Approach to a Neonate with Disorder of Sex Differentiation

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Introduction:

Disorders of sex development (DSD) are a heterogeneous group of conditions which are a result of atypical development of internal and external genitalia. It is important to have a systematic approach as well as a sensitive attitude towards these disorders due to the social implications they entail. These situations can be very difficult to manage especially when the gender of rearing of the baby is uncertain. Informing and educating the parents regarding the condition and building a good rapport with the family is extremely important throughout the process of investigation and management.

Definition: The term defines a condition in which, "development of chromosomal, gonadal or anatomic sex is atypical". It is more appropriate to use the term "atypical genitalia" or "disorder of sex development" rather than "ambiguous genitalia" .

Incidence: The condition is known to occur in 1:4500 live births.[1]

Criterion for diagnosis of DSD in a newborn:

- Bilaterally non palpable testes
- Hypospadias and unilateral non palpable gonad

- Micropenis (stretched penile length less than 2.5cm in a full term newborn baby, (< -2.5 SD for gestational age based on population specific normative data)[2]
- Perineal hypospadias with bifid scrotum
- Clitoromegaly (length of clitoris > 9mm and/or width of clitoris more than 6mm)[3,4]
- Posterior labial fusion (anogenital ratio > 0.5)
- Gonads palpable in labio scrotal folds
- Discordant genitalia and sex chromosomes.

Sexual differentiation

Sexual differentiation is a complex process, which involves a precise spatiotemporal interplay of various promoting and repressing transcription factors .

Chromosomal sex:determined at time of fertilization.

Gonadal sex: The development of the bipotential gonad into testis or ovary occurs at around4-6 weeks gestational age.

Sexual differentiation: The internal and external genitalia are differentiated by 12th gestational week.

Fig. 1. Graphic representation of sexual differentiation

Table. 1 Classification of DSD

INITIAL EVALUATION

History:

- Prenatal exposure of the fetusto exogeneous androgens or endocrine disrupters.
- Virilization of mother during pregnancy (placental aromatase deficiency, androgen producing tumors)

- Female relatives with primary amenorrhea/ childless
- Unexplained infant deaths in family
- Consanguinity (recessive disorders like congenital adrenal hyperplasia, androgen biosynthetic defects)

Physical examination:

- Inspection for number of urogenital openings, hyperpigmentation and fusion oflabioscrotal folds. The findings may need confirmation by cystoscopy/vaginoscopy and/or imaging.
- Palpation of labioscrotal folds and inguinal region for gonads.
- Measurement of phallic length and width; and anogenital ratio.

  The **penile length** is usually measured on dorsal surface, right from the pubic rami to the tip of penis (foreskin should be excluded), after stretching the penis. It is important to press the ruler down against the pubic ramus to ensure adequate depression of supra pubic fat. The width is measured at midshaft.

  To measure the Clitoral width, the shaft of clitoris is gently pressed between the thumb and forefinger (so that excess skin and subcutaneous tissue can be excluded)
- Anogenital ratio = $\frac{\text{Distance between anus and posterior fourchette}}{\text{Distance between anus and base of clitoris}}$[5]
- Severity of virilization has been graded by Prader's classification depending upon stages of virilization of the external genitalia and urogenital sinus.[6]

Investigations:

Determination of chromosomal sex: Karyotype / FISH for SRY

Imaging:Determination of internal genital anatomy and position of gonads: USG pelvis helps in identifying Mullerian structures. MRI Pelvis may be necessary in some situations to have an exact idea of anatomy.

Hormonal evaluation:

46 XX DSD:17 OH Progesterone (to be sent 48 hrs of life) , Testosterone, ACTH, Cortisol, S. electrolytes to confirm a diagnosis of Congenital adrenal hyperplasia (commonest cause). Treatment may be started after collection of the critical sample especially if the child presents with salt wasting crisis.

46, XY DSD:AMH (antimullerian hormone) levels correlate with testicular tissue.Urinary steroid profile helps in detecting the enzymatic defect in steroidogenic pathway of testosterone biosynthesis. Hormonal profile is best interpreted between 1month – 5months of age coinciding with minipuberty in infancy. Hormonal profile includes : LH, FSH, Testosterone,Dihydrotestosterone and Androstenedione. Assessment of cortisol levels, ACTH and a synacthen test may be required in some cases when steroidogenesis defect is suspected. Other investigations include Urine for proteinuria.

HCG simulation test: The test is usually required which evaluating infants beyond the minipuberty period or if the baseline values are equivocal.The protocol includes 500-1500 iu IM for 3 days. S. Testosterone is measured on day 0 and 4. Dihydrotestosterone and androstenedione on day 4.[7]

Testosterone: DHT Ratio > 30 is suggestive of 5 alpha reductase deficiency

Testosterone: Androstenedione Ratio> 0.8 is suggestive of 17 beta hydroxysteroid dehydrogenase

Surgical exploration. It may be necessary to understand the internal anatomy, confirm presence of gonads and take a biopsy if necessary.

Genetic analysis: With the availability of micro array and next generation sequencing, it has been possible to arrive at a genetic diagnosis. However it is important to understand that a provisional diagnosis based on hormonal evaluation is more likely to yield a positive result.

Management

Management involves a multidisciplinary team with experience in managing this condition.

1. Pediatrician / Neonatologist
2. Pediatric Endocrinologist
3. Pediatric Surgeon
4. Gynecologist
5. Geneticist
6. Psychologist
7. Social worker

Communication between all members of the team, with one specialist being the nodal point of contact is crucial so that a clear message is given to families. Documenting discussions with the family, maintaining privacy of information and obtaining consent when required is equally important. Maintaining a sensitive attitude with careful use of language (eg. “your baby” instead of he/she until gender is determined) is necessary during all discussions.

Aspects of management:

Gender assignment: It depends on various factors including diagnosis, appearance of external genitalia,outcome of reconstruction surgery and hormonal treatment, functionality, fertility, cultural factors and understanding of family. An individualized approach is necessary in each case (exceptions being, congenital adrenal hyperplasia and complete androgen insensitivity syndrome where the preferred gender of rearing is female)

Medical treatment:

Immediate management includes management of salt wasting crisis in congenital adrenal hyperplasia in an infant with 46, XX DSD

Long term management includes hydrocortisone replacement for Congenital adrenal hyperplasia, testosterone hormonal replacement in puberty (46, XY DSD) and dihydrotestosterone cream application (in boys with 5 alpha reductase deficiency).

Surgical treatment:

The timing of surgery would depend upon the understanding of the parents, cultural factors. Some parents prefer early surgery to protect their baby from social stigma. The pros and cons of early vs late surgery must be explained to parent. Surgical interventions include correction of internal and external anatomy, gonadal biopsy, orchidopexy and gonadectomy(in 46XY, DSD with intraabdominal gonads)

Psychosocial support:

It is an ongoing process which continues throughout the management years into adult hood to help these families and patients deal with the implications of this condition.

Conclusion

An individualized approach is necessary for each patient to decide for gender of rearing, timing of surgery, hormonal therapy and fertility. Advances in genetic analysis such as microarray analysis and next generation sequencing have contributed to accurate diagnosis and clear management plan in many patients.

References:

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Figure 1. Sexual differentiation in the fetus

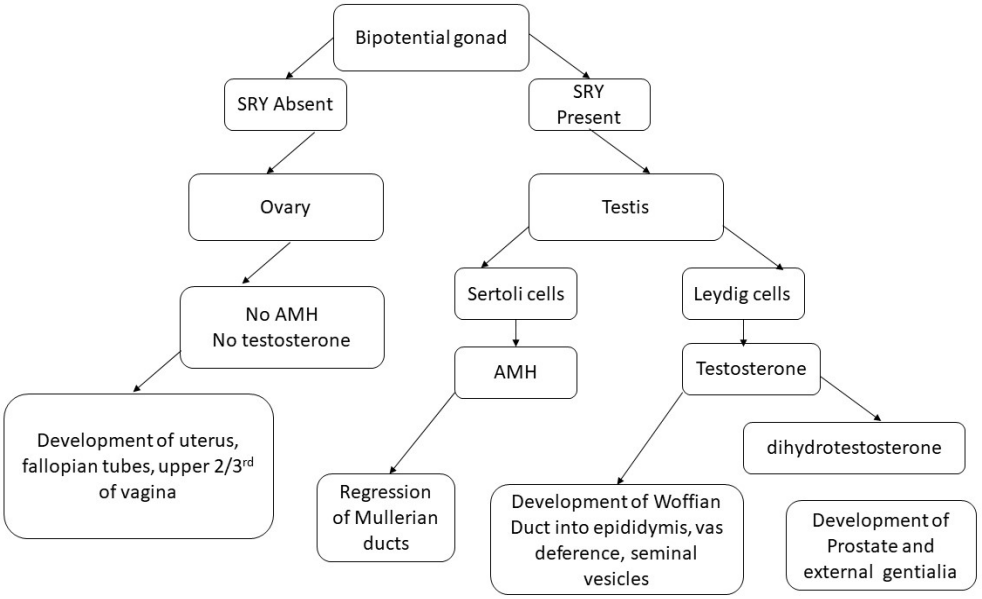

Table 1. Classification of DSD

46, XX DSD	46, XY DSD	Sex chromosome DSD	XX or XY disorder of gonadal development
1. Virilizing Congenital adrenal hyperplasia 2. Placental aromatase deficiency 3. Maternal androgen secreting tumor 4. Virilizing luteoma 5. Glucocorticoid receptor mutation 6. Exposure to norethisterone, medroxyprogesterone acetate, ethinodrel, danazol 7. Ovotesticular disorders	1. Leydig cell agenesis 2. LH receptor defect 3. Lipoid adrenal hyperplasia 4. 17alpha hydroxylase deficiency 5. 3 beta HSD 6. 17 beta HSD 7. Smith lemliopitz syndrome 8. P 450 oxidoreductase 9. 5 alpha reductase 10. Androgen receptor defects	1. Turner (45, X) 2. Klinefelter (47, XXY) 3. Mosaicism	1. Complete gonadal dysgenesis 2. Partial gonadal dysgenesis 3. Ovotesticular DSD

Persistent mullerian duct syndrome	Malformation syndromes
Low AMH	1. MURCS

Normal or High AMH	2. MRKH syndrome 3. CHARGE 4. Hand foot genital syndrome 5. Aphalia 6. Peno scrotal transposition 7. Isolated hypospadias 8. Bladder exstrophy

2. Interpretation of HCG stimulation test in 46, XY DSD

Testosterone	Precursors	Diagnosis
Low	Low	**Normal Cortisol response:** Leydig cell hypoplasia, Gonadal dysgenesis, SF-1 gene defect **Low Cortisol :**StAR, P450scc
Low	High	**Normal Cortisol:**17 Beta HSD **Low Cortisol:** 17 alpha hydroxylase, 3 beta HSD
Normal/ High	Normal	Androgen receptor defect