Review Article

Imaging in short stature

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ABSTRACT

Short stature can be a sign of disease, disability, and social stigma causing psychological stress. It is important to have an early diagnosis and treatment. Short stature may result from skeletal dysplasias, endocrine disorders, may be familial, or may be the result of malnutrition and chronic illnesses. A team effort of the healthcare professionals like pediatricians, endocrinologists, radiologists, and pathologists is required to diagnose, treat and monitor various pathological conditions associated with growth abnormality. In this review, we have discussed the role of imaging in diagnosing and characterizing various pathological conditions associated with short stature.

Key words: Computed tomography, dwarfism, imaging, magnetic resonance imaging, short stature, X-ray

Introduction

Short stature is defined as a height that is 2 or more standard deviations below the mean for age and gender within a population (below the 2.5th percentile).[1] Short stature may be caused by skeletal dysplasias and endocrine disorders; it may also be familial, or the result of malnutrition and chronic illnesses.[2,3]

Short stature may be proportionate or disproportionate. *Disproportionate dwarfism* is characterized by one or more body parts being relatively large or small, with growth variation in specific areas being apparent. The condition is typically caused by one or more genetic disorders involving bone or cartilage development, as seen in skeletal dysplasias. Hypotonia, or low muscle tone, is common, but intelligence is usually normal. In case of *proportionate dwarfism*, the body appears normally proportioned, but is unusually small. Extreme shortness with proportional body parts usually has a hormonal cause, such as growth hormone deficiency, called pituitary dwarfism. Unlike disproportionate dwarfism, intelligence impairment may be seen in some of these cases.[2,3]

Radiological evaluation of a short statured patient includes (i) a skeletal survey to identify a dysplasia or exclude it as a cause, (ii) anteroposterior radiograph of left hand and wrist to determine bone age (to assess skeletal maturity and give an estimate of potential residual growth), and (iii) magnetic resonance imaging (MRI)/ computerized tomography (CT) scan brain (pituitary-hypothalamic axis) if hypopituitarism is suspected.[4]

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Skeletal Dysplasias

"Dysplasia" is a scientific word that means disordered growth. Skeletal dysplasia is the term used to describe conditions in which there is abnormal or disordered growth of skeleton. Skeletal dysplasias are due to inherited faulty genes; and account for about half of over 300 genetic conditions that affect growth and development. The majority of skeletal dysplasias are diagnosed in children. They are characterized by short stature that may be proportionate or disproportionate. Short stature condition can be classified according to the parts of body in which there is reduced growth:[3-5]

i. Short limb conditions (there is reduced rate of growth of the limbs, example: achondroplasia, hypochondroplasia),

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ii. Short trunk conditions (reduced growth rate of the torso or trunk, example: spondyloepiphyseal dysplasia),
iii. Proportionate short stature conditions (generalized short stature in which both limbs and the trunk are shortened, example: osteogenesis imperfecta type-4).

Skeletal dysplasia with disproportionate short stature (short limb/short trunk conditions)

The diagnosis of disproportionate short stature is based on clinical features, and genetic testing is therefore not required. Clinical diagnosis depends on anthropometric measurements (i.e. arm span, upper to lower segment ratio). This assessment helps to determine if the disproportionate shortening affects primarily the trunk or the limbs. Short-limb disproportionate dwarfism can be further subdivided into proximal (rhizomelic), middle (mesomelic) or distal segment (acromelic) limb shortening. The next step in evaluation of disproportionate dwarfism is a complete radiographic skeletal survey including views of the skull, spine, pelvis, extremities, hands, and feet.[4,5]

Achondroplasia (ACH) is a common non-lethal form of skeletal dysplasia. It is known as *short limb dysplasia* because children with this condition have an average sized torso (chest and abdomen) but smaller arms and legs. It affects about 1 in 20,000 babies and is generally diagnosed at birth or early infancy. ACH is due to a defect of endochondral bone formation resulting in rhizomelic dwarfism. Boys and girls are affected equally. Patients are of normal intelligence with normal motor function; few patients may have specific neurological deficits. There is increased risk of infant death from cord compression and/or upper airway obstruction.[6,7]

Radiographically, almost all bones of the skeleton are affected in ACH. Antenatally, it is difficult to diagnose achondroplastic features until 3rd trimester. *Antenatally detectable sonographic features* include decreased femur length (FL) to biparietal diameter (BPD) ratio below the 5th percentile, trident hand (2nd, 3rd, and 4th fingers appear separated and similar in length) and frontal bossing.[7,8] *Postnatally, plain film features* include enlarged head with frontal bossing, depressed nasal bridge, mid-face hypoplasia and skull base abnormalities on skull X-ray; spinal curvature abnormalities with bullet shaped vertebra(e) (anterior wedging of vertebral bodies), posterior vertebral scalloping and progressive narrowing of lumbar interpedicular distance on X-ray spine; horizontal acetabular roof (decreased acetabular angle), small squared (tombstone) iliac wings, short sacroiliac notch, small trident pelvis, champagne glass type pelvic inlet on X-ray pelvis; the femora and humeri are particularly shortened (rhizomelic shortening), metaphyseal flaring (giving trumpet bone appearance to femora and humeri), V-shaped growth plates, and trident hand on X-ray extremities; and narrow thorax with anterior rib flaring on chest x-ray.[6,7] *MR/CT imaging brain* reveals small skull base, narrowed foramen magnum with compressive myelopathy at cervico-medullary junction, syringomyelia, cord changes of myelomalacia, hydrocephalus, and lumbar canal stenosis.[7,9,10] Classic images of ACH are described in detail by Renton, *et al.* and Aglan, *et al.*[11,12]

Hypochondroplasia (HCH) has been described as a milder form of achondroplasia, which presents with short limb condition usually during 2nd to 3rd year of life. The characteristic facial features of achondroplasia are absent, and both short stature and rhizomelia are less pronounced. Common features include genu valgum and mild lumbar lordosis.[13]

Skeletal dysplasia with disproportionate short stature (short trunk conditions)

Spondyloepiphyseal dysplasia (SED) is a *short trunk dysplasia,* which is characterized by shortening of the torso or trunk. As the name indicates, it affects growth of spine (vertebrae) and proximal epiphyseal centers. Two major types of SED are recognized, namely, SED congenita and SED tarda. The condition primarily affects boys. The clinical and radiographic findings differ in the two types of SEDs. SED congenita is characterized by vertebral changes and occasionally vision/hearing defect. The condition is present from birth and has autosomal dominant inheritance; hence males and females are affected equally. In contrast, SED tarda is milder than SED congenita and late in onset (in childhood or adolescence). It is x-linked recessive; hence, generally only males are affected. SED is a nonlethal form of skeletal dysplasia, hence life expectancy is not reduced. However, due to increased morbidity, regular monitoring and follow-up care should be encouraged.[14,15]

Children with *SED congenita* are short-statured from birth, with very short trunk and neck, and shortened limbs. Their hands and feet, however, are usually average sized. Radiological evaluation with complete spine survey and hip joint assessment is warranted in patients with SED congenita. Radiographic imaging findings include: spine changes such as kyphoscoliosis and lordosis, platyspondyly (flattened vertebrae), and cranio-vertebral junction (CVJ) anomalies like odontoid hypoplasia or os odontoideum leading to atlantoaxial instability. Cervical myelopathy due to cord compression may be present. The spine changes may be associated with breathing problem. Hip joint deformity includes delayed ossification of capital femoral

epiphysis, metaphyseal flaring, horizontal acetabular roof, broad femoral neck and coxa vara.[14]

Radiographic changes may not be apparent in children *with SED tarda* before the age of 4-6 years. The imaging findings are similar to those seen in patients with SED congenita, however, in SED tarda, the thoracic spine is typically involved to a greater extent and the epiphyseal involvement is primarily in shoulders. The changes in the hip may mimic bilateral Legg-Calve-Perthes disease; in doubtful cases, abnormalities of other epiphysis and spine help to establish the correct diagnosis of SED tarda.[15]

Skeletal dysplasia with proportionate short stature (generalized short stature conditions)

Osteogenesis imperfecta (OI) type 4 is a condition in which bones are extremely fragile leading to many fractures, especially before puberty. These patients are born with defective connective tissue formation due to deficiency of type-I collagen. All the bones of skeleton are affected; hence, the short stature is generalized. Associated abnormalities include: barrel-shaped rib cage, spinal curvature abnormality, vertebral compression fracture(s), basilar invagination deformity of skull with consequent brainstem compression, triangular face and brittle teeth (dentinogenesis imperfecta). The sclera is normal in these patients.[16]

Endocrine Disorders Causing Short Stature

Pediatric endocrine disorders may have serious impact on growth (height and weight) and development of a child. Children with endocrine disorders usually have extreme shortness with proportionate body parts (i.e., proportionate dwarfism). The hallmark of endocrine disease is linear growth failure that occurs to a greater degree than weight loss. Common endocrine disorders causing short stature include:[17,18]

i. Congenital hypopituitarism,
ii. Hypothyroidism,
iii. Cushing's syndrome, and
iv. Precocious puberty

Congenital hypopituitarism

Congenital hypopituitarism (CHP) is an important cause of short stature (SS). It may present with isolated growth hormone deficiency (IGHD) or multiple pituitary hormone deficiencies (MPHDs). MRI is the modality of choice in evaluation of pituitary-hypothalamic axis (PHA) in children with CHP. The primary role of MRI is to detect tumors of PHA that may require urgent surgical intervention. MRI has a secondary role in identifying PHA related structural abnormalities responsible for IGHD or MPHDs. CNS tumors [Figures 1 and 2] account for ~23% of abnormal findings in patients with growth failure; these include craniopharyngioma, hypothalamic/optic chiasm glioma, hypothalamic hamartoma, pituitary adenoma, germinoma and leukemia/lymphoma. Structural anomalies of PHA causing growth hormonal deficiency include pituitary hypoplasia, pituitary stalk interruption, ectopic posterior pituitary, and empty sella syndrome [Figure 3]. Congenital hypopituitarism (CHP) may also be associated with midline CNS defects [Figures 4 and 5] like anencephaly, holoprosencephaly, septo-optic dysplasias, corpus callosum dysgenesis, agenesis of septum pellucidum and arachnoid cyst. MRI is extremely helpful in selection and management of patients with hypopituitarism by early diagnosis of the evolving pituitary hormone deficiencies.[19,20]

Hypothyroidism

Thyroxine deficiency has a detrimental effect on the growing child. Delay in commencing thyroxine replacement therapy results in short stature and irreversible brain damage. The most common cause of *congenital hypothyroidism (CHT)* is thyroid dysgenesis or complete absence leading to severe CHT. Ectopic or maldescent of thyroid gland may lead to milder form of CHT. Cretinism is a medical condition in which untreated CHT can lead to severe growth failure and permanent mental retardation. Epiphyseal dysgenesis (irregular, deformed and stippled epiphysis) is the radiological hallmark of longstanding untreated hypothyroidism. Spine may show platyspondyly and thoraco-lumbar kyphosis. Diagnosis of CHT is generally confirmed by measuring serum TSH and thyroxine concentrations. *Acquired hypothyroidism (AHT)*

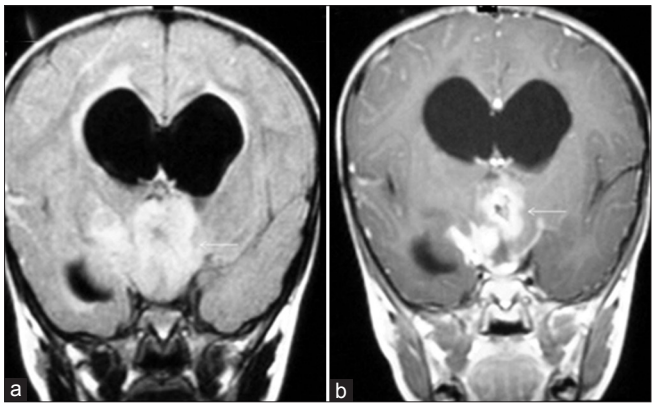

Figure 1: Opticochiasmatic–hypothalamic pilocytic astrocytoma in a child with growth failure due to isolated growth hormone deficiency. Coronal FLAIR (a) and T1W post contrast (b) MR images show a large heterogeneous enhancing sellar-suprasellar mass lesion (arrow) with resultant upstream obstructive hydrocephalus. Note, it is difficult to differentiate whether the tumor originates from chiasma or hypothalamus, as typically both of these structures are involved. Post surgical biopsy proved astrocytoma

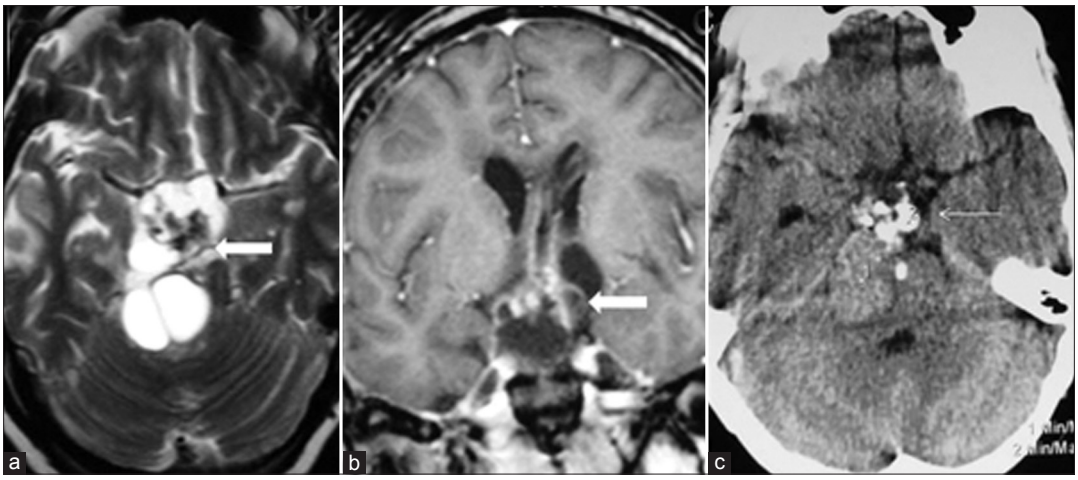

Figure 2: Cystic craniopharyngioma in a young child with panhypopituitarism. Axial T2W (a) and coronal post contrast T1W (b) images show a large complex cystic sellar-suprasellar mass (thick arrow). Note intratumoral calcification (thin arrow) on non-contrast axial computerized tomographic (CT) image (c). Hyperdense cyst on non-contrast CT suggests presence of high protein content within the cyst

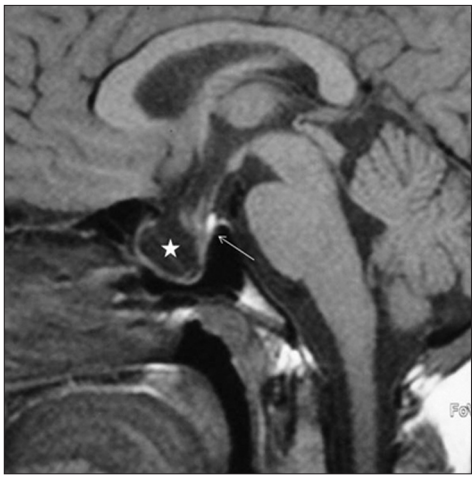

Figure 3: Empty sella syndrome in an adolescent with retarded growth due to isolated growth hormone deficiency. Sagittal T1W image of brain reveals enlarged sella filled-up with cerebrospinal fluid (CSF) (asterisk). Pituitary gland appears flattened along the floor of sella (arrow). The sella is also expanded due to CSF pulsations

is largely due to autoimmune thyroiditis (Hashimoto's thyroiditis) [Figure 6] which rarely occurs under the age of 3 years. Clinically, autoimmune thyroiditis may present with formation of a goiter with or without disturbance of thyroid function. Patients with AHT usually have growth failure and delayed puberty. Diagnosis of Hashimoto's thyroiditis is confirmed by demonstration of serum thyroid antibodies and antithyroglobulin antibodies. Bone age is significantly delayed in both types of hypothyroidism and the degree of delay of skeletal maturation is often indicative of duration of illness. Anteroposterior radiograph of hand and wrist is used to determine the bone age and assess skeletal maturity. Thyroid scan may be indicated to assess congenital thyroid anomalies (e.g., agenesis/hypoplasia) or if a thyroid mass is palpable (e.g., goitrous enlargement of thyroid in Hashimoto's thyroiditis).[21,22]

Cushing's syndrome

Paediatric Cushing's disease (CD) is a rare cause of short stature. ACTH secreting pituitary microadenoma is the most common cause of CD. Clinically, patients have growth failure, weight gain, moon facies, truncal obesity, adrenarchal signs (acne, pubic/axillary hair) and hypertension. Increased serum cortisol level and pituitary MRI demonstrating ACTH-secreting microadenoma [Figure 7] are important diagnostic tests to confirm the clinical suspicion. However, because of co-existence of an ACTH secreting microadenoma and a pituitary incidentaloma, bilateral inferior petrosal sinus sampling (BIPSS) with corticotrophin-releasing hormone (CRH) stimulation test may be needed for preoperative localization of the microadenoma. Transsphenoidal surgery with selective microadenomectomy allows complete remission of hypercotisolism.[23]

Precocious puberty

Precocious puberty is defined as pubertal development occurring before the age of 8 years in girls and before 9 years in boys. The major concern in precocious puberty is accelerated bone maturation leading to reduced stature. Idiopathic central precocious puberty is more common in girls, whereas, in boys there may be an underlying pathology, such as CNS lesion. CNS causes [Figure 8] of precocious puberty include congenital anomalies (such as hypothalamic hamartoma, arachnoid cyst, septo-optic dysplasia), hydrocephalus, infection, trauma or tumors (like hypothalamic astrocytoma, craniopharyngioma, ependymoma, and rarely a pituitary adenoma). Central precocious puberty may be associated with McCune-Albright syndrome and Neurofibromatosis type-1 (NF-1). Non-CNS tumors [Figure 9] causing precocious puberty include adrenal adenoma or carcinoma, gonadotropin

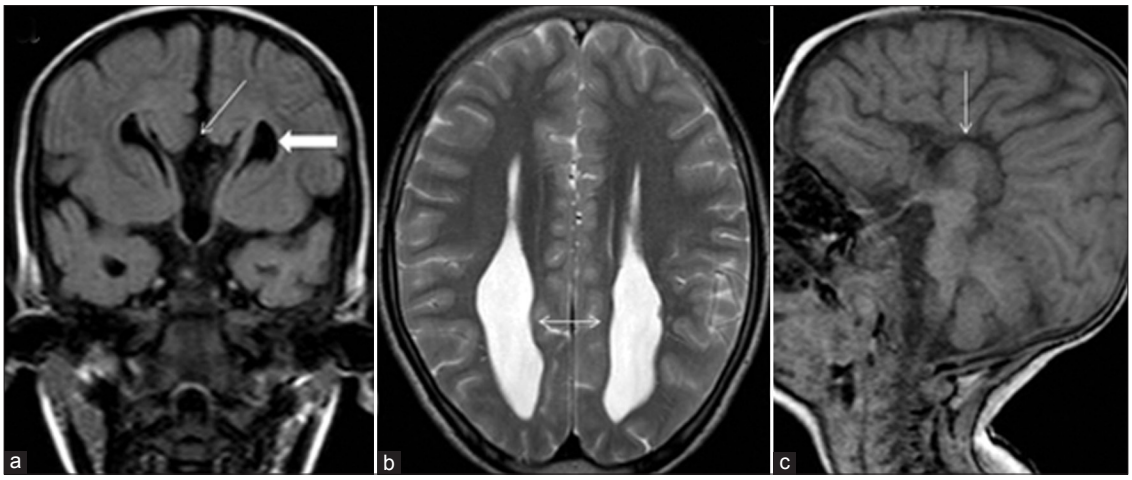

Figure 4: Corpus callosum agenesis (complete) in a child with abnormal growth and development. Coronal FLAIR (a) image shows high riding third ventricle communicating with the interhemispheric fissure (thin arrow), and crescent shaped frontal horns indented medially by white matter tracts of Probst's bundles (thick arrow); axial T2W image (b) shows widely separated and parallel lateral ventricles with colpocephaly (double arrow); and sagittal T1W (c) image shows complete absence of the corpus callosum and cingulate sulcus (thin arrow). Pituitary gland was, however, normal (not shown)

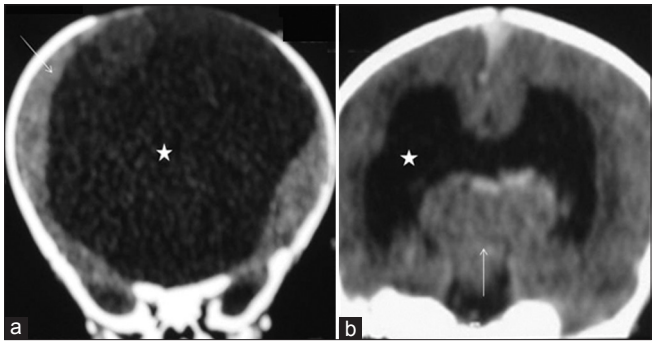

Figure 5: Holoprosencephaly in a child with abnormal growth and development. CT coronal images of brain show (a) alobar holoprosencephaly with a large central monoventricle (asterisk) and thin cortical mantle (arrow); (b) semilobar holoprosencephaly with H-shaped monoventricle (asterisk). Basal ganglia and thalami are partially fused (arrow). Pituitary gland (not shown) appeared normal

producing choriocarcinoma, teratoma, hepatoblastoma, and ovarian or testicular neoplasm. The primary role of imaging (MRI/CT/USG) is to detect or exclude structural abnormalities causing precocious puberty.[24]

Conclusion

Although a number of simple diagnostic measurements (including weight/height ratio and U/L limb ratio) and associated clinical findings (including dysmorphic features and growth retardation) may be helpful in identifying the disorders causing short stature, the radiological imaging techniques provide useful diagnostic clue to the physicians and help them to confirm their diagnosis. Skeletal survey with plain X-ray is particularly useful to identify or exclude a dysplasia as a cause of short stature, X-ray hand and wrist is used to determine the bone age, ultrasound helps in evaluation of thyroid

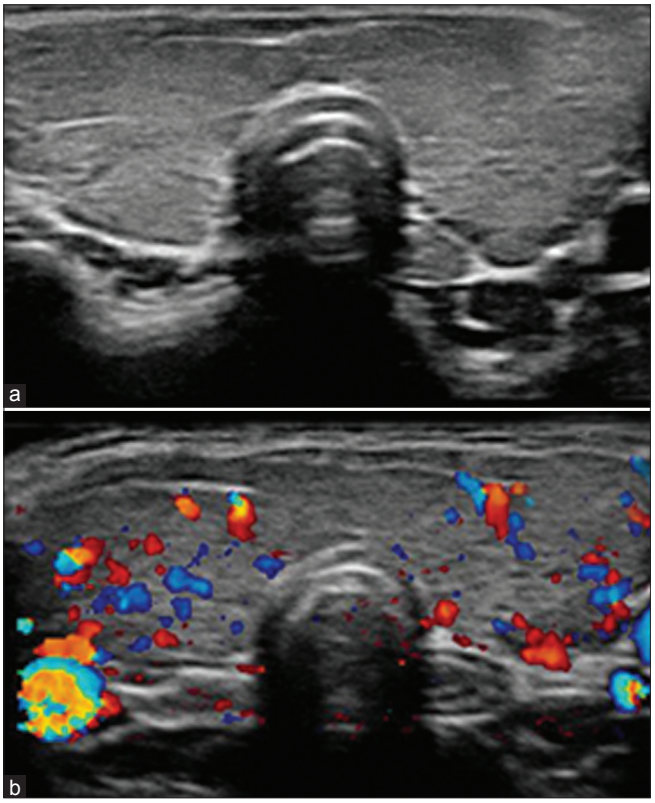

Figure 6: Hashimoto's thyroiditis in a female patient who presented with features of hypothyroidism and had antibodies positive for the disease. Gray scale ultrasound image (a) shows diffuse glandular enlargement with coarse parenchymal echotexture. Note, echogenic fibrous septae giving pseudolobulated appearance to the parenchyma. Color flow imaging (b) demonstrates normal parenchymal vascularity. [Reproduced with permission from Indian Journal of Endocrinology and Metabolism]

pathology, and MRI/CT brain primarily demonstrates pathologies of pituitary-hypothalamic axis causing paediatric neuroendocrine dysfunction and consequently short stature.

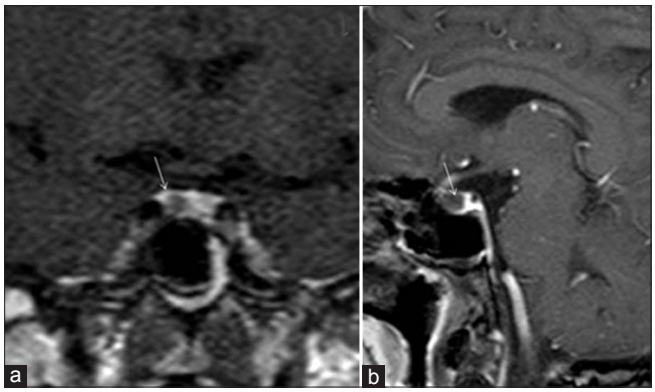

Figure 7: ACTH secreting pituitary microadenoma in a patient with clinical features of Cushing's disease and increased serum cortisol level. High resolution dynamic contrast enhanced T1W coronal (a) and sagittal (b) images of brain (at 60 seconds) show a small non enhancing (dark) microadenoma (arrow) lateralized to right side of the pituitary gland. The normal pituitary gland shows marked homogenous enhancement

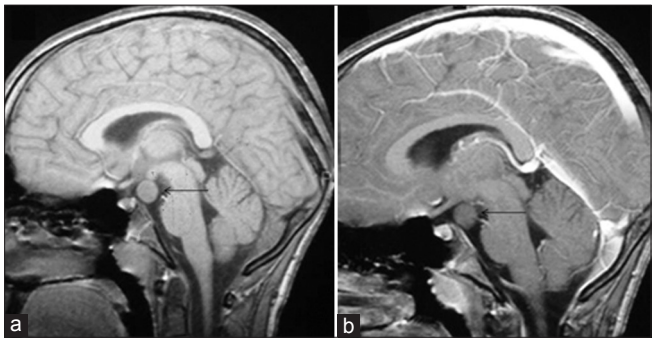

Figure 8: Hypothalamic hamartoma in a male child with central precocious puberty and short stature. Magnetic resonance imaging (MRI) brain, plain (a) and post-contrast (b) sagittal images demonstrate a small well-defined, non-enhancing rounded suprasellar mass arising from hypothalamus (arrow). Note that the lesion is isointense to normal brain parenchyma

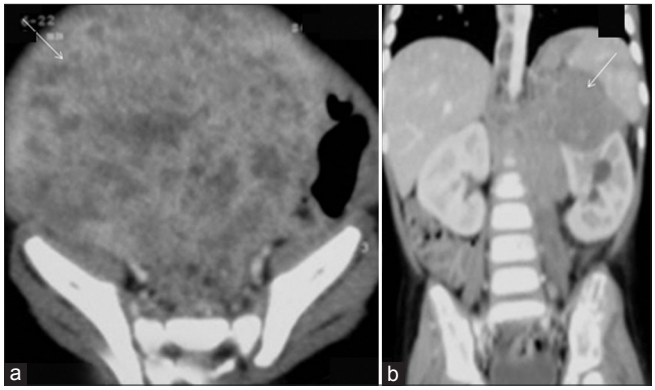

Figure 9: Post-contrast CT abdomen showing (a) retroperitoneal teratoma (arrow), and (b) infiltrating left adrenal carcinoma (arrow), in two different children. Both the children had precocious puberty (due to non-CNS cause) and short stature

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