HAEMOPHILIA IN SINGAPORE—A Study of the Clinical and Haematological Features in 36 Patients

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A clinical syndrome affecting males usually and characterised by an inherited tendency to bleed excessively following slight injury has been recognised for many years. Described by the term "haemophilia", the condition was originally believed to be caused by a specific defect of coagulation. However, recent advances in the knowledge of the clotting mechanism have altered these views and it would now appear that the term "haemophilia" as used in the past covered a group of conditions in which similar clinical manifestations are produced by different basic defects in the clotting mechanism. Thus, in addition to a deficiency of antihaemophilic globulin (AHG), deficiencies of Factor V or proaccelerin, Factor IX or plasma thromboplastin component (PTC), and Factor XI or plasma thromboplastin antecedent (PTA) can all give rise to a clinical picture not unlike mild haemophilia.

Today the term "haemophilia" is generally used to describe a clinical condition in which there is an inherited deficiency of a specific factor, antihaemophilic globulin. Deficiency of Factor IX or plasma thromboplastin component, also known as Christmas Disease, is clinically indistinguishable from haemophilia due to AHG deficiency and some workers describe the latter condition as Haemophilia A and Christmas Disease as Haemophilia B.

Up till recently the diagnosis of haemophilia was mainly a clinical one depending on the history of a haemorrhagic tendency usually starting in infancy and showing a definite sex linked pattern of inheritance. From the laboratory point of view, the only abnormality usually found is a prolonged clotting time. The platelet count, bleeding and prothrombin times are usually normal. With these criteria, it is not unusual to find a number of cases with a suggestive clinical history but with no conclusive proof of the condition.

For many years, proof of AHG deficiency depended on the use of blood from a known haemophiliac patient as an indicator. Thus in doubtful cases, the ability or otherwise of the patient's blood to correct the clotting defect of blood from a haemophiliac was taken to indicate whether the deficiency in the patient was the same as in the haemophiliac. This technique obviously has its limitations and it was not until the development of the thromboplastin generation test by Biggs and Douglas (1953), that it became possible to make a confident diagnosis of haemophilia or AHG deficiency without the use of haemophilic blood.

Haemophilia has been reported with greatest frequency in the European races of Northern Europe, Great Britain, North America and Australia, Biggs and Macfarlane (1958), Sjolin (1959), Stefanini and Dameshek (1962), Fantl and Sawers (1954), Wilkinson et al. (1961). Its incidence in other countries is less certain. It is known to occur in Japanese, South Americans and in Negroes, Bullock et al. (1957). Wintrobe (1961), stated that haemophilia seems to be very rare among Chinese.

In Singapore and Malaya, apart from a report of a single case of haemophilia in an Indian boy reported by Lie-Ingo et al. (1964), no other case reports on the condition have been recorded. This is not because haemophilia is rare in these countries but because of the lack of diagnostic facilities which up till recently were not available.

This paper reports on the clinical features and haematological findings of a series of 36 proved cases of haemophilia due to AHG deficiency seen by the authors between 1963 to 1965.

Because the condition as seen in Singapore has not been recorded previously, it is our intention to record in some detail the symptomatology and clinical manifestations of our cases to enable a comparison to be made with the clinical description of the condition from other countries.

These 36 patients, derived from 31 families, represent all cases admitted into the various hospitals in Singapore during the period with the provisional diagnosis of "haemophilia". They were subsequently referred to the Haematological Laboratories of the Blood Transfusion Service for investigation for evidence of a coagulation defect. In most instances these patients have had many previous admissions into hospital for various bleeding episodes.

TECHNICAL METHODS

The methods employed in this study in general are those described by Biggs and Macfarlane, (1962), and Dacie and Lewis (1963). Given below is a summary of the techniques used and the range of normal values as obtained in our laboratories.

The Platelet Count was carried out as described by Brecher and Cronkite (1950). Normal range 150,000 to 300,000/c.mm.

The Bleeding Time was recorded by the method of Ivy. Normal range 3 to 7 minutes.

The Tourniquet Test was carried out as described by Biggs and Macfarlane (1962). Normally 0-10 petechiae may be found.

The Whole Blood Clotting Time was estimated by a modification of the Lee and White (1913) method. Normal range 5 to 10 minutes.

The One Stage Prothrombin Time was that of Quick (1935), using a commercially produced extract of rabbit brain (Difco) as the source of thromboplastin. Normal range 12 to 15 seconds.

The Prothrombin Consumption Index was that of Merskey (1950). Normal range 0-30%.

A modified Partial Thromboplastin Time Test (P.T.T.), Langdell et al. (1953), Nye et al. (1962), was used as a screening test throughout the studies. Two sources of commercially produced partial thromboplastin reagent, Thrombofax (Ortho) and Cephaloplastin (Dade) were used for the test. The methods employed were as described by the manufacturers. Normal times are 100 seconds or less for Thrombofax and 80 seconds or less for Cephaloplastin.

The Thromboplastin Generation Test (T.G.T.) was carried out as described by Biggs and Douglas (1953).

The AHG assay was carried out by the method described by Pitney (1956). Normal range 60-200%.

In addition to the above, the ability or otherwise of small amounts of fresh normal plasma, barium sulphate or aluminium hydroxide, Al $(OH)_3$ adsorbed plasma and normal serum to correct the abnormal Thromboplastin Generation Test was routinely carried out.

Plasma from confirmed haemophiliacs and patients with Christmas Disease was also used in these studies.

CLINICAL FEATURES

Ethnic Distribution and Incidence

The ethnic distribution of the 36 patients and of the Singapore population is shown in Table I.

It will be seen that 32 or 88·9% of the patients were Chinese, 3 or 8·3% were Indians, 1 or 2·8% was a Malay. No example of haemophilia in an Eurasian who make up the fourth major ethnic group in Singapore or in the Europeans was recorded. The overall incidence of haemophilia in Singapore is 1 haemophiliac patient per 51·8 thousand of population.

Age Incidence

The age of the patients as recorded at the time full haematological investigation was carried out is shown in Table II.

It will be seen that 61·2% are below the age of 10 and that the majority, 30 or 83·4% are under 20 years of age. The youngest patient was a two day old Indian baby, Case No. 14, presenting with a cephalhaematoma and subarachnoid haemorrhage. The oldest was a male Chinese aged 82, Case No. 34, presenting for the first time with an extensive haematoma of the arm.

TABLE I

SHOWING ETHNIC DISTRIBUTION CF SINGAPORE POPULATION AND HAEMOPHILIAC PATIENTS AND THE CALCULATED INCIDENCE

	Population* in thousands	No. of haemophiliac patients	Incidence
Chinese	1,396·5	32	1 per 43·6 thousand
Malays†	266·6	1	1 per 266·6 thousand
Indians¶	153·7	3	1 per 51·2 thousand
Eurasians	15·1	-	-
Europeans & others	33·0	-	-
Total	1,864·9	36	1 per 51·8 thousand

† include Indonesians

¶ include Pakistanis

* population estimates as on 30th. June, 1965 obtained from Department of Statistics, Singapore.

TABLE II

SHOWING DISTRIBUTION OF PATIENTS IN VARIOUS AGE GROUPS

Age in years	10 & Below	11-20	21-30	31-40	41-50	50 & Above
No. of patients	22	8	2	1	1	2
% of series	61·2	22·2	5·5	2·8	2·8	5·5

TABLE III

SHOWING AGE AT ONSET OF INITIAL SYMPTOMS

Age in years	< 1 year	1-5	6-10	11-20	21 · Above
No. of patients	8	17	7	3	1
% of series	22·2	47·2	19·5	8·3	2·8

Age at Onset of Initial Symptoms

Most of the patients have had previous admissions into hospital for various bleeding episodes. The age at onset of the first manifestations of a bleeding tendency were recorded and shown in Table III.

The great majority, 32 or 89% had developed symptoms suggestive of a bleeding tendency by the time they had reached 10 years, 8 or 22% of whom developed symptoms under the age of 1. The earliest age of onset of symptoms was at 2 days, Case No. 14.

In the majority of cases, the commonest initial symptoms noticed were a tendency to bruise easily from an early age. Bleeding from the gums was the next most common initial symptom followed by the occurrence of hemarthroses and prolonged bleeding after minor injury.

In two cases, No. 14 and No. 11, the initial symptoms were those of an intra cranial haemorrhage.

Symptomatology and Clinical Manifestations

The clinical manifestations and symptomatology encountered in the series of 36 patients are shown in Table IV below.

TABLE IV

FREQUENCY OF SYMPTOMS ENCOUNTERED IN SERIES OF PATIENTS

Symptomatology	No. of Patients	% of series
Ecchymoses	26	72·2
Bleeding Gums	23	63·9
Haematoma	16	44·4
Hemarthroses	14	38·9
Bleeding Lips & Tongue	9	25·0
Epistaxis	8	22·2
Hematemesis & Melaena	6	16·7
Hematuria	4	11·1
Retro Peritoneal Hematoma	4	11·1
Haemoptysis	2	5·6
Subconjunctival Haemorrhage	2	5·6

Ecchymoses or Bruising

This was complained of in 72·2% of cases. In most instances the bruising had been noticed from a very early age usually within the first year or two of life. Whilst often of traumatic origin when it would be localised to the exposed surfaces and bony prominences of the body, in the more severe case the ecchymoses were often of spontaneous onset when they would be found in the less exposed portions of the body as well. Ecchymoses were seldom the reason for seeking admission although in a few instances the patients have been brought up by their parents for investigation because of the tendency to bruise easily. Petecheal haemorrhage is very uncommon and was seen in only two patients.

Bleeding Gums

It will be seen that 23 or 63·9% complained of bleeding from the gums at some stage or other. Bleeding gums were most often the presenting complaint and was the commonest cause for hospitalisation. In most instances the bleeding was present in association with very carious teeth. In a good proportion of our cases, the most troublesome bleeding was encountered in association with carious primary dentition often precipitated by some degree of trauma.

Bleeding from the tooth sockets after extraction is almost invariable in haemophiliacs and is a frequent reason for admission into hospitals. In 5 patients, bleeding after tooth extraction was the first manifestation of the disease which resulted in the patient being hospitalised for investigation and treatment. In some of the milder cases it constituted the only symptom of a bleeding disorder.

Haematoma

Subcutaneous or intramuscular haematoma following minimal injury and sometimes spontaneous in the more severe haemophiliac occured in 44·4% of the cases. The haematoma were most often found in the muscular portions of the upper and lower limbs and less commonly they would be subcutaneous over the body. The extent to which bleeding can occur into these muscular haematoma is often not realised and in one instance, Case No. 34, extensive subcutaneous and intramuscular haemorrhage producing marked anaemia and symptoms and signs of a circulatory deficit were recorded.

A complication following haemorrhage into muscle tissue is sometimes seen in the development of a flexion contracture of the muscle. In one patient, No. 17, repeated haemorrhage into the calf muscles ultimately led to an equinus deformity of the ankle.

Haemorrhage into soft tissue can often produce pressure symptoms. Thus pressure occlusion of the arterial blood supply to the toes was responsible for the development of gangrene of the big toe in one of our patients, No. 21, which necessitated an amputation.

Haemorrhage into the soft tissue of the mouth and pharynx producing extensive hematoma involving the pharyngeal and laryngeal walls was seen in only one patient, Case No. 34. This is one of the few emergencies in haemophilia because of the possibility of the rapid occurrence of respiratory obstruction.

Hemarthroses

A feature characteristic of haemophilia but also known to occur in other clotting defects is the presence of repeated haemorrhage into synovial joints or hemarthroses. Hemarthroses usually become evident when the child begins to walk. Hemarthroses was the third most common reason for patients being admitted into hospitals. Hemarthroses were present in 14 or 38.9% of the cases. In the mild or moderately severe case it was often associated with a definite strain or injury whilst in the severe case it was often spontaneous in onset. The joints most often affected were the knee 12 cases, ankle 7 cases, elbow 6 cases. Less commonly the hip 4 cases, wrist 2 cases, shoulder 1 case and interphalangeal joints 1 case were affected.

In six cases only a single joint was involved whilst in eight cases there was multiple joint involvement.

In the severe case permanent joint damage usually results from repeated haemorrhage leading to a disorganisation with ankylosis of the joint with atrophy of the surrounding muscles. In only 3 cases was there a marked involvement and disorganisation of the joint whilst in 8 others a less severe involvement was present.

In 2 instances, Case No. 2 and Case No. 15, the lone hemarthroses of the knee was originally thought to be a septic arthritis or osteomyelitis. Open drainage and currettage was attempted resulting in persistent and severe bleeding necessitating transfusion of blood.

Other Less Common Symptoms

Prolonged bleeding following trivial injury is characteristic of haemophilia. Bleeding from the lips and tongue following accidental biting is a common complaint in little children, whilst haemorrhage following minor cuts and lacerated wounds to the scalp and other parts of the body were recorded on a number of occasions.

Epistaxis was complained of by 8 of the patients and was generally not severe. In 5 patients the epistaxis or bleeding gums was associated with a hematemesis and melaena due to the blood being swallowed. In 1 patient, Case No. 13, there were symptoms suggestive of a definite peptic ulcer associated with hematemesis although a barium meal examination did not confirm the presence of an ulcer.

Hematuria was reported in 4 adult patients all of whom had a severe clinical disability. Although frequently painless, it was sometimes associated with severe colic. The hematuria is often persistent and if left untreated may last for days giving rise to marked anaemia.

In 1 patient, Case No. 9, hematuria was associated with the presence of a ureteric stone.

Intracranial haemorrhage occured in 2 patients, Case No. 11 and Case No. 14. In both instances they were of traumatic origin, one of which was sustained following a fall when the patient developed transient drowsiness and signs of cerebral irritation. Investigation showed the presence of a blood stained spinal fluid. In the second patient, Case No. 14, the intracranial haemorrhage was associated with a birth injury and the development of a large cephalheruatoma.

One patient, Case No. 39, was operated upon for paraplegia thought to be due to a paraspinal abscess. However, at operation a large hematoma was found. Patient bled excessively during and after operation necessitating a large number of transfusions. Subsequent investigation showed the patient to be a haemophiliac.

Retro peritoneal hematoma was seen in 4 adult patients. In one Case No. 13, a large perinephric hematoma developed spontaneously. The patient was admitted into a surgical unit where he was diagnosed as a perinephric abscess and an incision and open drainage was performed. No pus except for blood clots was evacuated. Patient bled persistently thereafter requiring massive transfusions. Subsequent investigation showed the patient to be a haemophiliac.

The other retro peritoneal hematomas were situated over the right iliac fossa simulating an acute appendicitis. The presence of limitation of movement and the position of the mass suggests a haemorrhage into the psoas muscle.

Family History of Bleeding Tendency

A family history suggestive of a bleeding tendency was carefully looked for in every case. In only 18 patients was a positive family history suggestive of a bleeding tendency definitely elicited. This gives an incidence of 50% in whom no definite family history could be elicited. The full family studies of these 36 patients will be presented in another paper.

LABORATORY FINDINGS

The diagnosis of haemophilia depends on the triad of a history of bleeding beginning in early life, a characteristic hereditary pattern and the demonstration of a specific deficiency of AHG. The platelet count and morphology, tourniquet and bleeding time tests are usually normal. The one stage prothrombin time is always normal. The whole blood clotting time is typically prolonged in severe haemophiliacs, whilst in the mild case it is sometimes abnormal, but usually normal. The prothrombin consumption index is usually abnormal. The thromboplastin generation test using the patient's adsorbed plasma is usually abnormal except in the very mildest grades of deficiency when an assay of AHG level may be necessary to demonstrate the deficiency, Biggs and Macfarlane (1958).

Given below are the results of the various tests carried out on the 36 patients:—

Platelet Count

The initial platelet count was found to be below 150,000/c.mm. in 6 patients, the lowest count being 65,000/c.mm. All these patients were having an acute bleeding episode. Stefanini and Dameshek (1962) states that a mild transitory thrombocytopenia is known to develop in these cases as the result of severe bleeding and the rapid utilisation of platelets often coupled with the transfusion of large quantities of platelet poor blood.

In 15 other patients, the platelet count was higher than the upper limit of 300,000/c.mm. In 6 of these, the counts were over 400,000/c.mm. the highest count recorded being 500,000/c.mm. A moderate increase in platelet count is often seen as a response following an acute haemorrhage. In the remaining 15 patients the platelet count was within the normal range.

The Bleeding Time Test and Tourniquet Test

The bleeding time was found to be normal in all except for two patients—Case No. 18 and 22 in both of whom they were persistently prolonged to beyond the upper limit of normal. In both these cases the prolonged bleeding time was associated with a positive tourniquet test. The tourniquet test was normal in all the other patients.

The significance of the positive results will be discussed later.

The Whole Blood Clotting Time Test

This test is the simplest and most widely used test for screening for coagulation deficiency states.

The results of the test as estimated by the method of Lee and White (1913) is shown in Table V.

It will be seen that in 6 or 17% of the patients, the clotting time was within normal limits. Of the 6 patients, 4 were cases with a mild to moderate disability, whilst the remaining two patients were of severe disability with AHG levels of less than 1%.

In 18 or 50% of patients the clotting time was greater than 20 minutes. Although in the majority of instances a prolonged clotting time is generally found in association with a severe disability and low AHG levels of less than 1% there were 2 patients with clotting times of over 60 minutes with AHG levels of between 3-4%. Both of these patients had a mild to moderate disability. One third of the patients had clotting times of between 11 and 20 minutes.

It is therefore apparent that the value of the clotting time test as a diagnostic test is limited. A prolonged time would however generally indicate haemophilia, as it is the commonest disorder in which a prolonged clotting time is encountered. The presence of a greatly prolonged clotting time usually indicates a severe clinical condition although the reverse does not always hold true and many cases with a severe or moderately severe clinical disability and low AHG levels have shown normal or near normal times. It is generally true, however, that cases with a mild disability tend to have normal or near normal times.

The One Stage Prothrombin Time

Using the method of Quick (1935), the one stage prothrombin time was found to be normal in all 36 patients. However, when a modified method using Russel's Viper Venom as a source of thromboplastin was carried out by the various Unit Clinical Laboratories, no less than 14 of the 36 patients were found to give abnormal times of 4 seconds or more over the control. However, these 14 cases when re-investigated by the Quick one stage method all gave unequivocally normal results.

The Prothrombin Consumption Index

The results of the prothrombin consumption index and their correlation to the clotting times are shown in Table VI.

TABLE V

RESULTS OF WHOLE BLOOD CLOTTING TIME (LEE & WHITE) ON 36 PATIENTS

Clotting Times (mins.)	< 10	11-20	21-30	31-40	41-50	51-60	60+
No. of Patients	6	12	3	2	5	1	7

TABLE VI

RESULTS OF PROTHROMBIN CONSUMPTION INDEX AND THEIR CORRELATION TO WHOLE BLOOD CLOTTING TIME

Clotting Time (mins.)	Prothrombin Consumption Index (%)				
	0-30	31-40	41-60	61-80	81-100
10	2		4		
11-20	4	3	5		
21-30			1	1	1
31-40		1	1		
41-50		2	1	1	1
51-60					1
61 and above		1	3	2	1

Of the 36 patients, 6 had normal prothrombin consumption indices of less than 30%. The remaining 30 patients had values of over 30%. The number of patients with a normal consumption index is the same as the number found to have a normal clotting time. It will be seen that of the 6 patients with normal clotting times 4 had an abnormal consumption index, and of the 6 patients with normal consumption index, 4 had a slightly prolonged clotting time.

From the diagnostic point of view, it was our experience that neither of these tests was superior to the other in picking up the mildly affected patients, although Biggs and Macfarlane (1958) found the prothrombin consumption index to be a more sensitive index of an underlying coagulation defect.

The other points to be noted are that patients with clotting times of less than 20 minutes, all had consumption indices of less than 60%, whilst those with prolonged clotting times tended to have indices of 60% or more. It would thus appear that there was some degree of correlation, though not complete, between the prothrombin consumption index and the whole blood clotting time.

The Partial Thromboplastin Test

The partial thromboplastin test carried out on all 36 patients gave unequivocally abnormal results. In most instances, the clotting times recorded were prolonged to over 200 seconds and in the mild haemophiliacs the clotting times in this test were always over 150 seconds.

The Thromboplastin Generation Test

So far all the tests discussed do not allow any distinction to be made between the various factor deficiency states.

With the development of the thromboplastin generation test by Biggs and Douglas (1953), there was now for the first time a test which allowed a distinction to be made between different deficiency states without the use of haemophilic blood as an indicator.

In patients with haemophilia, prolonged clotting times are obtained in the thromboplastin generation studies when patient's adsorbed plasma is used in place of normal plasma. The minimum plasma clotting times obtained in the 36 patients is shown in Table VII.

Using reagents from the normal, the minimum clotting times obtained in our laboratory are always less than 10 seconds. It will be seen that all haemophiliacs including those of mild disability had a minimum plasma clotting time of more than 10 seconds. The lowest minimum time recorded was 11 seconds in a patient with a very mild disability and a AHG level of 5%. The longest plasma clotting time was 61 seconds in a haemophiliac with moderately severe disability and an AHG level of 2%. The majority of patients however had minimum clotting times of between 21-50 seconds.

It will therefore be seen that the thromboplastin generation test apart from its diagnostic value is a more sensitive indicator of a coagulation deficiency when compared to the clotting time test and the prothrombin consumption index.

Assay of AHG Activity

The results of the Assay of AHG activity in the plasma of the 36 patients are shown in Table VIII.

17 patients had AHG levels of less than 1%. 8 of these patients had a complete absence of AHG in the plasma and in 9 others only small traces amounting to less than 1% could be detected. Of these 17 patients, 15 had whole blood clotting times, of more than 10 minutes, whilst 2 patients had clotting times within the normal range (see Table IX). All these 17 patients had a severe clinical disability.

16 patients had AHG levels of between 1-4%, 11 of whom were of moderate clinical disability and 5 had a severe disability. 3 patients had AHG levels of over 4% all of whom had a mild disability. There were no cases with AHG levels of over 5%.

The relation of AHG level to prothrombin consumption index is shown in Table X.

Of the 6 patients with normal prothrombin consumption index, 2 had AHG levels of less than 1% and 4 had levels of between 1-5%.

Circulating Anticoagulants

The presence of circulating anticoagulants which have been demonstrated in some cases of haemophilia was looked for in every case investigated. The presence of a circulating anticoagulant would be shown by abnormal times in the T.G.T. when using either the plasma or the serum from the patient. Confirmation is usually obtained by demonstrating the failure of small amounts of normal plasma to correct the prolonged clotting times or alternatively by demonstrating the prolongation of the clotting of normal blood, when small amounts of patient's plasma are added. It was not possible to demonstrate the presence of a circulating anticoagulant in any of the patients.

DISCUSSION

Incidence of Haemophilia

Haemophilia due to AHG deficiency is the commonest of the hereditary disorders of coagulation seen in medical practice. Biggs and Macfarlane (1962) gave the incidence of haemophilia in England as 2-3 per 100 thousand. In Australia, the incidence is 1 per 5 thousand male births, De Gruchy (1964). The incidence in Denmark is given as 1 per 27 thousand or about 1 haemophiliac per 14 thousand males, Sjolin (1959). Hecht (1955), quoted by Sjolin gave the incidence in Holland as 1 per 10 thousand. Ratnoff (1960) gave the incidence in Cleveland USA as 1 per 20 thousand.

During the 3 year survey, 36 cases of haemophilia were seen by the authors. The population as at 1965 is 1·87 million of which 967·5 thousand were males. This gives an overall incidence of 1 haemophiliac per 51·8 thousand population or 1 haemophiliac per 26·9 thousand males.

The true incidence of haemophilia in Singapore is probably higher for two reasons; firstly, it is very likely that there are very many mild haemophiliacs with no symptoms leading very normal lives having never consulted a doctor because of the disease; secondly, it is known that the bleeding tendency in the severe haemophiliac tends to have a seasonal or periodic variation and it is not unusual for some severe haemophiliacs to remain symptom free for many years. As this study covers only a 3 year period, it is possible that a few severe haemophiliacs may have been missed.

The study recorded haemophilia in the three major ethnic groups in Singapore with the exception of the Eurasians who form a very small proportion of the population estimated at 15·1 thousand. The point of interest is that only one Malay haemophiliac was detected from a population of 266·6 thousand. This would sug-

TABLE VII

SHOWING MINIMUM CLOTTING TIMES USING $Al(OH)_3$ ADSORBED PLASMA IN T.G.T. STUDIES

Ad. Plasma Minimum clotting time (secs.)	< 10	11 - 20	21 - 30	31 - 40	41 - 50	51 - 60	60 +
No. of Patients	0	7	17	7	3	1	1

TABLE VIII

SHOWING AHG LEVELS IN PLASMA OF 36 HAEMOPHILIACS

Plasma AHG Levels % of Normal	< 1 %	1.1-2.0 %	2.1-3.0 %	3.1-4.0 %	4.1-5.0 %
No. of Patients	17	8	4	4	3

TABLE IX

SHOWING AHG LEVELS IN RELATION TO WHOLE BLOOD CLOTTING TIMES IN SERIES OF 36 PATIENTS

Whole Blood Clotting Times (mins.)	Plasma AHG Levels % of Normal				
	< 1%	1-2%	2·1-3·0%	3·1-4·0%	4·1-5·0%
less than 10	2	3		1	
11-20	4	2	3		3
21-30	1	1		1	
31-40	2				
41-50	4	1			
51-60	1				
61 and above	3	1	1	2	

TABLE X

SHOWING AHG LEVELS IN RELATION TO PROTHROMBIN CONSUMPTION INDEX IN SERIES OF 36 PATIENTS

P.C. Index	Plasma AHG Levels % of Normal				
	< 1%	1·1-2·0%	2·1-3·0%	3·1-4·0%	4·1-5·0 %
0-30%	2	1	1		2
31-40%	4	1		1	
41-60%	6	4	3	2	
61-80%	3			1	
81-100%	2	2			

gest that haemophilia is less common among this particular ethnic group. As the Malays tend to live in the outlying rural areas and are generally recognised to be more conservative and have not come to accept western medicine as readily as the other ethnic groups, it is possible that a number of cases could have been missed thereby accounting for the relatively low incidence of the disease among them.

On clinical grounds, a haemophilia patient may be classified as "severe" if he suffers from repeated haemorrhages with serious crippling, frequent deep tissue haemorrhage with little provocation; as "moderate", if he has few hemarthroses and no serious crippling and an occasional hematoma; as "mild" if he has no hemarthroses or other spontaneous bleeding and merely gave a history of abnormal bleeding after definite injury. The clinical grading can generally be correlated to the AHG levels in the plasma, severe cases having less than 1%, moderate cases 1-5% and the mild cases 5-20% of AHG activity, Biggs and Macfarlane (1962).

In terms of clinical disability, 22 or 61% of our cases were of severe disability whilst 11 or 30·5% were moderate to mild disability, 3 patients had a very mild disability. The majority of the severe cases were under the age of 10 years. Of the 6 patients over 30 years, 3 were mild cases and 2 had a moderate to mild disability and 1 had a severe disability.

The observation that the majority (83·4%) of the series are under 20 years of age would suggest that the prognosis is poor for these patients. Birch (1937) quoted by Ratnoff (1960) estimated that 35% died within the first year of life and 57% within the first 5 years and 95% by the age of 40. However, with the increasing availability of fresh blood, plasma and AHG concentrates and the advancements that have been made in the understanding and management of these cases, the present day outlook is certainly not as gloomy as reported. Biggs and Macfarlane (1966) state that only 2 of their 520 patients have died under the age of 18 during the past 10 years and that the mean age at death of 56 patients recorded by the Registrar General for the years 1959-1962 is between 36 and 37 years.

Figures obtained from the Department of Statistics, Singapore showed that between the years 1956 to 1965 there were 3 deaths certified as due to haemophilia. All these three cases died before 1963 when conclusive haematological proof of the disease was not available, although it was fairly certain from the clinical features that they were cases of "haemophilia". During the period of survey, only one death was recorded, Case No. 34.*

What is often not realised is that there are varying degrees of disability from the very mild haemophiliac who only bleeds on definite injury to the very severe with very frequent and repeated spontaneous bleeding. In the mild or mild to moderate cases there is a very good outlook with very little incapacity and many die of entirely unrelated conditions, Biggs and Macfarlane (1958), Pitney (1957).

The clinical symptomatology of our cases are no different from the descriptions given in various monograph and reviews, Davidson (1949), Biggs and Macfarlane (1958, 1962), Sjolin (1959), Ratnoff (1960), Wilkinson et al (1961), Stefanini and Dameshek (1962).

The majority (89%) of the patients had developed symptoms suggestive of a bleeding tendency by the age of 10, though 1 patient Case No. 34 apparently did not have any symptoms till the age of 83 before being admitted with extensive hematoma of the forearm.

The late onset of symptoms has been recorded occasionally and Ratnoff (1960) describes one patient who was in the seventies before it was established that he was a bleeder. Wilkinson and associates (1961) from a study of 267 haemophiliacs found that most cases had been diagnosed by the age of 5 years, only 13% being diagnosed later than this age.

About the only feature frequently described which was not recorded in this series was the development of damage to peripheral nerves following compression by large hematoma. Hematuria which was reported to occur in as much as 90% of a series of patients, Davidson (1949) was only seen in 4 or 11% of our cases.

Two of our cases No.18 and 22 were found to have persistently prolonged bleeding times coupled with a positive tourniquet test. The platelet counts were always normal. Prolonged bleeding times have been noted in some cases of haemophilia, Biggs and Macfarlane (1958), Harmon et al. (1957). This could suggest the diagnosis of von Willebrand's disease, a condition characterised by an inherited haemorragic tendency of an autosomal dominant pattern affecting both males and females. Apart from a

* ADDENDUM: Since this paper was written another death was recorded. Case No. 27, who died of intra cerebral haemorrhage following a fall from a bicycle.

prolonged bleeding time, most of the other investigations including the platelet count are usually normal, though in some cases a slightly prolonged clotting time has been recorded. Recently, low AHG levels similar to those found in mildly affected haemophiliacs have been demonstrated in a number of these cases, Alexander and Goldstein (1953), Biggs and Macfarlane (1958), Pitney and Arnold (1960), Blackburn (1961).

The lack of a positive family history in our two patients, especially the absence of an affected female in the family makes it difficult for a confident diagnosis of von Willebrand's disease to be made. The AHG levels in the two patients were less than 1% and 2% respectively.

One of the striking features of haemophilia is its sex linked pattern of inheritance. It is now reasonably certain that the defect is carried by the X chromosome. The condition is thus transmitted to affected males by the mother who although a carrier of the defect does not show any haemorrhagic tendency, though examples of carriers with slightly low AHG levels have been reported. The disease is exclusively seen in males although an occasional case of a female haemophiliac has been described, usually resulting from the marriage of a haemophiliac male and a female carrier, Israels et al (1951), Merskey (1951), Mellman et al (1961). All our 36 cases were males.

The large proportion, 50%, of our cases with a negative family history is to be noted. Biggs and Macfarlane states that 25%-30% of the total recorded cases did not have any previous medical history. This lack of a positive history may be accounted for by the fact that spontaneous mutations could occur giving rise to new cases of either haemophiliac males or of female carriers. Another possibility is that many patients are entirely ignorant of their predecessors or relatives. This factor is particularly true in Singapore where many of the patients were not able to volunteer any information about their predecessors with whom they have lost contact since their parents emigrated from China to settle in Singapore.

The laboratory findings in the series of cases described are fairly characteristic of haemophilia. Apart from the mild cases where the whole blood clotting time and the prothrombin consumption index may be normal, there was no difficulty of establishing the diagnosis from the characteristic T.G.T. pattern and the AHG assay.

The significance of the various laboratory findings have been discussed together with the results. Of the screening tests employed the partial thromboplastin time test was found to be of greater value than the clotting time test or prothrombin consumption index in the detection of patients with a coagulation factor deficiency. This test which is very simply carried out has the advantage that it can be performed using either venous or capillary blood. In a recent report Nye and associates (1963) was able to show that with the exception of Factor VII deficiency, this test is sensitive to deficiencies of all factors involved in the 3 stages of coagulation including the presence of circulating anticoagulants. It is a very suitable test as a broad spectrum test to be used in conjunction with the platelet count, bleeding time and prothrombin time tests for detection of coagulation deficiency states. The ability to use capillary blood makes it very useful in the investigation of paediatric cases where there is always difficulty of obtaining blood for investigation.

Our results confirm those of other workers in emphasizing the value of the T.G.T. as a diagnostic tool for differentiating the various deficiency states. All cases including those with a mild deficiency gave clearly abnormal results.

The assay of AHG activity showed that all the cases in the series had AHG levels of below 5%, with approximately 50% having a total absence of AHG. The absence of cases with AHG levels above 5% is rather surprising. Biggs and Macfarlane (1958) reported 63 out of 115 patients of haemophilia with absent AHG, whilst 52 cases had AHG levels of between 5% and 40%. The absence of cases with AHG levels higher than 5% suggests the possibility that many of the milder cases may not have been detected probably because of their lack of symptoms.

SUMMARY CASE REPORTS

Case No. 2: First seen at the age of 8 months with a swelling of the right knee. Has had no history of previous bleeding episodes. Negative family history. Diagnosed as a case of septic arthritis and submitted for aspiration drainage. Bled persistently after operation requiring a number of blood transfusions. Subsequent investigation showed a slightly prolonged clotting time (CT) of 13 minutes, a prothrombin consumption index (PCI) of 15%, and a partial thromboplastin time (PTT) of 200+ sec., Assay of plasma AHG activity showed a level of $2\frac{1}{3}$%.

Case No. 9: A 35 year old male, first seen in 1960 for hematuria. Investigation revealed the presence of the stone in the right ureter. He was submitted for surgery during which he bled excessively necessitating a large number of transfusions. A careful inquiry into his history revealed that he had an episode of prolonged bleeding after a dental extraction many years ago, and that his sister's son living in China also has a similar history of a bleeding tendency. He has never had any spontaneous bleeding or hemarthroses. Laboratory investigation showed him to be a mild case of haemophilia with a CT-14 mins., PCI-42%, PTT-148 sec., and an AHG level of 3%.

Case No. 11: First seen at the age of 3 years when he was admitted into hospital in coma following a fall from a lorry. Investigation showed the presence of a blood stained spinal fluid. He has a positive history of recurrent bleeding from the gums and frequent spontaneous bruising. Family history was negative. Laboratory investigation revealed CT-24 mins., PCI-76%, PTT-200+ secs., AHG assay-0%.

Case No. 13: Male Chinese aged 16 was first seen in June 1964 with a mass in the left flank associated with some pain and fever. Diagnosed as a perinephric abscess and submitted for aspiration drainage when 200 ml. of stale clotted blood was obtained. He bled persistently thereafter requiring blood transfusions. Subsequently he was referred for investigation when he was found to have a prolonged CT-36 mins., PCI-45% and AHG activity of less than 1% in the plasma. Inquiry revealed that he had one episode of swelling of the knee when young and occasional bleeding from the gums. Family history was negative.

In November 1965 he was readmitted for hematemesis and melaena when he was treated with plasma and blood transfusions. Subsequent barium meal examinatiion failed to reveal any peptic ulcer.

Case No. 14: An Indian boy, first seen 2 days after a normal delivery when he was noticed to be drowsy and restless and to refuse feeds. Examination revealed a large cephalhematoma, some degree of pallor and signs of meningeal irritation. Lumber puncture revealed a blood stained spinal fluid. Following some blood transfusions he recovered uneventfully. Subsequent investigation revealed a negative family history. He had a CT-110 mins., PCI-86%, AHG assay-0%.

Case No. 15: A 4 year old boy with a negative family history. First seen at the age of 8 months with swelling of the right knee. Diagnosed as a septic arthritis. Submitted for aspiration when only blood clots were obtained. Later an open drainage operation was performed. He bled profusely post operatively requiring transfusions of blood and plasma. Subsequent investigation showed a CT-43 mins., PCI-85%, PTT-200+ sec., AHG assay-$1\frac{1}{2}$%.

Case No. 17: A 14 year old boy with a history of recurrent bleeding episodes from the age of 2. Has had a repeated haematoma into the buttocks and calf muscles and recurrent hemarthroses of the knees, ankles, elbows, and hips. There was a positive family history of the sex linked pattern. The repeated haemorrhage into the calf muscles over the years led to a fibrosis and contracture of the calf muscles resulting in an equinus deformity of the foot. Laboratory investigation revealed a CT-114 mins., PCI-50%, PTT-200+ sec., AHG assay $1\frac{5}{6}$%.

Case No. 18: First seen at the age of 3 for spontaneous bleeding from the gums. Has had prolonged bleeding following accidental biting of the lips and tongue. No hemarthroses. Patient comes from a family of 7 with 2 elder brothers and 4 sisters, all of whom are well with no history of a bleeding tendency. No history of similar bleeding in any of the relatives. Investigation showed a normal platelet count, prolonged bleeding time of beyond 10 mins. Capillary resistance test negative. CT-11 mins., PCI-50%, PTT-200+ sec., AHG assay less than 1%.

Case No. 21: 20 year old student who has had bleeding symptoms from the age of 2. Has had frequent bruising and haematoma formation, epistaxis bleeding from the gums, and hematemesis. Has had multiple joint involvement affecting both ankles, knees, elbows and hips. He has spent an equivalent of more than 2 years in hospital because of this symptoms. Severe haematoma around the ankle and foot led to vascular obstruction and gangrene of the big toe with ulceration and controllable bleeding. Finally he had to be submitted for a below the knee amputation. He has a positive family history of a bleeding tendency. Laboratory investigation showed a CT-82 mins., PCI-50%, PTT-200+ sec., AHG assay less than 1%.

Case No. 22: 5 year old boy, first seen at the age of 3 with a history of recurrent spontaneous bleeding from the gums and epistaxis. Has had a total of over 33 admissions into hospital amount-

ing to about 120 days. Admissions invariably were for epistaxis and bleeding gums. Has had one episode of hemarthrosis of the right ankle. On most admissions he has been given fresh blood or plasma transfusions with good response and was able to be discharged within a day or two. Investigation revealed a persistently prolonged bleeding time of over 12 mins. with a positive capillary resistance test. CT-7 mins., PCI-19%, PTT-200+ sec., AHG assay-2%.

The bleeding appears to be that due to a capillary defect although he has had one episode of hemarthrosis. Inquiries did not reveal a history of a bleeding tendency in any other member of the immediate family or in the relatives of the father or mother.

Case No. 27: 12 year old school boy, first seen at the age of 4 years for excessive bleeding after a tooth extraction. Negative family history. Investigation revealed a CT-9 mins., PCI-56%, PTT-200+ sec., AHG assay-1%. Readmitted in May 1966 for increasing drowsiness of one day's duration. He had a fall from a cycle 7 days before admission. Examination revealed signs of meningeal irritation with irregular pupils. A blood stained spinal fluid was obtained on lumber puncture. He died within hours of admission into hospital. Autopsy showed an extensive intra cerebral haemorrhage. No bony fractures were detected.

Case No. 34: 83 year old male Chinese was seen for the first time in November 1965 with severe bruising and hematoma formation following a fall. Examination revealed extensive hematoma covering the whole left side of the body and left thigh as well as the right arm and forearm. He has never had any bleeding episodes in the past. 3 months previously he was seen by the ENT surgeon for nasal obstruction and epistaxis. A tumour was found which on biopsy showed the histology to be that of a malignant lymphoma. He received a course of radiotherapy.

Laboratory investigation revealed a Hb. of 6·6 gm.%, CT-21 mins., PCI-50% and a plasma AHG activity of 4%.

Whilst in hospital he developed an extensive sublingual and pharyngeal hematoma for which he was given fresh whole blood and human AHG concentrates. He also developed melaena for which further plasma and blood transfusions were given. After a turbulent period the bleeding was finally arrested and his condition gradually improved. He was about to be discharged from hospital when he unexpectedly died in his sleep. The family history was negative.

Case No. 39: First seen at the age of 5 years with progressive weakness of both lower limbs and incontinence of urine and faeces. Clinical examination showed a flaccid paralysis of both lower limbs with absent reflexes. Diagnosed as a case of transverse myelitis due to paraspinal haematoma. He was submitted for operation when a mass of fibrous haemangioma-like tissue was removed. He bled excessively post operatively requiring repeated plasma and blood transfusions. Subsequent investigation revealed a history of a bleeding tendency from the age of 3 when he bled profusely from a cut lip requiring hopitalisation and blood transfusions. Family history was negative. Laboratory investigation revealed a normal clotting time, PCI-53%, PTT-200+ sec., AHG assay less than 1%.

SUMMARY

The clinical and haematological features of 36 cases of haemophilia due to AHG deficiency seen over a 2 year period have been described. The incidence in Singapore has been estimated at 2 per 100 thousand population or 1 per 26·9 thousand males. The relative value of the various laboratory investigations has been discussed.

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