A survey of pregnancies that ended in haemoglobin Bart's hydrops foetalis and Cooley's anaemia

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Recent advances allow detection of the homozygous states of α- and ß-thalassemia in early pregnancy, thus giving couples at risk the option of early abortion. However, at the Prince of Wales Hospital, no reduction has occurred in the number of births of infants with haemoglobin Bart's hydrops foetalis. A survey by us has revealed a total of 33 cases during the seven years from 1987 to 1993. Antenatal records were available for 20 of the 33 cases and none of these showed that a thalassemia risk had been recognised prior to the development of hydrops. In some cases, mothers had failed to attend antenatal clinics early in pregnancy. However, in others, there was apparent failure of vigilance on the part of the doctors concerned because the thalassemia risk was not identified and appropriate referral for prenatal diagnosis was not made. During the same period, only five new cases of Cooley's anaemia were diagnosed, mostly after the first year of life. Antenatal records were unavailable for review.

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Introduction

Thalassemia includes a heterogeneous group of diseases caused by an imbalance in the production of globin chains, and is manifested by a wide spectrum of clinical syndromes.[1] Individuals with the mildest forms, such as α- and ß-traits, lead normal healthy lives. Those with moderate forms, such as thalassemia intermedia and haemoglobin H (Hb H) disease, are anaemic, but not transfusion-dependent—except during periods of stress or illness—and can expect to lead productive lives. The most severe forms are Cooley's anaemia (CA) which is a homozygous ß-thalassemia and haemoglobin Bart's hydrops foetalis (Hb Bart's) which is a homozygous α-thalassemia. With the former condition, affected individuals are totally transfusion-dependent throughout life and in the latter, death invariably occurs perinatally, at birth, or soon afterwards.

From the public health point of view, the two diseases that require prevention are CA and Hb Bart's; the former because of the immense burden on society and the family in caring for a transfusion-dependent patient, and the latter because of the futility in carrying to term a pregnancy which invariably results in stillbirth or early infant death, and which is frequently associated with maternal risks such as pre-eclampsia, antepartum haemorrhage, and placenta praevia.[2]

With the availability of population screening methods and the advent of molecular genetics in prenatal diagnosis, it is possible to drastically reduce the incidence of these two diseases, as has been done elsewhere.[3] However, at the Prince of Wales Hospital (PWH) in Hong Kong, these blood disorders still appear regularly, with no signs of a decline in incidence. We conducted a survey of these cases in order to determine the incidence of these two entities at PWH in recent years, the problems leading to their occurrence, and to develop a strategy for their prevention.

Subjects and methods

Patient selection

Our laboratory records were referred to and all cases diagnosed as CA and Hb Bart's between January 1987 and December 1993 were included. Typically, with CA, the diagnosis was made after the first year of life when the child became symptomatic of anaemia. Diagnosis

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was based on a profound microcytic, hypochromic blood picture with a haemoglobin pattern showing more than 95% foetal haemoglobin (Hb F) and no normal haemoglobin (Hb A). With Hb Bart's, the diagnosis was made at birth, based on a leucoerythroblastotic and microcytic hypochromic blood picture with a haemoglobin pattern comprising approximately 90% haemoglobin Bart's and the remainder haemoglobin Portland.[1]

The survey

Information required for the survey was obtained from antenatal records and delivery charts. Data extracted included the mother's age, when and where the first antenatal care was received, the history of previous pregnancies, complications associated with the pregnancy, and outcome.

Results

Table 1 shows the number of cases of CA and Hb Bart's seen between 1987 and 1993. There were very few cases of CA and the number of cases of Hb Bart's fluctuated over the years, but with no trend apparent. The number of births at the PWH did not vary significantly during this period (Table 1).

Antenatal and delivery records were available in 20 of the 33 cases of Hb Bart's but in none of the cases of CA. Table 2 profiles 20 of the mothers who gave birth to babies diagnosed as suffering from Hb Bart's. They were divided into four groups according to where they first received antenatal care.

Group 1 (15 cases) attended government Maternal and Child Health clinics (MCH). This group commenced their antenatal visits much later (mean = 19 weeks, range 13 to 25 weeks of gestation) than the optimal gestational age of less than 10 weeks for prenatal diagnosis. Those who attended private hospital antenatal clinics (group 2) were early in gestation, as was the one patient who attended PWH (group 4). The two mothers from China (group 3) received no antenatal care in Hong Kong.

The obstetrical history was indicative of past problematic pregnancies in six cases, but in none of the charts viewed was there any mention of thalassemia as a potential risk for the impending birth. At least 16 of the 20 mothers suffered from complications. Whether or not the two mothers from China had experienced complications could not be documented. The outcome of the pregnancies in all cases was similar in that they all ended in spontaneous or induced premature labour, and resulted in stillbirth or early infant death. Ultrasonography detecting hydrops was usually the first clue in the diagnosis of Hb Bart's.

Discussion

The strategy for prevention of thalassemic disorders has been fully discussed in the literature.[4] In this paper, we considered the extent of the problem locally, the available laboratory tests for identifying pregnancies at

Table 1. Number of cases of Cooley's anaemia and haemoglobin Bart's hydrops foetalis from 1987 to 1993 at the Prince of Wales Hospital

Year	Cooley's anaemia	Haemoglobin Bart's	Number of births
1987	0	4	6392
1988	1	2	7294
1989	1	7	7354
1990	1	3	8042
1991	1	8	7672
1992	1	5	7968
1993	0	4	8004
1987 - 93	5	33	52 726

Table 2. Profile of pregnancies ending in haemoglobin Bart's hydrops foetalis, 1987 - 1993

Case number	Age (yr)	1st antenatal visit (weeks of gestation)	Pregnancy history	Complication	Outcome
Group 1					
1	25	13	$G^2 P^0$ Two spontaneous abortion	Oligohydramnios	USG*: hydrops. Induced labour at 25 weeks, stillbirth
2	30	14	$G^1 P^0$ One spontaneous abortion	Pre-eclampsia	USG: hydrops. Induced labour at 27 weeks, stillbirth
3	32	25	$G^3 P^3$ Past pregnancies normal	None	Normal spontaneous delivery at 37 weeks, hydropic baby died soon after
4	26	20	$G^1 P^1$	Early labour	Spontaneous labour at 32 weeks, hydropic baby died soon after
5	24	18	$G^3 P^0$ Induced labour three times, circumstances unknown	Pre-eclampsia	USG: hydrops. Spontaneous labour at 25 weeks, stillbirth
6	18	25	$G^1 P^0$ One abortion	Transverse lie of foetus	Spontaneous labour at 25 weeks, stillbirth
7	30	13	$G^2 P^2$ Previous pregnancies normal	Pre-eclampsia	Spontaneous labour at 29 weeks, baby died soon after
8	31	13	$G^3 P^3$ Previous pregnancies normal	No foetal movements	Induced labour at 30 weeks, stillbirth
9	19	24	$G^2 P^1$ One abortion	Anaemia	Induced labour at 37 weeks, stillbirth
10	25	19	$G^2 P^2$	Anaemia	USG: hydrops. Induced labour at 34 weeks, stillbirth
11	33	22	$G^5 P^3$ One spontaneous abortion One intrauterine death at 30 weeks	No foetal movement	Induced labour at 27 weeks, stillbirth
12	28	20	$G^4 P^2$ Two abortions	Placenta praevia antepartum bleeding	Caesarian section at 25 weeks, stillbirth
13	26	22	$G^2 P^2$	None	Spontaneous labour at 37 weeks, baby died soon after
14	26	22	$G^1 P^1$	Pre-eclampsia	Spontaneous labour at 30 weeks, stillbirth
15	33	14	$G^2 P^1$ One abortion	None	Spontaneous labour at 37 weeks, stillbirth
Group 2					
16	29	4	$G^1 P^1$	Antepartum bleeding	Spontaneous labour at 29 weeks, baby died soon after
17	28	10	$G^1 P^1$	Pre-eclampsia	Induced labour at 30 weeks, baby died soon after
Group 3					
18	23	na	$G^2 P^1$	Unknown	Spontaneous labour at 36 weeks, hydropic baby died soon after
19	34	na	$G^4 P^3$ One stillbirth	Unknown	Spontaneous labour at 35 weeks, hydropic baby died soon after
Group 4					
20	29	10	$G^3 P^1$ Two spontaneous abortions	Antepartum bleeding	USG: hydrops. Induced labour at 30 weeks, baby died soon after

Group 1 attended Maternal and Child Health clinics
Group 2 attended private hospitals
Group 3 received no antenatal care in Hong Kong
Group 4 attended the Prince of Wales Hospital
USG Ultrasonography
na not applicable

risk, premarital education, and prenatal diagnosis.

The extent of the problem locally

The prevalence of ß-thalassemia minor in the general community is 4% and that of α-thalassemia-1 trait (the trait responsible for Hb Bart's) is 2.2%.[5,6] The number of pregnancies annually in Hong Kong is approximately 80 000. Using this data, it can be calculated that the number of pregnancies at risk for CA is 0.04 x 0.04 x 80 000 = 128 per year; and that for Hb Bart's is 0.022 x 0.022 x 80 000 = 38 per year. If these pregnancies are allowed to be carried to term, the Mendelian mode of inheritance dictates that the number of babies born in the homozygous state of each disease should be one-fourth of the pregnancies at risk, i.e. 32 annually for CA and 10 annually for Hb Bart's.

We found in our survey that the incidence far exceeded the expected number of Hb Bart's cases, considering that the PWH only services part of the Hong Kong population (New Territory East region). A similar disproportion has also been recorded at the Queen Mary Hospital, Hong Kong Island.[7]

Screening for at-risk pregnancies

Currently, the method used in Hong Kong to initially screen for thalassemia traits is mean cell volume (MCV), one of the red cell indices included in a complete blood count generated by electronic blood cell counters. Using a standard cutoff value (MCV < 80 fL), practically all thalassemic individuals can be identified. Confirmatory laboratory tests include haemoglobin A_2 and F levels, and identification of Hb H inclusions. Technological advances have yielded high performance liquid chromatography (HPLC), which we recently evaluated and found to be extremely efficient and reliable in identifying ß-thalassemia trait.[8] Alpha-thalassemia trait still requires the labour-intensive method of looking for Hb H inclusions in red cells preincubated in Brilliant Cresyl Blue. Better methods may be forthcoming, based on the detection of another gene product inherent to the disease—ζ-globin, measurable by immunological or chromatographical methods.[9,10] Another potentially useful method is by direct DNA analysis of the α-ζ-gene cluster using the polymerase chain reaction.[11]

In our survey, a retrospective examination of parental blood was performed after each baby had been diagnosed as hydropic. All parents showed microcytic, hypochromic red cells with low MCV. The thalassemia trait should have been detected in the mother by the routine antenatal complete blood count, and the potential risk would have been diagnosed had the father been tested as well. However, routine testing of all pregnant mothers for MCV (and for those with low MCV, their husbands as well) would involve a considerable increase in workload for the regional laboratories.

Premarital education

From our survey, it appeared that none of the mothers were aware of their potential risk. Many of them attended their first antenatal visit late in gestation, not knowing that prenatal diagnosis at nine weeks of gestation is both possible and preferable.

Currently, there is no citywide programme offering universal counselling and education to young women on the risks of bearing a child with severe thalassemic disorders. However, premarital counselling and education may not be successful in completely preventing thalassemia as many pregnancies are out of wedlock, making premarital counselling irrelevant.[12]

Prenatal diagnosis

As early as nine to 10 weeks of gestation, foetal cells obtained by chorionic villus sampling can be used for DNA analysis. For more advanced gestational age (18 weeks or beyond), one can use amniocentesis to harvest foetal fibroblasts for DNA analysis.[13] Prenatal diagnosis early in pregnancy is more desirable because some couples find it morally and emotionally more acceptable to undergo an abortion in the first trimester. A detailed account of the techniques involved with prenatal diagnosis is beyond the scope of this article. Suffice to say, α-thalassemia-1 in Hong Kong is of the Southeast Asia (SEA) type, involving a deletional mutation which can be detected by the Southern Blot technique.[13] Beta-thalassemia among Hong Kong Chinese is due to point mutations and their characterisation is more complicated. It involves a step-by-step approach which starts with restriction analysis and linkage to restriction fragment length polymorphisms (if another sibling is available for the study), or synthetic oligonucleotide hybridisation (if the specific probes are available). In inconclusive cases, foetal blood is obtained at 18 weeks of gestation or beyond for ß/γ-globin ratio analysis.[14] This approach has met with great success at the Queen Mary Hospital, and referral is open to all medical practitioners in Hong Kong.[7]

From this work we found that, contrary to expectations, the number of Hb Bart's cases far exceed those with CA. It is possible that some children with CA were delivered at the PWH but were subsequently treated elsewhere when they became symptomatic, and these could account for this discrepancy. A large-scale prevalence study of these two diseases seems

necessary to evaluate the true extent of the problem in the territory.

Of the pregnancies that resulted in Hb Bart's, it was found that all cases were unsuspected and undiagnosed prenatally until late in pregnancy, when complications called for ultrasonographic examination of the hydropic foetus. Currently available laboratory tests could have accurately predicted the risk, and cases prenatally confirmed to be either CA or Hb Bart's could have been aborted. The missing link appears to have been vigilance on the part of MCH doctors and obstetricians. Ignorance of the mothers also resulted in many of them delaying their first antenatal visit.

In the future, the following tactics may be considered for reducing the incidence of these two disorders. There should be an educational programme on the risk of thalassemia in pregnancy directed at women of childbearing age. This may not be effective in preventing at-risk pregnancies, but could alert many young women to the importance of early antenatal appointments.

The most direct and effective way to prevent affected births is by prenatal diagnosis. Universal screening of all pregnancies using red cell indices as diagnostic indicators, followed by the confirmatory tests mentioned above, will detect most if not all pregnancies at risk. There should be continuing training for both private and public hospital-based obstetricians and most of all, MCH doctors should be instructed on the proper use of laboratory tests to identify thalassemic risk in pregnancy. Doctors should be aware that they need to make the appropriate referral for prenatal diagnosis in a timely manner.

Such a public health endeavour will involve additional workload for public health laboratories, prenatal diagnostic centres, and genetic counselling services. Consequently, increased funding from the government to support this endeavour is urgently needed.

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