International Journal of Contemporary Pediatrics
Ramalingam BA et al. Int J Contemp Pediatr. 2026 Feb;13(2):321-323
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20260108

Case Report

Functional hypogonadotropic hypogonadism in an adolescent male with neurofibromatosis type 1: a case report

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Received: 19 November 2025
Revised: 12 December 2025
Accepted: 02 January 2026

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ABSTRACT

Delayed puberty in males may result from permanent or reversible causes of hypogonadotropic hypogonadism. We describe a 16-year-old adolescent male with neurofibromatosis type 1 (NF1) who presented with delayed puberty. Baseline gonadotropins and testosterone levels were low; however, a robust luteinizing hormone response to leuprolide stimulation confirmed preserved pituitary reserve, consistent with functional hypothalamic suppression. The patient had undergone multiple major surgeries and demonstrated NF1-related sphenoid bone abnormalities on imaging. Testosterone therapy was initiated with gradual dose escalation. This case highlights the importance of identifying reversible causes of delayed puberty in adolescents with chronic multisystem disorders.

Keywords: Delayed puberty, Hypogonadotropic hypogonadism, Neurofibromatosis type 1, GnRH stimulation test, Testosterone therapy

INTRODUCTION

Delayed puberty in males is defined as the absence of testicular enlargement (testicular volume <4 ml) by 14–16 years of age.[1] Hypogonadotropic hypogonadism (HH) is an important etiology and is broadly classified into permanent and functional forms.[2] Permanent HH results from intrinsic hypothalamic or pituitary pathology, whereas functional HH represents transient suppression of the hypothalamic–pituitary–gonadal (HPG) axis due to chronic illness, undernutrition, psychosocial stress, or systemic disease.[3]

Several clinical studies have demonstrated that functional HH is potentially reversible, and dynamic GnRH or GnRH agonist stimulation testing plays a pivotal role in differentiating it from permanent causes.[4,5] Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder with skeletal and neurological manifestations. While precocious puberty has been well documented in NF1, delayed puberty is rarely reported.[6] Chronic disease burden, repeated surgical stress, and subtle central nervous system involvement may contribute to hypothalamic suppression in affected individuals. We report a case of functional GnRH deficiency in an adolescent male with NF1.

CASE REPORT

A 16-year-old boy with a known diagnosis of NF1 was referred for evaluation of delayed puberty. He had previously undergone posterior spinal instrumentation and scoliosis correction with right costoplasty, along with excision of an anterior chest wall neurofibroma (Figures 1 and 2). There was no history of anosmia, cranial irradiation, or chronic systemic illness apart from NF1.

On examination, anthropometric parameters were appropriate for age. Pubertal assessment revealed Tanner stage I pubic hair with testicular volumes of 3 ml (right)

and 4 ml (left). Baseline hormonal evaluation showed luteinizing hormone (LH) of 1.65 mIU/ml and serum testosterone of 0.707 ng/ml. Following leuprolide stimulation, LH increased to 73.50 mIU/ml and follicle-stimulating hormone (FSH) to 23.8 mIU/ml, indicating intact pituitary gonadotroph function. Bone age assessment demonstrated a delay, corresponding to 11 years. Brain magnetic resonance imaging (MRI) revealed abnormal curvature and focal signal alteration of the left greater wing of the sphenoid, consistent with NF1-related skeletal involvement (Figure 3).

Figure 1: Posterior view of the patient showing scoliosis, post-surgical scar, and trunk asymmetry consistent with neurofibromatosis type 1.

Figure 2: Anterior view demonstrating slender habitus and absence of secondary sexual characteristics, consistent with delayed puberty.

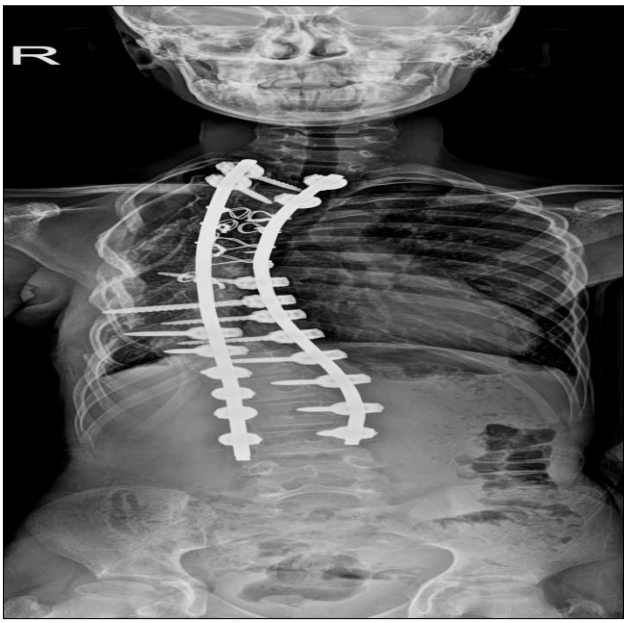

Figure 3: Plain radiograph showing post-operative status following scoliosis correction with spinal instrumentation and costoplasty.

Management and outcome

The patient was initiated on intramuscular testosterone enanthate at a dose of 100 mg monthly, with plans for gradual dose escalation. Regular follow-up was arranged to monitor pubertal progression, growth velocity, and potential recovery of endogenous HPG axis activity. Psychosocial support and counseling were also emphasized.

DISCUSSION

Differentiating functional hypogonadotropic hypogonadism from permanent forms is essential in adolescents presenting with delayed puberty.[1,2] In the present case, low baseline gonadotropin and testosterone levels suggested central hypogonadism. However, the marked rise in LH and FSH following leuprolide stimulation demonstrated preserved pituitary reserve, favoring functional hypothalamic suppression rather than permanent HH.[4,7]

In the present case, each evaluated parameter supports a diagnosis of functional hypogonadotropic hypogonadism. Baseline gonadotropin and testosterone levels were low, a pattern commonly reported in adolescents with functional suppression of the hypothalamic–pituitary–gonadal axis. Prior studies have demonstrated that an exaggerated luteinizing hormone response to GnRH agonist stimulation reliably excludes permanent hypogonadotropic hypogonadism and indicates preserved pituitary reserve. The marked LH surge observed in our patient is comparable to responses described in adolescents with constitutional delay of growth and puberty and functional hypogonadism. Delayed bone age, another important

parameter in this case, is a well-recognized feature of functional hypogonadotropic hypogonadism and reflects delayed skeletal maturation due to reduced sex steroid exposure. In contrast, patients with congenital or permanent hypogonadotropic hypogonadism often demonstrate less pronounced bone age delay. NF1 is more frequently associated with central precocious puberty, particularly in the presence of optic pathway gliomas; however, delayed puberty remains rarely reported. In this patient, extensive skeletal involvement, multiple major surgical interventions, and NF1-related craniofacial abnormalities may have contributed to chronic physiological stress and transient hypothalamic suppression. Short-term testosterone therapy has been shown in previous studies to safely induce pubertal progression, improve psychosocial outcomes, and allow spontaneous recovery of the hypothalamic–pituitary–gonadal axis in functional hypogonadotropic hypogonadism. Our findings are consistent with existing literature and further expand the phenotypic spectrum of pubertal disorders associated with NF1.

Dynamic GnRH or GnRH agonist testing has been shown to reliably distinguish reversible HH from congenital or permanent forms, as patients with functional suppression exhibit robust gonadotropin responses.[5,8] The magnitude of LH response in our patient was comparable to that reported in adolescents with constitutional delay and functional HH.[7]

Delayed bone age, as seen in this patient, is a recognized feature of functional HH and reflects delayed skeletal maturation due to reduced sex steroid exposure.[3,9] In contrast, patients with permanent HH may exhibit relatively less bone age delay. Although NF1 is more commonly associated with precocious puberty, delayed pubertal development has been rarely described.[6] Chronic illness burden, repeated major surgical interventions, and possible subtle hypothalamic involvement may contribute to transient suppression of the HPG axis in such patients.

Testosterone therapy is the recommended approach for pubertal induction in males with delayed puberty.[12] Low-dose regimens allow development of secondary sexual characteristics while minimizing suppression of endogenous gonadotropin secretion. In functional HH, short-term testosterone therapy may also facilitate spontaneous recovery of the HPG axis while providing psychosocial benefits.

CONCLUSION

Adolescents with NF1 presenting with delayed puberty should be evaluated for potentially reversible causes of hypogonadotropic hypogonadism. GnRH agonist stimulation testing is valuable in demonstrating preserved pituitary function. Timely initiation of testosterone therapy can safely induce pubertal progression while awaiting endogenous recovery.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ramalingam BA, Parvathy S. Functional hypogonadotropic hypogonadism in an adolescent male with neurofibromatosis type 1: a case report. Int J Contemp Pediatr 2026;13:321-3.