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REVIEW

GNRH NEURON BIOLOGY
AND CONGENITAL HYPOGONADOTROPIC HYPOGONADISM

Neuroradiological findings in hypogonadotropic hypogonadism

Alessandro SALVALAGGIO [1], Andrea ELEFANTE [2], Renzo MANARA [3]*

[1]Neurology Unit, Department of Neurosciences, University of Padua, Padua, Italy; [2]Neuroradiology Unit, Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; [3]Neuroradiology Unit, Department of Medicine and Surgery, University of Salerno, Salerno, Italy

*Corresponding author: Renzo Manara, Neuroradiology, Section of Neurosciences, Department of Medicine and Surgery, University of Salerno, Via S. Allende 1, Baronissi 89081, Salerno, Italy. E-mail: rmanara@unisa.it

ABSTRACT

Hypogonadotropic hypogonadism (HH) is a clinical hallmark of a heterogeneous group of acquired and inherited diseases. Patients with HH undergo brain imaging in order to investigate morphological or signal abnormalities at the level of the hypothalamic-pituitary structures. The presence of tumors, lesions or atrophy might be the explanation of the hormone dysfunction. Nonetheless, in most patients both the hypothalamus and the pituitary gland appear normal. In some cases, the presence of ancillary, not necessarily HH-related brain abnormalities might provide significant clues on the underlying condition. We addressed those conditions associated with HH subdividing them into acquired or inherited diseases, highlighting the neuroradiologic features that might help in the diagnosis.

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Hypogonadotropic hypogonadism (HH) is a clinical hallmark of a heterogeneous group of acquired and inherited diseases. Patients with HH undergo brain imaging in order to investigate morphological or signal abnormalities at the level of the hypothalamic-pituitary structures. The presence of tumors, lesions or atrophy might be the explanation of the hormone dysfunction. According to current Endocrine Society Guidelines, pituitary MRI is recommended when high-risk symptoms are present (headache and visual disturbance) or when the morning total testosterone is less than 5.2 nmol/L and LH and FSH levels are low or normal.[1] In fact, HH patients might encompass cases of pituitary pathology requiring surgical intervention, sometimes in the absence of clinical or biochemical "red flag" features. Nonetheless, in most patients both the hypothalamus and the pituitary gland appear normal.[2] In some cases, the presence of ancillary, not necessarily HH-related brain abnormalities might provide significant clues on the underlying condition.

We addressed those conditions associated with HH subdividing them into acquired or inherited diseases, highlighting the neuroradiologic features that might help in the diagnosis.

Acquired hypogonadotropic hypogonadism

The acquired conditions that might present HH are listed in Table I.[3, 4]

After having excluded functional, drug-

TABLE I.—*Acquired causes of hypogonadotropic hypogonadism*

Hyperprolactinemia
Drugs
Iron overload
Cushing syndrome
Severe and chronic illness
Pituitary gland and hypothalamic tumors
Pituitary apoplexia and abscess
Pituitary irradiation, chemotherapy or surgery
Neoplastic and inflammatory/infectious pituitary stalk lesions
Pituitary trauma

related or metabolic conditions such as iron overload, neuroimaging might detect or rule out tumors, lesions or atrophy of the hypothalamic-pituitary structures (Figure 1). MRI is certainly the most suitable tool for the morphological evaluation of the hypothalamic-pituitary gland axis.[5] The III-ventricle floor, pituitary stalk, T1-bright neurohypophysis, adenohypophysis, and pituitary sella (enlargement or bone remodeling/erosion) should be carefully evaluated, both before and after contrast medium administration. Acquired HH is rarely isolated; in most cases panhypopituitarism is present and laboratory assessment reveals multi-hormone involvement.

Pituitary gland and hypothalamic tumors

Pituitary macroadenomas might determine panhypopituitarism due to anterior pituitary gland compression and pituitary stalk disconnection. Prolactin-secreting adenomas might induce hypogonadism also because hyperprolactinemy *per se* decreases Gn-RH levels via abnormal feedback mechanisms and interferes with peripheral gonadal hormone effects.[6] MRI might present with signal abnormalities in the pituitary gland before or after contrast medium administration. Moreover, the pituitary gland might appear enlarged with remodeling of the pituitary sella and internal carotid artery siphon lateral displacement; the cavernous sinuses might be unilaterally or bilaterally invaded, the bone floor of the pituitary sella might be eroded, the pituitary stalk can be deviated and the suprasellar cisterns might be occupied by the tumor with subsequent optic chiasm compression.

The MRI evaluation is not limited to the pituitary gland and stalk as hypothalamic lesions might cause pituitary gland dysfunction and might be easily detected with conventional coronal sequences; craniopharyngiomas, low grade gliomas, germinomas, hamartomas and

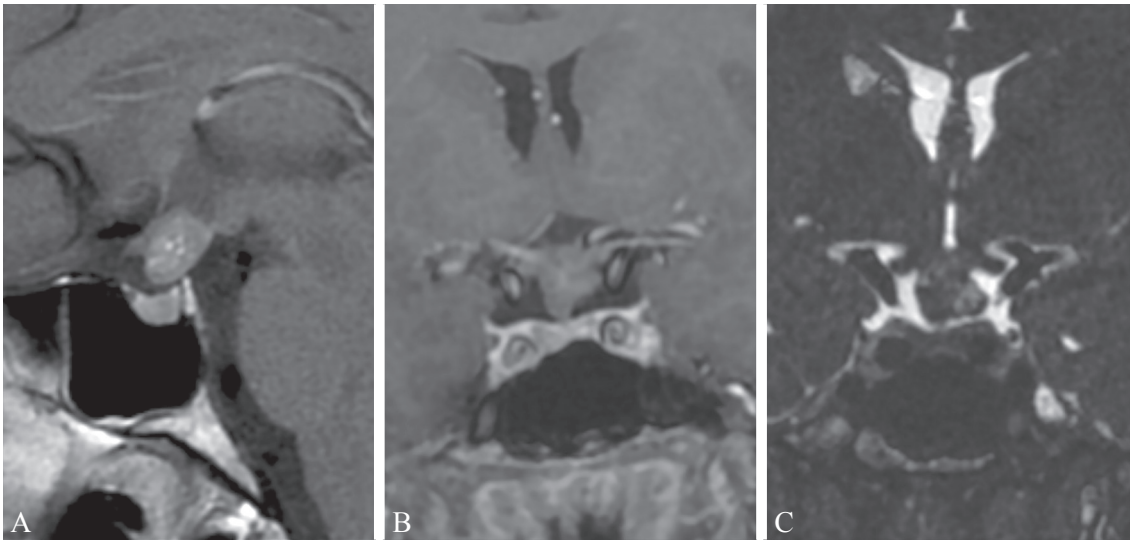

Figure 1.—Hypothalamic lesion-related hypogonadotropic hypogonadism. A 23-year-old boy with isolated hypogonadotropic hypogonadism. A and B) contrast enhanced midsagittal and coronal T1-weighted images showing a suprasellar ovoidal mass at the level of the pituitary stalk and the III-ventricle floor; the lesion presents inhomogeneous enhancement. C) coronal T2-weighted image confirming the intralesional signal inhomogeneity.

metastasis account for most hypothalamic tumors, but almost all central nervous system tumor might primarily or secondarily involve the hypothalamic region.[7, 8]

Pituitary apoplexy and abscess

These two rare conditions have to be considered due to the clinical relevance of an early diagnosis. Both present with panhypopituitarism, but the clinical onset might be insidious. Pituitary apoplexy occurs in pituitary glands harboring an (unknown) adenoma. Besides panhypopituitarism, sudden pituitary enlargement caused by intratumoral hemorrhage might present with visual deficits (due to chiasm compression), diplopia (due to III, IV and VI cranial nerve compression), headache, vomiting, altered consciousness up to coma (due to intracranial hypertension or chemical meningitis) and amenorrhea. The pituitary sella is usually enlarged and T1 sequences often show pituitary hyperintensity due to the presence of metahemoglobin.[9]

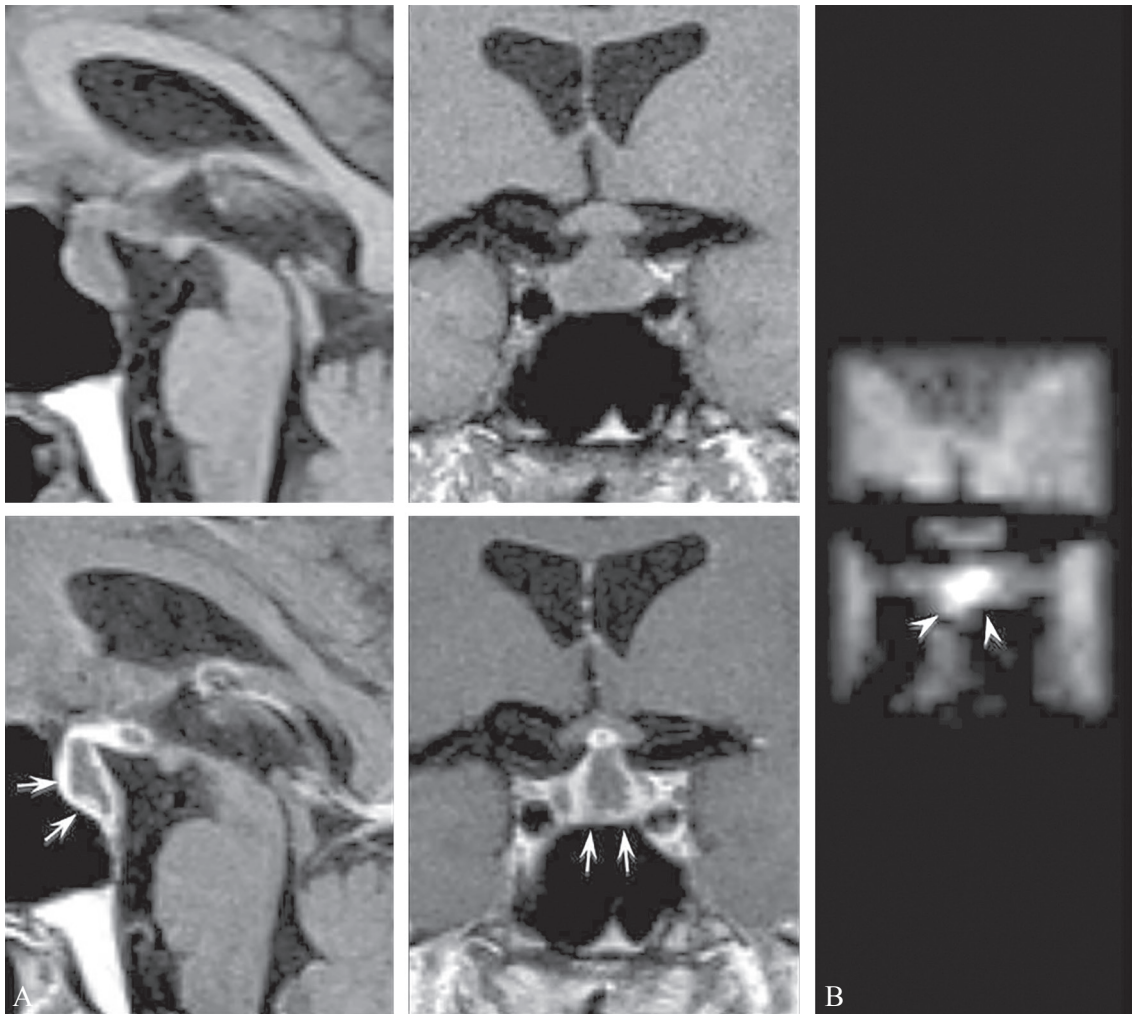

Figure 2.—Pituitary abscess. Brain MRI in a man suffering from panhypopituitarism. A) The pituitary gland and stalk are thickened and show striking ring-like enhancement after contrast medium administration (arrows); B) coronal diffusion weighted imaging discloses hyperintensity of the necrotic core (arrowheads) and decreased apparent coefficient values (not shown) consistent with purulent material. The lesion improved dramatically after treatment with antibiotics but the panhypopituitarism persisted.

The pituitary abscess is commonly associated to sphenoid sinusitis. The MRI shows an enlarged pituitary gland and stalk with necrotic core and a striking peripheral ring-like contrast enhancement. The necrotic core appears hyperintense on diffusion weighted imaging due to the presence of purulent material (Figure 2).[10]

Iatrogenic "empty sella"

HH might result from pituitary tumor resection, especially when dealing with craniopharyngiomas and macroadenomas.[11] In these cases an enlarged but empty pituitary sella is the most common finding (Figure 3).

Radiation and chemotherapy, both isolated or after surgery might be associated with early or delayed HH in up to 80% of those evaluated at a pubertal age. Gonadotropin deficiency and delayed puberty are dose related and most likely in children who receive 40 Gy or more of radiation.[12]

Empty sella is easily detected by MRI as this tool depicts both the pituitary sella and the pituitary gland. Total or partial empty sella is defined according to the portion of the pituitary sella occupied by the pituitary gland (less than one third or less than two thirds, respectively). In some cases, neoplastic remnants, scar tissue and soft tissue used to prevent rhinoliquorrhea might mimic the presence of pituitary gland tissue. Pre-surgery MRI, pre and post-gadolinium sequences and laboratory findings usually help to differentiate these conditions.

Pituitary stalk lesions

Neoplastic and inflammatory/infectious lesions might affect the pituitary stalk. The subsequent impairment of the hypothalamic-pituitary axis due to functional disconnection commonly presents with hypogonadism. Pituitary stalk involvement lacks of pathognomonic morphological and signal pattern before and after contrast medium administration. The pituitary stalk usually appears thickened, with striking contrast enhancement while the physiological precontrast T1-hyperintensity of the neurohypophysis is usually absent. Treatable lesions (for example histiocytosis, lymphocytic hypophysitis, sarcoidosis or tuberculosis) often result in thinning of the pituitary stalk with volume loss of the adenohypophysis; the physiological T1 brightness of the neurohypophysis most often does not normalize and hormone deficit might persist (Figures 4, 5).[13]

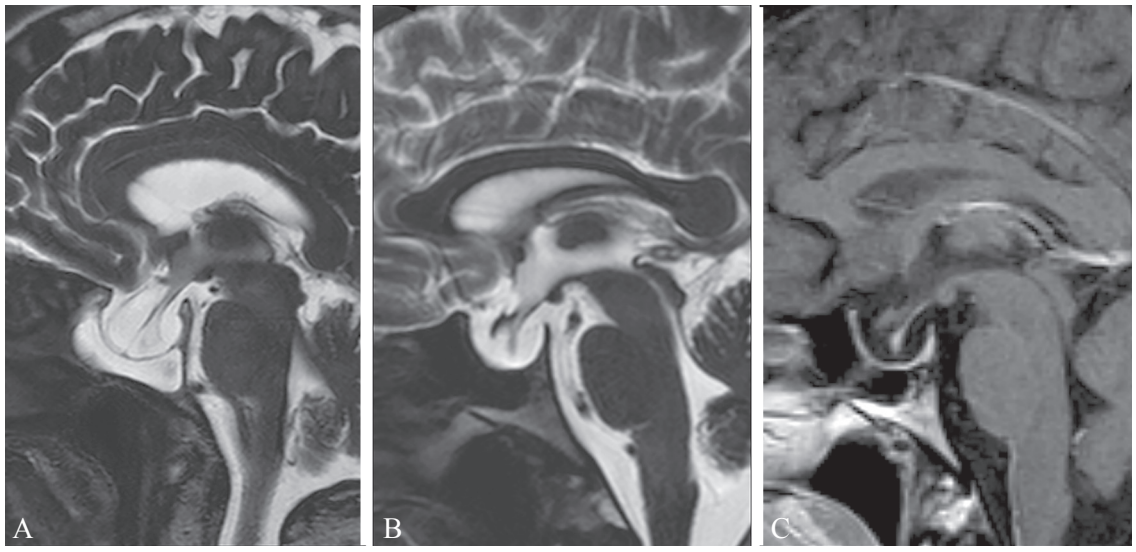

Figure 3.—Postsurgery empty sella. A) Midsagittal T2-weighted image showing postsurgery enlarged empty sella; B) midsagittal T2-weighted image showing the prolapse of the optic chiasm and III-ventricle floor within the empty sella; C) midsagittal contrast-enhanced T1-weighted image showing a thin pituitary gland along the floor of the pituitary sella.

Pituitary trauma

Traumatic brain injury might cause significant insufficiency of the anterior and posterior pituitary gland. Persistent gonadotropin deficiency has been detected in up to 44% of those with history of severe head trauma [14] but hormonal function might restore during follow-up.[12]

Even though a hypothalamic-pituitary gland axis dysfunction is usually considered

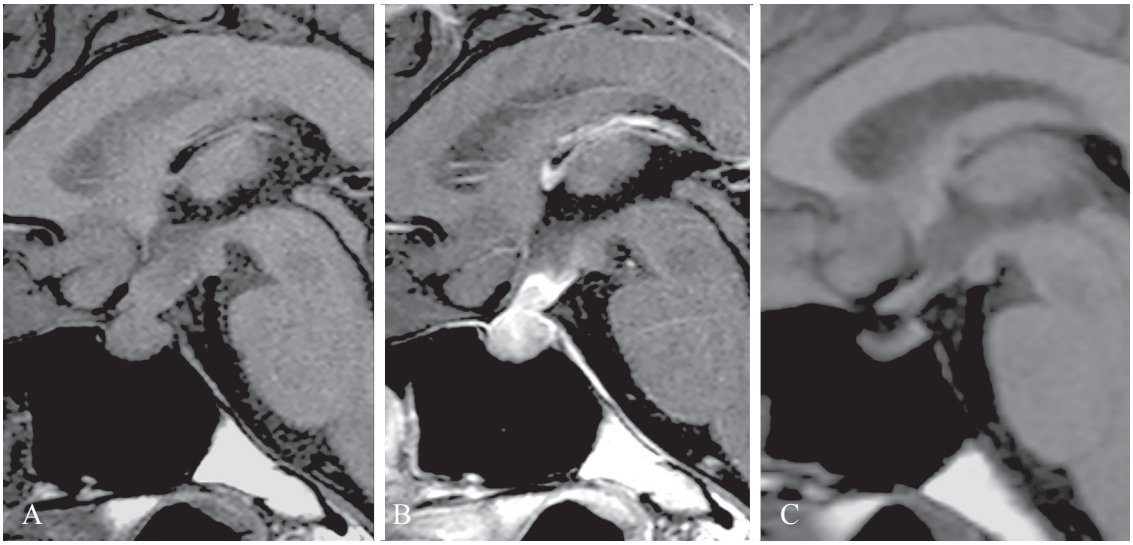

Figure 4.—Histiocytosis X. Brain MRI, midsagittal T1-weighted images of a 17-year-old girl affected with histiocytosis X. A) The pituitary gland and the pituitary stalk are thickened while the hyperintensity of the neurohypophysis is not recognizable; B) after contrast medium administration the pituitary gland and stalk show striking enhancement; C) one year later the pituitary gland and stalk have shrunken and the pituitary sella appears relatively empty.

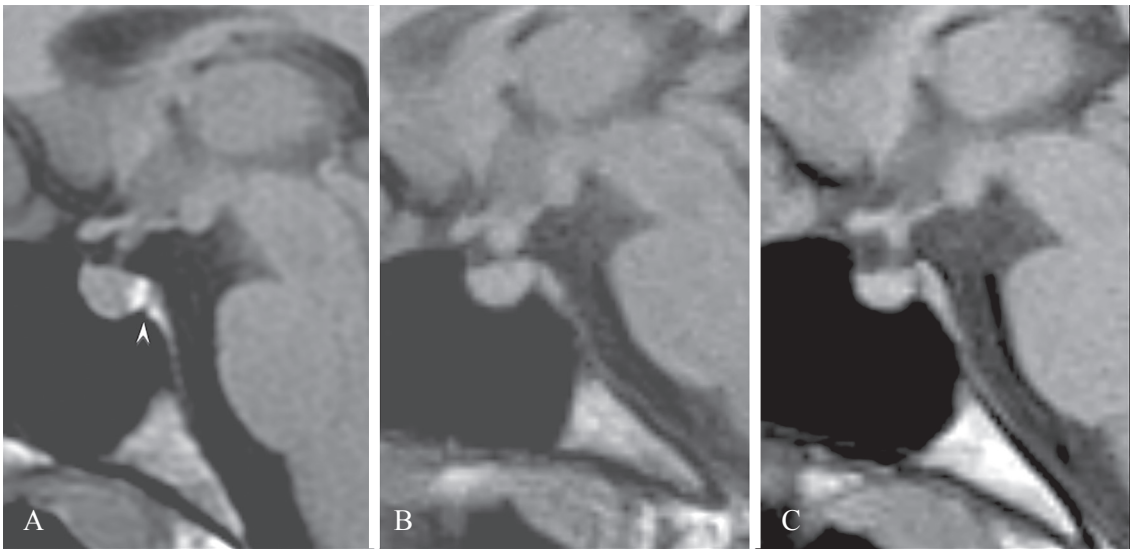

Figure 5.—Hypophysitis. Midsagittal T1-weighted images of a 21-year-old woman affected from hypophysitis. A) Presymptomatic brain MRI performed because of dizziness showing a normal pituitary gland (note the physiological hyperintensity of the neurohypophysis, arrowhead); the pituitary stalk distal narrowing is partially due to slight tilting of the image; B) MRI performed 4 months later because of diabetes insipidus showing pituitary stalk thickening while the hyperintensity of the neurohypophysis has disappeared; C) MRI performed one year later: the pituitary gland volume is slightly decreased while the pituitary stalk has partially normalized, the hyperintensity of the neurohypophysis is still absent.

the cause of post-traumatic HH, MRI of the pituitary gland and stalk mostly appears normal.[15] In contrast, cortical frontal-basal and temporal-polar contusions or subsequent degenerative cortical-subcortical changes on conventional imaging, skull fractures on CT, acute or subacute diffuse axonal injury on DWI and hypointense hemosiderin deposits on T2* or SWI sequences are typical concomitant hallmarks in neuroimaging studies.

Hypogonadotropic hypogonadism in inherited diseases

The inherited conditions that might present HH are listed in Table II.

Kallmann Syndrome

Kallmann Syndrome (KS) is a rare inherited disorder (affecting about 1/10.000 males and 1/40.000 females), clinically characterized by the association of HH and hypo/anosmia. Despite its low incidence, KS is the most common inherited condition associated with HH.[16] KS is related to mutations of several genes (KAL1, FGF8/FGFR1, PROK2/PROKR2, CHD7, NELF, HS6ST1 etc.) involved in the intrauterine migration process of olfactory axons and gonadotropin-releasing hormone (Gn-RH) neurons from the olfactory placode to the hypothalamus.[17] The failure of the migration process results in hypo/aplasia of the rhinencephalon (olfactory bulbs and tracts) and in altered gonadotropic axis function with low levels of sex hormones. In addition, distinctive KS brain and anterior cranial fossa bone changes might be detected by MRI and CT.[18, 19] The most known morphological brain feature is the reduction in depth and length of the olfactory sulcus, though concomitant fairly symmetric changes in the contiguous orbitofrontal sulcus and orbital-frontal regions (gyrus rectus, medial orbitofrontal gyrus) have been recently shown in KS male patients (Figures 6, 7).[19,20] The spatial and volumetric relationship between abnormal olfactory bulbs and forebrain morphological changes represents an intriguing model of genetically-driven developmental brain abnormalities and highlights the pivotal role of rhinencephalon in the forebrain morphogenesis.[21] Olfactory bulb and sulcus abnormalities are best investigated with coronal images at the level of the anterior cranial fossa. As these images might not be included in the standard pituitary MRI protocol, olfactory bulb investigation should be specifically requested whenever KS is suspected. KS patients have also been anecdotally reported to present with midline head and brain abnormalities such as palatal cleft, corpus callosum dysgenesis, Dandy-Walker malformation, holoprosencephaly and empty sella.[22] A possible association between KS and multiple sclerosis has been also reported [23] unveiling the wide spectrum of KS associated brain abnormalities. Some changes might be associated to specific subsets of KS patients. For example, cortical thickness decrease has been shown close to the hand motor cortex in KS patients with bimanual synkinesis (*i.e.* involuntary movements mirroring contralateral voluntary hand movements or mirror movements), a peculiar phenomenon that affect up to 40% of male KS patients, especially those with KAL1 and PROK mutations.[17]

From a diagnostic point of view, rhinencephalon and forebrain abnormalities are the hallmark of KS, but the phenotypic spectrum also includes rare KS patients with normal olfactory bulbs. In addition, in the same family there might be subjects with KS syndrome and subjects with isolated HH or isolated hypo/anosmia.[24]

In addition, a few KS patients might present

TABLE II.—*Inherited diseases with hypogonadotropic hypogonadism.*

Kallmann Syndrome
SOX2 Anophthalmia Syndrome
Bardet-Biedl Syndrome
Boucher-Neuhäuser and Gordon-Holmes syndromes
Prader Willi Syndrome
CHARGE Syndrome
Empty sella
Hypoplasia of the adenohypophysis
Idiopatic hypogonadotropic hypogonadism

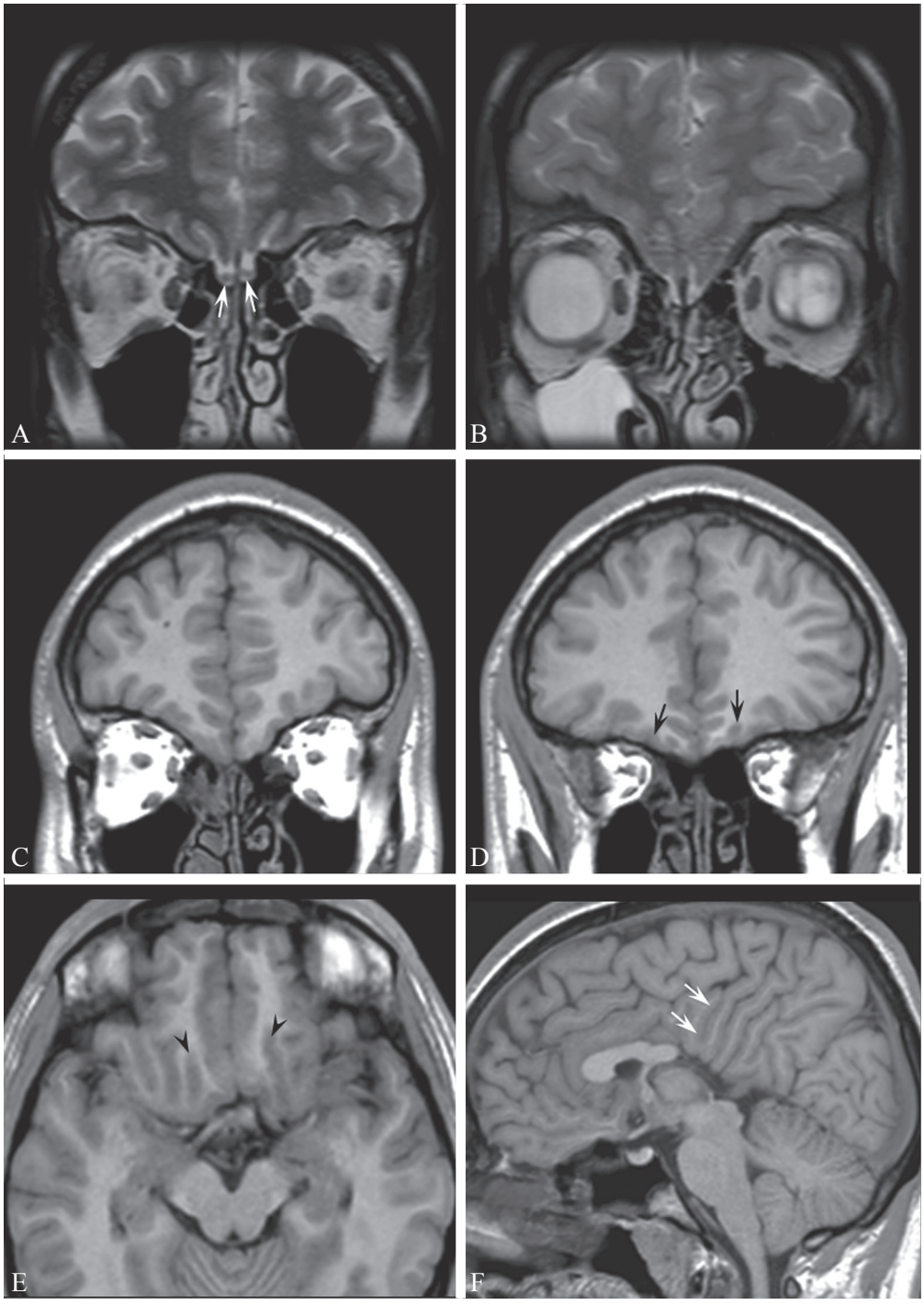

Figure 6.—Kallmann Syndrome, conventional MRI imaging. A) coronal T2-weighted image showing the normal appearance of the olfactory sulci and bulbs (arrows); B) coronal T2-weighted image in a Kallmann patient disclosing the aplasia of the olfactory bulbs with hypoplasia of the olfactory sulci; C, D) coronal T1-weighted images in a 32-year-old male Kallmann patient showing the absence of the olfactory bulbs and the hypoplasia of the olfactory sulci (black arrows) that appear shallow; E) axial T1-weighted image showing the hypoplasia of the olfactory sulci that appear short and recognizable only in their posterior portion (arrowheads); F) *corpus callosum* hypoplasia with absence of the splenium; note the radially oriented sulci at the level of the missing portion of the corpus callosum (white arrows).

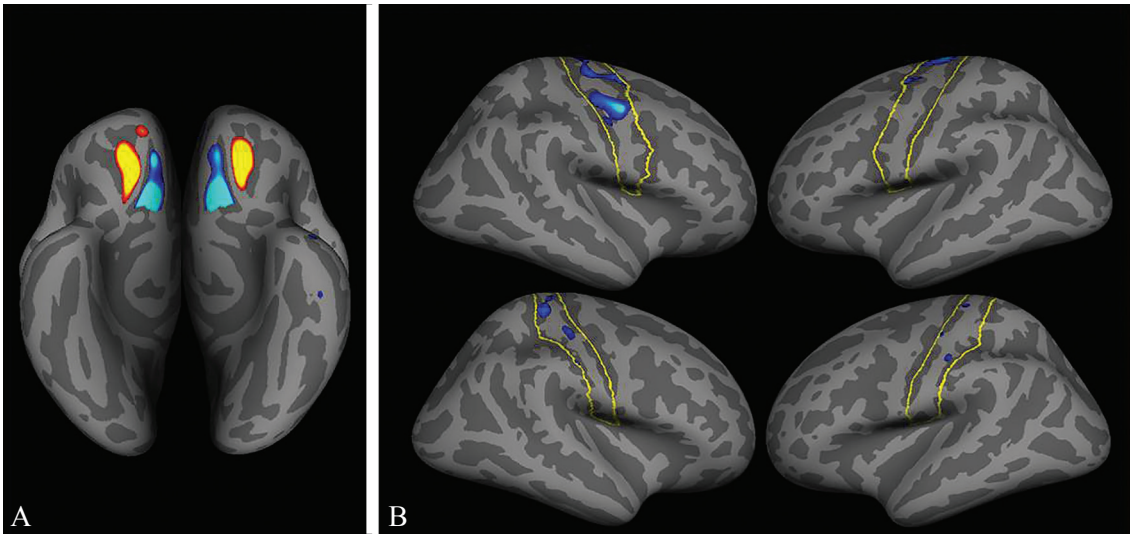

Figure 7.—Kallmann Syndrome: cortical abnormalities. A) Whole brain sulcation analysis showing the typical morphological cortical changes in Kallmann Syndrome at the level of the hypoplasic olfactory sulci (blue areas) with concomitant increased depth of the contiguous portion of the orbital-frontal sulci (yellow-red areas) B) decreased cortical thickness areas in Kallmann patients with mirror movements compared to Kallmann syndrome patients without mirror movements at the level of the primary motor (upper row) and somatosensory (lower row) cortices.

with sensorineural hearing loss, with or without skin and hair hypopigmentation. Beside olfactory bulbs hypo/aplasia and olfactory sulcus hypoplasia, neuroimaging usually detects bilateral semicircular canals development abnormalities and/or vestibular enlargement. About 30% of these patients harbor SOX10 gene mutations,[25] which are associated to the Waardenburg Syndrome, thus underlying the possible overlapping among different genetic syndromes (Figure 8).

SOX2 anophthalmia syndrome

This condition is characterized by anophthalmia and/or microphthalmia that is usually bilateral and severe. Ocular abnormalities also include coloboma or iris defects, optic nerve hypoplasia, retinal dysplasia, anterior segment dysgenesis (including sclerocornea or microcornea), glaucoma and cataract. Molecular genetic testing identifies a heterozygous SOX2 pathogenic variant in approximately 40% of

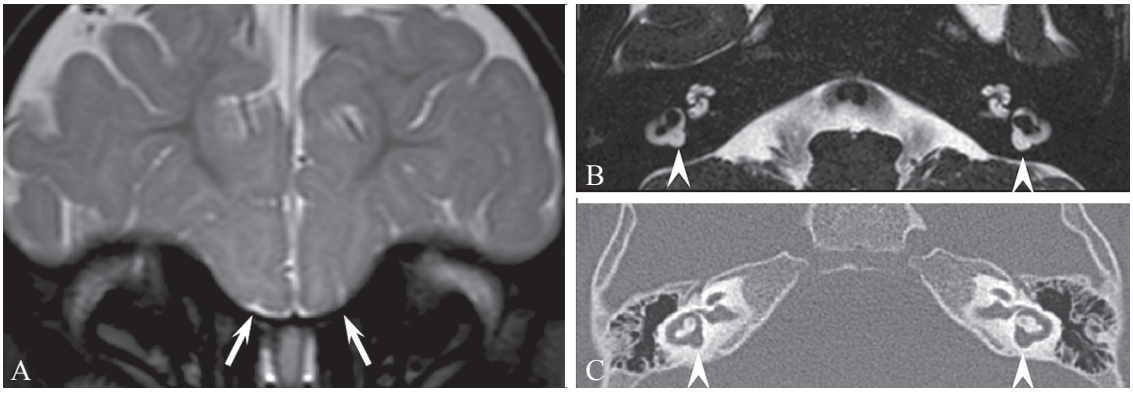

Figure 8.—Waardenburg Syndrome. A) coronal T2 image showing the absence of the olfactory bulbs (white arrows) and the hypoplasia of the olfactory sulci; B) high resolution axial T2 image revealing symmetric dysplasia of the vestibulum and posterior semicircular canals (arrowheads); C) CT image at the same level of B confirming the vestibular bone abnormalities.

individuals with bilateral anophthalmia/microphthalmia. Prevalence is approximately 1:250,000 (UK estimate). Other common findings include esophageal atresia, pituitary hypoplasia and HH in about 15% of cases.[26] HH is reported to be associated to Y110C and c905delC *SOX2* mutations Besides ocular abnormalities, neuroimaging of these patients might detect both hypothalamic-pituitary gland abnormalities (anterior pituitary hypoplasia, elongation of the anterior hypothalamus, *suprasellar teratoma* and ectopic neurohypophysis, hamartoma of *tuber cinereum*) and brain anomalies (*cavum septum pellucidum*, nonspecific periventricular white matter signal abnormalities, prominence of cerebrospinal fluid spaces in posterior fossa, prominent lateral ventricles, hypoplasia of the corpus callosum, hippocampal and parahippocampal malformations and heterotopic grey matter in the mesial temporal region.[27-31]

Bardet-Biedl Syndrome

Bardet-Biedl Syndrome (BBS) is a ciliopathy characterized by early onset *retinitis pigmentosa* (rod-cone dystrophy), polydactyly, obesity, renal abnormalities, cognitive impairment and HH. Recently, disorders of olfaction (anosmia, hyposmia) have been also described in BBS patients. Hypothalamus and pituitary gland are frequently abnormal [32] and tumor changes, hypophysis and/or sella hypoplasia, and Rathke cleft cyst have been reported. Brain imaging might reveal areas of abnormal gyration, cortical dysplasia, periventricular heterotopias,[33] supratentorial ventricle enlargement but in most cases conventional MRI is normal. Quantitative voxel based morphometry analysis showed contradictory findings in terms of global gray matter volume and regional atrophy of cerebellar hemispheres, occipital and parietal lobes, parahippocampal gyri, temporal lobes and orbitofrontal cortex.[34, 35]

Boucher-Neuhäuser and Gordon-Holmes syndromes

These forms are part of the spectrum of PNPLA6-associated diseases characterized by the co-existence of HH and progressive cerebellar degeneration. These forms differ according to the presence of chorioretinal dystrophy (Boucher-Neuhäuser) or spasticity (Gordon-Holmes).[36] The hypothalamus and the pituitary gland are usually grossly normal [37] though empty sella has been also reported. The majority of patients may present with atrophy of the superior and dorsal parts of the cerebellar vermis and, less frequently, of the cerebellar hemispheres. Brainstem and brain are mostly spared.[38]

Prader Willi Syndrome

It is a well-defined syndrome of childhood-obesity characterized by hyperphagia, HH, growth hormone deficiency, affecting about 1/10000-25000 children.[39] The genetic might be due to deletion on the paternal chromosome or due to maternal disomia. About 75% present subtle morphological abnormalities, mostly hypoplasia, of the pituitary gland. Concomitant intracranial abnormalities include ventriculomegaly (100%), incomplete insular closure (65%), sylvian fissure polymicrogiria (60%) and decreased brain tissue volume in the parietal occipital lobes (50%).[40] Recent studies have revealed a reduced cortical complexity and divergent brain developmental patterns according to the underlying genetics.[41, 42]

CHARGE (Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and development, Genital hypoplasia, Ear anomalies/deafness) Syndrome

CHARGE patients might show non-specific hypoplasia of the anterior pituitary gland.[43, 44] Notably, the majority of CHARGE patients with HH presents abnormal olfactory bulbs and sulci, thus sharing some of the features observed in Kallmann syndrome. Temporal bone CT or cone beam CT variably reveal semicircular canal, cochlear and ossicle chain dysplasia while cranial nerve abnormality detection requires high resolution T2-weighted sequences.[45, 46]

Empty sella

Empty sella syndrome is usually associated with GH deficiency, but it may rarely be associated with congenital or acquired hypogonadotropic hypogonadism.[47, 48] From a neuroimaging point of view, empty sella classification does not differ from that used in the acquired form (partial or total empty sella).

Hypoplasia of the adenohypophysis

Failure of the conjunction between the Rathke's pouch and the infundibulum, early traumatic transection of the pituitary stalk or ischemia of the hypothalamus are the most known hypotheses for the hypoplasia of the adenohypophisis.[49] Commonly these children present with growth hormone deficit, though panhypopituitarism has also been described (combined pituitary hormone deficiencies, CPHD). MRI typically shows a shallow pituitary sella, a variable decrease of the pituitary gland volume with medialization of the carotid siphons, a thin or absent pituitary stalk while the bright neurohypophysis position might range from the hypothalamus to the sella. According to our experience about 30% of children present with concomitant brain abnormalities encompassing septum pellucidum agenesia, optic nerve and/or chiasm hypoplasia, *corpus callosum* hypo-/agenesia, periventricular nodular heterotopia and polymicrogiria (Figure 9). Even though in

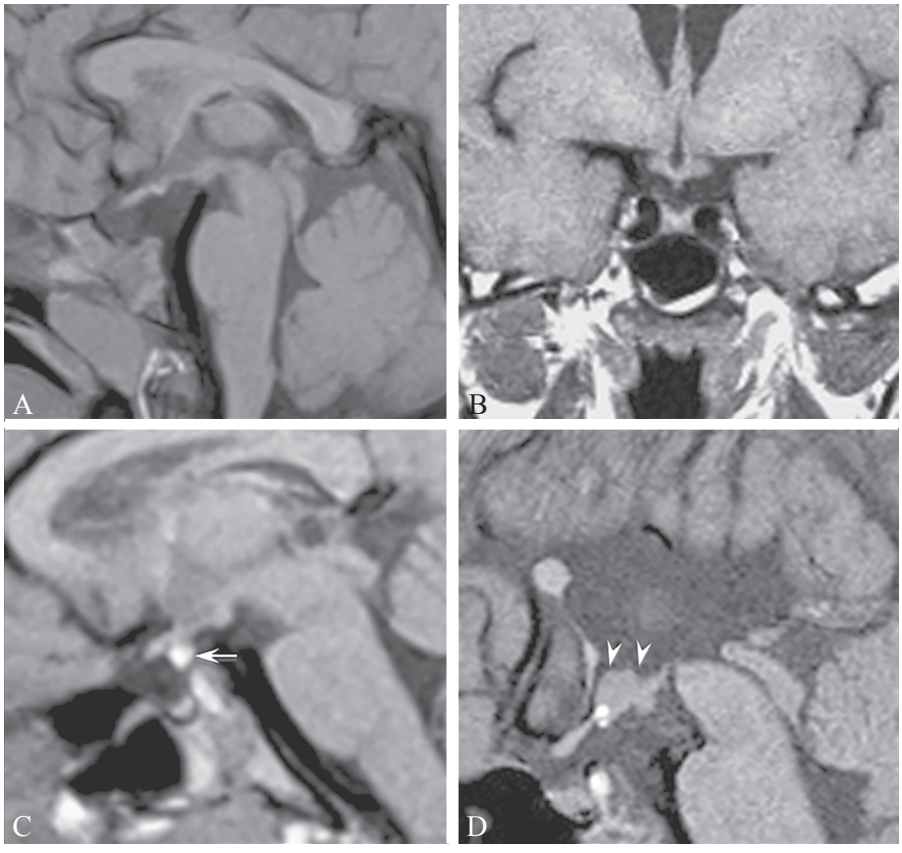

Figure 9.—Hypoplasic pituitary gland. A) Midsagittal T1-weighted image shows a shallow pituitary sella with a hypoplasic gland; the stalk is absent and a small ectopic neurohypophysis is present beyond the optic chiasm; B) coronal T1-weighted image disclosing a hypoplasic pituitary gland while the carotid artery are medialized; C) midsagittal T1-weighted image shows a prominent ectopic neurohypophysis along the short pituitary stalk (arrow); D) midsagittal T1-weighted image shows concomitant brain abnormalities that might be present in children with anterior pituitary hypoplasia such as corpus callosum hypo-/aplasia and hypothalamic hamartoma (arrowheads).

CPHD, the pituitary gland typically appears hypoplastic with absence of the bright spot of the neurohypophysis, enlarged adenohypophysis can be transiently found on initial pituitary MR imaging examinations during childhood.[50]

Conclusions

Several congenital and acquired conditions might be associated with HH. In some cases, the evaluation of the hypothalamic-pituitary region might directly reveal the cause of HH. In other cases, concomitant neuroimaging findings might address the underlying congenital or acquired condition and helps the physician in tailoring the proper management.

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