of the APC gene is stable, and the site of mutation determines the severity or associated features of FAP with strong parent-child correlation[10-13]. If the anticipation is the biological phenomenon in FAP, not only we need to investigate the cause of the anticipation in the APC gene, but also it has a considerable clinical meaning because colorectal cancer must be prevented by an early detection and treatment. Consequently, it has aroused our interest to study whether the anticipation phenomenon in FAP is a biological fact.

MATERIALS AND METHODS

Between January 1975 and December 1995, data were collected from 750 families from 1198 FAP patients registered at our Polyposis Registry[14]. These FAP cases fulfilled the diagnostic criteria by Bussey[15]. Turcot syndrome was excluded. Histories of their family members were obtained from their doctors who registered patients, death

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certificates and the National Family Registry[16]. All first-degree relatives of proved FAP patients were recruited and no selection was made in these collections. Among the families of 9626 members (4991 men, and 4635 women), 2161 were FAP patients with colorectal cancer, and 7465 were their first-degree family members. Their births and deaths were certified by the National Family Registry or from the documents of the registry, and causes of death were ascertained by death certificates or by inquiring the doctors. The 9626 members were divided into three generations. They were 2958 individuals in the generation of the index patients (the proband generation), 4273 in the generation of their parents (the parent generation), and 2395 in the child generation of the indicated patients (the child generation). The ages at death, causes of death, and cumulative mortality rates of the three generations were compared to evaluate the features of anticipation. The cumulative mortality rates were calculated for both the entire group and the FAP patients by the Kaplan-Meier method. Chi-square test was used for comparison of occurrence rate in pairs of groups, and *t* test was used for the comparison of age.

RESULTS

There were a total of 3891 deceased individuals in the entire group. The proportion of deceased individuals in each generation was 66. 0% in the parent generation, 39.5% in the proband generation, and only 10.5% in the child generation ($P<0.001$, Table 1). The mean age at death was 41.6 ± 26.2 years in the parent generation, 26.3 ± 22.3 years in the proband generation, and 15.8 ± 16.8 years in the child generation. These low age and large standard deviation in the age at death were the result of early childhood death occurring before five years of age, accounting for 18.4% of all deaths in the parent generation, 33.4% in the proband generation, and 47. 2% in the child generation (Table 1). We examined the causes of death in each generation and their age at death (Table 2). The death from unknown causes in the parent generation (0.84 to FAP deaths) was almost five times higher than that in the other two generations ($P<0.001$). In this generation, the mean age at death (36.7 ± 19.8 years) from unknown causes was significa ntly lower than that at death from other causes ($P<0.05$).

The number of FAP patients was 508 (17.2%) in the parent generation, 1316 (30.8%) in the proband generation, and 337 (14.1%) in the child generation (Table 3). Among them, the number of deceased FAP patients was 460 (90.6% of 508) in the parent generation, 675 (51.3% of 1316) in the proband generation, and 78 (23.1% of 337) in the child generation. There were significant differences among the groups in the FAP death rate ($P<0.001$). The age at death of FAP patients in each generation was 50. 9 ± 12.4 years, 42.3 ± 12.3 years, and 33.3 ± 8.8 years, respectively, and the differences among the generations were significant ($P<0.001$).These results showed that any random selection of deceased intergenerational pairing in FAP patients would produce anticipation caused by these differences between the generations.

The cumulative mortality rates of the FAP patients gave usa few clues to the anticipation (Figure 1). The generation included less young FAP patients, and the start of death was delayed as compared to other generations. It may be said pseudo-anticipation. Between the child and proband generations, the a cceleration of death was observed in the age between 22 and 40 years. Both a low detection rate of FAP patients (14.1%, Table 3) in the child generation, and a low portion of deceased FAP patients (23.1%) among them may cause this situation because many FAP patients were remained undiagnosed. This suggests a comparatively short observation period in the child generation. The incidence of colorectal cancer increased rapidly between 20 to 40 years of age, and this period might be overestimated in this generation.

In order to minimize these intergenerational biases in FAP patients, we calculated the cumulative mortality rates for the entire members as well as for the FAP patients to evaluate the anticipation. The cumulative mortality rates for the all subjects were plotted on Weible's probability paper according to each generation (Figure 2). If the mortality curve of a descendant shifts to the left, it means earlier death or anticipation, and if a mortality curve shifts downside, it means the improvement of the general health condition of the group. The cumulative mortalities for both the parent and the proband generations were almost the same and parallel, while there was a slight vertical shift in these two curves, no horizontal shift was observed. This calculation method revealed no anticipation between the parent and the proband generations. The mortality rate of the child generation differed from those of the other generations; the overall cumulative mortality rate was low becaus e of the lower infantile mortality in this generation. Although the mortality curve for the child generation showed a steeper slope line than those for the other two generations, the starting point of the steep slope, just after 20 years of age, was common to all the generations.

Table 1 Deceased subjects in each generation, *n* (%)

Generation	Total	Deceased	Age at death ($\bar{x}$ ± s, years)	Early childhood death* (% of the deceased cases)
Parent	2958	1952(66.0)[b]	41.6 ± 26.2	359(18.4)
Proband	4273	1687(39.5)[b]	26.3 ± 22.3	563(33.4)
Child	2395	252(10.5)[b]	15.8 ± 16.8	119(47.2)

[b]$P<0.001$, among the generations; *Death before the age of five years.

Table 2 The proportion of causes of death in each generation and their mean age at death (each number of deaths is shown as a proportion to the number of FAP deaths)

Generation	FAP	Extra colonic malignancies	Other diseases	Unknown cause	Death in childhood
Parent	1.00*	0.37	1.24	0.84[b]	0.78
n = 1952	(50.9 ± 12.4)	(57.6 ± 14.4)	(58.2 ± 19.6)	(36.7 ± 19.8)[a]	
Proband	1.00	0.11	0.37	0.19	0.84
n = 1687	(42.3 ± 12.3)	(46.2 ± 15.8)	(36.7 ± 19.0)	(22.7 ± 16.7)	
Child	1.00	0.13	0.44	0.14	1.53
n = 252	(33.3 ± 8.8)	(26.2 ± 16.3)	(22.9 ± 14.2)	(21.9 ± 14.2)	

FAP: Death from familial adenomatous polyposis and colorectal cancer.n: Total number of deaths.
*: Deaths from FAP were calculated as 1.00. ($\bar{x}$ ± s, years): Age at death.
[a]P<0.05, *vs* other causes of death; [b]P<0.001, *vs* other two generations.

Table 3 Age at death in the FAP patients, n(%)

Generation	Total number of subjects	Patients with FAP*	Deceased FAP patients	Age at death ($\bar{x}$ ± s, years)
Parent	2958	508(17.2)	460(90.6)	50.9 ± 12.4[b]
Proband	4273	1316(30.8)	675(51.3)	42.3 ± 12.3[b]
Child	2395	337(14.1)	78(23.1)	33.3 ± 8.8[b]

[b]P<0.001, among the generations
FAP: familial adenomatous polyposis.
*FAP patients and patients with colorectal cancer.

Table 4 Deceased parent-child pairs of FAP patients classified by the parental status of the child, and the anticipation

Age at death	Group A	Group B[b]
Parent>child	184	93
Parent≤child	57	5

Group A: Parent-child pairs in which the child had become a parent.
Group B: Parent-child pairs in which the child had not had any child.
[b]P<0.01, *vs* Group A.

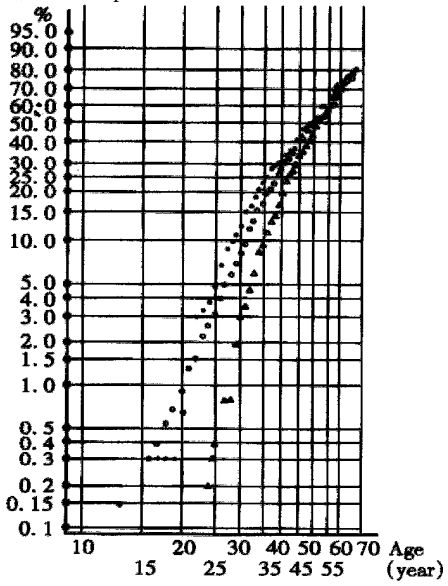

Figure 1 Age specific cumulative mortalities of FAP patients. Circles: the proband generation; Triangles: the parent generation; Black dots: the child generation

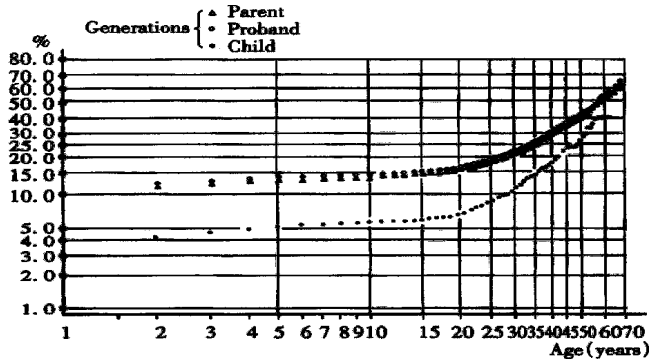

Figure 2 Age specific cumulative mortalities of all subjects, including FAP patients and their first-degree relatives.

DISCUSSION

The anticipation phenomenon is so powerful that it surmounts the improvement of medical standards over years, and it is easily detected in hereditary diseases[1,2,17-19]. Comparison of the age at death or onset in affected parent-child pairs is a conventional method in the study of the anticipation phenomenon[1,2,17,18]. McInnis *et al* [18] and Imamura *et al*[19] applied the life-table analysis or random pairs method only to diagnosed patients and excluded other family members. If this method was applied to our FAP patients, the mean age at death in the proband generation was 8.5 years lower than that in the parent generation, and that in the child generation was 9 years lower than that in the proband generation. These figures exceed a standard period of 5 years to calculate postoperative survival of patients with colorectal cancer. This apparent anticipation was we ll correlated to the proportion of deceased cases in these three generations. Th is indicates that any fair pairing method will produce the anticipation. Veale[2] estimated that a lack of parent-child correlation in onset of FAP was a major cause of sampling bias in his study over a limited period of time. He also concluded that the lack of correlation was due to the allele of the APC gene. Although his suggestions have not been denied as a contributor to the anticipation, some recent reports[10-12] have suggested an apparent relationship between the site of the APC gene mutation and colorectal polyp density and retinal pigments in FAP patients. In addition, the comparison of the age at onset or death in parent-child pairs inevitably has two selection biases besides the intergenerational biases. One is that the parent has already been selected because he or she has already had at least one child, and this child must necessarily have already developed a symptom or died in order to make a parent-child pair. The other one is that a patient with a severe condition is difficult to gain a child, and this patient cannot be treated as a parent. We

confirmed the effect of selection bias in analysis of our 339 deceased parent-child pairs with FAP (Table 4). When the pairs were classified according to whether the child of the pair had become a parent or not, the childless group showed a significantly higher incidence of the anticipation phenomenon.

Recent reports have revealed that the elongation of trinucleotide repeat sizes is correlated with the increased severity of several hereditary neurological diseases such as myotonic dystrophy[4], fragile X syndrome[5], Huntington's disease[6,7], and spinal and bulbar muscular atrophy[8]. Although it is proved that the meiotic elongation of trinucleotide repeats accelerates these diseases, it does not necessarily mean that the elongation is inevitable in the meiosis. If we take parent-child pairs, it may seem as if the meiosis in these diseases constantly increases the length of trinucleotide repeats as the cause of the anticipation. The anticipation is such a powerful phenomenon as Ashizawa *et al*[20] noted in 48% of 56 parent-child pairs that showed contractions of CTG repeat. Because anticipation is commonly encountered in clinical practice, its mechanism must be rather general. It is necessary to approach the elucidation of this phenomenon using some methods other than parent-child pair comparisons[21].We studied not only the FAP patients but also their first-degree relatives in our calculations of life tables. In this kind of studies, the change of medical environment among generations may influence the pattern of mortality. Besides its difficulty in taking the recent improvement of medical care in count, we h ave several reasons for not calculating this influence. ① parent-child pairing method in this series showed an apparent anticipation phenomenon; ② overall improvement of mortality in colorectal cancer was not so substantial as the anticipation phenomenon was diminished; and ③ proportion of early detection and preventive treatment in FAP patients was comparably small [14]. Bias was minimized by our method because the effect of deaths of undiagnosed FAP patients in the parent generation was taken into account. In the parent generation, inherent bias was present in the form of deceased but undiagnosed young FAP patients. In the child generation, the bias was present mainly in the form of premature observation period and unidentified FAP patients, picking up only young deaths.

As the anticipation phenomenon is observed only in the conditions that threat their life and reproductive ability, one of the methods to avoid these biases is to examine the anticipation phenomenon on the FAP specific phenotypes that do not affect the life of FAP patients. For example, congenital hypertrophy of the retinal pigment epithelium is specific to FAP, and it has no influence on optical function. Our experience did not show apparent anticipation phenomenon in number of the pigment areas[22]. Despite these results it will be wise to watch FAP patients for colorectal cancer before the age at which their parents had cancer.

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