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اسم المحاضرة السابعة والعشرون باللغة الإنكليزية :Puberty and its diorders

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Puberty and Its Disorders

The transition from childhood to adolescence and adulthood is one of the most dynamic changes that occur during the life of a woman. The changes are not only physical,but emotional, psychological, and behavioural and all these changes encompass the maturation of the female to become reproductively capable.

There is enormous variation between individuals in the processes involved in puberty but the five major physical changes are **growth, breast development, pubic hair development, axillary hair development and, ultimately, menstruation.** Whilst these changes occur temporally at different rates, there may be changes that occur prematurely or in a delayed fashion which alter this process. Finally, some girls may undergo pubertal change without menstruation and others may fail to enter puberty entirely.

Control of the onset of puberty

The age of onset of puberty in girls ranges from 8 to 13 years and **the appearance of secondary sexual characteristics before this age is known as precocious puberty; failure of appearance of any secondary sexual characteristics after 13 years in girls is considered delayed puberty**. A number of factors are known to play a role in the timing of puberty. Genetics has a clear and dominant role and there is a clear correlation between age at puberty of a woman and that of her daughter. However, there are racial differences, with black females showing an earlier age of pubertal onset compared with white. Furthermore, nutritional status in all ethnic groups seriously influences the age of onset of puberty. Children living in areas of malnutrition have significantly delayed onset of puberty and transfer of these girls to a socioeconomically superior environment reduces the age of onset of puberty significantly.

At the other extreme, evidence now exists to suggest that a high body mass index (BMI) is linked to earlier age of maturation, and the relationship between body fat and the onset of puberty is linked to the release of leptin from adipose sites. Leptin would seem to act as a primary signal to the hypothalamus to allow puberty to commence.

The hypothalamus–pituitary–gonadal axis is active during fetal life and quiescent during childhood. It is the reactivation of this axis that leads to sexual maturation, although the mechanism by which this occurs remains unclear. The arcuate nucleus in the basal hypothalamus is responsible for secretion of gonadotrophin-releasing hormone (GnRH) into the hypothalamus–pituitary portal circulation.

As puberty commences, the arcuate nucleus begins to secrete GnRH in a pulsatile manner, initially solely at night; however, as time progresses GnRH release adopts a low-frequency low-amplitude pulsatile pattern that starts to induce release of luteinizing hormone (LH) from the pituitary. The low-amplitude pulsatile pattern gradually extends to include daytime secretion and gonadotrophin levels themselves start to increase, reflecting higher pulse amplitude and increasing frequency of GnRH production. As the pattern of follicle-stimulating hormone (FSH) and LH release becomes established, so ovarian activity commences and initially this is disordered as it is uncoordinated.

This means that there is follicular growth without coordinated ovulation and although estradiol levels start to rise, there is no evidence of ovulation. The ovary may have appearances that are multicystic due to this chaotic gonadotrophin stimulation and, over time (about 5–10 years), coordinated pulsatile release of GnRH leads to adult frequency of FSH release (approximately every 90min). At this stage the ovulatory cycle is established.

From age 7, most girls will begin activation of adrenal androgen production, a phenomenon known as adrenarche. As with ovarian estradiol production, androgen production is initially at extremely low levels and increases over time.

Physical changes of puberty

Growth:

An increase in vertical growth is the initial physical sign of the onset of puberty. Growth during infancy is relatively rapid until age 3–4 and then it rapidly decelerates when the childhood phase begins. Growth velocity during infancy is approximately 15cm/year but in middle childhood, until the onset of puberty, slows to 5–6cm/year. Interestingly, childhood growth rates are usually at their slowest in the 12–18 months immediately preceding puberty and thus if puberty is delayed this effect is exaggerated. At puberty, girls may reach a peak growth velocity of 10cm/year and will gain approximately 25cm of growth during puberty. Males in contrast have their growth spurt approximately 2 years later than females but eventually gain approximately 28cm of added height.

Once the final stage of growth velocity decreases, epiphyseal fusion occurs which prevents further growth. During the adolescent growth phase, bone density increases rapidly. Control of the growth spurt is primarily through growth hormone and its major secondary messenger insulin-like growth factor (IGF)-1. Estradiol plays an important role in the increased secretion of growth hormone during puberty, particularly in the early stages. As bone growth and height are maximally achieved, estradiol initiates epiphyseal fusion as it reaches its maximum towards the end of puberty. Thyroid hormone also plays a key role in growth and development as illustrated in severe childhood hypothyroidism, which results in a dramatic decrease in the velocity of growth.

Breast development

Although the growth spurt is usually the first sign of the onset of puberty, in females it is breast change that is usually used as an indicator of development. The initiation of breast development is known as thelarche and Tanner has classified this into five stages. Breast growth is often unequal between the two breasts and Tanner stage 5 represents the mature end stage of breast development. This takes approximately 5 years.

Pubic and axillary hair growth

The adolescent development of female pubic hair occurs in conjunction with androgen release and it is the presence of androgen that determines both pubic and axillary hair growth. In approximately 20% of females, pubic hair growth may precede breast development.

Age of onset of puberty and subsequent health

Early age of menarche is associated with increased risk of breast cancer, cardiovascular disease, depression, behavioural disorders, diabetes and increased early mortality.

Precocious puberty

This phenomenon has received increased attention over the last few years with the belief that the age of onset of puberty has been falling. However, in accepting some guidance over age, the appearance of secondary sexual characteristics prior to 8 years should be considered precocious and prompt the clinician to carry out investigations.

Differential diagnosis of early onset of puberty

Premature adrenarche

This is due to the precocious increase in adrenal androgen secretion and is the most common cause of referral for precocious puberty. There seems to be an association between premature adrenarche and increased BMI, and in the overweight child referred with precocious puberty it is important not to assume that breast tissue is truly breast development and not adipose tissue. Signs of virilization such as clitoral enlargement, severe acne or increased muscle mass would lead to concerns of a virilizing ovarian or adrenal tumour or late-onset congenital adrenal hyperplasia (CAH). Late-onset CAH can present with pubic hair growth from the age of 1 and should be appropriately investigated.

Premature thelarche

Here, breast growth tends to appear earlier than age 8 and progresses very slowly and usually occurs in isolation of the growth spurt or any other secondary sexual characteristic. The cause of this condition remains unknown and although it is appropriate to exclude an ovarian cyst, these are rarely found.

Central precocious puberty

This refers to progressive breast development prematurely due to early activation of the hypothalamic–pituitary–ovarian axis and is accompanied by the growth spurt; pubic hair is frequently but not always found. This therefore mimics normal onset of puberty but at a very early age. A positive family history of early onset of puberty may be discovered where an MKRN-3 gene mutation can be found, but in the majority of cases the aetiology is idiopathic. Brain imaging is important, especially in girls with an onset of puberty before the age of 6, where 20% will be found to have a central nervous system (CNS) tumour.

Peripheral precocious puberty

This is far less common than central precocious puberty and is usually induced by excess production of sex steroids.

Causes include the following.

- Androgen secretion from a virilizing adrenal tumour.
- Late-onset CAH.
- Oestrogen-secreting tumour causing rapid breast development. If a large ovarian cyst is present, this may be part of McCune–Albright syndrome, with associated classical features of irregular café-au-lait spots and cystic bone lesions called polyostotic fibroid dysplasia.
- Exposure to exogenous hormones, e.g. inadvertent ingestion of birth control pills by children causing excess levels of oestrogens; topical androgen exposure.

Investigations

A number of hormonal studies may be carried out in children with precocious puberty. However, they are of limited value and should be focused on specific clinical entities. LH may be used to distinguish between premature thelarche and central precocious puberty. FSH is of limited value. Estradiol is usually elevated in girls with precocious puberty and very high levels may suggest a tumour. Dehydroepiandrosterone is always elevated in children with premature adrenarche; testosterone when markedly elevated would suggest an androgen-secreting tumour; and in those children who are considered to have late-onset CAH, the diagnosis can be confirmed by measuring 17-hydroxyprogesterone. Radiological studies have somewhat limited value, although pelvic ultrasound may be used if an abdominal tumour is suspected and brain MRI may be used in those children with extreme precocious puberty, where the chances of a positive finding are around 20% and MKRN-3 gene mutation should be screened for.

Treatment

The majority of girls with central precocious puberty do not require hormonal treatment, because most development is extremely slow and will result in maturity at an age which would be expected even though onset has been early. It is therefore prudent to review children with precocious development of secondary sexual characteristics 6 months later to see whether there has been rapid development of secondary sexual characteristics or not. In these cases, there is a high chance that sexual maturity will be reached by age 9 and therefore suppression of the progress of puberty would be sensible. While it is possible to suppress the pituitary, growth hormone cannot be suppressed and therefore treatment will result in adult height that is significantly greater than would be expected than if the child were left untreated.

Children with extremely early puberty are often tall at the time of diagnosis and they tend to finish their growth early but achieve normal adult height. It is appropriate in these young children to suppress the development of secondary sexual characteristics.

The standard treatment for central precocious puberty is GnRH analogues, which may be given nasally or by intramuscular injection. Three-monthly preparations are available and therefore four injections a year is all that is required to suppress puberty. GnRH analogues can then be administered until such time as the child reaches approximately age 11, when withdrawal will result in the normal resumption of pubertal changes. Peripheral precocious puberty, when due to an ovarian or adrenal tumour, requires surgical intervention; however, for girls with androgen excess due to CAH, suppression of the adrenal with hydrocortisone will reverse the changes.

Note:

Precocious puberty is usually idiopathic and requires treatment only if changes are accelerated such that completion of puberty will occur prematurely.

Delayed puberty

Delayed puberty is usually considered when girls have no secondary sexual characteristics by age 13.5years. Delay in puberty occurs in only 2.5% of the population but the identification of those children who do have a significant aetiology for this may be extremely important. It is mandatory to take a detailed history as the presence of chronic medical conditions or excessive athletic participation may be an explanation for delay in the onset of puberty. In females, approximately 50% will have constitutional delay with no explanation and the vast majority will commence the onset of puberty by age 18. A further 40% have been found to have a genetic defect.

It is due to either due to a central defect (hypogonadotrophic hypogonadism) or a failure of gonadal function (hypergonadotrophic hypogonadism).

Hypogonadotrophic hypogonadism

This is central and may be constitutional, but other causes must be excluded: these include anorexia nervosa, excessive exercise and chronic illness, such as diabetes or renal failure. Rarer causes include a pituitary tumour and Kalmans syndrome.

Associated with delayed puberty and primary amenorrhoea.

Hypergonadotrophic hypogonadism

This is caused by gonadal failure.

- The gonad does not function despite high gonadotrophins.
- Associated with Turner syndrome and XX gonadal dysgenesis.
- Premature ovarian failure can occur at any age, including prior to pubertal age, and may be idiopathic, but can also be part of an autoimmune or metabolic disorder or following chemo- or radiotherapy for childhood cancer.
- Associated with delayed puberty and primary amenorrhoea.
- Hypergonadotrophic hypogonadism can also occur later in life and will cause secondary amenorrhoea after normal sexual development.

In the presence of secondary sexual characteristics, menstruation ought to occur within 2 years of the establishment of Tanner stage 2 breast change. However, any child presenting at any stage because of concern over failure to establish either secondary sexual characteristics or menstruation should be investigated at that time. There are often extremely good reasons why a mother will bring her daughter for investigation and this often relates to the fact that a sibling completed her pubertal development at an earlier age or she herself went through puberty at an earlier age. **While investigations may not lead to a diagnosis of abnormality, proof of normality is extremely important**.

Thank you