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Interesting Cases of Pituitary Adenoma with Varied Presentations

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Abstract

Pediatric pituitary adenomas (PPAs) are rare neoplasms sometimes with unusualpresentations and varied clinical course. We describe 2 atypical PPAs to highlight the clinical examination, radiological, hormonal and management aspects.

A 6-year-old girl presented with bleeding per vagina with difficulty in walking with breast enlargement without visual disturbances. MRI revealed an enlarged anterior pituitary gland showing intense enhancement on contrast of size 11mm x 16mm without invasion of 3rd ventricle or parasellar extension into cavernous sinuswith USG Abdomen and pelvis revealing complex ovarian cyst with reduced TSH levels suggesting Primary Hypothyroidism.

Another 30-year-old male presented with blurring of vision in both eyes with bilateral temporal field defects with absence of secondary sexual characters and decreased libido with decreased testosterone levels and MRI Brain showing non diffusion restricting T1 iso T2 hyperintense lesion in sellarsuprasellar region suggestive of Cystic pituitary macroadenoma with haemorrhage,which was managed surgically.

Keywords: Adenoma; Medical; Pituitary; Surgery.

Introduction

Pediatric Pituitary adenomas (PPAs) are rare neoplasms that account for 2% of all pediatric brain tumors.[17] Typical clinical presentation depends on the extent of mass effect and, for secreting tumors, which trophic hormones are dysregulated. In addition to headaches, children frequently come to medical attention because of visual disturbances, growth failure, or abnormal pubertal onset.[15,16] Interestingly, PPA appears to have unusual presentations, atypical symptomatologies, or extremes of severity. When these tendencies are combined with the lesion's relative rarity, frequent misdiagnosis occurs with management challenges. We report two such cases with particularly striking presentations and/or extraordinary challenges in both diagnosis and

treatment of atypical PPA. This study was approved by our institutional review board, including a consent obtained from patients and their family members.

Case 1

A 6 year old female presented to the Neurosurgery outpatient department with progressive breast enlargement and episodes of irregular vaginal bleeding for past 3 months with gait disturbance in the form of left side high stepping gait since1 year. She was full-term delivered vaginally, was born of non-consanguineous marriage and was first in the birth order. Her birth weight was 2.5 kg (between 3rd and 15th centiles; WHO growth charts). She has not joined school because of her declining socialistic performances. There was no history of headache, vomiting, or visual symptoms. There was no other significant past history. There was no history of autoimmune disorder in the family.

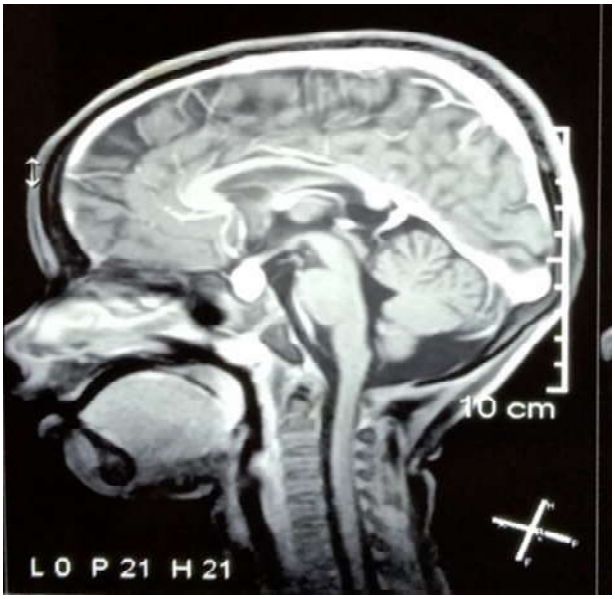
Her height was 114 cm (<3rd percentile, IAP chart), Her weight was 11 kg (between 25th and 50th centiles; IAP growth chart). Her pulse rate was 74/min and blood pressure was 100/62 mmHg (50th centile) She had dry skin, pallor and there were no café au lait spots. Child was having gait disturbances in the form of left high stepping gait with lateral deviation of left toes.

There was no goitre on palpation. She was having Tanner's staging II Breast enlargement, and there were no axillary or pubic hairs. Visual acuity and fields were normal.

Her hormonal profile is evaluated which showed TSH - > 1000 microIU/ml, Serum prolactin -75 ng/ml, Inhibin B level is 439.5 ng/l,LDH – 394 u/l and others hormonal values are normal.

Ultrasonography (USG) of the Abdomen and pelvis suggested multi-septated right ovarian cyst measuring around 4.9x 2.5 cm with bulky left ovary for the age with large follicles with mildly bulky left adrenal gland. USG screening of both breast shows prominent retroglandular areolar tissue, Screening of thyroid gland shows diffuse altered with increased vascularity.Skeletal survey was done of hands and feet which showed left deviation of toes.

Magnetic resonance imaging (MRI) scan of the brain revealed an enlarged anterior pituitary gland showing intense enhancement on contrast of size 11mm x 16mm without invasion of 3rd ventricle suprasellarextension into cavernous sinus.



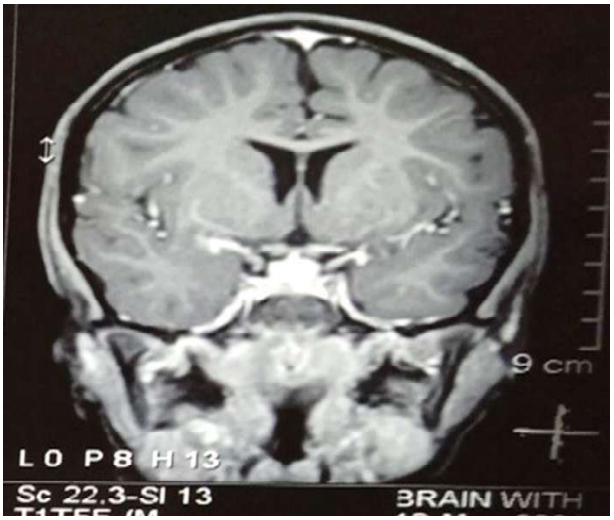


Fig. 1 and 2: MRI Brain contrast sagittal and coronal view showed enlarged anterior pituitary gland showing intense enhancement on contrast.

The child was managed with thyroid replacement therapy and was started on tablet L- thyroxine at a dose of 25 µg, which was escalated weekly to a daily dose of 50 µg, given in the early morning on an empty stomach and within a month of starting the therapy, her bleeding cycles stopped. She was referred to Pediatric surgery.

Department ICH Chennai for further treatment of ovarian mass.

Case 2

A 30 year old male presented to the Neurosurgery outpatient department with blurring of vision in both the eyes with bilateral temporal field defect since 3

months with lack of secondary sexual characters like absence of axillary and pubic hairs, h/o decreased ejaculation and loss of early morning tumescent. There was no history of headache, vomiting. There was no other significant past history. There was no history of autoimmune disorder in the family.

His height was 163 cm and absence of axillary and pubic hairs with long hands and feet with fingers and toes and Bilateral testicular atrophy.

Fig. 3: Showed absence of axillary and pubic hairs with long hands.

His pulse rate was 74/min and blood pressure was 120/82mmHg. Visual field testing showed bitemporalhemianopia.

His hormonal profile is evaluated which showed serum Testosterone is <0.025, serum cortisol is 4.74 and FSH is 0.64 and LH is 0.320and other hormones are in normal limits.

Ultrasonography (USG) of the Abdomen does not reveal any abnormality.

Magnetic resonance imaging (MRI) scan of the brain shows non diffusion restricting T1 iso and T2 hyperintense lesion not suppressing on FLAIR measuring 3.6x2.7x3.9 mm with blood fluid levels noted within the sellar and suprasellar region with lesion extending anteriorly upto anterior cranial fossa exerting mass effect over basifrontal region with erosion of dorsum sella and widening of sella without cavernous sinus invasion without involvement of internal carotid artery suggestive of cystic pituitary macroadenoma with haemorrhage.

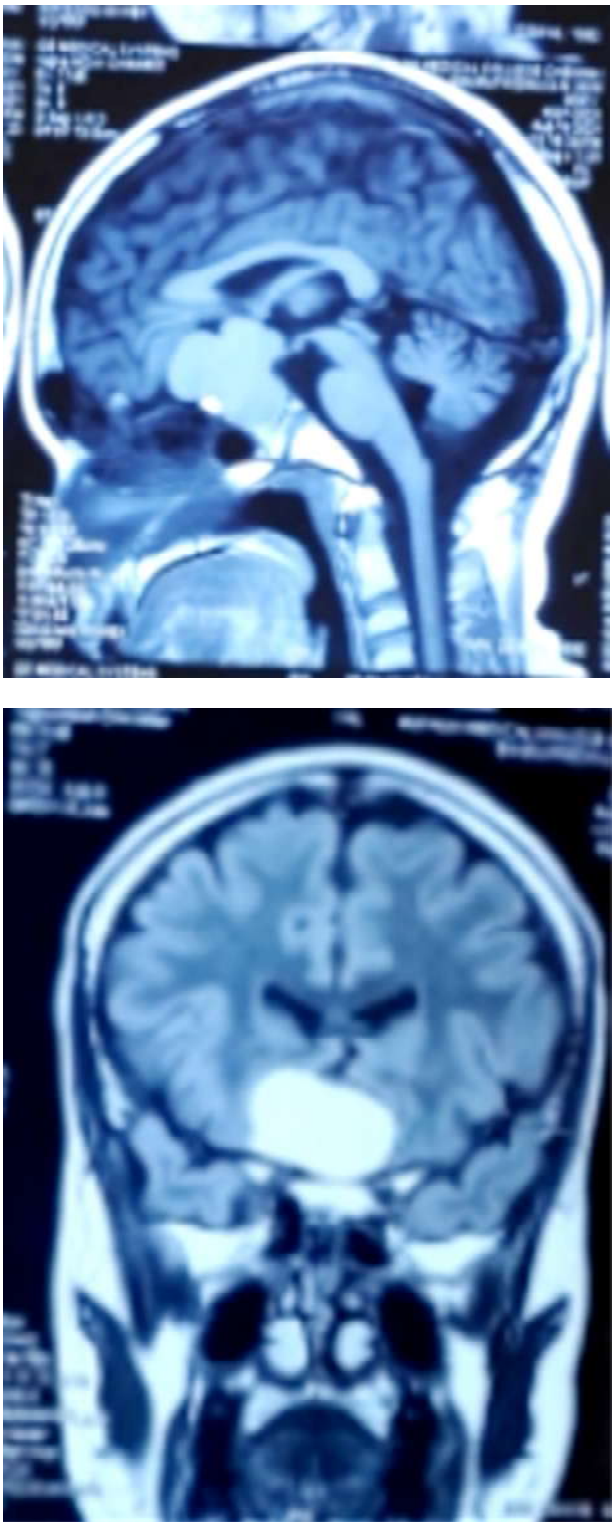


Fig. 4 and 5: MRI brain showsT1 iso and T2 hyperintense lesion with blood fluid levels noted within the sellar and suprasellar region.

The patient was managed medically and surgically with Transnasal microscopic excision of tumor and histopathology turned out to be pituitary

macroadenoma features and postoperatively patient recovered vision partially and discharged to be followed up in neurosurgery and endocrinology opd.

Discussion

Case 1

Our patient presented with features of growth retardation and a delayed bone age with iso-sexual peripheral precocious puberty. The most common differentials of growth failure were juvenile hypothyroidism, Cushing's disease and panhypopituitarism. Short stature without obesity initially pointed towards juvenile hypothyroidism as the diagnosis.

Precocious puberty with adnexal masses is always associated with an advanced bone age with an elevated basal cortisol level, which was not seen in the index case. Severe growth retardation is also observed in patients with panhypopituitarism (due to the combined deficiency of growth hormone and TSH). It is associated with secondary hypothyroidism and delayed puberty, which was not seen in this patient. Hence, we came to the diagnosis as primary hypothyroidism in view of the linear growth failure with a delayed bone age and features of thyroid hormone insufficiency with pituitary lesion. The association of long-standing thyroid insufficiency with sexual precocity has been described in literature as Van Wyk and Grumbach syndrome (VWGS).

The exact mechanism of the development of precocious puberty in VWGS remains undefined and has been explained with several theories.[1] The most widely accepted of which is hormonal overlap in the pituitary feedback mechanism due to molecular mimicry between TSH and follicle-stimulating hormone (FSH) receptors. TSH in high concentrations leads to stimulation of gonadal FSH, as they share the common alpha subunit, which, in turn, increases the oestrogen levels, thereby manifesting as peripheral sexual precocity in females and macroorchidism in males. Pubic and axillary hairs are characteristically absent as there is no effect on adrenal hormone synthesis, thus it is also known as incomplete sexual precocity.[2]

Multiple cysts in the ovaries develop secondary to the enhanced production and decreased clearance of FSH due to hyperstimulation of its receptors by elevated thyrotropin-releasing hormone (TRH). In addition, high circulating TSH acts on the FSH receptors present on the ovarian follicle due to specificity spillover, resulting in the follicular cyst formation.[3]

Pituitary adenoma reported on imaging is basically thyro-lactotrope hyperplasia, which is an indication of a long-standing, severe thyroid deficiency state. High circulating levels of TRH due to lack of thyroxine-mediated feedback inhibition result in hyperstimulation of thyro-lactotropes in the pituitary gland, thus presenting as a macroadenoma on imaging studies. The similar mechanism is also responsible for the stimulation ofprolactin secretion, thereby leading to hyperprolactinaemia.[4] Hyperplastic pituitary causes compression of the pituitary stalk that disrupts the hypothalamic inhibition of prolactin secretion, which further explains the presence of high prolactin levels with long-standing hypothyroidism.

The most common cause of thyroid insufficiency in an iodine sufficient area in young females has been attributed to immune-mediated destruction of the thyroid gland (Hashimoto's thyroiditis)[5] which is not the case in our patients as anti-TPO antibody titre was normal and screening of thyroid gland showed diffuse altered echopattern with increased vascularity. Hypothyroidism in our patient could have been due to severe iodine deficiency or a delayed onset dyshormogenesis. Several methods have been devised for the estimation of bone age in children, of which the most frequently used and practically feasible is through Greulich and Pyle atlas. In females aged 3 years and above, assessment of the bone age is done through comparison between ossification centres of the epiphysis and metaphysis of proximal and intermediate phalangeal joints, in an X-ray of hand. This can also be done by comparison with age-matched standards derived from healthy children, published in the atlas.[6-8]

Our patient at presentation had a bone age of 4 years, which was delayed by 2 years from the chronological age. Thyroxine is needed for the secretion and action of growth hormone. It acts directly on the growth plate and promotes differentiation of chondrocytes to hypertrophic chondrocytes, which is required for the growth of long bones.[9] Deficiency states as seen in primary hypothyroidism lead to growth failure and a delayed bone age, as was seen in our patient. Thyroid replacement therapy in VWGS will lead to complete resolution of all the symptoms along with complete regression of ovarian cyst and pituitary hyperplasia without any need of surgical management.

Case 2

In the evaluation of our patient with erectile dysfunction in pituitary macroadenoma, an endocrinopathy is the rarest of causes.[9,10] However, when an endocrinopathy does affect erectile function, it is almost always caused by hypogonadism.[9-11] Obtaining a serum testosterone (T) level is the most

costeffectiveway of screening for an endocrinopathy as the cause of erectile dysfunction.[10,11] Then additional evaluation should include obtaining serum luteinizing hormone, free T, and prolactin levels.[10] If the serum T is elevated, then a thyroid evaluation may be indicated.[10] In our patient, hypogonadism as well as an elevated prolactin level (prolactin was emanating from the lesion within the pituitary gland) were found. Hyperprolactinemia induces hypogonadism by interfering with the secretion of gonadotropinreleasing hormone (GnRH) from the hypothalamus.[12,13]

However, when the serum prolactin is corrected in patients with an elevated prolactin level, erectile function is usually restored (if erectile dysfunction was present).[10] Hyperprolactinemia is a very rare cause of impotence in a general population of men with impotence.[14] However, men who have hyperprolactinemia have a high incidence of sexual dysfunction, and the erectile dysfunction appears more likely to resolve in patients with the most severe hyperprolactinemiawith dopaminergic agonist like bromocriptine, cabergoline and after surgical excision of pituitary lesion.

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Case Report

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Brucellosis Spondylodiscitis

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Abstract

Brucellosis is neglected but important zoonotic disease when it comes about spondylodiscitis. Here, we are presenting rare case of 54 years old male with brucellosis spondylodiscitis which is diagnosed by serum agglutinin test and had undergone L5-S1 Level discectomy with L5 Partial coprpectomy with L4-L5-S1 Screw and rod fixation for the same. Postoperative period was uneventful and he was discharged on fourth postoperative day with complete neurological recovery. Due to atypical presentation and prevalence of spinal tuberculosis, diagnosis of brucellosis is challenging but with proper investigation battery and right treatment, patient can be saved from greater morbidity.

Keywords: Brucellosis; Spondylodiscitis; Zoonotic disease.

Introduction

Brucellosis is still an important zoonosis of both public health and economic significance in many developing countries. Each year, half a million new cases are reported worldwide, but according to the World Health Organization (WHO), these numbers greatly under-estimate the true incidence of human disease (1). In this era of advanced medicine, brucellosis spondylodiscitis has become anuncommon presentation that we have come across.

Case Report

A 54 years male patient, farmer by occupation, without history of recent animals/birds contacts, consuming unpasteurized milk known case of diabetes and ischemic heart disease, was brought with chief complain of fever (low grade,1 episode) lasted for whole days 3 months back, relieved on its own without any treatment. 5 days after fever patient developed complaint of low back pain, aggravating on sneezing, forward bending that later radiated to lateral aspect of thigh & then to calf up to ankle joint.

Since last 2 months patient had developed complain of bilateral lower limb weakness. Initially patient was any how able to walk with walker , which in next 10-15 days progressed such that he needed 2 persons support to walk, then was bed ridden for next 15-20 days. MRI and other routine investigations were done. So thinking it to be pott's spine he was started on AKT. But there was no improvement. His serum agglutination test for brucellosis came positive and treatment with doxycycline was started. On clinical examination, there was paraparesis and atrophy of left thigh muscle with depressed left ankle reflex. So clinical picture suggestive of neurological disorder but on MRI there was compressive radiculopathy on

L4-L5 and L5-S1 level with changes of spondylodiscitis with (10mmX6mm) epidural collection at L5 level.

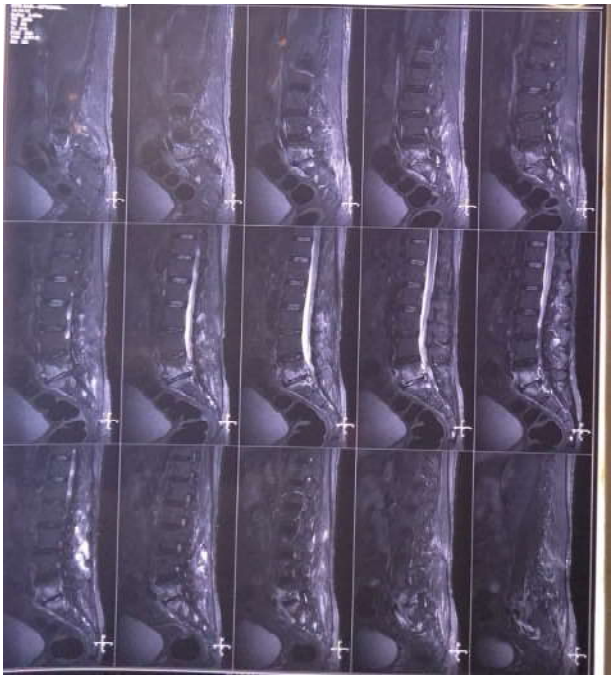

Fig. 1: STIR images (sagittal plane) showing collection at L5 level with changes of spondylodiscitis at L5-S1 level.

Fig. 2: T2WI (axial cuts) showing collection at L5 level and compressive radiculopathy of traversing root at L5-S1 level and impingement at L4-L5 level.

Patient's symptoms were resolving but there was persistent back pain which radiates to left for which operative intervention was planned. He was undergone L5-S1 Level discectomy with l5 partial coprpectomy with L4-L5-S1 screw and rod fixation.

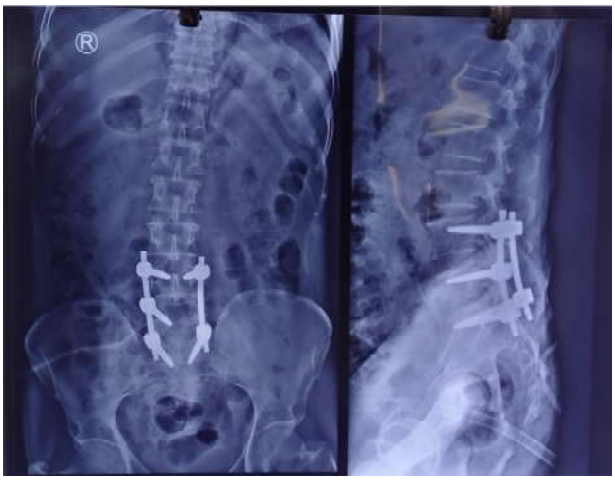

Fig. 4: Post-operative X-ray showing L4-L5-S1 screw and rod fixation.

Intraoperative there was minimal pus and necrotic changes involving L5-S1 disc and L5 vertebra which was removed and sent for culture and histopathological examination.

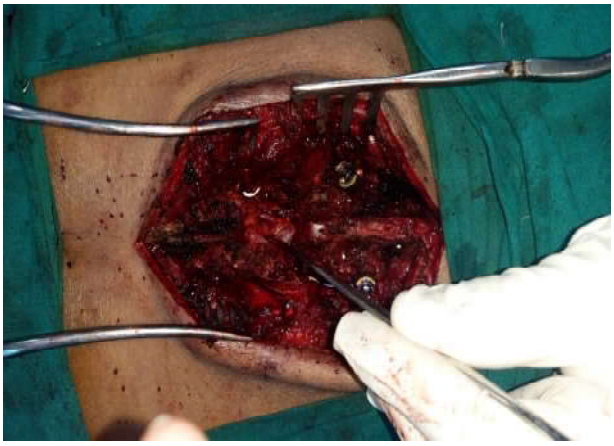

Fig. 3: Intraoperative picture with retracted spinal cord showing origin of left L5 root.

Histopathological report was suggestive of chronic inflammatory changes involving disc and vertebra and culture was negative for tuberculosis. Patient was discharged on fourth post-operative day with normal neurological examination.

Discussion

Human brucellosis, caused by small Gram negative, aerobic coccobacilli of the genus Brucella is a zoonotic infection and is transmitted most commonly through the ingestion of unpasteurized milk products

(especially cheese) or raw liver, or by direct contact with infected animals (direct inoculation through cuts and skin abrasions, especially from handling animal carcasses, placentas, or contact with animal vaginal secretions, via the conjunctiva or inhalation of aerosols)[2]. After entering the human body and being taken up by local tissue lymphocytes, Brucellae are transferred through regional lymph nodes into the circulation and are subsequently seeded throughout the body, with tropism for the reticuloendothelial system [3].

Patients with brucellosis also commonly present with musculoskeletal symptoms. The most common complications are peripheral arthritis, sacroilliitis and spondylodiscitis. Osteoarticular involvement ranges from 20% to 60%, and spondylitis is seen in 8% to 13%[4]. These osteoarticular complications are sometimes linked to a genetic predisposition, with recent data suggesting an association with HLA-B39[5]. Among the musculoskeletal involvements of brucellosis, vertebral involvement is the most difficult one to diagnose and treat. It can cause neurological complications and abnormal posture through vertebral destruction. A thorough clinical examination could have given important diagnostic clues. In the differential diagnose of himanshu back pain the examiner should also take into account that the disease has its most important prevalence in certain areas of the world but is also emerging in non-endemic areas due to importation through international travel or infected food products.

In patients who stayed in certain endemic areas tuberculosis or Brucella infections of the spine can be confused. Both are caused by intracellular pathogens which are difficult to isolate or identify in a short period. Since vertebral involvement is more frequent in chronic brucellosis, it is less likely that micro-organisms are isolated in the blood or bone marrow (which is the gold standard for confirming acute brucellosis because of the relatively high concentration of Brucella in the reticuloendothelial system). Differential diagnosis between spinal brucellosis and vertebral tuberculosis is usually made on the basis of clinical and routine laboratory and radiological findings.[4]

Routine laboratory data reported in most studies have been of little diagnostic value. Haemogram and ESR are not useful indicators for the diagnosis of brucellar spondylitis. CRP can be normal[6]. Leucocyte count and ESR are relatively lower in brucellar spondylitis than in tuberculous or pyogenic spondylitis [4].

Plain radiographs can show various degrees of bone involvement, with narrowing of the intervertebral disc space, gross destruction, patchy sclerosis of the vertebral end plate, syndesmophytes with or without paravertebral noncalcified soft tissue swelling, or displacement of the vertebral axis (4).As the earliest appearances of the destructive changes visible on plain radiographs begin approximately 3 months after the onset of symptoms, magnetic resonance imaging, which is more sensitive to demonstrate early bone infection, should be considered.

As mentioned above in our case, Brucella spondylitis may also be confused with spinal tuberculosis (Pott disease). Characteristic features of tuberculous spondylitis include involvement of a single vertebra or disc, predilection for the midthoracic region, severe vertebra body collapse, and extensiveassociated paraspinal abscess and gibbus deformity. In contrast to spinal involvement in brucellosis, tuberculous spondylitis is commonly seen in younger patients[6]. Distinguishing specific features of brucellar spondylitis included end-plate defects simulating Schmorl's nodules, obliteration of muscle-fat borders, a moderate amount of paraspinal granulation tissue, and disc gas [7]. A small collection of air is entrapped between the disc and the affected superior end plate, also known as the "peripheral vacuum phenomenon" (up to 18%, this is probably due to longstanding ischemia and avascular necrosis of the disc adjacent to the infected endplate)[8]. In this case serological tests and culture of Brucella were necessary to establish the diagnosis of brucellosis.

There are two broad categories of serological methods for diagnosing brucellosis: those based on antibody production against lipopolysaccharide and those based on antibody production against other bacterial antigens.

The serum agglutination test developed by Bruce remains the most popular diagnostic tool for brucellosis. These serum agglutination tests are also not suitable for patient follow-up, since titers can remain high for a prolonged period [9]. Another test is indirect enzyme-linked immunosorbent assay (ELISA). It uses cytoplasmic proteins as antigens. ELISA measures immunoglobulins class M, G, and A, which allows for a better interpretation of the clinical situation and overcomes some of the shortcomings of the serum agglutination tests. A comparison with the serum agglutination test yields higher sensitivity and specificity. The development of a specific polymerase chain reaction (PCR) is a recent advance. PCR is fast, can be performed on any body tissue, and can yield positive results as soon as 10 days after inoculation. PCR ELISA is a new promising variation. Although PCR offers new

possibilities for the future in diagnosing brucellosis, standardization of extraction methods and set-up is lacking, and a better understanding of the clinical significance of the results is still needed [10].

Brucella coccobacilli have a long doubling time (2.5 to 3.5h) and concentrations of circulating bacteria in the blood of infected patients are relatively low. Therefore, the recovery time of Brucellae can take up to 30 days using the classic Castaneda blood culture method. Automated blood culture systems have reduced the growth time of Brucella spp. The time to detection is now possible within 4 days but a positive culture depends on a variety of factors. The isolation of the organism from blood cultures is more difficult in patients with chronic brucellosis[11,12].

Conclusion

On the one hand, this case report illustrates an atypical presentation of Brucella spondylodiscitis which focused the neuro physician's attention at the mayopathy at First. On the other hand we emphasized the difficultiesto differentiate brucellosis from tuberculosis. Radiology techniques can point out some specific features, but serological tests and, if possible, cultures and PCR are helpful.

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Case Report

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Van Wyk-Grumbach Syndrome: Atypical Presentation in Childhood Pituitary Macroadenoma with Primary Hypothyroidism

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Abstract

Van WykGrumbach syndrome is a constellation of hormonal abnormalities which includes hypothyroidism, precocious puberty and ovarian cysts in pre and pubertal girls. The usual presentation is ascites, pericardial and pleural effusion, enlarged pituitary, elevated prolactin, ovarian hormones. Here, we present a 6 year old female, who presented with precocious puberty associated with hypothyroidism and had features suggestive of Van Wyk– Grumbach syndrome. This is presented to highlight the rare presentations of Pediatric Sellar Pituitary enlargement with bleeding PV, walking difficulty, thelarche her hormonal profile showed elevated TSH, Prolactin, Inhibin B and LDH, USG abdomen showed multiple ovarian cysts with adrenal mass, MRI brain showed enlarged pituitary gland and bone scans revealed a delayed bone age. This rare entity should be kept in mind in cases of ovarian cysts, especially those with isosexual precocity, to prevent delay in medical management and unnecessary surgical misadventures.

Keywords: Hypothyroidism; Pituitary; Vanwyk Grumbach.

Case Report

Written informed consent was obtained from the parent of the child. A 6 year old female presented to the Neurosurgery outpatient department with progressive breast enlargement and episodes of irregular vaginal bleeding for past 3 months with gait disturbance in the form of left side high stepping gait since 1 year. She was full-term delivered vaginally, was born of non-consanguineous marriage and was first in the birth order. Her birth weight was 2.5 kg (between 3rd and 15th centiles; WHO growth charts). She has not joined school because of her declining socialistic performances. There was no history of headache, vomiting, or visual symptoms. There was no other significant past history. There was no history of autoimmune disorder in the family.

Her height is 114 cm (<3rd percentile, IAP chart), her weight is 11 kg (between 25th and 50th centiles; IAP growth chart). Her pulse rate is 74/min and blood pressure is 100/62 mmHg (50th centile). She had dry skin, pallor and there were no café au lait spots. Child had gait disturbances in the form of left high stepping gait with lateral deviation of left toes.

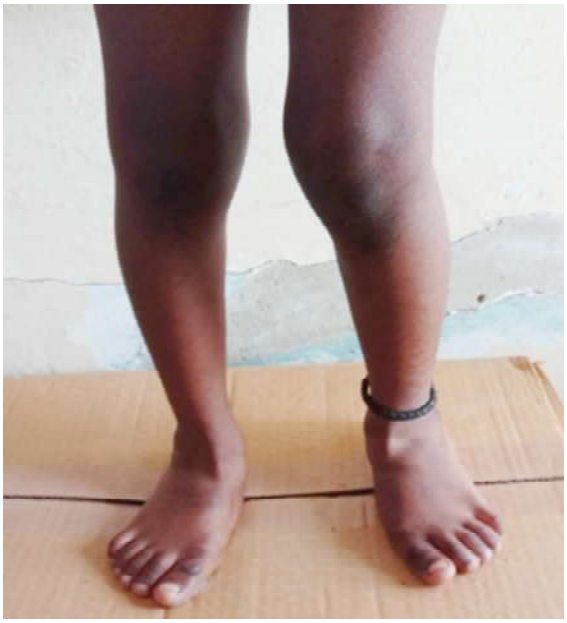
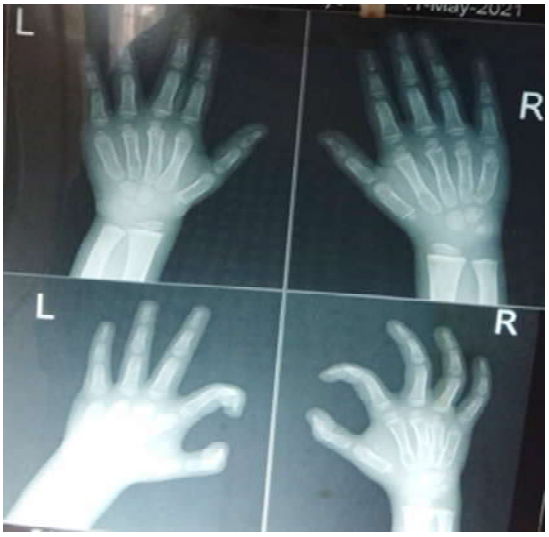


Fig. 1: Clinical picture showing left high stepping foot with lateral deviation of left toes.

There was no goitre on palpation. She was having Tanner's staging II, and there were no axillary or pubic hairs. Visual acuity and fields were normal. Her hormonal profile showed TSH - > 1000 micro IU/ml, Serum prolactin -75 ng/ml, Inhibin B level is 439.5 ng/l, LDH – 394 u/l and others hormonal values are normal.

Ultrasonography (USG) of the Abdomen and pelvis suggested multi-septated right ovarian cyst measuring around 4.9x 2.5 cm with bulky left ovary for the age with large follicles with mildly bulky left adrenal gland. USG screening of both breast shows prominent retroglandular areolar tissue, Screening of thyroid gland shows diffuse altered with increased vascularity. Skeletal survey was done of hands and feet



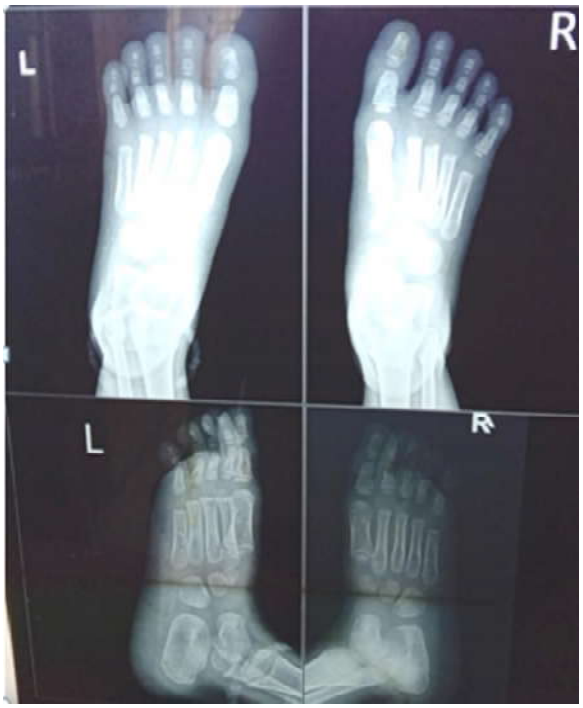


Fig. 2 & 3: x-ray of hand and foot.

Magnetic resonance imaging (MRI) scan of the brain revealed an enlarged anterior pituitary gland showing intense enhancement on contrast of size 11mm x 16mm without invasion of 3rd ventricle or parasellar extension into cavernous sinus.

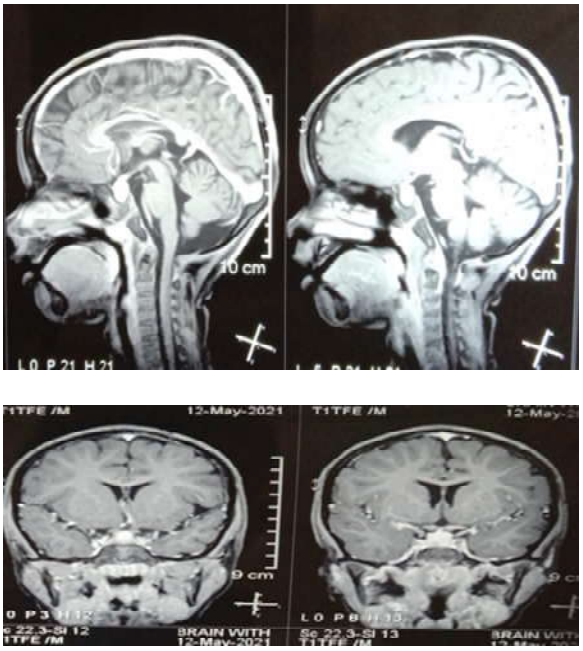


Fig. 4 & 5: Sagittal and coronal view of Magnetic resonance imaging brain contrast revealed an enlarged anterior pituitary gland showing intense enhancement on contrast of size 11mm x 16mm without invasion of 3rd ventricle or parasellar extension into cavernous sinus.

The child was managed with thyroid replacement therapy and was started on tablet L-thyroxine at a dose of 25 μg, which was escalated weekly to a daily dose of 50 μg, given in the early morning on an empty stomach and within a month of starting the therapy, her bleeding cycles stopped. She was referred to Pediatric surgery department ICH Chennai for further treatment of ovarian mass.

Discussion

Our patient presented with features of growth retardation and a delayed bone age with iso-sexual peripheral precocious puberty. The most common differentials of growth failure were juvenile hypothyroidism, Cushing's disease and panhypopituitarism. Short stature without obesity initially pointed towards juvenile hypothyroidism as the diagnosis.

Precocious puberty with adnexal masses is always associated with an advanced bone age with an elevated basal cortisol level, which was not seen in the index case. Severe growth retardation is also observed in patients with panhypopituitarism (due to the combined deficiency of growth hormone and TSH). It is associated with secondary hypothyroidism and delayed puberty, which was not seen in this patient. Hence, we came to the diagnosis as primary hypothyroidism in view of the linear growth failure with a delayed bone age and features of thyroid hormone insufficiency with pituitary lesion. The association of long-standing thyroid insufficiency with sexual precocity has been described in literature as Van Wyk and Grumbach syndrome (VWGS).

The exact mechanism of the development of precocious puberty in VWGS remains undefined and has been explained with several theories.[1] The most widely accepted of which is hormonal overlap in the pituitary feedback mechanism due to molecular mimicry between TSH and follicle-stimulating hormone (FSH) receptors. TSH in high concentrations leads to stimulation of gonadal FSH, as they share the common alpha subunit, which, in turn, increases the oestrogen levels, thereby manifesting as peripheral sexual precocity in females and macroorchidism in males. Pubic and axillary hairs are characteristically absent as there is no effect on adrenal hormone synthesis, thus it is also known as incomplete sexual precocity.[2]

Multiple cysts in the ovaries develop secondary to the enhanced production and decreased clearance of FSH due to hyperstimulation of its receptors by elevated thyrotropin-releasing hormone (TRH). In addition, high circulating TSH acts on the FSH receptors present on the ovarian follicle due to specificity spillover, resulting in the follicular cyst formation.[3] Pituitary adenoma reported on imaging is basically thyro-lactotrope hyperplasia, which is an indication of a long-standing, severe thyroid deficiency state. High circulating levels of TRH due to lack of thyroxine-mediated feedback inhibition result in hyperstimulation of thyro-lactotropes in the pituitary gland, thus presenting as a macroadenoma on imaging studies. The similar mechanism is also responsible for the stimulation of Prolactin secretion, thereby leading to hyperprolactinaemia.[4] Hyperplastic pituitary causes compression of the pituitary stalk that disrupts the hypothalamic inhibition of prolactin secretion, which further explains the presence of high prolactin levels with long-standing hypothyroidism.

The most common cause of thyroid insufficiency in an iodine sufficient area in young females has been attributed to immune-mediated destruction of the thyroid gland (Hashimoto's thyroiditis)[5] which is not the case in our patients as anti-TPO antibody titre was normal and screening of thyroid gland showed diffuse altered echo pattern with increased vascularity. Hypothyroidism in our patient could have been due to severe iodine deficiency or a delayed onset dyshormogenesis. Several methods have been devised for the estimation of bone age in children, of which the most frequently used and practically feasible is through Greulich and Pyle atlas. In females aged three years and above, assessment of the bone age is done through comparison between ossification centres of the epiphysis and metaphysis of proximal and intermediate phalangeal joints, in an X-ray of hand. This can also be done by comparison with age-matched standards derived from healthy children, published in the atlas.[6-8]

Our patient at presentation had a bone age of four years, which was delayed by two years from the chronological age. Thyroxine is needed for the secretion and action of growth hormone. It acts directly on the growth plate and promotes differentiation of chondrocytes to hypertrophic chondrocytes, which is required for the growth of long bones.[9] Deficiency states as seen in primary hypothyroidism lead to growth failure and a delayed bone age, as was seen in our patient. Thyroid replacement therapy in VWGS will lead to complete resolution of all the symptoms along with complete regression of ovarian cyst and pituitary hyperplasia without any need of surgical management.

Conclusion

Pediatric pituitary macroadenoma can be associated with Juvenile severe long-standing primary hypothyroidism with precocious puberty along with

the presence of pituitary hyperplasia and ovarian cysts. It is essential to know about this type of rare presentation and levothyroxine therapy can lead to complete resolution of all the signs and symptoms without any surgical intervention of non compressive pituitary tumors without hydrocephalus. Management of precocious puberty in a protocol-based algorithm not only helps in early diagnosis and management but also prevents any invasive surgical interventions for associated ovarian cystic lesions and pituitary hyperplasia.

Consent of patient and attenders

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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The second page should carry the full title of the manuscript and an abstract (of no more than 150 words for case reports, brief reports and 250 words for original articles). The abstract should be structured and state the Context (Background), Aims, Settings and Design, Methods and Materials, Statistical analysis used, Results and Conclusions. Below the abstract should provide 3 to 10 keywords.

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State the background of the study and purpose of the study and summarize the rationale for the study or observation.

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The methods section should include only information that was available at the time the plan or protocol for the study was written such as study approach, design, type of sample, sample size, sampling technique, setting of the study, description of data collection tools and methods; all information obtained during the conduct of the study belongs in the Results section.

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Include summary of key findings (primary outcome measures, secondary outcome measures, results as they relate to a prior hypothesis); Strengths and limitations of the study (study question, study design, data collection, analysis and interpretation); Interpretation and implications in the context of the totality of evidence (is there a systematic review to refer to, if not, could one be reasonably done here and now?, What this study adds to the available evidence, effects on patient care and health policy, possible mechanisms)? Controversies raised by this study; and Future research directions (for this particular research collaboration, underlying mechanisms, clinical research). Do not repeat in detail data or other material given in the Introduction or the Results section.

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Standard journal article

[1] Flink H, Tegelberg Å, Thörn M, Lagerlöf F. Effect of oral iron supplementation on unstimulated salivary flow rate: A randomized, double-blind, placebo-controlled trial. J Oral Pathol Med 2006; 35: 540-7.

[2] Twetman S, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, et al. Caries-preventive effect of fluoride toothpaste: A systematic review. Acta Odontol Scand 2003; 61: 347-55.

Article in supplement or special issue

[3] Fleischer W, Reimer K. Povidone iodine antisepsis. State of the art. Dermatology 1997; 195 Suppl 2: 3-9.

Corporate (collective) author

[4] American Academy of Periodontology. Sonic and ultrasonic scalers in periodontics. J Periodontol 2000; 71: 1792-801.

Unpublished article

[5] Garoushi S, Lassila LV, Tezvergil A, Vallittu PK. Static and fatigue compression test for particulate filler composite resin with fiber-reinforced composite substructure. Dent Mater 2006.

Personal author(s)

[6] Hosmer D, Lemeshow S. Applied logistic regression, 2nd edn. New York: Wiley-Interscience; 2000.

Chapter in book

[7] Nauntofte B, Tenovuo J, Lagerlöf F. Secretion and composition of saliva. In: Fejerskov O,

Guidelines for Authors

Kidd EAM, editors. Dental caries: The disease and its clinical management. Oxford: Blackwell Munksgaard; 2003. p. 7-27.

No author given

[8] World Health Organization. Oral health surveys - basic methods, 4th edn. Geneva: World Health Organization; 1997.

Reference from electronic media

[9] National Statistics Online—Trends in suicide by method in England and Wales, 1979-2001. www.statistics.gov.uk/downloads/theme_health/HSQ 20.pdf (accessed Jan 24, 2005): 7-18. Only verified references against the original documents should be cited. Authors are responsible for the accuracy and completeness of their references and for correct text citation. The number of reference should be kept limited to 20 in case of major communications and 10 for short communications.

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