Undoubtedly, each subsystem is interconnected either within the hypothalamus or with the reticular formation. Reciprocal connections for many of these increase the opportunity for modulation in each component.

There is a substantial body of literature on stress and sleep; however, the linkage between the two remains poorly understood. This is true especially in the context of animal studies. The fundamental problem is that the interventions used to enforce experimental sleep deprivation or restriction, such as forced locomotion [50], the flowerpot paradigm (and variations thereof) [51], the disk-over-water paradigm [52], and other methods, likely introduce nonspecific stressors that confound separating stress from sleep. For instance, some studies found no stress response during chronic sleep deprivation of rats [52, 53], whereas others document increased corticosterone release (see [54]). In human studies of experimental sleep deprivation, elevated cortisol is observed [55]. The literature is replete with considerable variability in such findings. Hence, it is not surprising that there is a plethora of popular websites addressing matters of stress and sleep. And at the same time, what continues to be a challenge is, "What came first – stress or insomnia?"

One cannot fully review the underpinnings of hypothalamic sleep disorders without consideration of the differences in responses to sleep disruption between males and females. Sleep deprivation can present with increased signs of depression and a variety of behavioral changes. Irrespective of the causes of sleep disruption, sleep-deprived men tend to display greater risk-taking behaviors than women. Women show increased signs of depression [56], whereas men show greater risk and acting out [57]. Even in adolescents and young adults, as sleep problems emerge, females display higher incidents and different behavioral patterns [58, 59]. There are clear effects of estrogen or its absence in the dynamics of sleep and the consolidation of wake states in both humans and animals [60]. A dissociation of the biological clock with corticosteroid rhythms as school and social activities shift the time individuals go to sleep has been proposed to trigger these responses but how is not fully understood. Nor does it explain the sex difference. In postmenopausal women [61], problems with sleep and hot flushes stem from the loss of estrogen. While hot flushes are not fully understood, they do have their roots in neural control of temperature provided by the median preoptic nucleus. It is likely that estrogenic effects on those neurons and their connections to the hypothalamic sleep systems are involved. Independent of estrogen, temperature can alter sleep. The proximity of systems within the hypothalamus that regulate temperature gives credence to the notion that sleep-related changes in body temperature are likely functions governed by hypothalamic systems. In support of this perspective, a subject who suffered a stab wound to the brain that coursed through the frontal lobe and ended within the anterior hypothalamus exhibited unilateral sweating and inner ear temperature changes as well as daytime sleepiness [62]. The fact that the knife blade had remained intact [Fig. 13.6] enabled precise determination of the lesion sites that could then be linked to the patient's behavior. In normal sleep, it is thought that the orexin/hypocretin system in concert with the median preoptic area permits sleep-related patterns of body temperature. Yet the connections of the anterior hypothalamus with the preganglionic neurons undoubtedly participated in the dysregulation of the temperature control and asymmetric sweating seen in that subject when he was exposed to elevated ambient temperatures. Conversely, ambient temperature can also interrupt sleep. New data is emerging that climate change with global warming is responsible for losses of sleep at night [63].

Overall, the present review presents sleep disorders with their roots in the hypothalamus. In addition, the integrative roles played by the hypothalamus set the stage for stimuli that arise outside of the hypothalamus to use hypothalamic efferents to reach centers that do affect sleep. Reciprocal connections of extrahypothalamic systems and the hypothalamus can then bring changes in sleep.

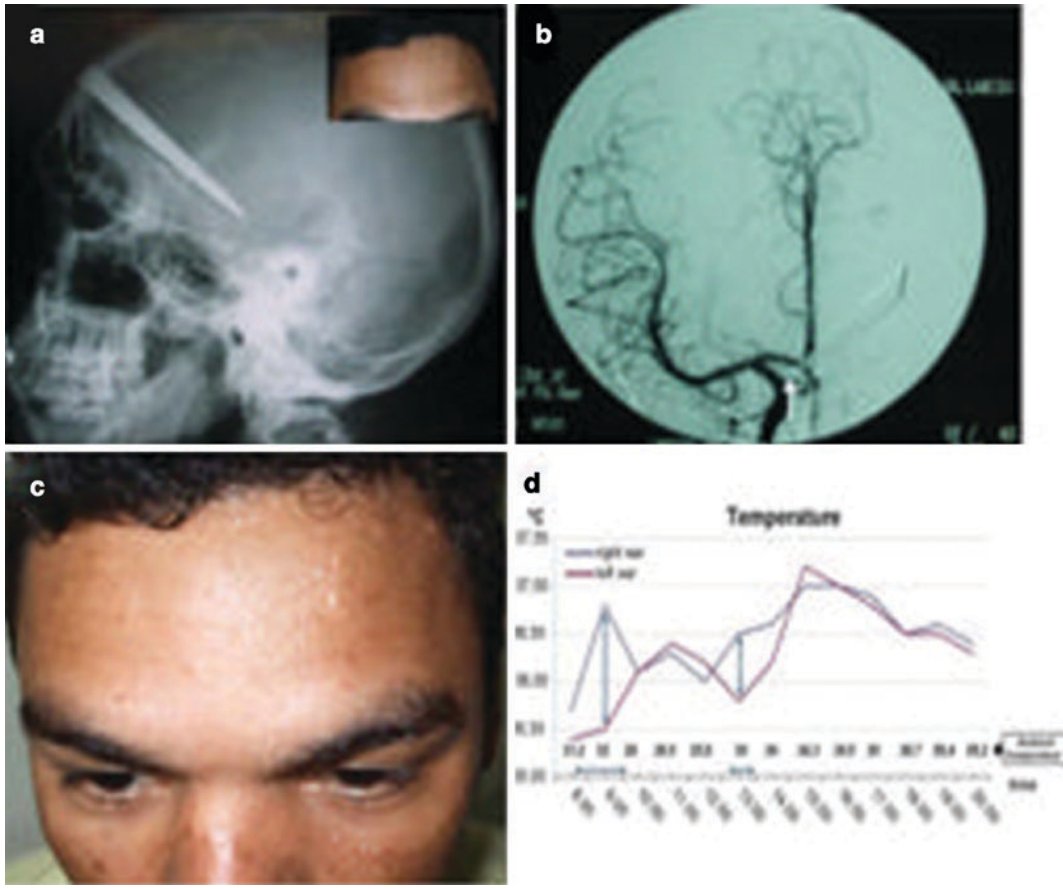

Fig. 13.6 Presence of a stab wound in an individual. (**a**) An X-ray shows the position of the knife blade. (**b**) Arteriography of the right internal carotid artery showing the position of the tip of the knife with respect to the anterior communicating artery. (**c**) The person displayed excessive unilateral sweating patterns limited to the left side in high temperature; (**d**) unilateral changes in temperature with elevations only on the right tympanic membrane. (From [62] with permission from J. Neurology)

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14 Genetic Syndromes of Hypothalamic Dysfunction

George William Moll Jr and Vishnu Garla

The adult hypothalamus is about 4 cm^3 in volume representing about 0.4% of the total central nervous system (CNS) volume. Although its 4 g mass is relatively small, hypothalamic activity is crucial to an individual's physical growth, maturation and development, and overall ability to survive, socially interact, and succeed [1]. Previous chapters in this book have reviewed anatomy, topography, neurophysiology, and neuroendocrinology related to the hypothalamus. This chapter presents an overview of genetic loci and mutations that can reasonably be implicated to influence hypothalamic development and function or to be the source for expression of clinically identifiable syndromes with hypothalamic dysfunction.

Genetic programming for hypothalamic development and function is complex. An individual's genes possibly consisting of multiple DNA exons must be transcribed into RNAs possibly requiring transport into the endoplasmic reticulum or processing for translation into proteins to form structural and functional elements that may also require specific processing in order to appear in appropriate spatiotemporal manner to support key steps in hypothalamic development and hypothalamic functions.

The hypothlamus connects the CNS to the endocrine system through its neurotransmitters and control of pituitary hormones which support an individual's physical growth, development and interaction with nature. The hypothalamus is essential for control of plasma osmolality related to water, sodium, and electrolyte balance, body thermoregulation, appetite, circadian rhythms including sleep cycles, central autonomic efferent and afferent neuronal signaling, and emotional and behavioral memory balance, along with control of anterior pituitary hormone secretions through hypothalamic-releasing factors or hormones.

Genetic control of an individual's appearance and metabolism requires multiple factors acting at several control points in space and time via intra- and extracellular metabolic pathways that may be altered through genomic and somatic mutations such as sporadic single-nucleotide polymorphisms (SNPs) and epigenetic events. An individual's age, gastrointestinal biome and diet, environment, and physical activity can directly influence gene expression through control factors such as DNA methylation and histone modifications, DNA-interactive microRNAs

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https://doi.org/10.1007/978-3-030-62187-2_14

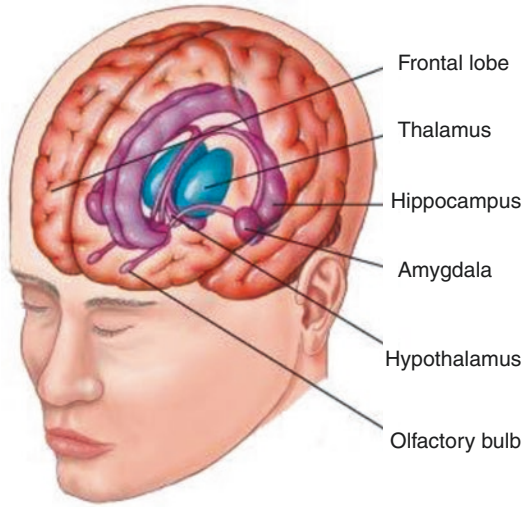

Fig. 14.1 The hypothalamus/limbic system within maturing forebrain

(miRNAs) and proteins, transcription control factors, posttranslational modifications, and enzyme conversions [2, 3]. Jackson and Bartek [4] review molecular surveillance and repair mechanisms for genome stability and repair responses to DNA damage in human biology and disease. During a pregnancy of about 9 months, the human fetus must experience delicately timed and spatially oriented molecular and cellular events including achievement of a functional hypothalamus and limbic system (Fig. 14.1) required for survival and recognition as a healthy human being.

Genetic Aspects of Hypothalamic Development

A recognizable primordial central nervous system (CNS) develops during the third week of human gestation. Complex spatiotemporally interactive signal molecules and transcription factors are critically important for development of the forebrain leading to the hypothalamus and pituitary and optic nerves from the anterior neural plate as it folds into the neural tube. The neural tube in early development of the nervous system is divided into the prosencephalon (forebrain), mesencephalon (midbrain), rhombencephalon (hindbrain), and spinal cord [5]. Location of the hypothalamus as part of the limbic system and as a structure within the diencephalon division of the maturing forebrain is shown in Fig. 14.1.

Sonic Hedgehog (SHH) signaling pathways are responsible for the dorsal/ventral orientation of the neural plate and serve central roles in fundamental CNS patterning, cell differentiation (especially ocular development), and responses to environmental stimuli [6]. Neural tube closure is complex and involves numerous inter- and intracellular communications especially involving Wnt signaling pathways responsible for induction and anterior-posterior axis orientation of the neural plate as well as many aspects of neural development and function [7, 8]. The common midline neural plate origin with balanced Wnt and SHH signaling pathway involvement in hypothalamus, pituitary, optic nerve, and forebrain development often associates hypothalamic-pituitary dysfunction with craniofacial midline anomalies ranging from incompatibility with life to holoprosencephaly (HPE), cleft lip and palate, and septo-optic dysplasia (SOD) [9].

Newborns presenting with mutations in SHH gene exhibit HPE often with cranial facial malformations and developmental delays. Successful hypothalamic-pituitary axis development requires close association between the ventral diencephalon (VD) neuroectoderm containing primordia of the hypothalamus, infundibulum, and posterior pituitary with the dorsal invagination of oral ectoderm as Rathke's pouch (RP) containing primordia of the anterior pituitary [10–13].

There is relatively little published regarding genetics, signaling, and marker molecules involved in human hypothalamus development, but parallels with human hypothalamus development are recognized within well-characterized murine (e.g., mouse and rat) and zebrafish models [14]. Genes such as Sim1, Sim2, Arx, and Nr5a1 (SF-1) are important for regional patterning of hypothalamic cells and achieve highest expression levels near the end of corresponding human embryo development stages. Major signaling pathways that include Wnt, SHH, bone

morphogenetic proteins, NOTCH, and Lhx transcription factors serve key roles in hypothalamic nuclei induction and patterning. Homeobox gene-encoded products and transcription factors are critically important for development of hypothalamic paraventricular (PVN), supraoptic (SON), anterior periventricular (aPeVN), and arcuate (ARC) nuclei [3, 14–17]. NOTCH is historically derived from a noted inheritance of a notch feature in the *Drosophila* wing and subsequent discovery of the evolutionary-conserved NOTCH signaling pathway recognized to play a major role in embryonic development of hypothalamic nuclei-specific neurons. Ratié et al. [18] present a current model for NOTCH signaling promotion of neuron progenitors that along with NUMB inhibitory activity differentiate into hypothalamic nuclei-specific neurons.

Hypothalamic neurogenesis is complete by late human fetal stages. Basic helix-loop-helix (bHLH) gene family encoded transcription factors play major roles in hypothalamic neurogenesis. While several gene mutations are associated with pituitary development anomalies, the bHLH gene ARNT2 novel homozygous frameshift mutation is the first genetic mutation implicated in a human hypothalamic dysfunction syndrome, Webb-Dattani syndrome [17]. This syndrome initially identified in a highly consanguineous family has a phenotype characterized by postnatal microcephaly, CNS frontotemporal lobe hypoplasia, multiple pituitary hormone deficiencies, seizures, severe visual impairment, and renal urinary tract abnormalities [17]. Some of the various genes and genetic mutations associated with hypothalamic development and hypothalamic dysfunction are listed in Table 14.1.

Hypothalamic Regions/Nuclei: Functions/Dysfunctions

The fully developed hypothalamus is divided into four regions anterior to posterior as it forms the lower walls and floor of the third CNS ventricle below the two lobes of the thalamus that form the upper walls and roof of the third ventricle. The hypothalamic sagittal anterior to posterior regions are preoptic, supraoptic, tuberal, and mammillary. The hypothalamic coronal zones from midline left or right are periventricular, medial, and lateral. Each region contains groups of distinct cells forming nuclei directed to perform specific control functions as presented in Table 14.2 [1].

Table 14.1 Mutations associated with hypothalamic development anomalies and dysfunction [14–16, 20]

Mutation	Affected neurons	Associated disorders
Otp (homeodomain TF) deletion	Agenesis of paraventricular and supraoptic nuclei	Dysfunctional stress response, circadian rhythm disruption, deficient hypothalamic hormones
Lhx1 (TF) deletion	Decreased vasopressin (AVP), Vip, Grp	SCN-deficient circadian rhythms, heat/neuron protection defect
Ngn3 (neurogenin-3 bHLH family TF) deletion	Decrease in POMC and SF-1 neurons and increase in NPY neurons	Obesity, appetite center dysfunction
NHLH2 (neuronal HLH family TF) deletion	Disrupted GnRH migration	Obesity-disrupted energy balance, infertility
Steroidogenic factor 1 (SF-1 nuclear receptor) deletion	Agenesis of VMN of the hypothalamus	Obesity and anxiety, appetite center dysfunction, adrenal insufficiency
Sim 1 (bHLH family TF) heterozygous deletion	Decrease in oxytocin (OXT)	Obesity, appetite behavior dysfunction
ARNT2 (bHLH family TF) homozygous frameshift mutation	Global CNS-deficient neuronal development, pituitary deficiency, frontotemporal hypoplasia	Hypopituitarism, multiple absent "bright spot" MRI visual impairment; severe microcephaly – postnatal
NOTCH deletion	Hypothalamic nucleus specific neuron progenitor promoter	Hypothalamic deficiencies, hypothalamic nuclei dysfunction

TF transcription factor; *bHLH* basic helix-loop-helix; *HLH* helix-loop-helix; *Vip* vasoactive intestinal peptide, also noted to be a CNS neurogenic factor; *GRP* glucose-regulated peptide, also a neurogenic factor; *SCN* suprachiasmatic nucleus of the hypothalamus, primary circadian rhythm generator

Table 14.2 Hypothalamic functions, associated nuclei or areas, and clinical disorders due to dysfunction [1]

Hypothalamic function	Hypothalamic regions/nuclei and hypothalamic neurotransmitters involved	Clinical disorders/symptoms due to dysfunction
Energy homeostasis	VMN (satiety center) – anorexigenic – and proopiomelanocortin (POMC) signaling	Defect: hypothalamic obesity or overactive cachexia
Appetite control	LH area (hunger center) – orexigenic – and neuropeptide Y (NPY)/agouti-related peptide (AGP)	Defect: anorexia nervosa or diencephalic syndrome, diencephalic glycosuria
Temperature control	Preoptic anterior hypothalamic area and posterior hypothalamic area	Defect: hyper-, hypo-, poikilothermia
Water/sodium/ osmolality	Supraoptic and paraventricular nuclei magnocellular neuron-produced vasopressin Circumventricular hypothalamic area	Defect: diabetes insipidus, essential hypernatremia, or overactive SIADH
Circadian rhythm center	Superchiasmatic nucleus (SCN) as primary circadian pacer Arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP) cycling neurotransmitters l-Norepinephrine neurotransmitter	Defect: coma or dysfunctional pituitary hormone cycling, more active in morning
Sleep-wake cycle	Posterior hypothalamic area + tuberomammillary nucleus (arousal center)	Akinetic mutism Fragmented sleep
	Ventrolateral preoptic anterior hypothalamic area (sleep center)	Somnolence, narcolepsy, reversal of sleep-wake cycle
Visceral (autonomic) activity	Posterior medial (sympathetic) and preoptic anterior hypothalamus (parasympathetic)	Defect: disrupted sympathetic and parasympathetic activity
Emotions, behavior, and memory modulation	Ventromedial nucleus (VMN) and mammillary bodies Medial, posterior, and caudal areas within the hypothalamus	Defect: inappropriate or uncontrolled rage Fear/panic/anxiety Apathy Hyper-libidinous behavior Short-term memory loss
Hypothalamic control of anterior pituitary-secreted hormones	Suprachiasmatic, paraventricular, and preoptic hypothalamic nuclei most sending hypothalamic hormones through arcuate nucleus to convey to the pituitary via neovascular zone (median eminence) Thyrotropin-releasing hormone (TRH) Corticotropin-releasing hormone (CRH) Growth-hormone-releasing hormone(GHRH) Gonadotropin-releasing hormone (GnRH) Inhibiting hormone somatostatin Neurotransmitter dopamine inhibits prolactin	Defect: dysfunction of pituitary hormone secretions that may be multiple, partial, or isolated hypo- or hyperpituitarism

Plasma Water/Metabolic Balance

Plasma water electrolyte (sodium)-osmotic balance is mediated by hypothalamic supraoptic and paraventricular nuclei-directed release of vasopressin in response to feedback signaling from the hypothalamic circumventricular region where increased vascular permeability about the third and fourth ventricles permits monitoring extracellular fluid sodium and osmolality. Dysfunction involving these nuclei and region mediating vasopressin can result in central diabetes insipidus (DI), essential hypernatremia, or syndrome of inappropriate antidiuretic hormone (SIADH).

Temperature Control

Thermoregulation is mediated by nuclei within preoptic anterior hypothalamic and posterior hypothalamic regions. Dysfunction involving these regions can result in hyperthermia, hypothermia, or poikilothermia.

Appetite Control

Appetite control is mediated by ventromedial nuclei within the satiety center balanced with lateral hypothalamic region nuclei within the feed-

ing center. Dysfunction involving these nuclei and region can result in hypothalamic obesity or cachexia and anorexia nervosa such as rare diencephalic syndrome to be considered in infants and children with failure to thrive progressing to emaciation despite near-normal caloric intake and found to have a CNS tumor [19].

Sleep/Circadian Rhythm Control

Sleep-wake cycle and circadian rhythm are mediated by ventrolateral preoptic anterior (VPA) hypothalamic region nuclei within the sleep center, the posterior hypothalamic (PH) region with tuberomammillary nuclei (TMN) within the arousal center, and the suprachiasmatic nuclei. Dysfunction involving the VPA can result in somnolence or narcolepsy and reversal of the sleep-wake cycle. Dysfunction in PH and TMN region can result in akinetic mutism and/or coma.

Central Autonomic Transmission Control

Visceral autonomic neural activity is mediated through the posterior medial hypothalamic region for sympathetic neural activity and through the preoptic anterior hypothalamic region for parasympathetic neural activity. Dysfunction involving these regions can result in inappropriate uncontrolled sympathetic and parasympathetic neural activity swings in emotions, heart and breathing rates, and bladder and digestive dysfunction.

Emotions, Behavior, and Memory Control

Emotions and behavior are mediated by ventromedial nuclei and medial and posterior as well as caudal hypothalamic regions. Dysfunction involving these regions can result in emotional instability from inappropriate rage and fear to apathy as well as unbalanced sexual behavior. Memory is assisted by neural networks throughout ventromedial nuclei and mammillary bodies. Dysfunction in these regions causes short-term memory loss.

Anterior Pituitary Control

Anterior pituitary hormone control is mediated by arcuate, preoptic, suprachiasmatic, paraventricular nuclei. The neovascular zone within the median eminence directs hypothalamic releasing hormones through the infundibulum to the pituitary. Dysfunction in these regions results in partial to complete hypopituitarism.

OMIM Hypothalamus Genetic Clinical Synopses Affecting Hypothalamic Functions

Genetic origins for hypothalamic dysfunction can be monogenic or part of clinically recognized complex polygenic syndromes. Online Mendelian Inheritance in Man (OMIM) website search on “hypothalamus” associates 525 genetic entries, but search on “hypothalamus – clinical synopses” associates 140 entries of which 113 associate with hypothalamic dysfunction [20]. NIH-based Genetics Home Reference (https://ghr.nlm.nih.gov/) and the Human Gene Database’s GeneCards (https://www.genecards.org/) websites offer assistance to literature searches on specific disease states and on specific genes and their reported mutations.

Hypothalamic Development/Midline Anomalies

Close proximity of the hypothalamus and pituitary requires their progenitor cells’ spatiotemporal interaction for normal hypothalamic development and functions summarized earlier in this chapter. More is known concerning pituitary development than that of the hypothalamus, but published research is progressing with extensive genetic data from animal (primarily murine,

mouse, and rat) models into human genetic origins for hypothalamic dysfunction [16].

Midline head and facial anomalies can relate to underlying diencephalic and associated hypothalamic developmental anomalies. Neonates with midline anomalies should raise interest in obtaining CNS imaging, preferably MRI, as soon as possible but not to delay starting panhypopituitary therapy if clinically indicated such as adrenal support for hypoglycemia. OMIM associates 29 clinical synopses of genetic loci scattered across nearly all 23 human haplotype chromosomes with hypothalamic development and midline anomalies [20]. Genes and mutation-associated hypothalamic disorders related to midline anomalies are summarized in Table 14.3.

The forebrain diencephalon subdivision contains progenitor cells for pituitary and hypothalamus spatiotemporal development. HESX1

Table 14.3 Summary of genes and mutation-associated hypothalamic disorders related to midline anomalies [20]

Gene	Gene product	Mutations' inheritance	Mutation-associated hypothalamic disorder
HESX1	Homeobox protein – transcript. repressor in forebrain and pituitary development	Autosomal heterozygous and homozygous	Hypopituitarism – complete, partial, isolated, infundibulum interruption Rare association septo-optic dysplasia
PAX6	Paired box protein + homeobox domain – transcription regulator Key neuron development, the eye	Autosomal heterozygous	Bilateral optic nerve hypoplasia, ocular disorders – aniridia, Peter's anomaly Potential hypothalamic dysfunction
SOX2	Intronless gene – transcription factors for embryo CNS development, stem cell fate	Autosomal heterozygous	Optic nerve hypoplasia, microphthalmia, hypothalamic dysfunction with anterior pituitary hypoplasia, Hhypogonad, HH
ARX	Homeobox subset protein – transcription factor required for CNS development	X-linked	CNS malformation – lissencephaly X-linked cognitive disability Epileptic encephalopathy
SHH	Peptides – inductive patterning neural ventral tube, long axes embryo into maturity	Autosomal heterozygous	Defects SHH or SHH signaling pathway, holoprosencephaly, facial deformity, VACTERL syndrome, polydactyly
ZIC2	Zinc finger protein member – transcript. repressor, supports neural tube, dopamine receptor	Autosomal heterozygous	Defect forebrain development, holoprosencephaly Coloboma
SIX3	Homeobox protein – transcript. regulator eye and CNS devel. Pathways circadian related	Autosomal heterozygous	Holoprosencephaly Schizencephaly association
TGIF	Homeobox protein – transcript. regulator CNS devel. likely nuclear signaling into adult	Autosomal heterozygous	Holoprosencephaly Semilobar holoprosencephaly
NKX2-1	Protein transcript. factor – reg. thyroid gene transcript. and morphogenesis genes	Autosomal heterozygous	Movement disorders Benign hereditary chorea
ARNT2	bHLH member protein transcript. factor reg. devel. and environment response genes	Autosomal homozygous	Dattani-Webb syndrome – postnatal microcephaly, hypothalamic dysfunction, severe eye impairment, seizures, etc.
PACS2	Multifunction protein – control ER-mitochondria interactions and ER homeostasis	Autosomal heterozygous	Epileptic encephalopathy Mental retardation syndrome
GSX2	Homeobox protein – transcript. factor embryo neurogenesis in the forebrain and hypothalamus	Autosomal homozygous	Diencephalic-mesencephalic junction dysplasia syndrome
BBS (1 to 7)	Proteins in BBSome required for ciliogenesis-dependent cell orientation, organogenesis	Autosomal homozygous/ recessive	Bardet-Biedl syndrome Ciliopathy ciliogenesis disorder disrupting neurons, organogenesis, cell orientation

Table 14.3 (continued)

Gene	Gene product	Mutations' inheritance	Mutation-associated hypothalamic disorder
MKS1	B9 domain containing protein – req. basal bodies and primary cilia for early embryogenesis	Autosomal homozygous/ recessive	Meckel-Gruber and Joubert syndromes and Bardet-Biedl syndrome-like phenotypes Bardet-Biedl syndrome type 13
TMEM216	Transmembrane protein 216 – for tissue specific ciliogenesis, cell cycling cilia	Autosomal homozygous/ recessive	ciliopathy – Joubert, Meckel-Gruber, and related Bardet-Biedl overlap syndromes, CNS with hypothalamic malformations

Homeobox large group of similar genes regulating morphogenesis. Estimate 235 functional human homeobox genes (NIH https://ghr.nlm.nih.gov/ & https://www.genecards.org/); *Transcript.* transcription, *Hhypogonad* hypogonadotropic hypogonadism, *HH* hypothalamic hamartoma, *VACTERL* at least three defects: vertebral, anal atresia, cardiac, TE fistula, renal, limb abnormalities

homeobox gene-encoded promoter-specific transcription repressor is expressed early in embryogenesis and related to the developing forebrain via required spatiotemporal gene expression pathways. Mutations within HESX1 gene are listed as autosomal dominant (heterozygous) or autosomal recessive (homozygous) inheritance, and some are considered synonymous gene mutations that associate with human disease via their potential influence upon temporal gene expression and RNA processing [21, 22]. HESX1 gene mutations are rare causes of septo-optic dysplasia (SOD) with reported 1 in 10,000 live births incidence. Clinical SOD may be partial or complete with all three phenotype components: optic nerve, pituitary hypoplasia, and midline anomalies (about 30%). About 62% SOD patients express hypopituitarism, and 60% have absent septum pellucidum [23, 24].

Birkebæk et al. [25] report a medical record study group of 55 children with optic nerve hypoplasia. Twenty-seven (49%) had through MRI abnormal septum pellucidum, and twenty-seven had endocrine dysfunction (59% growth hormone and 44% multiple pituitary hormone deficiencies, 26% vasopressin deficiency, and 15% precocious puberty). They point out that optic nerve hypoplasia is the most common optic disc congenital anomaly, either isolated or with midline anatomical and functional anomalies. PAX6 gene encodes a protein that contains two DNA-binding domains functioning as regulators of gene transcription that is key to the development of neurons, particularly the optic nerve. Heterozygous PAX6 gene mutations with autosomal dominant inheritance are associated with bilateral optic nerve hypoplasia and aplasia, aniridia 1, and possibly hypothalamic dysfunction [26].

SOX2 gene encodes a transcription factor involved in regulation of embryonic development and along with SOX2 gene product is required for central nervous system (CNS) stem cell maintenance. Kelberman et al. [27] report screening 235 patients with congenital hypothalamo-pituitary disorders for mutations in the SOX2 gene. They identify six patients with clinical anophthalmia or microphthalmia and heterozygous de novo SOX2 gene mutations and two patients with bilateral optic nerve hypoplasia and autosomal dominant inherited mutations. They note SOX2 gene mutations to be associated with hypothalamic dysfunction with hypogonadotropic hypogonadism, anterior pituitary hypoplasia, and hypothalamic hamartoma. They conclude that SOX2 gene product is necessary for normal hypothalamo-pituitary development and function.

ARX gene encodes a subset of homeodomain transcript factors that are crucial to cerebral development and neuronal patterning with particular attention to forebrain development including the hypothalamus [28, 29]. ARX is one of the most frequently mutated genes in a spectrum of X-linked disorders with mental retardation as a cardinal feature associated with lissencephaly [30]. Dobyns et al. [31] describe five children and Ogata et al. [32] an infant with X-linked lissencephaly. Two of these children demonstrate hypothalamic dysfunction including deficient temperature regulation.

Holoprosencephaly is reportedly the most common human forebrain structural malformation, occurring in up to 1 in 250 gestations but only 1 in 8000 live births. Several genetic loci have been associated with HPE variants. HPE1 is associated with mutations in the 21q22.3 gene region inherited in an autosomal dominant, recessive, or isolated pattern consistent with a multiple mutation hypothesis [10–12, 33]. Mercier et al. [12] review phenotype-genotype correlations in clinical expressions of HPE with individual genetic analyses on a European series of 645 HPE probands and 699 relatives. They note 25% to have a mutation in one of four major genes: SHH, ZIC2, SIX3, and TGIF. Most de novo mutations leading to HPE occur in ZIC2. SIX3 encodes a DNA-binding protein that supports eye development and is involved in pathways supporting embryo circadian rhythm development [34]. Xin Geng et al. [35] note that homeobox SIX3 gene mutations account for 1.3% HPE. Their research supports SIX3 gene product to be a direct regulator of SHH expression. Inadequate spatiotemporal SHH-encoded peptide expression can result in HPE.

The solitary median maxillary central incisor is historically involved in the naming of the SHH hedgehog gene family encoded proteins and SHH pathway dysfunction. SHH gene encodes proteins critical to patterning of embryonic ventral neural tube development. SHH gene mutations tend to have autosomal dominant inheritance [16]. Sasai et al. [6] review the SHH hedgehog gene family encoded proteins and their broad-spectrum involvement in cell and embryo development through transduction pathways for anterior-posterior orientation into maturity.

NKX2-1 gene encodes a transcription factor that regulates expression of genes involved in development of several organs including the thyroid, lung, forebrain and hypothalamus. Thorwarth et al. [36] summarize the clinical expression of 27 mutations in NKX2-1 in 100 patients. All of these patients express neurological symptoms generally presenting as movement disorders (chorea) inherited in an autosomal dominant pattern.

ARNT2 gene encodes a transcription factor contributing to control of embryonic development including hypothalamus, anterior and posterior pituitary, optic nerve, and renal development. Webb et al. [17] describe an autosomal recessive syndrome of postnatal microcephaly with hypothalamic dysfunction and multiple pituitary hormone deficiencies, severe visual impairment with seizures, and kidney abnormalities.

PACS2 gene product is important for endoplasmic reticulum ion channel regulation and associated brain and hypothalamic neural network development [37]. Olson et al. [38] describe PACS2 mutations in 14 patients with infantile epileptic encephalopathy. Aside from epilepsy, the patient clinical features include sleep and behavioral disturbances with hypothalamic developmental anomalies. The inheritance pattern appears autosomal dominant.

GSX2 is a homeobox gene encoding a transcript factor important for embryonic development of the forebrain and appropriate spatiotemporal neurogenesis and hypothalamus development. De Mori et al. [39] describe two unrelated girls, 5 and 14 years of age, with global developmental delay and that are nonverbal and have spastic tetraplegia. Their brain imaging reveals complex malformation involving hypothalamic-mesencephalic fusion. The inheritance pattern appears autosomal recessive.

Chromosome 18p deletion syndrome includes mental retardation, growth retardation, craniofacial malformation, and brain anomalies that may involve hypothalamus hypoplasia. Though most often sporadic in occurrence, Tsukahara et al. [40] note rare autosomal dominant pedigrees in at least three families.

Nearly all cell types genetically express primary cilium as a microtubule-based cellular membrane extension essential to cell orientation, communication, and organogenesis, including neuronal development [9, 41, 42]. Cilia are involved in protein trafficking, photoreception, embryo axis limb and digit patterning, and cell cycle regulation requiring cell division spindle microtubules. Sattar and Gleeson [43] review cil-

iopathies related to neuronal development. Bardet-Biedl syndrome presented in detail later is associated with mutations in BBS genes inherited in autosomal recessive or digenic recessive patterns [44]. As ciliopathies, Bardet-Biedl syndrome 1 to 7 (BBS1 to BBS7) genes each encode one of seven proteins in a protein complex, the BBSome, required for ciliogenesis. Scheidecker et al. [45] report detailed exome sequencing on a sporadic BBS patient's sample. Scheidecker et al. [45] suggest anomalies in BBSome assembly represent a unifying mechanism for Bardet-Biedl syndrome characterized by genetically heterogeneous expression of retinitis pigmentosa, kidney dysfunction, postaxial polydactyly, and hypothalamic dysfunction with behavior and hypogonadism concerns.

MKS1 gene encodes one of three known B9 domain-containing proteins that associate with basal bodies and primary cilia in early embryogenesis [46]. Functional mutations in MKS1 gene and in transmembrane protein 216 (TMEM216, essential for ciliogenesis required for cell cycling regulation) gene appear to have autosomal recessive inheritance and associate with ciliopathies such as Joubert, Meckel (Meckel-Gruber), and related syndromes with BBS phenotype overlap, severe developmental dysfunction, and CNS malformations possibly involving the hypothalamus [47]. Logan et al. [9] review the classic triad first described by Meckel in 1822: occipital encephalocele, cystic kidneys, and hepatic fibrosis.

Hypothalamic Tumor Genetics

Hypothalamic tumors are due to multiple causes that include genetic factors controlling cell growth. Hypothalamic tumors include gliomas, hypothalamic hamartomas, neuroglial cell-related low-grade astrocytomas, dermoid and epidermoid tumors, local tumor invasion such as craniopharyngioma, and infiltrative malignancies such as Langerhans cell histiocytosis and leukemia group [48]. Most childhood hypothalamic tumors are gliomas reflecting abnormal or uncontrolled growth of glial cells that normally are essential for brain development and neural network homeostasis [49]. Adults may also develop gliomas that tend to be more aggressive than those in childhood. Adult CNS tumors are more likely metastatic cancer that may cause hypothalamic dysfunction due to local invasive or compression effects [48–50]. Primarily, inherited hypothalamic tumors are rare. However, inherited conditions like neurofibromatosis type 1 (NF1) and multiple endocrine neoplasia type 1 (MEN1) may lead to tumors involving the hypothalamus [50]. Genes and mutations associated with hypothalamic tumors are summarized in Table 14.4.

NF1 gene encodes a cytosol protein, neurofibromin, predominantly expressed in neurons with capacity to regulate several intracellular processes including a tumor suppressor effect as a negative regulator of the RAS signal transduction pathway. NF1 inheritance appears autosomal dominant with estimated incidence of 1 in 2500–3000 [51, 52]. Optic pathway gliomas (OPG) occur in about 15% of NF1 patients and are the most common intracranial tumors in NF1 patients [52, 53]. Habiby et al. [54] report seven cases of central precocious puberty (CPP) in their review of 219 children with NF1 and conclude CPP is found exclusively in NF1 children who have optic chiasm and optic pathway tumors about the anterior hypothalamus. Neurofibromatosis type 1 patients also have an increased risk of developing a leukemia.

MEN1 gene encodes the nuclear scaffold protein menin that regulates gene transcription and associated genome stabilization, cell cycle, and growth. The incidence of one inherited MEN1 gene mutation is about 1:30,000. The second MEN1 gene mutation required for multiple endocrine tumor risk occurs in over 80% from 5 years of age to adult life, making multiple endocrine neoplasia syndrome inheritance autosomal dominant. About 94.5% of patients are diagnosed with MEN1 at presentation of a hyper-parathyroid adenoma followed by 40.5% pancreas adenoma and 29.5% pituitary adenoma that may interfere with hypothalamic-pituitary hormone control resulting in growth failure and obesity in children with MEN1 [49, 50].

Table 14.4 Summary of genes and genetic mutations related to hypothalamic tumors ([20], https://genecards.org/)

Gene	Gene product	Mutations' inheritance	Mutation-associated hypothalamic disorder
NF1	Neurofibromin cytosol protein – 1° neuron tumor suppressor neg. RAS path	Autosomal heterozygous/ dominant	Neurofibromatosis type 1, 1:2500–3000 incidence 15% optic pathway gliomas, CPP Juvenile myelomonocytic leukemia
MEN1	Menin – protein role in histone modification and epigenetic regulation	Autosomal[a] homozygous/ epigenetic two hit	Adenomas: PTH est. 94.5%, pituitary est. 29.5% MEN1 mutation, 1:30,000 incidence, >90% two hit Pancreas tumors 40.5%
GLI3	C2H2-type zinc finger protein – transcription factor, SHH mediator	Autosomal heterozygous/ dominant	Pallister-Hall syndrome, HH Greig cephalopolysyndactyly syndrome Pre- and postaxial polydactyly syndromes
CPLANE1	Protein – transmembrane ciliogenesis and cell axis polarity and migration	Autosomal homozygous/recessive	Orofaciodigital syndrome VI Joubert syndrome 17, HH risk Ciliopathy, neural tube anomalies
PTEN	Dual-specific phosphatase tumor suppressor, part of P13K/AKT/ mTOR path	Autosomal heterozygous/ dominant	Commonly lost PTEN in human cancer disrupts cell growth control, macrocephaly/ autism Cowden syndrome – PTEN hamartoma syndrome
FGFR1	FGF membrane receptor – binds acid/base FGF for neuron/limb growth	Autosomal heterozygous/ dominant	Hartsfield syndrome – rare holoprosencephaly Myeloproliferative stem cell disorder and rare leukemia lymphoma syndrome

HH hypothalamic hamartoma

[a]MEN1 mutation-related tumors follow two-hit autosomal dominant pedigree model in which >90% individuals born with one MEN1 gene mutation will develop the second MEN1 mutation and >80% tumor risk

Somatostatinoma is extremely rare (incidence of 1 in 40 million individuals per year) but frequently associated with NF 1 and MEN1. Some somatostatin produced in the ventromedial hypothalamic nucleus passes to the anterior pituitary where it inhibits release of growth hormone, thyroid-stimulating hormone, and prolactin [50, 55]. Breder et al. [56] describe differential expression of somatostatin receptor subtypes in the brain consistent with somatostatin regulation of many aspects of CNS function and neuroendocrine control, autonomic function and pain perception, and appetite and arousal behavior.

Hypothalamic hamartomas (HH) are congenital ventral hypothalamic mass lesions that tend to be nonprogressive and grow synchronously with the brain to maintain relatively constant proportionate mass to overall brain mass over time without metastases. HH can present in two distinct phenotypes that relate to hypothalamic location of the tumor. HH tumors developing in the posterior hypothalamus near the mammillary bodies associate with epilepsy, usually treatment-resistant gelastic seizures beginning in infancy. HH tumors developing in the anterior hypothalamus near the tuber cinereum associate with central precocious puberty [57]. HH syndrome is rare, occurring at about 1 in 200,000 children and adolescents, with slight male prevalence (1.5 male to every 1 female) but no racial or ethnic predilection [58].

GLI3 gene mutations associate with hypothalamic hamartoma development and Pallister-Hall syndrome in an autosomal dominant inheritance pattern. GLI3 encodes a zinc finger transcription factor that modulates the SHH (hedgehog) signal transduction pathway. Newborn babies born with hypothalamic hamartomas may have less than a few months to survive. A variant holoprosencephaly-diencephalic hamartoblastoma is similarly a rare tumor occurring early in embryogenesis and lethal in about 50% of cases [59]. About 5% of patients with hypothalamic hamartomas and epilepsy have features consistent with Pallister-Hall syndrome (presented in detail later) characterized by post-

axial polydactyly, bifid epiglottis, and imperforate anus [57, 58].

Parisi [60] reviews the genetic and phenotypic heterogeneity of ciliopathies including orofaciodigital syndrome VI (OFD6) associated with CPLANE1 gene mutations and hypothalamic hamartoma risk inherited in an autosomal recessive pattern. CPLANE1 encodes a protein that appears transmembrane in location and is widely expressed as involved with ciliogenesis and establishment of cell polarity and associated directional cell migration as required for hypothalamic nuclei organization. CPLANE1 mutations associate with neural tube anomalies and ciliopathy phenotypes.

PTEN gene encodes a dual-specific phosphatase enzyme that is ubiquitously expressed as a tumor suppressor with autosomal dominant inheritance pattern. PTEN mutations disrupt cell growth control allowing for multiple hamartomas as seen in PTEN hamartoma syndrome and Cowden syndrome. Orloff and Eng [61] review genetic and phenotypic heterogeneity expressed in PTEN hamartoma tumor syndrome and importance of understanding this pathway to individualize cancer therapy. Overgrowth with PTEN mutations is also demonstrated in PTEN macrocephaly/autism syndrome.

FGFR1 encodes a fibroblast growth factor receptor with autosomal dominant inheritance pattern. FGFR1 transmembrane acid/base FGF-binding receptor contributes to control of neural tissue growth and development and participates in limb induction. Simonis et al. [62] report six patients with Hartsfield syndrome as a unique association of holoprosencephaly and ectrodactyly (ECCL). Bieser et al. [63] present the 4th and youngest (3 months old) male patient expressing ECCL with a hypothalamic low-grade glioma. FGFR1 mutations are also associated with stem cell myeloproliferative disorder and rare stem cell leukemia lymphoma syndrome [20].

Fibroblast growth factors (FGF) as basic FGF2 and embryonic-tissue-expressed FGF4 may increase tissue blood supply and contribute to tumorigenesis such as pituitary adenomas possibly assisted by hypothalamic hormones as reviewed by Shimon and Melmed [64]. FGF2 stimulates prolactin secretion from normal pituitary prolactin-secreting cells and pituitary prolactin adenoma cells. Human pituitary adenomas secrete FGF2, but FGF2 does not stimulate pituitary adenoma growth. Adenoma tumor growth appears more correlated with FGF4 expression.

Hypothalamic Neurodevelopment/Neurodegenerative Dysfunction

Although only 4 ml in volume, the hypothalamus is an individual's control center for physiologic and emotional homeostasis. The hypothalamus consists of several groups of neurons organized into distinct nuclei appropriately interconnected within the hypothalamus and then to higher CNS centers and distant sites through afferent and efferent autonomic nerve fibers. The normal spatiotemporal development of hypothalamic nuclei and their interconnectivity are crucial to an individual's survival and maturation. Thereafter, control of neuronal aging is crucial to an individual's longevity [1]. Genes and mutations associated with hypothalamic neuron development and neuron degenerative dysfunction are summarized in Table 14.5.

MYT1L gene product is a member of the zinc finger family of transcription factors that appears to be expressed only in neuronal tissue [20]. Pang et al. [65] and other investigators report MYT1L to induce and control cell-fate changes (programming) in diverse progenitor somatic cell types (e.g., human fibroblasts and pluripotent stem cells) into functional neurons [66, 67]. Somatic cell programming is a tool in the evolving field of regenerative medicine where it has potential to assist development of effective therapy for neurodegenerative diseases [68]. Mall et al. [69] employing a mouse model demonstrate that the MYT1L gene product safeguards the resultant neuronal identity of a mouse fibroblast undergoing reprogramming to become a functional neuron. They find the neuron-directing transcription factor encoded by the MYT1L gene represses many different somatic lineage programs while preserving the appropriate mouse fibroblast to

Table 14.5 Summary of genes and genetic mutations related to hypothalamic neurodevelopment and neurodegenerative dysfunction ([20], https://genecards.org/)

Gene	Gene product	Mutations' inheritance	Mutation-associated hypothalamic disorder
MYT1L	Zinc finger protein – TF expressed in developing CNS neurons	Autosomal heterozygous/ dominant	Cognitive disability – autosomal dominant form Autism spectrum disorder Obesity contribution
MAGEL2	Ubiquitin ligase protein – endosomal recycling and promote axonal network	Autosomal heterozygous/ dominant	Prader-Willi syndrome (PWS) Schaaf-Yang syndrome Circadian rhythm dysfunction
DMXL2	Rab connect in three subunit in NS essential for neuronal secretion and housekeeping	Autosomal homozygous/ recessive	Polyendocrine polyneuropathy syndrome and deaf Hhypogonad, MR, non-autoimmune DM, central hypothyroid, peripheral polyneuropathy
PHOX2B	Homeobox protein TF – neuron hypothalamic network and autonomic	Autosomal heterozygous/ dominant	Congenital central hypoventilation syndrome Autonomic neuropathy-Hirschsprung disease, neural crest-derived tumors in 5%–20% CCHS
D2HGDH	D2HGDH enzyme – intramitochondrial neuron acid reduction	Autosomal homozygous/ recessive	Neuro-metabolic disorder – rare – features developmental delays, epilepsy, hypotonia, dysmorphology
WFS1	Wolframin protein – ER transmembrane calcium, Glu/energy metabolism	Autosomal homozygous/ recessive	DIDMOAD – diabetes insipidus, DM, optic atrophy, deafness Wolfram-like syndrome
SNCA (PARK1,4)	α-Synuclein protein – high in the brain, assists integrate signaling/ trafficking, inhibit phospholipaseD2	Autosomal heterozygous/ dominant	Parkinson's disease – accumulation of amyloid Lewy body inclusions in neurons and progressive selective depletion of midbrain dopamine neurons
PRKN (PARK2)	Protein in E3 ubiquitin ligase – direct targeting substrate proteins for proteasome degradation	Autosomal homozygous/ recessive	Parkinson's disease contributor Juvenile Parkinson's disease

TF transcription factor, *NS* neuronal synaptic vesicle, *Hhypogonad* hypogonadotropic hypogonadism, *MR* mental retardation, *DM* diabetes mellitus, *CCHS* congenital central hypoventilation syndrome, *Homeobox* large group of similar genes regulating morphogenesis. Estimate 235 functional human homeobox genes (NIH https://ghr.nlm.nih.gov/ and https://www.genecards.org/), *D2HGDH* D-2hydroxyglutarate dehydrogenase (gene), *ER* endoplasmic reticulum, *Glu* glucose

neuron identity program. Blanchet et al. [70] report nine children with heterozygous MYT1L mutations (four loss of function and five missense single-nucleotide variants) to clinically show intellectual disability (IQ less than 70 points) and obesity (BMI greater than 95th centile). Blanchet et al. [70] then employ a zebrafish model to demonstrate mutation-reduced MYT1L levels result in abnormal hypothalamus development and reduction in oxytocin levels that can possibly be associated in humans with disrupted thought processing. They conclude that heterozygous MYT1L mutations can contribute to clinically observed human intellectual disability and syndromic obesity through dysregulated hypothalamic neurodevelopment.

MAGEL2 gene encodes ubiquitin ligase required for endosomal protein recycling and functional in promoting axonal outgrowth required for hypothalamic neural networking that appears deficient in Prader-Willi syndrome where MAGEL2 gene is inactivated [71, 72]. Schaaf et al. [73] present four patients with Prader-Willi syndrome (PWS presented in detail later) phenotypes and autism associated with truncating mutations of MAGEL2 that along with joint contractures and more frequent occurrence of autism than seen with PWS defines Schaaf-Yang syndrome. Schaaf-Yang syndrome and PWS are clinically similar and considered neurodevelopmental disorders with molecular overlap at the MAGEL2 gene [74]. Kozlov et al. [75] offer a

mouse model to support hypothalamic expression of MAGEL2 and its role in regulating normal hypothalamic circadian output.

DMXL2 gene encodes rabconnectin-3 as a subunit of rabconnectin protein complex that concentrates in neuronal synaptic vesicles where it is essential for hypothalamic neurosecretion. Rabconnectin-3 also contributes to cell housekeeping as autophagy through its support of a multi-subunit proton pump governing intracellular organelle acidification [76]. DMXL2 gene mutation inheritance follows an autosomal recessive pattern. Tata et al. [77] present detailed assessment of a DMXL2 homozygous in-frame mutation found in each of three brothers in a consanguineous family with five children. Each of the three brothers shows similar new syndromic features of progressive endocrine and neurodevelopment dysfunction: hypogonadotropic hypogonadism, central hypothyroidism, peripheral polyneuropathy, mental retardation, and progressive development from hypoglycemia to non-autoimmune insulin-dependent diabetes mellitus. Tata et al. [77] also report investigation of this DMXL2 gene mutation in a mouse model where they find it to associate with loss of hypothalamic neurons resulting in central hypothyroidism and hypogonadotropic hypogonadism.

PHOX2B is a paired-like homeobox gene necessary for autonomic nervous system development. Amiel et al. [78] present data from a mouse model supporting dependency of central hypothalamic neural network and peripheral autonomic nervous system reflex circuitry upon PHOX2B gene products. Based upon these data and human clinical observations, they conclude heterozygous PHOX2B mutations are major causes of isolated congenital central hypoventilation syndrome (CCHS, Ondine's curse) with an autosomal dominant inheritance pattern. Trochet et al. [79] associate autonomic nervous system impairment due to PHOX2B mutations with Hirschsprung disease and autonomic neural crest-derived tumors that occur in 5%–20% of congenital central hypoventilation syndrome. Trochet et al. [79] encourage PHOX2B mutation screening as a reliable tool to assist diagnosis of CCHS.

D2HGDH gene encodes D-2-hydroxyglutarate dehydrogenase as an intramitochondrial enzyme expressed in the liver, kidney, heart, and brain to reduce acid build-up with D-2-hydroxyglutaric aciduria. Wajne et al. [80] report an infant with intermittent D-2-hydroxyglutaric aciduria died at 10 months of age from cardiomyopathic cardiogenic shock. Cerebral MRI reveals hypothalamic lesions and similar multiple CNS lesions to correlate with clinical developmental delay and hypotonia but intermittent generalized tonic seizures. Biochemical assessment is consistent with D-2-hydroxyglutarate dehydrogenase deficiency. Struys et al. [81] report genetic assessment of two unrelated patients with D-2-hydroxyglutaric aciduria that reveal D2HGDH gene (one patient homozygous missense and other patient compound heterozygous missense) mutations. Their overexpression studies of these mutations in HEK-293 cells support their conclusion that D2HGDH gene mutations cause D-2-hydroxyglutaric aciduria.

WFS1 gene encodes wolframin as a transmembrane protein that localizes in the endoplasmic reticulum. Osman et al. [82] report wolframin to be associated with calcium transmembrane transport activity in the endoplasmic reticulum. Wolframin is involved in various pathways including unfolded protein response (UPR) and glucose/energy metabolism [20]. WFS1 mutations appear to have autosomal recessive inheritance and associate with Wolfram syndrome presented in detail later to combine diabetes insipidus, diabetes mellitus, optic nerve atrophy, and sensorineural hearing loss (DIDMOAD syndrome) with progressive neurodegeneration that includes the hypothalamic neural network.

Huntington's disease is an autosomal dominant progressive neurodegenerative disorder characterized by chorea, dystonia, and cognitive decline tending to occur at 30–40 years of age. Huntington's disease is associated with Huntington gene (HTT) mutations that relate to neuronal death in select brain regions including the hypothalamus [83]. Petersén et al. [84] report atrophy and loss of orexin neurons in the lateral hypothalamus of a Huntington's disease mouse model that supports noted loss of orexin neurons in Huntington patients contributing to their weight loss. Cepeda et al. [85] review Huntington's disease neuron loss including

within the hypothalamus that focuses attention to alterations in dopamine neurotransmission and dopamine and glutamate receptor dysfunction in neurodegenerative disorders including Parkinson's disease.

Parkinson's disease is second to Alzheimer's disease as the most common neurodegenerative disorder, and Parkinson's disease affects about 1% of adults over 50 years of age [86]. Parkinson's disease involves progressive loss of midbrain dopamine neurons resulting in characteristic signs of motor dysfunction including muscle rigidity with bradykinesia, resting tremors and postural instability, dysautonomia, and dementia. Parkinson's disease cases are mostly sporadic and of uncertain etiology, but there is a suspected role for oxidative stress causing mitochondrial dysfunction [87]. Definitive Parkinson's disease pathology includes distinctive intra-neuron Lewy body inclusions and depletion of selective midbrain dopamine neurons. Three familial Parkinson's disease-related mutated genes encode proteins that contribute to the characteristic progressive intra-neuron Lewy body inclusions and hypothalamic dysfunction.

PARK1 and PARK4 gene designations are aliases for the SNCA gene that encodes alpha-synuclein. Synucleins are abundant in the brain where alpha-synuclein assists selective inhibition of phospholipase D2. Alpha-synuclein may also integrate neuronal signaling and membrane trafficking. Heterozygous, autosomal dominant mutations in SNCA gene contribute to clinically progressive Parkinson's disease [20].

PARK2 gene designation is an alias for the PRKN gene that encodes a protein component of E3 ubiquitin ligase multiprotein complex. E3 ubiquitin ligase complex directs targeting of substrate proteins for proteasomal degradation. PARKN gene mutations contribute to Parkinson's disease and cause autosomal recessive juvenile Parkinson's disease [20].

Hypothalamic Behavior and Memory Modulation

The hypothalamus is a major regulatory center for neuronal network activity and endocrine homeostasis. Hypothalamic nuclei and closely interconnected pituitary regulate a broad array of physiologic and behavioral activities via neuronal and hormonal signaling networks. Genes and mutation-associated hypothalamic disorders related to behavior and memory modulation are summarized in Table 14.6.

Table 14.6 Summary of genes and mutation-associated hypothalamic disorders related to behavior and memory ([20], https://genecards.org/)

Gene	Gene product	Mutations' inheritance	Mutation associated hypothalamic disorder
HCRT	Hypothalamic neuropeptide – orexin A, orexin B, sleep, and feeding	Autosomal heterozygous	Narcolepsy syndrome Potential appetite center interactions
BHLHE41	Basic helix-loop-helix protein – circadian cycles, cell differentiation	Autosomal heterozygous	Familial normal variant short sleep behavior Less sleep over any 24 h than average for age
AR	Androgen receptor – binds sex steroid, transcription androgen respond genes	X-linked recessive	Complete androgen insensitivity Rare spinal bulbar muscular atrophy
MAOA	Mitochondrial enzyme – oxidative deamination dopamine, NorEpi, Ser	X-linked recessive	Impulsive, antisocial behavior Cognitive concerns Brunner syndrome
COMT	Catechol-O-methyltransferase – metabolize neurotransmitters	Autosomal heterozygous	Prefrontal cortex dysfunction with disturbed dopamine neurotransmitters, risk for schizophrenia
CRF (CRH)	CRH preproprotein – PVN mature CRF neuropeptide release pituitary ACTH	Autosomal mixed	Hypothalamic CRH deficiency Nocturnal frontal lobe epilepsy Postpartum depression

NorEpi norepinephrine, *Ser* serotonin, *CRF* (*or CRH*) corticotrophin-releasing factor or hormone

Narcolepsy is a disruption of normal sleep-wake cycle by attacks of disabling drowsiness not connected with light-dark cycles in the absence of underlying metabolic or physiologic imbalance such as diabetes insipidus or diabetes mellitus. Human narcolepsy cases are mostly sporadic but tend to carry a specific haplotype [88]. Familial cases with monozygotic (identical) twins reveal 25%–31% concordance suggesting environmental effects and possible immune system involvement with a noted association of human narcolepsy-cataplexy with HLA-DQB1*0602 [89]. Narcolepsy syndrome 1 (NRCLP1) is associated with heterozygous mutations in the orexin A and B precursor HCRT gene. Hagan et al. [90] report a wide distribution of orexigenic neurons from the lateral hypothalamus in the rat brain including appetite centers but with most concentrated innervation from orexinergic nerves in the locus coeruleus-arousal center. Thannickal et al. [91] present postmortem hypothalamus sections from four narcoleptic patients that demonstrate 85%–95% reduction in number of hypocretin neurons relative to control sections from 12 neurologically normal human brains. These data support roles for orexins in modulating neuroendocrine function, arousal, sleep-wake cycle establishment, and possibly appetite center.

BHLHE41 (alias DEC2) gene is associated with familial natural short sleep behavior. DEC2 is a basic helix-loop-helix transcription factor that assists circadian rhythm control primarily regulating mammalian sleep-wake cell with suppression of orexin and potential control of cell differentiation. Hirano et al. [92] present results of a mouse model to explore effects of human DEC2 mutations. They observe reduced orexin suppressor effect with missense BHLHE41 mutation leading to short sleep behavior. This result supports DEC2 regulation of sleep/wake duration at least in part by modulating hypothalamic orexin levels.

Psychopathology and human behavior in general involve complex multi-genetic neuroendocrine, epigenetic, and social interactions that must involve processing through the hypothalamus [93]. An individual's sexuality and potential gender dysphoria involve genetic influences including those upon the hypothalamus. Sex steroids are noted to alter hypothalamic morphology with variable interpretations of male and female differences in size of some nuclei of the anterior hypothalamus (postmortem anterior medial nuclei trending larger in men than women) and the anterior commissure (postmortem midsagittal area larger in women than in men) [94, 95]. Cunningham et al. [96] review several aspects of hypothalamic sex steroid interactions with particular attention to androgen receptors that are in high concentration in the medial preoptic area and ventromedial hypothalamus. They support physiologic levels of androgen interacting with androgen receptors to be the primary drive for virtually all reproductive-related behavior. Lee and Chang [97] review clinical implications of genetic and other mechanisms related to androgen receptor (AR) signaling pathway interactions in males and females and note areas for further investigation. Mutations in the AR gene are X-linked recessive in inheritance pattern and associate with clinical expressions of androgen insensitivity syndrome and rare X-linked spinal and bulbar muscular atrophy or Kennedy's disease [98, 99].

MAOA gene X-linked recessive mutation and COMT gene heterozygous mutation are associated with anxious impulsive behavior and social and cognitive concerns [100, 101]. MAOA gene encodes a mitochondrial enzyme that catalyzes oxidative deamination of amines: dopamine, norepinephrine, and serotonin. COMT gene encodes catechol-O-methyltransferase that facilitates major catecholamine neurotransmitter degradation pathways: dopamine, epinephrine, norepinephrine, and catechol drug (used in treating hypertension and asthma) metabolism. Brunner et al. [102] describe an association of MAOA deficiency due to MAOA gene point mutation in 14 males clinically expressing mental retardation, antisocial behavior, disturbed sleep, and mood swings with disturbed monoamine neurotransmission. Similarly, COMT deficiency due to COMT gene mutation is associated with altered prefrontal cortex function, risk for schizophrenia, and disturbed dopamine neurotransmission.

Meyer-Lindenberg et al. [103] report multimodal limbic-hypothalamic examination of healthy volunteers separated into MAOA gene low-expression polymorphism (MAOA-L) and high-expression polymorphism (MAOA-H) due to their population's common variable number of tandem repeats in the MAOA gene altering its transcriptional efficiency. They find about 8% decrease of gray matter volumes in the cingulate gyrus, amygdala, insula, and hypothalamus in MAOA-L compared to MAOA-H. Since these data identify differences in limbic circuitry for emotion regulation and cognitive control, they propose level of MAOA gene expression as a biomedical mechanism to relate to socially expressed impulsive aggression.

Panic is a common anxiety disorder with a general population prevalence of about 4%. Schumacher et al. [104] review the genetics of panic disorder and estimate its heritability about 48%. They note that most panic disorder patients show complex multi-genetic inheritance of interest for future research. Johnson et al. [105] report their exploration of hypothalamic response to panic attacks with a rat anxiety-like model. They note that the rich in orexin-containing neurons dorsomedial/perifornical hypothalamus must generate orexin as a key signal for arousal, vigilance, and stimulant for autonomic neuroendocrine components of panic attack. Their results support an important orexin system involvement in pathophysiology of panic anxiety.

Pleil and Skelly [106] review CNS/hypothalamic corticotrophin-releasing factor (CRF) signaling in alcohol addiction, anxiety, and mood disorders. They note that hypothalamic CRF neurons have an essential role in initiating the hypothalamic-pituitary-adrenal (HPA) response to stress. But extra-hypothalamic CRF (particularly stria terminalis area) can regulate drinking behavior and stress responses independent of the HPA. This observation demonstrates the effectiveness of CRF as a neurotransmitter in addition to its role as a hypothalamic-releasing factor. Researchers report hypothalamic CRF and HPA activity tends to be suppressed while extra-hypothalamic CRF is upregulated in neuropsychiatric diseases including alcohol addiction. Genetic mutations affecting hypothalamic CRF and HPA activity need to be explored.

Hypothalamic Neuroendocrine Secretion Control

The hypothalamus is well positioned as a major control point for emotional, physiologic, and metabolic homeostasis. There are five specific hypothalamic-pituitary gland or organ axes: (1) hypothalamic thyrotropin-releasing hormone (TRH) to pituitary thyroid-stimulating hormone (TSH), (2) hypothalamic corticotrophin-releasing factor or hormone (CRF or CRH) to pituitary adrenal corticotropic hormone (ACTH), (3) hypothalamic growth-hormone-releasing hormone (GHRH) to pituitary growth hormone (GH), (4) hypothalamic gonadotrophin-releasing hormone (GnRH) to pituitary gonadotrophins (luteinizing hormone [LH], follicle-stimulating hormone [FSH]), and (5) hypothalamic general inhibitory somatostatin and dopamine to inhibit pituitary prolactin release. Each axis requires appropriate spatiotemporal genetic expression for successful physiologic and environmental survival from conception to newborn and newborn to adult and appropriate aging. Genes and mutation-associated hypothalamic disorders related to neuroendocrine secretion control are summarized in Tables 14.7, 14.8, and 14.9.

TRH gene encodes a 225 amino acid prepro-TRH directed into the rough endoplasmic reticulum with signal peptide cleavage into pro-TRH that in humans contains six copies of TRH progenitor sequences translated into TRH along with non-TRH peptides that have biologic activity likely contributing to diversity in TRH neurotransmitter and neurohormone activity [107]. TRH tripeptide primarily produced in hypothalamic paraventricular nucleus is released to accumulate in the median eminence near the arcuate nucleus for appropriate conveyance via hypothalamic-pituitary portal system to anterior pituitary where it promotes thyroid-stimulating hormone (TSH) secretion. The variety of peptides derived from pro-TRH in various CNS regions likely contribute to how TRH neurons

Table 14.7 Summary of genes and mutation-associated hypothalamic disorders related to neuroendocrine thyroid, adrenal, and growth hormone secretion control ([20], https://genecards.org/)

Gene	Gene product	Mutations' inheritance	Mutation-associated hypothalamic disorder
Thyroid			
TRH	Prepro-TRH – six TRH to prompt pituitary TSH and prolactin secretion, prompt hair growth	Autosomal homozygous/ recessive	Congenital TRH deficiency Hyperprolactinemia
IGSF1	Immunoglobulin-like domain protein – regulate cell interactions	X-linked mixed	Central hypothyroidism Testicular enlargement
IRS4	Insulin receptor (IR) substrate 4 protein – IR phosphorylated interacts signaling molecules	X-linked mixed	Congenital hypothyroid, nongoitrous 9 Exostosis
TBL1X	Transducin β-like 1 protein – signal transduction, RNA and gene reg., vesicle trafficking	X-linked mixed	Ocular albinism with late-onset sensorineural deafness Similar to Y-chromosome TBL1Y
TRHR	G-protein-coupled TRH receptor – activates inositolphospholipid calcium-protein kinase C path	Autosomal mixed/ dominant	Generalized TRH resistance
TSHB	β-subunit TSH – thyroid structure and metabolism, hypothalamus feedback loop	Autosomal mixed	Congenital central and secondary hypothyroidism Hashimoto's thyroiditis
Adrenal			
MC2R	G-protein melanocortin receptor – ACTH selectively activates, signaling pathways	Autosomal homozygous/ recessive	Glucocorticoid deficiency 1 Familial glucocorticoid deficiency
MRAP	MCR interacting protein – MCR trafficking and signaling, Aldo synthesis/secretion path	Autosomal homozygous/ recessive	Glucocorticoid deficiency 1 Glucocorticoid deficiency 2
NNT	Nicotinamide nucleotide transhydrogenase – integral inner mitochondrial protein	Autosomal homozygous/ recessive	Glucocorticoid deficiency 4 +/− mineralocorticoid deficiency Familial glucocorticoid deficiency
ABCD1	ATP binding cassette ALD1 – peroxisome import very long-chain FA-CoAs, mito function	X-linked recessive	Adrenoleukodystrophy Familial hypoadrenocorticism
NROB1	DNA-binding protein dominant neg. transcription regulator, anti-testis to Sry	X-linked	X-linked congenital adrenal hypoplasia Hypogonadotropic hypogonadism 46, Xy sex reversal
NR3C1	Gluc receptor – binds promoter Gluc response genes and regulate other transcription factors	Autosomal heterozygous/ dominant	Generalized glucocorticoid resistance – anxiety and adrenal rest tumor potential Diverse cytoplasm-to-nucleus trafficking
GH			
GHRH	Preproprotein cleaved to GH-releasing hormone – promotes pituitary GH secretion	Autosomal	No definite isolated GHRH mutation-related disease but short stature and gigantism related through its receptors
GPR101	G-protein-coupled receptor – uncertain function but related GHRH growth dysfunction	X-linked	Pituitary adenoma 2 GH secreting and Xq26.3 dup. syndrome X-linked acro-gigantism (X-LAG)

MCR melanocortin receptor, *Aldo* aldosterone, *Gluc* glucocorticoid, *GH* growth hormone

influence their targets and to TRH regulation of other hormones: prolactin, growth hormone, vasopressin, and insulin. TRH is observed in many brain loci outside the hypothalamus and in non-neuronal tissues such as the GI tract, heart and human skin, and hair follicles where TRH promotes healthy hair growth.

Sugisawa et al. [108] review mutation screening for congenital isolated TSH deficiency, and Tajima et al. [109] report recent research on iso-

Table 14.8 Summary of genes and mutation-associated hypothalamic disorders related to neuroendocrine puberty and sexual maturation control ([20], https://genecards.org/)

Gene	Gene product	Mutations' inheritance	Mutation-associated hypothalamic disorder
KISS1	Kisspeptin/metastin – stimulate GnRH, promote puberty GnRH neurons, FSH, LH secretion	Autosomal homozygous/ recessive	Hypogonadotropic hypogonadism 13 +/– anosmia and normosmic congenital hypogonadotropic hypogonadism
KISS1R (GPR54)	G-protein-coupled receptor – binds KISS1, role promoting puberty onset and progression	Autosomal homozygous/ heterozygous	Hypogonadotropic hypogonadism 8 +/– anosmia Central precocious puberty 1
MKRN3	Ring (C3HC4) zinc fingers protein – puberty control with paternal imprinting	Autosomal heterozygous/ dominant	Central precocious puberty 2 Idiopathic precocious puberty Potential PWS association
GnRH	Preproprotein – gonadotropin-releasing hormone promoting LH and FSH pituitary secretion	Autosomal mixed	Hypogonadotropic hypogonadism
KAL1 (ANOS1)	Anosmin-1 protein – promote neural cell adhesion and axonal migration	X-linked recessive	Kallmann syndrome X-linked Hypogonadotropic hypogonadism 1 +/– anosmia
FGFR1	FGF receptor 1 protein – binds acidic and basic FGF limb induction, Pl3K, MAPK paths	Autosomal heterozygous/ dominant	Autosomal dominant Kallmann Syndrome 2, Pfeiffer, Jackson-Weiss, Antley-Bixler Osteoglophonic dysplasia
FGF8	FGF family protein – cell growth and development, tissue repair, morphogenesis	Autosomal heterozygous/ dominant	Hypogonadotropic hypogonadism 6 +/– anosmia
NELF	Nasal embryonic protein – guide olfactory axon and GnRH neuron development	Autosomal heterozygote	Idiopathic hypogonadotropic Hhypogonad 9 +/– anosmia
PROK2	Protein in suprachiasmatic nucleus (SCN) – likely GnRH development and circadian clock	Autosomal heterozygote/ dominant	Kallmann syndrome 4 +/– anosmia Normosmic congenital hypogonadotropic hypogonadism
PROKR2	G-protein-coupled receptor – prokineticins that can promote angiogenesis	Autosomal heterozygote/ dominant	Hypogonadotropic hypogonadism 3 +/– anosmia
SEMA3A	Semaphorin 3A protein – secreted to direct normal neuronal development	Autosomal heterozygous/ dominant	Hypogonadotropic hypogonadism 16 +/– anosmia Aberrant release – progressive Alzheimer's
RAB3GAP2	Protein subunit of Rab3 GTPase activator – CNS release hormones, neurotransmitters	Autosomal homozygous/ recessive	Martsolf syndrome – mild MR, congenital cataracts and hypogonadism
CHD7	Chromodomain helicase DNA-binding protein 7 – olfactory hypothalamic development	Autosomal heterozygous/ dominant	Hypogonadotropic hypogonadism 5 +/– anosmia CHARGE syndrome

PWS Prader-Willi syndrome, *FGF* fibroblast growth factor, *G-protein* guanine nucleotide-binding protein

lated congenital central hypothyroidism with incidence of 1/16,000–30,000 in the general population. Five genes are listed whose mutations are responsible for isolated TSH deficiency with otherwise normal hypothalamic function: immunoglobulin superfamily 1 (IGSF1), insulin receptor substrate 4 (IRS4), transducing β-like protein 1 X-linked (TBL1X), thyrotropin-releasing hormone receptor (TRHR), and thyroid-stimulating hormone β-subunit (TSHB).

Corticotrophin-releasing hormone (CRH) gene (Table 14.6) is transcribed in hypothalamic paraventricular neurons as a 191 amino acid preprohormone that is enzymatically cleaved to a 41 amino acid peptide for appropriate conveyance via the portal system to the anterior pituitary

Table 14.9 Summary of genes and mutation-associated hypothalamic disorders related to neuroendocrine puberty and sexual maturation control (continued) and vasopressin ([20], https://genecards.org/)

Gene	Gene product	Mutations' inheritance	Mutation associated hypothalamic disorder
TAC3	Preproprotein – proteolytic to neurokinin B neurotransmitter assists GnRH and reproduction	Autosomal homozygous/ recessive	Hypogonadotropic hypogonadism (HH) 11 Severe congenital HH normosmic
TACR3	Neurokinin B receptor protein – G-protein-coupled, related signaling pathways	Autosomal homozygous/ recessive	As listed with TAC3
WDR11	WD repeat protein – GnRH and cell processes, SHH signaling, ciliogenesis, Golgi activity	Autosomal heterozygous/ dominant	Hypogonadotropic hypogonadism 14 +/− anosmia
HS6ST1	Heparan sulfate 6-O-sulfotransferase 1 – supports neuron branching and communications	Autosomal heterozygous	Hypogonadotropic hypogonadism 15 +/− anosmia
SPRY4	Protein regulatory factor – inhibitor MAPK signal path in control of GnRH	Autosomal heterozygous	Hypogonadotropic hypogonadism 17 +/− anosmia Normosmic congenital HH
FGF17	FGF protein – embryonic cell growth and development, GnRH control path	Autosomal heterozygous	Hypogonadotropic hypogonadism 20 +/− anosmia Normosmic congenital HH
IL17RD	Interleukin 17 receptor membrane protein – MAPK path interactive, GnRH	Autosomal heterozygous	Hypogonadotropic hypogonadism 18 +/− anosmia Normosmic congenital HH
DUSP6	Dual-specificity phosphatase protein – inactivate target kinases, interact MAPK, GnRH	Autosomal heterozygous	Hypogonadotropic hypogonadism 19 +/− anosmia Normosmic congenital HH
FLRT3	Fibronectin Leu-rich transmembrane protein – embryo Devel., CNS neuron networks	Autosomal heterozygous	Hypogonadotropic hypogonadism 21 +/− anosmia Congenital HH
FEZF1	Forebrain embryonic zinc finger protein – TF repressor, GnRH neuron migration	Autosomal homozygous	Hypogonadotropic hypogonadism 22 + anosmia Kallmann syndrome
PNPLA6	Patatin-like phospholipase protein – neuron development, support acetylcholine	Autosomal homozygous/ recessive	Neurodegenerative L-O-F PNLA6-Boucher-Neuhäuser, Gordon Holmes with hypogonadotropic hypogonadism
C2orf37	Nuclear transmembrane protein – damage DNA repair, support neuronal activity	Autosomal homozygous/ recessive	Woodhouse-Sakati syndrome- alopecia, MR, extrapyramidal syndrome, DM, hypogonadotropic hypogonadism
Posterior pituitary AVP	Prepro-AVP protein – cleaved to AVP, neurophysin II, copeptin AVP antidiuretic hormone	Autosomal homozygous, dominant	Familial neurohypophyseal (central) DI

Leu leucine amino acid, *Devel.* development, *TF* transcription factor, *MR* mental retardation, *DM* diabetes mellitus, *AVP* arginine vasopressin, *DI* diabetes insipidus

where it promotes release of adrenocorticotropin (ACTH) into the circulation to stimulate adrenal production and release of glucocorticoid primarily in response to stress [110]. CRH also acts as a neurotransmitter with receptors throughout the brain and other tissues [111, 112]. Kovács et al. [113] report their study of a rat model to quantify acute restraint stress (ARS) and chronic variable mild stress (CVMS) evoked neuronal activity in hypothalamic CRH cells throughout the whole life span. They find paraventricular nucleus CRF neuronal ARS sensitivity decreases with aging, but these neurons maintain their responsivity to CVMS. Dedie et al. [112] review the CRF family of neuropeptides and their receptors throughout the CNS as detailed in the mouse brain to mediate the central stress response. Jokinen et al. [114] relate CRH gene epigenetic site-specific

methylation changes with severity of general psychiatric risk score and suicide attempts in cohorts of high-risk 18 years of age or older and adolescents with a recent suicide attempt. In their cohort of 93 subjects, 14–16 years of age, 49 were classified high risk by psychiatric testing. Jokinen et al. [114] find individual CRH gene site-specific methylation to be significantly higher ($p < 0.01$) in high-risk subjects. Human Gene Mutation Database (https://genecards.org/) lists three mutations in CRH gene related to glucocorticoid deficiency.

MC2R gene encodes melanocortin 2 receptor that serves key roles to register adrenal and other tissue responses to ACTH as well as to function within the feedback loop to the hypothalamus. Guran et al. [115] report their genetic assessment of a cohort of 95 children (0–18 years of age, 48 female/47 male) with clinical primary adrenal insufficiency diagnosis. They identify a molecular genetic diagnosis for primary adrenal insufficiency in 77 (81%) of the children in this cohort. They report 80% of the genetic mutations to be homozygous with only one patient heterozygous and 18% (14 patients) X-linked. The majority of the genetic mutations are in MC2R gene distributed as follows: MC2R $n = 25$, NROB1 $n = 12$, Star $n = 11$, CYP11A1 $n = 9$, MRAP $n = 9$, NNT $n = 7$, ABCD1 $n = 2$, NR5A1 $n = 1$, and AAAS $n = 1$. Ninety-five percent of the genetic mutations associating with primary adrenal insufficiency in this cohort occur in six genes: MC2R, NROB1, Star, CYP11A1, MRAP, and NNT. STAR and CYP11A1 mutations involve primarily the interference with adrenal steroidogenesis.

MC2R, MRAP, ABCD1, and NNT are mutations that would be generally involved with neuronal metabolism including the hypothalamus. ABCD1 mutation causes X-linked adrenoleukodystrophy with potential to disrupt axonal transmission. Nicotinamide nucleotide transhydrogenase (NNT) mutation would affect cellular oxidation. MRAP mutation would interfere with essential MRAP trafficking of MC2R to the cell membrane where it can interact with ACTH. The MC2R mutation-related primary adrenal insufficiency presents in the newborn with markedly elevated ACTH that must be treated with glucocorticoid soon after birth for survival supporting a benefit to prenatal genetic testing.

NROB1 gene encodes the dosage-sensitive sex reversal, adrenal hypoplasia congenital (AHC) critical region on the X-chromosome, gene 1 (DAX1) protein containing a DNA-binding domain. This protein acts as a dominant negative transcription regulator. It also acts antagonistically to testis-supporting Sry gene. It is expressed at all levels of the hypothalamus-pituitary-adrenal and gonadal axis. Mutations in NROB1 gene result in X-linked congenital adrenal hypoplasia and hypogonadotropic hypogonadism or prolonged or absent puberty possibly with psychiatric concerns reflecting hypothalamic neuronal network dysfunction [116, 117].

NR3C1 gene encodes the cytoplasmic glucocorticoid receptor (GCCR) that upon binding glucocorticoid traffics into the nucleus to bind glucocorticoid response elements in promoters of glucocorticoid-responsive genes and thereby influence the transcription of these genes. GCCR also functions as a regulator of other transcription factors and influences inflammatory responses, cell proliferation, and differentiation in target tissues. NR3C1 heterozygous mutations associate with degrees of generalized glucocorticoid resistance in an autosomal dominant pattern.

Chamandari et al. [118] review molecular mechanisms and clinical aspects of varying degrees of glucocorticoid resistance reported in MEDLINE literature in 1975–2008 to better understand the clinical influence of glucocorticoid resistance-related markedly increased hypothalamus-pituitary-adrenal axis activity. They conclude that hypersecretion of CRH and ACTH in the presence of generalized glucocorticoid resistance can cause serious anxiety and adrenal rest tumors.

Growth-hormone-releasing hormone (GHRH) gene is transcribed in the hypothalamus as a preprohormone with N-terminal signal peptide that is cleaved prior to release of GHRH as a mature 40 or 44 amino acid peptide for conveyance via the portal system to the pituitary where it promotes growth hormone (GH) secretion from

somatotropes in a cyclic pattern predominantly over night with sleep. Although GHRH is a likely candidate for mutations related to isolated GH deficiency, no functionally significant GHRH gene mutation is yet reported with isolated GH deficiency. Alatzoglou et al. [119] and Mullis [120] review genetic causes of isolated GH deficiency that aside from GH deficiency with multiple deficiencies related to hypothalamic development anomalies reviewed earlier tend to be due to GH gene mutations and pituitary anomalies. Daly et al. [121] present clinical observations and extensive hormonal profiles on a 2-year-old female with X-linked acro-gigantism (X-LAG) syndrome. They relate persistently elevated circulating GHRH levels to her pituitary hyperplasia and acro-gigantism, and they confirm her GPR101 gene micro-duplication mutation to relate to her GHRH hypersecretion X-LAG syndrome.

Hypothalamic control of puberty progressing to sexual maturity and reproduction requires multiple gene product interactions. Puberty is timed to physiologically start between about 8 and 13 years of age for girls and about 9 and 14 years of age for boys to optimize growth and physical as well as behavioral sexual maturation to achieve healthy adulthood with option for normal human reproduction [122, 123]. Skorupskaite et al. [124] review the kisspeptin-GnRH pathway as key to current understanding of neuroendocrine regulation of puberty and human reproduction. Uenoyama et al. [125] compile data from their literature review regarding DNA and histone modifications in KISS1 gene promoter region to reveal molecular and epigenetic mechanisms regulating hypothalamic KISS1 gene expression. They propose a molecular and epigenetic mechanism regulating KISS1 gene expression in two hypothalamic neuron groups that can reasonably interact to govern puberty onset, cycling, and reproduction via the kisspeptin-GnRH pathway maturing to GNRH pulse cycling. Silveira et al. [126] report their survey of the KISS1 gene in 83 children with CPP (77 girls, 6 boys) to reveal two novel missense mutations in three unrelated children with CPP, and both these mutations are not found in 400 control alleles. KISS1 gene mutations can cause disorders of puberty.

The kisspeptin-GPR54 ligand-receptor complex is a neuro-regulator for onset of puberty, and some rare mutations in GPR54 gene (KISS1R) are noted to associate with central precocious puberty. Autosomal recessive inheritance pattern of other mutations in KISS1R is associated with variable expression of idiopathic hypogonadotropic hypogonadism (iHH) with or without anosmia [127]. KISS1 gene mutations also associate with iHH with or without anosmia [126]. Topaloglu et al. [128] are the first to report a kisspeptin loss-of-function mutation with autosomal recessive inheritance pattern in four sisters with HH demonstrating importance of functional kisspeptin for human puberty and reproduction.

Precocious puberty is traditionally defined as development of any secondary sexual characteristics before 8 years of age for girls and before 9 years of age for boys. However, there are noted trends for onset of normal puberty as early as 6–7 years of age for girls though their age of menarche is considered within current norms at about 12 years of age. It is important to distinguish central precocious puberty (hypothalamic focused initiation) from peripheral precocious puberty [123, 129].

Hypothalamic gonadotropin-releasing hormone (GnRH) pulsatile secretion activation is key for onset of central (normal) puberty initiation and progression. Pituitary-expressed GnRH receptor gene mutations tend to associate with idiopathic hypogonadotropic hypogonadism with or without anosmia. Kisspeptin-GPR54 ligand-receptor complex is an excitatory neuro-regulator for onset of puberty. Lee et al. [130] report isolation of kisspeptin G-protein-coupled receptor (GPR54) from a human DNA library and then localize GPR54 within rat brain sections including the hypothalamus. Koemeter-Cox et al. [131] employ a mouse model to demonstrate the key role of KISS1R (human GPR54) localized on GnRH neuron primary cilia (mammalian central neuron typically has a solitary or primary cilia to assist neuronal networking). They report GPR54-positive cilia increase in parallel with pubertal maturation and increase GnRH neuron firing rate.

These observations support kisspeptin-GPR54 control of GnRH pulses for puberty and reproduction. Teles et al. [132] report a heterozygous GPR54 gene puberty-activating mutation in an 8-year-old girl with OMIM classified central precocious puberty 1 (CPPB1) inherited in an autosomal dominant pattern. Ojeda et al. [133] review the wealth of available data regarding gene networks and the neuroendocrine regulation of puberty.

Abreu et al. [134] report four mutations in MKRN3 gene to associate with central precocious puberty 2 inherited in a paternal imprinted autosomal dominant pattern. MKRN3 gene encodes for makorin ring protein 3 and is located within the Prader-Willi syndorme region of chromosome 15. MKRN3 protein has a puberty suppressive influence to assist childhood until normal age for onset of puberty. MKRN3 gene mutations cause lack of functional MKRN3 protein expression and resultant central precocious puberty (CPP).

Hypogonadotropic hypogonadism is most frequently encountered as a genetic hypothalamic dysfunction. There are 24 OMIM genetic associations with hypogonadotropic hypogonadism. Olfactory nerve development is in close embryologic time and space proximity with hypothalamic development in a pattern often associating anosmia with hypogonadotropic hypogonadism such as classic Kallmann syndrome. Bianco and Kaiser [127] review genetic and molecular data related to idiopathic hypogonadotropic hypogonadism (iHH). Since GnRH pulses are essential for normal onset and progression of puberty progressing to maturity and successful reproductive capacity, GnRH gene mutations would be obvious candidates for iHH. Chan et al. [135, 136] report their survey of DNA from 310 patients with normosmic iHH and 192 healthy control subjects. They identify five patients out of the 310 with normosmic iHH to have GnRH gene mutations, one homozygous with severe iHH, and the four others heterozygous. GnRH1 gene mutations can be mild and possibly reversible with transient hormonal therapy of idiopathic hypogonadotropic hypogonadism to severe lifelong forms of GnRH deficiency.

KAL1 gene, also termed ANOS1 gene, expresses anosmin-1 protein that has a key role in migration of GnRH neurons and olfactory nerves into the hypothalamus [137, 138]. Located on the X chromosome, KAL1 mutations tend to be inherited in an X-linked recessive pattern, but the majority appear sporadic with only about 30% showing a familial pattern with higher prevalence in males in part attributed to partial escape of normal KAL1 from X inactivation and the variable phenotypic expression of iHH with or without anosmia due to autosomal gene mutations [139].

Fibroblast growth factor receptor 1 (FGFR1) and its ligand FGF8 and NELF gene product have key roles in embryonic development of neurons in several brain areas but especially the hypothalamic GnRH-producing neurons. FGFR1 gene mutations and FGF8 gene mutations associate with iHH with or without anosmia and are inherited in autosomal dominant patterns. Pitteloud et al. [140] report three individuals with loss-of-function FGFR1 gene mutation-associated iHH. Trarbach et al. [141] report two familial iHH patients that associate FGF8 gene mutations with human GnRH deficiency. Xu et al. [142] identify nasal embryonic LHRH factor (NELF) gene mutations in 3 of 168 (1.8%) patients with normosmic iHH and Kallmann syndrome. Two of the three males have heterozygote NELF gene mutations. NELF gene product assists embryo olfactory-hypothalamic neuron/axon migration and development of GnRH hypothalamic neurons.

PROK2 and its receptor PROKR2 are critical regulators of reproduction in mice and humans. Isolated mutations in these genes with appearance of autosomal dominant inheritance are associated with variable expressions of Kallmann syndrome or normosmic iHH as variants of GnRH deficiency [143]. Cole et al. [144] report their genetic exploration of 324 patients with iHH consisting of 170 KS and 154 normosmic IHH. They identify four mutations in PROK2 gene, ten mutations in PROKR2, and one patient with mutations in both PROK2 and PROKR2.

They note that a subset of these patients appear to have some recovery of their GnRH to the extent that 10% note full maturation of GnRH neuronal network in late adult life [145]. The mechanism of how PROK2 gene and PROKR2 gene products influence GnRH neuron development in the preoptic hypothalamus remains an area for research and likely involves circadian rhythm output.

SEMA3A gene encodes semaphorin 3A that along with neuropilin receptors serves to direct migration of neuronal axons into various areas of the cortex and hypothalamus [146]. Young et al. [147] report their study of a family in which the father expressed congenital hypogonadotropic hypogonadism with anosmia but became fertile in young adult life only after intensive hormonal therapy. They conclude that pubertal failure in the 17-year-old son and 18-year-old daughter is due to their hypogonadotropic hypogonadism with anosmia-associated SEMA3A mutation with autosomal dominant inheritance pattern.

RAB3GAP2 gene expresses non-catalytic protein subunit 2 that helps regulate intracellular GTPases among which RABs are involved in release of hormones and neurotransmitters in the brain and hypothalamus. Aligianis et al. [148] present a pedigree identifying three patients with mild mental retardation, congenital cataracts, and hypogonadism (Martsolf syndrome) associated with autosomal recessive pattern inherited RAB3GAP2 gene mutation.

CHD7 gene encodes chromatin-remodeling protein that functions as a transcription modulator. CHD7 mutations have variable expression of developmental anomalies including neuronal development ranging from multi-organ CHARGE syndrome (1:8500–10,000 newborn, coloboma, heart defects, atresia choanae, retardation of growth, genital and ear abnormalities) to focused olfactory-hypothalamic region with iHH or Kallmann syndrome in an autosomal dominant inheritance pattern [149]. Kim et al. [150] report screening for CHD7 mutations in 197 patients with idiopathic hypogonadotropic hypogonadism or Kallmann syndrome and find CHD7 mutations in 6%.

TAC3 encodes the preproprotein that is proteolytically cleaved to neurokinin B as a neurotransmitter, and TACR3 encodes neurokinin B receptor. Neurokinin B and its receptor in the hypothalamic arcuate nucleus assist GnRH secretion as a marker of puberty activation as well as a key modulator in human reproduction. TAC3 and TACR3 mutations are associated with hypogonadotropic hypogonadism +/− anosmia. Neurokinin B is also expressed in the placenta where it likely has an influence upon reproduction. Topaloglu et al. [151] report four human pedigrees with several members expressing severe congenital hypogonadotropic hypogonadism associated with TAC3 or TACR3 mutations inherited in autosomal recessive patterns. They conclude that neurokinin B is a critical central control regulator of human gonadal function and human reproduction.

WDR11 gene encodes WDR11 protein (containing wheel-like structural domains) that is expressed throughout the mouse embryo model central nervous system including progenitor cells for hypothalamic GnRH neuron development. WDR11 gene expression in adults is seen primarily in olfactory bulbs, olfaction-related cortex, and hippocampus-related neurons. Function of WDR11 protein is not clear, but it appears critical for the developing hypothalamic nuclei required for later expression of normal puberty. Kim et al. [152] report six patients with five different WDR11 mutations inherited in an autosomal dominant pattern and associated with iHH and Kallmann syndrome.

HS6ST1 gene encodes cell membrane protein heparan sulfate 6-O-sulfotransferase 1 that in *C. elegans* plays a role in neural branching in vivo supporting cell-cell communication model required for GnRH neuronal development. Tornberg et al. [153] report their genetic screening of 338 GnRH-deficient patients revealing five heterozygote mutations in HS6ST1 gene in seven patients, five patients anosmia (Kallmann syndrome), and two patients normosmic iHH.

Miraoui et al. [154] report screening 386 unrelated individuals with congenital hypogonadotropic hypogonadism for multiple associated gene mutations. They report finding 11 patients with heterozygous mutations in the SPRY4 gene. SPRY4 gene encodes a protein regulatory factor

as an inhibitor of the receptor-transduced mitogen-activated protein kinase (MAPK) signaling pathway. As one of many intracellular interactions, MAPK pathway is involved in the FGF8-FGFR1 control of GnRH neurons. Miraoui et al. [154] report finding multigene mutations involved in the FGF8-FGFR1 control of GnRH neurons to include fibroblast growth factor 17 (FGF17) gene mutation in three, interleukin 17 receptor D (IL17RD) gene mutation in eight, dual-specificity phosphatase (DUSP6) gene mutation in five, and fibronectin-like domain-containing leucine-rich transmembrane protein (FLRT3) gene mutation in three.

FEZF1 gene encodes a transcription repressor forebrain embryonic zinc finger protein 1 that is noted in a mouse model to be required to enable olfactory receptor neuron axons to penetrate CNS basal lamina essential for GnRH neuron development for later pubertal development. Kotan et al. [155] report screening 30 individuals with Kallmann syndrome to find four patients with FEZF1 homozygous mutations.

PNPLA6 gene encodes patatin-like phospholipase domain-containing protein 6 (PNPLA6) that de-esterifies phosphatidylcholine as a major component of biologic membranes into its fatty acid components and glycerophosphocholine leading to acetylcholine biosynthesis. Acetylcholine is a key neurotransmitter critical for CNS cell signaling and motor neuron and autonomic neuron activity. PNPLA6 protein is also thought to support neurite outgrowth and neuronal differentiation including GnRH neurons. Synofzik et al. [156] report screening for PNPLA6 gene mutations in families with homozygous inheritance of neurodegenerative Boucher-Neuhäuser syndrome or Gordon Holmes syndrome. They note ten patients (nine Boucher-Neuhäuser, one Gordon Holmes) with hypogonadotropic hypogonadism and PNPLA6 gene mutations. They propose that the two syndromes are due to variable PNPLA6 mutations as part of a broad neurodegenerative spectrum. Topaloglu et al. [157] confirm loss-of-function PNPLA6 in six patients from three unrelated families to associate with the patients' neurodegenerative disorders, failure to complete puberty, and hypogonadotropic hypogonadism. They conclude PNPLA6 loss-of-function alters phospholipid homeostasis causing neurodegeneration and impairs LH release.

C2orf37 homozygous gene mutations are associated with rare Woodhouse-Sakati syndrome that combines hypothalamic neural network dysfunction and resultant hypogonadotropic hypogonadism with alopecia, mental retardation, extrapyramidal syndrome, and diabetes mellitus [158]. C2orf37 encodes a nucleolar protein that appears to assist maintenance of normal hypothalamic neuronal activity as well as other multiple key organs via C2orf37 general presence in nucleolus and nucleoplasm of most cells throughout the body.

Hypothalamic Water/Metabolic Balance Control

The posterior pituitary is a neuroectoderm extension from supraoptic and paraventricular nuclei of the hypothalamus in which magnocellular neurons are specifically for synthesis and secretion of arginine vasopressin (AVP) with its "transporter" neurophysin II or oxytocin with its neurophysin I. Oxytocin assists attainment of appropriate social/reproductive behavior balance. AVP is transported in vesicles along the axon from its specific magnocellular neuron to the posterior pituitary where osmoreceptor input regulates AVP secretion for water osmotic/sodium homeostasis. Oxytocin is transported in vesicles along the axon from its specific neuron to the posterior pituitary for release into the general circulation to attain social, reproductive, and parenting behavior balance [159]. AVP gene mutation-associated hypothalamic disorders related to diabetes insipidus (DI) are summarized in Table 14.9.

AVP gene encodes prepro-AVP that consists of AVP, neurophysin II, and glycoprotein (copeptin). Osmoreceptor cells in the lateral preoptic anterior hypothalamic region monitor the need for AVP action. About 40 mutations in the AVP gene are associated with rare familial neurohypophyseal (central) diabetes insipidus (FNDI)

presented in detail later. The majority of FNDI-associated AVP gene mutations have an autosomal dominant inheritance pattern with a few reported autosomal recessive pattern. The majority of AVP gene mutations associated with FNDI occur in the neurophysin-encoding region. Ito et al. [160] report that FNDI-associated AVP mutations stably expressed in neuro2A neuroblastoma cells exhibit mutant AVP precursor accumulation in the endoplasmic reticulum that interfere with AVP trafficking and provide a potential cause for reported magnocellular neuronal cell toxicity in FNDI patients. Wahlstrom et al. [161] report similar magnocellular toxicity with an AVP gene mutation causing histidine for tyrosine substitution in AVP itself and AVP trafficking dysfunction.

Hypothalamic Nutrition/Appetite/ Body Weight Control

Claude Bernard published in 1854 [162] his observation that discrete puncture of the floor of the cerebral 4th ventricle in animals caused a transient hyperglycemia for no more than a day. He termed it "pique diabetique" or diencephalic hyperglycemia and initiated interest in brain influence upon glucose metabolism. Lam et al. [163] review literature and their rat model data supporting the hypothalamic arcuate nucleus as a major site for multiple nutritional and hormonal signal integration contributing to modulation of liver glucose homeostasis through neuroendocrine signaling as well as appetite. They conclude neurons have physiologically significant mechanisms for glucose sensing.

Glucose consumption is recognized to be tightly linked to brain neuronal activity. Kasischke et al. [164] present their use of multiphoton microscopy to image subcellular neuronal metabolism in hippocampal brain slices. Utilizing intrinsic fluorescence of β-nicotinamide adenine dinucleotide (NADH), they demonstrate neural activity triggers neuronal oxidative metabolism supported by lactate shuttled between astrocytes and neurons known as the astrocyte-neuron or neuron-astrocyte lactate shuttle. Lam et al. [163] utilize their rat model to study the influence of intracerebral-ventricular infusions of glucose or lactate upon hypothalamic glucose levels and signaling. Their results support hypothalamic blood glucose regulation through neuronal lactate conversion to pyruvate followed by tricarboxylic acid cycle-generated high-energy ATP. Lam et al. [163] note that inhibition of hypothalamic lactate metabolism reduces hypothalamic inhibition of hepatic glucose production by 40% (i.e., reduction in hypothalamic response to hyperglycemia). They offer this observation as an area to explore for management of type 2 diabetes mellitus. Genetic mutations interfering with pyruvate metabolism would influence hypothalamic regulation of blood glucose.

Schwartz and Porte Jr [162] review research and offer a viewpoint on the brain's key role in control of glucose homeostasis, body fat, and mechanisms linking obesity and type 2 diabetes mellitus. Current data support the hypothalamus receiving and processing information from insulin and leptin levels proportionate to absorbed glucose and related food nutrients and to free fatty acids and adipose stores proportionate to an individual's body fat mass. To accomplish this pivotal role in establishing energy balance, the brain and especially hypothalamic neurons must respond to digestion-related signals, insulin through insulin receptors and inter/intracellular pathways for pyruvate metabolism noted above, and hypothalamic sensing of lipid levels resulting in appropriate hypothalamic neuroendocrine activity to control energy homeostasis and hepatic glucose production. Genes and mutation-associated hypothalamic disorders related to nutrition/appetite/body weight control are summarized in Table 14.10.

Genetic influences upon hypothalamic involvement in energy homeostasis and related weight control can be appreciated through studies of human syndromes focused upon weight imbalance and mouse modified gene models. Insulin receptor substrates play critical roles in intracellular insulin signaling pathways. Employing insulin receptor substrate 2 (IRS2) partial knockout mouse model, Kubota et al. [165] report their studies of heterozygous IRS2

Table 14.10 Summary of genes and genetic mutations related to hypothalamic nutrition/appetite/weight control ([20], https://genecards.org/)

Gene	Gene product	Mutations' inheritance	Mutation associated hypothalamic disorder
IRS2	Insulin receptor Sub. 2 – signaling mediator Ins, IGF1, other cytokines	Autosomal homozygous/ recessive	Type 2 diabetes mellitus Fatty liver disease
LEP	Leptin – major regulation hypothalamic appetite and energy centers	Autosomal homozygous/ recessive	Severe obesity, morbid obesity, link T2DM Hypogonadism Leptin dysfunction eating disorder
LEPR	Leptin receptor – stimulate gene transcription, act on hypothalamic centers	Autosomal homozygous/ recessive	Obesity Hypogonadotropic hypogonadism Eating disorders – anorexia nervosa
POMC	Pre-proopiomelanocortin hypothalamic arcuate neuronal satiety center	Autosomal mixed	Obesity – early onset with adrenal insufficiency and MSH deficiency Associated hair pigment aberrations
PCSK1	Proprotein convertase 1 – hypothalamic neuron cleaves POMC-ACTH	Autosomal homozygous	PCSK1 deficiency – congenital adrenal insufficiency, link monogenic early-onset severe obesity
MC4R	MSH membrane receptor hypothalamic satiety, multi-signaling paths	Autosomal heterozygous/rare recessive	Obesity – autosomal dominant as most common monogenic cause of human obesity BMI family traits

Sub. substrate, *Ins* insulin, *IGF1* insulin-like growth factor-1, *T2DM* type 2 diabetes mellitus, *MSH* melanocyte-stimulating hormone, *BMI* body mass index

gene knockout mice as a model of type 2 diabetes mellitus as well as leptin sensitivity and obesity. They conclude that IRS2 appears crucial for hypothalamic leptin sensitivity and associated weight control. Stefan et al. [166] report human polymorphisms in IRS2 gene to be less consistent but suggest an association of homozygous Asp1057 allele in IRS2 with type 2 diabetes mellitus in Pima Indians that may be mediated by degree of individual obesity.

Human obesity is multifactorial involving environmental factors, food intake, energy expenditure, and establishment of a hypothalamic individual energy balance set point. Inheritance accounts for 40%–70% of an individual's predisposition to obesity. Ranadive and Vaisse [167] review monogenic mutations associated with extreme human obesity. Although only about 20 distinct genes are associated with extreme monogenic human obesity and account for about 5% of all severe human obesity, results from studies of monogenic extreme human obesity support the critical involvement of the hypothalamic leptin-melanocortin system in an individual's energy balance.

Leptin gene encodes the human leptin that is secreted by adipocytes in proportion to an individual's body fat mass. There are only a few individuals with reported congenital leptin deficiency involving two known homozygous (autosomal recessive inheritance) mutations reviewed by Farooqi and O'Rahilly [168]. Functional leptin and melanocortin receptors must be available in the hypothalamus to appreciate leptin's positive influence upon anorexigenic POMC-producing neurons balanced with leptin's negative influence upon orexigenic neuropeptide (NPY)/agouti-related peptide (AgRP) neurons forming the appetite and energy homeostasis control center within and about the hypothalamic paraventricular nucleus [169].

LEPR gene encodes the leptin receptor that is critical to hypothalamic appetite center function and to achieving energy balance. LEPR gene mutations resulting in LEPR dysfunction are inherited in an autosomal recessive (homozygous) pattern. Clement et al. [170] offer the first description of human congenital leptin receptor deficiency due to a homozygous LEPR mutation in three sisters from a consanguineous family.

The three sisters had normal birth weights but rapid weight gain by 6 months of age and hyperphagia with severe obesity by adolescence with 65% body fat and BMI 50–70 kg/m^2. Farooqi et al. [171] describe results of their LEPR gene sequencing in 300 subjects that included 90 probands from consanguineous families. Of the 300 subjects they report seven (2–3%)with homozygote LEPR mutations. Severe obesity, hyperphagia, and altered immune function are attributed to altered LEPR reducing its interaction with immune response as a single-transmembrane-domain receptor of the cytokine receptor family hypogonadotropic hypogonadism-associated delayed.

POMC gene encodes pre-proopiomelanocortin that after removal of N-terminal signal sequence leads to proopiomelanocortin (POMC) protein. POMC is sequentially cleaved into several bioactive peptides in cells primarily in the hypothalamus, anterior pituitary, and skin where proprotein convertase 1/3 cleaves POMC to form ACTH, joining peptide and N-proopiomelanocortin. Both homozygous and compound heterozygous POMC mutations cause complete POMC deficiency presenting as profound adrenal insufficiency in the newborn requiring early recognition and glucocorticoid replacement for survival [172]. Krude et al. [173] report the first patients diagnosed with complete POMC deficiency and note their presentation with severe early-onset obesity, adrenal insufficiency, and red hair pigmentation due to lack of POMC cleavage products especially hypothalamic α-melanocyte-stimulating hormone (α-MSH) to promote satiety, ACTH to stimulate adrenals, and skin cleavage of ACTH to α-MSH to influence skin/hair pigmentation though not necessarily red hair color. POMC is cleaved into pro-ACTH and β-lipotropin by PCSK1 gene-encoded proprotein convertase 1/3. PCSK1 homozygous mutation is associated with proprotein convertase 1/3 deficiency and congenital adrenal insufficiency with ACTH deficiency and a link to monogenic early-onset severe obesity [172].

Leptin signaling targets POMC-expressing neurons in the hypothalamic arcuate nucleus as key components in the leptin-melanocortin system with particular attention to appetite control as shown in Fig. 14.2. Following proprotein convertase 1/3 release of ACTH and β-lipotropin from POMC, PC2 prohormone convertase expressed in hypothalamic POMC neurons cleaves ACTH into α-MSH that promotes satiety through interactions at the MC4R receptor. However, PC2 also cleaves β-lipotropin into β-endorphin that can promote cannabinoid-induced feeding at the cannabinoid receptor 1 [174].

MC4R heterozygous mutations are considered the most common monogenic cause of human obesity. Farooqi et al. [175] report screening 243 subjects with severe, early-onset obesity in whom they find 3%–4% have pathogenic mutations in MC4R gene. The typical presentation of these pathogenic MC4R gene mutations is heterozygous with autosomal dominant inheritance pattern, but they find a homozygous or autosomal recessive pattern in five children with severe obesity. Andermann and Lowell [169] present a 2017 update for understanding appetite regulation as an evolving wiring diagram as a synthesis of neural network data from new technologies. Millbank and López [176] present a 2019 review of the orexins/hypocretins (HCRT gene products orexin A and orexin B summarized in Table 14.6) as key regulators of appetite and energy homeostasis depicted in Fig. 14.2.

Summary of Genetic Syndromes of Hypothalamic Dysfunction

Hypothalamic Hamartoma Syndrome (HHS)

Introduction

Hypothalamic hamartomas (HH) are congenital lesions of the ventral hypothalamus: floor of third ventricle, tuber cinereum, or mammillary bodies [49, 57]. HH tend to grow synchronously with the brain and do not metastasize, maintaining their size constant in relation to the brain. HH can present in two distinct ways, either with central

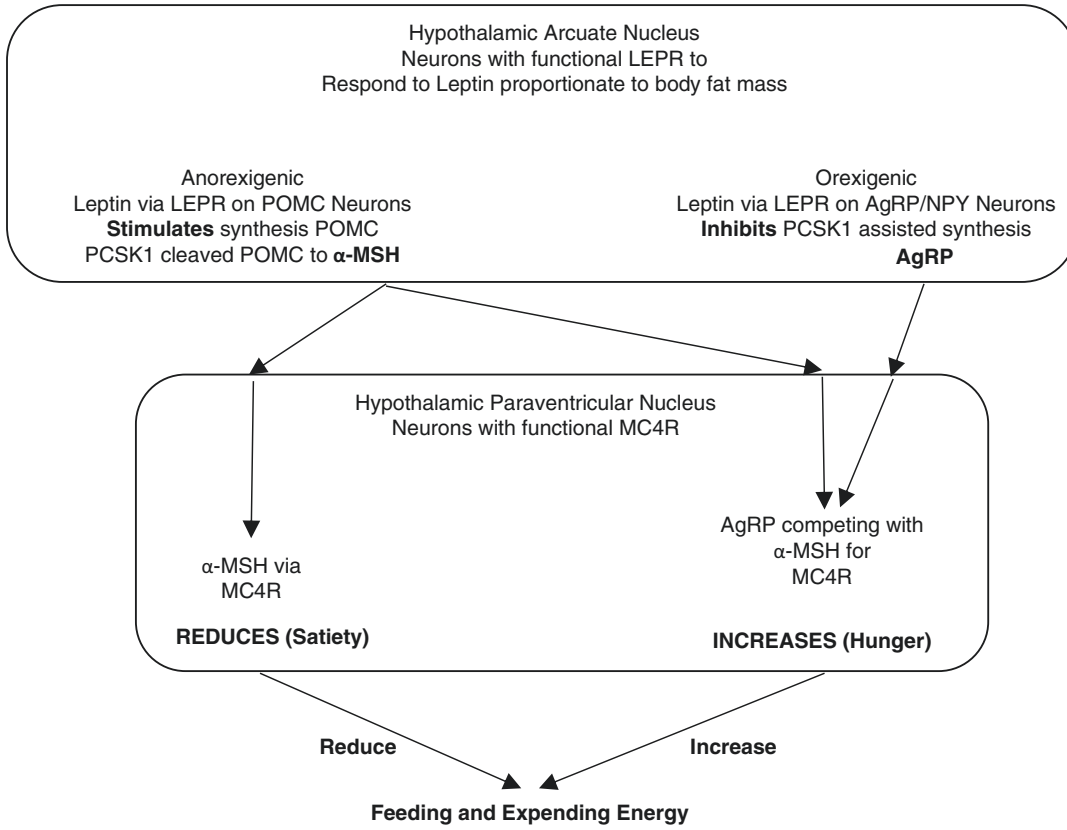

Fig. 14.2 Hypothalamic pathways assisting regulation of feeding and expending energy. LEPR leptin transmembrane catalytic leptin receptor, POMC proopiomelanocortin, AgRP agouti-related peptide, NPY neuropeptide Y, PCSK1 PCSK1-encoded proprotein convertase subtilisin/kexin type 1, MC4R melanocortin 4 receptor

precocious puberty (CPP) favoring anterior hypothalamic tumor location or with seizures favoring posterior hypothalamic tumor location. MRI and video EEG monitoring are useful tools to make the diagnosis. The management of HH includes the use of gonadotropin antagonists to treat CPP and surgery/antiepileptic drugs to treat the seizures [57].

Epidemiology

HHS is a rare condition with estimated prevalence of 1 in 200,000, no published racial or ethnic predilection, and boys more often affected than girls (estimated ratio 1.5:1). HH is potentially underdiagnosed due to the small nature of lesions possibly missed on imaging or atypical seizures possibly not immediately recognized [57, 177–182].

Genetics

HHS is usually sporadic and not associated with other congenital anomalies. However, in about 5% of cases, it is associated with Pallister-Hall syndrome [178], which is characterized by postaxial polydactyly, bifid epiglottis, and imperforate anus. Pallister-Hall syndrome is due to mutations in the GLI3 gene (Table 14.4), which is a modulator of the sonic hedgehog (SHH) pathway (Table 14.3). Somatic GLI3 mutations are noted in 10%–20% of sporadic HH cases [58]. As genotyping technology evolves, more mutations of the GLI3 gene in association with HH may be uncovered.

Pathophysiology

Hamartomas consist of nonneoplastic disordered collections of mature neurons, glia, and fiber bun-

dles that do not metastasize. HH is characterized by clusters of neurons, and these clusters are made of small neurons (90%) and large neurons (10%). The small neurons have pacemaker activity, making them potential epileptogenic foci. The larger neurons have numerous dendrites which may help propagate seizure potentials [57, 177–182].

Gonadotropin-releasing hormones (GnRH)-secreting neurons are present in the medial basal hypothalamus. GnRH-secreting neurons may be part of an HH secondary to defects in the axon guiding molecules (including KAL-1), resulting in flawed migration from the olfactory neural plate to appropriate hypothalamic nuclei. Lack of the usual inhibitory CNS mechanisms in these ectopic neurons allows them to secrete GnRH prematurely, resulting in CPP [181].

HH can be classified based on whether they are pedunculated or sessile. Pedunculated or para-hypothalamic HH are attached to the tuber cinereum by a stalk and usually associated with CPP. Sessile or intra-hypothalamic HH locate within the fornix and mammillary bodies and are associated with seizures and behavioral issues but generally not CPP. Large HH, which involves both the anterior and posterior hypothalamus, can present with both CPP and seizures [57].

Clinical Features

The clinical features of HHS can be divided into two main categories:

1. Seizures and behavioral changes: Gelastic seizures are characteristic but not exclusive to HH. They present early in life around 2 years. The patients appear to be laughing during these gelastic seizures; however, in most instances, there is no reasonable social setting for their laughter that is not shared by their companions or family. HH-associated gelastic seizures are brief, lasting only 10–20 seconds, and are not associated with distinctive electroencephalogram (EEG) anomalies. Occasionally, dacrystic seizures in which the seizure events resemble crying or a combination of gelastic and dacrystic seizures again without reasonable social setting may be noted. Many other seizure types are associated with HH and present around 4–10 years of age. Temporal lobe seizures (50%–60%) are the most common; however, tonic-clonic (40%–60%), atypical absence (40%–50%), and tonic (15%–30%) seizures can also be seen [177, 179, 180, 182].

   HH can be associated with mood lability and aggression. Cognitive decline is seen in association with seizures in HH, and its severity is related to the size of the HH, seizure frequency, and age of onset of the seizures. Prigatano [180] presents results of psychometric method testing of 49 patients with treatment-resistant epilepsy due to HH and notes the following patterns of cognitive dysfunction:
   A. Pattern 1 (35%) has normal IQ but may have mild attention deficits.
   B. Pattern 2 (18%) has normal IQ but significant defects in verbal and performance domains.
   C. Pattern 3a (22%) has mental retardation as measured on standard scales.
   D. Pattern 3b (14%) has mental retardation that cannot be measured on standard scales.

Endocrinological

A key endocrine dysfunction noted with some HH is precocious puberty that may present in boys or girls with HH. Precocious puberty is defined as the occurrence of a secondary sexual characteristic at an earlier age than generally agreed normal onset for those puberty stages for age and gender (any characteristic less than 9 years for boys, 8 years for girls) [122, 129]. HH can be associated with CPP depending on the size and location of the hamartoma. The initial CPP symptom in girls is usually breast enlargement, while in boys, it is testicular enlargement. There is also early onset of pubertal growth spurt with associated bone age advancement primarily due to estradiol-influenced stimulation of insulin-like growth factor-1 (IGF-1). However, untreated CPP can lead to premature fusion of epiphysis with reduced adult height for biologic parents' midparental height projection [181].

Diagnosis

Gelastic or dacrystic seizures may be the initial manifestation of HH. However, due to the atypical nature of the seizures and no interval EEG abnormalities, patients have the potential to be initially misdiagnosed. HH are isodense tumors and may be missed on MRI evaluation. High-resolution MRI with T2-weighted (tissue density enhanced) fast spin-echo sequence is ideal for identifying HHS. Neurodevelopment testing is also recommended to evaluate cognitive deficits and to document any significant progressive neurodegeneration [57, 177–179].

CPP is diagnosed when secondary sexual development is observed in girls younger than 8 years and boys younger than 9 years of age. Enlargement of the breasts is usually the first sign of CPP seen in girls, while in boys, the initial sign of CPP is usually testicular enlargement. CPP differs from peripheral precocity in that the typical sequence of gender-appropriate pubertal events is preserved. Laboratory assessment of CPP includes measurement of testosterone, estradiol, LH, and FSH. High levels of testosterone or estradiol with low levels of LH (<0.2 mIU/mL) are indicative of peripheral precocious puberty, whereas high levels of LH (>0.3 mIU/mL) are indicative of central precocious puberty. A GnRH stimulation test can be performed if the initial labs are unclear [129, 181].

Treatment

1. Seizures: Gelastic seizures tend not to respond to antiepileptic drugs (AEDs). However, secondary seizures may respond to AEDs. Early surgery is recommended in cases resistant to AEDs. The early surgical intervention also prevents the "rundown phenomenon" where secondary epileptogenic foci develop due to constant stimulation from the primary foci in the HH. The pre-surgical evaluation includes a 24 hour EEG monitor, MRI to obtain the anatomic alignment of HH, visual field assessment, endocrine evaluation for CPP, and comprehensive psychometric testing. Various surgical approaches to HH are used, including transcallosal anterior intraforniceal resection, transventricular endoscopic resection, and pterional/orbitozygomatic resection. Other less invasive modalities include gamma knife radiotherapy and stereotactic radiofrequency/laser thermoablation [57, 182].
2. Central precocious puberty: The goal of treatment of CPP is to ensure the child with CPP reaches reasonable adult height (general North American 2000 CDC health statistics average height for males is 5′10″ with about 95% adult males 5′5″ or taller, and average height for women is 5′4 1/2″ with about 95% adult women 5′ or taller). Therefore, the decision to treat or not is based on age of pubertal onset, rate of maturation, and predicted adult height from bone age and clinical data in comparison to biologic midparental height, if available. Treatment with GnRH agonists is most likely to be helpful in patients who are younger by bone age than anticipated age for gender-appropriate pubertal stage and have a rapid rate of maturation [123, 129]. Various formulations of GnRH agonists are available for treatment of CPP; however, leuprolide acetate is most commonly used. It is started at a dose of 7.5 mg every 28 days. Pubertal development, growth velocity, and bone age are monitored. If adequate CPP suppression is not obtained, then the dose of leuprolide can be increased. Treatment with GnRH agonists should be continued up to about 12 and 11 years of age in boys and girls, respectively. However, treatment duration should be individualized for each patient's behavioral adaptation and growth potential considerations [123, 129, 181].

Familial Neurohypophyseal Diabetes Insipidus

Introduction

Diabetes insipidus (DI) is a disorder due to the lack of action of an antidiuretic hormone, arginine vasopressin (AVP). Clinically, it is characterized by excessive excretion of inappropriately hypotonic urine. The lack of action of AVP can be due to a decrease in the synthesis of AVP (neurohypophyseal DI), resistance to the action of AVP

(nephrogenic DI), or rarely due to increased metabolism (gestational DI) [159]. Neurohypophyseal DI, in most instances, develops as a complication of pituitary surgery or radiation; rarely, DI can be secondary to genetic defects (Table 14.9) [159, 183].

Physiology of Arginine Vasopressin Secretion

AVP is a nonapeptide synthesized by the magnocellular neurons of the hypothalamus. It is synthesized as a pre-prohormone (164 amino acids) consisting of a signal sequence, neurophysin II carrier protein (NIIM), AVP, and C-terminal glycopeptide copeptin. The AVP gene is located in the short arm of chromosome 20. The gene consists of three exons that encode the abovementioned four segments. Posttranslational modification occurs in the endoplasmic reticulum where the signal sequence is cleaved, and the molecule undergoes folding by the formation of eight disulfide bonds. The prohormone so formed is packed into neurosecretory granules and transported along the axons. The enzyme prohormone convertase acts to separate the three remaining segments: NIIM, AVP, and copeptin [183]. AVP is released in response to hyperosmolarity, hypovolemia, or hypotension [159, 160].

Genetic Forms of NDI

Lacombe is historically the first to describe a hereditary form of DI in 1841 [184]. Genetic localization of autosomal dominant neurohypophyseal DI (ADNDI) to an AVP gene is attributed to Repaske et al. in 1990 when they hypothesized the basis for ADNDI could be a genetic mutation-derived deficiency of AVP [183–185].

Autosomal Dominant NDI

ADNDI is hypothesized to result from cumulative neurotoxic degeneration of magnocellular neurons due to accumulation of AVP fibrillary aggregates. Postmortem studies in ADNDI patients show selective degeneration of magnocellular neurons, and transfection studies demonstrate decreased viability of neurons with AVP mutations. [183, 185].

Clinically, ADNDI may manifest in the first months of life with polyuria and polydipsia. However, the onset and severity of ADNDI symptoms are variable even in patients who have the same AVP mutation. ADNDI can progressively become more severe as AVP production declines with progressive degeneration of magnocellular neurons. Infants with inherited ADNDI can present with failure to thrive and growth retardation [159, 183]

Autosomal Recessive NDI (ARNDI)

ARNDI is rarer than ADNDI with published reports in only a few families. Willcutts et al. [186] describe three children of a consanguineous marriage who develop DI between 1 and 2 years of age. Genetic analysis reveals a proline to leucine substitution (P7L) at position 7 of AVP. This mutation impairs the ability of AVP to activate cyclic AMP after binding to the V2 receptor. Christensen et al. [187] report an infant clinically expressing DI in the first few days of life. They report their genetic analysis to reveal a large deletion of exon 3, intron 2, and exon 2 of the AVP gene.

X-Linked NDI

To date, only one family (four adult males and two boys) with X-linked NDI is published in the world literature as an abstract. The males with this X-linked NDI tend to develop clinical DI years after birth. This form of DI resolves with the administration of desmopressin confirming NDI. The published report notes the posterior pituitary bright spot to be absent in the adult males but present in the boys with X-linked NDI consistent with slower onset of the disease. None of the mothers of the affected males are developing clinical DI that supports X-linked recessive mode of inheritance for this expression of late-onset DI [188].

Prader-Willi Syndrome (PWS)

Introduction

Historically, A Prader, A Labhart, and H Willi are given credit for first description of PWS in 1956.

The estimated prevalence of this disorder is 1/10,000–1/30,000. PWS is due to hypothalamic dysfunction resulting in a variety of symptoms and associated disorders. Genomic imprinting is the selective loss of expression of genes derived from one or the other parent. PWS is secondary to the loss of expression of paternal genes in the 15q11–q13 region. Loss of maternal genes with preservation of paternal genes in the region results in Angelman syndrome which is clinically distinct from PWS [189–197].

Genetics

PWS is a contiguous gene disorder which is localized to a 2.5 Mb differentially imprinted gene disorder on chromosomes 15q11.2–q13. The expression of genes in this region is mostly dependent on parental origin. PWS is an imprinted disorder wherein there is loss of expression of the paternal genes in the region. The maternal contribution of genes to this region in PWS is distinguishable from paternal genes as the maternal genes are heavily methylated and therefore mostly not expressed [189].

There are four distinct domains in the 15q112.2–q13 region on chromosome 15 that are delineated by three common break points [189]:

1. Four non-imprinted genes expressed on both chromosomes located between two proximal break points (BP1 and BP2): GCP5, CYFIP1, NIPA1, and NIPA2. There are other genes similarly expressed on both chromosomes located between more distal break points (BP2 and BP3).
2. The PWS imprinted genes (only paternal expression and therefore altered or deleted with PWS clinical expression) between two distal break points (BP2 and BP3): MKRN3, MAGEL2, NDN, bicistronic SNURF-SNRPN, and a cluster of RNA processing involved genes key to PWS as small nucleolar RNAs or snoRNAs and some antisense transcripts.
3. The Angelman syndrome region containing the maternally expressed genes: UBE3A and ATP10A genes.
4. A distal non-imprinted region containing a cluster of GABA receptor genes, oculocutaneous albinism gene, HERC2, and distal break point BP3.

Deletions are the most common mechanism resulting in PWS (65%–75%). Most of these deletions involve one of the proximal break points and the distal break point. Unbalanced translocations and deletions in the promoter region and proximal SNRPN can also result in PWS.

Clinical Features

Neonatal Period Hypotonia, impaired suck, failure to thrive, thick saliva, increased head/chest circumference ratio, small genitalia, and cryptorchidism [189–191].

Childhood Obesity, short stature, almond-shaped eyes, thin upper lip, downturned mouth, and small hands and feet [189–191].

Sleep Disorders

Neurons containing hypocretin (HCRT gene, Table 14.6) in the hypothalamus are responsible for wakefulness. Developmental disorders of the hypothalamus and mutations of HCRT and BHLHE41 genes can affect these neurons and potentially cause sleep disorders. PWS is associated with sleep disruption and sleep-disordered breathing. Hypotonia, chest wall deformities, craniofacial dysmorphia, and brain anomalies all contribute to the prevalence and severity of sleep disorders in PWS [192]. PWS is also associated with excessive daytime sleepiness. For children with PWS and obstructive sleep apnea, adenotonsillectomy is the preferred treatment, whereas in adults, the treatment of choice is well-maintained continuous positive airway pressure (CPAP) [192, 193].

Growth Hormone Deficiency

Short stature is a cardinal manifestation of PWS. While obese non-PWS children may have low growth hormone (GH) but normal IGF-1, PWS children have low levels of both growth hormone and IGF-1 consistent with true growth hormone deficiency [194, 195]. Treatment with recombinant growth hormone helps children

attain normal range adult heights. GH therapy is also associated with a decrease in fat mass and increase in lean mass, muscle strength, and exercise capacity. It is also associated with a decrease in hemoglobin A1c, blood pressure, and insulin resistance [194]. Prader-Willi recommended starting dose of GH is 0.18–0.3 mg/kg/week [194]. Potential side effects of GH therapy include lymphoid hyperplasia which may worsen obstructive sleep apnea. Scoliosis is highly prevalent in PWS (20%–30%) and previously considered a contraindication for GH therapy. However, recent studies have found no increase in progression of scoliosis with GH therapy [196].

Hypogonadism

Hypogonadism is a common feature of PWS and is a combination of primary and secondary hypogonadism. Males present with micropenis, cryptorchidism, and hypoplastic scrotal sac. Females present with clitoral and labia minora hypoplasia. Progression of puberty is delayed both in males and in females. Premature adrenarche is a common feature of PWS, and careful assessment of testicular size (>4 ml) and breast development (>tanner stage 2) must be done to confirm the onset of true puberty [197].

HCG administration is approved for the treatment of cryptorchidism. Sex steroid replacement is based on the patient's chronologic and bone age anticipated sexual development and associated comorbidities [123, 189, 197].

Hypothyroidism

Central hypothyroidism is reported in 20%–30% of PWS patients. However, other studies reported higher levels in children (72%) and lower levels in adults (2%). Due to this heterogeneity, levothyroxine therapy is not routinely prescribed [189, 190].

Adrenal Insufficiency

Isolated adrenocorticotrophic hormone (ACTH) deficiency is rare, but it can occur along with deficiencies of other pituitary hormones. In children with PWS, the sequence of hormonal loss usually is GH, TSH, LH/FSH, and lastly ACTH. Patients who are at risk of adrenal insufficiency need to be counselled about the symptoms associated with adrenal crisis and the appropriate individual emergency response to adrenal crisis and to immediately seek medical help [189, 190].

Pallister-Hall Syndrome (PHS)

Introduction

PHS is a syndrome characterized by hypothalamic hamartomas (HH) and mesoaxial polydactyly. PHS is secondary to a defect in the GLI3 gene (Table 14.4) and inherited in an autosomal dominant manner. Around 25% of cases are due to de novo mutations. The clinical spectrum of PHS is wide-ranging from asymptomatic to neonatal death secondary to adrenal insufficiency [178, 198–202].

Clinical Features

1. Hypothalamic hamartomas: These are benign malformations occurring in the hypothalamus. HH are slow-growing but, over time, can become quite large. They can occur in isolation or as a part of PHS. Generally, surgical intervention is not recommended and can result in complications such as panhypopituitarism and serious CNS injury.
2. Polydactyly: Both postaxial and mesoaxial polydactyly are observed in association with PHS; however, the presence of mesoaxial polydactyly is classically needed to make the diagnosis of PHS. Postaxial polydactyly is characterized by the presence of a well-formed digit or nubbin on the medial side of the limb, while mesoaxial polydactyly is the presence of six well-formed digits with a Y-shaped metacarpal.
3. Seizures: HH can be associated with gelastic seizures, which are partial complex seizures that simulate laughter. Seizures secondary to HH associated with PHS are milder as compared to those caused by non-syndromic HH, which is often refractory.
4. Endocrine abnormalities: HH can be associated with panhypopituitarism, isolated growth hormone deficiency, precocious puberty, and

adrenal insufficiency. Adrenal insufficiency is more common with sporadic PHS and presents in the neonatal period. Prompt diagnosis is crucial to prevent an adverse outcome.

5. Other malformations associated with PHS include craniofacial dysmorphology, abnormal lung lobulation and glottis-epiglottis anomalies, renal hypoplasia/dysplasia, ureter abnormal implantation, congenital heart defects, and anal defects.

Diagnosis

PHS is diagnosed by finding a pathogenic variant in the GLI3 gene in a patient with HH and mesoaxial polydactyly.

Management

1. HH: MRI to evaluate size and extent of tumor. Electroencephalogram for seizures as needed.
2. Polydactyly: Obtain radiographs of affected limbs. Consultation with a hand surgeon for surgical fixation of polydactyly.
3. Endocrine abnormalities: Assessment of hypothalamic-pituitary-adrenal axis and treatment with steroids, especially if there is no family history of PHS. Monitoring for growth hormone deficiency, hypothyroidism, and precocious puberty.
4. Laryngoscopy to visualize the epiglottis and surgical correction if needed.
5. Renal ultrasound to assess renal anomalies.
6. Surgical consultation for an imperforate anus if present.
7. Consultation with a geneticist to assess future recurrence.

Wolfram Syndrome

Introduction

Wolfram syndrome is a disorder characterized by diabetes mellitus, diabetes insipidus, optic atrophy, hearing loss or deafness, and progressive neurodegeneration. Historically, the first clinical description of diabetes mellitus with simple optic atrophy in four patients is attributed to DJ Wolfram and HP Wagener in 1938. Wolfram syndrome is a rare disorder with a prevalence of 1 in 160,000 to 1 in 770,000. It has a poor prognosis with progressive neurodegeneration including the hypothalamus and with the median age of death being 30 years [203–209].

Clinical Features and Management

Diabetes Mellitus (DM) Wolfram syndrome is associated with non-autoimmune, non-HLA-linked insulin-dependent DM. DM is usually clinically apparent around 6 years of age and aside from lack of autoimmune markers differs from type 1 DM by having a lower prevalence of ketoacidosis, persistent residual insulin secretion, and slower progression.

Diabetes Insipidus About 75% of patients with Wolfram syndrome present with DI by the age of 14. The presence of inappropriate hypo-osmolar urine generally makes the diagnosis of DI. Wolfram syndrome patients respond well to desmopressin.

Urological Manifestations Urological manifestations include large atonic bladder, low-capacity high-pressure bladder with sphincter dyssynergia, and hydroureteronephrosis. Currently, cholinergic medications and intermittent catheterization are the initial therapeutic options. Patients with Wolfram syndrome are prone to recurrent urinary tract infections and must be monitored and treated appropriately.

Optic Nerve Atrophy Optic atrophy is one of the cardinal manifestations of Wolfram syndrome and appears around 11 years of age. Surveillance in the form of an annual eye examination, color vision assessment, visual fields, and optical coherence tomography is recommended. Retinal thinning is a marker of disease progression. Docosahexaenoic acid or idebenone may be useful in delaying the progression of optic atrophy.

Hearing Loss Sensorineural hearing loss is observed in at least 70% of patients with Wolfram syndrome. The hearing loss typically affects high frequencies first. Annual routine audiometry with consideration of brainstem response audiometry is recommended. Low-frequency sensorineural

hearing loss is reported without DI though still risky for non-autoimmune diabetes mellitus and optic atrophy as a clinically distinct autosomal dominant heterozygous mutation in the WFS1 gene. Neurodegeneration appears to be more limited or slower with autosomal dominant WFS1 Wolfram-like syndrome than the severe clinical progression seen with autosomal recessive WFS1 Wolfram syndrome noted above [206, 209].

Neurological Manifestations Neurodegeneration can present with diverse symptoms depending on the population of neurons involved. Ataxia due to cerebellar involvement is common. Dysphagia and dysarthria can occur and need evaluation by a speech pathologist. Central sleep apnea is indicative of brain stem involvement. Orthostatic hypotension, anhidrosis or hyperhidrosis, gastroparesis, and temperature dysregulation can occur. Patient anxiety with their perception of progressive neurodegeneration should be appropriately referred early for psychology and/or psychiatry assessment and support.

Genetics

The WFS1 gene on chromosome 4 at about 4p16.1 encodes wolframin, a transmembrane protein primarily located in the endoplasmic reticulum with highest levels in brain, pancreas, and heart cell lines. Wolframin activity is essential for ER calcium homeostasis and associated cell survival, particularly high-energy-requiring cells such as neurons. Mutations in WFS1 gene encoding dysfunctional wolframin leading to Wolfram syndrome (WFS1, OMIN#222300) show autosomal recessive inheritance. An autosomal dominant mutation in WFS1 is reported to result in Wolfram-like syndrome (WFSL, OMIN#614296) described above without DI and with initial low-frequency hearing loss instead of WFS1-associated high-frequency loss. Another expression of autosomal recessive diabetes mellitus, high-frequency sensorineural hearing loss, and optic nerve atrophy without DI but added risk for bleeding peptic ulcer and labelled Wolfram syndrome 2 (WFS2, OMIN#604928) is attributed to mutations in CISD2 gene also located on chromosome 4 at 4q24. CISD2 gene encodes a zinc finger protein localized to ER and involved in calcium homeostasis [20]. All forms of Wolfram syndrome show varying degrees of progressive neurodegeneration and, although rare, should be diagnosed early to inform patient and institute with appropriate monitoring and current therapy.

Diagnosis

In addition to the medical history to include family history with attention to potential Wolfram syndrome occurrence, WFS1 gene sequencing is required to confirm the diagnosis of Wolfram syndrome. If there are no mutations in the WFSI 4p16.1 gene, CISD2 (alias WFS2) gene sequencing should be considered.

Bardet-Biedl and Related Syndromes

Introduction

Bardet-Biedl syndrome (BBS) is an autosomal recessive ciliopathy first reported by G Bardet and A Biedl in the 1920s. The prevalence of this disorder is estimated to be 1:160,000; however, it is more common in some ethnic communities like Kuwaiti Bedouins (1:15,000). The cardinal features of this disorder are tapetoretinal degeneration (ocular rod-cone dystrophy), obesity, learning difficulties or mental retardation, polydactyly, and hypogonadotropic hypogonadism. Several syndromes closely resemble BBS (Laurence-Moon, Biemond, and Alstrom-Hallgren), likely reflecting heterogeneous expression of closely related genetic anomalies [210–218].

Pathogenesis

BBS is a rare autosomal recessive complex disease caused by several genes. Most of these genes are involved in the formation and function of the BBSome multi-subunit complex. BBSome is made of eight subunits, and it is required for the proper formation and function of cilia as eukaryotic organelles critical for neuronal development and networking. Hypothalamic dysfunction seen with BBS is currently considered in large part

due to mutation-derived BBSome dysfunction and resultant ciliopathy. Each neuron has a primary cilium that is essential for neuron axial orientation, dendrite and axon development, and establishment of organized neural networks critical to development of the normal hypothalamus [6, 215]. The BBS ciliopathy appears to disrupt embryonic forebrain development resulting in a diencephalic lesion adversely affecting hypothalamus progenitor cells with resultant neuron disorientation and dysfunctional neural networks [6, 214–216].

Clinical Features and Diagnosis

1. Polydactyly: It is one of the primary diagnostic features of BBS. Postaxial polydactyly is present in 63%–81% of BBS patients. Polydactyly may involve all four limbs (21%), only lower limbs (21%), and only upper limbs (9%).
2. Retinal degeneration (RD): RD affects about 90% of BBS patients and can cause severe visual issues leading to blindness. It can manifest as either rod-cone dystrophy or cone-rod dystrophy. In the former, the degeneration first affects rods than cones and vice versa in the latter [211, 218].
3. Obesity: Obesity affects 72%–92% of BBS patients. It begins in childhood and progresses with age. BBS proteins are required to localize leptin receptors in the brain, and they also play an important role in the differentiation of adipocytes.
4. Genitourinary anomalies: Hypogonadism is present in 59%–98% of BBS patients. Males have a micropenis and small or undescended testis. Females may have genital anomalies such as hypoplastic uterus, ovaries, and fallopian tubes.
5. Renal anomalies: Cystic tubular disorder is the most common in BBS patients (25%–30%).
6. Mental retardation: It affects 50%–61% of BBS patients. Normal ciliary function is essential for neurogenesis and subsequent neural networking. The hippocampal volume is reduced in BBS patients. Affected patients may have speech and learning deficiencies, autistic tendencies, and psychosis, as well.

Secondary features of BBS include hepatic fibrosis, diabetes mellitus, cardiac anomalies (aortic stenosis and patent ductus arteriosus), and facial dysmorphism (brachycephaly, big ears, small eyes, long philtrum, hypodontia, high arched palate, and retrognathia).

Leptin/Leptin Receptor Syndromes

Introduction

Leptin is a hormone produced by adipocytes and secreted in proportion to body fat mass. Leptin serves a key role in maintaining energy homeostasis and body weight via binding with its leptin receptors in the hypothalamic appetite, energy, and body weight homeostasis centers (Fig. 14.2). Leptin deficiency or resistance is associated with severe obesity. Zhang et al. [219] are historically among the first to identify the "OB" (obesity) now leptin gene in mice and to isolate the gene-encoded product, leptin [168, 219–223].

Physiology of Leptin Interactions

Leptin mediates its action on appetite and energy homeostasis by binding to leptin receptors (LR) in the hypothalamus and thereby activating janus kinase-2 (JAK2). JAK2, in turn, phosphorylates tyrosine residues along the intracellular portions of LR. JAK2 itself can be phosphorylated that modulates JAK2 activity (serine phosphorylation inhibits JAK2, and tyrosine phosphorylation stimulates Jak2 activity). JAK2 also facilitates the binding of Src homology 2 B adapter protein 1 (SH2B1) which recruits insulin receptor substrates (IRS) 1 and 2. IRS 1 and 2 further activate phosphoinositide 3-kinase feeding into a MAPK pathway to influence energy homeostasis center [220].

Leptin stimulates neurons in the arcuate nucleus of the hypothalamus expressing pro-opiomelanocortin (POMC). POMC is cleaved into several peptides including α-melanocyte-stimulating hormone (α-MSH). α-MSH binds to

melanocortin receptor 4 (MC4R). α-MSH is involved in mediating satiety (Fig. 14.2). Leptin also inhibits agouti-related peptide (AGRP)/neuropeptide Y (NPY) synthesis. AGRP/NPY is a competitive inhibitor of MSH binding to MC4R, thus increasing hunger over satiety [219–223] (Fig. 14.2).

Clinical Features

Leptin deficiency is associated with the development of early-onset obesity and hyperphagia. The birth weight is normal but soon rapid weight gain develops over the next few months. Children exhibit food-seeking behaviors and become aggressive when food is denied. This food-seeking behavior may persist into adulthood. There is an accumulation of subcutaneous adipose tissue over the trunk and limbs. T-cell defects are seen in association with leptin deficiency making children more prone to childhood infections. Adolescents do not undergo puberty secondary to mixed hypogonadotropic hypogonadism. Inherited leptin deficiency patients may develop type 2 diabetes mellitus, hepatic steatosis, and dyslipidemias.

Diagnosis and Treatment

Leptin-related disorders should be suspected in instances of early-onset obesity. Leptin levels may be low or undetectable in cases of leptin deficiency; however, in leptin resistance, the levels are markedly elevated.

Leptin injections are available for patients as a recommended therapy for leptin deficiency. Administration of recombinant leptin in the presence of fully functional leptin receptor activity resolves hyperphagia, induces weight loss, and improves immunity.

Farooqi et al. [221] report beneficial effects of leptin administration to humans with congenital leptin deficiency. They note leptin injections decreased the patients' ad libitum food intake by 84% with a decrease in hunger scores. In leptin deficiency, food images are associated with increased neuronal activation in the anteromedial and posterolateral ventral striatum, indicating pleasure and reward mechanism has a role in encouraging appetite. This appetite encouragement in leptin-deficient states is abolished within seven days of initiating leptin administration.

Licinio et al. [223] report leptin administration is associated with the development of secondary sexual characteristics and restored pulsatile secretion of gonadotropins. This observation adds to the potential benefits of leptin injections for congenital leptin deficiency and possibly other serious obesity situations as well.

Genetics of Hypothalamic Programming of Systemic Aging

Aging can be viewed as progressive loss of strength and control of physiologic functions as well as increasing susceptibility to age-related disorders and diseases. As a critical brain region connecting neuroendocrine signaling to physiologic functions, the hypothalamus is well positioned to moderate various aspects of physiologic aging in general [224]. There is mounting evidence for placement of the hypothalamus as a master regulator for systematic aging. This makes the hypothalamus a prime target for understanding the aging process with potential for aging control and potential antiaging therapy.

Cross sectional studies from Norway [225] and longitudinal Korean [226] population research consistently demonstrate variation in metabolic activity and body composition of even healthy aged people often results in decline into sarcopenic (muscle weakness with reduced muscle mass) obesity (increased fat mass in part replacing reduced muscle mass). An imbalance develops between nutrition and energy metabolism in the elderly. This progressive imbalance along with the observed loss of appetite in old age contributes to declining health in the elderly [227, 228].

Aging can be viewed as a gradual decline from an organized efficient metabolic control of energy cycling to a chaotic inefficient metabolism and energy utilization. Extensive research is ongoing and published utilizing transgenic mice lines to model human aging. Rudman et al. [229] report aging humans given growth hormone (GH) to improve their age-related decline in GH and associated decline in somatomedin-C (IGF-1)

experience increased lean body mass and bone density with decreased body fat mass. However, a transgenic mouse line overexpressing GH consistently exhibits shortened life spans, while a Pit1 mutated gene transcription factor blocked GH production transgenic mouse line exhibits prolonged life spans [230–232].

Kim and Choe [224] present a 2019 review of the underlying cellular mechanisms involved in the role of the hypothalamus in aging. They note five cellular components that relate to age adjustments in the murine (mouse and rat) aging model hypothalamus and show significant changes in their measureable levels with old age.

The autosomal MTOR gene encodes a phosphatidylinositol kinase-related kinase that mediates cellular responses to stresses like DNA damage and nutrient deprivation and is located in hypothalamic POMC (anorexigenic) neurons. This mechanistic target of rapamycin (mTOR) kinase activity is noted to increase in POMC neurons with old age [233] and contributes to age-dependent obesity [234]. Increased mTOR activity enlarges hypothalamic POMC neurons while reducing neural networking to contribute to obesity through increased feeding drive, adipogenesis, and glucose tolerance. Aging mice given intracerebral mTOR-inhibiting rapamycin demonstrated reduced food intake and body weight, significantly extended male and female median and maximal life span, and improved hypothalamic POMC neuronal appearance and activity.

The autosomal NFKB1 gene encodes a protein that undergoes co-translational processing to become a DNA-binding subunit (nuclear factor kappa B subunit 1) of transcription factor NFKB. NFKB nuclear factor contributes to the age-associated increase in microglial cell activity as a sign of inflammation pathway activation. Blagosklonny et al. [235] offer observations that prolonged activation of CNS pro-inflammatory cytokine microglia cells associated with hypothalamic neuron communications causes loss of hypothalamic homeostatic regulation with age. Chronic microglial-neuronal inflammation pathway activation leads to loss of hypothalamic homeostatic regulation of energy and general metabolic homeostasis contributing to age-related metabolic syndrome with declining longevity, cognition, and muscle strength [224, 236].

Progressive loss of hypothalamic neural stem cells with age reduces neurogenesis and associated ability to replace, repair, or improve functional neurons. Zhang et al. [236, 237] report their research with mouse aging models and their hypothalamic neural stem cell populations to suggest declining stem cell number with age contributes to age-associated CNS inflammation and associated physiologic and mental decline. Zhang et al. [237] report that viral facilitated depletion of two specific hypothalamic stem cell lines results in mice exhibiting significant decline in physiologic functions including decline in muscle endurance and cognition and reduced life span.

Controlled autophagy is critically important to healthy intracellular turnover of no longer needed by-products of metabolism and maintenance of cellular (neuronal) homeostasis [224]. Kaushik et al. [238] report their research into imposed loss of autophagy from mouse hypothalamic POMC neurons. They note that specific loss of autophagy reduces α-MSH levels and signaling from POMC neurons that promotes adiposity, impairs lipolysis, and alters glucose homeostasis.

The autosomal SIRT1 gene that encodes sirtuin 1 protein is a NAD-dependent deacetylase that can assist regulation of diverse physiologic pathways including epigenetic gene responses to environmental stimuli and control of hypothalamic circadian rhythm [224, 20]. Chang and Guarente [239] report their studies of SIRT1 knockout and control mice to conclude SIRT1-encoded protein in the hypothalamic superchiasmatic nucleus (SCN) mediates central circadian control within a pathway that decays with aging. The SCN is considered a master clock for circadian rhythms. The SCN clock is established primarily through interactions between SCN-located arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP) neurons. Several published reports indicate the SCN volume and its AVP neuron population decline in aged rats [240–243]. Similarly, published reports indicate that rat hypothalamic reproductive cycle-related GnRH pulse generator neurons (KNDy) decline

in number with age in both male and female rats while GnRH neuron number remains stable with age [236, 243]. Stoh et al. [244] report their exploration of sirtuin 1 protein activity in brain-specific SIRT1-overexpressing (BRASTO) transgenic mice. Both male and female BRASTO mice show significant life span extension. Stoh et al. [244] find enhanced neural activity in BRASTO dorsomedial (DMH) and lateral hypothalamic (LH) nuclei to be supported through SIRT1/Nkx2-1 homeobox/orexin type 2 receptor gene interactions mediating slowing of aging and promoting longevity.

There are many opportunities for research into hypothalamic age-associated adjustments in neuron function, intercellular communication and alterations due to immune glial interference, intracellular proteostasis and general housekeeping, and stem cell cycling and replacement. Better understanding of hypothalamic mechanisms for aging to include genetic and epigenetic input should lead to effective individualized therapies to control and possibly reverse aging.

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Neuroendocrine Neoplasms and Lesions of the Hypothalamus

15

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Introduction

While the hypothalamus makes up a minute percentage of the entire central nervous system by weight, it has a very significant effect on the processes occurring within the brain and subsequently throughout the entire human body. This is evidenced by the large number of neurotransmitters that are found and produced within the hypothalamus itself, including but not limited to dopamine, serotonin, histamine, neurotensin, cholecystokinin, vasoactive intestinal peptide (VIP), substance P, angiotensin II, gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GHRH), corticotrophin-releasing factor (CRH), luteinizing hormone-releasing factor (LHRH), thyrotropin-releasing factor (TRH), somatostatin, dynorphin, and enkephalin [1]. Before the use of targeted electrical stimulation and lesioning in animal models, our understanding of the hypothalamic functions grew out of postoperative lesion studies in patients suffering various traumas or tumors [2].

Neoplasms of the hypothalamus generally present with symptoms that fall into two broad categories: those brought about by the mass effect and infiltrative properties of the tumor and those related to the intrinsic processes and function of the hypothalamus leading to hypersecretion of hypothalamic hormones [3]. As opposed to tumors leading to hypothalamic destruction or dysfunction, which generally lead to hypopituitarism (aside from hyperprolactinemia if the pituitary remains intact), the downstream effects of those leading to increased hypothalamic hormone production often mimic the effects of functioning neuroendocrine neoplasms of the pituitary gland.

Neoplasms causing hypersecretion of hypothalamic hormones are rare. The endocrinological consequences of these neoplasms vary widely, and given the hypothalamus's delicate interplay with the pituitary gland, they are often observed through the lens of pituitary dysfunction. Most of the neoplasms documented to release hypothalamic hormones are shown to produce GHRH, CRH, or vasopressin. Sellar and suprasellar lesions will produce symptoms related to mass effect and infiltrative properties of the neoplasm, as opposed to those brought about by the intrinsic hypothalamic endocrine function of the lesion. This category of tumors manifesting from mass effect or infiltrative processes makes up a larger piece of this pie. Thus, throughout most of this chapter, we will be discussing sellar and suprasellar pathologies and their effect on the hypothalamus.

The sellar region is located in the midline of the skull base, posterior to the sphenoid sinus and medial to the cavernous sinuses [4]. Within the

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G. I. Uwaifo (ed.), *The Human Hypothalamus*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-030-62187-2_15

sella turcica lies both the adenohypophysis and neurohypophysis (anterior and posterior pituitary glands, respectively), each of which has a separate embryological origin. Although they frequently infiltrate laterally into the cavernous sinus, sellar neoplasms can extend through suprasellar growth and compress or infiltrate the hypothalamus. Sellar region neoplasms account for approximately 10–15% of all intracranial neoplasms and are most commonly pituitary adenomas [4]. Sellar pathology has a wide range of differential diagnoses, and even after narrowing it down to a strictly neoplastic process, one must complete a thorough workup to determine the specific etiology of the presenting pathology as optimal therapeutic strategies may vary considerably. Table 15.1 provides a comprehensive overview of the spectrum of different causes that can present as hypothalamic mass lesions.

Table 15.1 Mass lesions of the hypothalamus

Neuronal neoplasms
Gangliocytoma
Neurocytoma
Gangliogliomas
Glial neoplasms
Pituicytoma
Gliomas
Optic pathway hypothalamic glioma
Astrocytomas
Infiltrative neoplasms
Pituitary adenoma
Craniopharyngioma
Germ cell tumors
Pituitary carcinoma
Meningioma
Chordoma
Dermoid cyst
Epidermoid cyst
Rathke's cleft cyst
Arachnoid cyst
Metastases
Nonneoplastic lesions
Hypothalamic hamartomas
Granulomatous lesions
Neurosarcoidosis
Wegener's granulomatosis
Giant cell reparative granuloma
Langerhans histiocytosis
Lymphocytic hypophysitis
Rosai-Dorfman disease
Erdheim-Chester disease
Cavernous angioma

Clinical Presentation

The clinical presentation of these lesions is a consequence of their unique location. The clinical consequences of sellar and suprasellar neoplasms generally fall into three categories: endocrine, ophthalmological, and neurological [4]. Space-occupying lesions cause hypopituitarism by destroying the hypothalamic nuclei or by disrupting the hypothalamic-hypophysial portal venous system. Although specific tumors may present with a subset of symptoms, given the location of these lesions and the adjacent structures, we can discuss the common clinical presentations that they may manifest. Patients with suspected hypothalamic tumors should undergo an MRI to determine the extent and nature of the tumor.

Neurological Symptoms

Some of the most commonly observed presenting symptoms are those related to increased intracranial pressure (ICP), such as headache, vomiting, and papilledema [5]. These symptoms are frequently encountered with cases of craniopharyngiomas (CP) and optic pathway gliomas (OPG) and other lesions with propensity to block the flow of cerebrospinal fluid (CSF) causing obstructive hydrocephalus [6, 7]. The headache itself can have variable presentations, and there is no one pathognomonic headache indicative of sellar/suprasellar lesions. Several other possible etiologies of these headaches have been described, including stretch and displacement of local structures (such as blood vessels, dura mater, and cranial nerves), as well as increased ICP [8, 9]. Other neurological symptoms such as anosmia, cognitive deficits, and memory impairment can also be seen given the extent of growth of the mass [4]. Cystic lesions such as Rathke's cleft cyst and epidermoid cysts can also produce an aseptic meningitis manifesting with symptoms of headache, photophobia, and neck pain. This is due to rupture and spillage of cyst contents into the subarachnoid and ventricular space.

Visual Disturbances

Given the proximity of these lesions to the optic nerve, tract, and chiasm, ophthalmological symptoms are a frequently observed sequela as well [10, 11]. Depending upon the location and size of the lesion, a variety of neoplastic optic neuropathies can be seen. Tumors in the region of the optic pathway or infundibulum may cause optic atrophy, visual deficits, or visual hallucinations [12]. The visual symptoms typically develop over the course of weeks to months; however, the patient may not notice a more insidious defect initially and describe its onset as sudden. Intratumor hemorrhage or necrosis presenting as pituitary apoplexy can lead to a sudden visual field loss. Afferent pupillary defect and dyschromatopsia are typically early abnormalities. When field deficits present, the typical presentation is that of bitemporal hemianopsia; however, quadrantanopsia, central scotoma, junctional scotoma, and superotemporal defects have all been described [13]. Diplopia may present given increased ICP and compression of cranial nerves III, IV, and/or VI. Additionally, facial pain and/or numbness may present if there is trigeminal nerve involvement. However, these symptoms occur less frequently and may signify a particularly aggressive neoplasm with increased involvement of local structures [14].

Neuroendocrine Disturbances

In 1954, Bauer was the first to compile and publish a large case series of 60 autopsy-proven cases of hypothalamic disease. In his series, 43 had sexual abnormalities (hypogonadism or precocious puberty), 21 diabetes insipidus (DI), 21 psychic disturbances, 20 obesity or hyperphagia, 18 somnolence, 15 emaciation or anorexia, and 13 disorders of temperature regulation [15]. This breakdown of symptoms has remained an important stratification of neuroendocrine clinical manifestations of lesions in the hypothalamus. Complete assessment of hypothalamic-pituitary axis (HPA) and hormone function is necessary in these patients, because deficiencies are present in the great majority, and the evaluation will establish the requirements for replacement therapy.

Neuroendocrine symptoms stemming from sellar/suprasellar pathology have been documented in the literature for over 100 years when Babinski reported sexual infantilism and adiposity in patients with CPs [16]. Endocrine dysfunction is present in the majority of patients with sellar/suprasellar lesions, and while it often precedes other symptoms, it is frequently undiagnosed initially [17]. The specific alterations vary in prevalence depending upon the type of lesion, but most commonly, they involve growth hormone (GH) deficiency, precocious puberty, gonadotrophin deficiency, adrenocorticotropic hormone (ACTH) deficiency, thyroid-stimulating hormone (TSH), hyperprolactinemia, and DI. Growth hormone deficiency is a particularly common dysfunction in this population, especially if radiotherapy is utilized during treatment [18]. All of the aforementioned endocrine dysfunctions occur at varying frequencies depending upon the population and specific etiology of the neoplasm.

In his account of tumors of the hypothalamus, Bauer was able to make some associations between tumor types and clinical manifestations, which were later more clearly identified in the literature. It was noted that in addition to gelastic seizures, hypothalamic hamartomas may typically affect the posterior region of the hypothalamus with precocious puberty [15]. Germ cell tumors and gangliogliomas have high likelihood of causing precocious puberty by accelerating LHRH maturation, respectively [19, 20]. Tumors of the tuberal and preoptic region of the hypothalamus are often found in hypogonadism. This is especially the case for craniopharyngioma and germ cell tumors [21]. Symptoms of ventromedial hypothalamic tumors are hyperphagia and obesity, fits of rage, amnesia, and attacks of laughter or crying [22]. Markedly elevated leptin plasma levels, with increasing body mass index, are found in patients with hypothalamo-pituitary damage, which suggests unrestrained leptin secretion [23]. In a patient with a probable hypothalamic germ cell tumor, hypoadrenalism, hypogonadism, DI, and hypercalcemia have been found [24]. Cushing described patients with

hypothalamic tumors associated with a duodenal ulcer and proposed the existence of a parasympathetic center in the hypothalamus, which would send fiber tracts to the vagal center [25]. Hypothalamic lesions due to craniopharyngioma or pilocytic astrocytoma may be accompanied by decreased nocturnal melatonin levels and increased daytime sleepiness [26].

The remainder of this chapter will be spent discussing specific neoplasms that commonly affect the hypothalamus and its neuroendocrine function. They represent lesions from a wide range of classifications including neuronal neoplasms, glial neoplasms, and infiltrating neoplasms. We will also address some common nonneoplastic lesions that find themselves among the differential for hypothalamic lesions and can cause similar symptoms. Some present with hypersecretion of hypothalamic hormones, while most lead to endocrine dysfunction through compression, destruction, and infiltration of normal CNS architecture. Their specific neuroendocrine implications vary considerably, which serves to highlight the far-reaching responsibilities of the hypothalamus. This also has severe consequences on the neurosurgical approach to the treatment of these lesions, as any further damage to this area could have devastating consequences.

Neuronal Neoplasms

Neoplasms of neuronal origin intrinsic to the hypothalamus are overall rare but are important group of primary central nervous system (CNS) tumors. These tumors are usually benign and often curable with surgical resection. This small cohort of tumors includes gangliocytomas, neurocytomas, and gangliogliomas, which are in fact mixed neuronal-glial cell tumors but will be discussed in this section.

Gangliocytomas

Gangliocytomas are classified as World Health Organization (WHO) grade I tumors composed of mature neurons that are generally well differentiated and slow growing [27, 28]. The tumor can arise within the cerebrum, pituitary gland, hypothalamus (near the floor of the third ventricle), pineal region, or brain stem. Tumors confined to the cerebellum may also occur as dysplastic gangliocytomas (Lhermitte-Duclos disease). Gangliocytomas affecting the sellar region are extremely rare and represent less than 1% of all sellar tumors [29]. The majority of gangliocytomas become symptomatic within the first three decades of life, with a mean of 25 years of age.

Histologically, they are formed by large multipolar neurons which arise from ganglion cells and have been shown to stain for NeuN and MAP2 (markers of mature neurons), S100, neurofilament proteins, and synaptophysin [28, 30–32]. The most common sequela of increased hormone production associated with gangliocytomas is acromegaly; however, Cushing's disease, precocious puberty, and hyperprolactinemia have also been noted [3, 28]. Immunohistochemical testing of these tumors has identified the presence of several hypothalamic hormones including but not limited to GHRH, CRH, GnRH, gastrin, vasopressin, oxytocin, and somatostatin [28, 31, 33–36]. A review in 2016 of 111 cases of sellar gangliocytoma in the adult population found that 85% of sellar gangliocytomas were associated with pituitary adenomas, and of the cases in which the gangliocytoma component was assessed for the presence of GHRH, 28 tumors tested positive. While prolactinomas are the most common functional pituitary adenoma, in this large case review, it was found that GH-secreting adenomas were the most common lesion in these mixed sellar lesions [28]. Although there may have been some selection bias given the predilection for prolactinomas to be medically treated, surgical intervention is normally first line for cases presenting with acromegaly. This association between gangliocytomas and pituitary adenomas has been shown in multiple case reports and studies, but the causative agent remains unclear [28, 31, 32, 37, 38]. Many theories have been put forward in an effort to explain these findings including the possibility of incidental findings following abnormal hypothalamic neuronal migration, hypothalamic hor-

mones promoting adenoma formation, and somatotroph plasticity and transdifferentiation; however, none of them are without their faults, and further research is required [38]. Treatment for these lesions typically involves surgical resection, and complete tumor resection is considered curative. Postoperatively, patients are managed with careful clinical observation and follow-up MRIs. Radiotherapy and/or chemotherapy is considered only for deep, inaccessible tumors with persistent recurrence and an aggressive clinical phenotype [39].

Neurocytomas

Another hypothalamic neoplasm that has been associated with hypersecretion of hypothalamic hormones is neurocytomas, classified as WHO grade II. Neurocytomas are typically defined as central, which originate in the lateral ventricles, or extraventricular. Central neurocytomas typically develop within the ventricular walls or septum pellucidum, with more than 50% of cases arising in the lateral ventricles adjacent to the foramen of Monro. Another 15% involve the third ventricle adjacent to the hypothalamus. The majority of these tumors present as mass lesions causing obstructive hydrocephalus.

Cases of extraventricular neurocytomas have been reported and shown the syndrome of inappropriate antidiuretic hormone (SIADH) due to hypersecretion of vasopressin [30]. One case of acromegaly related to neurocytoma due to GHRH release has also been reported in the literature [40]. Extraventricular neurocytomas can present with varying morphologies ranging from sheets of small-medium-sized monotonous cells to ribbons, clusters, and broadly dispersed neuropils. Extraventricular neurocytomas typically contain a larger population of ganglion than do central neurocytomas [41]. Pale eosinophilic to chromophobic cytoplasm with round to oval nuclei containing finely granular chromatin and multiple nucleoli is often seen. Areas of calcification, fibrosis, and acidophilic hyaline globules within the neuropil may also be seen [3]. Radiologically, it presents as a contrast-enhancing lesion that is well circumscribed and frequently associated with a cyst-mural nodule. Given the limited data on these neoplasms in the literature, pathogenesis is hard to determine, but multiple chromosomal loci gain and loss mutations have been documented, as well as epidermal growth factor receptor gene polysomy [41].

First-line treatment for these lesions is surgical resection with adjuvant radiotherapy in cases of incomplete or questionable resection. However, there is lack of evidence regarding the ability of adjuvant radiotherapy to prevent recurrence or mortality. Typically, recurrence rate is 36% [42].

Ganglioglioma

Another low-grade neoplasm that may arise in the hypothalamus is ganglioglioma. It is classified as WHO grade I. Gangliogliomas are well-differentiated, slow-growing tumors with a mixture of neoplastic glial and neuronal elements. These make up 1.3% of all brain tumors and contain both neuronal and glial elements, while gangliocytomas are composed predominantly of neoplastic neurons [43]. The most common location is the supratentorial brain, usually within the temporal lobes. Gangliogliomas are also known to occur in the thalamus, pineal gland, and cerebellum, but there have also been cases in the third ventricle, optic chiasm, and hypothalamus [44–46].

Histologically, they are composed of irregular groups of large, multipolar neurons with dysplastic features and intermixed with regions of neoplastic glial cells, usually of astrocytic origin. MRI appearance on T1 is hypointense and T2 is hyperintense; the mass is well circumscribed. Enhancement is variable and may be solid, rim, or nodular [47].

Symptoms can be related to raised intracranial pressure despite slow, indolent growth of these tumors. They typically do not exhibit neuroendocrine dysfunction, but may present with DI from mass effect [48, 49]. They may also arise similar to other neuronal CNS tumors [50]. Similar to other neuronal CNS tumors, these tumors are

usually non-infiltrative and well delineated from surrounding neural tissues. Thus, gross total resection is often possible [43].

Glial Neoplasms

Tumors originating from glial cell of the CNS typically give rise to astrocytomas. However, other glial tumor precursors such as pituicytes and granule cells are also noted. In this section, we will be discussing neoplasms of the sellar and suprasellar region arising from glial cells, namely, pituicytomas and gliomas.

Pituicytomas

Pituicytes are highly specialized glial cells that occupy perivascular zones within the neurohypophysis and engulf axons and axon terminals acting as a physical barrier to hormone release [51]. This barrier can be lifted in physiological states requiring increased hormone levels. Pituicytoma is considered a rare low-grade (WHO grade I) glioma of the sellar/suprasellar region that is thought to be a derivative of neurohypophysis or infundibulum, pituicytes. In fact, they are referred to as astrocytomas of the pituitary gland. Altogether, fewer than 300 cases of all types of pituicytomas have been reported, mostly in case reports or small case series [52].

They often appear as solid, uniformly contrast-enhancing lesions within the domain of the neurohypophysis that are isointense to gray matter on T1-weighted image and hyperintense on T2-weighted image [4, 53]. MRI shows extension of the tumor into the stalk. These masses are sometimes mistaken for pituitary adenomas on radiographical studies; however, unlike pituicytomas, these adenomas are typically uniformly reactive for synaptophysin and are negative for S-100 and GFAP [53].

Patients presenting with pituicytoma often exhibit visual disturbances, headaches, and/or hypopituitarism [54]. Despite their location, they are hormonally inactive and typically do not present with DI although rare cases of DI and galactorrhea have been noted in the literature [55–57]. More commonly, they can present with hypopituitarism [58]. Signs of hyperprolactinemia have also been reported.

Histologically, they present as interlacing fascicles or sheets of spindle cells with mildly fibrillar cytoplasm and elongated nuclei. Mitoses are often rare or absent with low MIB-1 labeling indices (0.5–2%) [53]. Five different variants of pituicytes have been described based upon their ultrastructural characteristics: major/light pituicytes, dark pituicytes, ependymal pituicytes, oncocytic pituicytes, and granular cell pituicytes [59]. These tumors were recognized as new and separate brain tumor entities in the fourth edition of the WHO Classification of Tumors of the Nervous System [60]. These different variants can often produce varying phenotypes of pituicytoma which has led to some confusion regarding classification of neoplasms in the past. Most notably, there has been evidence supporting the fact that spindle cell oncocytomas and granular cell tumors are quite possibly derivatives of different variants of pituicytes and may constitute a spectrum of a single biological tumor entity given their immunohistochemical similarities to known variants of normal pituicytes [61]. Similar to normal pituicytes and pituicytomas, these neoplasms have the common denominator of expressing thyroid transcription factor-1 (TTF-1) [52, 62].

Surgical resection is usually advocated when the lesion is symptomatic. Complete excision is generally believed to be curative; however, recurrence has been shown in cases of subtotal resection despite this neoplasm's low proliferative activity [53].

Gliomas

Gliomas that arise in the hypothalamus, in the nearby optic pathway, or in the region of the inferior third ventricle are rare. The majority of the gliomas affecting the hypothalamus are diffusely infiltrative fibrillary or pilocytic astrocytomas and thus low grade (WHO grade I). They can mimic anterior pituitary neuroendocrine tumors, presenting as a parasellar and sellar mass. The

most aggressive gliomas in this location have been reported as sequelae of radiation therapy for primary pituitary tumors [63]. Depending on their location, hypothalamic gliomas may manifest themselves in the form of eating disorders, disturbances of temperature regulation, precocious puberty, somnolence, rage, visual impairment, or hydrocephalus [19].

Optic Pathway Hypothalamic Gliomas

Most pilocytic astrocytomas arise within the visual system. Optic pathway hypothalamic gliomas (OPHG) are rare astrocytic neoplasms that account for approximately 2% of all CNS neoplasms [64]. They are more common in pediatric populations with a median age of diagnosis of 7 years (3–5% of all pediatric intracranial neoplasms, 20% of all intracranial neoplasms in those under 2 years of age), and surgical intervention is commonly deemed not feasible [65, 66].

The two principal differing pathological varieties of OPHG are pilocytic astrocytoma (PA) and pilomyxoid astrocytoma (PMA). PA, the more common etiology of OPG, is a WHO grade I neoplasm, whereas PMA is a WHO grade II neoplasm that is more commonly seen in infants (median age 10 months). PMAs are typically seen in infants, are associated with leptomeningeal dissemination, and generally have a worse prognosis [64, 67, 68]. Overall, nearly one-third of cases are associated with neurofibromatosis type I (NF1), which is an autosomal dominant disease that results in an inactivating mutation of the tumor suppressor gene encoding neurofibromin on chromosome 17q [69]. Five to fifteen percent of patients with NF1 develop OPHG [70]. OPHGs associated with NF1 typically run a more indolent course and require decreased intervention, with decreased rates of visual impairment and HPA axis dysfunction [71].

OPHGs can affect the optic pathway, hypothalamus, pituitary gland, limbic system, diencephalon, and third ventricle depending on their size and extent [72]. Presenting symptoms may be brought about by invasion or compression of the optic pathway and/or diencephalon and include ophthalmological symptoms, weight changes, cognitive problems, behavioral disturbances, hydrocephalus, and endocrinological dysfunction [72]. While changes in vision are frequently the presenting symptom, endocrine disturbances are often present and are typically manifested in hyposecretion of GH and precocious puberty. DI is also seen but generally after significant tumor growth. Pilocytic astrocytoma causing hypothalamic lesions may be associated with decreased nocturnal melatonin levels and increased daytime sleepiness [26].

Symptoms may also vary depending upon the location of the lesion. Those with lesions in the anterior optic pathway often present with vision loss, strabismus, and proptosis. Those with lesions affecting the optic chiasm generally present with field loss, decreased visual acuity, and nystagmus. Finally, those with lesions affecting the diencephalon can present with diencephalic syndrome, precocious puberty, endocrine dysfunction, and hydrocephalus [72]. The diencephalic syndrome, first described by Russell in 1951, may lead to infant failure to thrive, characterized by emaciation, weight loss, and hypothalamic dysfunction [73].

On MRI, these lesions generally appear hypointense/isointense on T1-weighted images and hyperintense on T2-weighted images with variable contrast enhancement [74]. MRI screening of asymptomatic patients with known histories of NF1 is not currently recommended [75]. Given their histologically benign nature and central location, the risks of surgical intervention have generally outweighed the benefits; however, there are certain patient populations, such as those with cystic tumors, large tumors, exophytic tumors, or hypothalamic tumors, in which debulking procedures may be possible with acceptable risk [76].

Complete surgical resection is generally only deemed to be possible if the tumor only affects the optic nerve unilaterally [65]. Much of the current literature on OPHGs focuses on initial management of these tumors with observation, chemotherapy, or radiotherapy. A wait-and-watch tactic may be appropriate initially, especially in patients with a history of NF1, as these tumors tend to stabilize and spontaneous regres-

sion has been noted to occur [77]. Increased ICP, declines in vision, tumor progression, and the presence of diencephalic syndrome are all indications to begin specialized intervention. Thus, neurosurgery only has a role in diagnosis, tumor control, and relief of mass effect in selected cases [71].

Chemotherapy regimens are considered the first-line treatment for OPGs. Currently accepted regimens include carboplatin and vincristine, as well as cisplatin and vincristine [78, 79]. Those regimens that include cisplatin require that patients be hospitalized but treatment duration is decreased, and therapeutic effect manifests in early stages when compared to carboplatin [79]. Radiotherapy is effective against OPGs; however, it can lead to hormonal dysfunction, decreased cognitive function, and development of secondary tumors especially given the young age of this patient population, and as such, a risk-benefit analysis should first be performed on an individualized basis. Specifically, there have been reports of vasculopathies and moyamoya syndrome [80]. Radiation is generally considered a viable option in patients over 5 years of age whose tumor has progressed despite chemotherapy and is not amenable to surgical resection [65].

Other Gliomas

High-grade gliomas have been reported in the hypothalamus although exceedingly rare. H3 K27M mutant gliomas that typically present in midline structures have been shown in the hypothalamus [81, 82]. Other rare types of glioma found and reported to involve the hypothalamus include chordoid glioma [83, 84], glioblastoma [85–87], and diffuse astrocytomas that have also been reported in case reports [88]. There have been fewer than 30 reported cases of WHO grade IV astrocytomas reported in the literature as of 2018. They typically affect adults unlike low-grade gliomas. These patients also tend to have rapid deterioration of visual symptoms and endocrine dysfunction, notably DI [86].

Infiltrating Neoplasms

This is a group of tumors that arise from adjacent regions of the hypothalamus and do not involve neuronal or glial cells of the hypothalamus or neurohypophysis. We will discuss the most common including pituitary adenomas, CP, germ cell tumors (GCT), epidermoid cysts, dermoid cysts, and Rathke's cleft cysts. Others that may also exert mass effect in that region include meningiomas, chordomas, pituitary carcinomas, and arachnoid cysts.

Pituitary Adenomas

Pituitary adenomas are the most common intracranial neoplasms of the sellar and suprasellar region. They have been noted to have an autopsy prevalence of 15%. Most are sporadic. However, they can be associated with rare genetic conditions such as multiple endocrine neoplasia type 1 or familial isolated pituitary adenomas [89]. They are composed of adenohypophyseal cells. Clinically, they are classified as functioning or nonfunctioning adenomas. Functioning adenomas are more common (65%) and most are prolactinomas, secreting PRL. They present commonly in women during the reproductive period and present with oligomenorrhea or amenorrhea, galactorrhea, and infertility. In men and elderly women, prolactinomas are mostly macroadenomas and present with visual symptoms. Impotence and decreased libido are common in men but are usually not the revealing complaint [90]. The next most common functioning adenomas are GH secreting (leading to acromegaly or gigantism) followed by ACTH secreting (leading to Cushing's disease) making up 20% and 15% of functioning adenomas, respectively. Other functioning adenomas include TSH-secreting adenomas (secondary hyperthyroidism) and FSH/LH-secreting adenomas (hypogonadism).

About one-third of PAs are not associated with clinical evidence of hormone hypersecretion or are clinically silent. Thus, they have usually reached a significant size at the time of diagnosis,

most often present with visual symptoms and signs of hypopituitarism, with 60% to 85% of patients presenting at least one pituitary deficiency [91]. Headache is a common early symptom attributed to stretching of the diaphragma sellae, a structure innervated by the first division of the trigeminal nerve. A common objective finding is visual loss, a consequence of suprasellar growth and compression of anterior visual pathways. It is these adenomas that may inflict hypothalamic disturbance as the optic chiasm and hypothalamus rest just above the pituitary gland. With continued suprasellar growth, pituitary tumors may encroach upon the hypothalamus, causing a variety of vegetative disturbances that include disorders of sleep, alertness, eating, behavior, and emotion [92]. An important laboratory finding is moderately elevated PRL (<150 ng/mL). This is known as the *stalk effect* and is the result of compressive lesions involving the pituitary stalk or hypothalamus due to the impaired release of dopamine from the hypothalamus, leading to loss of inhibitory effect on pituitary lactotrophs.

Based on size on imaging, adenomas are categorized as microadenomas if <1 cm in diameter or macroadenomas if equal or greater than 1 cm. A popular classification schemes based on imaging findings of tumor extension by Hardy [93] and modified by Wilson [94]. Intrasellar microadenomas are grade I, macroadenomas causing diffuse enlargement but no perforation of the sella are grade II, those causing focal perforation through the sella are grade III, those causing extensive destruction of the sella are grade IV, and those that exhibit CSF or hematogenous spread are grade V. Tumors with suprasellar or parasellar extension are further divided into stages A to E: stage A tumors reach only the suprasellar cistern, stage B tumors encroach upon the anterior recesses of the third ventricle, stage C tumors elevate the floor of the third ventricle, stage D tumors extend to intradural growth, and stage E tumors invade the cavernous sinus laterally.

Surgical resection has been a mainstay for nonfunctioning pituitary macroadenomas and functioning adenomas refractory to medical management. Pioneer neurosurgeons such as Harvey Cushing, Walter Dandy, and Fedor Krause used open subfrontal and frontotemporal craniotomies for sellar lesions. Although developed in the early twentieth century, transsphenoidal techniques gained popularity in the 1980s and 1990s [95], and further, endoscopic approaches have gained traction as the primary method of tumor resection. It should be noted that a complication of pituitary surgery is hypothalamic damage. This may result from direct surgical injury or from hemorrhage and ischemia. This can result in coma, DI, memory loss, and disturbances of vegetative functions (e.g., morbid obesity, uncontrollable hunger or thirst, disturbances in temperature regulation) [96].

Pituitary apoplexy is a serious acute complication of typically nonfunctioning pituitary adenomas. Patients present with acute symptoms characterized by a sudden onset of headache. It is frequently associated with nausea and vomiting. Visual symptoms such as diplopia, ptosis, visual acuity, and visual field impairment are also common manifestations. Decreased consciousness and obstructive hydrocephalus may also occur. The incidence of pituitary apoplexy is around 2% of all surgically treated patients with pituitary adenoma [97]. Since pituitary apoplexy is frequently associated with hypopituitarism, hydrocortisone replacement should be initiated immediately after diagnosis. Etiology has been attributed to ischemic necrosis of a rapidly growing lesion, intrinsic vascular abnormalities within the tumors, and compression of the superior hypophysial artery against the diaphragma sella [98].

Craniopharyngiomas

CPs are rare (incidence of 0.5–2 cases per million persons per year) and generally benign, WHO grade I, epithelial lesions arising from either the hypophysis or the pituitary stalk [99]. They are commonly partially cystic and calcified neoplasms with a bimodal age distribution (peak rates of onset 5–14 years and 50–74 years). They represent the third most common pediatric brain

neoplasm [100]. Calcifications are found in nearly 90% of CPs, and thus, CT is an important tool in its diagnosis when combined with MRI [101]. CPs commonly infiltrate local structures including the hypothalamus. This can lead to devastating postoperative complications if caution is not exercised during resection. If key structures are not damaged during excision, long-term survival rates are generally very high (87–95% 20-year survival in child-onset cases), and malignant transformation is rare [101]. When malignant transformation does occur, the average time scale is 8.5 years from time of benign diagnosis [100].

CPs are low-grade developmental neoplasms. The embryogenetic theory of this neoplasm purports that CPs originate from an ectodermal remnant of Rathke's pouch, whereas the metaplastic theory states that they result from metaplasia of cells in the pars tuberalis [4]. There are two histological subtypes of CPs: adamantinomatous, which is more common in children and young adults, and papillary, which is more frequently seen in adults and rarely presents calcifications. Both frequently extend up toward the third ventricle, stretching the optic chiasm and causing mass effect on the hypothalamus.

CP has a predilection to spread using CSF and along the path of least resistance which can occasionally lead to obstruction of the foramen of Monroe, aqueduct of Sylvius, or even the third ventricle, ultimately leading to hydrocephalus and increased ICP [4]. At the time of diagnosis, patients may present with symptoms of increased ICP either due to tumor burden or hydrocephalus. Nearly 62–84% of children will also experience visual disturbances, whereas 58–87% will experience some form of endocrine dysfunction generally leading to hyposecretion rather than hypersecretion [101]. These endocrine abnormalities may precede presenting symptoms by months or years. The endocrine hyposecretions can lead to short stature, amenorrhea, DI, and hypothyroidism. Gonadotropin deficiency leading to absent or arrested puberty is usual in older children and adolescents. In the adult population, endocrine dysfunction is generally more advanced at the time of presentation. Most commonly, GH secretion is affected followed by gonadotropins, ACTH, TSH, and vasopressin in decreasing order of prevalence [101]. Additionally, patients may suffer from obesity from high leptin levels due to disturbed hypothalamic feedback to adipose tissue [102]. New-onset DI is a common postsurgical adverse outcome, and many patients will require supplementation of multiple hormones following excision of the mass [103, 104]. The risk of endocrine dysfunction after resection increases with involvement of or proximity to the HPA, and if caution is not taken, significant postsurgical morbidities are common. Hypothalamic disturbances are common with suprachiasmatic and posterior hypothalamic area involvement [105]. Permanent consequences of alterations to hypothalamic projections can also present in both pre- and postsurgical patients, often leading to sequelae of obesity, sleep disturbances, behavioral alterations, and dysregulation of thirst, heart rate, blood pressure, and body temperature [103].

CPs are usually treated with surgery with or without adjuvant radiotherapy. The decision for radiotherapy depends on extent of resection as well as the age of the patient. At times, complete resection of craniopharyngioma is usually not feasible given the location, and neurological complications can be devastating with aggressive intervention. Multiple endocrine abnormalities are quite common postoperatively, and patient will likely need lifelong hormone replacement and close follow-up with an endocrinologist. While survival rates are good, recurrence and progression rates are generally high. This is thought to be due to the neoplasm's highly infiltrative nature and subsequent subtotal resection given future quality of life concerns [106]. As mentioned, endocrine disturbances are common after radical resection as a result of hypothalamic manipulation and pituitary stalk sectioning. Recurrence is common, and the single most important factor associated with recurrence is the extent of resection at index surgery [107]. Most recurrences occur within 2–3 years of initial surgery, and subtotal resection without adjuvant radiation unequivocally results in recurrence. Patients must be monitored with serial MRIs.

Germ Cell Tumors

CNS germ cell tumors (GCTs) are thought to originate from primordial germ cells and represent 3% of all pediatric CNS tumors with peak incidence between 10 and 12 years of age [108]. Germinomas account for approximately two-thirds of the broader category of CNS GCTs, which also includes non-germinomatous germ cell tumors (NGGCT): mixed malignant germ cell tumors and mature teratomas [108]. Germinomas are the least differentiated of the germ cell group, whereas teratomas differentiate along all three germ cell layers. The male/female ratio of those presenting with CNS germinomas is 1.88:1. Males seem to be specifically prone to development of germinomas in the pineal region, whereas females tend to present with suprasellar lesions [109, 110]. CNS germinomas tend to be found in midline structures such as the pineal gland and the sellar/suprasellar region, and there seems to be an association between CNS germinomas and both trisomy 21 and Klinefelter syndrome [111, 112]. A bifocal presentation involving both the pineal gland and suprasellar region can be seen in 25–30% of cases [113].

Patients who present with a lesion in the suprasellar region will often have a history of insidious endocrine dysfunction which may include DI, growth failure, decreased cortisol production, and diminished thyroid function [108]. In men, germinomas may cause precocious puberty because they may secrete β-HCG, which stimulates the secretion of testosterone. Increased tumor growth may lead to visual disruptions as well as nausea, vomiting, and headaches as a sequela of obstructive hydrocephalus. Pineal gland involvement may lead to increased ICP, diplopia, and Parinaud's syndrome, and these lesions typically present with a more protracted time course than that of suprasellar lesions [108].

Radiographically, germinomas often appear as enhancing solid masses on MRI, whereas teratomas frequently show a heterogenous mix of signal intensities [114]. GCTs can secrete both AFP and β-HCG into the systemic circulation and CSF. Nearly 40–60% of patients with CNS germinomas show mildly elevated β-HCG levels, most often in the CSF, whereas patients with NGGCTs may show elevated AFP levels [115]. These include y*olk sac* or *endodermal sinus tumor*, *choriocarcinoma*, and *embryonal cell tumor* that represent the less common NGGCTs. CSF should also be evaluated for disseminated neoplastic cells as this is a possible site of spread [114].

Germinomas are not only malignant but also highly radiosensitive, which makes early diagnosis of vital importance. In fact, most GCTs respond very well to radiotherapy and chemotherapy and, as such, the role of surgical intervention is generally limited except for NGGCT [116].

Dermoid and Epidermoid Cysts

Dermoid and epidermoid cysts are benign and slow-growing lesions that may arise to compress the hypothalamus and cause hypopituitarism, DI, or cranial nerve deficits. Sellar and parasellar dermoid and epidermoid tumors make up only 0.2–0.7% of major transsphenoidal series. Dermoid cysts are well-circumscribed, ectodermal inclusion cysts [117]. They are more common in children and most commonly located in the fourth ventricle or the vermis and are less commonly seen in a juxtasellar position. They arise as a result of a defect in gastrulation in development causing disruption in neural tube closure [118]. They are benign, often asymptomatic, and found incidentally. The problem arises intracranially when they exert mass effect on adjacent structures. The cyst walls of these tumors contain dermal appendages, hair follicles, sebaceous glands and sweat glands, and stratified squamous epithelium. The yellow contents of the cyst consist of a waxy material containing desquamated keratin products, hair, and cholesterol crystals. Symptomatic lesions usually present with symptoms related to local mass effect, seizures, or recurrent meningitis, depending on the specific location of the lesion [119]. Surgical resection is the treatment of choice for symptomatic cysts, although there is risk due to cyst wall adhesions against neural structures.

Epidermoid cysts typically occur in adults in the fourth to fifth decades of life. They are found in the basal cisterns or cerebellopontine angle but may also present in the parasellar region and produce remarkably few pressure effects. They often present in a paramedian location in contrast to the typically midline dermoid cysts. The cyst walls of these tumors contain a simple stratified squamous epithelium. The cyst contains a waxy material with desquamated keratin products and cholesterol crystals. The cholesterol shines through, giving a silvery appearance, so that they are sometimes called "pearly tumors." The cyst contents of epidermoid cysts can be caustic to the surrounding tissue and produce an aseptic meningitis. Epidermoid cysts may also invaginate into adjacent intracranial structures, making gross total resection more difficult.

While both intracranial dermoid and epidermoid cysts have fairly classical features and locations, dermoid cysts can sometimes present with atypical imaging findings [120]. On CT, dermoid cysts are usually hypodense and avascular, and they do not show contrast enhancement. MRI characteristics may be variable, depending on the fat content of the lesion, but they usually show high signal levels on both T1- and T2-weighted images [121]. Both dermoid and epidermoid cysts almost never produce edema. Epidermoid cysts are less homogenous on T2-weighted imaging compared to arachnoid cysts and exert more mass effect. Standard MRI cannot be reliably used in all cases to definitively establish a diagnosis of epidermoid or dermoid cysts, but restricted diffusion on diffusion-weighted imaging has been shown to play a useful role in allowing the differentiation of epidermoid lesions from other types of cystic pathology [122]. Gross total resection is the treatment of choice, and no adjunctive radiotherapy or chemotherapy has been proven to be of significant benefit in the management of these lesions.

Rathke's Cleft Cysts

Rathke's cleft cysts are benign and relatively common findings, reported in 12–33% of normal pituitaries at autopsy, and are now more frequently diagnosed with the use of CT and MRI [123]. Occasionally, the cysts may enlarge and cause symptoms from compression of surrounding structures such as the hypothalamus, pituitary gland, and visual pathways. These cysts occur in the zona intermedia of the pituitary and may derive from remnants of the developmental Rathke's pouch, thus sharing a similar origin with craniopharyngioma. The cyst may contain mucoid yellow and grumous material, serous or CSF-like contents, or cellular debris [124]. These cysts are usually confined to the sella and were previously described as intrasellar craniopharyngiomas [125]. However, they can also be located entirely in the suprasellar region [126]. Histologically, one may distinguish Rathke's cleft cysts from craniopharyngiomas by staining for cytokeratins [127]. On imaging, they do not have calcifications. Like other sellar and suprasellar lesions discussed, symptoms of Rathke's cleft cysts may include multiple endocrinopathies, headaches, and visual disturbances. The most common symptoms were those caused by pituitary hypofunction. Growth retardation was noted in more than 70% of pediatric patients. A few cases have been described with symptomatic pituitary hemorrhage into a Rathke's cleft cyst with sudden, severe retro-orbital headache, nausea, and visual loss [128]. Rupture of cyst into the subarachnoid space can lead to aseptic meningitis. If symptomatic, surgical aspiration of cyst content is advocated through an endoscopic transnasal approach [129]. Recurrence is between 8% and 30%, with higher rates seen in microsurgical approaches compared to endoscopic [130].

Nonneoplastic Lesions

Hypothalamic Hamartomas

While not considered a neoplastic proliferation, hypothalamic hamartomas (HH) are rare congenital malformations in which there is heterotopic gray matter within the tuber cinereum or inferior hypothalamus associated with the mammillary bodies [131]. On MRI, they generally appear as nonenhancing lesions that are isointense to gray matter on T1-weighted images and

hyperintense/isointense on T2-weighted images [132]. The typical triad of HHs incorporates epilepsy, precocious puberty, and developmental delays. Children with a HH typically present first with gelastic seizures in infancy, and as they age, this will generally evolve into a more severe seizure disorder, usually between 4 and 10 years of age [133]. The neurons reported to be responsible for this seizure activity are of a GABAergic phenotype and exhibit an intrinsic pacemaker-like activity [134]. Commonly, the seizure semiology suggests the involvement of temporal or frontal lobe regions. HHs can also be asymptomatic or be associated with precocious puberty, behavior disturbances, and cognitive impairment. Medically refractive epilepsy, cognitive impairment, and behavioral disturbances, such as oppositional defiant disorder and ADHD, are common in children who present with seizures due to HH [135, 136].

Very few patients with an intrahypothalamic HH and epilepsy will successfully control their seizures using antiepileptic drugs alone, and vagal nerve stimulators have been utilized with mixed results [137, 138]. Stereotactic radiosurgery resection as well as endoscopic, transcallosal, pterional, and subfrontal lamina terminalis approaches has been utilized to try and disconnect the HH seizure focus from the mamillary bodies [131, 139]. Surgical intervention may result in seizure freedom in up to 50% of patients and may lead to significant improvements in quality of life, cognition, and behavior even with only partial resection [132]. HHs can be associated with Pallister-Hall syndrome, an autosomal dominant disorder which is characterized by central polydactyly as well as several midline defects including imperforate anus, panhypopituitarism, and bifid epiglottis [140]. Preoperatively, many patients will present with neuroendocrine dysfunction, nearly all of which experience precocious puberty, as well as developmental disabilities [139, 141]. Postoperatively, hormonal problems reported include decreased libido, sodium abnormalities, temperature dysregulation, obesity, and thyroid dysfunction [139].

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) is generally considered a myeloid origin neoplasm in which there is a proliferation of pathological dendritic cells [142, 143]. These dendritic cells typically express both CD207 and CD1a (1,3). Classically, there have been three major syndromes associated with LCH: Abt-Letterer-Siwe disease (hepatosplenomegaly, pulmonary involvement, lymphadenopathy, cytopenias, and seborrheic rash), eosinophilic granuloma (lytic bone lesions), and Hand-Schüller-Christian disease (DI, exophthalmos, and lytic craniofacial bone lesions) [144]. Contemporary classification has moved away from these terminologies toward a system that classifies based upon specific sites of involvement and local/multifocal nature of disease. For the purposes of this chapter, we will focus on LCH with CNS involvement. Infiltration of the hypothalamic pituitary region is frequently associated with DI. Less frequently, GH deficiency may develop as well as occasional hyposecretion of TSH, hyposecretion of ACTH, hypogonadism, and panhypopituitarism [145]. Roughly half of patients with LCH will have craniofacial osseous involvement, particularly in the calvaria, skull base, and temporal and maxillofacial bones [146].

Sellar and suprasellar LCH will often present with enlargement of the pituitary stalk and may progress to present as a space-occupying lesion with possible infiltration of the hypothalamus. In patients presenting with DI, T1-weighted images will frequently lack the normal hyperintense signal within the neurohypophysis. This is often referred to as the loss of the bright spot and is correlated with the loss of vasopressin-containing granules [147]. Pineal gland abnormalities are also often seen in patients with LCH [148]. Changes to these two areas may be brought about given their lack of a traditional blood-brain barrier. The presence of osteolytic skull lesions coinciding with a soft tissue mass is highly suggestive of a diagnosis of LCH [149]. Involvement of these areas will often present with symptoms of increased ICP [145].

Less commonly, LCH may also present as neurodegenerative syndromes typically affecting the cerebellum, pons, and basal ganglia [150]. Symmetric patchy hypointense areas on T1-weighted images with hyperintensity on T2-weighted images involving the periventricular area, pons, and cerebellum with or without atrophy may also infrequently be seen [151]. When symptoms do present, they can affect a wide variety of processes and may include tremor, gait abnormalities, dysphagia, dysarthria, ataxia, behavioral abnormalities, deep tendon reflex augmentations, and psychiatric ailments [145]. Patients who develop DI seem to be at an increased risk of also presenting with/developing neurodegenerative changes [152].

The goal of therapy with hypothalamic pituitary region lesions is to prevent further infiltration, endocrine dysfunction, and neurodegeneration [150]. Current standard of care for CNS LCH mass lesions is similar to that outside of the CNS. Curettage may be utilized for isolated lesions, whereas those that are multifocal are generally treated with vinblastine/prednisone [142]. Cladribine has also shown efficacy for CNS LCH mass lesion [153]. For those presenting with DI, treatment is recommended promptly even if the only radiographical evidence is that of minimal pituitary stalk thickening to minimize further endocrine dysfunction [150]. Treatment for those presenting with neurodegeneration syndromes is still not well established and has been looked at mostly through the lens of case reports and case series to date.

Neurosarcoidosis

Sarcoidosis is a disease process that can affect multiple organ systems within the body, most commonly the eyes, skin, and lungs, and is characterized histologically by development and accumulation of noncaseating granulomas [154]. These granulomas typically form to limit inflammation and confine pathogens and in some cases lead to sclerosis and alterations of local architecture. Peak incidence is in the third and fourth decade of life [154]. Within the American population, Black Americans tend to have an annual incidence that is approximately three times higher than that of White Americans, and the disease course tends to be more chronic and fatal among this population [155, 156]. Neurosarcoidosis includes cases of sarcoidosis that affects both the CNS and PNS. While histological evidence of neurosarcoidosis is found in nearly a quarter of patients with a history of sarcoidosis at autopsy, only 10% of all patients will show symptoms of neurological function including headache, ataxia, weakness, seizures, cognitive dysfunction, and cranial nerve palsies [157]. NS involvement of the hypothalamic pituitary region can be seen in 10–26% of NS cases, and when it occurs, HPA dysfunction can be seen [158].

Observed sequelae of HPA dysfunction brought about by NS predominantly include central hypogonadism and primary polydipsia/polyuria (possibly brought about by a combination of destruction of osmoreceptors and vasopressin hyposecretion), whereas hypothyroidism, GH deficiency, corticoadrenal insufficiency, hyperprolactinemia, and obesity have been observed but are less frequently seen [159]. Hypothalamic involvement can also lead to somnolence, insomnia, body temperature dysregulation, changes in appetite, and personality changes. These endocrinopathies appear to be due to the direct granulomatous invasion of the hypothalamic pituitary region or fibrous deposition [160]. NS also seems to have a predilection for the anterior visual pathway and optic chiasm. While the ophthalmological deficits brought about may resolve with treatment, they often lead to profound impairment [161]. Gadolinium contrast-enhanced MRI is an important diagnostic tool for the recognition of NS and often shows multiple white matter lesions and occasionally pituitary stalk thickening; however, it cannot be used to unequivocally exclude NS, and biopsy is required for definitive diagnosis [160]. While some patients fully recover after corticosteroid treatment, others will continue to experience recurrent relapses and continue on a chronic progressive course [162]. Certain immunosuppressive drugs have also been shown to reduce relapse rates, such as IV cyclophosphamide, methotrexate, and infliximab [163].

Conclusion

The hypothalamus plays an integral role in the homeostatic functions of the entire human body. One of its principal roles is that of neuroendocrine regulation. Neuroendocrine dysregulation brought about by sellar and suprasellar pathology has been noted in the literature for centuries. Neoplasms leading directly to hypersecretion of hypothalamic hormones are exceedingly rare. While still a rare occurrence, more commonly, hypothalamic endocrine dysfunction is brought about through the mass effect and/or infiltration of local processes. The etiologies of the lesions leading to this dysfunction incorporate both neoplastic and nonneoplastic processes. Within the neoplastic domain, lesions can be characterized into broad classifications including neuronal neoplasms, glial neoplasms, and infiltrating neoplasms. The various etiologies of, and locations affected by, these sellar/suprasellar pathologies lead to a very diverse set of possible clinical presentations.

Often the resultant endocrine dysfunction does not produce the patient's initial presenting symptoms; however, their occurrence often precedes the development of other symptoms. They will often present with various signs of ophthalmic disturbances and neurological symptoms. When endocrine dysfunctions are recognized, they typically present as disturbances to the hypothalamic-pituitary axis including sequelae such as GH deficiency or acromegaly, precocious puberty or gonadotrophin deficiency, ACTH deficiency or Cushing's disease, thyroid hormone abnormalities, hyperprolactinemia, and DI or SIADH.

Different tumor types will often have varying symptom and associated endocrine dysfunctions. While a wide range of dysfunctions are typically seen among all classifications, their typical locations and cell types often lead to a predominance of a select few prevalent dysfunctions. Given the endocrine implications not just of the lesion itself but also of the treatment, it is vital to understand the far-reaching consequences of hypothalamic damage when investigating potential causative agents and possible therapeutic options. While these tumors are rare, their massive impact upon patient quality of life and homeostatic functioning makes them an important area of study. The scope of the processes within the human body that can be affected by neuroendocrine dysfunction is immense. It often presents with devastating impacts to our patients, and thus, every effort should be made to recognize and limit its effects. This is not done solely through recognition of certain symptoms and pathology, but also through recognizing the safest and most effective modalities of therapy for a given lesion.

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Non-endocrine Neoplasms of the Hypothalamus

16

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Intrinsic CNS Lesions

Glioma

Gliomas of the hypothalamus and optic chiasm are considered pediatric tumors with up to 75% of patients presenting before the age of ten. These tumors do not show a specific gender predilection, but they are more common in patients with neurofibromatosis type I. Clinical presentation includes visual problems due to optic nerve atrophy and growth delay due to hypothalamic pituitary axis dysfunction. In children under three, diencephalic syndrome can be observed, which includes emaciation, locomotor hyperactivity, and increased alertness. Patients with associated neurofibromatosis have a better prognosis with stable lesions in half of the patients, while sporadic cases are less favorable with 5% of patients with stable disease. The lesions are round or lobulated and hypointense on T1-weighted MR images and hyperintense on T2-weighted sequences with heterogeneous enhancement. Cystic components are frequent in sporadic cases [1]. Specific glioma types in this region include high-grade diffuse glioma, chordoid glioma, pilocytic astrocytoma, and pilomyxoid astrocytoma.

Adult gliomas in this region are rare and make up the majority of malignant gliomas. Glioblastoma and anaplastic astrocytomas have been rarely reported, with a total of six publications describing specific cases. Two of the cases described children initially diagnosed with low-grade gliomas which later progressed at a higher grade. Clinically, these lesions typically present with rapid, progressive visual field defects, weight loss, and fatigue [2–7]. Radiographically, these tumors are solid with cystic components that are known to displace nearby structures and are heterogeneously enhancing. T1-weighted sequences are typically iso- to hypointense, but intertumoral heterogeneity makes it difficult to have a centralized description [6–8]. High-grade gliomas are characterized, histologically, as infiltrating glial neoplasm composed of tightly packed tumor cells staining positively for glial fibrillary acidic proteins (GFAP) that are pleomorphic and mitotically active. Necrosis and microvascular infiltration are common [7].

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G. I. Uwaifo (ed.), *The Human Hypothalamus*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-030-62187-2_16

Chordoid glioma is a distinct entity diagnosed based on histopathologic analysis revealing similarities to chordoma and staining with glial fibrillary acidic proteins (GFAP) unique to glial cells [9]. Chordoid gliomas are considered rare, intra-axial, grade II neoplasms that are not known to display anaplastic or necrotic features and are not infiltrative. These lesions are exclusive to the third ventricle and hypothalamus [10]. Choroid glioma presents between the third and sixth decade of life and is more prevalent in women with a ratio of 2:1 further separating it clinically from hypothalamic glioma [11]. Patient presentations vary and include headache, memory loss, homonymous hemianopsia, diplopia, psychosis, obstructive hydrocephalus, nausea and vomiting, lethargy, ataxia, urinary incontinence, diabetes insipidus, amenorrhea, hypothyroidism, and weight loss. This tumor appears similar to and can often have the preoperative diagnosis of glioma, meningioma, craniopharyngioma, lymphoma, pilocytic astrocytoma, ependymoma, or aneurysm [12].

Radiographically, the mass is described as well-circumscribed ovoid, solid hypothalamic, and third ventricular mass that is hyperdense and uniformly enhancing on CT imaging. The infundibulum is often displaced posteriorly unlike Rathke's cleft cysts and hamartomas, and the tumor itself does not extend into the optic chiasm or the optic tracts as can be observed in hypothalamic glioma [12]. Pomper et al. reported on a series of twelve cases with 17% of cases displaying surrounding vasogenic edema, 25% of cases with obstructive hydrocephalus, and 25% of cases containing central cystic- or necrotic-appearing areas which did not indicate necrosis on histopathologic analysis [9]. Surrounding edema, reactive astrocytosis, Rosenthal fiber formation, and inflammatory cell infiltration can be observed, characterizing reactive parenchymal changes to long-standing compression seen in a slowly growing lesion [13].

Histopathologic analysis reveals noninfiltrating, clusters and cords of epithelioid tumor cells with eosinophilic cytoplasm and round to oval nuclei, Russell bodies, and lymphoplasmacytic infiltrate. Necrosis and mitotic activity are not generally observed. Immunohistochemical analysis shows positive staining for GFAP, vimentin, EMA, cytokeratin, CD34, and S-100 [13–15]. Several investigations have supported the theory of ependymal origin of the neoplasm, with some cases arguing for a multipotent stem cell with glial and neuronal cell differentiation as the cell of origin. Ni et al. suggest a majority of chordoid gliomas with an ependymal origin with a minority arising from a multipotent stem cell with ependymal and neuronal cell differentiation based on immunoreactivity for D2-40, an epithelial membrane antigen specific for ependymal cells, and CD34, an epithelial membrane antigen seen in undifferentiated neural precursors [15].

Genomic analysis characterizes chordoid gliomas as having fairly stable genomes with no chromosomal imbalances, aberrations in the TP53 and CDKN2A genes, or amplification in the EGFR, CDK4, and MDM2 genes frequently seen in diffuse gliomas [13].

Choroid gliomas represent tough surgical targets as they are often tightly adherent to the hypothalamus, despite their non-infiltrative, well-circumscribed nature. While histopathologically low grade, choroid gliomas are associated with poor outcomes due to the nature of the location, resulting in subtotal resections and regrowth or severe hypothalamic injury at the time of resection [10, 16]. Maximally safe surgical excision remains the cornerstone of treatment, with adjuvant radiosurgery showing improved overall survival, while chemotherapy has not been shown to improve outcomes [16–18].

Pilocytic Astrocytoma

Pilocytic astrocytoma is a WHO grade I glioma most commonly observed in the pediatric and young adult population. Pilocytic astrocytoma is the second most common malignant brain tumor in children, with two-thirds of all pilocytic astrocytomas diagnosed in patients under the age of eighteen. Two-thirds of these lesions occur in the cerebellum in children, with an even split between infra- and supratentorial tumors in adults. These lesions are generally associated with a good

prognosis, with 90% of patient alive at 10 years post diagnosis. Hypothalamic pilocytic astrocytomas make up 10–15% of supratentorial tumors in the pediatric population with no gender predilection. One-third of cases are associated with neurofibromatosis type I. Visual deficits are the most common presentation followed by growth restriction and, in cases of extension to the third ventricle and blockage of the foramen of Monro, obstructive hydrocephalus [19, 20].

Radiographically, these lesions are well-circumscribed, cystic masses with a discrete mural nodule that are moderately to markedly enhancing [21]. These tumors are hypointense on T1-weighted sequences and hyperintense on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences [20].

Histologically, these tumors show a biphasic pattern where compact areas associated with bright eosinophilic Rosenthal fibers alternate with more loose areas characterized by microcysts. Eosinophilic granular bodies are found in both areas as well as hairlike projections that radiate from the neoplastic astrocytes. Poorly formed microvascular proliferations and hyalinized blood vessels can be observed as well as rare mitotic activity. Rarely, anaplastic features can be observed, which include at least four mitotic figures per ten high-powered fields and pseudopalisading necrosis [19, 20].

Pilomyxoid astrocytoma is a glioma closely related to pilocytic astrocytoma. It is a WHO grade II tumor that is more aggressive than pilocytic astrocytoma and characterized by intratumoral hemorrhage, local recurrence, and leptomeningeal dissemination. The mean age of onset is 1.5 years old, and this tumor type has a predilection for the diencephalon. Histologically, pilomyxoid astrocytomas show myxoid stroma with angiocentric arrangement of neoplastic astrocytes [22–24].

Craniopharyngioma

Craniopharyngiomas are intracranial tumors derived from the remnants of Rathke's pouch. These developmental tumors are most frequently encountered in the pediatric population, commonly between 5 and 14 years of age, followed by a second peak in incidence between the fourth and sixth decade of life. The incidence is about 1.3 cases per million. Craniopharyngioma comprises 5–10% of pediatric intracranial tumors and 1% of adult intracranial tumors [25].

Histologically, these tumors are broken down into the adamantinomatous and papillary tumors. Pediatric craniopharyngiomas are almost exclusively of the adamantinomatous histology as well as up to 85% of adult tumors (50–85%) [26]. Currently, no difference in response to therapy has been noted between the two histological subtypes. Genomic analysis of craniopharyngiomas identified activation of the Wnt pathway, specifically the CTNNB1 gene mutations, as the major driver in the adamantinomatous subtype with up to 96% of tumors sharing this genetic feature [27]. Mutations in the BRAF gene are often identified in the papillary subtype, with mutations found in up to 95% of these tumors. Of note, these pathways do not appear to predict the histology in all cases, with some adamantinomatous tumors harboring mutations in the BRAF gene and vice versa [28].

Hypothalamic craniopharyngioma presents with a wide range of symptoms, many due to compression of nearby structures as the tumor expands. Patients typically present with visual symptoms due to compression of the optic chiasm and/or adjacent structures. In cases of extension of the hypothalamic craniopharyngioma into the sellar space, deficiencies in growth hormone, gonadotropin, thyroid-stimulating hormone, or adrenocorticoid hormone are encountered. Diabetes insipidus occurs due to the compression of the pituitary stalk. Due to common extension of the tumor into the sellar space, hormone-related symptoms are a common initial presentation. These include growth failure in children and sexual dysfunction in adults (erectile dysfunction, amenorrhea, etc.). Headache is another common presenting symptom, found in up to 50% of patients. This is presumed to occur due to compression of pain-sensitive structures, meningeal irritation, or increased intracranial pressure.

Treatment of craniopharyngioma includes a surgical resection followed by radiotherapy depending on the initial extent of resection.

Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) accounts for up to 2% of all intracranial lesions, with immunocompromised patients at an increased risk of the disease. The most common location is the periventricular region with less common locations including the thalamus, basal ganglia, corpus callosum, cerebellum, and spine [29]. Hypothalamic PCNSL is a rare entity with 21 cases reported at this time. There is a higher ratio of male to female (13 males to 6 females) patient affected with a broad age at presentation, from preschool age to 71 years old. The median age at presentation is 50 for the twenty-one reported cases [30–38].

Clinically, PCNSL presents as hypopituitarism and diabetes insipidus as well as memory and personality changes. Radiographically, primary CNS lymphoma is isodense to hyperdense on CT imaging. On diffusion-weighted MR sequences, there is restricted diffusion due to the hypercellularity of the lesion [38].

Non-Hodgkin large B-cell lymphoma makes up the majority of primary CNS lymphoma. Histologically, these lesions are commonly composed of large lymphoma cells with prominent nucleoli, amphophilic cytoplasm, increased mitotic activity, and positive immunostaining for cytoplasmic CD20 with intertwined nonneoplastic T cells [38].

With genome sequencing of the tumors becoming a common practice, key genes have been identified that not only differentiate PCNSL from other diseases but also offer specific targets for treatment. The most common and clinically significant gene mutations observed in PCNSL (based on COSMIC database) are PIM1, MYD88, CD79B, and CDKN2A, among others [39, 40].

Treatment is centered around radiotherapy in conjunction with chemotherapy. Surgical intervention is usually limited to biopsy, as large resection has not been shown to lead to improved outcomes and is associated with higher rates of morbidity. Surgery is reserved in cases of mass effect on nearby structures, including in emergent cases with risk of brain herniation. Recently, research into the clinical merit of surgery has resurfaced due improved surgical techniques [41, 42].

Radiotherapy is the backbone of treatment for many malignancies, including PCNSL, although in the recent years there is a movement away from the accepted protocols. With the introduction of methotrexate into the treatment guidelines, it was questioned whether there was still a benefit of continuing radiotherapy. Not only was methotrexate found to be more effective at prolonging overall survival, but it also prolonged survival to the point where radiotherapy-related neurocognitive deficits became an important consideration in long-term quality of life. It became imperative to look into ways to preserve cognitive function. Three paths have emerged. The first is a decrease in total radiation dose as well as radiation dose per session. Use of radiotherapy only after methotrexate-based chemotherapy fails to reach complete remission is the second option [43]. The third pathway is to use agents which can reduce the radiotherapy-induced damage (mainly creation of free radicals), such as statins [44].

Median overall survival in patients with PCNSL without treatment is around 2–3 months, but prognosis has significantly improved with the advent of new therapies. With radiation alone, overall survival is reported to increase to 12 months with a 48% survival at 1 year after diagnosis [45]. Chemotherapy regimens including high-dose methotrexate have become the mainstay of therapy, increasing overall survival to more than 5 years. Unfortunately, in many cases, there is a recurrence of the disease with no standard guidelines for treatment.

Pituicytoma

A type of low-grade glioma, pituicytomas can be classified into oncolytic, granular cell (often referred to as choristomas) and ependymal subtypes that arise from the different variants of pituicytes (modified astrocytes) of the posterior pituitary. As in normal pituicytes, all variants of pituicytoma share a hallmark expression of the thyroid transcription factor 1 (TTF1).

Common presenting symptoms include visual field defects, headaches, and endocrinological abnormalities, including panhypopituitarism, galactorrhea, loss of hair, infertility, amenorrhea, personality changes, memory problems, and rarely diabetes insipidus. These tumors are slow growing and do not infiltrate the surrounding parenchyma. Spontaneous hemorrhage intratumorally and intraventricularly has been noted as the initial presentation as well as postoperatively in patients with subtotal resection [46–48].

Histologically, pituicytomas are composed of elongated eosinophilic spindle-shaped cells that form interlacing fascicles and low level of nuclear atypia. The oncolytic subtype is distinguished due to its plump epithelioid cells with a more abundant eosinophilic granular cytoplasm. Granular cell tumors are characterized by polygonal cells with prominent granular eosinophilic cytoplasm. Ependymal pituicytomas are associated with ependymal-type rosettes.

Immunohistochemistry of pituicytomas reveals focal positivity for S100 protein, GFAP, and vimentin. Epithelial membrane antigen is often positive as well as stain for TTF1. These tumors are known to express galectin-3. They do not stain for synaptophysin, chromogranin, neurofilaments, keratins, adenohypophysial transcription factors, CD34, bcl-2, smooth muscle actin, and desmin. Granular cell tumors can be distinguished immunohistochemically by their positivity with the periodic acid-Schiff (PAS) stain as well as reactivity for biomarkers of lysozymes, such as CD68, alpha-1-antitrypsin, alpha-1-antichymotrypsin, and cathepsin B [49, 50]. The oncolytic subtype has a strong reactivity for mitochondrial antigens [49].

Choristoma is a type of low-grade glioma that is also referred to as granular cell tumor and infundibuloma; this tumor arises from the neurohypophysis, including the infundibulum and the posterior pituitary gland. They are derived from pituicytes, which are modified astrocytes. These tumors are rare (under 100 cases) with most of the data available in the form of case reports and small case series [51]. In available series of autopsies, choristomas were incidentally diagnosed in 6.5–17% of patients [52]. Adults between the ages of 40 and 60 are most commonly affected with females diagnosed at double the rate of males [53]. Three reports of pediatric-age patients have been reported to date [54–56]. These tumors have also been reported in the spinal meninges, third ventricle, and cerebral hemispheres [57–59].

Radiographically, choristomas are well-circumscribed extra-axial or exophytic lesions that can present with cystic and solid components or completely solid. The solid component of the tumor is isointense to the gray matter on T1-weighted MR sequences and isointense to white matter on T2-weighted MR sequences and is homogeneously to heterogeneously enhancing. Lesions appear isodense or slightly hyperdense on computed tomography imaging with moderate contrast enhancement. Rarely, calcification and erosion of the dorsum sella have been reported [51]. These lesions are not associated with infiltration of the parenchyma, surrounding edema, or extension along the dura.

Treatment is centered at decompression of the affected structures surgically. Due to the firm and easily hemorrhagic nature of the lesion as well as the eloquent location, subtotal resection is sufficient in most cases. Total resection has an added implication of severance of the pituitary stalk in many cases, leading to iatrogenic panhypopituitarism. Recurrence rate of these tumors is debated. Studies with prolonged follow-up of patients post subtotal resection report a median progression-free survival around 100 months. In studies with shorter follow-up times, recurrence is seldom seen, indicating the need for prolonged follow-up in these patients. Radiotherapy has been used in some cases where biopsy was the procedure of choice or atypical histology was noted. Radiotherapy has not been shown to benefit patient with extracranial choristoma, was associated with no recurrence at 5 years in a patient who underwent biopsy, and showed no effect on the lesion at autopsy in a patient initially treated surgically who passed away three months postoperatively. Thus, no definite conclusion about the role of radiotherapy in treatment of choristoma currently exists [51, 60, 61].

Meningioma

Meningiomas are mostly benign, extra-axial CNS lesions that most likely arise from the arachnoid cap cells. Meningiomas account for up to 33.9% of all primary central nervous system tumors. These tumors have a latency of 20–30 years and have a high prevalence of subclinical disease as shown by autopsy findings where up to 2.8% of the female population is affected [62–64]. It is estimated that the incidence rate per 100,000 persons is 8.36 in women and 3.61 in men [65]. These lesions are more common in women, with a ratio of 1:2–3 in male to female patients, with the exception of WHO grade III meningiomas. Such profound gender predilection can be in part explained by the estrogen receptors associated with these tumors. Age-specific rates of diagnosis show an increase in risk with age in women and men. The majority of meningiomas are WHO grade I, with 5% higher-grade tumors [65]. Tuberculum sellar meningiomas make up 5–10% of intracranial meningiomas. These specific meningiomas arise from the tuberculum sellar, chiasmatic sulcus, limbus sphenoidale, and diaphragma sellae. The growing tumor can elevate or displace the optic chiasm, leading to visual symptoms.

Possible risk factors include ionizing radiation, hormone use, breast cancer, and head trauma. Ionizing radiation in the form of dental x-rays has been associated with an up to tenfold increase in meningioma incidence [66]. Due to the higher rate of meningioma incidence in pre-menopausal women compared to age-matched men, exogenous hormone use has been explored as a possible risk factor, with studies thus far pointing to positive association with long-acting contraceptives when used for ten or more years, but not oral contraceptives [67–69]. The association between head trauma and meningioma can likely be attributed to detection bias [70]. Breast cancer does not appear to be a risk factor, but instead likely shares similar risk factors as meningiomas occurring prior to breast cancer diagnosis confer a similar increased risk as breast cancer occurring prior to meningioma [71].

Patients most commonly present due to visual symptoms. These include loss of vision in one eye, objective decrease in visual acuity, decreased color perception, afferent pupillary light defect, decreased visual fields, pallor of the optic discs, Foster-Kennedy syndrome, abnormal extraocular movements, and orbital pain. Other symptoms include memory and concentration problems, headaches, dizziness, and endocrine abnormalities, such as hypogonadism, hypothyroidism, and diabetes insipidus [72, 73].

Histologically, meningiomas are broken down by WHO grade based on the number of mitotic figures as well as invasion and atypia. WHO grade I tumors are identified as less than four mitoses per ten high power fields and are broken down into nine subtypes based on histology and include the meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic. Survival in these patients is 80–90% at 10 years. Grade II meningiomas are characterized based on four possible diagnostic 4–19 mitoses per ten high-power fields or presence of three of the following: necrosis, high nuclear/cytoplastic ratio, prominent nucleoli, architectural sheeting, hypercellularity or clear cell/chordoid histology, or brain invasion. The grade II histological subtypes include atypical, chordoid, and clear cell. The overall survival at 10 years is between 50% and 79%. WHO grade III meningiomas are characterized by greater than 20 mitotic figures per ten high-power fields. Histological subtypes of grade III include anaplastic, papillary, and rhabdoid. The overall survival in this group is between 14% and 34% at 10 years [74–76].

Sporadic, low-grade meningiomas are frequently associated with focal chromosomal deletions, while atypical and malignant grades are driven by multiple chromosomal copy number aberrations and demonic instability [77]. Sporadic meningiomas are most frequently associated with inactivation of the NF2 gene (33% of cases), but loss of 14q, 1p, 6q, and 18q have also been cited [78–80]. Familial cases are associated with germline NF2 mutations and less commonly NF1, PTCH, CREBBP, VHL, PTEN, and CDKN2A [80]. Recent look at the epigenetic

landscape of meningiomas has led to the observation that DNA methylation may have a greater impact compared to mutation events in development of meningioma [81]. Meningiomas are associated with genetic alternations in the DNA repair genes, specifically repair of DNA double-stranded breaks (breast cancer susceptibility gene 1-interacting protein 1, BRIP1) and homologous and nonhomologous DNA break repair (ATM) [82–84]. Other possible genes include those of the apoptotic repair and immune regulatory pathways [85, 86].

Meningiomas are homogenously enhancing on MR imaging, providing an important distinction from pituitary adenomas. They are isointense on T1-weighted sequences and hypointense on T2-weighted sequences [87–89]. Meningiomas are associated with dural-based tail and suprasellar epicenter [89]. In a series reported by Nakamura et al., radiographically, these lesions were associated with bone hyperostosis, calcification, and peritumoral edema in about 20% of patients. Encasement of the internal carotid artery was observed in 28.6% of patients, and cavernous sinus involvement was observed in 6.3% of patients [73].

Treatment is aimed at maximally safe surgical resection in order to improve or prevent worsening of visual symptoms [90]. Recurrence rate is based on the grade at diagnosis with current rates between 0% and 25%, with higher-grade tumors associated with shorter progression-free survival as well as overall survival. Studies have shown improved visual symptoms in 50–60% of patients, with 30–40% of stabilization of symptoms [90, 91].

Solitary Fibrous Tumor

Solitary fibrous tumors are masses most commonly originating from the lung pleura but can develop virtually anywhere in the body. They are mesenchymal and derived from fibroblasts. Solitary fibrous tumors have also been referred to as glomangiomas in the literature but are considered to be different entities in the sellar region [92, 93]. The lesions are relatively rare in the CNS and account for less than 1% of meningeal-based tumors [94]. Reported intracranial sites include the clinoid process, middle cranial fossa, parasellar region, falx cerebri, lateral ventricle, and cerebellopontine angle [95–97]. Suprasellar and sellar involvement of solitary fibrous tumors has been reported by Cassarino et al. [92], Furlanetto et al. [93], Lo et al. [98], Pakasa et al. [99], Rubacha et al. [100], Yang et al. [101], Yin et al. [102], and Wu et al. [103]. These lesions arise from dural fibroblasts and can invade the parenchyma, nerve roots, and bone [104, 105]. The age distribution is quite wide with the earliest diagnosis reported in a 6-month-old male and the oldest in a 73-year-old patient. The median age of onset specific to the CNS is 47.6 years with an equal gender distribution [100, 106].

Clinical presentation varies widely; lesions in the hypothalamic-pituitary region have been reported to present as hyponatremia, headaches, and visual disturbances. While less aggressive than hemangiopericytomas, a couple cases of recurrence and malignant transformation have been reported and have been associated with subtotal resection [100, 107, 108].

Histologically, solitary fibrous tumors are hard to distinguish from hemangiopericytomas and are considered to be the same entity histopathologically, even though clinically hemangiopericytomas exhibit a more aggressive nature [109]. Histological examination frequently reveals moderately hypercellularity within a collagen matrix. The polygonal, spindled, fibroblast-like tumor cells are arranged into fascicles, and the nuclei are small spindled to fusiform [100, 110]. Dilated vascular spaces can be observed [93]. Immunohistochemistry provides the best data for differentiation from hemangiopericytoma as well as fibrous meningioma. Solitary fibrous tumors stain positive for CD34 and vimentin and focally positive for CD99 and bcl-2. They stain negatively for S100 and EMA [98]. A fusion of NAB2-STAT6 is shared between solitary fibrous tumors and hemangiopericytomas [109]. Genetic analyses of a small set of solitary fibrous tumors have shown various chromosomal aberrations, including translocations t(2;3),

t(2;17), t(9;22), and t(4;9) and gains of chromosomes 5, 8, and 21 [111–113].

Radiographically, the differential includes meningiomas, cavernous hemangiomas, and hemangiopericytoma. These lesions are iso- to hypointense on T1-weighted MR sequences and hypointense on T2-weighted sequences. The lesions are well defined with lobulations with a prominent heterogeneous enhancement, although more homogeneous enhancement has also been reported. Cystic changes, hemorrhage, and necrosis can be seen [114]. Cavernous hemangiomas without hemorrhage can be differentiated from solitary fibrous tumors as they exhibit prolonged T2 relaxation [98]. Dural attachments are observed in the majority of intracranial solitary fibrous tumors but only in one-third of spinal tumors [115].

Gross total resection is the mainstay of treatment, and in cases where this is achieved, no further therapy is generally indicated. In subtotal resection, radiotherapy is a good adjunct with some reports of success with chemotherapy [116–118]. Surgically, these tumors can be complicated with adherence to intracranial structures as well as hemorrhagic potential due to the relatively high vascularity. Postoperative hemorrhage can further complicate surgical management [118].

Choroid Plexus Papilloma/Carcinoma

This is a rare benign neuroectodermal tumor that makes up around 0.5% of adult intracranial tumors. The majority of these lesions arise in the lateral and 4th ventricles with rare extraventricular lesions most likely to arise at the cerebellopontine angle. Few case reports of hypothalamic involvement of these tumors have been published with most cases describing extension from intraventricular tumors, metastatic recurrence, and ectopic tissue [119, 120].

Clinical presentation in hypothalamic choroid papilloma includes visual problems [120]. Radiographically, a round well-circumscribed, isodense lesion with marked enhancement on CT imaging is the classic finding. MR imaging shows isointense signal on T1- and T2-weigthed sequences with homogenous enhancement on post-gadolinium T1-weighted sequences. Partial calcification can also be noted. Radiographically, these lesions are similar to tuberculum sellae meningiomas 121].

Histological analysis exhibits thin papillary structures lined by a single layer of nonpleomorphic cuboidal or cylindrical cells within a fibrous stroma. PAS, S-100, SYN, and GFAP staining is negative, with positive prealbumin, vimentin, and EMA staining [119, 121]. Treatment includes surgical resection with local recurrence and metastasis, a known concern in intraventricular lesions but has not been well studied in intraparenchymal lesions.

Hematologic Malignancies

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis, formerly known as histiocytosis X, is characterized by clonal proliferation of dendritic cells that resemble normal epidermal Langerhans cells derived from the bone marrow as part of the dendritic cell line and are able to present as well as process antigens [122]. As part of the hematologic cell lines, these cells are able to lead to widespread systemic disease as well as localized lesions. The prevalence of the disease is 0.2–2.0 cases per 100,000 patients under the age of 15. This is a pediatric disease with less than 30% of cases diagnosed in adults [123]. Langerhans cell histiocytosis in the CNS has a predilection for formation of lesions in the hypothalamic pituitary region, following by bilateral symmetric lesions in the cerebellum and basal ganglia as well as extra-axial lesions [124]. Hypothalamic involvement in this disease occurs in chronic multiorgan disease, as part of the Hand-Schuller-Christian disease and rarely as an isolated eosinophilic granuloma [125–128]. Hand-Schuller-Christian disease manifests as a triad of exophthalmos, diabetes insipidus (in up to 50% of these patient), and osteolytic lesions [129]. Diabetes insipidus is a common symptom in Langerhans histiocytosis and presents in up to 50% of all patients with this disease [130–132].

Clinically, Langerhans histiocytosis with hypothalamic involvement can present as diabetes insipidus, delay in growth in prepubertal patients, hyperprolactinemia, hypogonadism, and hyperphagia [133]. These presentations are thought to be related to the neurodegenerative changes in the infundibulum leading to interference of the axonal transfer of vasopressin and other hormones from the hypothalamus as well as direct damage by the granuloma [134].

Radiographically, these lesions often present as thickening and enlargement of the infundibular stalk or a hypothalamic mass centered in the superior portion of the stalk. The lesions are brightly enhancing on T1-weighted MR imaging [134, 135]. Other common radiographic signs include empty sella, loss of hyperintensity of the posterior pituitary gland, and narrowing of the infundibulum to a maximum width of less than 1 mm [136]. The combination of hypothalamic or infundibular mass and absence of hyperintensity of the posterior pituitary has a wide differential, including tumors (commonly germinomas) as well as other granulomatous diseases (sarcoidosis, granulomatosis with polyangiitis), leukemia, autoimmune disease, and idiopathic diabetes insipidus [137]. A case of LCH lesion of the optic chiasm has been reported, in which the lesion was enhancing on T1-weighted MRI sequence and hyperintense on T2-weighted sequence [138].

Histologically, the lesion is similar to other systemic lesions and includes a mixture of histiocytes with features of Langerhans cells, neutrophils, macrophages, lymphocytes, eosinophils, and plasma cells [138]. Lesions involving the hypothalamus are granulomas within the connective tissues with partial infiltration of the brain parenchyma. The area of infiltration was associated with a large area of inflammation, characterized by high number of CD8+ T cells, and partial loss of neurons and oligodendrocytes. The inflammatory damage can be due to multiple potential mechanisms. Dendritic cells can act as the sources of proinflammatory cytokines which in turn recruit inflammatory cells to the surrounding of the lesion. The weakness of this theory is the fact that the inflammatory process continues even once the granulomas no longer harbor the dendritic cells. The other theory is autoimmune response to the granuloma, which can persist once the Langerhans cells are no longer part of the lesion. They are sharply demarcated due to glial scarring at the periphery of the lesion. In contrast, granulomas in other organs contain a higher ratio of CD8+ T cells to CD3+/CD8- T cells. Lesions involving the hypothalamic region also exhibit CD1a+ cells (a dendritic cell surface marker) in most of the patients studied by Grois et al., a cell marker that has been associated with the age of the lesions, with younger lesions having a higher number of CD1a+ Langerhans histiocytes. These lesions can be distinguished from multiple sclerosis by the process of demyelination. While multiple sclerosis leads to primary demyelination, LCH lesions lead to secondary demyelination due to neuronal and axonal destruction [134].

Depending on the extent of the disease, systemic therapy is the mainstay of treatment. In patients with hypothalamic involvement, low-dose radiotherapy and chemotherapy have been used, but these measures have not been shown to be successful in reversing diabetes insipidus and other hormonal imbalances. In some adult patients studied by Kaltsas et al., LCH lesions developed in other regions of the CNS with no progression of the hypothalamic pituitary region lesions [135]. Common chemotherapeutic agents used include vinblastine, etoposide, cytarabinoside, methotrexate, vincristine, cyclosporine, and prednisone and bisphosphonates [134].

Leukemia

Hypothalamic involvement is usually due to diabetes insipidus caused by thrombosis of hypothalamic vessels or direct infiltration although cases of hypothalamic obesity have also been reported. The most common etiology is acute non-lymphoblastic leukemia (75%), acute lymphoblastic leukemia (14%), chronic myeloblastic leukemia (10%), and chronic lymphocytic leukemia (3%). Due to high likelihood of CNS involvement in acute lymphoblastic leukemia,

prophylactic treatment with radiation and intrathecal chemotherapy leads to relatively lower frequency of hypothalamic infiltration [139]. In cases of acute myeloid leukemia, imaging findings include hyperintensity on fluid attenuation inversion recovery (FLAIR) MR sequences with contrast enhancement post-gadolinium administration [140].

A case of chronic lymphocytic leukemia with hypothalamic involvement has been reported. The patient presented with lethargy, disorientation, and abnormal upward eye gaze. CT scan revealed a hyperdense lesion in the suprasellar region that extended into the third ventricle and occluded the foramina of Monro with enlarged lateral ventricles. CSF analysis performed after ventricular drain placement showed increased cellularity with the cell population composed of atypical monoclonal lambda B-cells [141].

Extrinsic Tumors: Other

Germinoma

Germinomas are tumors derived from germ cells that fail to migrate during fetal development. These tumors are potentially infiltrative and can spread throughout the CNS. The incidence in the United States is 0.75 cases per 1,000,000 and is the most commonly encountered germ cell tumor in the CNS [142]. They are usually located at the midline; suprasellar (49%) location is the most common followed by the pineal gland (37%). In about 8% of cases, both locations are involved, which is referred to as bifocal or multifocal germinoma. These are primarily pediatric tumors with 90% of cases occurring before the age of 20 [142]. While males are more commonly affected overall for CNS germinomas, the hypothalamic region has an even gender distribution. Male patients are at a 1.88 times increased risk for any CNS germinoma and at a 13 times increased risk for pineal germinoma [143–145]. An increased risk of germinoma development has been reported in patients with Klinefelter, Noonan, and trisomy 21 syndromes [146, 147]. Overall survival is cited between 85% and 94% at 5 years [148, 149]. Additionally, Matsutani et al. reported survival to be 95.4%, 92.7%, 87.9%, and 80.6% at 5, 10, 15, and 20 years, respectively [147].

Clinical presentation includes diabetes insipidus in the majority of the cases as well as other metabolic derangements; visual symptoms depend on the extent of the disease [144, 148]. Onset of diabetes insipidus can occur prior to positive MRI findings; thus, a child who presents with otherwise unexplained diabetes insipidus should undergo a repeat MRI at 3- to 6-month intervals for the first 3 years post-diagnosis [150].

Macroscopic examination shows gray solid nodules which can be either well circumscribed or poorly defined at an equal rate. Histologically, these lesions consist of large, epithelioid, polygonal cells with pale or clear cytoplasm staining positively for PAS. These tumors are associated with lymphocytic infiltrate. Immunohistochemistry often reveals positive staining for placental alkaline phosphatase (PLAP) as well as, virtually, always positive staining for c-kit (CD117) and OCT4. Staining for CK AE1/3 is usually negative or focally, weakly positive. Blood germ cell tumor marker, alpha-fetoprotein (AFP), is always negative in pure germinomas, and low levels of beta-HCG can be noted [148, 149].

Radiographically, these lesions are best assessed using MR imaging. They are homogenous, well-circumscribed solid masses associated with infundibular thickening and loss of contrast enhancement of the posterior pituitary on T1-weighted sequences. Suprasellar germinomas are not associated with calcification or cystic components. On T1-weighted sequences, these tumors are iso- to hypointense. On T2-weighted sequences, they are iso- to hyperintense with short relaxation time [144]. Germinomas show prominent and homogeneous contrast enhancement, with larger lesions exhibiting more heterogeneous enhancement due to the inhomogeneous blood supply or necrosis [151].

Treatment is dependent upon staging at initial presentation. MR imaging of the brain and spine as well as serum and CSF cytology and tumor markers are used for staging. Stage M0 is consistent with no evidence of metastatic spread, stage

M1 is consistent with positive cytology, intracranial metastases are consistent with stage M2, and spinal metastases increase the staging to M3. Germinomas are highly radio- and chemosensitive. Surgical management is usually isolated to stereotactic or open biopsy in cases where the diagnosis is unclear in order to minimize the risk of iatrogenic seeding. Radiotherapy, alone, has been used historically, but with longer survival and late effect of radiation, lower doses of radiation therapy are being combined with chemotherapy. Etoposide and carboplatin have been used in combination with various doses of radiotherapy as adjuvant treatment depending on response to chemotherapy. Recurrence and relapse are treated based on the initial treatment strategy. In patients receiving only chemotherapy, a combination of radio- and chemotherapy is usually employed. Chemotherapy regimens include cisplatin-etoposide-ifosfamide, cisplatin-etoposide, and carboplatin-etoposide. In patients who were additionally treated with radiotherapy at initial presentation, autologous stem cell rescue was conditioned with carboplatin-etoposide or etoposide-thiotepa in addition to high-dose chemotherapy [152]. Two independent studies show a relapse time of 37 and 32 months following chemotherapy and limited radiotherapy [153, 154].

Metastatic Disease

Metastatic lesions are the most common CNS tumors. Metastasis to the hypothalamic-pituitary axis has been cited to make up 4% of all intracranial metastatic tumors. More specifically, hypothalamic involvement has been cited to be as high as 3% of intracranial metastatic lesions in a retrospective review of 895 patients with metastatic brain lesions by Janssen et al. [155]. Unfortunately, not many case reports are available, and most involve the pituitary gland with spread to the infundibulum [156, 157]. From the available data, there is no predilection for gender, and the mean age at presentation is 64 (including 26 hypothalamic and nine pituitary lesions with infundibular spread). The most common primary pathology in the combined hypothalamic-pituitary axis was non-small cell lung cancer (46%), followed by small cell lung cancer (14%) and breast cancer (12%), and more rarely melanoma (7%), colorectal carcinoma (4%), and renal cell carcinoma (3%). Hypothalamic lesions were statistically significantly more likely to be diagnosed in patients with more than ten intracranial metastatic lesions [155]. Possible avenues of spread to the hypothalamic-pituitary axis include hematogenous spread through the hypophyseal arteries and portal vessels, direct extension from juxtasellar and skull base lesions, and CSF seeding through the suprasellar cistern [158, 159].

Many of the presenting symptoms include metabolic dysfunction, including diabetes insipidus and growth hormone insufficiency which presents as fatigue. Many of these symptoms are shared between hypothalamic-pituitary axis disorders, oncologic diseases, and chemotherapy side effects; thus, it is often difficult to delineate the true cause of the symptoms in these patients [159].

The histopathologic analysis is not often available as these lesions are usually not treated surgically, but rather with a combination of radio- and chemotherapy. The diagnosis is frequently based on patient history of metastatic cancer as well as the radiographic findings.

Radiographically, important characteristics of metastatic involvement include infundibular thickening, lack of contrast enhancement of the posterior pituitary in cases of infundibular involvement, isointensity on T1- and T2-weighted MR sequences, and strong contrast enhancement on post-gadolinium sequences [159].

Treatment is centered around palliative goals as metastatic spread to the CNS is a poor prognostic factor with the mean survival from time of brain metastasis diagnosis of 6–8 months [160] with survival around 15 months reported in individual cases as well as most commonly presence of other extracranial metastatic lesions. Symptomatic patients are treated with localized radiotherapy as well as hormone replacement [159, 161, 162].

Lipomas and Osteolipomas

Intracranial lipomas are rare and make up less than 0.5% of all intracranial tumors. The majority arise in the corpus callosum (greater than 50%), the ambient cistern (15%), and the suprasellar region (15%) [163]. Lipomas in the suprasellar legion are more likely to exhibit partial ossification, with up to half of suprasellar lipomas containing ossified portions. Intracranial lipomas envelope blood vessels and nerves leading to the theory that these are slow-growing, congenital malformations versus neoplastic lesions [164–170].

Radiographically, on CT scan, the lesion shows partial calcification with no enhancement and a hypodense adipose region. On MR imaging, lesions were hyperintense on T1-weighted sequences and iso- to hypointense on T2-weighted sequences. Again, the lesions are non-enhancing. Histologically, these lesions are composed of mature adipocytes within a bony shell and connective tissue containing vessels. Few osteoblasts and osteoclasts can be observed as well [165].

Treatment is reserved to symptomatic lesions due to the otherwise slow growth of the lesions and high risk of surgery. In symptomatic cases, careful debulking and subtotal resection are appropriate due to the benign course of the lesions. It is important to consider the high risk of hemorrhage due to the highly vascularized nature of the tumors and their adherence to adjacent structures [165].

Vascular Tumors

Hemangioblastoma

These are benign (WHO grade I), noninfiltrating vascular tumors that make up 2% of primary CNS tumors. Median age of onset is in the third and fourth decades of life [171]. These tumors are usually sporadic although approximately 30% are associated with von Hippel-Lindau disease. This genetic disorder is characterized by inactivation of a tumor suppressor gene on chromosome 3p25 leading to overexpression of VEGF and thus overproduction of erythropoietin [172]. It is associated with hemangioblastomas of the central nervous system as well as a retinal angiomas, renal cell carcinoma, pheochromocytomas, pancreatic tumors, endolymphatic sac tumors, and epididymis cysts [173]. The patient typically presents, at an earlier age, multiple lesions and worse prognosis. Most common locations in the CNS include the posterior fossa followed by the cervical and thoracic spinal cord [172]. Hemangioblastomas affecting the hypothalamic region are rare, with under ten cases reported in the literature, and have a higher chance of diagnosis as part of von Hippel-Lindau disorder [174–182].

Clinically, these lesions present due to either mass effect of obstructive hydrocephalus, in the cases affecting posterior fossa. Hemangioblastomas are not associated with high risk of hemorrhage but can occasionally present as symptomatic polycythemia induced by erythropoietin production by the lesion [183].

Histologically, this is characterized by proliferating capillaries of variable size. Cells are large and stromal with pink to clear cytoplasm containing fine vacuoles, large hyperchromatic nuclei, and lack of atypia. The lesions are not associated with fibrillar cells, necrosis, or mitotic figures [184]. Mast cells can be noted within the tumor mass [185]. Immunohistochemically, hemangioblastomas stain positively for NSE, VEGF, inhibin alpha, reticulin, and CD34 with occasional positive stain for S100, GFAP, and erythropoietin and negatively for EMA cytokeratin, and CD10, allowing histological differentiation from renal cell carcinoma metastasis [186, 187]. Hemangioblastomas can be further differentiated from paragangliomas as the latter tumors stain positively for chromogranin.

Radiographically, these tumors are best assessed with contrast-enhanced MR imaging. Hemangioblastomas are well-circumscribed and composed of solid contrast-enhancing mural nodules with some cystic components [136]. Hypothalamic hemangioblastomas are more likely to consist of only solid components with only one out of nine lesions from available case reports showing a cystic component [188]. On

CT imaging, these lesions are described as solid with intense enhancement [180, 181]. On T1-weighted MR sequences, the tumors appear isointense and on T2-weighted sequences hyperintense and heterogeneously enhancing post-contrast administered images [188].

Surgical excision is often curative with very low risk of recurrence in sporadic cases. On the other hand, patients with von Hippel-Lindau disease experience frequent de novo hemangioblastomas and thus need close follow-up with comprehensive surveillance MR imaging. Timing of surgery is more sensitive in the case on von Hippel-Lindau, as the risks and benefits of multiple potential surgeries are considered. One major drawback of deferring surgical intervention is the possibility of tumor growth and expansion to critical structures, especially in the suprasellar and sellar region [189]. Primary and secondary (post-subtotal resection) radiotherapy has been associated with good outcomes [190–193]. Stereotactic radiotherapy shows good results in most cases with solid tumors at up to 5-year follow-up but is not effective on cystic components [194]. Endovascular embolization alone or more commonly in conjunction with surgery has been shown to have good results in hemangioblastomas in other locations, but no data on the effects of hypothalamic hemangioblastomas is currently available [195]. No clear guidelines regarding postoperative follow-up have been established for sporadic cases, but repeat imaging in 12–24 months has been suggested.

Hemangiopericytoma

Central nervous system hemangiopericytomas make up less than 1% of all primary CNS tumors. These are often dural-based cranial tumors, with up 10% occurring in the spine. At this time, 11 documented cases of suprasellar/sellar hemangiopericytomas have been reported [196–205]. The age of affected patients ranges from 18 to 60, with a mean age at presentation of 40 years old. Unlike their benign counterparts, solitary fibrous tumor, hemangiopericytomas are usually either WHO grade II or grade III. Three of the 11 reported suprasellar/sellar lesions were diagnosed as grade III and eight as grade II, although one of these was diagnosed as grade III at recurrence [198]. These tumors have a high rate of recurrence (6/11) at a mean follow-up of 6 years. Hemangiopericytomas are also known for distal metastases within the central nervous system in the general affected population.

Clinically, these lesions present due to mass effect on the optic apparatus, facial pressure and headache, and symptoms of metabolic dysfunction in some cases.

Histologically, hemangiopericytomas are characterized by ovoid cells arranged in a haphazard manner with variable number of mitoses, necrosis, and "staghorn" vessels. WHO grade II tumors are defined as having less than five mitoses per ten high-power fields, while grade III has five or more mitotic figures. Immunohistochemistry shows positive stain for STAT6 ,and genomic analysis is significant for inversion at 12q13 leading to fusion of *NAB2* and *STAT6* genes [206, 207].

Radiographically, hemangiopericytomas are contrast-enhancing and often diagnosed preoperatively as pituitary adenomas.

Gross total resection with subsequent radiotherapy is the currently accepted treatment with a recurrence rate of up to 10 years in the general hemangiopericytoma population. Radiosurgery is a good alternative to re-resection as has been shown by Sheehan et al. as well as Chang and Takamoto who achieved a 75% local control [208, 209]. Radiosurgery is an attractive alternative to surgery especially in the suprasellar and sellar regions as critical structures are at risk with each surgery. Also, the well delineation of these tumors from the brain parenchyma increases the accuracy and completeness of radiosurgery. Although good local control was achieved in these studies, metastatic rate was not reduced. Chemotherapy has not shown to be effective in treating this tumor nor was neoadjuvant radiotherapy [210].

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Nonneoplastic Mass Lesions of the Hypothalamus

17

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Cystic Lesions

Epidermoid and Dermoid Cysts

Epidermoid and dermoid cysts are congenital lesions and are composed of keratinizing stratified squamous epithelium that are filled with keratin and in the case of dermoid cysts, additional materials such as fat, hair, or sebaceous glands. The tissue of origin is ectoderm that fails to separate as the neural tube closes at around the fourth week of embryonic development. These lesions, while formed during neural tube closure, do not usually present until early to late adulthood as the cysts accumulate desquamating tissue and keratin from the inner capsule and enlarge slowly during the first decades of life [1, 2]. Patients with suprasellar cysts usually present with visual and endocrinologic disturbances. Epidermoid and dermoid cysts are more common in the midline intracranial structures below the tentorium [3].

Epidermoid cysts make up between 0.2% and 1.8% of all primary intracranial mass lesions [4]. Dermoid cysts are even less common, making up between 0.04% and 0.7% of all primary intracranial mass lesions [5]. Epidermoid and dermoid cysts occur at a slightly higher frequency among males than females with no difference in prognosis, which is generally very good. These cysts are sporadic with a small number of dermoid cysts associated with Goldenhar syndrome. Goldenhar syndrome is characterized by the anomalous formation of the first and second branchial arches [6, 7].

The clinical course of epidermoid and dermoid cysts is the slow development of symptoms, based on location, over a median of 47 months prior to diagnosis. The growth of the cysts is linear as compared to malignant lesions. Initial presentation due to spontaneous or traumatic cyst rupture and chemical meningitis due to the inflammatory response to the cystic components in the subarachnoid space has also been reported [4]. In a very small percent of epidermoid and dermoid cysts, malignant progression has been reported either post cyst rupture, after the excision of the primary epidermoid cyst, but has also been reported to occur spontaneously in a handful of cases. Malignant transformation leads to the development of squamous cell carcinoma. Epidermoid and dermoid cyst transformation is the third leading cause of this rare intracranial tumor type, after metastasis and extension from the cranial base [8].

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G. I. Uwaifo (ed.), *The Human Hypothalamus*, Contemporary Endocrinology,
https://doi.org/10.1007/978-3-030-62187-2_17

Histopathology of dermoid cysts consists of an outer connective tissue layer of squamous cells that surround a collection of mixed adnexal structures including hair follicles, sebaceous droplets and glands, fat globules, and sweat glands [4]. Epidermoid cysts are composed of a connective tissue outer capsule with keratin and desquamated epithelium and a core composed of water and cholesterol droplets [9].

Radiographically, the MR imaging characteristics of dermoid cysts defer from epidermoid cysts depending on the contents of the cyst. Dermoid cysts containing fat can take on a similar appearance to lipomas on both T1- and T2-weighted images. Unlike lipomas, dermoid cysts exhibit less signal intensity suppression on fat-suppression sequences. Dermoid cysts with less fat content can resemble other cysts, such as arachnoid cysts as they demonstrate a CSF-like signal intensity. Unlike arachnoid cysts, dermoid cysts appear hyperintense relative to CSF on FLAIR sequences [5, 10]. On CT imaging, dermoid cysts are well-circumscribed hypodense masses with 20% of cysts exhibiting capsular calcification [8].

Epidermoid cysts are more likely to deviate from the midline compared to dermoid cysts. Parasellar region is the second most site for intracranial epidermoid cysts with the most common location being the cerebellopontine angle cistern. Radiographically, epidermoid cysts appear similar to arachnoid cysts. On T1- and T2-weighted MR images epidermoid cysts are more hyperintense and exhibit a more heterogeneous signal intensity compared to the arachnoid cysts. Epidermoid cysts are rarely calcified (10%) and do not show contrast enhancement. When calcification is present, it is usually located at the periphery of the cyst [1, 11].

Definitive treatment is surgical resection, although due to the slow growth and benign characteristics of these cysts, they are often followed clinically with serial imaging. Resection is pursued in cases of worsening symptoms including neurological deficits and is focused on gross total resection including the cyst capsule and dural attachments with consideration of any neighboring neurovascular structures especially in the region of the hypothalamus. It is important to inform patients of the possibility of cyst rupture which presents a host of other concerns, such as the aforementioned chemical meningitis as well as vasospasm, seizures, coma, and infarction [3, 12]. Malignant transformation is less likely in stable cysts with no prior exposure of the intracystic material to the outside of the cyst wall [8]. The rate of recurrence based on the extent of resection has not been formally explored, although it is generally accepted that gross total resection leads to lower rates of recurrence. In a review by Lynch et al., the rate of gross total resection was reported to be between 0% and 95.4% and the rate of recurrence to vary between 0% and 26%, although the time of follow-up was inconsistent [13].

Arachnoid Cyst

Arachnoid cysts are benign intracranial masses that usually remain asymptomatic throughout life and are commonly diagnosed as incidental findings. They are thought to form due to splitting of the arachnoid layer during fetal development which leads to the accumulation of CSF within the potential space created [14]. While the vast majority of arachnoid cysts are formed during the fetal period, inflammatory environment can lead to secondary arachnoid cyst formation in an adult. Some examples of inflammatory causes include adhesions, neoplastic process, and trauma. A rare complication of an arachnoid cyst is spontaneous rupture into the subdural space [15].

Overall, arachnoid cysts make up 1.4% of intracranial masses and are more common in men. Suprasellar arachnoid cysts are considered rare with the most common locations being the middle cranial fossa in 50–60% of cases (involvement of the Sylvian fissure is common), followed by retrocerebellar cysts, which account for an additional 30–40% of all intracranial arachnoid cysts [16]. While suprasellar arachnoid cysts are rare (5–12%), they become symptomatic at a higher rate than the aforementioned locations due to the sensitive nearby structures, such as the optic pathway and the ventricular system [17]. Suprasellar arachnoid cysts have an even

distribution between male and female patients and have an early onset of symptoms with the average age of 9.8 years old, although the range of ages at presentation spanned from 1 month to 83 years of age in a study by Mattox et al. [18].

Clinical course is similar to other suprasellar mass lesions and often manifests as visual disturbances due to compression of the optic pathways. As they increase in size, arachnoid cysts extend superiorly into the third ventricle and can obstruct the flow of CSF through the foramen of Monro, leading to obstructive hydrocephalus and associated symptoms of increased intracranial pressure (nausea, vomiting, headache, etc.) [17, 19]. Occasionally, the pituitary infundibulum can be compressed by the cyst leading to endocrine abnormalities [20].

Upon histological examination, the primary, or congenital, cysts are composed of flattened arachnoid cells forming a thin translucent layer. Secondary arachnoid cysts are characterized by scarred arachnoid layer surrounding CSF loculations. No epithelial lining, capsule, or solid component is present. Surgery is considered in symptomatic cases [21].

Radiographically, arachnoid cysts have a very thin wall, making it difficult to see except on high-resolution T2-weighted MR imaging. These cysts do not enhance and have no solid component, and no calcification has been reported. While these cysts are benign, it has been found that over time, they can not only displace intracranial structures but also cause remodeling of adjacent bone. In CSF flow studies, such as CT cisternography, communication between the arachnoid cyst and subarachnoid space becomes apparent [16, 19].

Treatment is focused on freeing the course of CSF flow from the lateral ventricles and decreasing the mass effect on surrounding structures. Endoscopic approach has become a popular approach as it allows for a safe and effective third ventriculostomy. Cyst fenestration is another popular surgical technique [18].

Rathke's Cleft Cyst

Rathke's cleft cysts (RCCs) are benign, congenital, non-obliterated remnants of the primitive craniopharyngeal duct and are usually located intrasellar or with extension into the suprasellar region. Pure suprasellar RCCs are rare and have only been reported as individual case reports [22]. While RCCs are relatively common, with as much as 33% of randomly selected autopsies containing an RCC (the range varies between 2% and 33%), symptomatic RCCs requiring treatment are relatively rare and make up less than 10% of all lesions resected in the intrasellar region. Intrasellar RCCs are formed between the pars anterior and the pars intermedia of the pituitary gland. The purely suprasellar RCCs are thought to arise from the pars tuberalis of the pituitary gland, which is superior to the diaphragma sellae [23–27].

The clinical course of these lesions is relatively benign, with most diagnosed at autopsy. In cases where the RCCs become symptomatic, this is thought to be due to the accumulation of mucinous fluid leading to an increase in size. Suprasellar RCCs produce symptoms due to the compression of the nearby structures, resulting in visual disturbances and occasional endocrine imbalances [28, 29]. Other symptoms reported at presentation and resolved postoperatively include vertigo, ataxia, and diminished libido [22].

Histologically, RCCs are composed of a single-cell layer of cuboidal or columnar epithelium with mucin-secreting goblet cells and cilia interspersed. The cyst contents are variably viscous and mucous [26].

Radiographically, RCCs can present differently depending on the contents of the cyst. RCCs are hypointense on T1-weighted sequences and hyperintense of T2-weighted sequences in cases where the cyst contents resemble cerebrospinal fluid. RCCs that are composed of a higher ratio of mucopolysaccharides, cellular debris, intracystic hemorrhage, and cholesterol crystals can be hyperintense on T1-weighted sequences and iso- to hypointense on T2-weighted sequences. No enhancement of the cyst or the cyst wall has been reported [28, 29].

Treatment of RCCs is pursued in symptomatic cases, while incidental findings are followed radiographically and symptomatically. In the case of RCCs, partial resection of the cyst wall

with draining of the cyst contents leads to resolution of symptoms and only rarely leads to recurrence [27].

Colloid Cyst

Colloid cysts are slow-growing lesions of neuroepithelial or endodermal origin. They are often located in the anterosuperior third ventricle close to the foramen of Monro but can also rarely be found in the suprasellar cistern, lateral ventricles, parietal convexity, and cerebellar regions. Even though these lesions originate intraventricularly, these lesions have been shown to have a significant effect on the hypothalamus and are thus discussed here [30].

Colloid cysts remain asymptomatic in many patients, especially with cysts less than one centimeter. Colloid cysts, while most likely congenital lesions, present in adults between the third and sixth decade of life. These lesions make up 1–2% of all intracranial tumors and 15–20% of intraventricular lesions [31, 32]. Only 1–2% of all colloid cysts present in the pediatric population. Common presenting symptoms include paroxysmal headaches, visual disturbances, nausea and vomiting, behavioral changes, memory changes, lower extremity weakness, gait disturbances, and in some cases sudden death [33]. Sudden death has been attributed to a sudden increase in intracranial pressure, neurogenic pulmonary edema, and neurogenic stunned myocardium due to prolonged, bilateral stimulation of the hypothalamus [34, 35]. While estimates of risk of rapid deterioration and death in patients with colloid cysts are hard to establish, 3–35% of patients are at risk of sudden deterioration with an associated 5–38% risk of death [36, 37]. Symptoms specific to colloid cysts in the intra- and suprasellar region include galactorrhea, hypogonadism, and headaches due to compression of parts of hypothalamic-pituitary axis [30].

Histologically, colloid cysts are lines with a single layer of pseudostratified squamous, cuboidal, or columnar epithelium. The wall of the cyst is composed of collagenous connective tissue stroma, and the contents vary within the mucoid inner core [38].

Radiographically, colloid cysts are heterogeneous lesions. The most common appearance is hyperintensity on T1-weighted MR-sequences and iso- to hypointensity on T2-weighted sequences. On CT imaging, these lesions are commonly hyperdense but can also present as iso- and hypodense. These lesions are not known to enhance and are not associated with calcification. The heterogeneity in imaging of colloid cysts can be attributed to the various substances that have been found within the cyst, including blood products, macrophages, cholesterol crystals, cerebrospinal fluid, metallic ions, and mucus [39, 40].

Treatment of colloid cysts has been focused on symptomatic relief. In patients with an incidental diagnosis of colloid cysts, nonoperative management with serial imaging has been the general recommendation if the size of the lesion is under 1 cm as the dangers of surgery outweighed the possible benefit of prevention of possible symptoms in the future. Since there have not been many studies looking at the growth potential of colloid cysts, it is hard to know how many cysts will go on increasing in size and how many people are actually at risk of future symptom development. On the other hand, surgical techniques have improved tremendously in the recent years with endoscopic approaches minimizing possible side effects and damage to the nearby structures. Aspiration of the colloid cyst without the resection of the capsule often leads to recurrence and is thus not recommended [37].

Vascular Lesions

Cavernoma

Cavernomas are benign vascular congenital malformations that arise during embryonic vascular development. These lesions make up 10–25% of intracranial vascular malformation and have an overall prevalence between 0.4% and 0.8% in the general population based on autopsy studies [41].

Cavernomas are more frequently encountered in the frontal, temporal, and parietal lobes but can