monitored further, using a larger sample size in a subsequent study.

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References

Haemophilia A and B are recessive X-linked genetic diseases. In haemophilia A there is deficiency of factor VIII (FVIII) and in haemophilia B of factor IX (FIX), resulting in a clotting disorder. Haemophilia occurs in approximately 20/100,000 male newborns in all ethnic groups, of whom 80 - 85% have haemophilia A and 10 - 15% haemophilia B. Classification of severity is based on the patient’s blood level of FVIII or FIX. In the severe form the level of plasma-clotting factor is < 1.0%, in the moderate form 1.0 - 4.0%, and in the mild form 5.0 - 25.0% of normal.1

Patients with severe haemophilia develop spontaneous joint and muscle bleeds. Without adequate treatment this may result in chronic arthropathy. In patients with moderate haemophilia bleeds usually result from minor trauma. Patients with mild haemophilia usually present with prolonged bleeding after trauma or operations.2

Haemophilia can cause severe disability and a reduced life expectancy. After effective replacement therapy with clotting factors was introduced in 1960, the complications of haemophilia decreased in adequately treated patients. At first pooled factor concentrates (i.e. using a pool of donors) were used for the treatment of acute bleeding episodes. Later prophylactic treatment with these concentrates was used to prevent disability and increase life expectancy. Unfortunately viral diseases such as hepatitis B, hepatitis C and HIV have been transmitted to patients, especially in those treated with concentrates made from a large pool of donors. To prevent these possible complications, recombinant DNA-produced FVIII and FIX concentrates are used preferentially if affordable and available.2

Early diagnosis and adequate treatment are of utmost importance in preventing severe disability and morbidity. Early diagnosis can be achieved by focusing on early bleeding events and the family history.3 One-third of all patients have haemophilia as a result of a spontaneous genetic mutation, and are considered sporadic. In some cases designated as sporadic, the mother may be unaware of the fact that she is a carrier.3 Subcutaneous rather than joint or muscle bleeding is the most important initial presenting symptom in haemophilia.4 Unawareness of the clinical signs and limited laboratory facilities may add to a delay in diagnosis in developing countries.5

The Haemophilia Care Centres (HCCs) for children in the Western Cape (WC) are located at the Tygerberg Children’s Hospital, Red Cross Children’s Hospital and Groote Schuur Hospital, all public tertiary care hospitals. The South African Western Cape (WC) haemophilia registry listed 53 children with haemophilia A and 20 with haemophilia B aged 0 - 18 years, resident in the WC, on 28 February 2002. The recorded incidence of haemophilia A was 7/100,000 and that of haemophilia B 1.1/40,000 male newborns in the WC (C D Karabus — personal communication). In the WC patients are routinely treated with either intermediate-purity small-pool (heat-treated) concentrate produced by the WC Blood Transfusion Service, or with intermediate-purity large-pool concentrate (solvent detergent-treated) produced by the Natal Bioproducts Institute. These non-profit organisations produce approximately 18 million IU of FVIII per annum, which represents about 12,000 IU per South African patient per year, at a cost of approximately R1.60 per IU of FVIII.6 These locally produced plasma products have no significant risk of transmitting transfusion-transmitted virus (TTV), although infection with B19 parvovirus may occur.7 Mean use of FVIII was 20,000 IU per patient, and that of FIX 6,000 IU per patient in the WC for the year 1 October 2000 - 31 September 2001 (CD Karabus — personal communication). Three kinds of treatment protocols are used in the WC. The majority of patients receive clotting factor ‘on demand’ after a bleed. Some patients with recurrent severe bleeds in a joint are given clotting factor three times a week as ‘periodic prophylaxis’ until the joint has improved, and a few patients receive ‘continuous prophylaxis’ with clotting factor from shortly after birth.

Objectives

Objectives of the study were to identify all children with haemophilia A and B aged 0 - 18 years in the WC and to record how the diagnosis had been made, the severity of disease, the treatment used and the functional status of the joints. Impact of the disease on the family was also investigated.

Methods

This descriptive, cross-sectional study was performed between 28 January 2002 and 30 April 2002 as a research project by two elective students (MHH and JHJ). Patients’ clinical data, addresses and telephone numbers were obtained by reviewing patient records at the three HCCs in the Cape metropole, and at the regional hospitals of the WC. The event that led to the first medical consultation, the age of the child at that time and the age when the diagnosis was confirmed, were recorded.

Guardians were asked if they had been suspected of abusing or molesting their child. The type and severity of haemophilia, number of joint bleeds in the past 12 months and the frequency of therapy during that 12-month period were recorded. The status of the patients’ joints was classified as ‘functionally limited’ if the normal range of movement was decreased in one or more joints.

The socioeconomic status of the family was assessed, in part by determining the employment status of the guardian(s), and by the availability of private medical insurance. Guardians were asked if they had made minor or major changes to the education (and upbringing) of the child after they had learnt of
the diagnosis, and whether or not the disease had impacted significantly on their family life. The questionnaires were conducted at home, at the hospital or at the guardian's workplace by MHH and JJH. The presence of a family history was determined. If there were two affected brothers in a family where the mother had a negative family history, the first boy was included in the group with a negative, and the second boy in the group with a positive family history. Informed consent was obtained from all guardians and the study was approved by the Ethical and Research Review Committee of the Faculty of Health Sciences at Stellenbosch University, South Africa.

**Results**

**Study population**

We identified 59 boys with haemophilia A and 19 with haemophilia B (total 78) aged 0 - 18 years in the WC. We studied 49 children (63% of the total), 37 with haemophilia A and 12 with haemophilia B. The remaining 29 patients were not studied because it had not been possible to arrange an interview with the guardian or a home visit in the time available. Twenty-one patients (43%) had severe, 14 (29%) moderate and 11 (22%) mild haemophilia. The severity of 3 patients (6%) was unknown.

**Diagnosis**

A positive family history was obtained in 24 patients (49%), of whom 8 had severe, 7 moderate 8 mild disease and 3 disease of unknown severity. The mean delay between the first medical consultation and the time of diagnosis was 2 months (range 0 - 9 months) in severely affected patients, 0.5 month (range 0 - 1.5 months) in moderately affected patients, and 2 months (range 0 - 8 months) in mildly affected patients. The mean age at diagnosis was 9 months (range 1.5 - 22 months, median 11.8 months) in severely affected patients, 11 months (range 0.5 - 33 months, median 16.8 months) in moderately affected patients, and 21 months (range 1 - 48 months, median 24.5 months) in mildly affected patients.

The most common symptoms that led to the diagnosis of haemophilia were subcutaneous and mucosal bleeds (45% and 15% respectively). Twelve per cent of patients were diagnosed after a blood test because of a positive family history. Events that led to the diagnosis differed according to the severity of disease. The most common events leading to diagnosis were subcutaneous haematomas (51%) and iatrogenic causes (14%) in severely affected patients, a blood test because of a positive family history (30%) and subcutaneous bleeds (21%) in moderately affected patients, and subcutaneous bleeds (64%) and mucosal bleeds (18%) in mildly affected patients (Table I). Guardians had been suspected of child abuse in 14 cases (29%). Bruises or bleeding at immunisation sites had been observed in 14 patients (29%).

**Table 1. Factors that led to the diagnosis in patients with severe, moderate and mild haemophilia**

<table>
<thead>
<tr>
<th>Factors leading to diagnosis</th>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous haematomas</td>
<td>51 (1)</td>
<td>21 (3)</td>
<td>64 (7)</td>
</tr>
<tr>
<td>Iatrogenic causes</td>
<td>14 (3)</td>
<td>7 (1)</td>
<td>9 (1)</td>
</tr>
<tr>
<td>Mucosal bleeds</td>
<td>10 (2)</td>
<td>21 (3)</td>
<td>18 (2)</td>
</tr>
<tr>
<td>Family history</td>
<td>10 (2)</td>
<td>30 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Intra/extracranial bleeds</td>
<td>10 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Joint or muscle bleeds</td>
<td>5 (1)</td>
<td>21 (3)</td>
<td>9 (1)</td>
</tr>
</tbody>
</table>

*Severity unknown in 3 patients.

**Treatment and clinical status**

Of 36 patients treated ‘on demand’, 30 (83%) had suffered one or more joint bleeds in the preceding 12 months and 17 (47%) had one or more functionally restricted joints. Eight of 10 patients (80%) receiving ‘periodic prophylactic treatment’ had suffered one or more joint bleeds, and 2 (20%) had one or more functionally restricted joints. Continuous prophylactic treatment was given to 3 patients, 1 of whom had experienced a number of joint bleeds and 2 of whom had functionally restricted joints.

**Impact on the family**

Twenty-nine female guardians (59%) were gainfully employed, 18 (37%) were not, and in 2 (4%) the employment status was unknown. Thirty-three (68%) of the male guardians were gainfully employed, 5 (10%) were not and in 11 cases (22%) the father’s work status was not applicable (mother a single parent). Only 14 guardians (29%) had some form of medical insurance. Although guardians who are medically insured are billed for service, and poor parents are requested to pay a nominal fee whenever they attend a health care facility, treatment was provided free of charge to every patient who could not afford to pay for hospital treatment.

Twenty-three sets of guardians (47%) made major changes in the household, such as resigning from employment to care for the child, preventing the child from participating in sport and confining the child to the home. Thirteen of 24 guardians (54%) with a positive family history and 16 of 25 (64%) with a negative family history said that haemophilia had had a major impact on their family life. The remainder said there was little or no impact on their family life.

**Discussion**

We identified 78 children with haemophilia in the WC, including 5 children who were not listed in the national registry. These 5 children were known at regional hospitals, but the registry had not been notified and they had not been
referred to a HCC. Internationally, haemophilia A is four times as common as haemophilia B. In the WC it is three times as common, indicating under-diagnosis of haemophilia A. The categorisation of severity of haemophilia depends on an assay of the blood level of the clotting factor and may be influenced by laboratory techniques. We accepted the different hospital laboratory reports as accurate for the purposes of this study.

We were unable to find a clear definition of a ‘positive family history’ in the literature. In the case of two brothers with haemophilia the oldest may have a negative family history, but the younger will have a positive family history by virtue of his affected brother. For this reason we did not compare our family history incidence rate with that of the literature. It is known from the literature that about 50 - 60% of mothers are known carriers.

The mean age at diagnosis for severe haemophilia patients was 9 months, which is similar to the age recorded by Ljung et al., while patients with moderate haemophilia were diagnosed earlier (mean age 11 months) compared with 21 months in the study by Ljung et al. Clinical presentation in the WC patients was similar to that recorded by Pollmann et al. In that study 47% of severe haemophiliacs presented with subcutaneous haematomas compared with 52% in this study. In Pollmann’s study 24% of severe haemophiliacs were diagnosed because of a positive family history, compared with only 10% in this study, despite the fact that 38% of patients in the WC had a positive family history. Interestingly, 14% of our patients were diagnosed after iatrogenic trauma, mainly immunisation. In moderately severe haemophiliacs a family history led to the diagnosis in 4 of 7 children, and in 0 of 8 children with mild haemophilia. Poor counselling may explain why families are unaware of a family history and the role of heredity, which in turn may explain why children with a positive family history were not commonly diagnosed shortly after birth. Unfamiliarity on the part of the attending physician or nursing sister with regard to the clinical presentation of haemophilia may also contribute to delay in the diagnosis. Wrongfully accusing guardians of child abuse is disconcerting, and a diagnosis of a bleeding disorder should always be considered first when children are investigated for non-accidental injuries.

The majority (73%) of children in the WC received clotting factor on demand, that is only after a bleed. Eighty-three per cent of this group had experienced joint bleeds in the preceding year, and almost half of the patients had functionally restricted joints. Children who received periodic prophylactic treatment because of repeated serious joint bleeds had a much lower rate of non-functional joints (20%), but 80% had still experienced joint bleeds in the preceding year. Periodic prophylaxis therefore appears to be helpful in maintaining joint function, but not in preventing bleeds. Continuous prophylaxis, which is the accepted best treatment, was only used in 3 patients, making comments on the possible benefit inappropriate. The South African national annual production of FVIII is approximately 12 000 IU per patient per year. This fact, and the high cost of imported products, cannot support a local continuous prophylaxis programme for all severe haemophiliacs. Prophylactic therapy with recombinant FVIII from birth onwards largely prevents arthropathy, and is given to 80% of children with severe haemophilia in the Netherlands. This is currently unaffordable in the public sector in South Africa.

The extra demands on parents and children in these families are clear, and guardians need active support to raise their child with the minimum amount of physical and emotional damage, and to assist the child to achieve the best possible educational level. Family income is often inadequate because a guardian may have to give up his/her work to look after the child. The national budget for 2003 has fortunately increased the age up to which children will qualify for financial support from the Ministry of Social Affairs. Guardians need to be fully informed on all aspects of the disease, and be encouraged to use the expertise of the nearest HCC. Two specially trained nursing sisters have been appointed in the WC to counsel and assist patients and parents, to train them in home therapy and to promote optimal therapy at the HCC. The principle of optimal treatment is to diagnose and plan treatment at an HCC, and to involve the local public health care facility at community level in the day-to-day management.

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References

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