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BCH ASSIGNMENT

1. What do you understand by primary or simple obesity.

Simple or primary obesity is due to excessive energy intake and too little consumption of energy, also known as diet induced obesity and has the largest proportion in all types of obesity.

2. How does congenital syndrome and drug therapy affect obesity

Constitutional obesity occurs in several multiple congenital anomaly syndromes including;

1. Prader - Willi Syndrome
2. Bardet - Biedl Syndrome
3. Albright Hereditary Osteodystrophy ~~and~~
4. Wilson Turner Syndrome and
5. Foresman - Lehmann Syndrome

As well as some rarer disorders.

1. Prader - Willi Syndrome (PWS)

PWS is a complex neurodevelopmental genetic condition due to paternal loss of imprinted genes on chromosome 15 and characterized by a range of mental findings including obesity that can be life threatening

Obesity is the most common cause of metabolic complications and poor quality of life in PWS. It develops after an initial phase of poor feeding and failure to thrive

Several mechanisms for the manner of causation (aetiology) of obesity in PWS are proposed which include;

i. Disruption in hypothalamic pathways of satiety control resulting in hyperphagia (excessive eating from excess hunger or increased appetite.)
ii. Aberration in hormones regulating food intake
iii. Reduced energy expenditure because of hypotonia, which prevents PWS patients from becoming physically active causing reduced muscle

movements and hence reduced energy expenditure.

2 Bardet - Biedl Syndrome (BBS)

BBS is a highly pleiotrophic (producing or having multiple effects) autosomal recessive disorder associated with a wide range or array of phenotypes, with six clinical features that are considered the cardinal manifestations.

Despite the wide spectrum of disorders that BBS patients may carry, obesity; truncal obesity (disproportional fat deposition along / onto the abdomen and chest) appears to be one of the most disturbing symptom of the syndrome and highly prevalent in BBS heterozygous individuals.

The mechanisms by which BBS genes may influence adiposity is not clear, but this may occur in conjuction with other known genes [eg MC4R (melanocortin 4-receptor) and FTO (fat mass and obesity associated gene)

Alterations in hypothalamic action of leptin is a major abnormality accounting for energy imbalance in this syndrome. (Leptin is a 167 amino acid protein expressed mainly by adipocytes and released in the blood in proportion to fat mass. Leptin action in the central nervous system promotes weight loss by reducing food intake and increasing energy expenditure)

Increased circulating levels of leptin (hyperleptinemia) associated with leptin resistance is seen in BBS patients.

The alteration of leptin action was associated with changes in the downstream neuropeptides involved in the control of energy homeostasis. Several brain regions ranging from cortex to brainstem are known to be involved in leptin regulation of energy homeostasis with the hypothalamus playing a key role.

3 Albright Hereditary Osteodystrophy (AHO)

A disorder caused by heterozygous inactivating mutations in GNAS, the gene encoding the alpha chain of the stimulatory G protein Gs, and is associated with short stature, obesity, brachydactyly, subcutaneous ossifications, dental abnormalities and cognitive impairment.

Patients with AHO with GNAS mutations on maternally inherited alleles often manifested resistance to multiple Gs protein-coupled hormones (eg PTH, TSH, LH, FSH, GHRH) a variant termed pseudohypoparathyroidism type 1a (PHP1a)

Those patients who inherit mutations on the paternal allele have the AHO developmental defects and phenotype alone without hormonal resistance a variant termed pseudopseudohypoparathyroidism (pseudoPHP)

It was observed that obesity is not only more common in PHP1a than in pseudoPHP, but is marked by significantly greater mean weight (SDS) as well as BMI percentiles which is as a result ~~in~~ of decreases in resting energy expenditure.

Wilson-Turner Syndrome

A very rare X-linked multisystem genetic disease characterized by intellectual distability, truncal obesity, gynecomastia, hypogonadism, dysmorphic facial features and short stature.

The described phenotype overlaps with Borjeson-Forssman Lehmann syndrome a form of X-linked intellectual distability. Differences between the 2 described families are small but there's a possibility that they are different entities as little is known of them.

Medications associated with weight gain / Drug therapy include certain

A. Antidepressants (medications used in treating depression)

Experts say that for up to 25% of people most antidepressant medications including: The popular SSRI (selective serotonin reuptake inhibitor) Eg citalopram (Celexa), fluoxetine (Prozac), paroxetine (Brisdelle, Paxil, Pexeva), Sertraline (Zoloft), Cyclic antidepressants - TCAs eg amitriptyline (Elavil), amoxapine, desipramine (Norpramin), doxepin (Adapin), Imipramine (Tofranil-PM), nortriptyline (Pamelor), Protriptyline (Vivactil), trimipramine (Surmontil), Monoamine oxidase inhibitors (MAOIs)

They do this by interfering with serotonin, the neurotransmitter then regulates anxiety and mood while also controlling appetite. In particular, these changes may increase cravings for carbohydrate rich foods such as bread, pasta and desserts.

B. Anticonvulsants (medications used in controlling seizures) such as carbamazepine (Tegretol, Tegretol XR, Equetro, Carbatrol), valproate (Depacon, Depakene), vigabatrin, gabapentine

Body weight gain is a common and frequent undesirable effect associated with the use of anticonvulsant drugs.

i Potential mechanisms of anticonvulsant associated weight gain are not the same and differ with drug used but include

I The involvement of lowered blood glucose level, which may stimulate eating through an effect on the hypothalamus, constitutes one of the possible mechanisms. Lowered blood glucose levels may result from

i A competition between the binding of the drug and long chain fatty acids. An increased availability of the latter stimulates insulin production and lowers the serum glucose levels.

II A deficiency in carnitine directly caused by the drug,

that would result in a reduction of fatty acid metabolism and an increase in glucose consumption

2 Enhancing effect of gamma aminobutyric acid-mediated neurotransmission may increase appetite for carbohydrates reduce expenditure

c. Medications used in lowering blood sugar such as insulin, sulfonylureas and thiazolidinediones)

Insulin's basic function in the body is to help it absorb nutrients ushering glucose from the blood into cells for use and storage and so it inherently promotes weight.

The other diabetes medications that trigger weight gain primarily do so by increasing the amount of insulin in the body they include:

1 Sulfonylureas

They are a class of oral hypoglycemic agent used for the treatment of type 2 diabetes. They are described as insulin secretagogues they act on a set of receptors on β cells, thereby increasing insulin secretion

2 Repaglinide and Nateglinide.

Often described as being in the same class of drugs, repaglinide and nateglinide actually have very different chemical backgrounds but have similar mechanisms of action. Repaglinide is a meglitinide and nateglinide is a D- phenylalanine derivative. Both drugs fall into the category of insulin secretagogues and have their effect by stimulating the β-cell. The action of both drugs is glucose dependent, and, in contrast to the sulfonylureas, they stimulate insulin secretion only in the face of elevated glucose levels. These drugs are given before meals and decrease post prandial glucose levels.

Weight gain is seen with both drugs These drugs caused a decrease in urinary glucose excretion that

may play the major role in weight gain

3 Thiazolidinediones

They are a class of drugs that activate the peroxisome proliferator - activated receptor - γ (PPAR-γ). Activation of this receptor decreases insulin resistance and promotes glucose uptake by the cell in patients with type 2 diabetes. Drugs that are currently available in this class include rosiglitazone and pioglitazone.

The improved glucose control seen with these drugs may result in weight gain and in some cases substantial weight gain. The cause of this weight gain is unclear. Decreased glycosuria may play a role, but these drugs appear to also have a direct effect on the PPAR receptors on the adipocyte and thus stimulate adipogenesis.

D Certain hormones such oral contraceptives, and corticosteroids such as prednisone.

E Some high blood pressure medications and antihistamines

3. Outline the aetiology of cancer and its molecular basis.

Cancer is a disease of controlled growth and proliferation whereby cells have escaped the body's normal growth control mechanisms and have gained the ability to divide indefinitely.

It is a multi-step process that requires the accumulation of many genetic changes overtime. These genetic alterations involve activation of many genetic changes overtime. These genetic alterations involve activation of proto oncogenes to oncogene, deregulation of tumour suppressor genes and DNA genes and immortalisations.

Cancer is a group of disease characterized by an autonomous proliferation of neoplastic cells which have a number of alterations including

1. Mutations and genetic instability :- mutations in protein synthesis and therefore abnormal gene formation and malignant transformation require two or more abnormalities occuring on the same cell or different cells.
2. Resisting cell death :- Cell death occurs in healthy tissues through a) apoptosis which is programmed cell death and is markedly reduced in cancers.
b) Autophagy which is a catabolic process during which cellular constituents are degraded by lysosomal machinery with the cell. It is physiologically occurring at low levels in cells but can be induced in response to environmental stresses, particularly radiotherapy and cytotoxic chemotherapy which induce elevated levels of autophagy that are cytoprotective for malignant cells, thus impeding rather than perpetuating the killing actions of these stress situations and c) necrosis which is a premature cell death. It is characterised by the release of cellular contents into the local

tissue microenvironment. Necrotic cell death results in the recruitment of inflammatory immune cells, promotion of angiogenesis, cell proliferation and tissue invasion. Necrotic cells also release stimulatory factors which promote proliferation of neighbouring cells and can promote rather than inhibit carcinogenesis.

3 Sustaining Proliferative Signaling:- Cancer cells can sustain proliferation beyond what would be expected for normal cells, typically due to growth factors, which are able to bind to cell surface bound receptors that activate an intracellular tyrosine kinase mediated signalling cascade, ultimately leading to changes in gene expression and promoting cellular proliferation and growth.

Cell cycle is regulated by a number of molecular mechanisms, most importantly by cyclins and cyclin dependant kinases (CDKS). The complexity of cell cycle control is susceptible to dysregulation which may produce a malignant phenotype. Many cancer cells produce growth factors which drive their own proliferation by a positive feedback known as autocrine stimulation

4 Evading growth suppressors:- cell to cell contact in dense cell populations acts as an inhibiting factor on proliferation. This is typically absent on many cancer cell populations.

5 Enabling replicative immortality - For cancer cells to evolve into macroscopic tumours, they need to acquire the ability for unlimited proliferation. Telomerase, a specialized polymerase enzyme, adds nucleotides to telomeres allowing continued cell division and thus preventing arrest of cellular replication. The telomerase enzyme is almost absent

in normal cells.

6 Inducing angiogenesis :- All cancers require a functional vascular network to ensure continued growth. They require sustenance in the form of nutrients and oxygen as well as an ability to evaluate metabolic waste products and carbon dioxide. This entails the development of new blood vessels.

7 Activating invasion and metastasis :- It involves multiple discrete steps. It begins with local tissue invasion, followed by infiltration of nearby blood and lymphatic vessels by cancer cells. Malignant cancer cells are eventually transported through haematogenous and lymphatic spread to distant sites within the body

8 Reprogramming energy metabolism :- Cancer cells can reprogramme their glucose metabolism to limit energy production to glycolysis even in the presence of oxygen termed aerobic glycolysis. Increased production of glycolytic intermediates occurs and can be fed into various biosynthetic pathways including those that generate nucleosides and amino acid necessary for the production of new cell cells.

9 Tumour - promoting inflammation :- Tumor - associated inflammatory responses promote tumour formation and cancer progression.

10 Evading immune destruction :- The immune system operates as a significant barrier to tumour formation and progression and the ability to escape from immunity is a hallmark of cancer development. Deficiences in the development of function of CD8+ cytotoxic T lymphocytes, CD4+ Th1 helper T

cells or natural killer (NK) cells can each lead to a demonstrable increase in cancer incidence. Also highly immunogenic cancer cells may evade immune destruction by disabling components of the immune system.

Cancers develop and progress when there is loss of recognition by immune system, lack of susceptibility due to escape from immune cell action and induction of immune dysfunction often via inflammatory mediators.

There could be mutations in mechanisms responsible for DNA maintenance and repair, the basic structure of DNA and the order of nucleotides. These mutations can be inherited or can occur sporadically. At nucleotide level, these mutations can be substitutions, additions or deletions. Also several oncogenes examples P53, C-Fms and Ras genes can be activated by point mutations that can lead to amino acid substitution in critical portions of the protein.

Aetiology of Cancer.

The majority of cancers do not have a ~~simple~~ single cause but rather are the result of a complex interaction between genetic factors and exposure to environmental carcinogen.

A) Environmental factors

1. Occupational exposure -
Dye and rubber manufacturing - aromatic amines, asbestos mining, vinyl chloride (PVC) Manufacturing, Petroleum industry - benzene

2. Chemicals - Chemotherapy - melphalan, cyclophosphamide

3. Cigarette smoking

4 Viral Infection - Epstein - Barr Virus, Human papillomavirus, Hepatitis B and C virus

5 Bacterial infection - Helecobacter Pylori

6 Parasitic infection - Liver fluke, Schistoma haematobium

7 Dietary factors - Low roughage or high fat content diet > high nitrosamine intake, aflatoxin

8 Radiation - Ultraviolet exposure, nuclear fallout following explosion, therapeutic radiation

9 Inflammatory diseases - Ulcerative colitis

10 Hormonal - use of diethylstilbesterol, oestrogens

B Genetic factors

Due to inherited mutations of in genes that regulate cell growth cell death (apoptosis) Examples BRCA 1, BRCA 2 and AT genes.

C Biological or internal factors - age, gender.