Inter Sex

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Introduction

One of the most difficult and challenging problems for a gynaecologist is the management of intersex. By definition the true intersex applies to hermaphroditism and intersexuality. These terms are applicable to persons with one or both sexes and some degree of ambisexual differentiation of the accessory sexual organs. In intersexual presentations what is more challenging is the anomalous manifestation of sex.

Stages Of Sexual Development

1. Chromosomal Sex: This state is entirely dependent on genetic sex which is determined at the time of fertilization
2. Gonadal Sex: The gonad of the embryo normally develops as determined by the genetic sex.
3. Phenotypic Sex: This is again dependent on the influence of the gonad which elaborates the typical endocrinological substances determining the phenotypic appearance of sex. For example- A male gonad by its influence of the HY antigen which determines the organisation of testis is responsible not only for elaborating the testicular hormones but also for secreting a substance known as Mullerian inhibiting factor (MIF) responsible for disappearance of the Mullerian system. On the other hand a gonad differentiating in the form of ovary is responsible for future labia formation of the female genital tract and inactivation of the vestiges of the Wolffian system.

Embryology of Gonadal Differentiation

The early embryo is sexually undifferentiated. In the gonad both Wolffian and Mullerian systems exist. The result is no sex can be assigned to the gonad at this stage.

In the course of time with further development, the germ cells migrate into the undifferentiated gonad from the chromosomal complement after fertilization. This starts the sequence of sexual differentiation and the subsequent sex differentiation is completely organised and controlled by the chromosomal sex. Further sex development takes place by the signals arising from gonadal sex. At this stage the endocrine effect of the gonad organises and determines the phenotypic sex. Presence or absence of 'Y' chromosome determines the gonadal differentiation If 'Y' is the chromosome present it produces a testicular differentiation which changes the undifferentiated gonad into the testis. The differentiation starts at the 7th week of the embryo with a crown rump length of 14-16 mm. The presence of 'Y' chromosome promotes testicular differentiation by elaboration of what is known as HY antigen which is probably the product of the testis determining factor of the 'Y' chromosome.

Factors Contributing To The Development Of Anomalous Sex

1. Abnormal sex chromosome-
   a) in ovum b) or in sperm c) or the zygote of fertilization.
   All these three factors may contribute towards conditions like the Turner Syndrome and Klinefelter Syndrome.
2. Genetic Factor- Mutant genes may be responsible for abnormal end organ receptors which make the end organ nonresponsive to specific hormone.
   Example-Androgen insensitivity syndrome (Testicular Feminisation).
3. Translocation of sex determining genes- The 'Y' and 'X' chromosome may be affected by translocation as in true hermaphroditism with gonads of both sexes This condition is characterised by differentiation of both testis and ovaries.
4. Extrinsic Factor affecting the foetus at critical stages of development.
   Example- Female pseudohermaphroditism due to abnormal enzyme biosynthesis in adrenals.
5. Idiopathic or unknown environmental and genetic abnormalities affecting the differentiation of primitive genital tract.

Characteristics Of Intersex

a) A true hermaphrodite (TH) possesses both testicular and ovarian tissue.

b) A Male Pseudohermaphrodite (MPH)
This subject is basically a male with testis with female phenotype of either external or internal genitalia but more commonly these subjects have female phenotypes. External genitalia on MPH could be (a) with mild hypospadias, glandular and phallic (b) micropenis which measures less than 1.9 cm at term. These new born babies may also be a case of cryptorchidism (c) severe hypospadias, penoscrotal or perineal with palpable gonads (d) these male subjects may clinically have feminine pattern labia with or without palpable gonads.

c) Female Pseudohermaphrodites (FPH)
FPH is characterised by existence of ovaries with masculine characteristics namely labio-scrotal fusion, clitoromegaly with funnel shaped urogenital sinus or penile urethra opening at the tip of the phallus.

Critical Periods Of Gestation For Gonadal Development

Critical gestation period for normal sexual development is seven weeks of the embryo. At this stage the effect of 'Y' chromosome takes place on the gonad which matures and liberates testicular determining factor responsible for conversion of the undifferentiated gonad to testis. The differentiation process starts at seven weeks.

Critical period for the male gonad to manifest androgen activity is most important. It is at this period of seven weeks if the androgen activity of the male gonad is deranged, it will lead to incomplete masculinization of the genitalia.

Similarly at the same period, congenital adrenal hyperplasia (CAH) takes place resulting in clitoral hypertrophy.

Up to ten weeks of intrauterine life, the external genitalia look similar both in the male and the female. Subsequently the differentiation into male and female takes place after this period of ten weeks. At this period the normal shape and size of the gonads takes place.

Pathogenesis Of Chromosomal Abnormality

It is usually believed that the missing 'X' in XX female is likely to be maternal (77% maternal 23% paternal).
Viability – Ninety five per cent of all 45 X conceptuses are aborted. Only in 5-10% of all abortuses, 45 karyotype was found.

Family History And Inheritance

Turner's syndrome is generally of sporadic occurrence. Mosaic Turner's syndrome may have familial incidence.

The speciality of this syndrome is instability of X chromosome in both male and female members of the family. Mosaic karyotype is rare amongst abortuses. It is only in full fledged XO will there be the true Turner syndrome.

Cytogenic Abnormality

The true Turner syndrome occurs only in the short arm of the X chromosome which is deleted.

It has further been established that the chromosome is derived from both male and female members of the family particularly amongst the mother and daughter with mosaic constitution.

Abortuses And Cytogenetics

The abortuses do not show significantly high incidence of Turner's amongst the abortuses. Early conception with Turner's features survive and grow up in the form of typical Turner's syndrome.

Turner Syndrome

True Hermaphroditism (TH)
This condition is rather rare with combined existence of testis and ovary or bilateral ovotestis. While searching for location of gonads specially at laparoscopy or ultrasonography the testis should be looked for in the line of descent. The ovary is usually found in its normal position.

External Phenotype

The external genitalia may show a wide range of abnormalities starting from all masculinised features with hypospadias and incomplete labioscrotal fusion. If the phenotype is that of female marked clitoral enlargement

and urogenital sinus could be detected.

Development Of Puberty

Variable feminisation or virilisation takes place at puberty. Some may have gynaecomastia and some of them may have cyclical menstruation manifest in the form of cyclical haematuria in male.

Function Of Gonad

Ovulation is more common than spermatogenesis.

Cytogenetics

Fifty per cent are found with XX, 20% with XY and 30% may be mosaics.

Danger Of Neoplastic Change In Gonad

In some cases of XX subjects the Y chromosome may translocate to the X chromosome and may have XY cell line. These patients with X cell line may develop gonadoblastoma.

Female Pseudohermaphroditism (FPH)

Female pseudohermaphroditism have normal sex chromosome in the form of XX karyotype with Mullerian ducts and ovaries associated with abnormalities of urogenital sinus and external genitalia.

FPH consists of various enzymatic abnormalities :

a) Congenital adrenal hyperplasia (CAH).
b) Foetal virilization by maternal androgens.

Abnormalities Of Enzyme Deficiency In Androgen Synthesis:

Five enzyme defects are encountered in female pseudohermaphroditism.

Enzyme Defect In Adrenal Of FPH

Seventeen alpha hydroxylase deficiency and enzyme defect due to 21 hydroxylase deficiency:

This is a condition which interrupts the pathway for synthesis of hydrocortisone. This enzyme is the link between pregnenolone, 17 alpha hydroxy coticosteroid, 21 alpha corticosteroid completing the pathway for synthesis of cortisol (Fig II). Cortisol deficiency provides the feedback to hypothalmus resulting in over production of adrenal androgens. This is the basis of congenital adrenal hyperplasia with virilization. If the high ACTH stimulates only zona-fasciculata than only a partial deficiency occurs. But if the stimulation affects both zona fasciculata and reticularis, then the new born becomes a salt loser in addition to virilisation because of the deficient androsterone synthesis. The gene for this enzyme deficiency is located on chromosome 6 with HLA-B locus.

There are three types CAH due to 21 hydroxylase deficiency:-

1. The classical type
2. A cryptic type and
3. Late onset type.

a. These differences are to be attributed to the allelic variability of this enzyme.
b. Enzyme defect in adrenal due to derangement of 11 beta hydroxylase: The females with this enzyme defect are born with severe virilization defect and hypertension due to increased deoxycorticosterone (DOC) which is a patient mineralocorticoid substance.
c. 3 beta hydroxysteroid dehydrogenase deficiency (3-BHSD) – This condition is a severe form of deficient production of cortisol and increase production of cortisol with androgens and oestrogens with severe salt loss and early neonatal death.
d. 17 alpha hydroxylase deficiency affecting both adrenal and ovary.

In this condition production of cortisol, androgen and oestrogens are completely deranged and this condition is incompatible with life.

Laboratory Investigation For Virilisation Due To Enzymatic Aberration

a. High 17 ketosteroid indicates 21 hydroxylase, 11 beta hydroxylase and 3 beta HSD defects. Normal values are 16-50 mg in 24 hours in offsprings at age of 10-15 years.
b. Elevated pregnanetriol – This is the characteristic of 21 beta hydroxylase blocks.
c. 17 alpha hydroxy progesterone – This enzyme can be easily estimated by RIA and it proves to be useful for

Fig I-

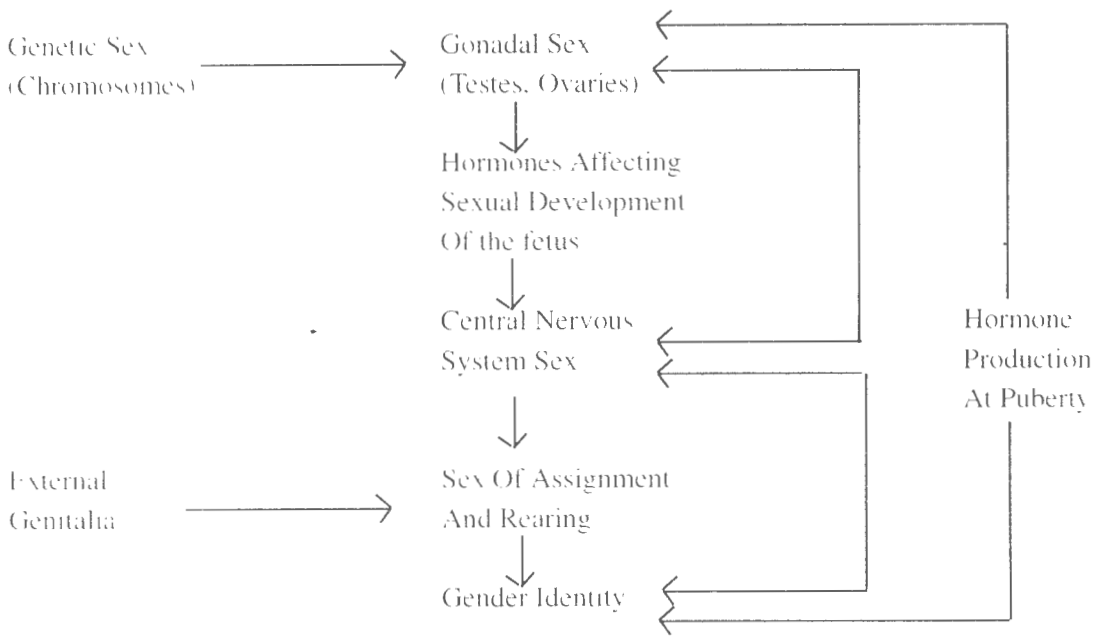
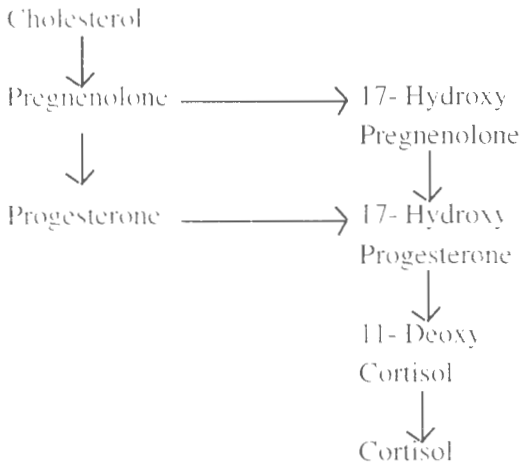


Fig II



diagnosis and management of CAH.

d. Serum cortisol and urinary excretion of its break down products does not increase with ACTH stimulation.

Virilisation Due To Increased Material Androgens

Androgen producing tumours like adrenal adenoma and androblastoma or luteoma of the ovary are other neoplastic causes of virilization.

Virilisation can also be produced by exogenous therapy with Medroxy Progesterone Acetate (MPA) and other androgens.

The characteristic picture of such condition is the fusion of labia minora. There is some degree of clitoral hypertrophy. Surgical correction in such correction by clitoroplasty is recommended.

Diagnosis Of Abnormal Sex Differentiation

1. History – Family history provides a clue to adrenal virilisation with hypertension due to 17 alpha hydroxylase deficiency.

2. Examination of external genitalia may reveal labial fusion or testis in the labia or in the inguinal canal. This condition is characteristic of androgen insensitivity syndrome.
3. Oral mucosal smear for sex chromosome and karyotype study. Serum electrolytes may reveal salt retaining CAH.
4. High urinary 17 ketosteroid indicates hydroxylase deficiency.
5. Ultrasound scan of pelvis for uterus tubes ovaries and streak gonads as also renal abnormalities may be of great value
6. Lastly gonadal biopsy with laparoscopic evaluation is helpful.

Some Conditions Characteristics Of Basic Disorder Manifesting In The Form Of Intersex.

Androgen insensitivity to androgenic hormones

a. Testicular feminization syndrome This condition is transmitted as 'X' linked disorder. Basic pathology in this syndrome consists of :
1. Persistent mullerian inhibitory factor (MIP).
2. Abnormal intracellular receptors These two factors are responsible for absent or incomplete androgen induction of Wolffian duct system.

Clinical features are external genitalia having female characteristics, occasional clitoral hypertrophy with fusion of labia and blind vaginal pouch. Uterus and tubes are usually absent. Testes are located in inguinal canal or labial folds.

The gonads secrete oestrogen at puberty- Testosterone levels are within normal levels. There is a basic abnormality which controls the receptor activity in the cytosol.

Incomplete Variant Of Testicular Feminization

The characteristics of incomplete variant are various degrees of breast development and non functioning androgen receptor. Testosterone levels are normal. Skin fibroblast receptors reveal low androgen binding.

5 alpha reductase defect

These patients have XY with well differentiated testis and external genital with varying degree of hypospadias. Basic abnormality in this condition is failure of testosterone to be converted into dihydrotestosterone due to enzyme defect. Finally there is no receptor activity.

Management

Management Usually Involves Mutidisciplinary Assistance- most important amongst which will be endocrinological.

Hormonal Treatment- Hormonal treatment with oestrogens is the most important line of management. Small dosage of ethinyl oestradiol in 100g/kg/day increases the growth rates temporarily. The recommended starting age of oestrogen therapy is usually 9 10 years. But long term therapy after the age of puberty should consist of oestrogen combined with progestogens obviously to avert the possibility of neoplastic change in the endometrium.

Recently cyclical oestrogen progestogen therapy has been found to be very beneficial. This line of management helps in the development of breast and uterine growth with cyclical withdrawal bleeding. Recently such patients have been given the benefit of assisted reproductive technology with ovum donation programme when the uterus and the endometrium achieve the optimum growth.

In the management of intersex the most important issue involves three things

1. The type and cause of intersex.
2. The way the child has been brought up in the family or society either as male or female.
3. Elaborate dialogue with the parents of the intersex.

If a child has been brought up as a female and the subject is a FPH, the patient would be well advised to be assigned the female identity. Moreover, this may help in the future child bearing if properly managed.

Ideally the sex of child should be decided for intersex by 2 ½ years of age before the child has grown up in with a

particular gender role.

In all cases the preliminary approach to the problem should be cytogenetic study, endrocrinological study and psychological makeup.

Special Management Of MPH

The size of the phallus in response to testosterone therapy and the pattern of the external genitalia with secondary sexual development should receive important consideration.

The gonads of MPH may have germ cells which may not be functioning or may not be responsive to endocrine therapy. This results in germ cell failure.

Androgen Insensitivity Syndrome

These subjects should be reared as females. MPH due to 5 alpha defect have a problem. These intersex subjects are usually brought up as girls and later suddenly during puberty there is a reversal to male type with virilization. Therefore the patient with 5 alpha defect must be diagnosed early and the proper line of management with regards to the final assignment of sex must be done.

True Hermaphroditise (TH)

TH needs to be assigned a particular sex after the gonadal biopsy. In these cases the external genitalia needs to be considered. It is easier and perhaps proper to bring up these subjects as females after submitting them to gonadectomy if 'Y' chromosome is detected in these gonads. This measure will prevent the neoplastic change in the gonad.

Surgical Measure

1. Perineal reconstruction in females may be required.
2. Clitoral reduction with clitoroplasty performed by Bayer's flaps leaving the neurovascular bundle intact should be carried out. Simultaneous division of corporacavernosa followed by reanastomoses of divided portions of the clitoris should be performed.
3. Hypospadias should be corrected if it is of the perineal type.
4. Vaginoplasty may have to be carried out in cases where it would be indicated.

Hormonal Replacement

Oestrogen replacement should be done for Turner's syndrome or other cases of male MPH at puberty, if the subjects are brought up as females. Later ovum donation may be considered.

Medical Management

The glucocorticoids in proper dosage based on body weight must be administered to the FPH due to enzyme deficiency in the adrenal cortex. Oestrogen therapy is recommended for promoting the development of breast.

Conclusion

The problem of intersex is a medical, cytogenetic, endocrinological and surgical problem for the profession not leading to easy solution. At the same time a thorough dialogue with perfect understanding on the part of the family has to be established. Lastly, correct social understanding and approach needs to be promoted so that an intersex may not be looked down upon as a social outcast.