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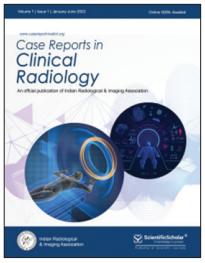

Case Series

Pituitary hypointensity: Hemochromatosis as an overlooked cause of hypogonadotropic hypogonadism

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ABSTRACT

Hemochromatosis (HFE) is caused by abnormal accumulation of iron in the parenchymal cells, eventually leading to dysfunction of the involved organs. It can be either primary (or genetic) or secondary (or acquired). Due to the presence of the blood-brain barrier (BBB), iron deposition in the central nervous system is rare but structures lying outside the BBB such as choroid plexus, pituitary, and circumventricular organs are commonly involved. This case series describes 2 cases of pituitary HFE, both presenting with hypogonadotropic hypogonadism, which were diagnosed by magnetic resonance imaging (MRI). In both the cases, T2-weighted and susceptibility-weighted imaging (SWI) images demonstrated markedly low signal in anterior pituitary and choroid plexus with patchy areas of non-enhancement seen on post contrast images. Hence, contrast-enhanced MRI with SWI sequences should be used as non-invasive tool in patients suspected of pituitary gland iron overload.

Keywords: Pituitary hemochromatosis, Hypogonadotropic hypogonadism, Iron deposition, Magnetic resonance imaging

INTRODUCTION

Hemochromatosis (HFE) is caused by abnormal accumulation of iron in the parenchymal cells, eventually leading to dysfunction of the involved organs.[1] The liver, pancreas, heart, skin, and pituitary are some of the most common sites of iron deposition.[2-4] The presence of the blood-brain barrier (BBB) does not allow deposition of excess iron in the central nervous system (CNS), but structures lying outside the BBB such as choroid plexus, pituitary, and circumventricular organs are commonly involved.[5-9] Although, involvement of cortical surface and basal ganglia has also been reported.[5] Iron deposition in various organs leads to liver cirrhosis, diabetes mellitus, bronzing of the skin, cardiomyopathy, and hypogonadism.[1-4,10] We report two cases of pituitary HFE with involvement of choroid plexus, pituitary, basal ganglia, and dentate nuclei of cerebellum in the first case and involvement of choroid plexus and pituitary in second case.

CASE SERIES

Case 1

A 36-year-old male presented with complaints of decreased hair on beard and moustache. No associated comorbidities were noted. On blood examination, ferritin levels were raised to 1260.00 ng/mL (Normal for males: 17.9–464 ng/mL) with reduced total iron binding capacity of

150 ug/dL (Normal range: 265–497 ug/dL). The hormonal workup of the patient was normal. Contrast-enhanced magnetic resonance imaging (MRI) dynamic pituitary was done on Siemens MAGNETOM Verio 3T MRI machine. Anterior lobe of the pituitary gland appeared small in size for age of the patient. The gland appeared intermediate signal intensity on T1-weighted (T1W) and hypointense on T2-weighted (T2W) images [Figure 1a-b]. On dynamic post contrast images, there was normal enhancement of pituitary stalk with patchy areas of non-enhancement seen within the anterior pituitary gland [Figure 1c-d]. Posterior pituitary T1 hyperintense spot was seen at its expected location.

Bilateral symmetric T2 hypointense and T1 hyperintense signal in the globus pallidi of basal ganglia and the dentate nuclei of the cerebellum was noted. Few tiny blooming foci were seen in the globus pallidi of basal ganglia, bilateral temporal horns and trigones of lateral ventricle, and the dentate nuclei of the cerebellum [Figure 1e-f]. The findings raised suspicion of pituitary iron/hemosiderin deposition. Further, clinical laboratory correlation was suggested. Genetic workup confirmed mutation in *HFE* gene confirming the diagnosis of primary (genetic) HFE.

Case 2

An 18-year-old female, known case of thalassemia major, on repeated blood transfusions since childhood, presented with complaints of amenorrhea. On blood examination, ferritin levels were raised to 4500.00 ng/mL (Normal for females <50 years: 6.24–137 ng/mL) with reduced total iron binding capacity of 167 ug/dL (Normal range: 265–497 ug/dL). The hormonal workup of the patient was normal. Contrast-enhanced MRI dynamic pituitary with conventional MRI brain sequences was done on Siemens MAGNETOM Aera 1.5T MRI machine. The gland appeared intermediate signal intensity on T1W and hypointense on T2W images [Figure 2a-b]. On post-contrast images, there was normal enhancement of pituitary stalk with lack of enhancement seen within the anterior pituitary gland, [Figure 2c-d] suggesting changes related to pituitary HFE. Blooming seen along the choroid plexus of bilateral lateral ventricles [Figure 2e], third, fourth ventricle, along the foramen of Luschka and Magendie [Figure 2f] was seen likely suggesting iron deposition in clinical settings of thalassemia.

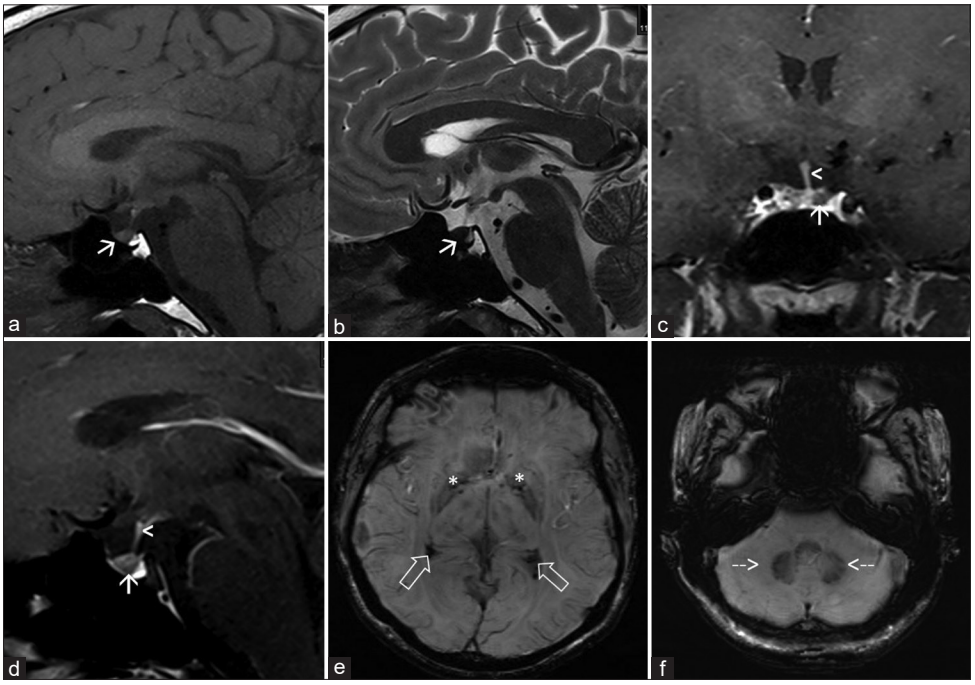

Figure 1: A 36-year-old male presented with features of hypogonadotropic hypogonadism. On contrast-enhanced magnetic resonance imaging dynamic pituitary. (a) T1 sagittal images showing small intermediate signal intensity anterior pituitary (white arrow) with normal hyperintense spot of posterior pituitary seen. (b) T2 sagittal images showing hypointense anterior pituitary (white arrow). (c and d) T1 coronal and sagittal post contrast images showing patchy areas of non-enhancement within anterior pituitary (white arrows) with normal enhancement of pituitary stalk (white arrowheads) seen. (e and f) Susceptibility-weighted imaging images showing blooming foci in bilateral globus pallidi (white asterisks), trigone of bilateral lateral ventricles (white open arrows), and bilateral dentate nuclei of cerebellum (white dashed arrows).

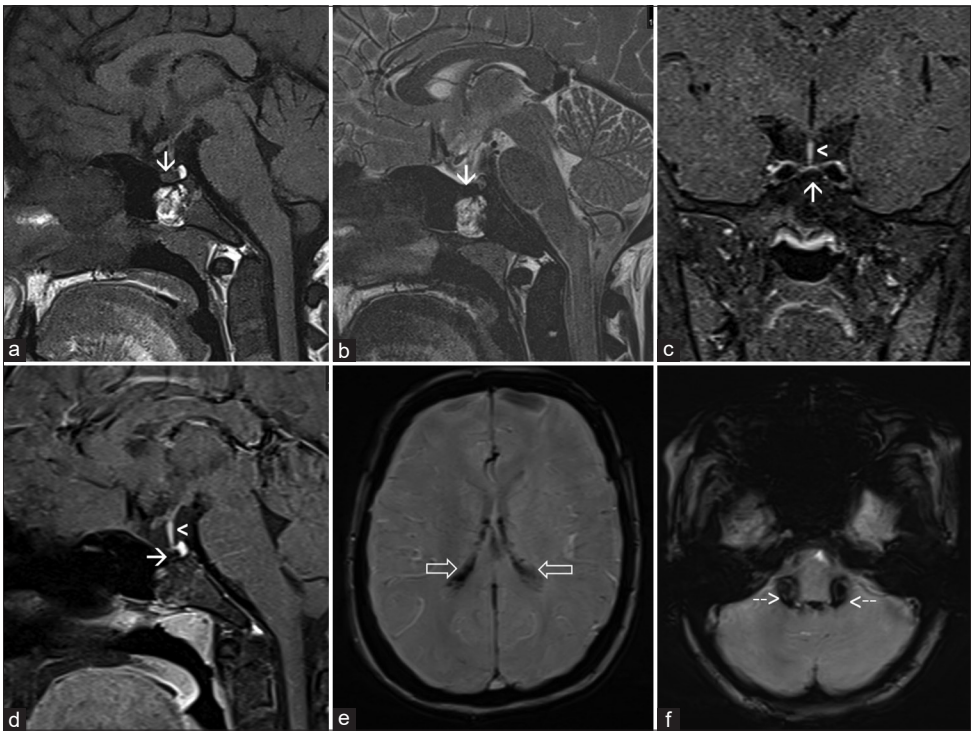

Figure 2: A 18-year-old female, known case of thalassemia major, on repeated blood transfusions since childhood, presented with complaints of amenorrhea. On contrast-enhanced magnetic resonance imaging dynamic pituitary. (a) T1 sagittal images showing small intermediate signal intensity anterior pituitary (white arrow) with normal hyperintense spot of posterior pituitary seen. (b) T2 sagittal images showing hypointense anterior pituitary (white arrow). (c and d) T1 coronal and sagittal post contrast images showing non-enhancement of anterior pituitary (white arrows) with normal enhancement of pituitary stalk (white arrowheads) seen. (e and f) Susceptibility-weighted imaging images showing blooming foci in bilateral lateral ventricles (white open arrows) and along the foremen of Luschka and Megendie (white dashed arrows).

DISCUSSION

HFE is a systemic disorder causing abnormal accumulation of iron in various organs of the body eventually leading to organ dysfunction. It can be either primary (or genetic) or secondary (or acquired). Primary (or genetic) HFE is most commonly caused due to mutation in *HFE* gene.[4] Secondary HFE is an acquired cause of iron accumulation most commonly associated with chronic disorders of erythropoiesis, treated with iron and blood transfusions.[1]

Iron plays an important role in cellular function and various physiological processes, such as the production of hemoglobin, oxygen transport, and adenosine triphosphate (ATP) generation. Humans have no physiologic pathway for iron excretion; hence, iron hemostasis is maintained by fine regulation of iron absorption, circulation, utilization, and storage.[2,3] Primary (or genetic) HFE, caused due to mutation in *HFE* gene, leads to dysregulation of iron absorption through interactions with transferrin and hepcidin, leading to systemic manifestations of iron overload.[4,10] Hemostatic iron balance requires only 1–2 mg of iron per day; however, chronic disorders of erythropoiesis treated with iron and blood transfusions lead to significant iron accumulation.

As discussed earlier, liver, pancreas, heart, skin, and pituitary are some of the most common sites of iron deposition.[2-4] The presence of BBB does not allow deposition of excess iron in the CNS, but structures lying outside the BBB such as choroid plexus, pituitary, and circumventricular organs are commonly involved.[5-9] The hypogonadism is caused due to deposition of iron in anterior pituitary leading to malfunctioning of the gonadotrophs with relative sparing of the posterior pituitary seen.[1,10]

MRI has been an effective imaging modality for evaluating iron deposition. Excess iron leads to local distortions in the magnetic fields and spin relaxations, resulting in shortening of T2 relaxation time, leading to signal intensity similar to the flow void of adjacent internal carotid artery.[11] Brain MRI with a gradient response echo (GRE) sequence has shown heightened sensitivity in detecting CNS HFE. Susceptibility-weighted imaging (SWI) is a 3D-GRE MRI sequence with high spatial resolution and phase post-processing that improves

Table 1: Differentials of suprasellar lesion showing decreased signal intensity on T2W images with the differentiating features.[4,13]

Differential diagnosis	Differentiating features
Pituitary hemochromatosis	History; biochemical correlation; decreased parenchymal enhancement with sparing of posterior pituitary and stalk.
Aneurysm	Continuous with internal carotid artery
Rathke's cleft cyst or other mass lesion (Craniopharyngeoma or calcification or hemorrhagic pituitary adenoma)	Focal lesion; abnormal pituitary contour; mass effect on adjacent structures
Melanoma	History

the detection of paramagnetic properties, making it more sensitive for detecting hemosiderin compared to traditional 2D-GRE MRI.[12] Considering the artifacts caused by the air-filled sphenoid sinus encasing the sella turcica, SWI may not be ideal for assessing the pituitary gland. The decreased parenchymal enhancement of the anterior pituitary with sparing of posterior pituitary and stalk has shown consistency with hemosiderin deposition secondary to HFE.[13]

The deposition of iron within the anterior pituitary leads to signal intensity changes on T2 and T1W imaging. However, diagnosing pituitary gland lesions can be challenging given the diversity of lesions involving the pituitary gland [Table 1].[4,13] HFE is the only clinical entity associated with decreased signal intensity on T2W images and raised serum ferritin levels (usually >1000 ng/mL).[4]

CONCLUSION

Considering diverse variety of lesions affecting the pituitary gland, adequate know how of the imaging manifestations along with clinical correlation is required to diagnose iron deposition in the pituitary gland. Hence, Contrast enhanced MRI should be used as primary non invasive tool in patients suspected of pituitary iron overload in setting of hypogonadotrophic hypogonadism.

TEACHING POINTS

1. The deposition of iron within the anterior pituitary leads to local distortions in the magnetic fields and spin relaxations, resulting in shortening of T2 relaxation time.
2. HFE is the only clinical entity associated with decreased signal intensity on T2W images and raised serum ferritin levels (Usually >1000 ng/mL).
3. The decreased parenchymal enhancement of the anterior pituitary with sparing of posterior pituitary and stalk has shown consistency with hemosiderin deposition, suggesting use of contrast-enhanced MRI as primary non-invasive tool in patients suspected of pituitary iron overload in setting of hypogonadotropic hypogonadism.

MCQs

1. Which of the following can cause pituitary HFE?
   a. *HFE* gene mutation
   b. Blood transfusions
   c. Both of the above
   d. None of the above

Answer Key: c

2. Which of the following is not an imaging finding of pituitary HFE?
   a. Non-enhancement of pituitary stalk
   b. Normal enhancement of posterior pituitary
   c. Decreased T2 signal in anterior pituitary
   d. Blooming in anterior pituitary

Answer Key: a

3. Which of the following do not cause decreased T2 signal intensity in the suprasellar region?
   a. HFE
   b. Hemorrhagic pituitary adenoma
   c. Thrombosed internal carotid artery aneurysm
   d. Melanoma

Answer Key: c

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