CASE REPORT

Neurofibromatosis type 1 (NF1) presenting with dichotomous pubertal presentation: A case series

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Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder that is caused by a mutation in the NF1 gene, which is located on chromosome 17q11.2, which encodes for a protein known as "Neurofibromin", which acts as an inhibitor of oncogene RAS. This gene mutation causes tumours to grow on nerves which results in other systemic abnormalities such as skin changes, bone and eye abnormalities, hormonal imbalances, and diversity in achievement of puberty with neurologic complications. NF1 has a wide variety of associations in context with puberty. It is important to determine the cause of precocious and delayed puberty in order to establish an early treatment plan, to lead a successful prognosis, and decrease complications. The case reports of two patients presenting with dichotomous pubertal variation in association with NF1 are presented.

Keywords: Neurofibromatosis, Delayed puberty, Early puberty, Genetics.

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Introduction

Undoubtedly, one of the most prevalent genetic illnesses is neurofibromatosis (NF). This phacomatosis, which is inherited in an autosomal dominant manner and can manifest as numerous skin lesions or neoplasms of the peripheral and central nervous systems, is divided into two genetically different subgroups. About one in 3,500 people have neurofibromatosis type 1 (NF1), commonly known as Recklinghausen's disease.[1] The disease's broad clinical spectrum also includes various consequences such as bone dysplasia, convulsions, mental retardation, learning difficulties, and optic glioma. Extreme clinical diversity, especially in family situations, is an NF1 feature.[2-4] The well-known diagnostic criteria have been revised, and having a minimum of two of those features is sufficient for the diagnosis.[5] Precocious puberty (PP) is a common NF1 consequence that mostly affects people with optic pathway tumours (OPT). However, it has also been observed in patients with no evidence of optic gliomas, with a prevalence that is likely comparable to that of the general population.6 Delay in puberty has also been regularly documented in NF1 besides PP.[6]

Here, we describe the case reports of two patients who demonstrated contrasting patterns of puberty in NF1.

Case 1

A 19-year-old female presented to the endocrinology OPD in June 2023 at National Institute of Child Health, Karachi, with complaints of a sizeable lumpy skin lesion over the back and for not achieving menarche yet. She was developmentally normal and did not have a history of seizures. On examination, she was short-heighted (below -2SDS) and had a kyphoscoliosis deformity. She had a large irregular skin lesion (Plexiform Neurofibroma, [Figure 1]) measuring about 6x8 cm at the back, multiple cafe'-au-lait spots (Figure 2) (most prominent of which measured 3x4 cm), multiple neurofibromas (Figure 3) and axillary freckling (Figure 4). Genital examination revealed normal female genitalia with prepubertal tanner staging [B1, A1, P1=0] (as per Marshall and Tanner scale 1969)[7] and the absence of axillary hair. She was investigated extensively in regards to NF1 and delayed puberty and her work up

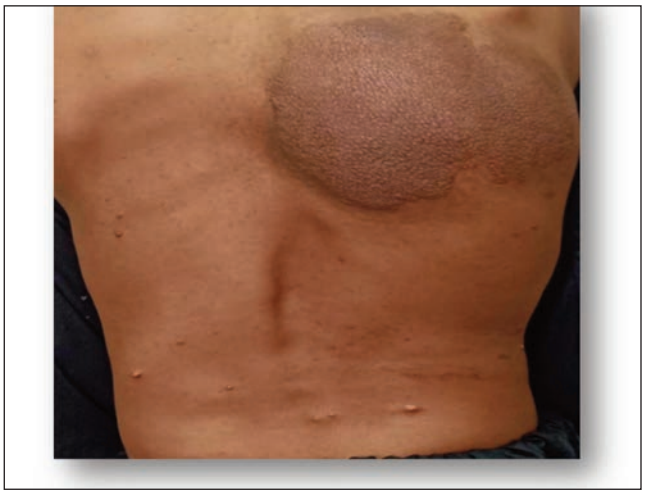

Figure-1: (Plexiform neurofibroma.

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showed bone age of 12 years that was less than her chronological age. Ultrasound of the pelvis showed a slit-like uterus and streak ovaries. Serum FSH and LH were high (114.67 mIU/ml (0.2-2.4) and 25.41 mIU/ml (0.8-1.3) respectively), with decreased levels of serum oestrogen and IGF-1 (5.0 mIU/ml and 85 ng/ml respectively). NORMAL VALUES IGF (27.4-113.5) Estrogen 30-400ng/ml. This hypergonadotrophic hypogonadism type of delayed puberty was managed by hormonal replacement therapy i.e., tablet Ethynyl Estradiol, and the patient was referred to the orthopaedic surgeon for the management of kyphoscoliosis deformities.

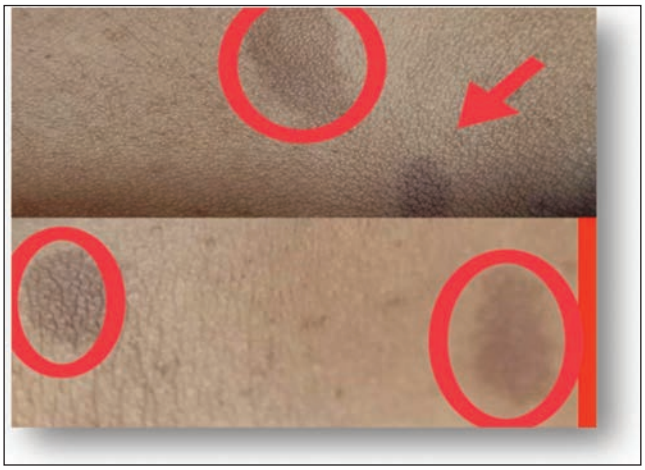

Figure-2: CAFÉ-EU-LAIT macules.

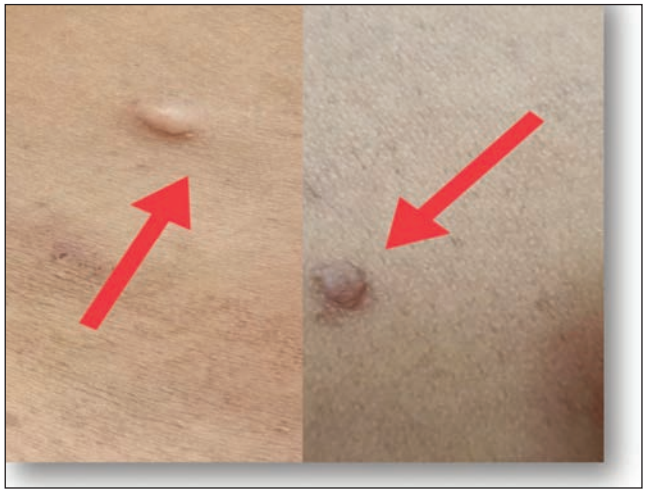

Figure-3 Neurofibromas.

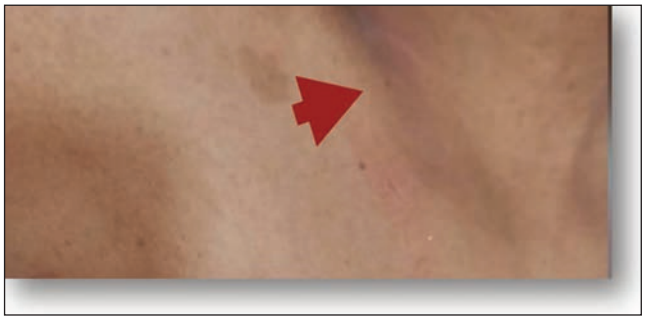

Figure-4 Axillary freckling (Crowe's sign).

Case 2

An eight-year-old male child presented with multiple cafe'-au-lait spots on the back and typical signs of precocious puberty at the endocrine OPD of National Institute of Child Health, Karachi, in February 2023. He was developmentally delayed and had decreased visual ability. On genital examination, he had bilateral testicular volume of 7ml, stretch penile length was 6cm, and dark pigmented genitalia with denser, coarse, and curly pubic hair with tanner staging of IV as per Marshall and Tanner scale 1969. MRI of the brain with pituitary protocol showed bilateral optic pathway gliomas with FASI (Focal areas of signal hyperintensity) which were strongly suggestive of the neuroimaging feature of NF1 (figure 5). His hormonal analysis showed markedly elevated levels of LH, FSH, prolactin, and testosterone, while serum cortisol and thyroid profile were normal as shown in Table 1. His genetic workup revealed a pathogenic heterozygous mutation in the NF1 gene with variant (c. 1756_1759del). He was then treated with GnRH analogue injection Lectrum 3.75 mg every month. On follow-up visits after six months of treatment his testicular volume, stretch penile length, and

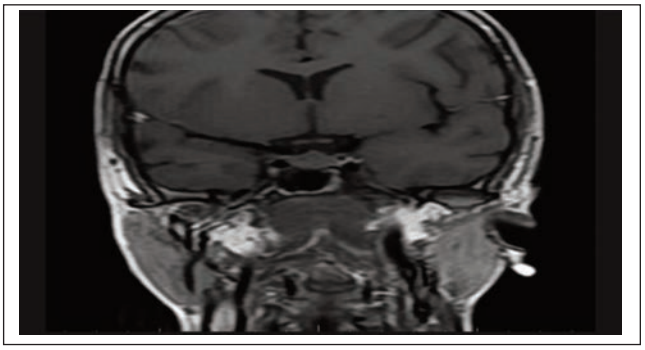

Figure-5 Pituitary microadenoma.

Table: Findings from a review and analyses of 37 reported cases of *Candida tropicalis* endocarditis in the peer reviewed literature from 1974 to 2021.

Investigations	Case 1	Case 2
Serum FSH	114.67 mIU/ml (0.0-0.15)	5.83 mIU/ml (0.0-5.0)
Serum LH	25.41 mIU/ml (1-3.5)	4.40 mIU/ml (1-3.5)
Serum Estrogen	5.0 mIU/ml (7.63-42.6)	-
Serum Testosterone	-	902.5 ng/ml (3-30ng/ml)
Serum Prolactin	-	24.55 ng/ml (2.9-9.2)
TSH	1.5uIU/ml (0.9-6.2)	1.42 (0.9-6.2)
U/S Pelvis	Streak Ovaries	Normal
MRI Brain	Pituitary Microadenoma	Optic Pathway Gliomas
Bone Scan	BA < CA	BA > CA
Slit Lamp Examination for Iris Lisch Nodules	Present	Normal

pubic hair growth were static and hormonal levels had decreased but still in pubertal range.

Table 1 summarises the investigations of both the cases.

Discussion

The NF1 tumour suppressor gene, which spans around 300 kb of DNA within the genome at locus 17q11.2, is the root cause of NF1.[8,9] Because there are a lot of coding exons and there is a lot of mutational diversity, the NF1 gene's mutational gamut is complicated. The majority of alterations cause neurofibromin to be truncated and lose its functionality. There is no discernible genotype/phenotype relationship.[10-12] Neurofibromatosis, a genetic disorder affecting nerve tissue growth, can influence the timing of puberty, leading to either precocious or delayed onset of sexual maturation. Precocious puberty, characterised by early development, may occur due to disruptions in the hypothalamus and pituitary gland, impacting hormone regulation. This early onset requires a multidisciplinary approach for management, including hormonal therapy and addressing any underlying causes such as tumours. Conversely, delayed puberty in neurofibromatosis can result from hormonal imbalances, physical complications, or psychosocial stressors.[10,11] Management of delayed puberty involves a comprehensive evaluation to address both physical and emotional needs, potentially including hormone therapy, surgical interventions, and supportive care.[12] Understanding these dynamics is crucial for providing effective treatment and support for individuals living with neurofibromatosis and its associated puberty-related challenges.[13,14] Precocious puberty may be caused more by optic pathway glioma than by the existence of the NF1 abnormality. Long-term monitoring is required because individuals with optic glioma and premature puberty may subsequently develop gonadotropin insufficiency.[6,15]

Because of the diverse and unpredictable complications associated with NF1, close multidisciplinary follow-up is necessary. Most people with NF1 will start puberty at the expected age range, but some may have precocious or delayed puberty, and affected children also face short stature in 30% of the cases.[6] Patients with NF1 should have regular clinical assessments yearly, focusing on developing potential complications and their timely management. These assessments include ophthalmologic examination, neurologic assessment, blood pressure monitoring, and endocrinologic assessment.[1]

Conclusion

In conclusion, there is a dichotomous presentation of puberty in patients with NF1. The presence of optic pathway glioma in a patient of NF1 warrants the workup of precocious puberty, and while dealing with a case of NF1, delayed puberty must also be kept in mind. Fortunately, both variations of puberty in NF1 patients are treatable. To develop an early treatment strategy, ensure a good prognosis, and reduce complications, it is critical to identify the underlying causes of precocious and delayed puberty.

Consent: Informed and written consent was taken from the guardians of both cases for case sharing and pictures.

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Conflict of Interest: None.

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