Why are thalassaemia patients born when prenatal screening is available?

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Thalassaemia major is a classic example of a disease that is preventable by prenatal diagnosis. Although the technology was introduced to Hong Kong more than a decade ago, new patients are continuously seen in the Hong Kong Special Administrative Region. This retrospective review concerns children who were diagnosed to have severe β-thalassaemic syndromes at the Tuen Mun Hospital from 1990 to 1996. Seventeen children (including a pair of identical twins) with homozygous β-thalassaemia and five children with double heterozygous β-E thalassaemia were identified. All except three children were transfusion-dependent. Thirty-six parents were available for the thalassaemic study. Thirty-one of them had β-thalassaemic traits and the other five were carriers of haemoglobin E. Two of the parents with β-thalassaemic traits and all five haemoglobin E carriers had a mean corpuscular volume above the cut-off for screening in antenatal diagnosis (>75 fL). Of the 21 at-risk pregnancies, seven were managed by public hospitals, 11 by maternal and child health centres, and two by private practitioners. Thalassaemia had not been diagnosed prenatally because of the lack of maternal screening (n=9), lack of paternal screening (n=3), late antenatal visit (n=7), and parental refusal (n=1). Thus, many of our patients are not benefiting from the availability of prenatal screening.

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Introduction

Thalassaemia major requires life-long blood transfusion and bears risks of transfusion haemosiderosis, but it is amenable to prenatal diagnosis.[1] The affected child appears to be normal at birth, when foetal haemoglobin ($\alpha_2\gamma_2$) is still the major component in the red blood cells. At around 6 months of age, the child becomes progressively anaemic because of the failure to produce adult haemoglobin ($\alpha_2\beta_2$). To sustain life and normal growth, the child must be given a blood transfusion at monthly intervals. In addition to the risks of infection, the child is also susceptible to iron deposition (haemosiderosis). Without adequate chelation therapy, transfusion haemosiderosis can lead to heart failure, cirrhosis, diabetes mellitus, or variable forms of endocrinopathies. Children with thalassaemia major receive continuous home treatment with desferrioxamine—an infusion that is given subcutaneously for at least 8 hours per day, 5 days or more per week, for the rest of the child's life. Consequently, patients and their families suffer tremendously in different ways.

A severely affected child may have inherited two β-thalassaemia alleles from his or her parents, or be double heterozygous for β-thalassaemia and haemoglobin E (HbE). By screening expectant couples for their thalassaemia status, we can identify at-risk pregnancies that carry a 25% chance of conceiving a severely affected foetus. Once confirmed, the at-risk pregnancy may be aborted therapeutically.[2]

The technology for prenatal screening and diagnosis has been available in Hong Kong since 1983,[3] yet new cases of thalassaemia major are being seen in the major public hospitals.[4] The reasons why thalassaemia is not

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Potential causes for failure of prenatal screening for thalassaemia

Parental factors
- Delayed first antenatal visit
- Parental refusal for prenatal diagnosis

Haematological factors
- Silent carrier
- MCV* above the cut-off value
- Co-existing iron deficiency anaemia

Gestational factor
- Complicated pregnancy

Diagnostic factors
- Failure to check MCV during antenatal visit
- Microcytosis mistaken as or solely ascribed to iron deficiency
- Laboratory error

*MCV mean corpuscular volume

always detected by screening vary from case to case (Box); these reasons have not been studied systematically. The Tuen Mun Hospital was opened in 1990, when prenatal screening was readily available. Because a substantial number of patients were diagnosed to have thalassaemia in our hospital, we wanted to review these patients to understand the reasons why they were not diagnosed before delivery.

Subjects and methods

All children who were diagnosed to be homozygous for the β-thalassaemic trait, or double heterozygous for β-thalassaemia and haemoglobin E (β-E thalassaemia) between January 1990 and June 1996 were included in a retrospective review. Patients' demographic data, transfusion status, and pattern of antenatal care were examined. The thalassaemic status of the parents, subject to their consent, were also evaluated when the children were diagnosed to have thalassaemia. The data, when available, were included in the analysis. An attempt was also made to identify the most direct cause for not establishing the prenatal diagnosis, by using the questioning scheme shown in the Figure.

Results

A total of 22 children from 21 pregnancies were identified. These included a pair of identical twins and two other pairs of siblings. There were 12 boys and 9 girls; their mean age at diagnosis was 1.9 years (range, 0.1-5.9 years). Seventeen (77%) of the children were homozygous for the β-thalassaemic trait. All 17 required regular transfusion therapy to sustain life and growth (ie they had thalassaemia major). The other five (23%) children had β-E thalassaemia; two of them were transfusion-dependent. The other three β-E thalassaemia patients required intermittent transfusions (less than six per year); splenectomy was contemplated for two of them.

The data on 36 (95%) of the 38 parents were available for study. Thirty-one had β-thalassaemic traits and 29 of these had mean corpuscular volumes (MCVs) below 75 fL. The MCVs of the other two parents were between 75 and 80 fL. Five parents were HbE carriers and had MCVs above 75 fL—one had an MCV of 83.3 fL. Four of the parents originated from provinces or countries other than Guangdong. They included three with β-thalassaemic traits who were from Guangxi, Jiangxi, and Indonesia, and one HbE carrier from Thailand.

The places of antenatal care for the affected pregnancies included public hospitals (n=7, 33%), maternal and child health centres (n=11, 52%), and private practitioners or private hospitals (n=2, 10%); the institution was unknown in one case (5%). The majority (85%) of the cases were thus managed by the public health sector. The most probable reasons for not performing antenatal diagnosis are listed in the Table. Except for one pair of parents, none received counselling for thalassaemia

Fig. A working algorithm to define the most likely cause of failure to establish prenatal diagnosis

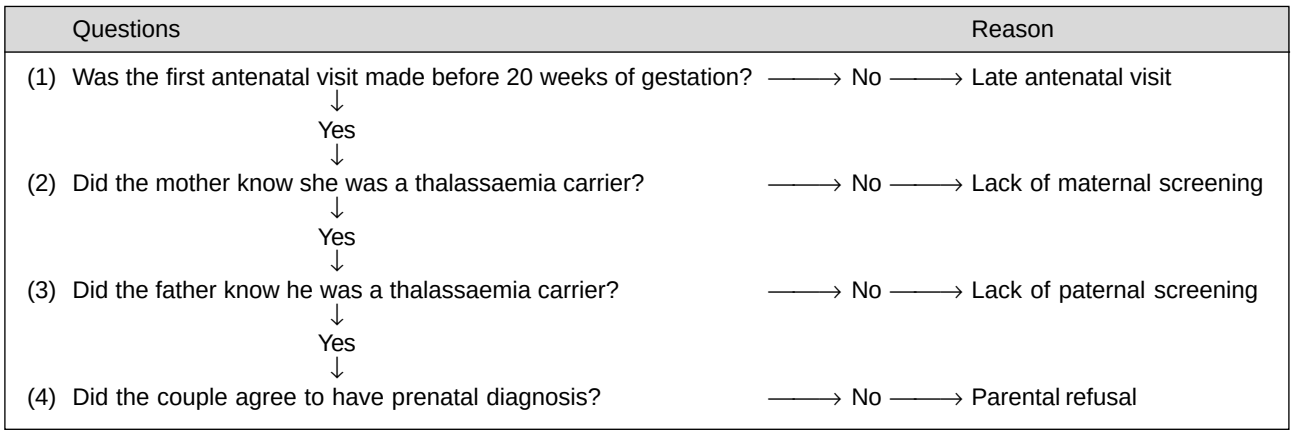

Table. Reasons why prenatal diagnosis was not performed

Factor	Cases, n=21 No. (%)
Lack of maternal screening	9 (43)
Lack of paternal screening	3 (14)
Late antenatal visit*	7 (33)†
Parental refusal	1 (5)
Unknown	1 (5)

* Defined as first antenatal visit beyond 20 weeks of gestation
† Includes two cross-border deliveries where the mother was resident in China

before confinement. When asked if they would opt for prenatal diagnosis in a subsequent pregnancy, all parents responded affirmatively.

Discussion

The thalassaemic syndromes represent the most commonly occurring single-gene disorder in the world. The treatment for thalassaemia major is palliative and expensive, and is notorious for its complications.[1] Although allogeneic bone marrow transplantation may be curative,[5] it is available only to a minority of patients, and the rejection rate appears to be high in non-Italian recipients.[6] Consequently, programmes on prenatal screening have been implemented in various regions of the world where the disorder is prevalent.[2] In Hong Kong, thalassaemia is one of the congenital diseases that are amenable to prenatal screening and diagnosis.[7]

Most programmes on prenatal screening start with the identification of the thalassaemia carriers.[2] Theoretically, screening may be targeted at the whole population, premarital couples, or expectant women. In Hong Kong, prenatal screening starts with the first antenatal visit and the approach has been shown to be technically feasible.[8] The pregnant woman is first tested for microcytosis (MCV <75 fL; the cut-off has been changed recently to 80 fL).[9] If the result is positive, the woman's partner will also be tested. If both parents are positive, they will be further tested for α-thalassaemia, β-thalassaemia, and iron deficiency anaemia. In the case where both parents are β-thalassaemia carriers, prenatal diagnosis can be accomplished by chorionic villi biopsy and molecular diagnosis in the first trimester of pregnancy. In the early second trimester, prenatal diagnosis can be achieved by foetal blood sampling, followed by molecular analysis and/or globin chain synthesis. In both trimesters, the sensitivity and specificity of the tests are high. The service is provided by the Prenatal Diagnosis Unit at the Tsan Yuk Hospital and is available for referral to all medical practitioners in Hong Kong.

The extent to which prenatal screening is practised in Hong Kong is unknown. Statistics from the major public hospitals show that the number of children with thalassaemia major has remained fairly constant for the past decade.[3] This suggests that prenatal screening is not widely practised in our locality. The lack of prenatal screening in at-risk pregnancies was shown in a recent study by Lau et al.[10] By screening school-aged children, they found that 3.4% of the 1800 subjects carried β-thalassaemia mutations. Based on an annual number of births of 70000, they estimated the annual number of pregnancies at risk for severe β-thalassaemia to be 80.[10] However, the corresponding numbers of prenatal screens performed during the years 1993, 1994, and 1995 were 45, 28, and 46, respectively. A significant proportion of the screens was for couples who previously had had affected offspring.

The findings of the present study provide some of the reasons why prenatal screening was not performed in a group of thalassaemic children living in the north-western New Territories. As therapeutic abortion is generally contra-indicated after the second trimester of pregnancy, women who received antenatal care late (33%) would not have benefited from prenatal screening. Even in these cases, screening may have been helpful in monitoring the newborn at risk and in further family planning. Nevertheless, more than half (57%) of the women who received antenatal care early in the pregnancy did not receive the appropriate screening. This, coupled with the fact that the majority of parents has not been counselled for thalassaemia, implies that prenatal screening has not been fully incorporated in the routine antenatal care programme of the public health sector in our region. The single pregnancy in which the parents refused prenatal diagnosis occurred in a family where there was a history of previously affected offspring.

The study also reveals an important pitfall in prenatal screening for thalassaemia. The cut-off MCV value of 75 fL used previously during antenatal screening may not be sensitive enough to detect all cases of β-thalassaemia (6% of the parents in this series would have been missed). It is certainly too low for detecting HbE carriers. An MCV of 80 fL would be more sensitive, but the cost-effectiveness and the anxiety aroused due to false positive cases must also be taken into consideration.

While reliable prenatal screening and diagnosis for thalassaemia is readily available in Hong Kong, it is clear that many families are not benefiting from this technological advancement. The problems, which

probably lie in public education and logistics of screening and referral, had been pointed out by Chan et al almost a decade ago.[3] The formal incorporation of screening during routine antenatal care is a pre-requisite for a successful screening programme. Public education is necessary to encourage early antenatal visits. Given that 8% (3% for the β-thalassaemic trait and 5% for α-thalassaemic trait) of the local population are carriers of some form of thalassaemia, it is desirable to launch some form of population screening.[10] The cost-effectiveness of such an approach awaits further evaluation.

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