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INCIDENCE OF BIRTH RATES AMONG MUTANT MOTHERS AND ITS RELATIONS TO CARRIER AND NORMAL MOTHERS: A STUDY BASED ON TWENTY-FOUR PEDIGREES OF CLASSICAL HAEMOPHILIA (AHG FACTOR VIII DEFICIENCY)

ABSTRACT — The mutational effect on birth rates and its relation to carrier and normal mothers of 24 pedigrees with the evidence of classical haemophilia has been discussed. The relative incidence of births is higher in the case of mutant mothers, followed by carrier and normal mothers. The reasons for the higher male birth rate as compared to the female birth rate are also dealt with in this paper.

KEY WORDS: Birth rates — Pedigree.

A deleterious gene like haemophilia is usually transmitted from generation to generation through the female line and such a trait is expressed within the male offsprings of the heterozygous/carrier mothers ($_{x}heA_{y}$). As the trait like haemophilia is a genetical disorder and usually causes early death of the hemizygous males, the chances of a genetical bridge through affected male ($_{x}heA_{x}$) descendants are absolutely minimal, the occurance of such a trait is maintained either through its inheritance from the female line or by a fresh mutation. Since the trait is not caused by any viral infection, the chances of a mutational effect cannot be denied. Boggs (1934) is of the opinion that cases of carrier mothers with at least one affected issue and without any traces of other haemophilic issue are usually caused due to mutation. Although, to identify a viable reason for the mutational effect is at least at present very difficult. The only reason we can assume is that the change due to mutational pressure took place at the blood plasma level of the assumed carrier mother, later being transmitted to the male issue which ultimately became affected. Schaffer (1970) specifically states that "...mutation is the ultimate source of the raw materials of evolution. While the majority of mutation may have unfavourable effects on the survival of their bearers, occasionally an advantageous mutation will occur." So from the present study we can see that the advantage of the occurence of haemophilia within the family as a whole is not yet apparent but rather its manifold disadvantages are evident. It is, therefore, a question for further researches th t when a trait does not have a beneficial aspect, then why it exists within the population. Of course, its higher male mortality rates are compensated by a higher incidence of male births. So, the natural loss and higher birth rates are maintained at the family level as well as at the population level to satisfy the natural law of population equilibrium. In this connection it can be said that Kimura, Maruyama and Crow (1963) showed that the genetic load due to deleterious mutations in a small population is much larger than that in large populations (in Nei, M. 1968).

However, in this present paper an attempt has been made to ascertain the relative fertility and mortality rates in the case of mothers with evidence of mutation and they were subsequently compared with the carrier and normal groups of mothers. Altogether 24 pedigrees of classical haemophilia were collected from the out-patients department of the School of Tropical Medicine, Calcutta (INDIA) during the

years 1973—75. The serological investigations of each of the probands and a few of their kin were made by the clinical/technical experts of the hospital by means of *Thromboplastin generation* tests (TGT). Thus the chances of any flow regarding the detection of haemophilia issue and identification of their carrier mothers from the collected pedigrees are minimal.

The 24 pedigree included in the present study come from two different communities of India, i.e. the Hindu (70.8 %) and the Muslim (29.2 %) ones and we can therefore presume that a trait like haemophilia is neither restricted to any particular community nor limited to any religious group, though its incidence may vary to some extent for a number of reasons:

1. Social isolation,
2. Sharing a common gene through marriage, and
3. population limitation, etc.

An analysis was made on the basis of mothers who were classified into three different categories:

1. *Mutant mothers* (after Boggs 1934) who have one affected issue or more, and without any other incidence of haemophilic sons in their ascending and descending generations.

2. *Carrier mothers* i.e. mothers with affected children and where a genetical chain of continuity can be traced in both ascending and descending generations.

3. *Normal mothers* (controls), i.e. either sisters or daughters of carrier and mutant mothers without any evidence of heamophilic births (*Table 1*).

TABLE 1. *Incidence of birth rates in different groups of mothers*

	— Average Livebirths —		
MOTHERS	HINDU	MUSLIM	TOTAL
MUTANT	7.5 (4)	5.3 (3)	6.6 (7*)
CARRIER	4.6 (27)	4.0 (8)	4.4 (35)
NORMAL	3.3 (58)	3.9 (12)	3.5 (70)

Number in the parenthesis (.) indicates the number of mothers in different groups.
** Two other mutant mothers were excluded for technical reasons.*

Apart from this, all the births of the different categories are again subdivided into three different categories a) *normal males;* b) *affected males* and c) *normal females*. Each of them is again divided into two, i.e. *living* and *dead*.

From the analysis of the data it is evident that the fertility rate of the mutant mothers is higher (6.6) as compared to that of the carrier (4.4) and normal mothers (3.5). This apparent higher incidence of births in respect of mutant mothers occurred probably due to sudden acceleration of genetic disturbances. On the other hand, if we compare the incidence of male and female births among mothers of different selective types it can be seen that the incidence of male births is higher in both mutant and carrier mothers, whereas the fertility rate is almost the same as that in normal mothers (*Table 2*). So, it can be hypothetically estimated that the chances of affected male births are higher in the case of mutant mothers as well as in carrier mothers, so that the male birth rates are being stimulated at least at this stage where the genetic equilibrium is disturbed due to the effect of deleterious gene(s).

TABLE 2. *Sex specific birth rates in different groups of mothers*

	SEX SPECIFIC BIRTH RATE		
	No. of MOTHERS	MALE	FEMALE
MUTANT	*7	4.0	2.6
CARRIER	35	2.8	1.6
NORMAL	70	1.5	1.9

** Two other mutant mothers were excluded for technical reasons.*

The incidence of normal male birth rates of the respective mothers of the different groups shows that its occurence is apparently higher among mutant mothers while it is comparatively smaller in both carrier and normal mothers (*Table 3*).

As regards the incidence of haemophilic issue it is evident that it is the same in both carrier and mutant mothers. It can therefore be presumed that the incidence of haemophilic births has the same proportions in both carrier and mutant mothers (*Tab. 3*). Similarly, if we compare the normal female birth rates in all the groups it can be seen that its incidence is comparatively higher in the mutant group (2.6) followed by the normal (1.9) and the carrier groups (1.6). From *Tab. 3* it can also be seen that the female birth rates are comparatively higher than those of normal male births in all cases. This may be one of the stages for elimination of defective male births. But in reality the male birth rates are comparatively higher in both mutant and carrier groups, while the female birth rates are higher in normal groups (*Table 3*). The incidence of higher male birth rates occurred among mutant and carrier mothers to compensate the loss caused by deleterious gene(s).

Now, if we compare the mortality rate caused by haemophilia it is evident from the analysis (*Table 4*) that the incidence of death is comperatively higher in the carrier group than in the mutant group. The only reason we can deduce from the present analysis is that when the number of subjects affected is higher, the chances of genetical loss are greater, otherwise it would create a problem from the point of view

TABLE 3. *Incidence of different type of births in different groups of mothers*

TYPES	TOTAL No. of MOTHERS	RELI-GIOUS GROUP	No. of MOTHERS	AVERAGE BIRTH RATES ($\bar{x}$)			SEX SPECIFIC	BIRTH RATES
				NORMAL MALE	AFFECTED MALE	NORMAL FEMALE	MALE	FEMALE
MUTANT	*7	HINDU	4	2.3	1.7	3.5	4.0	3.5
		MUSLIM	3	2.3	1.7	1.3	4.0	1.3
		TOTAL	7	2.2	1.7	2.6	4.0	2.6
CARRIER	35	HINDU	27	1.3	1.7	1.7	2.9	1.7
		MUSLIM	8	0.62	2.0	1.4	2.6	1.4
		TOTAL	35	1.2	1.7	1.6	2.8	1.6
NORMAL	70	HINDU	58	1.5	—	1.8	1.5	1.8
		MUSLIM	12	1.7	—	2.6	1.7	2.6
		TOTAL	70	1.5	—	1.9	1.5	1.9

* *Two other mutant mothers were excluded for technical reasons.*

TABLE 4. *Fertility and mortality rate in different groups of mothers*

TYPES	TOTAL No. of MOTHERS	RELI-GIOUS GROUP	No. of MOTHERS	NORMAL MALE		AFFECTED MALE		NORMAL FEMALE	
				LIVING	DEAD	LIVING	DEAD	LIVING	DEAD
MUTANT	*7	HINDU	4	2.0	0.3	1.2	0.5	3.2	0.3
		MUSLIM	3	1.3	1.0	1.7	—	1.0	0.3
		TOTAL	7	1.7	0.6	1.4	0.3	2.3	0.3
CARRIER	35	HINDU	27	1.2	0.07	0.9	0.7	1.6	0.04
		MUSLIM	8	0.6	—	1.0	1.0	1.4	—
		TOTAL	35	1.1	0.06	0.9	0.7	1.6	0.03
NORMAL	70	HINDU	58	1.4	0.1	—	—	1.7	0.1
		MUSLIM	12	1.5	0.2	—	—	2.4	0.2
		TOTAL	70	1.4	0.1	—	—	1.8	0.1

* *Two other mutant mothers were excluded for technical reasons.*

of natural balance; while natural death is comparatively lesser in all other cases.

As the relative significance of genetic and exogenous factors varies from disease to disease, so also do the causes of classical haemophilia. It is, therefore, suggested that when the mutant mother can be identified and also the carrier mothers, then we should extend our research to stop the effect of deleterious genes, if not the mutation, in countries like India where families with incidence of haemophilic births can be tackled through the amniocentatis procedure to stop the inborn error of metabolism (McKusick 1972: 189) rather than the effect of the deleterious gene(s).

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