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# Case Reports

## Down syndrome with Disorder of Sex development (DSD): A Rare Presentation

FARZANA SHARMIN[1], SURAIYA BEGUM[2], ISMAT JAHAN[1], ROKSANA PARVIN[1], DHIRAJ CHANDRA BISWAS[1]

**Abstract:**
*Down syndrome is the most common genetic disorder among live born infants, which is associated with a number of congenital malformations and requires a huge medical and social cost. Here, we report a very rare association in an infant with Down syndrome and XY disorder of sex development (DSD).*

**Introduction:**
Down syndrome is the most familiar chromosomal abnormality occurring at a frequency of about 1/800 live births.[1] It has more genetic complexity and phenotypic variability.[2] Disorder of sex development poses as a social emergency for both family and health care professionals during decision making for sex assignment.[3]

**Case Report:**
Alif, 4 months old infant, 5th issue of non - consanguineous parents, presented with atypical genitalia since birth. The child did not have any history of vomiting, convulsion or unconsciousness. There was no significant event at neonatal period. Mother's age was 38 years. On examination- the infant had facial dysmorphism like flat nasal bridge, upward slanting of palpebral fissure, epicanthic fold, low set ears. The infant also had broad and short hand with clinodactyly, simian crease, wide sandal gap. There was no dehydration and abnormal skin pigmentation. Weight was 5.2kg (just below 3rd centile), length was 60 cm (on 5th centile), OFC was 39 cm (below 3rd centile, Z score was - 2.4),weight for length in between 10th and 25th centile. The length of his phallus was a 1.5 cm (>- 2.5 SD), glans was not well formed, no pit at tip, urethral opening was at perineum, scrotum was bifid, both testes were palpable at scrotum and size of each testis was 2ml. The child had a systolic murmur along left upper sternal edge and he was hypotonic and had global developmental delay.

**Fig.-1:** *Typical facial features of Down syndrome*

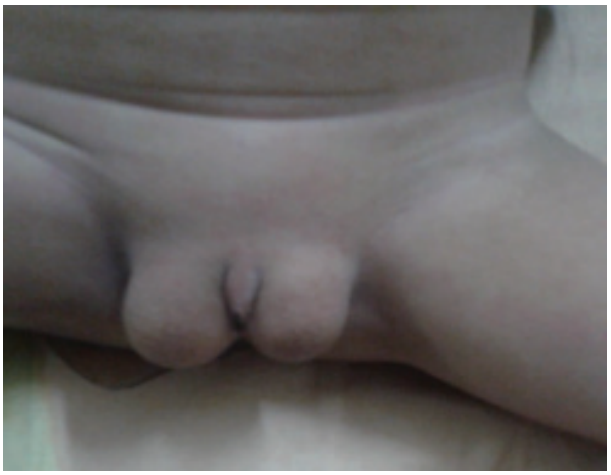

**Fig.-2:** *Bifid scrotum with palpable gonads and micropenis*

1. Phase B, Resident, General paediatrics, Bangabandhu Sheikh Mujib Medical University.
2. Professor, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University.

**Correspondence:** Dr. Farzana Sharmin, Phase B, Resident, Department of General paediatrics, Bangabandhu Sheikh Mujib Medical University. Mob.01681825433, email: sharminfarzana 348@gmail.com

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**Table-I**

*His laboratory evaluations were summarized*

| Tests | Result | Normal values |
|---|---|---|
| Serum Electrolytes | | |
| Serum Sodium | 135 mmol/L | 135-145 mmol/l |
| Serum Potassium | 4.2 mmol/L | 3.5-5.1 mmol/l |
| Serum Chloride | 105 mmol/L | 95-107 mmol/l |
| Serum Tco2 | 24 mmol/L | 22-30mmol/l |
| Random blood sugar | 5.8 mmol/L | 3.5-6.0 mmol/L |
| Basal Cortisol | 170nmol/L | 138-690nmol/L |
| Basal ACTH | 20.50 pg/mL | Not detectable to 46 pg/ml |
| DHEA-S | 15 ug/dl | 13-83ug/dl |
| 17 -OHP | 66 ng/dl | 3-90ng/dl |
| Serum Testosterone | 0.23nmol/l | <0.1-0.35 nmol/l |
| FSH | 0.09 U/L | 0.02- 0.3 U/L |
| LH | 1.2 U/L | 0.26- 3 U/L |
| **TSH** | **11.76 mIU/L** | 0.47- 5.01mIU/L |
| FT4 | 3.87 pmol/L | 9-19.05 pmol/L |
| **Anti Thyroglobulin Ab** | **121.2 IU/ml** | Upto 40 IU/mL |
| Anti Thyroid peroxidase Ab | < 10 IU/mL | Upto 35 IU/mL |
| Echocardiography | Moderate size PDA(3.4mm), small PFO with L-R shunt | |
| USG of KUB with scrotum | Kidneys and urinary bladder were normal. Scrotum was bifid and both testes were seen in the scrotal sac. | |
| **Karyotyping** | **47,XY,+21** | |

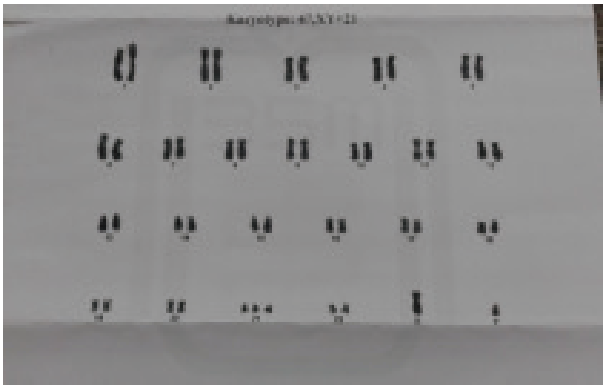

**Fig.-3:** *Karyotyping of this infant*

We diagnosed the case as Down syndrome with Disorder of sex development (47, XY, + 21, DSD) with autoimmune thyroiditis with patent ductus arteriosus (PDA). Tab Levo-Thyroxine (10µg/kg/day) was started along with frusemide, digoxin and enalapril. Developmental therapy was also ensured. Counseling for his overall condition was done in multiple sessions and further follow up plan and treatment option was also discussed with family.

**Discussion:**

Trisomy 21 or Down Syndrome (DS) is the most frequent type of viable human aneuploidy, prevailing at about 1/800 live births. Data for prevalence rate of DS is not available in Bangladesh, but prevalence rates in India are (0.81-1.2/1000 live births),[4,5,6] which is lower than the US prevalence (1.43/1000 person)[7,8] for DS. DS is characterized by presence of extra chromosome due to non-disjunction of chromosome 21 during meiosis, which is the most common type and responsible for 94% of the total DS population, translocation of chromosome 21 to another chromosome (4%) and mosaicism (2%) resulting from nondisjunction during mitosis of the fertilized

egg. Phenotypes are variable in Down syndrome, but the more common physical findings are hypotonia, small brachycephalic head, epicanthal folds, flat nasal bridge, upward-slanting palpebral fissures, brushfield spots, small mouth, small ears, excessive skin at the nape of the neck, single transverse palmar crease and short fifth finger with clinodactyly and wide spacing, often with a deep plantar groove between the first and second toes.[9,10] In addition to characteristics physical features, Children with DS are predisposed to various chronic disorders, infections and disabilities.[11]

Congenital and autoimmune hypothyroidism, euthyroid autoimmune disease, hyperthyroidism are observed with increased frequency in DS compared to general population.[11] The incidence of hypothyroidism is 13-63% in DS[12] and Pierce, LaFranchi and Pinter (2017) had found that thyroid antibodies were positive in 46% of subclinical hypothyroidism and 100% of overt hypothyroidism in DS.[13] Popova et al. stated that Hashimoto's thyroiditis was the most prevalent autoimmune thyroid disease in DS compared to age matched normal children : respectively 13-34% vs 1.3%. People with DS are at risk of developing thyroid dysfunction from infancy through adult life.[14]

In the south -western India, a study had found the incidence of congenital heart disease was 45% in DS. The most common congenital heart disease (CHD) associated with DS was ventricular septal defect (40%), followed by endocardial cushion defect (24.4%), atrial septal defect (17.7%) and patent ductus arteriosus (11.1%) [15.] Another study was also revealed that CHD was present in DS and the most common heart diseases were atrial septal defect (42.1%); total atrioventricular septal defect (15.1%); atrial septal defect and ventricular septal defect (14.6%); ventricular septal defect (12.7%); patent ductus arteriosus (6.6%); patent foramen ovale (5.6%) patients; tetralogy of Fallot (2%); and other diseases (1.3%).[16]

The overall incidence of DSDs is one in 5,500; though there are limited data.[16,17] Classifications of 46,XY DSD include the following: a) Disorders of testicular development (complete and partial gonadal dysgenesis), b) Disorders of androgen synthesis (complete and partial androgen insensitivity, disorders of antimullerian hormone (AMH)/ receptor, androgen biosynthesis defect) , c) Other (severe hypospadias, cloacal exstrophy).[18] Variations of external genitalia from a male looking phallus to almost normal female genitalia with mild cliteromegaly are present in patients with 46XY DSD at birth. Testes may present in abdomen or at inguinal region. The development of male genitals will depend on multiple factors like the capacity of testosterone synthesis of testicles, of the transformation of testosterone in dehydrotestosterone (DHT) by 5-alpha-reductase enzyme or of the presence of receptors sensitive to testosterone. Clinical findings and results of relevant investigations help in diagnosis of 46, XY DSD and multidisciplinary approach is required for treatment.[19] Mota et al. demonstrated clinical profile of 93 46XY DSD patients, among them 62 (63.4%) had been initially recorded as males, 31 (33.3%) as females; 50.5% had no defined etiology and 20.4% had androgen insensitivity syndrome (AIS).[20] Walia et al. also stated that among patients with 46,XY DSD, 32 (31.4%) had androgen insensitivity syndrome and 26 (25.5%) had androgen biosynthetic defect.[21] Our patient presented with small phallus and palpable gonads which indicates 46XY DSD and probable causes of DSD in this case are - Congenital adrenal hyperplasia ( 3 â hydroxysteroid dehydrogenase deficiency or 17á hydroxylase deficiency), Partial androgen insensitivity syndrome, 5 alpha reductase deficiency, Leydig cell aplasia. Ovotesticular DSD may also present with ambiguous genitalia with palpable gonads but in 10% of cases, chromosomes are 46XY. In this case, karyotype was 47XY, +21 and testosterone level was normal, FSH and LH levels were also normal and no raised DHEA-S and 17 OHP level. Normal DHEA-S and 17 OH-P levels excluded CAH in this case. Normal testosterone, low LH and FSH levels ruled out hypopituitarism. Normal testosterone level also ruled out leydig cell aplasia. Features of under virilized male genitalia, normal testosterone level and normal Mullerian duct regression evidenced by absence of uterus and fallopian tubes indicated that this case may be partial androgen insensitivity syndrome (PAIS) or 5 reductase type 2 deficiency. Usually, phenotypic differentiation between partial androgen insensitivity syndrome (PAIS) or 5 reductase type 2 deficiency are very difficult before puberty. Presence of consanguinity indicates 5 reductase type 2 deficiency as it has autosomal recessive inheritance and presence of family history from maternal side suggests PAIS since inheritance is X- linked

recessive. Both consanguinity and positive family history were absent in this case. At puberty, phenotypic differentiation between PAIS and 5 reductase type 2 deficiency is possible. Patients with PAIS usually have gynaecomastia, sparse body hair and less genital virilization, where as, patient with 5 reductase type 2 deficiency, have more genital virilization, absence of gynaecomastia, and absent or hypoplastic prostate. In patients with PAIS, high testosterone and LH are seen during puberty. But in prepubertal age, presence of normal LH and testosterone do not help to confirm PAIS. In 5 reductase type 2 deficiency, ratio of testosterone to dihydrotestosterone are elevated even in prepubertal age. Unfortunately, dihydrotestosterone (DHT) level and ratio of testosterone to dihydrotestosterone were not done as facilities for these tests were not available in our country. In 50% of children with 46 XY DSD, identification of recognized cause is not possible even after completing sophisticated laboratory evaluations [22]. Few case reports of DSD in Down syndrome patients are available. Jospe et al. (1999) reported a case of DSD associated with Down syndrome.[23] This is the 1st reported case of an infant with Down syndrome and (47, XY, +21) DSD in Bangladesh to our knowledge.

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