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Case Report

A JAPANESE PATIENT WITH X-LINKED α-THALASSEMIA/MENTAL RETARDATION SYNDROME: AN ADDITIONAL CASE REPORT

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Summary X-linked α-thalassemia/mental retardation syndrome (ATR-X) is characterized by severe mental retardation, wide range of minor abnormalities, and association with an unusual form of α-thalassemia. Fifty patients in Caucasian origin have been reported. This is the second report of the syndrome demonstrated in Oriental patients.
Key Words X-linked α-thalassemia/mental retardation syndrome (ATR-X), HbH inclusions

INTRODUCTION

In 1981 Weatherall *et al.* (1981) described three males with severe mental retardation and hemoglobin H disease. In 1991 Gibbons *et al.* (1991) defined a new, X-linked form of mental retardation in 16 individuals with characteristic dysmorphic features and α-thalassemia (ATR-X). XH2, the gene for the disorder, mapped to Xq13, was recently identified (Gibbons *et al.*, 1995a). To date there have been 50 published cases from 28 unrelated families in Caucasian origin and from clinical observations a well-defined phenotype has emerged (Lefort *et al.*, 1993; Gibbons *et al.*, 1995b). Here we report an additional patient with the ATR-X in Oriental origin next to our previous report (Kurosawa *et al.*, 1996).

CLINICAL REPORT

The patient was born as the second child to non-consanguineous healthy

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Japanese parents. Pregnancy was complicated by severe edema from 34 weeks. He was born at 39 weeks after breech presentation with apgar scores 3 at 1 min and 5 at 5 min. Birth weight, length, and head circumference were 3,015 g, 47 cm, 32 cm respectively. Because of marked floppiness and apneic spells, he was transferred to the neonatal unit and was ventilated for 7 days. An atrial septal defect with patent ductus arteriosus, hypotonus, and poor feeding was documented. Global developmental delay ensued. At the age of 2 years 4 months, head control and rolling over was achieved but incompletely. His comprehension was very poor, but he was aware of his parents. He had no speech and no bowel or bladder control. His psychomotor development was below that of 6-month-old. Constipation and recurrent blepharitis are major problems in his management. There has been no episode of convulsion or recurrent vomiting.

His dysmorphic features included a triangular nose with upturned nares, a broad nasal bridge, and nasal alae extending lower than the columella and septum (Fig. 1). The mouth was carp-shaped with full lower lip. Teeth were widely spaced and small. The antihelici of the ears were prominent. Scoliosis and sacral dimple was noted. External genitalia showed normal male pattern with descending testes. Digits were flexionally contractured. His karyotype was 46,XY.

The phenotypic similarity to ATR-X, in particular the severity of intellectual handicap, prompted more extensive hematological examination. He had mild hypochromic, microcytic anemia (Hb 12.6 g/dl; MCV 80.6 fl; MCH 25.2 pg; MCHC 31.3%). HbH inclusions seen on staining with brilliant cresyl blue (BCB) were 0.1% of red blood cells. Further examination of carrier status of his mother was rejected.

DISCUSSION

The hallmarks of the X-linked α-thalassemia/mental retardation (ATR-X)

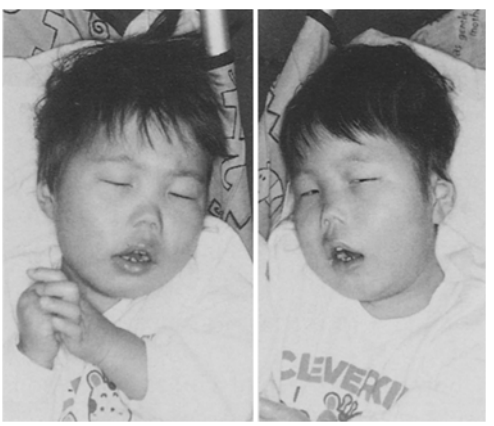

Fig. 1. Patient at age 2 years 4 months.

syndrome are severe psychomotor retardation, minor facial anomalies, genital abnormalities, and an unusual form of α-thalassemia. Although the component parts of this facial dysmorphism are rather nonspecific, the final appearance is strikingly uniform (Wilkie *et al.*, 1990). The demonstration of HbH inclusions in red blood cells after incubation with 1% brilliant cresyl blue confirms the diagnosis. The proportion of cells with HbH inclusions also varies widely from 0.01% to 12.2% (Gibbons *et al.*, 1995b). In the case of high index of suspicion from the family history and phenotype, a careful search for HbH inclusions should be made and repeated.

Fifty cases from 28 unrelated families have been reported (Table 1). All the families are of Caucasian origin (Lefort *et al.*, 1993; Gibbons *et al.*, 1995b). Our present case is the second in Oriental origin next to our previous report (Kurosawa *et al.*, 1996). Both cases are sporadic ones. Further studies are necessary to elucidate the prevalence of the syndrome among mentally retarded individuals.

XH2/XNP, the gene for the ATR-X, encoding a putative DNA helicase, was recently cloned (Stayton *et al.*, 1994; Gibbons *et al.*, 1995a). With single-strand conformation polymorphism analysis on cDNAs from 24 ATR-X patients, muta-

Table 1. Clinical findings in our present case, compared to those from the literatures (Lefort *et al.*, 1993; Gibbons *et al.*, 1995b; Kurosawa *et al.*, 1996).

Findings	Present case	Kurosawa *et al.*	Lefort *et al.* & Gibbons *et al.*
Facial anomalies			
Telecanthus	+	+	11/28
Epicanthic fold	+	+	38/45
Flat nasal bridge	+	+	35/48
Mid-face hypoplasia	+	+	37/42
Small triangular nose	+	+	42/48
Anteverted nares	+	+	42/47
Triangular mouth	+	+	42/43
Wide spaced incisors	+	+	15/23
Abnormal ears	+	+	34/44
Genital abnormalities			
Cryptorchidism	−	+	32/46
Hypospadias	−	−	9/48
Skeletal abnormalities			
Brachydactyly	+	+	7/47
Fixed flexion deformity	+	+	15/45
Kyphosis/scoliosis	+	+	22/47
Miscellaneous abnormalities			
Cardiac defect	+	−	9/49
Vomiting/reflux	−	+	28/49
Constipation	+	+	14/46
Recurrent chest infection	−	−	11/24
Blepharitis/conjunctivitis	+	+	4/16
Aberrant behavior	−	+	11/13

tions in nine pedigrees (7 for missense mutations, 2 for premature in-frame stop mutations) were detected (Gibbons *et al.*, 1995a). In addition, two mutation reports, one is a splicing mutation of the gene XNP in a dysmorphic mental retardation patient without α-thalassemia (Villard *et al.*, 1996a), and the other is a point mutation of the gene in a large family with Juberg-Marsidi syndrome (Villard *et al.*, 1996b), were presented. The complex ATR-X phenotype suggests that the gene, XH2/XNP, regulates the expression of several genes including the α-globin genes indicating that it could be a global transcriptional regulator. Thus, other dysmorphic mental retardation, which are linked to the Xq12-q21 region, could be due to mutations in XH2/XNP.

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