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SCIENTIFIC LETTERS

Acromegaly and type 1 neurofibromatosis. Is association of both conditions due to chance?☆

Acromegalia y neurofibromatosis tipo 1. ¿Es casual la asociación entre ambas entidades?

Type 1 neurofibromatosis (NF1), also known as von Recklinghausen disease, is the most common of the so-called neurocutaneous syndromes. It is a genetic disorder of autosomal dominant inheritance with complete penetrance and highly variable clinical expression. Its incidence rate is 1/3000–4000. Approximately half the cases are inherited, and the rest are *de novo* mutations.[1]

The most characteristic clinical features are café-au-lait spots and cutaneous neurofibromas. The diagnostic criteria established require at least two of the following: café-au-lait spot, neurofibromas, axillary or inguinal ephelides, optic glioma, iris hamartomas, and typical bone lesions.[2]

Patients with NF1 more frequently develop benign and malignant tumors during their life. Optic gliomas are the predominant type of intracranial tumors, but other tumors may appear inside and outside the central nervous system.[3]

The case of a patient with NF1 who developed a GH-secreting pituitary adenoma is reported.

This was a 42-year-old woman with a history of menarche at 12 years and no menstrual changes or fertility problems. She was diagnosed in 2005 with a small multinodular goiter with normal thyroid function, with a predominant 14-mm nodule. Manifestations of NF1 included café-au-lait spots, disseminated neurofibromas, mainly in the chest and abdomen, and scoliosis. A genetic study showed a mutation in the NF-1 gene consisting of a guanine for adenine substitution in intron 4b (IVS4b + 5G→A) causing a truncated NF-1 smaller than normal. She has one daughter and one son. The daughter carries the mutation and has café-au-lait spots and an optic nerve glioma as manifestations of the disease. There are no other relatives affected.

Because of the presence of galactorrhea on expression, which persisted since breast-feeding of her son nine years before, two prolactin measurements were performed, which provided slightly elevated levels of 36.8 and 44.1 ng/mL (6–29.9). A pituitary MRI performed on February 2009 revealed a 7-mm adenoma on the right side with slight bulging of sellar diaphragm.

She was then referred to us. Baseline pituitary hormone tests confirmed high prolactin levels of 46.2 ng/mL and an elevated IGF-I level of 459 ng/mL (55–329). All other hormone levels were normal: FT4 1.2 ng/dL (0.8–1.8), TSH 1.6 μU/mL (0.27–4.2), LH 3.09 mU/mL (2.4–12.6), FSH 5.75 mU/mL (3.5–12.5), estradiol 50.75 pg/mL (2.5–166), and cortisol 13.7 μg/dL (6.2–19.4).

When questioned again, the patient only reported swelling of the fingers in recent years, and some increase in facial hair in the preceding months. No increase in shoe size or other symptoms suggesting acromegaly were reported.

Examination found no clear dysmorphic changes in the face and only a moderate finger enlargement.

An oral glucose tolerance test showed a baseline GH level of 9.4 ng/mL with a paradoxical increase to 10.4 ng/mL at 120 min, with normal blood glucose levels. In a second test, an IGF-I levels of 580 ng/mL was found.

No changes in adenoma size were noted in a second pituitary MRI performed on September 2010 or in the preoperative MRI.

On October 2011, patient underwent surgery through an endoscopic endonasal transsesphenoidal approach, which allowed for apparently complete resection. Immunohistochemistry was positive for GH in 100% of cells, and for prolactin and TSH in 5% and 1% of cells respectively, and was negative for FSH, LH, and ACTH.

Postoperative laboratory tests (December 2011): free T4 1.1 ng/dL, TSH 2.15 μU/mL, prolactin 63.7 ng/mL, cortisol 19 μg/dL, IGF-I 242 ng/mL, oral glucose tolerance test: baseline GH 9.67, with maximum decrease of 1.19 ng/mL at 120 min.The case reported is quite exceptional, because there are few reported cases of pituitary adenomas, and more specifically acromegaly, associated to NF1.[4–10]

The vast majority of pituitary adenomas are sporadic and only rarely occur as part of genetic syndromes such as multiple endocrine neoplasia type 1, McCune-Albright syndrome, Carney complex, or in families with isolated pituitary adenomas such as those associated to AIP mutations. The number of cases of pituitary adenoma reported in NF1 is very small, and this is therefore not included in the list of these genetic syndromes. In fact, we may wonder whether this is only a chance association or is related to the capacity of NF-1 to promote tumor development.

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NF-1 is caused by mutations in the NF1 gene encoding neurofibromin, a protein with a tumor suppressant effect because it negatively regulates the p21 ras proto-oncogene. Loss of function of mutated neurofibromin increases activity of ras, and thus of signaling pathways depending on this activity such as Raf/MEK/ERK (MAPK), and Akt/mTOR. These two pathways mutually interact and have a key role in regulation of cell proliferation and growth.[11] These changes are involved in the wide spectrum of clinical manifestations of NF-1, including tumor development.[3]

In sporadic pituitary adenomas, mutations in genes of the abovementioned genetic syndromes are not usually seen. By contrast, changes in the cell signaling pathways PI3 K/Akt/mTOR, and Raf/MEK/ERK are being implicated in their pathogenesis in recent years.[12] In this regard, increased B-Raf and Akt expression has been noted in pituitary adenomas, as well as increased activity of some components which are activated form them.[13]

Thus, common changes in certain points of cell signaling pathways related to tumor growth and genesis appear to be involved in the pathogenesis of tumors associated to NF1, such as sporadic pituitary adenomas. Although there are few reported cases of acromegaly or other pituitary adenomas in NF1, these data suggest that this is not a chance association and that, although infrequently, this disease may also promote the occurrence of this type of tumors.

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Hypogonadotropic hypogonadism in a male with McCune-Albright syndrome☆

Hipogonadismo hipogonadotropo en un varón con síndrome de McCune-Albright

McCune-Albright syndrome (MAS) is a heterogeneous, uncommon condition caused by postzygotic, somatic, and sporadic mutation of the GNAS gene, encoding the stimulatory alpha subunit (α_s) of the G protein-coupled receptor.[1] Clinically, this syndrome consists of a triad characterized by bone fibrous dysplasia, café-au-lait spots and hyperfunctioning endocrinopathies such as early puberty, hyperthyroidism, excess growth hormone (GH), hyperprolactinemia, and hyperadrenocorticism. However, a diagnosis of MAS is made when two of the three clinical signs are present.[1,2]

We report the case of a 16-year-old male patient from Mérida (Venezuela) with no family history and a personal history of multiple femoral fractures secondary to polyostotic fibrous dysplasia diagnosed at three years of age who attended the endocrinology unit for tall height. He also reported continuous sever holocranial headache and hyposmia which had intensified in recent years.

Physical examination revealed 93 kg of weight (greater than the 97° percentile), 183 cm of height (greater than the 97° percentile) with a genetic height potential (sum of the height of both parents + 12.5 cm/2) of 169 ± 10 cm, a body weight index (IMC) of 26.6 kg/m^2, and 120/70 mmHg of blood pressure. Café-au-lait spots 5.5 and 7 cm in diameter, both with irregular margins, were seen in the back of the neck and the right buttock respectively. He also had craniofacial

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