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Case Report

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Central precocious puberty in Neurofibromatosis Type 1: A case study

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Abstract

The premature onset of secondary sexual characteristics defines precocious puberty (PP). Neurofibromatosis type 1 (NF1), an autosomal dominant genetic disorder, has been associated with a variety of systemic manifestations, including endocrinopathy like precocious puberty. In children with NF1, there is an increased risk of developing an optic chiasmal tumor, which is the primary cause of central precocious puberty (CPP) but not the only one. Here we present a case of CPP due to NF1. A 6-year 10-month-old boy presented to us with a growth spurt and premature appearance of secondary sexual characteristics with aggressive behavior, occasional headaches, hyperphagia, café-au-lait spots & a positive family history of nodular skin disease. During thorough evaluation, pubertal gonadotropin response was established after gonadotropin-releasing hormone (GnRH) stimulation and imaging studies revealed an optic pathway glioma. This known NF1 complication can disrupt hypothalamic-pituitary axis function and trigger hormonal imbalances; in this patient, it specifically affected the GnRH axis. Subsequently, the patient was managed with GnRH analog therapy while awaiting definitive management. *[J Assoc Clin Endocrinol Diabetol Bangladesh, January 2025; 4 (1): 43-47]*

Keywords: Precocious puberty, Neurofibromatosis, Optic nerve glioma

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Introduction

Precocious puberty is an uncommon manifestation of neurofibromatosis type 1 (NF1). NF1 is associated with a higher chance of optic chiasmal tumor development, which is the primary cause of central precocious puberty (CPP) but not the only one.[1] Central precocious puberty in boys is mostly pathologic (ranging from 20-75%) compared to girls. Of the tumors that cause precocious puberty, the hypothalamic hamartoma is the most common.[2] NF1 is a highly variable condition, manifestations such as café-au-lait spots and cutaneous neurofibromas occur in most (95%) patients. In contrast, other features, e.g. optic glioma, occur in fewer than 1%.[3] Even though CPP is more common in NF1, it becomes even more prevalent when an optic pathway tumor (OPT) is present.[4] Here we present a case of CPP in a boy where the etiology was evident early from the physical examination.

Case Summary

A 6-year 10-month-old boy was brought by the worried parents to the Department of Endocrinology with accelerated growth for one year & appearance of secondary sexual characteristics including pubic hair, phallic, and testicular enlargement. His parents also complained of his aggressive behavior, occasional headaches, hyperphagia, multiple skin spots & a positive family history (Figure-1) of nodular skin disease. His antenatal, natal, and postnatal period was uneventful except for an accidental head trauma on 4th day of age. Though he achieved his developmental milestones on time, his scholastic performance was poor. On examination: pulse – 78 bpm, BP – 110/70 mmHg without a postural drop. Regarding

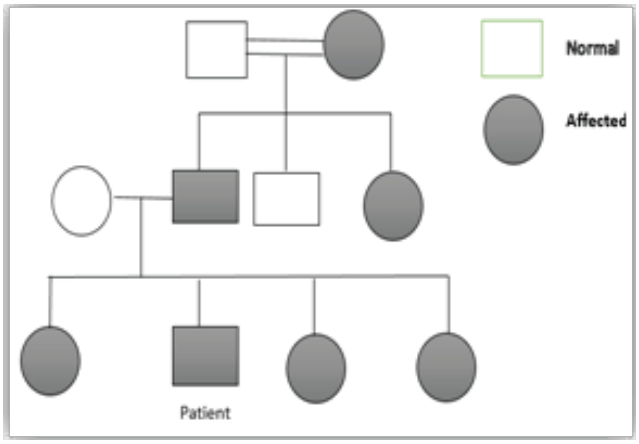

Figure11: Pedigree of nodular skin disease showing consanguinity of marriage in great grandparents with affected family members in three successive generations

anthropometry: weight – 47.10 kg (+6.8 SD), height-141 cm (+4.4 SD), BMI – 23.7 kg/m² (Table-I, Figure-2). His testicular volume was 20 mL bilaterally (Figure-3). He also had multiple (>10 in number) light to dark brown pigmented patches of variable size with irregular margins, involving the trunk and limbs, the largest one in the left thigh (Figure-4) & freckles in both axillae. On ophthalmologic examination: visual acuity, anterior chamber & fundus were normal.

On routine investigations: hemoglobin- 12.1 g/dL, erythrocyte sedimentation rate- 16 mm in 1st hour, hematocrit-32.8%; urine routine examination-normal; serum glutamate pyruvate transaminase-11U/L; serum creatinine- 0.59 mg/dL; fasting plasma glucose- 5.0 mmol/L; HbA1c- 5.4%; serum electrolytes: sodium- 138 mmol/L, potassium- 4.07 mmol/L, chloride- 101 mmol/L. Hormonal evaluation showed gonadotropin-releasing hormone (GnRH)

Table-I: Anthropometric findings of the patient

Parameters	Index case	Median for age	SD
Height	141 cm	121 cm	+4.4
Weight	47.1 kg	23 kg	+6.8
Pubic hair	Tanner stage 03	01	
Stretched penile length	10 cm	4.7 cm*	
Testicular volume	Right: 20 mL	1.8 mL*	+26#
	Left: 20 mL	1.8 mL*	+26#

* According to Jaiswal et al. 2019[5]
\# According to Joustra et al. 2015[6]

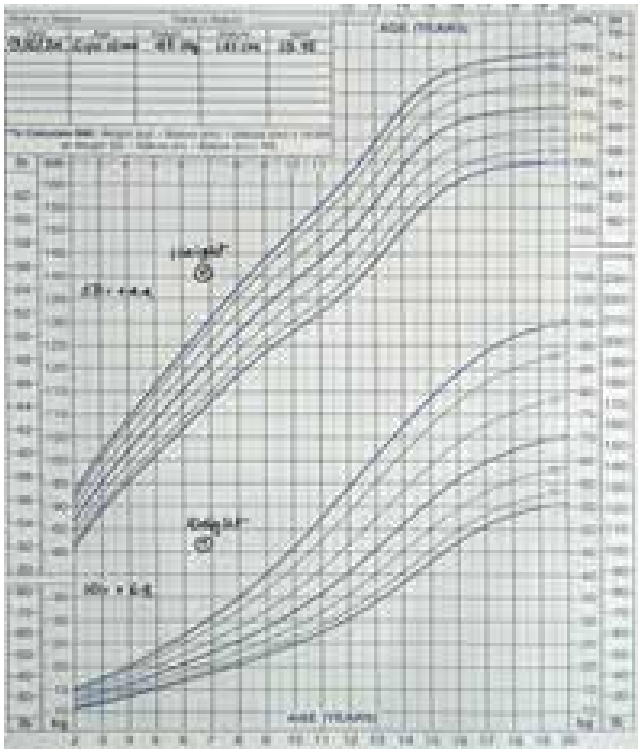

Figure-2: Growth chart of the patient showing height +4.4SD, weight +6.8SD

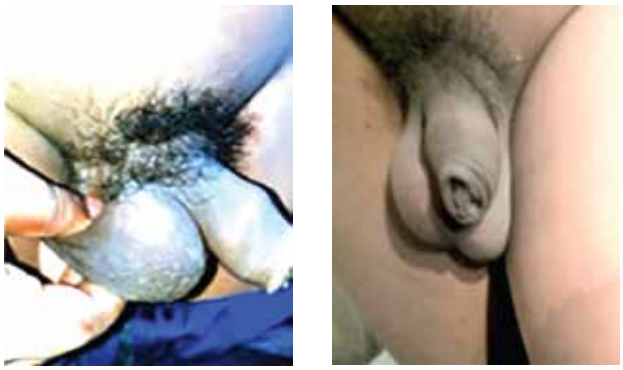

Figure-3: Tanner staging of the patient showing enlarged testis & phallus along with pubic hair stage 3: darker, coarser, and more curled hair, spreading sparsely over the junction of pubes

dependent isosexual pubertal response (Table-II).
In imaging studies, radiological bone age was between 11 and 12 years, and there were no bony deformities (Figure-5). A magnetic resonance imaging (MRI) of the pituitary showed a lobulated mass measuring about 2.8 (anteroposterior) x 2.7 (craniocaudal) x 3.9 (trans diameter) cm at the supra-sellar region inseparable from the anteroinferior aspect of the hypothalamus, superior

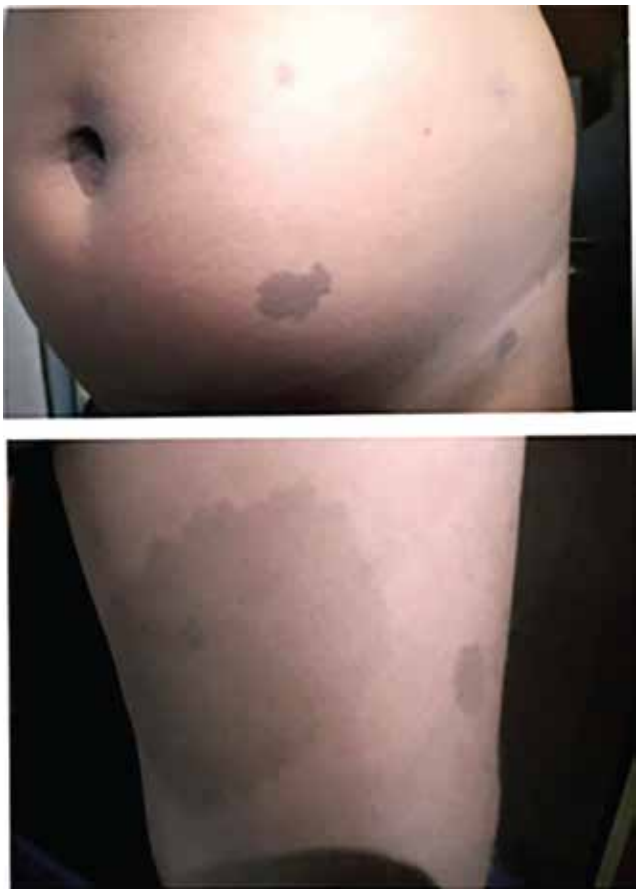

Figure-4: Café-au-lait spots (Multiple, crossing the midline & largest one in left thigh)

Table-II: Hormone profile of the patient

Test name	Result	Normal values
TSH	1.61 µIU/mL	0.70-5.50 µIU/mL
FT4	1.35 ng/dL	0.89-1.76 ng/dL
ACTH	54.1 pg/mL	ND- 46 pg/mL
Basal cortisol	185.09 nmol/L	55- 469 nmol/L
Cortisol, 30 min after SST	667 nmol/L	
Testosterone	244.74 ng/dL	< 13 ng/dL
LH	2.29 mIU/mL	<0.3 mIU/mL
LH (01 hr after GnRH)	9.49 mIU/mL	
FSH	1.94 mIU/mL	< 3 mIU/mL
17-OH-Progesterone	1.70 ng/mL	0.1- 1.70 ng/mlL
Prolactin	20.58 ng/mL	2.10-17.70 ng/mL
Growth hormone	0.739 ng/mL	0.06-5 ng/mL

TSH: Thyroid-stimulating hormone FT4: Free thyroxine
ACTH: Adrenocorticotropic hormone LH: Luteinizing hormone
GnRH: Gonadotropin-releasing hormone FSH: Follicle-stimulating hormone

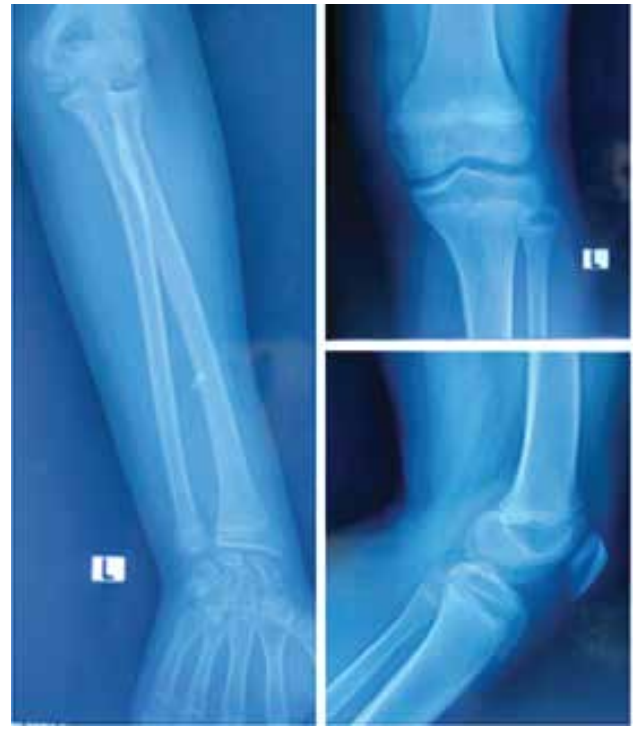

Figure-5: X-ray for bone age showing the presence of all carpal bones of the hand corresponding to radiological age between 11-12 years

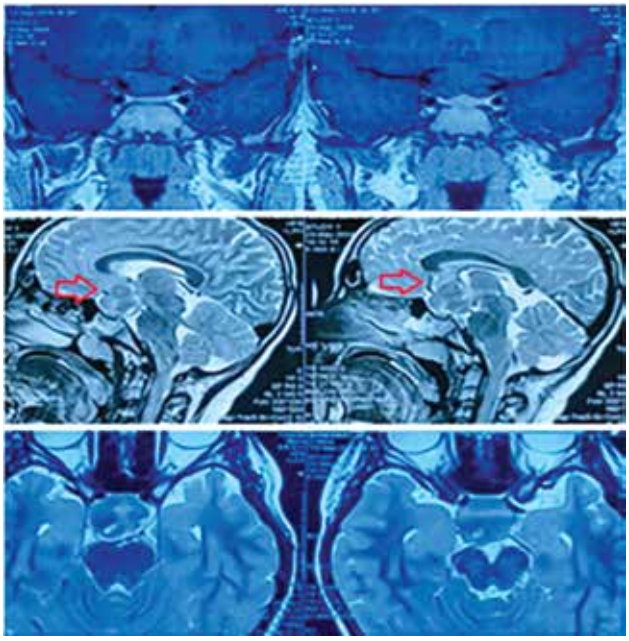

Figure-6: Magnetic Resonance Imaging of the pituitary (Arrowhead showing suprasellar mass lesion)

aspect of the optic chiasma & pituitary infundibulum, suggestive of optic pathway glioma (Figure-6). The patient was initiated on GnRH agonist therapy to halt pubertal progression. A multidisciplinary team was formed to plan his management, and he is currently under close monitoring while awaiting definitive surgery.

Discussion

Precocious puberty is a condition where secondary sexual characteristics develop before the age of 8 years for girls and 9 years for boys and is more common in girls than counterparts.[7] In this instance, our patient presented at the age of 6, which is significantly younger than the typical age for pubertal onset. In boys, one of the most obvious markers of pubertal orientation is testicular size. A testicular volume of 4 mL or more & length >2.5 cm usually suggests (central) gonadotropin stimulation.[8] Our patient's 20 ml testicular volume at presentation strongly suggests central etiology. Boys are more likely to have an underlying pathological cause for CPP, whereas girls typically experience it idiopathically without any nervous system abnormalities.[7] One of the most common observed pathologies of the central nervous system is hypothalamic hamartoma. Other known risk factors for CPP are NF1, hydrocephaly, meningomyelocele, neonatal encephalopathy, and low-dose cranial radiation exposure.[9]

Prevalence of NF1, is 2 to 3 people per 10,000. Varieties of features may be present. Frequent ones are café-au-lait macules, neurofibromas, intertriginous freckling, lisch nodules, and learning disabilities. Optic and other gliomas, malignant peripheral nerve sheath tumors, and osseous lesions can also be present.[3] Though the responsible gene of NF1 has already been identified, still a diagnosis of NF1 is made usually- based on clinical criteria. The National Institutes of Health Diagnostic Criteria is recommended for diagnosing NF1.[10] Based on this criterion, our patient was diagnosed as NF1, as he had multiple café-au-lait spots with a positive family history, axillary freckling, along with optic pathway glioma on pituitary MRI.

Another diagnosis to be considered in a precocious patient with café-au-lait spots is McCune-Albright Syndrome (MAS). Though its phenotype is far more complex, fibrous dysplasia of bone (FD) is another component of the classical triad, which is excluded in our patient, as he had no bony deformity with a normal x-ray appearance. Additionally, café-au-lait macules in MAS are characterized by their location respecting the body's midline and their irregular jagged edges which are sometimes compared to the 'Coast of Maine'.[11]

In children with NF1 optic pathway gliomas occur in about 15% of cases, but only one-half to one-third of these patients become symptomatic. In patients without NF1, optic gliomas behave differently from those of a benign nature of NF1. In an NF1 patient, optic gliomas usually arise in the first 4 years of life. It is usually bilateral and involves the optic nerve at the intraorbital portion, typically with or without optic chiasmal involvement. A relatively frequent presenting symptom of optic glioma in children with NF1 is precocious puberty.[12] Optic glioma may present with various symptoms, including diminished visual acuity, visual field defects, swelling of the optic disc, proptosis, alterations in visual evoked potentials, abnormalities in optical coherence tomography, strabismus, nystagmus, precocious puberty, and various neurologic signs. Here our patient with optic glioma presented with precocious puberty, possibly disrupting the hypothalamic-pituitary-gonadal axis due to the close proximation of the tumor to the hypothalamus. Optic pathway gliomas when symptomatic, cause significant morbidity but there is no evidence that they increase the risk of premature death in NF1 patients.[12]

Regarding the treatment of optic pathway glioma in NF1, watchful waiting followed by systemic cytotoxic chemotherapy is the treatment of choice in children with progressive symptoms.[13] Despite availability, targeted treatment and radiotherapy are infrequently employed and due to the possibility of severe visual and neurological impairments, surgery is usually avoided. Long-acting GnRH analogs are the effective & safe treatment of CPP & widely used for many years.[14] They can be instituted while awaiting definitive therapy. In our patient, we also initiated GnRH agonist and formed a multidisciplinary team for subsequent management.

Conclusion

In children with NF1, most optic gliomas are usually discovered by screening neuroimaging rather than by the presence of symptoms. So, children with NF1 should be followed up for the early signs of puberty, such as growth acceleration. Besides, patients with central precocious puberty should be examined carefully to look for any peripheral signs that may point toward the underlying etiology. This way, an etiological diagnosis can be suspected before undergoing troublesome investigations.

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Disclosure
The authors declare that no conflict of interest could be perceived as prejudicing the impartiality of the research reported.

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Data Availability
Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author upon reasonable request.

Ethical Approval and Consent to Participate
Written informed consent was obtained from the patient. All methods were performed in accordance with the relevant guidelines and regulations.

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