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Question 1: **What do you understand by primary or simple obesity.**

Simple obesity also known as primary obesity is an obesity resulting when caloric intake exceeds energy expenditure. OR This is due to excessive energy intake and too little consumption also known as diet-induced obesity and has the largest proportion (95%) in all types of obesity.

The simple obesity are generally caused by the hereditary factor, the nutrition surplus and a lack of exercise and characterized by the even distribution of the whole body fat.

Question 2) **How does congenital syndrome and drug therapy affects obesity?**

a) Congenital Syndrome can be said to be often-inherited medical condition that occurs at or before birth.

b) Drug Therapy is the treatment of any substance, other than food, that is used to prevent, diagnose, treat or relieve symptoms of a disease or abnormal condition.

Some congenital syndrome and drug therapy that affect Obesity are;

1). Leptin (LEP) and Leptin Receptor (LEPR) Deficiency: Leptin is a product of adipocytes in fatty tissue and its level increases with increased amounts of fatty tissue. It is bound to LEPR in the arcuate nucleus and other parts of the brain. Hunger acutely lowers the level of LEP, which strongly stimulates appetite and

reduces energy consumption. Individuals with a homozygous inactivating mutation of the LEP gene have an excessive food intake and develop severe obesity with very low LEP levels at an early age. Heterozygotes can only be presented with slightly lower levels of leptin.

In children with leptin receptor mutation, Hyperplasia begins in the first weeks of life and in those with mutation of leptin after several months. Leptin deficiency will also cause frequent infection, mild hypothyroidism and postponed puberty.

2). Brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) gene mutations: BDNF is very important for neuronal development and function. It exerts its effect on food intake and body mass through the TrkB receptor in the leptin signalling pathway, after MC4R. Heterozygosity for BDNF is considered to be responsible for early development of obesity in patients with Wilms tumor-aniridia syndrome (23).

Heterozygous carriers of an inactivating TrkB gene mutation are reported among patients with obesity, psychomotor retardation and convulsions.

3). Prader-Willi Syndrome (PWS): This is based on Congenital Syndrome and Drug therapy.

A rare and complex genetic disorder that affects many organ systems, is a consequence of the lack of expression of paternal genes in the 15q11-q13 region. From the earliest age it causes reduced muscle tone that impairs feeding and development. Due to excessive food intake, severe obesity develops. In spite of the obesity these children lag in growth and are of short stature, there is no sexual development and psychomotor development is also delayed. The disease is characterized by numerous complications, primarily obesity associated, which significantly impair the quality of life and shorten life expectancy.

Early confirmation of the diagnosis by genetic testing and initiation of treatment by multidisciplinary approach are of crucial importance for the course of the disease. First of all, it is necessary to ensure control of food intake and thereby prevent the development of severe obesity and, by applying habilitation measures, to enhance the psychomotor development of the child.

Growth hormone has been introduced in the treatment, since GH deficiency was recorded in approximately 80% of PWS children. This therapy accelerates growth,

improves final height and has a positive effect on body composition, primarily by reducing the amount of fat tissue. Therapy is maintained until the final height is achieved, but its positive effect on the patient's metabolic status persists several years after its discontinuation.

4) Carpenter syndrome: Besides obesity, includes mental retardation, short stature, brachicephalus, polydactyly, foot syndactyly, cryptorchidism, hypogonadism in boys, umbilical hernias and high palate. The RAB23 gene is located on chromosome 6p11. Like in Alström's and Bardet-Biedl's syndromes, this gene mutation also causes an impaired function of proteins involved in the ciliary body important for intercellular communication in mammals. The disorder also seems to disrupt communication between the neurons involved in the leptin signal pathway, crucial for energy homeostasis.

5) Proopiomelanocortin (POMC) gene mutation: By acting on neurons in the hypothalamus, leptin stimulates the production of POMC, whose cleavage originates from adrenocorticotropic hormone (ACTH), alpha-, beta- and gamma-melanocyte stimulating hormone (MSH), beta-lipoprotein and beta-endorphin. Alpha-MSH regulates appetite and energy consumption by binding to the melanocortin-3 and -4 receptors (MC3R and MC4R) in the arcuate nucleus. Inactivating mutations of POMC prevent its cleavage to alpha-MSH or ACTH. Patients, homozygotes or complex heterozygotes for the POMC mutation, have hyperphagia (probably due to a lack of signals on MC3R and MC4R), red hair (absence of peripheral binding of alpha-MSH to melanocortin-1 receptor) and adrenal insufficiency.

6) Cushing's syndrome: Cushing syndrome occurs as a result of either excessive cortisol-like medication or a tumor that either producesor results in the production of excessive cortisol by the adrenal glands. Cushing syndrome in children is very rare, and most commonly iatrogenic as the consequence of glucocorticoid therapy of malignant or rheumatic diseases. However, in rare cases it may be the result of a pituitary or adrenal gland tumour. Ectopic secretion of ACTH is exceptional in children and adolescents.

Adiposity caused by hypercortisolism is associated with a reduction in the growth rate (growth almost ceases). This clinical sign has to be the main reason for hypercortisolism screening. Unlike in adults, whose adiposity is predominantly

centripetal, involving the trunk and fatty tissue pad on the neck, in children the adiposity is mostly generalised. Physical examination will reveal a round face with red cheeks, hirsutism, acne and purple striae.

Increased glucocorticoid levels increase gluconeogenesis, and thus insulin secretion and insulin resistance, simultaneously inhibiting lipolysis and stimulating lipogenesis. Therefore a glucose tolerance disorder, hypertension, headache, hyperphagia, emotional instability and depression are often concomitant. In the case of simple obesity, hypercortisolism may also be present, making it difficult to distinguish it from Cushing's syndrome. This can be managed by monitoring the daily cortisol rhythm, with the most relevant and lowest level at midnight, and by means of the dexamethasone suppression test.

Question 3) **Outline the aetiology of cancer and its molecular basis.**

Cancer is an uncontrolled growth of abnormal cells in the body. Cancer develops when the body's normal control mechanism stops working whereby, old cells do not die and instead grow out of control, forming new, abnormal cells. Cancer cells are characterized by certain key properties: they proliferate rapidly, they display diminished growth control, they display loss of contact inhibition in vitro, they invades local tissues and spread or metastasize to other parts of the body.

Aetiology of Cancer

a) Radiant Energy such as Ultraviolent rays, x-rays and gamma rays.
b) Chemicals examples; Beno[a]pyrene, 2-acetylaminofluorene, Dimethylnitrosamine, Aflatoxin B1.
c) Viruses that cause cancer include human papilloma virus, human herpes virus, hepatitis B virus, human T-cell leukaemia virus, Human immunodeficiency virus, Hepatitis C virus

Molecular Basis of Cancer

ONCOGENE: An oncogene can be defined as an altered gene whose product acts in a dominant manner to accelerate cell growth or cell division. Oncogenes are

generated by “activation” of normal cellular proto-oncogenes; that is, genes encoding growth stimulating proteins.

TUMOR SUPPRESSOR GENE: A tumor suppressor gene produces a protein product that normally suppresses cell growth or cell division. When such a gene is altered by mutation, the inhibitory effect of its product is lost or diminished. This loss of tumor suppressor gene function leads to increased cell growth or cell division.

Most cancer mutations alter signals even when more cells are not needed, switching on cell growth, DNA replication and cell division inappropriately. The cancer-critical genes that regulate cell division exert their effects by acting on the central cell-cycle control machinery and many cancer cells proliferate inappropriately by eliminating ***Rb (the product of the tumor suppressor gene)*** protein entirely.

Cells in the multicellular organism commit suicide when they sense that something has gone wrong-when their DNA is severely damaged or when they are deprived of survival signals that tell them they are in their proper place. Therefore, resistance to apoptosis is thus a key characteristic of maglinant cells, essential for enabling them to increase in number and survive where they should not. A number of mutations that inhibit apoptosis have been found in tumors. One protein that blocks apoptosis is called ***Bcl-2***, as it targets chromosome translocation in a B-cell lymphoma.

The ***p53*** gene may be the most important gene in human cancer. This tumor suppressor gene is mutated in about half of all human cancer. The reason why p53 is so crucial is because of its triple involvement in cell-cycle control, in apoptosis and in maintenance of genetic stability. When normal cells are deprived of oxygen or exposed to treatments that damage DNA, such as Ultraviolent light or gamma rays, they raise the concentration of p53 protein by reducing the normally rapid rate of degradation of the molecule. The p53 response is seen in also where oncogens such as Ras and Myc are active, generating an abnormal stimulus for cell division.

Cells defective in p53 fail to show these responses. They tend to escape apoptosis and if their DNA is damaged-by radiation by some other mishap, they carry on

dividing, plunging into DNA replication without pausing to repair the breaks and other DNA lesions that the damage has caused.

Many cancer cells contain large quantities of mutant p53 protein. The loss of p53 activity can thus be trebly dangerous in relation to cancer. It also allows faulty mutant cells to continue through the cell cycle. It allows them to escape apoptosis and it leads to the genetic instability characteristic of cancer cells, allowing further cancer-promoting mutations to accumulate as they divide.

DNA tumor viruses cause cancer mainly by interfering with cell-cycle controls including those that depend on p53 and in more than 50% of all human tumors the p53 pathway is aberrant resulting in increased survival of cancer cells.

Malignant transformation of normal cells can be attributed to the presence of ***telomerase***, the enzyme responsible for maintaining telomeres at the ends of chromosomes. By extending telomeric DNA, telomerase is able to counter the progressive telomere shortening that would otherwise lead to cell death. Approximately, 90% of human tumors consists of cells that contain anactive telomerase enzyme.