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Brief Clinical Report

Homozygous Alpha-Thalassemia Associated With Hypospadias in Three Survivors

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We report three cases of homozygous α-thalassemia (αTH) who survived beyond the neonatal period, all with hypospadias. A review of literature identified two additional male cases of homozygous αTH who survived, and both had hypospadias. The simultaneous occurrence of the two conditions seems beyond coincidence and may be causally related. Possible pathogenesis for the association may be 1) homozygous αTH-induced in utero and/or edema secondary to hydrops fetalis, both leading to the failure of proper fusion of the urogenital folds, or 2) defect of another gene located at a chromosome 16p13.3 region. Thus, parents who request intrauterine therapy for a male fetus with homozygous αTH should be informed about this association and its prognosis. Am. J. Med. Genet. 82:225–227, 1999.

KEY WORDS: hypospadias; α-thalassemia; homozygosity; genital anomaly; contiguous genes

INTRODUCTION

The α hemoglobin locus contains two contiguous α chain genes, *HBA1* and *HBA2,* which are on chromosome 16 at band q13.3 [Liang et al., 1985]. Alpha thalassemia (αTH) results from either deletions or point mutations in the α chain genes. In South-East Asia (SEA), there are four classes of persons who have deletions of the genes: those with three intact alleles that are clinically silent; those with two normal alleles that are heterozygous αTH; those with one normal allele that have hemoglobin (Hb) H disease; and those with deletion of all 4 alleles (SEA-type deletion) who are called homozygous αTH.

The commonest cause of hydrops fetalis in South-East Asia is homozygous αTH. Affected fetuses usually die in utero during the third trimester or in the early neonatal period [Nakayama et al., 1986]. Association of congenital genital anomalies with homozygous αTH has been previously reported [Nakayama et al., 1986; Abuelo et al., 1997]. Nakayama et al. [1986] reported that 37.5% of autopsied male and female fetuses with homozygous αTH-related hydrops fetalis had genital anomalies, such as hypospadias, undescended testes, and ambiguous genitalia [Nakayama et al., 1986]. However, the prevalence of genital anomalies in patients with the disease may be underestimated, because the anomaly tends to be overlooked in grossly hydropic fetuses. A study of long-term survivors may provide an advantage in observing these anomalies. Here, we report three cases of homozygous αTH with hypospadias who survived the neonatal period.

CASE REPORTS

Patient 1

A boy weighing 1,400 g was delivered by Cesarean section at 29 weeks of gestation because of suspected intrauterine infection. At 22 weeks of gestation, the fetus was found to suffer from hydrops fetalis. The parents are αTH carriers, i.e., heterozygotes for SEA-type, as detected by polymerase chain reaction–based DNA analysis according to the method of Chang et al. [1991]. Fetal blood examinations (hemoglobin level, 9.6g/dl with 74% of hemoglobin Barts, and 26% of hemoglobin Portland) and DNA analysis confirmed that the patient had αTH with homozygous SEA-type deletions. Repeated intrauterine exchange transfusions were performed prenatally. After the delivery, there was no evidence of hydrops or anomalies other than glandular hypospadias. His karyotype was normal (46,XY). He is now 9 months old and waiting for bone marrow transplantation.

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Patient 2

This patient is a 12-year-old, mentally normal boy. He was delivered with a weight of 1,820 g at 34 weeks of gestation by Cesarean section because of prenatally diagnosed hydrops fetalis. The mother and father were known to have Hb H disease and αTH trait, respectively. Fetal blood examination at 30 weeks' gestation showed that the fetal hemoglobin level was only 3.7 g/dl; therefore intrauterine transfusion was performed. Molecular analysis of the fetus revealed SEA-type deletion of one chromosome 16, but no deletion was detected in the other chromosome. Thus, the fetus was a compound heterozygote for the deletion and an unidentified mutation which could produce an unstable α globin chain. After birth, he was found to have hypospadias, bifid scrotum, and bilateral undescended testes at the groin region. Chromosome analysis showed a 46,XY karyotype.

Patient 3

This patient is a 6-year-old mentally normal boy. He was diagnosed as suffering from hydrops fetalis at 34 weeks' gestation by ultrasonography. Fetal blood sampling confirmed the diagnosis of homozygous αTH (8 g/dl hemoglobin with 85% of hemoglobin Barts and 15% of hemoglobin Portland), and DNA analysis revealed that he was homozygous for SEA-type deletions. He was delivered vaginally at 35 weeks' gestation with a weight of 1,900 g. Immediately after birth, he required exchange transfusion for severe anemia, and was noted to have penoscrotal hypospadias without other abnormalities. His karyotype was 46,XY. Both parents had Hb H disease.

DISCUSSION

There have been, to our knowledge, only six phenotypical males with homozygous αTH, including three of our cases, who survived beyond the neonatal period [Beaudry et al., 1986; Carr et al., 1995; Westgren et al. 1996]. Of the six patients, five were karyotypically male and the other a karyotypical female (46,XX). All the karyotypical male patients had hypospadias (Table I). The prevalence of isolated hypospadias is estimated to be 0.26 to 2.11 per 1,000 births, although it varies geographically [Kallen et al., 1986]. The prevalence by perinatal statistics between 1991 and 1996 in our hospital (The Prince of Wales Hospital) gave a similar value of 0.41 per 1,000 births. In Hong Kong, prevalence of αTH carriers is estimated as 5% [Lau et al., 1997], and that of homozygous αTH patients is approximately 1 per 1,550 births [Liang et al., 1985]. The simultaneous occurrence of hypospadias and homozygous αTH by chance would be 0.2 to 1 per million births. Therefore, hypospadias in three karyotypically male patients in our series seems more than coincidental, and may be causally related to homozygous αTH.

The etiology of hypospadias is still unknown [Stoll et al., 1990]. Hypospadias results from a failure of either canalization of the glandular plate of fusion of the urogenital folds occurring between 11 to 16 weeks of gestation [Moore and Persaud, 1993]. Various mechanisms, such as severe anemia, vascular occlusion, or mechanical force, have been proposed to cause hypospadias [Abuelo et al., 1997]. Normally, erythropoiesis begins to shift to the production of Hb F ($\alpha 2\gamma 2$) at 9 to 10 weeks of gestation. In fetuses with homozygous αTH, this process does not occur, resulting in the production of Hb Barts ($\gamma 4$) which has much higher oxygen affinity but minimal oxygen delivery capacity. The failure of the shift could lead to tissue hypoxia, which potentially may affect organogenesis of the external genitalia during this period, i.e., hypospadias. Animal studies demonstrated that interruption of blood supply to the corpus spongiosum and urethra may also result in shortening of the corpus spongiosum [Kizilcan et al., 1994]. In addition, a vasoconstrictive effect by in utero exposure to cocaine has been known to increase the occurrence of hypospadias in humans [Battin et al., 1995].

All of the five male patients mentioned above had suffered from hydrops fetalis in their fetal lives, although its onset was unknown. Since hydropic changes may occur as early as 12 weeks of gestation [Lam et al., 1997], it is speculative that edema of the urogenital folds secondary to hydrops fetalis in early pregnancy may have impaired the fusion of the developing genital organ in the five reported patients with homozygous αTH. However, only 7% and 33% of αTH are repoted to show hydropic changes at 12 to 14 weeks and 17 to 18 weeks of gestation respectively [Lam et al., 1997]. Therefore the chance that all of the patients had hydrops in such an early gestation that led to hypospadias is relatively low.

TABLE I. Patient Characteristics of the Homozygous αTH Survivors Beyond the Neonatal Period

Author	Sex	Gestational age at delivery (weeks)	Hydrops fetalis	Hypospadias	Other abnormalities
Beaudry et al., 1986	Male	32	Yes	Yes	Cardiomegaly, pulmonary hypertension with right to left shunting, patent ductus arteriosus
Carr et al., 1995	Male	34	Yes	Yes	Right scrotal hypoplasia with an undescended right testicle, valgus of the right ankle, foreshortened left foot with only one distal phalanx and two metacarpal bones
Westgren et al., 1996	Male (46,XX)	37	No	Unknown	Hypotonia only
Our Patient 1	Male	29	Yes	Yes	Nil
Our Patient 2	Male	34	Yes	Yes	Bifid scrotum, undescended testes
Our Patient 3	Male	35	Yes	Yes	Nil

Alternatively, hypospadias might be explained by a defect in one or more genes that may control genital development. Wilkie et al. [1990] found deletions involving a 16p13.3 region in eight patients with αTH/mental retardation syndrome. Among them, two patients had genital abnormalities and chromosomal rearrangements (one with undescended testes and a 46,XY,der(16),t(1;16)(p36.3;p13.3) karyotype and the other with hypospadias/undescended testes and a de novo 46,XY,del(16)(p13.3) karyotype), while another patient with a normal karyotype had no genital abnormality. These findings may support the existence of a gene or genes at the 16p13.3 region that may affect genital development. If the five homozygous αTH survivors had deletions that extend beyond the α globin gene cluster to encompass such a gene or genes, hypospadias could be explained by contiguous gene deficiency. Four of the five patients had homozygous SEA deletions which would involve at least the α_1, α_2, $\psi\alpha_1$, $\psi\alpha_2$, and θ1 globin genes [Fischel-Ghodsian and Higgs, 1986]. The $\psi\alpha_1$ gene and $\psi\alpha_2$ gene are believed to be nonfunctioning genes [Whitelaw et al., 1983; Hardison et al., 1986]. Although the θ1 globin gene is believed to be functional [Shaw et al., 1987], its role is still unknown [Clegg, 1987]. The homozygous deletion of the θ1 globin gene in a girl has been reported to cause no phenotypical abnormalities. [Fischel-Ghodsian and Higgs, 1986]. However, in boys, its role is still unknown. Thus, the θ1 globin gene may be a candidate gene for the development of male genitalia.

Apart from the possibility of deletion within the SEA deletion, there are also a possibility that the genes nearby may be involved. From the proximal end of the SEA deletion, there is the ψζ1 gene which is considered to be a pseudozeta gene [Proudfoot and Maniatis, 1982], while from the distal end of the SEA deletion are the Alu-family repeats, and no other particular gene has been identified [Nicholls et al., 1987]. Further analysis, especially mapping of deletion breakpoints, may be useful if there are cases of homozygous αTH caused by deletions other than SEA deletions.

In conclusion, hypospadias is a common feature of male babies with homozygous αTH who survive the neonatal period. Thus, parents who request therapy with intrauterine blood transfusion for a male fetus should be informed about this association and its prognosis.

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