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QUESTION 1

What do you understand by primary or simple obesity?

ANSWER

Primary Obesity is a nutritional disorder that is characterized by high accumulation of fat as a result of excessive food intake, lack of physical activity and genetic susceptibility. Primary obesity is however not associated with clinical disorders.

QUESTION 2

How does congenital syndrome and drug therapy affect obesity?

ANSWER

CONGENITAL SYNDROMES AND HOW THEY AFFECT OBESITY

Some congenital syndromes are obesity-related syndromes and in these syndromes, obesity begins after infancy. Other than obesity, basic syndrome features include dysmorphia, psychomotor retardation and anomalies of certain organ systems. They can occur due to gene or larger chromosomal abnormalities. Autosomal or X chromosomes can be affected. Some of these congenital syndromes are explained as follows:

- **Prader-Willi syndrome (PWS):** This is a rare and complex genetic disorder that affects many organ systems and it is a consequence of the lack of expression of paternal genes. From the earliest age it causes reduced muscle tone that impairs feeding and development. Due to excessive food intake, severe obesity develops and 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 characterised by numerous complications, primarily obesity, which significantly impair the quality of life and shorten life expectancy. In the last few years, 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. The appetite regulation disorder in PWS is manifested by the inability to stop eating, repeated food intake soon after the previous meal and consumption of inedible items. This is not a consequence of an increased sense of hunger, but of a lack of satiety because of a hypothalamic disorder and increased stimulation of the ventromedial prefrontal cortex region as a response to food.

- **Bardet-Biedl syndrome (BBS):** This is a heterogeneous autosomal recessive disorder due to mutations in one of the 15 possible genes that control ciliary function. The role of cilia in regulating body mass has been confirmed in mice. Primary ciliary disorders by inactivating mutations of the Tg737 and Kif3a genes in POMC neurons, i.e. the leptin signal pathway, lead to hyperphagia and obesity. Classical clinical features include severe early-onset obesity, retinitis pigmentosa, hypogonadism, mental retardation, glucose intolerance, and postaxial polydactyly, deafness and kidney disorders. Mortality is a consequence of obesity and kidney disease complications.
- **Alström's syndrome (AS)**: This is a rare autosomal recessive disorder due to the mutation of the ALMS1 gene located on chromosome 2p13, which also disrupts ciliary function. In addition to early central obesity like in children with BBS, children with AS also have visual impairment and deafness. Central obesity develops by 5 years of age, and the affected children have acanthosis nigricans and type 2 diabetes more often than children with BBS. Other endocrinopathies include hypothyroidism, primary hypogonadism in boys and GH deficiency. However, intellectual development is normal.
- **Carpenter syndrome:** In this syndrome, besides obesity there is 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 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.
- **WAGR syndrome**: This syndrome includes Wilms tumour, aniridia, genitourinary tract abnormalities and mental retardation, while obesity is present only in some patients. The syndrome is caused by a deletion on chromosome 11p11.4, near the gene responsible for BDNF production. BDNF is regulated by nutritional status and included in the leptin signal pathway in the hypothalamus where it stimulates the production, differentiation and survival of neurons, but also body mass regulation. Most WAGR syndrome patients with the deletion which includes BDNF are obese, unlike those with no deletion, in whom the frequency of obesity is consistent with that in the general population.

HOW DRUG THERAPY AFFECTS OBESITY

The mandatory statement is that lifestyle modifications including dietary habits modification, physical therapy and behavioural therapy are the basis of all weight loss strategies. If the patient is not losing weight using these methods (at least 0.45 kg/week during 6 months), drug therapy should be considered. It is indicated for patients with BMI equal or higher than 30 kg/m^2. Patients with BMI 27 kg/m^2 and higher and concomitant obesity-related diseases (hypertension, dyslipidaemia, coronary heart disease, type 2 diabetes, sleep apnoea) could also be considered for drug therapy. The efficacy of the drug

should be reconsidered after therapy introduction. In situations when the drug is not efficacious enough, it should be re-evaluated and possibly discontinued. There are not many available drugs treating obesity on the market today. They could be divided into three categories. The first one is the group of drugs that suppress appetite (eg. sibutramine); the second is the group of drugs that interfere with digestion (eg. orlistat); and the third category is an inhomogeneous group of drugs that are actually used for other indications than weight loss, but with a concomitant weight loss effect. Such drugs are for example incretins used in the treatment of diabetes (eg. exenatide, liraglutide), antiepileptic drugs (eg. topimarate) and antidepressants (eg. fluoxetin, sertaline).

QUESTION 3

Outline the aetiology of cancer and its molecular basis

ANSWER

AETIOLOGY OF CANCER

All cancers are multifactorial in origin. They include genetic, hormonal, metabolic, physical, chemical and environmental factors. This factors cause gene mutation that result in cancer. Most human cancers are spontaneous and about 50% is due to mutation/deletion of this repair gene called the anti-oncogene or oncosupressant gene.

CAUSES OF CANCER

1. **CARCINOGENS**

   Carcinogens are mutagens and vice versa. Carcinogens, whether physical or chemical cause DNA damage that leads to mutation and these mutations can cause cancer. Examples are X-rays, gamma rays, ultraviolet rays. Some human cancers are caused by chemicals such as polycyclic aromatic hydrocarbons (Benzopyrenes, Cholanthrenes & Dimethyl benzanthracene (DMBA)), Aromatic amines (N-Methyl-4aminoazobenzene), Nitroso compounds (Dimethyl nitrosamine) and Natural compound (Aflatoxins). These may be introduced into the body by means of occupation (aniline, asbestos), diet (aflatoxins) or lifestyle (smoking). Chemical carcinogens act cumulatively. Tobacco, food additives, coloring agents, and aflatoxins are common carcinogens in our environment.

   - **Physical Carcinogens:** X-ray, gamma ray and UV ray may cause: (a) formation of pyrimidine dimers, (b) apurinic sites with consequent break in DNA, and (c) formation of free radicals and super oxides which cause DNA break, leading to somatic mutations. Exposure of x-ray in foetal life will increase the risk of leukaemia in childhood. In population studies, 1 rad per year will increase the cancer incidence by 40/million people per year.
   - **Aflatoxins:** They are a group of chemically related compounds synthesized by the fungi, Aspergillus flavus. The mould grows on rice, wheat and groundnut, when kept in damp conditions. The fungi may grow in cattle fodder, which

may enter into human body through the cow's milk. Aflatoxins are powerful carcinogens, which produce hepatomas.

- **Cigarette**: Lung cancer is associated with the habit of cigarette smoking. Cigarette contains many carcinogens, the most important group being benzopyrenes. Other important deleterious substances in cigarette smoke are nicotine, carbon monoxide, nitrogen dioxide and carbon soot. Statistically, it is estimated that one cigarette reduces 10 minutes from the lifespan of the individual. The incidence of lung cancer is increased to 15 times more in persons smoking 10 cigarettes per day and 40 times more when smoking 20 cigarettes per day.

2. ONCOGENIC VIRUSES

Another etiological factor of carcinogenesis is the integration of viral genes into the host DNA. The circularization of virus DNA will help in this process. Thus, the virus genes become part and parcel of the cellular DNA. The drive for multiplication by the virus genome overrules the regulatory checks and balances of the cellular mechanism. So, there is uncontrolled multiplication of the cells. This is called transformation by oncogenic virus.

For example, we have the HPV (Human Papilloma Virus) which is the most common sexually transmitted infection in adults. It has a circular double stranded DNA. More than 100 HPV types are known. HPV types 16 and 18 are associated with human uterine cervical cancer; they cause 70% of all cervical cancers. Harald zur Hauzen (Nobel Prize, 2008) showed the HPV DNA in the cancer cells. HPV infects epithelial cells in the cervical mucosa; the virus multiplies and lyses the host cells, causing a lesion. In 99% of such cases healing occurs within 6 months to 2 years. But in about 1% cases, the HPV DNA is integrated into some of the host cells. After about 10–30 years, these cells develop invasive cancer. Vaccines against high risk HPV16 and 18 types are now developed that provide 95% protection from infection of HPV, thereby reducing the chances of developing cervical cancer. HPV vaccine is now recommended for all girls and women between the ages of 9–25 years in Western countries.

SOME VIRUSES AND THEIR ASSOCIATED CANCERS

Human Virus	Abbreviation	Associated human cancer
Epstein-Barr virus	EBV	Burkitt's lymphoma (BL); Nasopharyngeal carcinoma (NPC)
Human papilloma virus	HPV	Uterine cervical carcinoma
Hepatitis B virus	HBV	Hepatoma
Hepatitis C virus	HCV	Hepatocellular carcinoma
Human immunodeficiency virus	HIV	Kaposi's sarcoma

3. **HEREDITARY**
   Mutated genes causing cancer has a 50% chance of getting to the offspring e.g. Xeroderma Pigmentosa (XP) and colon cancer. These cancers are known to be highly hereditary.

MOLECULAR BASIS OF CANCER

Cancer is a disease of uncontrolled growth and proliferation whereby cells have escaped the body's normal growth control mechanism, and gained the ability to divide indefinitely. It is a multi-step process that requires accumulation of many genetic changes over time. These changes include: activation of proto-oncogenes to oncogenes, deregulation of tumour suppressors and DNA repair genes and "immortalization".

- In normal cells, proliferation and progression through cell cycle is strictly regulated by groups of protein that interact with each other in a specific sequence of events. The re-entry of cells into the cycle is a decision influenced by extracellular mitogenic signal which are transmitted via signalling pathway to key regulatory proteins. These proteins ultimately trigger the start of DNA synthesis. In normal cells, activation of the p53 gene which is known as the guardian of the genome will impose cell cycle arrest or induce apoptosis depending on the damage to the cell. However in the case of 50% of human tumors, the p53 pathway is aberrant and inactivation of the p53 protein renders it unable to signal and activate the cell's apoptotic machinery resulting in increased survival of cancer cells

- Normal somatic cells proliferates a limited number of times before undergoing senescence. Senescent cells may remain metabolically active even though they have permanently ceased proliferation. However immortalization is an essential step in the malignant transformation of normal cells and can be attributed to the presence of telomerase, the enzyme responsible for maintaining telomeres at the ends of chromosomes by extending telomere DNA. Telomerase is able to counter the progressive telomere shortening that would otherwise lead to cell death. Unlike normal cells that lack detectable levels of telomerase activity, approximately 90% of human tumors consist of cells that contain an active telomerase enzyme which prevents cell death and makes the cancer cell *"immortal."*
- Growth factors play an important physiological role in normal process of growth control of cells by transmitting growth signals from one cell to the other signalling pathways to activate target molecules that promote proliferation. In cancer, this pathway is derailed allowing wayward cells generate their own internal signals that stimulate uncontrolled proliferation and become independent of their environment. Cancer cells are able to induce their own growth stimulating signals when mutations in the GFR gene occur.