Mini Review

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Endocrine Implications of Neurofibromatosis 1 in Childhood

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Key Words
Neurofibromatosis · Growth · Growth hormone · Precocious puberty · Gigantism · Glioma

Abstract
In 1882, von Recklinghausen described a group of patients with multiple tumors arising from the 'endoneurium' of peripheral nerves, and called them 'neurofibromas'. The term von Recklinghausen disease was used up to the end of the 20th century, when the gene of neurofibromatosis (NF1) was cloned on chromosome 17q11.2. The gene product is a cytoplasmic protein termed neurofibromin, regulating proliferation and maturation of both glial and neuronal progenitors during embryogenesis. Loss of neurofibromin function determines the hyperactivation of the proto-oncogene RAS, leading to an increased risk of tumor formation, predominantly affecting the skin, bone and the nervous system. NF1 is clinically and genetically distinct from neurofibromatosis type 2, characterized by bilateral vestibular schwannomas and other nervous system tumors. An increased incidence of central precocious puberty, diencephalic syndrome, GH deficiency and GH hypersecretion has been described in NF1 children. These conditions are commonly complications of optic pathway gliomas (OPG) involving the hypothalamic and sellar region. Nevertheless, these endocrine disorders have been observed also in children without evidence of OPG at magnetic resonance imaging. Clinical and laboratory follow-up is crucial in all children with NF1, particularly in those with an OPG, aiming at the early identification of signs suggestive of secondary endocrine alterations.

Introduction

In 1882, von Recklinghausen first described a group of patients carrying multiple tumors arising from the 'endoneurium' of the peripheral nerves, and called them 'neurofibromas' [1]. The term von Recklinghausen disease was used up to the end of the 20th century, when molecular genetic techniques allowed cloning of the gene of neurofibromatosis (NF1) on chromosome 17q11.2 [2]. NF1 is distinct on clinical and genetic grounds from type 2 neurofibromatosis, a rare disorder due to mutations of a gene located on chromosome 22q11.2 characterized by bilateral vestibular schwannomas and other benign tumors of the nervous system [3]. NF1 is an autosomal dominant multisystemic neurocutaneous disorder characterized by an increased risk of benign and malignant tumor formation. The disease primarily affects skin, bone and the nervous system. The incidence has been described to be around 1 in 2,500–3,500 live births, and the estimated prevalence is 1 in 4,000–5,000. The penetrance is complete, but the severity of the clinical manifestations is variable and unpredictable, even within affected families.

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Table 1. Diagnostic criteria for NF1 (at least 2 criteria are required to make diagnosis) adapted from Tonsgard [5]

Criterion	Description	Timing of the appearance	Frequency
Six or more café-au-lait spots, >0.5 cm in prepubertal children, >1.5 cm in postpubertal individuals	oval or rounded hyperpigmented flat spots	often present at birth, increasing number and size over the first 5–7 years of life	>99%
Freckling	freckling of the axillary regions and groins	usually after 5–7 years of age	85%
Two or more cutaneous neurofibromas	tumors of the nerve sheath, comprised of fibroblasts, Schwann cells, perineural cells, mast cells, axons and blood vessels	late childhood or adolescence, increasing number and size in adulthood	99%
One plexiform neurofibroma	histologically similar to cutaneous neurofibromas with more extracellular matrix, arising from dorsal spinal roots, nerve plexi, large nerve trunks, sympathetic chains, they may involve skin or be completely internal	infancy and early childhood	60%
Two or more iris Lisch nodules	proliferations of melanocytes and fibroblasts appearing as reddish brown spots in the iris in people with blue or green eyes and hypopigmented spots in people with brown eyes, commonly found in the lower pole of the iris without effect on vision	adolescence	>95%
One optic pathway glioma	commonly low-grade pilocytic astrocytomas	over the first 5–7 years of life; more aggressive forms involving the postchiasmatic pathway can occur after 8 years of age	15%
One distinctive osseous lesion	pseudoarthrosis, sphenoid dysplasia, severe kyphoscoliosis	childhood and adolescence	10%
First-degree relative with NF1			50%

Half of all cases arise from spontaneous mutations. Germline NF1 mutations are inherited or occur before fertilization in classical NF1, but somatic mutations may also occur after fertilization in mosaic NF1. The timing of postzygotic mutations during embryogenesis dictates the extent of the disease. Earlier somatic mutations result in mild widespread manifestations indistinguishable from classical NF1. Late mutations determine segmental or monosystemic NF1. Although recent advances in genetic testing allow the molecular diagnosis, in as many as 95% of cases, the diagnosis is still made on the basis of clinical features. Diagnosis requires the presence of 2 or more major criteria (table 1). In some children, the diagnosis can be easily reached early after birth, while other children must be followed for a few years for the appearance of additional criteria [4, 5]. The first descriptions of endocrine disorders complicating NF1 date back to the 1970s, most of them are isolated case reports or case series. In this review, PubMed and Web of Knowledge databases were used to identify studies analyzing endocrine disorders in NF1. The results of large controlled studies were selected and summarized. For the topics about which large and controlled studies are not available, data from case reports have been analyzed.

Neurofibromin, Hypothalamic-Pituitary Axis and Somatic Growth

The protein product of the NF1 gene is a large cytoplasmic protein that has been called 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. Furthermore, neurofibromin

positively 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. Brain-specific loss of CREB results in hypopituitarism and poor growth in animal models [4, 6]. During embryonic differentiation, neurofibromin regulates proliferation and maturation of both glial and neuronal progenitor cells. Recently, a mouse model (Nf1BLBPCKO mice) has been generated in which the NF1 gene inactivation occurs in neuroglial progenitor cells [7]. These mice show significantly reduced body weight and small anterior pituitary gland, while the posterior pituitary lobe is normal in size. The anterior pituitary hypoplasia reflects loss of neurofibromin expression in the hypothalamus, leading to reduced growth hormone-releasing hormone (GHRH), pituitary growth hormone (GH) and liver insulin-like growth factor-1 (IGF1) production. GHRH gene expression was analyzed by immunohistochemistry in hypothalamic-pituitary tissue from Nf1BLBPCKO mice. A significant reduction in GHRH staining within the median eminence (the primary capillary network of the hypophyseal portal system) was found. A 40–60% reduction in the GHRH mRNA was evident in the hypothalamic cells of Nf1BLBPCKO mice, compared with wild-type controls. The hypothalamic homogenates from Nf1BLBPCKO mice showed a 50% decrease in the levels of cAMP, in comparison with littermate controls [7].

Growth of Children with NF1

Short stature and macrocephaly have long been known to be specific clinical features of NF1 children [4]. Short stature has been associated both with normal endocrine status and with different degrees of GH deficiency (GHD) [8]. The growth profile was analyzed in a sample of 528 NF1 children, collected by a population-based registry covering three adjacent regions of North-East Italy [9]. The study was performed with the aim of drawing disease-specific growth charts for height, weight, and head circumference (HC). No differences in height were evident between NF1 and normal children up to the age of 7 years in girls and 12 years in boys. Subsequently, the 50th centile of NF1 children tended to overlap with the 25th centile of healthy children, and the 3rd centile was significantly lower in NF1 subjects, in comparison with healthy peers. During childhood, the median height velocity in NF1 subjects was found to be similar to that of healthy controls. Pubertal spurt occurred 1 year earlier than in healthy controls, and it appeared to be mildly reduced in boys but not in girls. No difference in the 97th centile for height was evident between NF1 charts and Tanner-Whitehouse standards. NF1 and normal subjects showed a similar median weight during the whole growth period. In NF1 subjects, the 3rd centile for weight was consistently lower during adolescence, and the 97th centile became higher when adulthood was reached. HC was found larger in NF1 subjects during the whole childhood, as well as in adulthood. It must be remembered that a rapid increase in HC in the first years of life that deviates from the normal growth curves deserves attention because it can be the presenting sign of a growing intracranial tumor or of an evolving hydrocephalus. The shape of the head growth curve was similar in NF1 and normal girls, whereas NF1 boys presented an HC pubertal growth spurt much more pronounced and delayed than control boys, with a significant increase in head size during adolescence. The disproportion between head size and height became more evident with advancing age, mainly in boys [9]. A recent retrospective study in 80 Finnish NF1 children aged 0–7 years analyzed the incidence and diagnostic accuracy of the elevated HC-to-height ratio (HCHR). The median age when the first elevated (≥2.0 SDS) HCHR value was detected was 0.3 years (range 0.0–5.3). At the median age of NF1 diagnosis (3.6 years), 53.8% of children showed elevated HCHR. The diagnostic accuracy of HCHR alone was 0.78 (95% CI 0.72–0.84). Considering the seven diagnostic criteria for NF1 (table 1), elevated HCHR was the second most common clinical manifestation after café au lait spots [10].

Optic Pathway Gliomas and Endocrine Disorders

Fifteen percent of NF1 children are affected by brain gliomas involving the visual pathways and/or the hypothalamic region. Optic pathway gliomas (OPG) identified on magnetic resonance imaging (MRI) scan are contrast-enhanced masses, commonly grade I pilocytic astrocytomas. Usually, OPG do not show clinical progression. Most of them are asymptomatic and do not require intervention. Biopsy and chemotherapy are indicated only in symptomatic lesions, in which there is evidence of radiologic progression and/or worsening of visual impairment [4, 5]. Chemotherapy stabilizes visual acuity in the majority of patients. Tumor regression or improvement in visual acuity are less common but may occur.

Central precocious puberty (CPP), diencephalic syndrome (DS), GHD and GH hypersecretion have been de-

scribed in NF1 children as complications of OPG, mainly involving the hypothalamic and sellar region, but they have also been observed in children without MRI evidence of OPG [11–13]. OPG should be distinguished from MRI hyperintensities on T2 sequences (formerly defined as unidentified bright objects, UBOs). These lesions are not associated with neurological defects, do not enhance after contrast administration, and do not exert any mass effect. They are common in young NF1 children and tend to disappear with increasing age [14]. It is unlikely that these lesions could be related to the development of CPP or other endocrine disorders because they are classically localized outside the sellar and suprasellar regions of the brain. UBOs probably represent areas of dysplastic glial proliferation and delayed myelination [5, 14].

GH Hypersecretion

GH excess has been observed in the presence of OPG located inside the hypothalamic area or close to it, mostly in patients with fully expressed NF1 [15–23]. Isolated OPG with GH hypersecretion in children without further clinical manifestations of NF1 have been supposed to be the monosystemic expression of mosaic NF1 due to late somatic mutations [4, 24]. The prevalence of GH hypersecretion is unknown. Table 2 reports available published data about NF1 children with OPG-related GH excess. GH hypersecretion is usually diagnosed by the evidence of the following criteria [23]: accelerated linear growth, high levels of IGF-1 and IGF-binding protein 3, and lack of GH suppression to levels <1 ng/ml, after oral glucose tolerance test.

The mechanism underlying OPG-related GH excess is unknown. The hypothesis of a GH-secreting mass has not been supported. In all the described cases, the pituitary gland was found normal in size, without evidence of adenomas on imaging. It has been supposed that the presence of OPG suppresses somatostatin tone, leading to an upregulated release of GH [19]. Other authors postulated the presence of overactive GHRH [17]. In contrast with this hypothesis, in several of the reported cases [15–17] tumor cells were negative at immunostaining for GHRH and GH. In the most recent case series by Josefson et al. [23], 1 patient had negative tumor staining for GHRH, GH, and somatostatin and weakly positive tumor staining for GH receptors (GHR). This evidence supports the hypothesis that the reduced somatostatin tone leads to GH hypersecretion. GH excess in such patients could also contribute to continued brain tumor growth. Josefson et al. [23] suggest medical treatment of GH excess by somatostatin analogs or GHR antagonists to reduce tumor growth and the long-term detrimental systemic effects related to uncontrolled GH excess (gigantism-related skeletal problems, hypertension, glucose intolerance, and cardiomegaly). Scarce data exist on the longitudinal course of patients treated with somatostatin analogs or GHR antagonists [20, 22]. Furthermore, NF1 patients with evidence of GH excess without OPG on imaging have never been reported, but it is likely that this condition can occur similarly to cases of CPP in NF1 children without evidence of OPG (see specific section).

GHD in NF1 Children

GHD has been described as more common in children with NF1 than in the general population, though the exact incidence has not been defined yet. The etiology of GHD in NF1 is not completely clear, but it has been demonstrated that GHD is much more common in the presence of an intracranial tumor. In some cases, it has been clearly correlated with treatment of these tumors with radiotherapy [25]. Data collected from the KIGS database concerning 102 NF1 children with GHD, who were receiving GH replacement therapy, were reviewed to assess the efficacy and safety of GH therapy in this condition [26]. GH was administered at a mean dose of 0.18 mg/kg/week. During the 1st year of treatment, 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. The height velocity was maintained well above baseline for the next 2 years, with a growth rate comparable with that of an age-matched population of healthy children. The response to therapy, however, was not as good as that observed in patients with idiopathic GHD. 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 [27–29]. Other adverse events were relatively minor and unlikely to be attributable to GH therapy. The authors concluded that the unsatisfactory response to therapy in children with NF1 probably cannot be explained by the use of a relatively low GH dose, but by additional disease-specific factors unrelated to endocrine abnormalities. They suggested that, within the limits imposed by a retrospective study lacking a control group, the safety data were reassuring [26]. Only a randomized prospective study would be able

Table 2. OPG and GH excess: reported cases

Reference	Patients	Presentation	Growth	GH levels	IGF-1 levels	Treatment	Outcome
Costin et al. [15]	2.8-year-old boy	OPG extending along the optic tracts Hydrocephalus	Accelerated growth	Paradoxical GH rise at OGTT[1] High GH response to arginine and insulin	Not reported	Radiotherapy	Normal fasting GH levels Blunted GH response to arginine and insulin No tumor relapse
Crawford and Buckler [16]	Twin boys aged 3.4 years	OPG involving the suprasellar region at CT scan in both twins	Accelerated growth since 3.4 years Precocious puberty at 4.9 months in one twin	Incomplete GH suppression at OGTT	Not reported	Radiotherapy	Improved biochemistry Progressive bone age advance
Duchowny et al. [17]	Female child	Presumed low-grade OPG	Rapid growth over 2.5 years	Elevated baseline GH No GH suppression at OGTT	Elevated	Bromocriptine 5 mg daily Radiotherapy	Bromocriptine reduced growth rate and improved biochemistry Radiotherapy arrested tumor enlargement and stabilized visual function
Fuqua and Berkovitz [18]	2.5-year-old boy	OPG in suprasellar cistern compressing the left optic nerve and encasing the right one	Rapid growth Central precocious puberty diagnosed at 6.2 years	No GH suppression at OGTT	Elevated	Partially resecting surgery	Improved growth rate after surgery Persistently high IGF-1 levels
Manski et al. [19]	16-month-old boy	Deteriorating vision OPG involving the optic chiasm	Rapid growth since 9 months of age	Not reported	+10 SDS	Actinomycin D and vincristine Ventriculoperitoneal shunt for hydrocephalus	Stabilization of height velocity Normal basal hormone levels Developmental delay
Drimmie et al. [20]	4.2-year-old boy	Large chiasmal OPG extending into the left optic nerve	Tall stature (+5.7 SDS) Precocious puberty at 6.1 years	No GH suppression at OGTT	Elevated	Octerotide therapy 62.5 μg twice daily, followed by long-acting octerotide 10 mg every 28 days	Unchanged MRI findings Normal height velocity at 7.4 years No progression of the visual defect
Drake et al. [21]	3.5-year-old girl	OPG extending into the hypothalamus	Tall stature (+3.69 SDS), coarse facial features Precocious puberty at 7.4 years	No GH suppression at OGTT	Elevated	Vincristine and carboplatin	Tumor shrinkage Improved biochemistry
Main et al. [22]	4-year-old girl	OPG of the optic chiasm and both optic nerves	Growth acceleration	Paradoxical GH increase (204.2 mIU/l) at OGTT	+6.9 SDS	Chemotherapy Long-acting octreotide Pegvisomant	Normalization of GH, IGF-1 SDS and height velocity SDS during pegvisomant therapy
Josefson et al. [23]	4 females 1 male, age range: 11 months to 4.3 years	OPG differently located (optic nerve, optic chiasm, optic tract, optic radiation, hypothalamus)	Height SDS >+2 SDS in 3/5 Precocious puberty in 3/5	No GH suppression at OGTT in 5/5	Above-normal range for age in 5/5	Vincristine and carboplatin in 3/5	Ventriculoperitoneal shunt in 2/5 Tumor progression on MRI in 3/5

[1] Normal levels to which GH is suppressed after oral glucose tolerance test (OGTT) are usually defined as <1.0 ng/ml as in adults, even if definitive age-specific cutoffs have not been defined in children and adolescents.

to definitively test the efficacy and safety of GH therapy in patients with NF1. In the following years, the better understanding of the molecular mechanisms leading to the disease, related to the de-repression of RAS proto-oncogene with a consequent increased risk of malignancies discouraged the use of GH therapy in NF1 children with short stature. To date, no randomized trial of GH therapy in NF1 children has been completed. Recently, GHR expression was investigated in 5 plexiform neurofibromas from NF1 patients using immunohistochemistry [30]. Four of the 5 tumors were found immunopositive for GHR. The discovery of GHR in plexiform neurofibromas does not necessarily prove that GH is implicated in the development of plexiform neurofibromas, but the presence of GHR suggests the capacity of these tumors to respond to GH. Plexiform neurofibromas are the most common precursors of malignant peripheral nerve sheath tumors, which have a very poor prognosis in NF1 patients [5].

Central Precocious Puberty

CPP linked to an early maturation of the hypothalamic-pituitary-gonadal axis represents the most common endocrine disorder associated with neurofibromatosis type 1 in childhood [13, 31, 32]. The prevalence of this disorder in NF1 patients is 3%, markedly higher than the prevalence of about 0.6% reported in the general population [11, 13]. CPP in the general population is sporadic and idiopathic in over 80% of females. In males, the condition is less frequent, with a female:male ratio of 20:1, but an underlying organic cause is more common [33–35]. Several papers on NF1 children reported a higher prevalence of CPP in boys. In the study by Cnossen et al. [13], CPP was diagnosed in 3/122 children (2.5%) with NF1, and all of them were boys. Habiby et al. [11] had previously found a female:male ratio of 2:5 in children with NF1 and CPP, suggesting that being a male somehow predisposes to CPP. Generally, it was thought that all endocrine disorders in NF1 could be related to central nervous system tumors compromising hypothalamic and pituitary function. In particular, CPP has been reported primarily in NF1 children with OPG [36, 37]. This observation is consistent with the theory that lesions located close to the hypothalamus interfere with tonic central nervous system inhibition of the hypothalamic-pituitary-gonadal axis, resulting in the premature onset of puberty [38, 39]. In the same paper, Habiby et al. [11] described the first epidemiological analysis of a large series including 219 patients with NF1 to better understand the prevalence of CPP and its relationship to OPG in this population. CPP was diagnosed in 7 (5 boys and 2 girls) of 219 children with NF1 (3%). All the 7 children presented OPG extending to the optic chiasm. Children with CPP represented 39% of children with NF1 and chiasmal tumors. Moreover, 11 prepubertal children between 2 and 10 years, with NF1 and OPG, and their age- and sex-matched NF1 control subjects without OPG, underwent luteinizing hormone-releasing hormone (LHRH) stimulation test. No child without OPG had either a pubertal response to LHRH or an elevated basal LH level. Two boys with OPG showed pubertal LH responses, and testosterone levels >10 ng/dl. In one child, the tumor was located inside the optic chiasm, while in the other one it was confined to the intraorbital portion of the optic nerve. According to the data from this study [11], CPP developed exclusively in those patients with NF1 who had OPG involving the optic chiasm. A further retrospective study by Virdis et al. [40] confirmed the higher incidence of CPP in patients with NF1 compared to the general population, and its association with OPG. Comparing data from these two studies, the global incidence of CPP in NF1 appears similar: 10/412 equal to 2.4% in the study by Virdis et al. [40] versus 7/219 equal to 3% in the study by Habiby's group. In contrast, the incidence of OPG-associated CPP reported by Virdis and colleagues (22%) seems to be lower than that described by Habiby's group (39%). Occurrence of CPP in NF1 children without documented OPG could be incidental. The 3 cases in the study by Virdis and colleagues represent 0.7% of all patients, and CPP incidence in the general population is just about 0.6%. On the other hand, a few authors had previously reported CPP in the NF1 population in the absence of OPG [41]. Saxena [31] firstly reported 2 examples of CPP in NF1 patients without OPG. It is noteworthy that neither computed tomography nor MRI were available at the time of the reported study, leaving open the possibility of undetected tumors. Laue et al. [32] described 4 children with NF-1 and precocious puberty; 3 of them had OPG. No further information was provided about how the presence of the tumor was excluded in the 4th child. In another study, Listernick et al. [42] analyzed the clinical manifestations and natural history of OPG in children with or without NF1. They reported CPP in 5 of 17 NF1children with OPG, in contrast to no cases of CPP in the group of children with OPG but no features suggesting NF1. These data seem to suggest an association between CPP and NF1 itself, independent of chiasmal involvement due to OPG. In the already re-

ported study by Cnossen et al. [13], CPP was diagnosed in 3 of 122 children (3%) but only 1 child presented an OPG at MRI.

Mild cerebral abnormalities, undetectable at MRI, such as slow-growing hamartomas, may lead to CPP in NF1 children without OPG. Considering that neurofibromin is part of a signal transduction chain extending from extracellular signals to transcriptional regulation in the nucleus, an abnormal signal transmission pathway has been suggested [6, 7, 43]. Therapeutic indications for NF1 children with CPP are similar to those approved for children with idiopathic or organic CPP not related to NF1.

Diencephalic Syndrome

DS is a rare clinical condition presenting in infancy and early childhood. It is characterized by loss of weight despite adequate or slightly decreased caloric intake, marked emaciation in spite of normal linear growth, hyperalertness and hyperactivity, correlated with supratentorial midline space-occupying lesions involving the anterior hypothalamus. Recurrent vomiting and nystagmus are often associated [44]. DS is globally very rare in NF1 children with OPG. In affected cases, it usually represents the presenting clinical manifestation of an undiagnosed OPG in an infant or young child. Less commonly, it may become evident later during the progression of an already known OPG due to the enlargement of the tumor which causes compression of the hypothalamus [44–49]. The median age of children diagnosed with DS not associated with NF1 has been reported to be around 10 months [44]. In contrast, the median age of the cases of DS occurring in NF1 patients was relatively advanced, with only 1 patient aged less than 12 months and a 39-year-old man [49]. GH hypersecretion has been frequently described in patients with DS [44, 48, 49].

Pheochromocytoma

The incidence of pheochromocytoma (PHEO) among NF1 patients is estimated to be 0.1–5.7%. It has been usually described in adult NF1 patients. This percentage rises up to 20–50% among hypertensive NF1 subjects compared to 0.1% of all hypertensive patients [50]. Biochemical screening to exclude or confirm PHEO is recommended in patients with NF1 in case of development of hypertension or other suggestive symptoms [50, 51]. Symptoms and signs of PHEO result from release of catecholamines and include the classical 'three H' of hypertension, headaches and hyperhidrosis as well as palpitations and weight loss [52]. In all NF1 patients and particularly in those with PHEO, an alteration in the circadian blood pressure rhythm represented by a 'non-dipping pattern' of blood pressure has been reported as an early marker of future hypertension [53]. Of the 48 NF1 patients evaluated in the study by Zinnamosca et al. [53], 11 patients (22.9%) presented arterial hypertension, and 7 patients had PHEO (14.6%). In the PHEO group, 6 patients (85%) had hypertension and 4 patients (57%) were symptomatic at diagnosis. The higher prevalence of PHEO in this study group (14.6%) compared to other reports in the literature seems to be correlated with the systematic screening for hypersecretion of catecholamines in all patients with NF1, regardless of the presence of hypertension or any other symptoms. A retrospective analysis compared NF1 patients undergoing PHEO resection with the non-NF1 PHEO patients treated by the same surgeon [54]. Of the 56 patients undergoing PHEO resection, 6 (11%) had NF1. The median age of NF1 PHEO patients was 46 years, compared to 53 years in the non-NF1 group. All the 6 NF1 PHEO patients received diagnosis incidentally during workup for another conditions in comparison with 28/50 (56%) non-NF1 patients. Hypertension was present in 1 (17%) NF1 PHEO patient and in 37 (74%) non-NF1 patients. This demonstrates that the majority of NF1 patients with PHEO do not have hypertension and that clinicians should not be reassured that the lack of this sign automatically indicates a lack of PHEO. The median tumor size in NF1 patients was smaller compared to non-NF1 patients (2.75 vs. 5.9 cm) [54]. The difference in tumor size could be related to earlier diagnosis in NF1 patients more frequently undergoing imaging for other reasons.

Gynecomastia

Gynecomastia is the growth of glandular breast tissue (both the fibrous and the epithelial components) in males. It is considered as a paraphysiologic condition when presenting during puberty and adolescence. Gynecomastia with prepubertal onset is very uncommon and suggests a different etiology (gonadal steroid-secreting tumors, congenital adrenal hyperplasia, aromatase excess) [55]. An increased frequency of unilateral and bilateral prepubertal gynecomastia has been described in NF1 patients

Table 3. Age-specific clinical follow-up of young NF1 patients (adapted from Tonsgard [5] and Walther et al. [50])

Parents must be examined. If a parent is affected, all of the children must be examined. Affected parents must be informed that there is a 50% risk of NF1 for each pregnancy. Assessment of patients for other issues is:

Age	Frequency of monitoring	Assessment
0–9 years	Yearly	Careful physical examination looking for long bone bowing, limb asymmetry, scoliosis Blood pressure monitoring (consider renal artery stenosis and pheochromocytoma) Eye examination by pediatric ophthalmologist (visual acuity, fundoscopy, color vision, visual field) Assessment of neuromotor development, language, and learning Growth assessment (height, weight, head circumference, pubertal staging)
9–15 years	Yearly	Careful physical examination looking for scoliosis, limb asymmetry, neurofibromas School performance evaluation looking for learning disabilities and attention deficit Discussion about NF1 and the impact of puberty on NF1complications Evaluation of socialization and self-esteem
16–21 years	Yearly	Careful physical examination looking for neurofibromas Imaging studies to evaluate any complaint or pain Evaluation of school performance, socialization and self-esteem Discussion of NF1 inheritance and risk for pregnancy Discussion of the effects of puberty, pregnancy, and birth control pills on NF1-related risk of tumors
>21 years	Yearly	Careful physical examination and blood pressure check Imaging studies to evaluate any complaint or pain Evaluation of cutaneous neurofibromas, pain and cancer risk

Brain MRI studies are indicated only in the case of signs suggesting neurological impairment (visual defects, progressive macrocephaly, etc.) or for the evaluation of specific complaints.

[56–59]. Endocrine workup was found normal in all the described cases. 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 [56]. A few cases of neurofibroma, hamartoma, lipomatous hyperplasia and pseudoangiomatous hyperplasia of the breast, mimicking gynecomastia (usually unilateral), have also been described in prepubertal NF1 children [57–59]. Surgery is indicated in cases of progressive breast enlargement.

Conclusions

Short stature and macrocephaly have long been known to be specific clinical features of NF1 children. CPP, GHD, GH hypersecretion and DS have been described in NF1 children, closely related to the presence of OPG involving the hypothalamic and sellar region. These endocrine complications may also be observed in children without MRI evidence of gliomas.

A careful diagnostic follow-up (table 3) is essential in all children with NF1 and particularly in those with an OPG to recognize early signs of secondary endocrine disorders.

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