Short Syndrome-An Expanding Phenotype

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The phenotypic description of SHORT syndrome (OMIM- 269880) is expanding since its initial description in 1975. There have been 26 case reports till date but the genetic locus of this syndrome is elusive. Involvement of PITX2 gene initially envisaged is probably is not the only gene involved but has an important role to play in ocular development. Our case did not demonstrate mutation in PITX2 gene. Here, we report a case of SHORT syndrome with two new unreported features – deviated nasal septum and cryptorchidism and stress on lipodystrophy, a cardinal feature but not a part of the pneumonic SHORT.

Key words: *SHORT Syndrome.*

SHORT syndrome (OMIM-269880) is an acronym consisting of following clinical features: S- short stature; H- hyperextensibility of joints/ hernia (inguinal); O-ocular depression; R-rieger anomaly; and T-teething delay. The most consistent finding, lipodystrophy of face and upper trunk, was first reported in 1975 [1]. The phenotype has been expanding since then.There have been a total of 26 case reports in English literature till date. Autosomal dominant inheritance has been proposed [2]. Locus of the gene has not yet been delineated. A recent study had shown that this may be a contiguous gene deletion syndrome requiring deletion of 1 or more other genes in addition to BMP4 [3].We report an adolescent with features of lipodystrophy, short stature, ocular depression, megalocornea, iris hypoplasia with previously two unreported features of deviated nasal septum (DNS) and bilateral cryptorchid testis.

CASE REPORT

A 14-year-old boy, product of consanguineous marriage was referred for work-up of short stature and associated dysmorphology. He was born as full term normal vaginal delivery at home, and was small at birth. At 3 years of age, he was evaluated for bilateral undescended testis. He underwent exploratory laprotomy with right orchidopexy and left incomplete orchidopexy with plan to follow up for second stage left complete orchidopexy later. At 11 years, left testis was found to atrectic and, left testicular implant was placed in scrotum. Surgeons noticed obvious short stature and dysmorphology and referred the case. Child was proportionately short with a height of 124 cm (<3rd centile as per WHO growth charts) and US/LS ratio of 0.9. Bone age and height age were 10-12 years (by Guerlich and Pyle method) and 7.5 years, respectively. Evaluation revealed thin built with progeroid facies with loss of subcutaneous fat mainly in face, trunk and shoulders, maxillary hypoplasia and dimpled chin (***Fig.*1**). His development had been normal but punctuated by delay in acquisition of speech. Ophthalmic evaluation revealed pseudoenopthalmos, megalocornea,

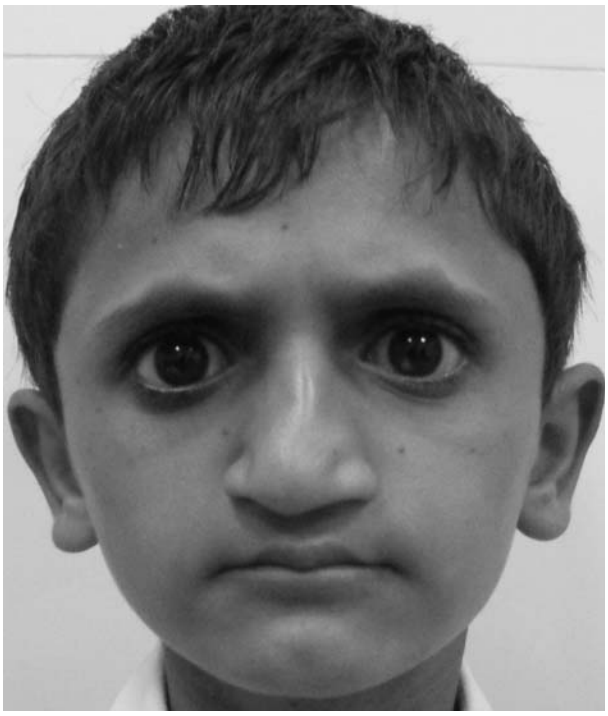
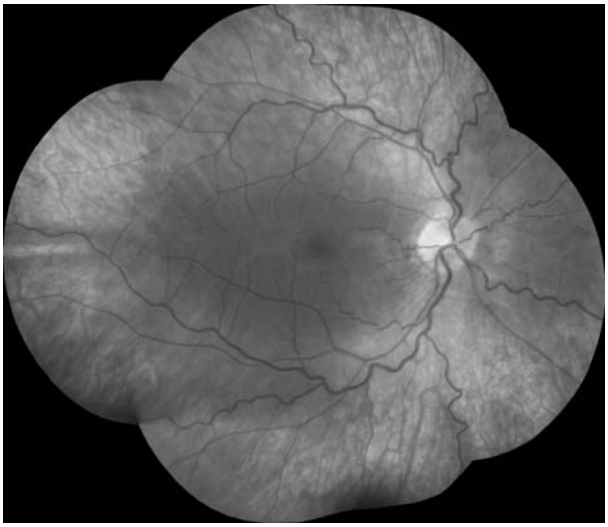


FIG. 1 *Shows loss of subcutaneous fat in face, megalocornea and deviated nasal septum.*



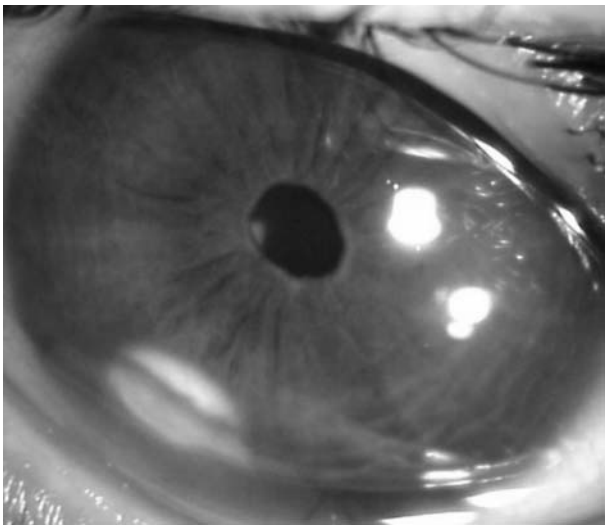


FIG. 2 *(a) Fundus showing disc pallor and venous tortousity. (b) Eyes showing sphincteric atrophy and iris hypoplasia.*

iris hypoplasia, sphincteric atrophy, venous tortousity with disc pallor (***Fig* 2**). There was no glaucoma or cataract. There was marked deviation of nasal septum to left side with secondary hypertrophy of turbinates. Secondary delay in eruption of permanent teeth was present. Rest of the systemic examination was not contributory.

Growth hormone stimulation tests, tests for thyroid function, hormones of pituitary axis and calcium homeostasis were in normal range. Sonographic examination of renal system revealed no pathology. Echocardiography, brain stem auditory evoked response and neuroimaging of brain were normal. The mother was a nondiabetic with normal insulin and HbA1C levels. The levels of glucose, insulin and HbA1C were normal in the proband but were not done in the father. Comparative array genomic hybridization was done on genomic DNA using Illumina Human CytoSNP. This test did not reveal any deletion or duplication of known pathogenic loci. There was no mutation in the *PITX2* gene either.

DISCUSSION

This case has all described features of acronym SHORT except hyperextensibility/hernia, which is not a consistent feature of this syndrome [2]. Joint hyperextensibility was found in only 35% of cases. Few cases of inguinal hernia have been reported [4,5]. The frequency of reported features mentioned in acronym SHORT has been reported as-Short stature (70%), Hyperextensibility (35%), Ocular depression (100%), Rieger anomaly (77%), and Teething delay (94%), [2]. Frequencies of other common features but not part of acronym SHORT in decreasing order of their occurrence are-lack of subcutaneous fat/very thin (100%), abnormal ears (95%), hypoplastic alae nasi (94%), normal intellect (90%), delayed bone age (82%), triangular face (80%), megalocornea (64%), micrognathia (65%). Clinical phenotype frequency suggest, that lipodystrophy and ocular depression are two unique and cardinal features present in all patients. Our patient also expressed this consistent phenotype besides two new previously unreported features viz., deviated nasal septum and bilateral cryptorchid testis.

Lipodystrophy is manifested mostly by lack of subcutaneous fat in face, chest and upper extremities, relatively sparing the legs. Lipodystrophy is not progressive, but seems to become apparent with age. Taken together, the predominant feature in SHORT syndrome is the lipodystrophy rather than short stature. Unfortunately, this cardinal feature is not mentioned in the mnemonic SHORT.

Autosomal dominant inheritance has been suggested but genetic basis of SHORT syndrome is currently poorly understood. Both autosomal dominant inheritance described by Gorlin, *et al*. [1] and autosomal recessive described by Sensenbrenner, *et al*. [4] have been postulated. Our case could be autosomal recessive as was born to consanguineous parents or could be sporadic [2]. A familial translocation t(1;4) (q31.2;q25) was identified, presumably disrupting the PITX2 locus, in a child with SHORT syndrome and his mother with Axenfeld-Rieger syndrome and polycystic ovary syndrome but the family demonstrated occurrence of both Reiger syndrome and insulin resistance[6].Our case did not demonstrate the insulin resistance and array was

not contributory in our case.

BMP4 loss of function mutations have been described in patients with SHORT syndrome, Axenfeld-Rieger malformation, growth delay, macrocephaly, and diaphragmatic hernia. The authors postulated the critical role of this in ocular development. Studies in animal models have shown that Bmp4 and Pitx2 act in a common pathway in craniofacial/dental and left-right asymmetry development [3]. However, the definite locus of SHORT syndrome gene still remains illusive.

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REFERENCES

1. Sensenbrenner JA, Hussels IE, Levin LS. A low birthweight syndrome,? Rieger syndrome. Birth Defects Orig Art Ser. 1975; 11:423-6.
2. Koenig R, Brendel L, Fuchs S. SHORT syndrome. Clin. Dysmorphol. 2003;12:45-9.
3. Reis LM, Tyler RC, Schilter KF, Abdul-Rahman O, Innis JW, Kozel BA, *et al* . BMP4 loss-of-function mutations in developmental eye disorders including SHORT syndrome. Hum Genet. 2011;130:495-504.
4. Gorlin RJ. A selected miscellany. Birth Defects Orig Art Ser. 1975;11:46-8.
5. Aarskog D, Ose L, Pande H, Eide N. Autosomal dominant partial lipodystrophy associated with Rieger anomaly, short stature, and insulinopenic diabetes. Am J Med Genet.1983;15:29-38.
6. Karadeniz NN, Kocak-Midillioglu I, Erdogan D, Bökesoy I.Is SHORT syndrome another phenotypic variation of PITX2? Am J Med Genet. 2004;130A:406-9.

Apparent Mineralocorticoid Excess (AME) Syndrome

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Apparent mineralocorticoid excess (AME) syndrome is a rare autosomal recessive disorder due to the deficiency of 11β hydroxysteroid dehydrogenase type 2 enzyme (11beta-HSD2). Mutations in this gene affect the enzymatic activity resulting to an excess of cortisol, which causes its inappropriate access to mineralocorticoid receptor leading to inherited hypertension.This is a potentially fatal but treatable disorder. We present clinical and molecular studies on two sisters diagnosed as AME.

Key words: *Hypertension,11β hydroxysteroid dehydrogenase type2 enzyme, Mutation.*

The syndrome of apparent mineralocorticoid excess (AME) arises from non-functional mutations in 11β hydroxysteroid dehydrogenase type2 enzyme (11beta-HSD2), an enzyme that inactivates cortisol and confers aldosterone specificity on the mineralocorticoid receptor. The imapaired conversion of cortisol (compound F) to cortisone (compound E) has been associated with low renin, low aldosterone hypertension with hypokalemia in children. The hypertension in the syndrome is presumed to arise from volume expansion secondary to renal sodium retention. This disorder is potentially fatal but treatable and hence early diagnosis is required to prevent the mortality.

CASE REPORT

Case-1: A one year old Kuwaiti girl, product of a consanguineous marriage; delivered by LSCS; IUGR with birthweight of 1.7 kg was admitted to our hospital with the history of polyuria and polydypsia for one week duration. On examination, the child's weight and height were both below 3rd centile. Her blood pressure was high (130/88 mmHg) at the time of admission. She had marked dystrophic squint and other systemic examination was unremarkable. Biochemical findings indicated hypokalemia with metabolic alkalosis. With this clinical and biochemical presentation Bartter syndrome was suspected, but the patient was further investigated to rule out other possibilities. Her plasma renin activity was low (<0.2 pmol/L/mL/h); serum aldosterone was low (<75 pmol/L); low serum renin and aldosterone level were against the diagnosis of Bartter syndrome. Chromatographic determination of urinary steroid