Aim of this module:
At the end of this module, the student will be able to
- Discuss the principles of development and maturation of the endocrine system and the major differences from adulthood;
- Understand and discuss the major influences affecting normal growth in childhood.

Introduction

The endocrine system is one of the regulatory systems of the body, which together with the nervous system and the immune system serves to promote and regulate the maintenance of the body’s internal environment, as well as energy balance, growth, puberty development and reproduction. In all of these, the state of nutrition has an important additional function through its influence on substrate availability.

From the time of conception through intra-uterine growth and postnatal development, childhood and adolescence is a period of progressive biological change. The genetically controlled differentiation of cells into tissues, organs and endocrine glands is followed by progressive growth and maturation. Thereafter, functional development and the establishment of the feedback and other controlling systems have to take place.

The patterns of hormone secretion are established with growth and maturation. With differentiation, the hormone producing cell gains the ability to secrete before the controlling loops and reactions (feedback control, periodicity, sleep-wake cycling, seasonality) are established. For example, the newborn infant sleeps for 16 to 18 hours a day without differentiation into day or night cycles, but by 6 months of age two thirds of the sleep time has been transferred to the night. A 2 year old sleeps only about 1 – 2 hours by day, and by 4 years just about all of the child’s sleeping is done at night. At this stage, the sleep-wake cycle assumes more controlling influence.

Infancy

At birth, the body is fully differentiated and has the potential to mature and develop into the independence of adulthood. Infancy is a period of very rapid growth and development. The normal baby grows nearly 50% of his starting
length by the end of his first year of life. Never again will there be such rapid growth.

The period at birth and early infancy is also a period of intense endocrine activity. The only other comparable time of life is the age of puberty. Just before birth, there is a rapid increase in ACTH secretion, this results in an increased output of cortisol. This is thought to be associated with rapid maturation of enzyme systems, including those of the lungs, in preparation for birth and extra-uterine existence.

Labour is followed by an increase in ADH, Renin and angiotensin levels. Postnatally, there is elevated catecholamine secretion, especially noradrenaline, which helps maintain the blood glucose level by its effect on the metabolism of brown fat before the onset of feeding.

The stress of birth is followed by a surge in thyrotropin activity which results in high levels of circulating thyroid hormone levels. These drop to usual levels only by the end of the first week. Premature or small for dates babies have thyroid hormone levels which are lower than but parallel to those of full-term infants.

Basal growth hormone levels are higher than expected for older children in the first 2 months of life. Thereafter there is a gradual decline till puberty, whereupon levels again increase.

Even the sex hormones are higher in the newborn baby than at any other time until puberty. In fact, on day 1 the blood levels of the androgenic steroid DHEAS (Dehydroepiandrosterone) are comparable to adult values. This period of increased gonadotrophins and sex hormone output lasts for a few months. It may be associated with some symptoms: in some girls there is a vaginal discharge and occasionally even a withdrawal bleed. Many babies develop gynaecomastia (enlargement of the breasts) and many newborn boys have quite pigmented rugous scrotal skin at this age.

**Childhood**

This is quite a stable period endocrinologically. Between early childhood and age about 8 – 9 years, the hypothalamo-pituitary-gonadal axis is dormant, with strong negative feedbacks inhibiting both gonadotrophin and sex hormone release. At the start of puberty, a gradual increase in sleep-associated pulsatile LH release occurs, followed by extension to day-time by mid puberty. Then, cyclic secretion and a change to a positive feed forward loop heralds the onset of menarche. The girl’s body mass has an influence on the pulsatile release of LHRH. In general, menarche occurs only after a mass of 46.5 Kg has been achieved with a specific ratio of fat to lean body mass.

During puberty, the secretion of growth hormone again increases, and together with the release of sex hormones is responsible for the puberty growth spurt. After puberty, growth hormone secretion persists at low levels.
The effect of growth hormone is mediated through IGF-1; this is acutely decreased by fasting, indicating the interaction between endocrine and nutritional events.

**Linkages between regulatory systems**

The different systems receive input from each other to fine tune the homeostatic control. Some neurons release chemical substances into the blood stream to act as hormones (e.g., hypothalamic releasing factors). The innervation of endocrine glands influences their secretion rate. In addition, hormone effects influence immune reactions and cytokines have an influence on neuroendocrine function.

One example of the above is the following interaction between inflammation and hormone response:

The pro-inflammatory mediator IL-1 is released from lymphocytes in response to infection. This IL-1 has an influence in the hypothalamus, where it increases the secretion of ACTH. This in turn results in increased cortisol secretion. The effect of cortisol is to increase the numbers of polymorph neutrophils and to decrease the numbers of lymphocytes, thus decreasing the production of IL-1 and antibodies and thus limiting the degree of inflammatory damage. In situations where IL-1 does not result in increased cortisol, patients have been seen to develop progressive inflammation and arthritis, which responds to treatment with cortisol.

**Measurement and evaluation**

Endocrine organs are commonly assessed by sonographic measurement. This depends on observer experience and the appropriate use of age-related standards.

The measurement of hormone blood levels demands a good laboratory and an understanding of the dynamic nature of the levels obtained, some of which can change acutely even in response to the excitement of having blood taken.

In infancy and childhood, the blood levels of many hormones are much higher than the usual normal adult range. It follows that the interpretation of hormone levels is dependent on the patient's age.

The normal ranges of hormone levels are therefore difficult to interpret in childhood. Ideally the relationship of the members of feedback loops should be measured together, such as T₄ and TSH, Insulin and Blood Glucose, Vasopressin and Plasma osmolality, Testosterone and LH. This can be then depicted in the form of a table, where the Y-axis represents the levels of trophic hormone, and the X-axis the levels of the target endocrine organ hormone.
Infancy is also the period in which the other controlling systems such as the nervous system and the immune system are still immature and developing rapidly. Many of the stable feedback systems and interactions mature at this age and are undoubtedly influenced by the state of stimulation or substrate availability occurring in each of the various systems.

**Endocrine Disorders**

Endocrine disease in childhood occurs as a consequence of one of the following processes:
- **Hormone deficiency:** Genetic (developmental or enzyme deficiency) or Acquired (destruction by infection, immune or vascular processes)
- **Hormone excess:** Genetic (eg adrenogenital syndrome) Acquired (immune or neoplastic)
- **Hormone resistance:** This manifests as a hormone deficiency syndrome in the presence of high circulating blood levels. Caused by a genetic or acquired receptor defect.
Module: Growth disorders in Childhood  
Block 3, Week 5

Department of Paediatrics and Child Health  
University of Pretoria

Tutor: Prof DF Wittenberg: dwittenb@medic.up.ac.za

Aim
At the end of this module, the student will be able to
- Discuss the central importance of growth in the assessment of a child's health;
- List and discuss major causes of poor growth in childhood;
- Discuss an approach to endocrine causes of short stature in childhood.

Key case
One Sunday morning, a nurse working in the paediatric department of a large hospital was travelling in the bus, when a boy got into the seat next to her. Assuming him to be about 8 years old, she enquired where he was attending school. His answer astonished her. He told her that he was a first year student at the Technikon and that he was 18 years old and had finished school with a first class matric pass.

On further questioning, he also said that he had always been very short and had always been mistaken to be much younger. His parents had taken him to doctors on a few occasions, but as he had not really been sick, they had always received the advice that he was ok and that he would “grow out of it”. Eventually, it had just been accepted that he was the way he was.

He has also not yet grown a beard and his voice has not broken. He is the same size and appearance as the 8 year old son of the next door neighbours. He gets depressed about himself.

Introduction

The above case illustrates a central aim of childhood: to grow up. Growing up is one of the most visible expressions of the continuous change taking place during childhood. Children change as they grow up; this applies not only to body size, proportions and composition, but also to physical, cognitive and social abilities, as well as to examination findings and laboratory test results.

The evaluation of a child therefore has to include a comparison of what he is or has achieved in terms of growth and development with what he should be at his given age in addition to the classical features of disease.

In the context of growth, this means that every child must be measured at each consultation, or at least frequently enough to recognize deviations from normal growth (approximately 3 – 4 times per year).

The growth and development of children follows identifiable patterns with a recognizable range of what is normal at each age. A child’s measurement in
comparison with this range is usually expressed as his/her position on a **percentile graph**:

| If 100 normal school children aged 6 years are lined up on the school grounds according to each child’s height starting with the shortest and ending with the tallest, the average or mean height of the whole group can be worked out by adding the height of each of the 100 children together and dividing by 100. This mean height will also correspond to the height measurement between the child on position 50 and that of child on position 51. In other words, of the 100 children, 50% will be shorter and 50% will be taller than the mean. The mean value for these children is called the 50th percentile (centile).
If a child stood very close to the shortest end of the line, his size could also be described in relation to the whole group by expressing it as a percentile. Thus if only 3% of the population were shorter, but 97% were taller than he, his height would correspond to the 3rd percentile. Similarly, a child on the 75th centile would be taller than 75% of normal children of his age.
Percentile graphs have been worked out for populations of normal children living under conditions of health and optimum nutrition. Any child’s measurement can then be compared with the standard by its position on the percentile graph. A percentile must not be confused with a mathematical comparison of the child’s height with the mean or average (also called expected height; on the 50th centile); that measurement could be expressed as \[
\frac{\text{Actual height}}{\text{expected height}} = X \text{ percent of the mean (expected)}.
\]

**Measurement of growth**

Before a child can stand upright, his length is measured. After 3 years of age, the height is recorded. There is a small difference in these two measurements in any one patient due to a sagging effect on the spine when standing.

For the length measurement, the baby is placed on a measuring board with a fixed head end and movable foot end. A second observer holds the head so that the line extending from the external auditory meatus to the lateral canthus of the eye is at right angles to the body plane and the top of the skull lies against the top end of the board. The legs are extended and straight and the heel rests on the board surface. The plane of the sole of the foot is at right angles to the board. The bottom movable end of the measuring board is moved up until it meets the plane of the foot including the heel. The child’s length is read off on a steel tape measure which is embedded in the floor of the board.

Height is measured against a perpendicular surface. The child must stand straight with heels, buttocks, scapulae, occiput all touching the wall. The head must be held in the so-called Frankfurt plane (external auditory meatus and lateral canthus of the eye in a horizontal plane).

Unless the technique of measurement is adhered to carefully, height or length measurements are subject to large errors and interobserver variation. If done carefully however, the failure to grow according to expected rates is a very important test of longterm health and normality.
Different types of growth charts

A *distance chart* is a height for age growth chart constructed around the actual heights of children at different ages. There are separate charts for boys and girls. A *velocity chart* relates the speed of a child’s growth in centimetres per year to its age. This shows the varying speed of growth at different ages: in the first year of life, a child will grow nearly 50% of its starting length, whereas a prepubertal child of age 8 years or so may grow at only about 4 – 6 cm per year.

**The child with poor growth**

Because there are so many influences on a child’s growth, it can be said that normal growth is a good indicator of a child’s long term health. Conversely, a child who is not growing normally must have a health problem even if no major symptoms or signs are present. The fact of poor growth is the clinical indicator of a problem.

**Genetic influences on growth**

Family stature is the strongest predictor of growth. Tall families tend to have tall children. But 3% of the normal population are short (less than the 3rd percentile) and if a child is of a normal length for his family he is probably quite normal.

**Short stature can be defined as a body length or height less than that expected for the family**

Genetic influences are additionally found in single gene disorders that alter growth expectation. Examples are disorders of bone associated with short stature (eg achondroplasia, osteogenesis imperfecta), or genetic diseases...
that interfere with growth through a number of other mechanisms (eg renal tubular acidosis).

**Intra-uterine environment and programming**
Babies who are born with a small body size relative to its gestational age (small for gestational age, SGA) are often found to remain small. A number of syndromes based on abnormal intrauterine development or teratogen exposure

**Bone and joint abnormalities**
Conditions like rickets or chronic diseases of bone lead to abnormal skeletal growth and therefore short stature.

**Chronic diseases**
Chronic disease interferes with growth through a number of mechanisms including increased energy expenditure on the disease and therefore too little available for growth; deranged cellular function, decreased tissue perfusion and oxygenation. Thus, poorly controlled asthma, congenital heart disease, chronic renal failure and chronic malabsorption are all associated with poor growth.

**Chronic emotional stress**
The emotional deprivation syndrome is a cause of poor growth where children suffer from chronic emotional stress. This may take the form of emotional neglect or exposure to continuous unhappiness and family tension. The mechanism is an interference with the hypothalamic releasing hormones.

**Malnutrition**
In children who are chronically undernourished, the building blocks for normal growth are missing. Protein energy malnutrition is the commonest cause of stunting worldwide.

**Endocrine diseases**
Growth hormone and thyroid hormone deficiency can cause short stature as isolated deficiencies or as part of multitropic pituitary deficiency. Clinical pointers exist to suggest the presence of an endocrine cause of short stature.

**Clinical approach to a child with short stature**

**Identification**
A growth problem can only be identified by regular measurement. Failure to measure is the commonest reason for delayed or inappropriate diagnosis. Once a measurement has been taken, it must be recorded and charted on an appropriate growth chart. Furthermore, if a child is repeatedly measured and the measurements recorded on the growth chart, visual inspection of its tracking will tell whether the child is progressing normally. A normal child continues more or less on or near its centile line. Progressive deviation from the centile line indicates a problem of growth and must trigger action.
Take the history
- Prenatal development: exposure to smoking, drugs, alcohol, infections.
  Prenatal growth. Gestational age at birth and birth weight.
- Postnatal growth and development: Nutritional status and weight gain.
  Appetite and food intake. Age at which height deficiency became evident.
  Developmental progress in learning and milestones.
- Evidence of disease of any organ system. Chronic medication.

Accurate measurement
This includes the proportions of the body relative to its age. Include arm span, upper segment to lower segment ratio. Disproportionate shortness of trunk or limbs refers to specific conditions affecting bones, such as the short-limbed syndromes (eg achondroplasia) or the short trunk conditions (eg mucopolysaccharidoses).

Careful clinical examination
To exclude disease of any organ system or a syndrome associated with poor growth (eg Foetal alcohol syndrome, Down syndrome)

Evaluate growth velocity
Unless the child is less than 3 standard deviations below the average for its age, or another feature is evident, it is useful to determine the growth velocity, i.e. the rate of growth in centimetres per year. This is done by repeating the growth measurement after 4 – 6 months and determining the difference. If the growth rate is normal, the patient has constitutional delay in growth and development, or familial short stature. A very short child should be evaluated immediately.

Where the growth rate is abnormally slow, and the other aspects above are sorted out, an endocrine cause of short stature or emotional deprivation must be considered.

Hormone tests for short stature
A thyroid hormone assay should be done immediately, even before observing the patient’s growth velocity.
Single random blood tests are of very little use in diagnosing growth hormone deficiency because it is secreted in pulsatile fashion. If a hormone assay is required at all, it should be done as a dynamic test to identify the hormone response to a releasing stress.

Solution of the key case
The young man presented with a number of problems: He was not growing, he had not developed puberty signs and he was continually being mistaken for a much more immature child. He had not received helpful advice. He was of normal or above normal intelligence. The lack of secondary sexual characteristics suggests a problem of sex hormone output. This could occur because his testes are not producing testosterone, or because of deficient gonadotrophic hormones from the pituitary.
He has always been short. This suggests that a hormone problem may have antedated the time by when puberty changes might have been expected. Growth hormone deficiency can often be associated with deficiency of other anterior pituitary hormones. After investigation, the diagnosis of anterior pituitary deficiency with growth hormone and gonadotropin deficiency was made.