With the backdrop of a major burden of preventable infections, malnutrition, a burgeoning population, and lack of resources, hereditary disorders are not a public health priority in India. National data on prevalence and types of genetic disorders and birth defects are unknown. Information on certain select disorders, primarily the haemoglobinopathies, is available from small studies.\textsuperscript{1–10} Data on the burden of specific genetic disorders on individuals, families, and society, and studies on mortality, morbidity, quality of life, and utilization of the health care system are unavailable.\textsuperscript{11}

This study focused on haemophilia, a sex-linked bleeding disorder that affects 4–6/100 000 males worldwide.\textsuperscript{1,12} Haemophilia takes an exceptional toll on the patient and family in India, since treatment with anti-haemophilic factor (AHF) is

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**OTHER ORIGINAL PAPERS**

**Modification of family size in families reporting history of haemophilia from Maharashtra, India**

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**Background** In India, genetic counselling services are largely unavailable. The question of whether awareness of the hereditary nature of the disorder leads to modified family size in affected families remains unanswered. The objective of this study was to determine whether family history of haemophilia resulted in modification of family size in families reporting haemophilia in the State of Maharashtra, India.

**Methods** The study was a retrospective cohort analysis from pedigrees collected from an earlier survey on haemophilia in Maharashtra. Pedigree data were manually defined into families with or without experience of haemophilia. Family size was defined as the number of live births per woman as documented in the pedigree. The data were analysed using Microsoft Excel package (version 2000) and SPSS package (version 10).

**Results** Family size of obligate carriers who were daughters of patients was significantly less than the family size of obligate carriers who reported haemophilia in a brother or maternal relative ($z = 7.14$, $P < 0.001$). As compared with parents from an older generation, a significant reduction in the number of children born to younger families with haemophilia was observed, irrespective of family history of the condition. In families with history of haemophilia, there was no significant reduction in the number of families with more than one affected son in between two generations of parents ($\chi ^2 = 1.43$).

**Conclusions** The results revealed a reduction in size of families with haemophilia over a generation, which possibly reflected the reducing fertility trends observed in the Indian population. Reduction in the number of children born to women with a haemophilic father suggested a comprehension of father to daughter transmission of haemophilia. This was not true when relatives other than the father were affected. The lack of significant reduction in the number of families with history of haemophilia of having more than one affected son may suggest a compensatory response to the high mortality associated with the disorder in India.

**Keywords** Haemophilia, India, reproductive decision-making
beyond the reach of most families and is only used in times of medical emergencies. As a consequence, patients suffer progressive crippling disability, which adds to the poor quality of life. With extreme economic deprivation, families have no other option but to use the less-expensive blood and blood products, enhancing the risk of transfusion-related infections.

Population data on haemophilia are unavailable in India except for our earlier survey based in Maharashtra, the second most populous State in the country. The objective of the study was to profile the haemophilia situation in the State, specifically to determine the total number of cases, the trends in case registrations, and to document the impact of the available haemophilia care services on haemophilia trends in the State. The study led to the identification of a total of 2192 known patients in the State, giving an observed period prevalence of 2.26/100 000 over a 10-year period. Geographical distribution revealed clustering of cases around three haemophilia clinics, which catered for all cases during the period 1989 to 2000. Case registrations were significantly absent from large areas where haemophilia care services had not been extended. The data revealed that there had been a 91% decrease in the number of new cases being registered over the 10-year period. In keeping with this profile of service delivery, clinicodemographic data of patients suggested that the longevity of severe patients was less than 25 years.

In India, haemophilia care services are delivered by a voluntary organization whose primary objective is to provide AHF to patients at subsidized cost. Haemophilia education for patients and families is a recent phenomenon, established after the haemophilia societies came into operation, which was after 1989 in Maharashtra. Genetic counselling services including prenatal diagnostic services are unavailable. The transmission of haemophilia is complex since it can either appear de novo in a family, or be transmitted from an affected patient through his daughter to a grandson (Figure 1a) or be transmitted from a carrier mother through her daughter to the grandson. With poor literacy rates (65% for both sexes, and 54% for women), and the dubious role of women in reproductive decision-making, there is no data available on whether knowledge of the hereditary nature of haemophilia results in modification in reproductive behaviour. Investigations on hereditary disorders in India are challenging since family history is a sensitive issue. This is especially true in the case of haemophilia, where it has gender-sensitive implications, since haemophilia is transmitted to the son from the mother. Furthermore, in the absence of psycho-social or genetic counselling services, the ethical aspects of a more qualitative approach towards analysing the impact of family history on reproductive decision making processes becomes pertinent. Thus, this study used pedigree data to determine whether family history of haemophilia affected the number of children being born to families reporting haemophilia in Maharashtra, India.

Materials and Methods

Materials

Clinical, demographic, and genetic data were collected from clinical records, National Registration forms from three haemophilia clinics in the State, and from blood bank records as described earlier. Using this method, 1467 patients, representing 1401 families, were documented. From pedigrees, 725 additional cases could be determined yielding a total of 2192 cases.

Of the 1467 case papers, family history could not be ascertained for 501 cases and 691 did not report haemophilia in the family. Of the remaining 275 cases, family history of the condition was recorded for 189 cases. Pedigrees were also available for 469 out of 691 families without haemophilia in earlier generations.

Measures of impact of past history on family size

Impact of family history on family size was determined through a retrospective analysis based on pedigree data. Family history was defined as affected relative(s) in earlier generations of the patient, indicating that the mother had experienced the consequences of haemophilia in a family member. The term pedigree is used to represent the shorthand genetic history of haemophilia in that family as reported by the patient/family member. Family size was calculated as the number of live births per woman.

The available pedigrees were defined into 996 nuclear families as explained in the legend to Figure 1. Of these, 353 families had reported haemophilia in an earlier generation, implying that the mother had experienced haemophilia in a family member (Figure 1a). The remaining 643 families had one or more affected sons but had not reported haemophilia in any other family member in the earlier generation (Figures 1b, 1c). The former families were categorized as families with history, whilst the latter group constituted families without history of haemophilia as explained in the legend to Figure 1. The number of children born to each category was compared to determine the impact of family history on reproductive choices.

By definition, obligate carriers are daughters of affected fathers, or mothers with either two affected sons, or one affected son and affected maternal relatives, or mothers of daughters with affected sons. From pedigrees, mothers were categorized into two groups. The two groups classified as having history of haemophilia were: (a) women who were daughters of haemophiliacs, (Figure 1a, III2), and (b) women with affected maternal relatives (Figure 1a, III3). Women without history of haemophilia included mothers of haemophiliacs without affected relative in earlier generations (Figures 1b, 1c). The family size of these three cohorts was analysed by determining the number of children born to each category of women.

Using the reported age of the patient at the time of registration, parents were categorized into two groups. Group I represented those parents where the age of the patient at the time of registration was above 25 years. Group II constituted those parents where the patient’s age at registration was between 8 and 12 years. The number of children born to group I families was compared with the number of children born to group II families.

In order to determine whether family history of haemophilia influences the number of affected sons born to a family, parents were categorized into two groups. Group III represented those parents where the patient’s age at registration was below 10 years. The number of affected sons born to both groups was compared against their family history status.
Individuals.

I, II etc. represent generations in the pedigree whilst 1, 2 etc. represent males, affected males, carrier females, and normal females respectively.

There was a significant difference in the sex ratio (i.e. the number of females per 1000 males); 657 for families with history of haemophilia, 701 for families without history of haemophilia, and 933 for the general Indian population.\(^4\)

**Family size of haemophiliacs**

Only 10% of families reported a haemophilic grandfather (Table 1, ii). Analysis of pedigree data revealed that over the 10 years, 154 out of 2192 patients had married. Of these, 27% were patients with severe haemophilia A. Our earlier data\(^13\) had shown that only 25% (i.e. 173/689) of severe patients survived after the age of 20 years. Thus, taking this into account, it appeared that 24% (41/173) of the severe haemophilic population that survived beyond 20 years had married over the 10-year period. Pedigrees revealed that these 154 married patients had 187 sons and 244 daughters (Table 2, i).

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**Table 1 Maternal history of haemophilia in families**

<table>
<thead>
<tr>
<th>Affected relative</th>
<th>(n = 996^a)</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. None</td>
<td>643</td>
<td>65%</td>
</tr>
<tr>
<td>ii. Father</td>
<td>97</td>
<td>10%</td>
</tr>
<tr>
<td>iii. One brother</td>
<td>114</td>
<td>11%</td>
</tr>
<tr>
<td>iv. More than one brother</td>
<td>57</td>
<td>6%</td>
</tr>
<tr>
<td>v. Maternal relative</td>
<td>53</td>
<td>5%</td>
</tr>
<tr>
<td>vi. Brother and maternal relative</td>
<td>32</td>
<td>3%</td>
</tr>
</tbody>
</table>

The available pedigrees were defined into 996 nuclear families as described in Methods.

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All data were analysed using either Microsoft Excel package (version 2000) or SPSS package (version 10).

**Results**

**Family history from pedigree data**

Of the 996 nuclear families defined from the pedigrees, 643 were families without any other affected relative in generations earlier to the mother, that is families without history of haemophilia (Table 1, i). In 353 families, the mother had experienced haemophilia either in the father (10%) or in another relative (25%) and these constituted families with history of haemophilia (Table 1, ii–vi).

**Impact of family history on family size**

The number of children in families who had reported history of haemophilia was 2.9 ± 1.5, which was significantly less than the size of families without history \((3.6 ± 1.9, \zeta = 6.36, P < 0.001)\). There was a significant difference in the sex ratio (i.e. the number of females per 1000 males); 657 for families with history of haemophilia, 701 for families without history of haemophilia, and 933 for the general Indian population.\(^4\)

**Family size of carriers of haemophilia**

The majority of mothers (65%) did not report any other haemophilic in the family (Table 1, i). In order to determine whether family history, i.e. experience of haemophilia in the family, influenced reproductive decisions, the family size of women with a haemophilic father \((n = 97; \text{Table 1, ii})\), or women who reported an affected brother or other maternal relative \((n = 256; \text{Table 1, iii–vi})\), was compared with that of women who did not report haemophilia in earlier generations in the family \((n = 643, \text{Table 1, i})\). The data revealed that the family size of women whose father had haemophilia \((2.5 ± 1.3; \text{Table 2, ii})\) was significantly less than that of women without history \((3.6 ± 1.9, \zeta = 7.23, P < 0.001), \text{(Table 2, iv)})\). The number of children born to women who reported haemophilia in a brother or other maternal relative \((n = 256, \text{family size } 3.0 ± 1.5)\) (Table 2, iii) was significantly more than the family size of obligate carriers whose father had haemophilia \((\zeta = 3.1, P < 0.05)\). These data suggested that the reproductive decision-making was influenced when a daughter had experienced haemophilia in her father. However, when the affected man was a brother or another maternal relative, these experiences did not affect the family size.

**Family size in older versus younger generation of haemophilic families**

In order to determine whether there had been a reduction in the number of children born to families with haemophilia, the family size of older versus younger generation was compared (Table 3a, group I versus group II). Analysis of these data revealed that there was a reduction in the number of children
of both sexes born to group II (younger) versus group I (older) parents (Table 3a). The reduction was significant irrespective of family history of haemophilia (Mann–Whitney U test, $z = 3.086$, $P < 0.05$ for males and $z = 2.345$, $P < 0.05$ for females).

Family history and number of affected sons in older versus younger generation of haemophilic families

In order to determine whether family history had an impact on the number of affected sons being born, the number of haemophiliacs born to older (group III) versus younger (group IV) families was compared against family history status. The data revealed that in cases of families without history of haemophilia, there was a highly significant reduction in the number of families with more than one affected son in the younger generation ($\chi^2 = 23.4$, d.f. = 1, $P < 0.001$). However, in families with history of haemophilia, the proportion of families with more than one affected son in older and younger generations remained unchanged ($\chi^2 = 1.43$).

Discussion

The factors leading to increase of haemophilia in the population are summarized in Figure 2. In our earlier study, two indicators of improved haemophilia care services in the State of Maharashtra had been identified, viz. a fourfold increase in referrals of severe cases over 10 years, and improved age of diagnosis of haemophilia. Furthermore, results of the earlier survey had shown that >90% severe haemophilia cases and >84% of all haemophilia patients were aged under 20 years. These two factors would be of prime importance in influencing the longevity of patients, leading to the addition of affected individuals to the total pool of haemophiliacs in the population. In haemophilia, the reproductive ability of the patient is not affected. Thus, uncontrolled reproduction of patients, in
addition to spontaneous mutations, would be other factors influencing the future trends of haemophilia. The role of carriers of haemophilia in producing affected sons due to lack of comprehension of the nature of transmission of the disorder or the absence of genetic counselling and prenatal diagnostic facilities would be a third important factor influencing the haemophilic load in the population.

This study revealed a general decline in the size of haemophilic families, over a generation, suggesting that families with haemophilia had experienced the same declining fertility trends observed in the Indian population. The major load of patients was from mothers who did not report any family history. Although over the last 10 years only 25% of the patients had had children, this low number was possibly a consequence of reduced longevity of patients. Of significance was the observation of reduced family size in daughters of haemophilic fathers as compared with obligate carriers with haemophilia in more distant relatives. These data suggested that while there was an awareness regarding father to daughter transmission of the disorder, there appeared to be a lack of comprehension regarding transmission of haemophilia through females, when more distant relatives were affected. Perhaps notably, the study identified that despite reducing trends in family size over generations, families with haemophilia showed no reduction in the number of families having more than one affected son. These data suggest that having experienced the high mortality of the disorder, families prefer to have more sons in order to compensate for the high fatality of haemophilia. In conclusion, while analysis of pedigrees revealed the demographic characteristics of the haemophilic population in the State of Maharashtra, the study highlights the need for a qualitative investigation to explore the reproductive decision-making of carriers of haemophilia.

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KEY MESSAGES

- In families with haemophilia a reduction in family size between older and younger generations of parents was observed.
- In families with history of haemophilia the number of families with more than one affected son did not show significant reduction across generations.
- Family size of daughters of haemophiliacs was significantly less than family size of obligate carriers who reported haemophilia in a brother or maternal relative.
- A qualitative study is necessary in order to explore the reproductive decision-making of carriers of haemophilia.

References