Dysmyelination of the Cerebral White matter with Microdeletion at 6p25

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A 6-year old boy presented with mental retardation, hypotonia, abnormal facies, impaired hearing, protuberant eyes, visual impairment, short stature, Axenfeld-Rieger anomaly, a bicuspid aortic valve, and bilateral sensorineural deafness. CT scan of head suggested dysmyelination of the subcortical and periventricular white matter. FISH revealed a subtelomeric microdeletion encompassing both FOXC1 and FOXF2 loci within 6p25. Dysmyelination of the central nervous system has been infrequently described earlier in patients with 6p25 deletion.

Key words: *6p25 microdeletion, Axenfeld-Rieger anomaly, Dysmyelination.*

Axenfeld-Rieger anomaly (ARA) is a spectrum of developmental anomalies of the anterior chamber of the eye that predispose to glaucoma in childhood. Axenfeld-Rieger syndrome (ARS) encompasses Axenfeld (anterior segment defect) and Rieger anomaly (anterior segment with iris defects) with systemic manifestations, including Rieger syndrome (ocular abnormalities, umbilical hernia and dental anomalies) and a variety of multiple congenital anomaly syndromes [1]. ARS is genetically heterogenous but an increasingly recognized cause of ARS is 6p deletion, which gives rise to an identifiable pattern of malformations, characterized by AR anomaly, sensorineural hearing loss, cardiac, cerebral and craniofacial anomalies [2-4]. Dysmyelination of the white matter has been infrequently described with ARS [3, 4].

CASE REPORT

A six-year old, the third child of healthy unrelated parents and born at term following an uncomplicated pregnancy. Immediate postnatal complications or feeding difficulty, had delayed acquisition of developmental milestones, particularly in the domains of gross motor and language. He presented with progressive deterioration of vision, hearing impairment, proportionate short stature and mental retardation. There was history of delayed descent of both testes noticed at 5 years. His parents were of average intelligence, normal stature and had no ocular or facial abnormalities.

On examination, he had proportionate short stature (100 cm, 3-4 SD below 50th centile), weight of 15 kg, and a head circumference of 50 cm. The child had a broad, high forehead, shallow orbits, proptosis, hypertelorism, down-slanting palpebral fissures, a flat nasal bridge, a short upturned nose, maxillary hypoplasia, a long featureless philtrum, thin upper vermillion border, open mouth and protuberant tongue (***Fig.* 1**). Generalized joint laxity was present. The umbilicus and external genitalia were normal. There was a grade III ejection systolic murmur at the aortic area that radiated to the neck. Central nervous system examination revealed hypotonia with normal reflexes with normal muscle power. The cranial nerve examination was normal with no cerebellar signs. He walked with a slightly broad based gait. The intelligence quotient (IQ) was 45 (WISC scale).

Slit lamp examination showed bilateral posterior embryotoxon. In the right eye, there was corectopia, pseudopolycoria (full-thickness colobomas of the iris which may appear to be multiple pupils) and generalized extensive areas of iris stromal hypoplasia with normal corneal clarity (***Fig.* 2*a***). The left cornea was hazy with a central opacity and severe edema with epithelial bullae (**Fig. 2*b***). Corectopia was identified but delineation of anterior chamber was limited by the degree of opacity. The

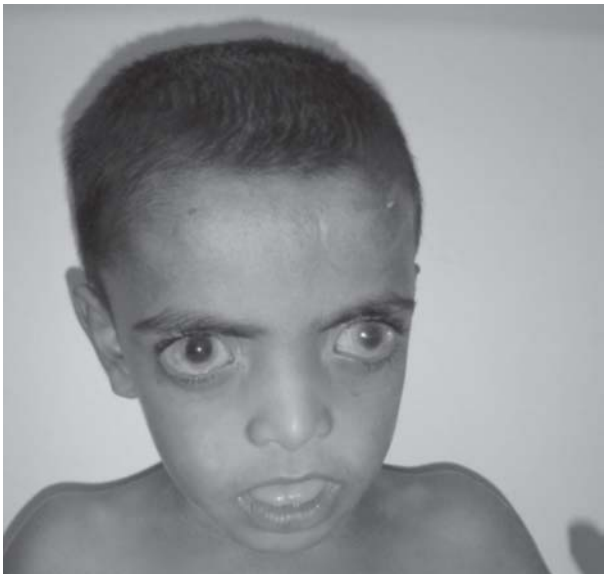


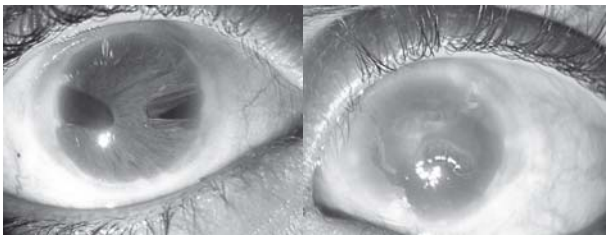
FIG. 1 *Photograph of the child showing hypertelorism, featureless philthrum, and open mouth.*

right and left intraocular tension was 26 mm Hg and 30 mm Hg, respectively. Visual acuity was 20/200 on the right with only hand movements close to face detected with the left eye. Radioimaging of the skeletal system revealed generalized osteopenia. The spine and skull were normal. The thyroid function tests were normal. Echocardiography revealed a mildly stenotic bicuspid aortic valve. The CT scan of the brain revealed dysmyelination of the subcortical and periventricular white matter. Renal ultrasound was normal. The BERA demonstrated bilateral moderate sensorineural deafness.

A high resolution (550 band) GTL karyotype from peripheral lymphocytes was 46, XY, with a normal banding pattern. FISH analysis was performed using Clone dJ668J24(FOXF2) and Clone dJ118B18(FOXC1), both of which hybridize to 6p subtelomere (Vysis, Des Plaines, IL) demonstrating deletion of both these p-arm sub-telomere loci, from one homologue of chromosome 6. This deletion extended proximally, to include the FOXC1 and FOXF2 loci within 6p25. No copies of the deleted loci were found on any other elements of the karyotype. The conventional karyotype of the parents were normal; FISH analysis could not be performed for economic reasons.

DISCUSSION

Fifteen mutations have been identified in the FOXC1 gene to date. Mutations in FOXF2 and FOXQ1 have also been reported. FOXF2 is expressed in the anterior segment of the eye, inner ear and pia mater indicating that it may contribute to the ocular, auditory and neurological



(*a*) (*b*)

FIG.2 *Right eye showing corectopia(a) and left eye showing hazy cornea with a central corneal opacity and severe corneal edema with epithelial bullae (b).*

phenotypes of this syndrome [5]. Lehmann, *et al*. [6] detected both interstitial duplications and deletions of 6p25 in Axenfeld-Rieger syndrome. All the rearrangements encompassed FOXC1. The consistent findings in the 6p25 deletions are developmental delay/mental retardation, hypotonia, craniofacial, ophthalmologic and cardiac anomalies. Genital, palatal, skeletal (clinodactyly), and central nervous system (CNS) manifestations are more variable. The CNS anomalies which have been reported are hydrocephalus, pachygyria, cavum septum pellucidum and hypoplasia of the cerebellum, brainstem, and corpus callosum.

The Axenfeld-Rieger malformation is seen in several other syndromes. Moog, *et al.*[7] reported two sisters who presented with Axenfeld-Rieger anomaly, hydrocephalus, leptomeningeal calcifications and mild mental retardation. Another entity with Reiger anomaly is SHORT syndrome [8].

Variable developmental defects have been reported from near normal cognition to severe developmental delay. Dysmyelination of the periventricular white matter has been infrequently reported and adds to the causes of delay seen in 6p25 phenotype, and may explain the developmental delay seen in our case. Recent studies in mice have reported the role of FOXC1 gene in cortical development in which hypomorphic mutations affect all the three meningeal layers with severe consequences in the development of the skull and underlying brain tissue, thereby explaining the cortical dysgenesis seen in our case. Since the breakpoint encompasses this gene the phenotype can be explained [9].

The constellation of clinical features reported and a distinctive phenotype should prompt the clinician to investigate for a 6p25 deletion. Submicroscopic 6p deletion appears to be a recognizable clinical phenotype, and this region should be thoroughly investigated with FISH probes, including at least a subtelomeric 6p probe and a probe covering FOXC1, for patients presenting

with these features.

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Satoyoshi Syndrome

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Satoyoshi syndrome is a rare autoimmune disease characterized by alopecia, painful muscle spasms, diarrhea and secondary skeletal changes. We report a 11-year old girl presenting with the typical features of alopecia totalis, severe muscle spasm and skeletal deformities.

Key words : *Alopecia, India, Muscle spasm, Skeletal deformity.*

Satoyoshi syndrome was first described by Satoyoshi and Yamada in 1967. It is common in Japanese population where it's colloquial name is *komura-gaeri* disease (komura implying *calf* and gaeri implying *spasm*) [1]. Our patient presented with the classical features of alopecia totalis, painful muscle spasms and skeletal anomalies but did not show any evidence of endocrinopathy.

CASE REPORT

This 11 year old girl, presented with progressively increasing alopecia for last 5 years and painful recurrent muscle spasms for last 3 months. These intense, painful muscle spasms often occurred in the thigh, neck, around the knees, and occasionally jaw spasms, and abdominal spasms simulating a visible ill-defined swelling over