Pituitary stalk lesions

Demetra Rupp and Mark Molitch

Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Correspondence to Mark Molitch, MD, Professor of Medicine, Division of Endocrinology, Metabolism and Molecular Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
Tel: +1 312 503 4130;
e-mail: molitch@northwestern.edu

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Purpose of review

To describe the diverse causes of pituitary stalk lesions, their diagnosis, and treatment.

Recent findings

Pathology of the pituitary stalk is often distinct from disease processes that affect the hypothalamus and/or pituitary. Pituitary stalk lesions fall into one of three categories: congenital, inflammatory/infectious, and neoplastic lesions.

Summary

Stalk thickening may be found incidentally or when evaluating pituitary functional abnormalities. The precise cause must be looked for to enable the proper form of therapy of the underlying process. Hormone replacement is often also necessary.

Keywords

diabetes insipidus, hyperprolactinemia, hypopituitarism, infundibulum, pituitary stalk

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Introduction

Disease processes that affect the pituitary stalk can be distinct from processes that affect the hypothalamus or pituitary. Pituitary stalk lesions fall into one of three categories: congenital and developmental, inflammatory and infectious, and neoplastic [1••]. Pituitary stalk lesions are often discovered on magnetic-resonance image (MRI) either incidentally or carried out to investigate symptoms such as those caused by diabetes insipidus (DI).

Before reviewing abnormalities of the pituitary stalk, one must understand its anatomy and physiology. The normal pituitary stalk is widest superiorly and tapers inferiorly. It measures 3.5 mm near the median eminence, 2.88 mm at its midpoint, and 1.9 mm at its insertion at the pituitary. On MRI T1-weighted images, the signal intensity of the stalk is less than that of the optic chiasm and neurohypophysis. Deviation or tilt of the pituitary stalk can be seen without any underlying abnormality. With administration of gadolinium, the pituitary stalk enhances intensely because it does not have a blood–brain barrier [2].

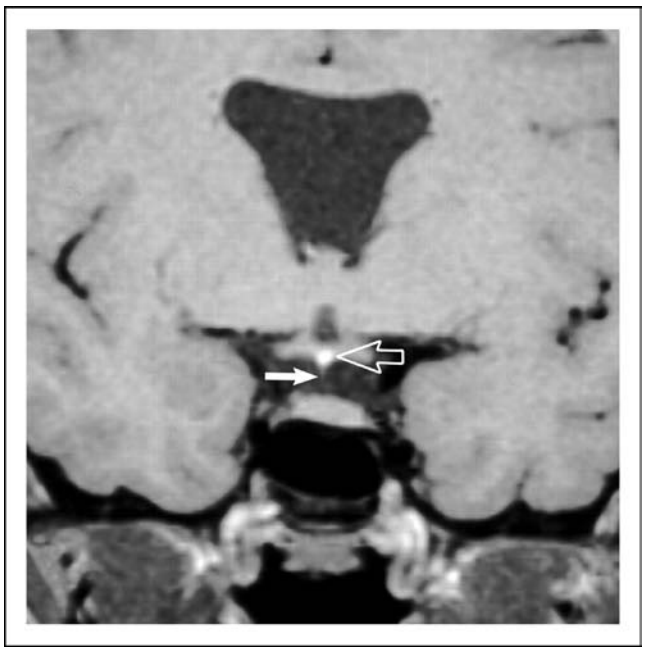
Within the pituitary stalk are the axons carrying vasopressin and oxytocin from the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus to the posterior pituitary. Interruption of this neural pathway, high in the stalk, can cause DI. Also within the stalk are the pituitary portal vessels that transport the various releasing and inhibiting factors collected in the venous plexus of the median eminence to the pituitary sinusoids. Interruption of these vessels causes loss of stimulation of all of the pituitary hormones, thereby causing hypopituitarism. As the hypothalamic influence on prolactin is predominantly inhibitory via dopamine, however, pituitary stalk disease commonly causes hyperprolactinemia along with deficiencies of the other hormones. As a consequence of this critical position of the pituitary stalk, patients who develop pathology involving the stalk commonly present with varying degrees of hypopituitarism, diabetes insipidus, and hyperprolactinemia.

Enlargement of the pituitary stalk greater than 2–3 mm on MRI is pathologic [3]. In a recent review of 65 infundibular lesions, the most common etiology was tumor or tumor-like lesions, which accounted for 37%, followed by congenital lesions, which made up 33% of lesions, and inflammatory and infectious causes, accounting for 30% of lesions [1••]. It is important to note that in this series, cases of Langerhans cell histiocytosis (LCH) were included in the neoplasm category, whereas in this review and in reports by other authors, LCH is included in the inflammatory/infectious category. This review will focus on the most common disorders affecting the pituitary stalk and is not meant to be inclusive of all possible abnormalities of the stalk.

Congenital lesions

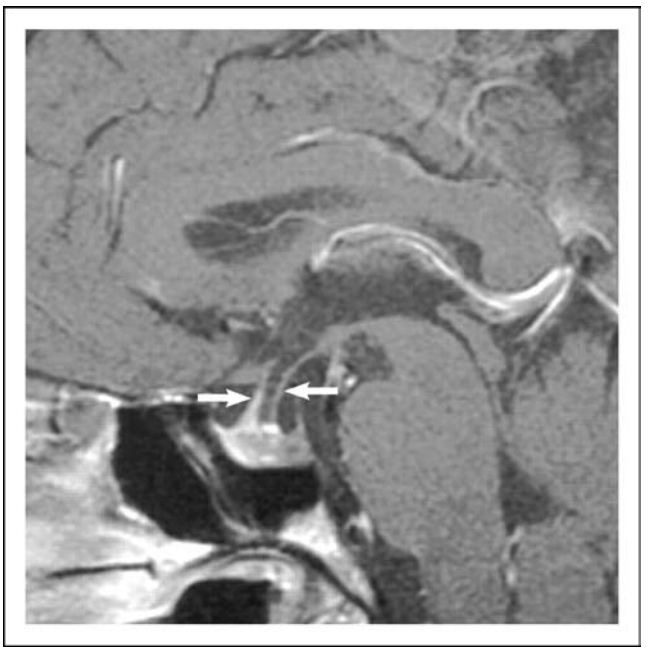
In the series of Hamilton *et al.* [1••], pituitary hypoplasia was the most common abnormality of the pituitary stalk in children and was found in five adults as well. Clinically, patients present with short stature because of growth hormone (GH) deficiency. On MRI, these patients can have a hypoplasic, absent, or a short, thickened stalk and an ectopic posterior pituitary (Fig. 1) [1••].

Figure 1 Pituitary hypoplasia



Seventeen-year-old patient with growth hormone deficiency and anosmia. Coronal unenhanced T1-weighted image: ectopic neurohypophyseal T1 hyperintensity (open arrow) and pituitary stalk is markedly attenuated (solid arrow). Reproduced from [1••].

Figure 2 Stalk duplication



Hypophyseal duplication in 69-year-old asymptomatic man. Arrows show pituitary and pituitary stalk duplication. Reproduced from [1••].

Pituitary stalk interruption syndrome is characterized by the following: an ectopic posterior pituitary, a hypoplastic anterior pituitary, and lack of or significant thinning of the pituitary stalk. On MRI, the ectopic posterior pituitary appears as a high-signal nodule in the area of the infundibular recess of the third ventricle. GH deficiency is a common feature; however, patients can have other anterior hormone deficiencies as well. Approximately 60% of children with idiopathic GH deficiency have an ectopic posterior pituitary. The etiology of pituitary stalk interruption is not completely understood. Several theories have been proposed including trauma or hypoxic injury to the stalk during delivery or disordered embyrogenesis of the hypothalamus and pituitary. Of note, there are reports of normal individuals found to have an ectopic posterior pituitary [4].

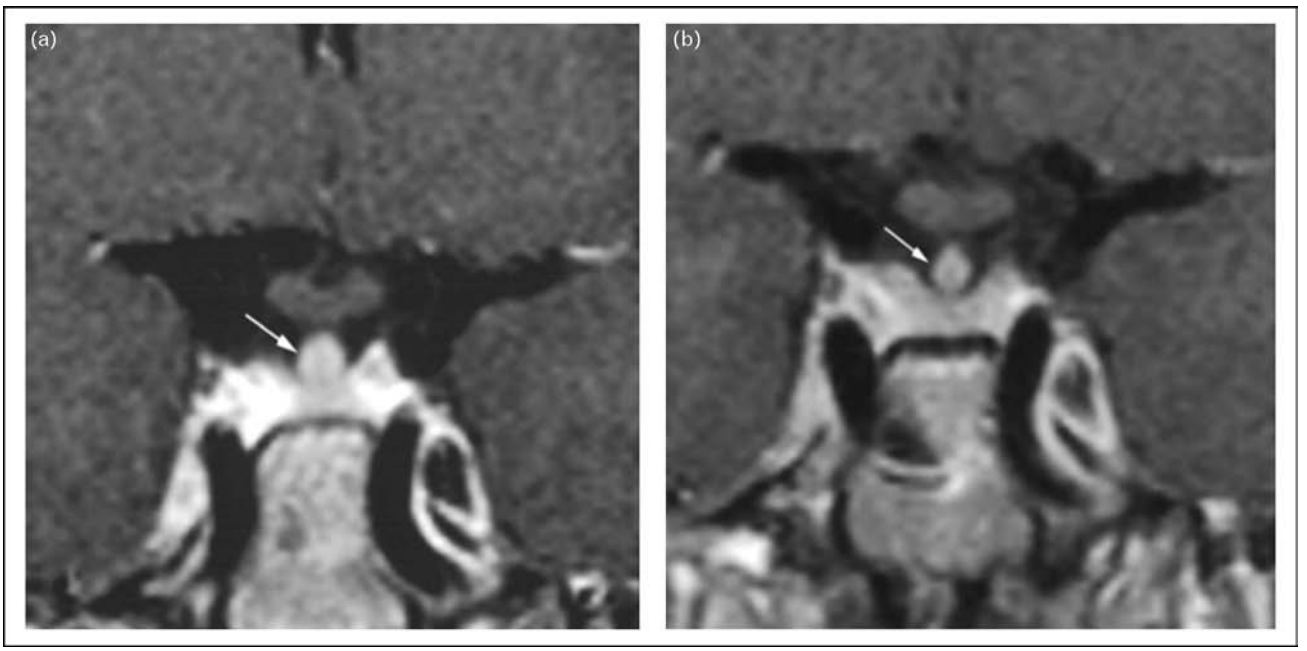
Another rare congenital anomaly, septooptic dysplasia, is characterized by midline forebrain abnormalities, optic nerve hypoplasia, and hypopituitarism. On an MRI of a patient with septo-optic dysplasia, one may see lack of an infundibulum, anterior pituitary hypoplasia, and an ectopic or undescended posterior pituitary. Clinically, GH deficiency is seen first, followed by deficiencies of thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) [5]. This phenotype has been found in patients with a mutation in the pituitary transcription factor HESX1. This disorder, however, has also been associated with maternal drug abuse during pregnancy and young maternal age. These factors have been postulated to cause vascular disruption during embryogenesis and result in septo-optic dysplasia [6].

Duplication of the pituitary, including the stalk has been reported (Fig. 2) [1••]. These cases are often associated with midline facial abnormalities and many of these patients die in infancy [1••]. Kandpal *et al.* [7] reported a case of a patient found to have two pituitary stalks but one pituitary, suggesting that this case may be a less severe form of pituitary duplication, thereby allowing the patient to survive and reach adult age.

Inflammatory and infectious lesions

Lymphocytic hypophysitis is an autoimmune condition involving the pituitary with a predilection for occurring in premenopausal women. When the inflammation is limited to the infundibulum and posterior lobe, the term lymphocytic infundibuloneurohypophysitis (LINH) is used. LINH is the most common inflammatory cause of pituitary stalk abnormalities [1••]. MRIs of patients with LINH will show thickening of the pituitary stalk, loss of the tapering at the pituitary insertion, and marked enhancement with gadolinium (Fig. 3) [8]. Furthermore, the normal enhancement of the neurohypophysis is absent on MRI, and clinically DI is present [8]. If the adenohypophsis is also involved, anterior pituitary deficiencies can occur. Corticotropin is the most common

Figure 3 Lymphocytic infundibuloneurohypophysitis

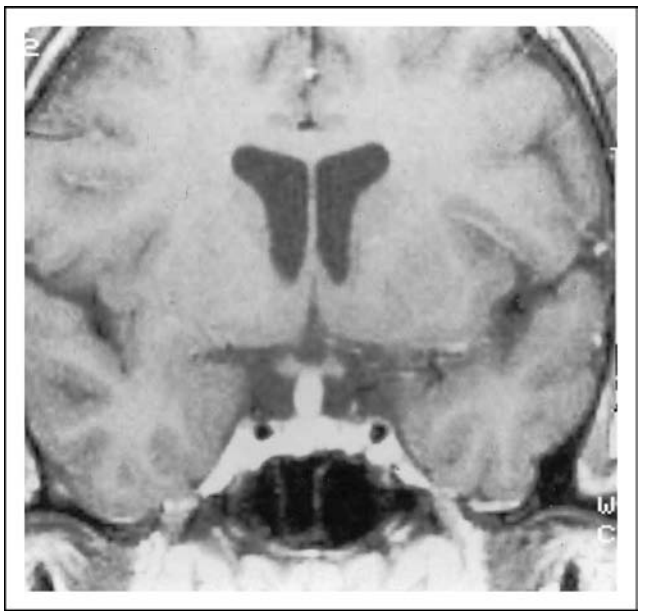


Gadolinium-enhanced coronal T1 magnetic-resonance images show pituitary stalk enlargement in a patient with lymphocytic infundibuloneurohypophysitis at (a) presentation and (b) 4 years later, which shows reduction in size of the pituitary stalk. Reproduced from [8].

anterior pituitary hormone affected, followed by thyrotropin, gonadotropins, and prolactin [9]. Pathologic examination of tissue in these patients shows lymphocytic infiltration [8]. In LINH, the inflammation can be self-limited and regression of the lesion can be seen on follow-up imaging. DI, however, tends to be permanent, likely because of neuronal damage [8]. In classic lymphocytic anterior pituitary hypophysitis, peripartum women are preferentially affected. In LINH, however, there may be a male predominance and the mean age of occurrence is 47 years [8]. It is thought that some cases of idiopathic DI may be cases of LINH. This hypothesis is supported by the presence of autoantibodies to vasopressin-secreting hypothalamic cells found in 31% of patients with idiopathic DI [10]. DeBellis *et al.* [11] noted that in patients with idiopathic DI, the thickness of the pituitary stalk correlated with the antivasopressin titers. The diagnosis of LINH is made based upon clinical, laboratory, and imaging findings; however, a definitive diagnosis can only be made with biopsy. Given the risks associated with pituitary biopsy, this is not done unless malignancy needs to be excluded. Glucocorticoids can be used to treat LINH. Kristof *et al.* [12] showed that high doses of methylprednisolone improved anterior pituitary function and DI. They also reported shrinkage of the sellar mass and pituitary stalk. Furthermore, the response to glucocorticoids was more pronounced in those with disease duration less than 6 months. Improvement in MRI findings occurred in the majority of patients within 6 weeks to 6 months of treatment [12]. There are other reports, however, in which the use of glucocorticoids resulted in little or no improvement in symptoms, hormone secretion, or MRI appearance. In case reports of patients who did not respond to glucocorticoids, azathioprine, methotrexate, and cyclosporine have been used successfully [8]. Overall, the utility of high dose glucocorticoids and immunomodulatory drugs in treatment of hypophysitis is controversial.

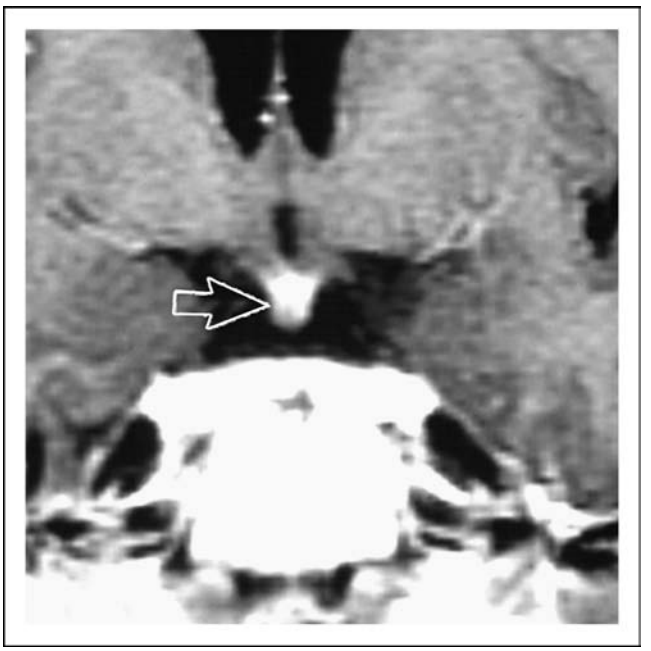
Langerhans cell histiocytosis (LCH) is a disorder that involves the skin, bones, orbit, lungs, and central nervous system (CNS). Granulomas are formed from a proliferation of histiocytes. These granulomas can be found in the hypothalamus and infundibulum [9]. DI is reported to occur in 5–50% of patients with LCH [13]. MRI reveals an asymmetrically thickened pituitary stalk or a hypothalamic mass that is isointense on T1 images, hyperintense on T2 images, and enhances with gadolinium (Fig. 4) [14]. Loss of posterior pituitary enhancement is seen as well [9,15]. There is disagreement as to whether or not LCH should be categorized as a tumor or as an inflammatory process. LCH is more common in children but can occur in adults as well. Kaltsas *et al.* [16] followed 12 patients with LCH and DI for a median of 11.5 years after the diagnosis of DI to determine the progression of anterior pituitary and nonendocrine hypothalamic dysfunction. They found that the majority of patients developed at least one other pituitary hormone deficiency; GH deficiency was the most

Figure 4 Langerhans cell histiocytosis



Eighteen-year-old woman with normal growth and development, who developed amenorrhea and galactorrhea 1 year previously, and then sudden onset of polyuria and polydipsia. Reproduced from [14].

Figure 5 Sarcoidosis



Thirty-six-year-old man with sarcoidosis. Axial image of contrast-enhanced T1-weighted images of the pituitary stalk. Reproduced from [1••].

common followed by gonadotropin, ACTH, and TSH deficiencies. In order to make the diagnosis of LCH, one must search for extracranial manifestations of LCH with a radiographic skeletal survey, skull series, chest radiograph, and bone scan so that these lesions can be biopsied. LCH can be treated with local radiotherapy (1000–2500 cGy) alone or with chemotherapy (etoposide, vinblastine, and/or cyclosporine). Treatment results in partial or temporary radiologic improvement; however, hormonal deficiencies do not improve [16].

Another inflammatory process affecting the pituitary stalk is sarcoidosis (Fig. 5) [1••]. CNS involvement occurs in approximately 5% of patients with sarcoidosis and precedes other symptoms in 30% of cases. DI occurs in 25% of patients with CNS sarcoid [17]. MRI can show pituitary stalk thickening and enhancement as well as pituitary enlargement. Periventricular lesions and leptomeningeal enhancement can be seen in sarcoidosis and this can help distinguish it from lymphocytic hypophysitis [17]. Sarcoidosis of the hypothalamus, pituitary stalk, and posterior pituitary is associated with DI, hyperprolactinemia, and decreased levels of testosterone, LH, and FSH [18]. Measurement of cerebral spinal fluid (CSF) angiotensin converting enzyme (ACE) may aid in the diagnosis of CNS sarcoid. A chest radiograph is also warranted to look for characteristic pulmonary lesions. In the series of Bullmann *et al.* [17], five patients with sarcoidosis and central DI were treated with prednisone (0.5–1.5 mg/kg) and radiologic improvement was seen with therapy; however, none recovered from DI.

Wegener's granulomatosis is a systemic vasculitis that causes necrotizing granulomas in the upper and lower respiratory tracts and kidneys. The mean age of onset is 40 and there is a 2 : 1 male to female predominance [19]. Cerebral and meningeal involvement is not common and occurs in 2–8% of patients [20]. Involvement of the pituitary can occur via direct extension from nasal, paranasal, or orbital disease, from remote granulomatous involvement, or from vasculitis of the hypothalamus. When the pituitary is involved, MRI reveals an enlarged pituitary with homogenous enhancement as well as thickening and enhancement of the pituitary stalk, and enhancement of the optic chiasm [9,20]. Clinically, patients most frequently have DI but hyperprolactinemia and panhypopituitarism have also been reported [9]. Wegener's granulomatosis can be treated with glucocorticoids and/or cyclophosphamide [19]. Czarnecki and Spickler [19] reported a case of Wegener's granulomatosis of the infundibulum in which treatment with high dose steroids resulted in remission of the patient's DI, hyperprolactinemia, and MRI findings. Finally, in the series of Murphy *et al.* [20], one patient with Wegener's and pituitary involvement had remission of DI after treatment with anti-CD 52.

Tuberculosis is an infectious entity that can affect the pituitary stalk via formation of a tuberculoma or granulomatous involvement. Tuberculomas are rare and occur

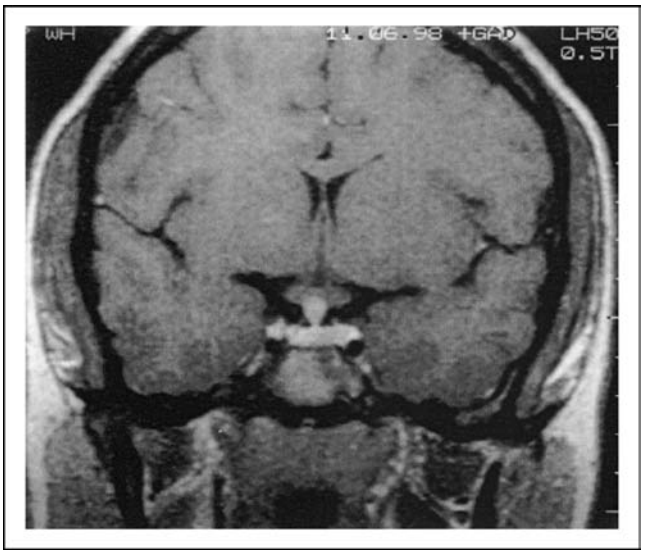
more frequently in women. Prior to the availability of antibiotics for tuberculosis, tuberculomas comprised 50% of intracranial tumors in adults. In industrialized nations, this rate is now 0.25–4% [21]. Imaging can reveal involvement of the paranasal sinuses or pititary fossa, thickening of the pituitary stalk, and adjacent meningeal enhancement. Pituitary abscesses may also have peripheral contrast enhancement. Furthermore, tuberculomas are isointense-to-hypointense on T1-weighted images and hyperintense on T2-weighted images. These signal characteristics, however, are not unique to tuberculomas and can be seen in pituitary adenomas as well [9]. Lam *et al.* [22] retrospectively studied 49 patients with a history of tuberculous meningitis in childhood for the development of pituitary deficiencies. Ten patients (20%) had abnormal pituitary function, GH deficiency being seen most commonly (seven of 10 patients), followed by gonadotropin deficiency (five of 10 patients), corticotropin deficiency (one of 10 patients), and hyperprolactinemia (one of 10 patients) [22]. Interestingly, none of the patients developed diabetes insipidus. Furthermore, five patients had abnormal MRI findings including enhancing lesions in the hypothalamus, the pituitary stalk, or suprasellar cistern and pituitary atrophy of varying severity. The authors postulated that the areas of abnormal enhancement likely represent granulation tissue, and that with increasing time from the infection, fibrosis occurs, and that the areas of fibrosis do not enhance [22]. Tien *et al.* [3] retrospectively studied the MRIs of 26 patients who presented with DI. Of these patients, one patient presented with acute onset DI and seizures. This patient's MRI showed a uniformly thickened pituitary stalk, diffuse enhancement in the basal cisterns, and a spinal epidural abscess was noted as well. CSF examination confirmed the diagnosis of tuberculosis. Of note, after treatment with antituberculosis medications, the patient's DI resolved. In summary, tuberculosis can affect the infundibulum via the presence of a tuberculoma, granulomatous involvement, or postinfectious fibrosis in the region.

Whipple's disease is a rare disorder caused by infection with the bacterium *Tropheryma whipplei*. There are only 1000 cases reported and this disease typically affects Caucasian, middle-aged men. Whipple's disease has been reported to cause pituitary stalk thickening. Treatment with steroids or tumor necrosis factor antagonists can exacerbate the condition [23]. Patients are treated initially with streptomycin and penicillin G or ceftriaxone for 2 weeks, followed by oral trimethoprim-sulfamethoxazole because it crosses the blood–brain barrier. In a patient with a history of Whipple's disease treated with tetracycline, which does not cross the blood–brain barrier, and a new pituitary stalk or hypothalamic lesion, one must suspect a recurrence of Whipple's disease in the CNS.

Neoplasms

Germ cell tumors account for 7.8% of pediatric brain tumors and are the most common brain tumor associated with DI in children [24,25]. Germinomas typically present as a hypothalamic or pineal mass, however, they can also manifest as isolated pituitary stalk thickening (Fig. 6) [26]. Patients typically present with germinomas in the first two decades of life and both sexes are affected equally. Germinomas can secrete human chorionic gonadotropin (hCG) or alpha-fetoprotein (αFP), which if present can assist in making the diagnosis. The clinical manifestations of suprasellar germinomas include DI, hypopituitarism, and vision changes [26]. Typically, germinomas progress within 1.3 years of the discovery of pituitary stalk thickening, and within 2.5 years of the diagnosis of DI [24]. Mootha *et al.* [25] reported nine pediatric patients with idiopathic, central DI, isolated pituitary stalk thickening, and anterior pituitary hormone deficiencies that were found either at presentation or during follow-up. Pituitary stalk lesions were biopsied in seven of nine patients when their MRIs showed extension of the lesion or when the CSF was positive for hCG. In six (of seven) patients, the biopsy was positive for germinoma. Mootha *et al.* recommend follow-up MRIs every 3–6 months and biopsy if the lesion enlarges or if CSF or serum hCG or αFP are positive. If biopsy cannot be done due to location or if the patient has positive tumor markers, a PET scan can be used to assist in making the diagnosis. The PET scan will be positive if the patient has a germ cell tumor, and can help distinguish from processes such as histiocytosis

Figure 6 Germinoma



T1-weighted coronal MRI with 17-year-old woman with germinoma, MRI shows pituitary stalk thickening. Reproduced from [26].

and granulomatous disorders that are not metabolically active [26]. In terms of treatment, germinomas are highly radiosensitive. Treatment with radiation, however, results in 5-year recurrence rates of 10–40% [26]. Adjuvant chemotherapy can be given to reduce the radiotherapy doses and this can also reduce future neurocognitive dysfunction [26]. In children with idiopathic DI, therefore, the literature supports following them with serial brain MRIs and some authors also recommend assessment of tumor markers hCG $\pm$ αFP in the serum and CSF in order to make a diagnosis of a germinoma prior to the development of visual and neurological symptoms [24,25].

Metastases to the infundibulum were the most common neoplastic cause of infundibular lesions in the series of Hamilton *et al.* [1••]. The most common malignancies that result in pituitary metastases are breast and lung cancers. Pituitary metastases typically occur in older patients and are often locally invasive and have rapid growth [1••].

Primary tumors that can involve the pituitary stalk include gliomas such as astrocytomas, ependymomas, and pleomorphic xanthoastrocytomas [1••]. A newly characterized tumor, the tanycytoma, can also involve the pituitary stalk. Tanycytomas are hypothalamic–suprasellar tumors that are biologically aggressive and have a high rate of recurrence. These tumors have a tendency to encase the circle of Willis and prognosis in children is worse than in adults [27]. There are case reports of meningiomas that arise from the pituitary stalk. Complete resection confers a good prognosis. This also involves, however, removal of the pituitary stalk; therefore, patients require lifelong hormone replacement [28].

Pituicytomas (also called infundibulomas) are benign tumors that typically arise from the infundibulum. They have a tendency to occur in men in the third to fifth decades of life. Clinically, patients present with panhypopituitarism and fatigue. On MRI, pituicytomas have the same isodensity as normal brain tissue, they enhance homogenously with contrast, and there is absence of the normal T1 hyperintensity of the posterior lobe. These tumors expand into the suprasellar cistern and can cause optic nerve compression. Pituicytomas do not cause enlargement of the sella and this fact can help distinguish them from pituitary adenomas. Treatment for pituicytomas is surgical resection, and long-term follow-up has shown no recurrence after total resection [1••].

Leukemia (chronic myelogenous leukemia and acute myelogenous leukemia) and lymphoma have been reported to involve the pituitary stalk. Typically the diagnosis is known by the time infundibular involvement occurs. Patients with leukemia and pituitary stalk thickening, clinically, also have DI [1••].

Conclusion

In conclusion, pituitary stalk lesions have diverse causes. The abnormalities of the pituitary stalk fall into three main categories: congenital lesions, inflammatory/infectious lesions, and neoplasms. Understanding the diverse pathology that can affect the pituitary stalk is imperative in making the correct diagnosis and implementing the proper treatment. In many cases, the diagnosis may not initially be apparent. The literature, therefore, supports following patients with pituitary stalk lesions and DI to determine if new symptoms arise and with imaging to determine if the lesion progresses over time.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 399).

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