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# Endocrine Conditions in Neurofibromatosis 1

*Shilpa Mehta and Resmy Palliyil Gopi*

## Abstract

Neurofibromatosis 1 (NF1) is an autosomal-dominant multisystemic neurocutaneous disorder primarily affecting the skin, bone and the nervous system. It has been long appreciated that NF1 is often associated with endocrine disorders. In this chapter, we will discuss the endocrine disorders associated with NF1. The most common endocrinological disorders in NF1 are short stature with or without growth hormone deficiency, central precocious puberty, growth hormone excess. Less common endocrine-related conditions in NF1 include gynecomastia, diencephalic syndrome and the presence of endocrine tumors like pheochromocytoma.

**Keywords:** NF1, endocrine conditions, short stature, GHD, growth hormone excess, central precocious puberty, endocrine tumors

## 1. Introduction

Neurofibromatosis 1 (NF1) is an autosomal-dominant multisystemic neurocutaneous disorder primarily affecting the skin, bone and the nervous system. The incidence has been described to be around 1 in 2500–3500 live births, and the estimated prevalence is 1 in 4000–5000. The penetrance is complete, but the severity of the clinical manifestations is variable and unpredictable, even within affected families [1]. Approximately one-half of the cases are familial and the remainder arise from a *de novo* NF1 mutation. The diagnosis of NF1 relies primarily on the clinical grounds, which is based on the National Institutes of Health (NIH) diagnostic criteria [2], as described in the other chapter.

In this chapter, we will discuss endocrine disorders associated with NF1. The association of NF1 with endocrinopathies has been reported since 1920 [3]. The data on the incidence and prevalence of endocrine disorders in NF1 are scarce [4]. The most common endocrine disorders in NF1 are short stature with or without growth hormone deficiency (GHD), central precocious puberty, growth hormone excess (GHE). Less common endocrine-related conditions in NF1 include gynecomastia, diencephalic syndrome and the presence of endocrine tumors like pheochromocytoma. The most endocrine disorders in NF1 are thought to be related to central nervous system tumors compromising the hypothalamic and pituitary function [1]. In a recent retrospective study, endocrine disorders were found in approximately one-third of patients with NF1 and optic pathway glioma [4].

## 2. Pathophysiology

The protein product of the NF1 gene is a large cytoplasmic protein, neurofibromin. The neurofibromin coding sequence comprises a 300-amino acid sequence, with the GTPase-activating protein domain. Loss of neurofibromin function results in hyperactivation of the proto-oncogene RAS, as well as enhanced activity of RAS downstream effectors. In animal studies with a mouse model, loss of neurofibromin alone is insufficient to cause nervous system tumor formation and that additional genetic or environmental changes are probably necessary for tumor formation [5].

Neurofibromin also regulates intracellular cAMP generation in the brain. Cyclic AMP and the transcription factor called cAMP response element-binding protein (CREB) represent key regulators of hypothalamic-pituitary axis development. In animal models, brain-specific loss of CREB is known to cause hypopituitarism and poor growth [5, 6]. During embryonic differentiation, neurofibromin regulates the proliferation and maturation of both glial and neuronal progenitor cells [7]. The animal studies with a mouse model (*Nf1<sup>BLBPCKO</sup>* mice) with NF1 gene inactivation in neuroglial progenitor cells showed significantly reduced body weight and a small anterior pituitary gland with normal posterior pituitary. The anterior pituitary hypoplasia reflects a loss of neurofibromin expression in the hypothalamus, leading to reduced growth hormone-releasing hormone (GHRH), growth hormone (GH) and insulin-like growth factor-1 (IGF1) production. GHRH gene expression analysis by immunohistochemistry in hypothalamic-pituitary tissue from these mice has shown a significant reduction in GHRH staining within the median eminence. About 40–60% reduction in the GHRH mRNA was evident in the hypothalamic cells of *Nf1<sup>BLBPCKO</sup>* mice, compared with wild-type controls.

## 3. Endocrine disorders in NF1

### 3.1 Short stature

Short stature is a well-recognized clinical feature of NF1. The risk factors for short stature in NF1 include suprasellar lesion, surgery or radiation for such lesions causing GHD and scoliosis or other skeletal abnormalities. Short stature has been reported in 13–33% of children with NF1 [8, 9]. After exclusion of risk factors, the short stature has been reported in 8% of children with NF1 [10]. Short stature in NF1 has been associated both with and without GHD.

The population with NF1 as a whole is significantly shorter than the general population and specific growth charts are available for children with NF1. Clementi et al. analyzed the growth profile of 528 children with NF1 based on the data collected through a population-based registry from three contiguous regions of North-East Italy, and created growth charts of height, weight and head circumference (HC) for children with NF1 [11]. There was no difference in height between children with NF1 and normal children up to 7 years in girls and 12 years in boys. Beyond that age, the 50th centile of children with NF1 overlapped with the 25th centile of normal children and the 3rd centile of children with NF1 was significantly lower than the normal children. The height growth velocity was normal for both sexes in children with NF1 during childhood, but pubertal spurt was reduced in NF1 boys. Children with NF1 and normal children showed a similar median weight during the whole growth period. The 3rd centile for weight was consistently lower in children with NF1 during adolescence, and the 97th centile was higher during adulthood. The HC was larger in children with NF1 during the whole childhood and adulthood.

These growth charts can be used in neurofibromatosis clinics for the identification of secondary growth disorders, for growth prognosis and the evaluation of the effects of various treatments in children with NF1 [11].

### **3.2 Growth hormone deficiency (GHD)**

The GHD is more common in children with NF1 compared to the general population. Cnossen et al. found a prevalence of 2.5% among patients with NF-1, which is higher than the 0.03% observed in the general pediatric population [12]. The cause of GH deficiency in NF1 is not clear, but it is much more common in the presence of an intracranial tumor and in some cases, it is clearly related to the treatment of these tumors with surgery and radiotherapy [13, 14]. GHD is also seen in children with NF-1 without suprasellar abnormalities, which suggests an association with NF-1 independent of organic pituitary damage [9].

As children with NF1 have a greatly increased risk of malignancy, there has been concern about the safety of GH treatment in children with NF1. Howell et al. reviewed the safety and efficacy of growth hormone therapy in a cohort of 102 children with both NF and biochemical evidence of GHD who had received GH replacement therapy at a mean dose of 0.18 mg/kg/week. During the 1st year, the median height velocity increased significantly from 4.2 cm/year before treatment to 7.1 cm/year, and the median height standard deviation score increased from -2.4 to -1.9. Children with NF1 and GHD respond favorably to treatment with GH, but not as good as that seen in patients with idiopathic GHD. Most of the adverse events reported in this cohort during GH therapy were either relatively minor or unlikely to be directly attributable to GH therapy. Five GH-treated patients had either a recurrence of an intracranial tumor or a second intracranial tumor. This incidence of tumor occurrence was comparable to that previously reported in similar NF1 patients not treated with GH. GH therapy did not influence the progression of any of the features of NF1, including intracranial tumors, and was not associated with an excess of other adverse events. Though controversial, GH treatment in NF1 patient is beneficial in terms of growth rate [15]. There is a need for prospective and randomized studies to test the efficacy, risk and safety of GH therapy in this population.

### **3.3 Central precocious puberty (CPP)**

Central precocious puberty is the most common endocrine disorder in children with NF1. The prevalence of this disorder in patients with NF1 is 3%, which is markedly higher than the prevalence of about 0.6% reported in the general pediatric population [1]. Central precocious puberty is reported more often in girls than in boys, while precocious puberty in NF1 is observed more in boys [12, 16].

Precocious puberty in NF1 almost occurred invariably in association with optic pathway tumors, especially when optic chiasm is involved [16]. This supports the theory that lesions located near the hypothalamus interfere with the tonic Central nervous system inhibitions of the hypothalamic-pituitary-gonadal axis, resulting in the premature onset of puberty [17]. However precocious puberty in NF1 has also been reported in the absence of optic glioma [12]. Saxena reported two cases of precocious puberty in patients with NF1 without tumors of the optic chiasm, but no imaging was available at that time, which leaves open the possibility of undetected tumors [3]. In the study reported by Cnossen et al., CPP was diagnosed in 3 of 122 children but only 1 child had an OPG at MRI showing that optic chiasm glioma is not a prerequisite for CPP [12]. This could possibly be due to some cerebral abnormality undetected by neuroimaging or due to abnormalities at the cellular level involving neurofibromin. Other tumors like hypothalamic hamartoma that causes



precocious puberty in the general population have also been reported to cause precocious puberty in patients with NF1 [18].

Treatment of NF1 children with CPP is similar to those approved for children with idiopathic or organic CPP not related to NF1. Pubertal progression in CPP is treated by administration of a gonadotropin-releasing hormone (GnRH) agonist. These agents act by causing continuous stimulation of the pituitary gonadotrophs, instead of physiologic pulsatile stimulation from hypothalamic GnRH and this continuous stimulation leads to desensitization of the gonadotroph cells and suppression of gonadotropins, resulting in decreased sex steroid production. These treatments are mostly effective in children with younger age at the onset of puberty or with a progressive decline in predicted adult height.

In contrast to precocious pubertal development, a very high incidence of delayed menarche among NF1 girls has been reported [19].

### **3.4 GH excess**

GH excess is generally a rare disease in children and adults but affects patients with NF1 at higher rates. It is mostly observed in the presence of OPG located inside the hypothalamic area or close to it. The prevalence of GH excess in patients with NF1 is unknown. Cambiaso et al. noted that 10% of the population with NF1 had abnormalities in the GH axis consistent with GH excess. All the affected patients studied by Cambiaso et al. had a tumor involving the optic chiasm, without pituitary involvement [20].

The mechanism underlying GH excess in NF1 is unknown. It has been postulated that the presence of OPT, particularly those involving the hypothalamic and sellar regions, inhibits somatostatin tone allowing for the unregulated release of GH. Some authors proposed the presence of overactive GH-releasing hormone in OPTs, although immunostaining for GHRH and GH were negative in some reported cases [21].

The diagnosis of GH excess in NF1 should be suspected in children with accelerated linear growth and clinical features of gigantism such as enlargement of the hands and feet, soft tissue thickening, coarse facial features, prognathism or worsening of clinical features such as neurofibromas, pain or endocrinopathies. Screening for GH excess in NF1 should be based on the existing guidelines for the diagnosis of gigantism and acromegaly. Initial screening includes the measurement of serum IGF-1 and GH levels that can be paired in a random sample. In patients with suspected GH excess with normal IGF1 and GH levels, a serial overnight GH sampling may be performed in specialized centers. GH excess is confirmed with elevated IGF-1 and lack of GH suppression to levels  $<1$  ng/mL after the oral glucose tolerance test. Once confirmed, brain imaging is recommended to evaluate for OPT and to assess for lesions in the pituitary and hypothalamus [21].

Growth hormone excess in children with NF1 has been reported to be a transient phenomenon in some children and thus may not need treatment [22, 23]. In children requiring treatment, somatostatin analogs and GH receptor antagonist have been used to reduce tumor growth and the long-term systemic effects related to uncontrolled GH excess. The outcome of the medical treatment has been reported only in a few cases [24] and there are limited data on the longitudinal course of patients treated with somatostatin analogs or GHR antagonists.

### **3.5 Diencephalic syndrome**

Diencephalic syndrome (DS) is a rare endocrine disorder reported in children with NF1 and OPG. It is a clinical condition present in early infancy and is characterized by failure to thrive despite adequate or slightly decreased food intake, severe

emaciation and hyper-alertness, associated with supratentorial midline space-occupying lesions involving the hypothalamus.

DS is commonly reported within the first 2 years of life. But the median age of children diagnosed with DS associated with NF1 is slightly advanced, with only one case reported at age less than 12 months [25]. DS in an infant or a child with NF1 usually indicates the presence of an undiagnosed OPG. Less often, it may become evident later with the progression of an already known OPG due to the enlargement of the tumor, which causes compression of the hypothalamus.

### **3.6 Gynecomastia**

Gynecomastia is the growth of glandular breast tissue in males. Gynecomastia seen during puberty is physiologic, but gynecomastia with prepubertal-onset is very uncommon and suggests a different etiology such as gonadal steroid-secreting tumors, congenital adrenal hyperplasia, aromatase excess [26]. An increased frequency of unilateral and bilateral prepubertal gynecomastia has been described in NF1 patients [27]. Endocrine workup was found normal in all the described cases, ruling out other etiologies of prepubertal gynecomastia. The exact etiology and pathogenesis of gynecomastia in NF1 are not clearly understood. It is thought to be due to pseudoangiomatous stromal hyperplasia of breast tissue secondary to a mutation in neurofibromin [28]. Distinct histopathologic features seem to be associated with gynecomastia related to NF1. Standard pubertal gynecomastia is characterized by hypocellular fibrous stroma, with proliferative multilayered ductal epithelium, while NF-1-related gynecomastia is characterized by hypercellular fibrous stroma and a single layer of ductal epithelium [27]. A few cases of neurofibroma, hamartoma, lipomatous hyperplasia and pseudoangiomatous hyperplasia of the breast, mimicking gynecomastia (usually unilateral), have also been described in children with prepubertal NF1 [29–31]. Surgery is indicated in cases of progressive breast enlargement.

## **4. Endocrine tumors in NF1**

Patients with NF1 are at an approximately 2–4-fold higher risk of developing tumors than the general population. The gastrointestinal tract may be involved in NF-1 and includes gastrointestinal stromal tumors (GIST), carcinoids, pheochromocytomas, paragangliomas and pancreatic neuroendocrine tumors. Gastrinomas, insulinomas and nonfunctioning pancreatic endocrine tumors have also been reported in patients with NF-1.

### **4.1 Pheochromocytoma**

The incidence of pheochromocytoma among patients with NF1 is estimated to be 0.1–5.7% [32]. It is usually seen in adult patients with NF1. NF-1-associated pheochromocytomas are predominantly epinephrine-producing, and thus, patients present with paroxysmal symptoms. Approximately 60% of patients with pheochromocytoma in the setting of NF-1 have sustained hypertension. Metabolites of epinephrine, such as metanephrines, can be measured in plasma by high-performance liquid chromatography with electrochemical detection. Biochemical screening *via* serum fractionated metanephrines is recommended in patients with NF1 in case of development of hypertension or other suggestive symptoms to exclude or confirm pheochromocytoma. If biochemical testing is positive, other imaging modalities such as CT, MRI and functional imaging with I123 metaiodobenzylguanidine (MIBG) scintigraphy may be utilized to further characterize the tumor.

## 4.2 Optic pathway gliomas

The Optic Pathway Gliomas occurs in 15-20% of children with NF1. These can involve the hypothalamus and lead to endocrine disorders [33]. A retrospective study by Sani et al. ( $n = 40$ ) reported endocrinopathies in 55% of children with NF1 and OPG by the mean age of 7.4 years. This study reported GHD in 36%, CPP in 33% and GH excess in 5%. This study also reported that GHD was transient in patients who were retested. A recent multicenter retrospective study in children with NF1 and OPG ( $n = 116$ ) showed 27% of children had endocrine dysfunction by age 7.8 years including CPP (72%) and GHD (10%), GHE (6%) and DS (12.5%) [4].

There are no specific recommendations for surveillance of patients with NF-1 for endocrine tumors. However, due to the association of NF-1 with endocrine tumors, physicians should have a high index of suspicion in patients with symptoms suggestive of a neuroendocrine tumor and appropriate screening tests should be performed.

## 5. Conclusion

Children with NF1 are at risk for developing endocrinopathies such as CPP, GHD, GHE and DS. A close follow-up is crucial in NF1 patients especially in children with OPG, for early identification of endocrinopathies.

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