Case Reports

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

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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

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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 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.

Table-I

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

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
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,
fecundities 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 DS12 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 atroventricular 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 extrophy).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
androgen. 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 17â 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
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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 gynecomastia, sparse body hair and less genital virilization, where as, patient with 5 reductase type 2 deficiency, have more genital virilization, absence of gynecomastia, 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.

Few case reports of DSD in Down syndrome patients are available. Jospe et al. (1999) reported a case of DSD associated with Down syndrome. This is the 1st reported case of an infant with Down syndrome and (47, XY, +21) DSD in Bangladesh to our knowledge.

References: