Genetics inMedicine | CORRESPONDENCE

Growth hormone excess in neurofibromatosis 1

The authors of the recent American College of Medical Genetics and Genomics clinical practice resource on the care of adults with neurofibromatosis type 1 (NF1) (ref. [1]) are to be commended for their comprehensive publication. However, an important comorbidity that affects patients with NF1 was left out and remains generally underrecognized by clinicians: growth hormone (GH) excess leading to either clinical or subclinical gigantism or acromegaly. These two disorders represent a continuum of clinical manifestations and are distinguished by the status of the epiphyseal growth plates with respect to GH excess.

GH excess is generally a rare disease in children and adults and is usually caused by a benign GH-secreting pituitary adenoma (somatotropinoma, with co-secretion of prolactin or PRL, it is referred to as "somatomammotropinoma"), pituitary hyperplasia secreting GH or PRL or both, or another neuroendocrine tumor elsewhere, releasing growth factors. GH excess likely affects patients with NF1 at higher rates, and across all ages, potentially increasing their oncological risk or growth of an existing tumor. This association was first recognized in the early 1900s and a few cases have been reported to date.[2] In the largest study on children with NF1 and overgrowth, Cambiaso et al. found that 10% of their population with NF1 had abnormalities in their GH axis, consistent with GH excess.[2] Interestingly, all of their affected patients had a tumor involving the optic chiasm, without pituitary involvement, as previously described.[2] Optic pathway tumors (OPTs) are usually identified on magnetic resonance image (MRI) scans as a contrast enhancing mass. Although the mechanism underlying GH excess in NF1 is unknown, it has been postulated that loss of somatostatinergic inhibition from OPTs, particularly those involving the hypothalamic and sellar regions, leads to a dysregulated GH secretion pattern. Others have proposed the presence of overactive GH-releasing hormone (normally produced in the arcuate nucleus of the hypothalamus) in OPTs, although staining for this hormone was negative in some cases.

The diagnosis of GH excess in NF1 should be suspected in children with accelerated linear growth, clinical features of gigantism such as enlargement of the hands and feet, soft-tissue thickening, prognathism, coarse facial features, presence of OPTs, or worsening of clinical features such as neurofibromas, pain, or endocrinopathies. Adults with GH excess and NF1 may also present with progressive clinical or coarse features suggestive of acromegaly, or worsening neurofibromas, pain, or endocrinopathies. Although short adult height is an important characteristic of NF1, clinicians should not be deterred from screening short individuals with NF1 for GH excess, particularly if the aforementioned features of overgrowth exist.

Biochemical screening for GH excess in NF1 should follow existing guidelines for the diagnosis of gigantism and acromegaly. This includes measurement of serum IGF-1 and GH levels that can be paired in a random sample. Normal IGF-1 and GH levels may be encountered in patients with NF1 and suspected gigantism and/or acromegaly; in such cases, serial overnight GH sampling may be performed in specialized centers.[3] 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, imaging of the pituitary, suprasellar, and optic tracts is recommended for evaluating pituitary lesions, hypothalamic infiltrations, or OPT, respectively.

Recently, we evaluated ten subjects with NF1 who were referred to the National Institutes of Health for workup of overgrowth.[3] Six children (median age = 3.9 years, range 4–10), one adolescent, and three adults (median age = 33 years, range 29–52) with NF1 had GH excess that was confirmed by failure to suppress GH on oral glucose tolerance tests ($n = 9$) and frequent overnight sampling of GH levels ($n = 6$) (ref. [3]). We showed pattern variability of serial overnight GH secretion in this group and confirmed a link between pituitary tumorigenesis, NF1, and GH excess.[3] One adult subject had radiographic evidence of pituitary hyperplasia (voluminous pituitary gland) and overnight secretion of GH and PRL (somatomammotroph hyperplasia),[3] as also seen in McCune–Albright syndrome, Carney complex, and multiple endocrine neoplasia type 1. Our data underline the need for early recognition and investigation for gigantism or acromegaly in patients with NF1, including a careful and thorough investigation of the pituitary gland through imaging. Evaluation of GH excess in NF1 is a forgotten comorbidity that is important to address in clinical practice and future guidelines, which has screening and treatment implications for the management of children and adults with NF1.

DISCLOSURE

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