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"GONADAL DYSGENESIS"-EMBRYOLOGICAL BASIS AND ITS CLINICAL IMPORTANCE

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ABSTRACT

Generally, Gonadal Dysgenesis is a condition which can be characterized by the underdeveloped or imperfect formation of the gonads. This occurs either due to the absence of the sex determining region of the Y chromosome (SRY) gene and therefore differentiation of the indifferent gonad would not occur. Hence, the other activities such as development of testes, production of its specific hormones and the formation of the other internal reproductive organs that needs those hormones in order to develop would be under developed.

Introduction

Any congenital developmental disorder of the reproductive system is called gonadal dysgenesis[33][39] while dysgenesis can be defined as the abnormal development of an organ during embryonic development and growth[37][40]. It can be characterized by the gradual depletion of the germ cells in the developing gonads of an embryo. This depletion leads to abnormality and also the underdevelopment of the gonads which may consist mostly of fibrous tissue which is given the name streak gonads.

Gonadal dysgenesis however, can be characterized in one of two gonadal morphologies as either complete gonadal dysgenesis or partial gonadal dysgenesis. This is likely to occur in male if there is an absence of antimüllerian hormone (AMH) and testosterone. Due to the absence of testosterone there would be a retrogradation of the duct system (Wolffian duct) which leaves the testis as a result the regular internal male reproductive tract would not develop. The absence of AMH will allow the primordial anlage of the female reproductive tract (müllerian duct) to differentiate into the uterus and oviducts. This individual would acquire a female like external and internal reproductive characteristics which means the lacking of the secondary sex characteristics. This would lead to the sexual organs that are not well formed or not clearly female or male.

Normally, the cells of an individual would consist of forty-six (46) chromosomes with one being, one (1) X and one Y or two X chromosomes. Sometimes, during the cell division and DNA replication one of the chromosomes can get lost. Due to the appearance and number of the chromosomes, that's how gonadal dysgenesis can be classified into: Turner Syndrome - XO gonadal dysgenesis (45, XO), XX gonadal dysgenesis (46, XX), Swyer syndrome (CGD) - XY gonadal dysgenesis (46, XY) and finally, mixed gonadal dysgenesis - XO or XY mosaicism [41][45].

Incidence

Generally, gonadal anomalies have been stated to occur at approximately one (1) in 4,500 births. In the case of the morphology characterization of gonadal dysgenesis, partial and complete gonadal dysgenesis, they have been estimated to occur in one (1) of every 20, 000 births

Ontogenesis of Normal Development of Male and Female Gonads

The morphologic structures of the male and female do not begin development until the seventh week. The gonads (testes and ovary) are the organs which produce the male and female sex cells (sperms and oocytes) [42]. The testis and ovary are similar in its early stages (indifferent stage) and only after this stage the ontogenesis continues in the male direction or female direction. In the indifferent stage the development of the gonads occurs in the intermediate mesoderm medial to the middle part of the mesonephros. The there are three components which helps in the development of the gonads are: the coelomic epithelium covering of the intermediate mesoderm, intermediate mesoderm medial to the middle part of the mesonephros and lastly, the primordial germ cells which differentiates in the wall of the yolk sac close the allontois. After differentiating, the primordial cells then migrate to the location where gonads develop [38].

The first indication of the development of the gonad is the generation and condensing of the coelomic epithelium which covers the intermediate mesoderm medial to the mesonephros. The mesoderm beneath also thickens and condenses. This activity (thickening of coelomic epithelium and condensation of underlying mesoderm) forms the genital ridge. Then, the coelomic epithelial cell invades the underlying mesoderm in the form of cords which are called sex cords. After the folding of the embryo the primordial cells which differentiated from the cells in the yolk sac close to the allontois, presents themselves in the wall of the hindgut.

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The then intern migrates along the dorsal mesentery of the hindgut by an active movement called amoeboid. The primordial cells then reach the developing gonad. The cells are then mixed with the sex cords which consist of coelomic epithelium and the primordial germ cells.

After this event the development of the testes and ovaries will follow their prospective path [37][38].

Development of testes

During this development the length of the sex cord increases and expands into the medulla (central part) of the gonad where they anastomose with each other. The sex cords develop a lumen which then converts it into the seminiferous tubule. The anamostosing cords form a network of canals called rete testis. The lining of the seminiferous tubules consist of two cells, the Sertoli cells which is derived from the coelomic epithelium and the spermatogenic cells which is derived from the primordial germ cells. It is important to note that only after puberty does spermatogenesis takes place and the other cells of the spermatogenic arrangement appears. The connection of between the seminiferous cord and surface epithelium disappears a thick fibrous capsule is formed called the tunica albuginea develops. This is a characteristic attribute to testicular development. The mesoderm forms the mediastinum testes, fibrous septa which arise from it and it also gives rise to the connective tissue which surrounds the interstitial cells of Leydig and the seminiferous tubules. These cells are responsible for the secretion the male hormone testosterone. The secretion of this hormone during the fetal period in turn influences the development of the genitalia and the duct system of the gonads.

As the development of the testes continues it projects in the coelomic cavity and here it is suspended from the posterior abdominal wall a mesentery called mesoorchium.

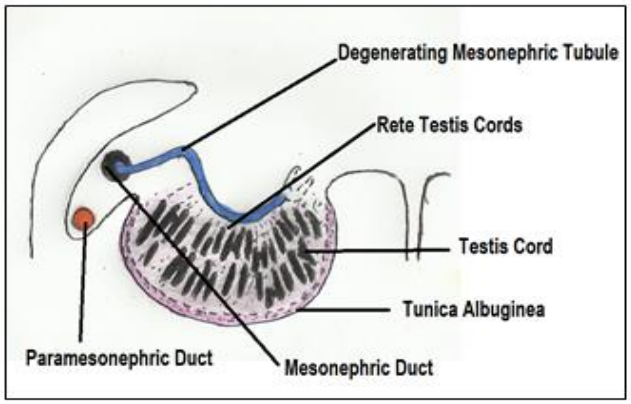

Fig1a. A schematic diagram showing transverse section of the testis, tunica albuginea, testis cords, rete testis and primordial germ cells.

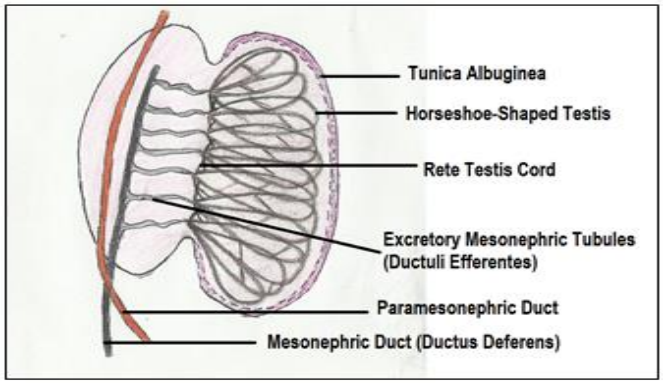

Fig 1b. A schematic diagram showing the testis and genital ducts.

Development of ovary

In females embryo gonadal development occurs slowly. During ovarian development the sex cords do not extends in the medulla as in the case of the development of the testes. The sex cords become fragmented instead and are converted into clusters of cells which contain primordial germ cells in its centers and coelomic epithelium surrounding them. The formation of the oogonia occurs from the primordial germ cells and the follicular cells from the coelomic epithelium hence, the primordial follicle. Numerous amounts of these cells are formed during fetal life by the division of the primordial germ cells and coelomic epithelial cells. No new follicles are formed after birth and further development of the follicles (primordial) do not occur until after puberty. The primordial cells are located in the cortex of the ovary which is enclosed in flattened coelomic epithelial cells which are called germinal epithelium even though they do not form germ cells. The mesoderm is responsible for the formation of the connective tissue covering the ovary and the stroma of the ovary. The mesentery which suspends the ovary from the posterior abdominal is called the meso-ovarium [43].

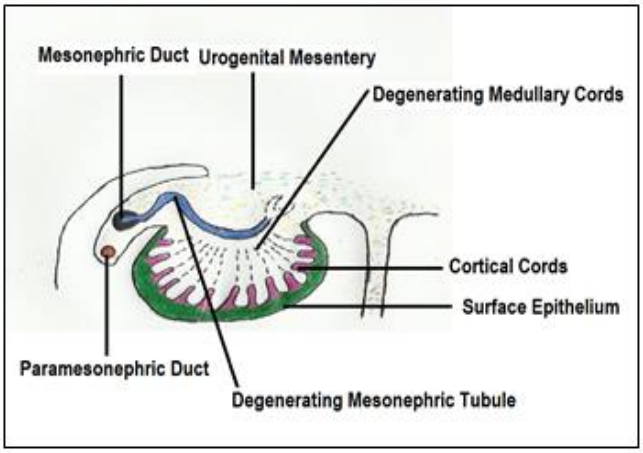

Fig2a. A schematic diagram showing cross section of an ovary, degeneration of the medullary cords and the formation of cortical cords .

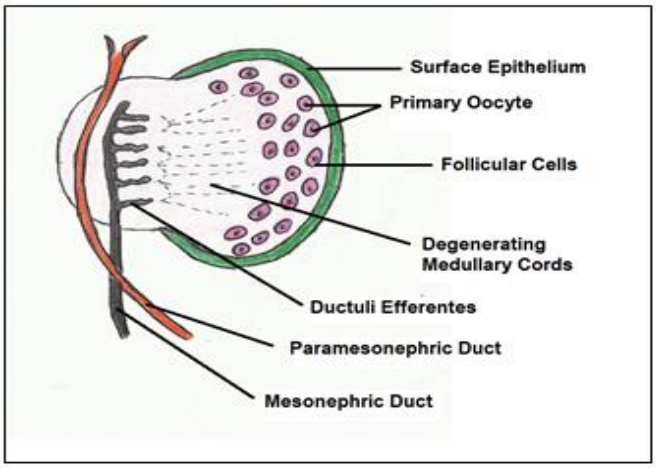

Fig 2b. A schematic diagram showing the ovary, genital duct and also the degeneration of the medullary cords.

Ontogenesis for the anomalous formation of Male and Female Gonads

Gonadal dysgenesis can be characterized by either the incomplete or defective development of the gonads. This can be as a result of the numerical or structural anomalies of sex chromosomes or the mutation of a gene that is involved in the gonadal development. It can be classified as either partial gonadal dysgenesis (PGD) or complete gonadal dysgenesis.

Partial Gonadal Dysgenesis (PGD)

In partial gonadal dysgenesis they chromosome is present but there is an incomplete determination of the testis and the external physical composition of would depend on the extent of the testicular function. Generally, it can be stated that PGD gives rise to uncertainty of the genitalia due to the upholding of some of the leydig cell function. There is also a remnant of the müllerian duct which reflects incompetent sertoli cells production of the AMH. Histologically the tunica albuginea would be thin and loosely organized and also there would be underdeveloped seminiferous tubules which would consist of wide intertubular space, scanty germ cells, abundance of infantile sertoli cells and also calcified psammoma bodies. Hence, PGD is basically the failure in gonad maturation [46].

Complete Gonadal Dysgenesis

In the case of complete gonadal dysgenesis there would be no development of the gonads and as a result the physical makeup of the individual would be completely female and there would also be a lack of the gonadal steroid production.

The first step of sexual differentiation that will occur of a normal male fetus is usually the development of the testes. This formation occurs in the second month of gestation depends on the activity of several genes. One of these genes is the sex determining region of the Y chromosome (SRY). In the absence of this gene the indifferent gonad would fail to differentiate into a testis. Without the testis there would be no production of the antimüllerian hormone (AMH) and testosterone. The wolffian ducts will fail to development due to the deficiency of testosterone and hence would result into the internal organs for males not being formed. The absence of testosterone also means that there would be no formation of dihydrotestosterone and therefore, external sexual organs would fail to virilize which would result into the formation of female external organ. On the other hand, absence of AMH the müllerian ducts would form into the normal female internal organs such as the uterus, fallopian tube, cervix and vagina.

Hence, an external female baby would be born and normal in all the structural aspects except that there would be nonfunctional streak gonads instead of testes or ovaries [45].

Discussion

Gonadal dysgenesis is correlated with the development of gonadoblastoma which is a tumor that contains nest of germ cells and also cells that appear like sertoli cells or granulosa cells. Other complications of gonadal dysgenesis may include infertility or impaired fertility, absence of the menstrual cycle, miscarriages and still births just to name a few.

In gonadal dysgenesis, there is no primary prevention. It is said to not be an inherited disorder and randomly occurs.

The loss of germ cells in gonadal development of an embryo advances to extreme underdeveloped and dysfunctional gonads which are composed of mainly fibrous tissue. Hence, the name streak gonads which is a form of aplasia whereby the ovaries is replaced by nonfunctional tissue. Hormonal failure also which accompanies it prevents growth of the secondary sex characteristics in one of the two sex resulting in infertility and also the infantile female appearance [3].

Some of the secondary sex characteristics which affect male individuals with gonadal dysgenesis are the increase strength and muscle mass, deepening of voice and enlarged larynx (Adam's apple), larger nose, hands and feet when compared to females and prepubescent males, waist is small but much wider than females and last but not least the growth of facial and body hair.

However, in females the waist to hip ratio is lower when compared to adult male, enlargement of the breast and also erection of nipples, waist is smaller than adult male, the inner lip of the vulva (labia minora) growth may be more prominent and may also undergo changes in color and lastly, muscle growth in the thigh would be greater behind the femur instead of in front [42].

When an individual is diagnosed with gonadal dysgenesis that individual is place on immediate estrogen and progesterone therapy. This helps to promote the growth of the normal sexual characteristics of a female and also to prevent possible cardiovascular complication and also osteoporosis. It is important to note that estrogen therapy would not make a female who has nonfunctional ovaries fertile but plays a major role in the assistance of reproduction [42].

Conclusion

Gonadal dysgenesis surrounds an array of conditions within the disorders of sex development which results in the abnormal formation of the gonads which may include Turner's syndrome, partial gonadal dysgenesis, mix gonadal dysgenesis etc [47].

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