Hypothalamic disorders

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Developmental Hypothalamic Dysfunction

- Kallmann Syndrome This syndrome results from defective hypothalamic gonadotropin-releasing hormone (GnRH) synthesis and is associated with anosmia or hyposmia due to olfactory bulb agenesis or hypoplasia (Chap. 335). The syndrome may also be associated with color blindness, optic atrophy, nerve deafness, cleft palate, renal abnormalities, cryptorchidism, and neurologic abnormalities such as mirror movements. Defects in the KAL gene, which maps to chromosome Xp22.3, prevent embryonic migration of GnRH neurons from the hypothalamic olfactory placode to the hypothalamus. Genetic abnormalities, in addition to KAL mutations, can also cause isolated GnRH deficiency, as autosomal recessive and dominant modes of transmission have been described. GnRH deficiency prevents progression through puberty. Males present with delayed puberty and pronounced hypogonadal features, including micropenis, probably the result of low testosterone levels during infancy (Chap. 335). Female patients present with primary amenorrhea and failure of secondary sexual development.
- Kallmann syndrome and other causes of congenitalGnRHdeficiency are characterized by lowLH andFSHlevels and low concentrations of sex steroids (testosterone or estradiol). In sporadic cases of isolated gonadotropin deficiency, the diagnosis is often one of exclusion after eliminating other causes of hypothalamic-pituitary dysfunction. Repetitive GnRH administration restores normal pituitary gonadotropin responses, pointing to a hypothalamic defect.
- Long-term treatment of males with human chorionic gonadotropin (hCG) or testosterone restores pubertal development and secondary sex characteristics; females can be treated with cyclic estrogen and progestin. Fertility may also be restored by the administration of subcutaneous, pulsatileGnRHusing a portable infusion pump.

- Laurence-Moon-Bardet-Biedl Syndrome This rare autosomal recessive disorder is characterized by mental retardation; obesity; and hexadactyly, brachydactyly, or syndactyly. Central diabetes insipidus may or may not be associated.GnRHdeficiency occurs in 75% of males and half of affected females. Retinal degeneration begins in early childhood, and most patients are blind by age 30.
- Frohlich Syndrome (Adipose Genital Dystrophy) A broad spectrum of hypothalamic lesions may be associated with hyperphagia, obesity, and central hypogonadism. DecreasedGnRHproduction in these patients results in attenuated pituitaryFSH andLHsynthesis and release.
- Prader-Willi Syndrome Chromosome 15q deletions are associated with hypogonadotropic hypogonadism, hyperphagia-obesity, chronic muscle hypotonia, mental retardation, and adult-onset diabetes mellitus (Chap. 66). Multiple somatic defects also involve the skull, eyes, ears, hands, and feet. Diminished hypothalamic oxytocin- and vasopressin-producing nuclei have been reported. DeficientGnRHsynthesis is suggested by the observation that chronic GnRH treatment restores pituitaryLH andFSHrelease.

Hypothalamic Infiltration Disorders

- These disorders -- including those associated with sarcoidosis, histiocytosis X, amyloidosis, and hemochromatosis -- frequently involve both hypothalamic and pituitary neuronal and neurochemical tracts. Consequently, diabetes insipidus occurs in half of patients with these disorders. Growth retardation is seen if attenuatedGHsecretion occurs before pubertal epiphyseal closure. Hypogonadotropic hypogonadism and hyperprolactinemia are also common.

Cranial Irradiation

- Cranial irradiation may result in long-term hypothalamic and pituitary dysfunction, especially in children and adolescents who are more susceptible to damage following whole-brain or head and neck therapeutic irradiation. The development of hormonal abnormalities correlates strongly with irradiation dosage and the time interval after completion of radiotherapy. Up to two-thirds of patients ultimately develop hormone insufficiency after a median dose of 50 Gy (5000 rad) directed at the skull base. The development of hypopituitarism occurs over 5 to 15 years and usually reflects hypothalamic damage rather than absolute destruction of pituitary cells. Though the pattern of hormone loss is variable,GHdeficiency is most commonly followed by gonadotropin andACTHdeficiency. When deficiency of one or more hormones is documented, the possibility of diminished reserve of other hormones is likely. Accordingly, anterior pituitary function should be evaluated over the long term in previously irradiated patients, and replacement therapy instituted when appropriate (see below).

Hypothalamic tumors

- Hypothalamic hamartomas and gangliocytomas may arise from astrocytes, oligodendrocytes, and neurons with varying degrees of differentiation. These tumors may overexpress hypothalamic neuropeptides includingGnRH,GHRH, orCRH. In GnRH-producing tumors, children present with precocious puberty, psychomotor delay, and laughing-associated seizures. Medical treatment of GnRH-producing hamartomas with long-acting GnRH analogues effectively suppresses gonadotropin secretion and controls pubertal development. Rarely, hamartomas are also associated with craniofacial abnormalities; imperforate anus; cardiac, renal, and lung disorders; and pituitary failure (Pallister-Hall syndrome). Hypothalamic hamartomas are often contiguous with the pituitary, and preoperativeMRIdiagnosis may not be possible. Histologic evidence of hypothalamic neurons in tissue resected at transsphenoidal surgery may be the first indication of a primary hypothalamic lesion.
- Hypothalamic gliomas and optic gliomas occur mainly in childhood and usually present with visual loss. Adults have more aggressive tumors; about a third are associated with neurofibromatosis.

METABOLIC EFFECTS OF HYPOTHALAMIC LESIONS

- The hypothalamus is subject to injury from mass lesions, granulomatous disorders, infections, and hemorrhage. Lesions involving the anterior and preoptic hypothalamic regions cause paradoxical vasoconstriction, tachycardia, and hyperthermia. Acute hyperthermia is usually due to a hemorrhagic insult, but poikilothermia may also occur. Central disorders of thermoregulation result from posterior hypothalamic damage. The periodic hypothermia syndrome comprises episodic attacks of rectal temperatures <30°C, sweating, vasodilation, vomiting, and bradycardia (Chap. 20). Damage to the ventromedial nuclei by craniopharyngiomas, hypothalamic trauma, or inflammatory disorders may be associated with hyperphagia and obesity. This region appears to contain an energy-satiety center where melanocortin receptors are influenced by leptin, insulin,POMCproducts, and gastrointestinal peptides (Chap. 77). Median eminence involvement results in diabetes insipidus in about 50% of patients. Hypothalamic gliomas in early childhood may be associated with a diencephalic syndrome characterized by progressive severe emaciation and growth failure. Polydipsia or hypodipsia are associated with damage to central osmo-receptors located in preoptic nuclei (Chap. 329). Slow-growing hypothalamic lesions can cause increased somnolence and disturbed sleep cycles as well as obesity, hypothermia, and emotional outbursts. Lesions of the central hypothalamus may stimulate sympathetic neurons, leading to elevated serum catecholamine and cortisol levels. These patients are predisposed to cardiac arrhythmias, hypertension, and gastric erosions.