

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.<sup>11</sup> These changes are involved in the wide spectrum of clinical manifestations of NF-1, including tumor development.<sup>3</sup>

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.<sup>12</sup> 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 from them.<sup>13</sup>

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.

## References

1. Jett K, Friedman JM. Clinical and genetic aspects of neurofibromatosis 1. *Genet Med*. 2010;12:1–12.
2. DeBella K, Szudek J, Friedman JM. Use of national institutes of health criteria for diagnosis of neurofibromatosis 1 in children. *Pediatrics*. 2000;105:608–14.
3. Lodish MB, Stratakis CA. Endocrine tumours in neurofibromatosis type 1, tuberous sclerosis and related syndromes. *Best Pract Res Clin Endocrinol Metab*. 2010;24:439–49.
4. Duchowny MS, Katz R, Bejar RL. Hypothalamic mass and gigantism in neurofibromatosis: treatment with bromocriptine. *Ann Neurol*. 1984;15:302–4.
5. Fuqua JS, Berkovitz GD. Growth hormone excess in child with neurofibromatosis type 1 and optic pathway tumor: a patient report. *Clin Pediatr*. 1998;37:749–52.
6. Drake AJ, Lowis SP, Boffet E, Crowne EC. Growth hormone hypersecretion in a girl with neurofibromatosis type 1 and an optic nerve glioma: resolution following chemotherapy. *Hormone Res*. 2000;53:305–8.
7. Drimmie FM, MacLennan AC, Nicoll JA, Simpson E, McNeill E, Donaldson MD. Gigantism due to growth hormone excess in a boy with optic glioma. *Clin Endocrinol*. 2000;53:535–8.
8. Kurozumi K, Tabuchi A, Ono Y, Tamiya T, Ohmoto T, Furuta T, et al. Pituitary adenoma associated with neurofibromatosis type 1: case report. *No Shinkei Geka*. 2002;30:741–5.
9. Main KM, Sehested A, Feldt-Rasmussen U. Pegvisomant treatment in a 4-year-old girl with neurofibromatosis type 1. *Hormone Res*. 2006;65:1–5.
10. Josefson J, Listemik R, Fangusaro JR, Charrow J, Habiby R. Growth hormone excess in children with neurofibromatosis type 1 associated and sporadic optic pathway tumors. *J Pediatr*. 2011;158:433–6.
11. Gottfried ON, Viskochil DH, Couldwell WT. Neurofibromatosis type 1 and tumorigenesis: molecular mechanisms and therapeutic implications. *Neurosurg Focus*. 2010;28:E8.
12. Suojun Z, Feng W, Dongsheng G, Ting L. Targeting Raf/MEK/ERK pathway in pituitary adenomas. *Eur J Cancer*. 2011, doi:10.1016/j.ejca.2011.11.002.
13. Dworakowska D, Wlodek E, Leontiou CA, Igreja S, Cakir M, Teng M, et al. Activation of RAF/MEK/ERK and PI3 K/AKT/mTOR pathways in pituitary adenomas and their effects on downstream effectors. *Endocr Relat Cancer*. 2009;16:1329–38.

Antoni Checa Garrido, Carlos del Pozo Picó\*

*Servicio de Endocrinología y Nutrición, Hospital Universitari Mútua de Terrassa, Terrassa, Barcelona, Spain*

\*Corresponding author.

*E-mail address: 11774cpp@comb.cat (C. del Pozo Picó).*

## Hypogonadotropic hypogonadism in a male with McCune-Albright syndrome<sup>☆</sup>

### Hipogonadismo hipogonadotrofo 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 ( $\alpha_s$ ) of the G protein-coupled receptor.<sup>1</sup> 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), hyperpro-

lactinemia, and hyperadrenocorticism. However, a diagnosis of MAS is made when two of the three clinical signs are present.<sup>1,2</sup>

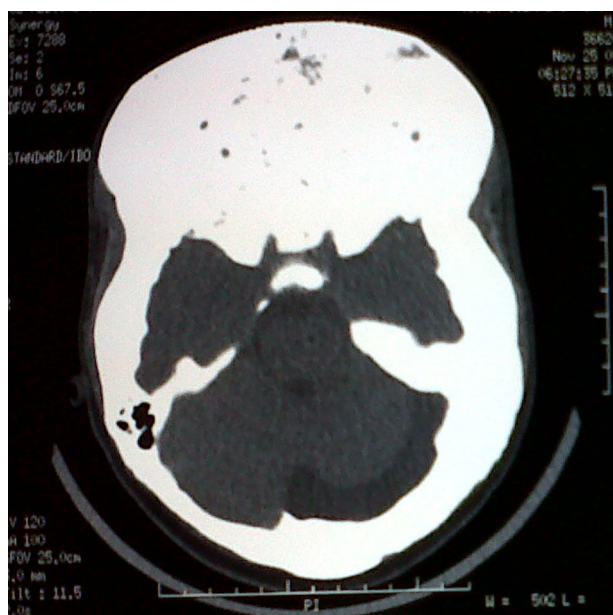
We report the case of a 16-year-old male patient from Mérida (Venezuela) with no family history and a personal history of multiple femoral fractures secondary to polyostotic fibrous dysplasia diagnosed at three years of age who attended the endocrinology unit for tall height. He also reported continuous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

Physical examination revealed 93 kg of weight (greater than the 97<sup>th</sup> percentile), 183 cm of height (greater than the 97<sup>th</sup> 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<sup>2</sup>, 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

<sup>☆</sup> Please, cite this article as: Lima-Martínez MM, et al. Hipogonadismo hipogonadotrofo en un varón con síndrome de McCune-Albright. *Endocrinol Nutr*. 2013;60:145–7.

deformity characterized by macrocephalia, frontal prominence and hypertelorism, and external supports in both lower limbs due to multiple fractures. An android distribution of body hair was also noted, with testes of 25 mL.

Clinical laboratory tests showed normal blood glucose, as well as the following results: calcium 8.8 mg/dL (normal range (NR), 8.7–10.3), magnesium 2.1 mg/dL (NR, 1.40–2.40), phosphorus 2.2 mg/dL (NR, 2.7–4.5 mg/dL), parathyroid hormone 35.1 pg/mL (NR, 10–69), alkaline phosphatase 1396.1 IU/L (NR, 98–271), basal somatotropin (GH) 7.1  $\mu$ g/L (NR, 0–2.5), GH of 5.4  $\mu$ g/L two hours after a 75 g glucose load (NR, less than 1), IGF-1 725 ng/mL (NR, 72–385), normal thyrotropin and free thyroxine, basal cortisol 8.7  $\mu$ g/dL (NR, 5–25), prolactin 57 ng/mL (NR in males, 0–15), follicle-stimulating hormone 0.35 mIU/mL (NR, 0.7–11), luteinizing hormone 0.2 mIU/mL (NR, 0.8–7.6), and total testosterone 92.8 ng/dL (NR, 286–1511). X-rays of the left hand and wrist revealed a bone age of 15 years. A computed tomography scan showed increased bone mass volume in the cranial vault and structures of the frontal, orbital, and mastoid regions consistent with fibrous dysplasia, and a thickening of sellar region bones, which prevented adequate visualization of the pituitary gland (Fig. 1). Pituitary magnetic resonance imaging with gadolinium could not be performed due to external supports and intramedullary nails in the lower limbs. Computed campimetry was therefore performed, showing reliability indices and a normal bilateral foveal threshold. However, slightly decreased retinal sensitivity, enlarged blind spot, and superior temporal focal scotoma consistent with prechiasmatic lesion were seen in the visual field of the right eye. The left eye in turn had slightly decreased retinal sensitivity, with a blind spot of normal size and no scotomas.



**Figure 1** Computed tomography of the reported patient showing increased volume of bone mass in the cranial vault and structures of the frontal, orbital, and mastoid regions consistent with fibrous dysplasia.

Based on the clinical and laboratory findings and imaging tests, octreotide LAR 20 mg once monthly, cabergoline 0.5 mg twice weekly, testosterone undecanoate 1000 mg every three months, and zoledronic acid 5 mg once a year were prescribed. At a new visit at three months, the patient reported a slight improvement in headache and showed a basal GH value of 2.4  $\mu$ g/L. Other test results included: GH of 2.5  $\mu$ g/L two hours after a 75 g glucose load, 2.5  $\mu$ basal IGF-1 105 ng/mL, prolactin 37 ng/mL, total testosterone 1290 ng/dL, and alkaline phosphatase 1126.2 IU/L. Based on these results, the monthly dose of octreotide LAR was increased to 30 mg, with no change in any of the other medical indications.

This patient had MAD due to the coexistence of polyostotic fibrous dysplasia, café-au-lait spots, and endocrinopathies such as excess GH and hyperprolactinemia. The prevalence of this disease is unknown, but it is estimated to occur in 1/100,000 to 1/1,000,000 newborns, being more common in females.<sup>1</sup> Fibrous dysplasia may be monostotic, affecting a single bone, or polyostotic when more than two bones are involved. The first form is more common and occurs in 7% of benign tumor bones.<sup>1,2</sup>

Approximately 20% of patients with MAS have excess GH. A high prevalence of concomitant hyperprolactinemia (71–92%) is found in these patients. Thirty-three percent of these cases are due to a pituitary microadenoma, and all the others to hyperplasia of mammosomatotroph cells.<sup>3</sup> Excess GH is particularly harmful in patients with MAS because it may accelerate fibrous dysplasia, especially in craniofacial bones, potentially causing vision and hearing loss.<sup>3</sup> First line treatment of excess GH and hyperprolactinemia is medical, consisting of the use of somatostatin analogs and dopamine D2 receptor agonists, because if pituitary adenoma occurs, (transsphenoidal) surgery is not effective due to massive thickening of the skull base resulting from craniofacial fibrous dysplasia<sup>3</sup>; it should be noted, however, that the response of this group of patients to medical treatment with cabergoline and octreotide LAR is usually consistent but inadequate, and hormone control criteria are not reached in most cases.<sup>4</sup> According to the consensus on acromegaly cure criteria published in 2010, disease control is defined as random GH levels less than 1  $\mu$ g/L with normal IGF-1 levels for sex and age. In the event of disagreement between these tests, it is recommended that the GH level be measured two hours after a 75 g glucose load. This should be less than 0.4  $\mu$ g/L.<sup>5</sup> It should be noted that when this patient was seen again three months after the start of treatment with octreotide LAR, he was found to have a basal GH of 2.4  $\mu$ g/L, with a GH level two hours after the load of 2.5  $\mu$ g/L, which despite the normal IGF-1 level revealed an inadequate response to the somatostatin analog and led to the dose being increased to 30 mg monthly.

The most common endocrinopathy in MAS is early puberty, but some cases of central hypogonadism have exceptionally been reported in both sexes.<sup>6,7</sup> In the reported patient, the cause must have been acquired because he showed good virilization and adequate testicular volume. Of note in the functional history was hyposmia, which is commonly associated with hypogonadism in Kallmann syndrome,

but may possibly be due in this case to severe cranial sclerosis obliterating the cribriform cartilage of the ethmoid bone, thus damaging the olfactory fibers. While this patient had high prolactin levels, these were not so high as to explain hypogonadism. It is therefore likely that the cause could be related to gonadotroph cell damage due to fibrous dysplasia of the sella turcica.

Fibrous dysplasia results from GNAS gene mutation and causes abnormal proliferation and differentiation of osteoblasts together with increased osteoclastic activity. This mutation is also associated with increased expression of fibroblast growth factor 23, which increases renal phosphate excretion, causing hypophosphatemia and aggravating the bone mineralization defect.<sup>2,8</sup> It should be noted that this patient had mild hypophosphatemia upon admission. Based on pathophysiological understanding of the disease, bisphosphonates have been increasingly used in recent years. Pamidronate and zoledronic acid are the most commonly used bisphosphonates.<sup>9,10</sup> The prognosis of polyostotic disease is usually good, but tends to be worse in patients with MAS having excess GH.<sup>2</sup> Monitoring is based on bone turnover markers such as alkaline phosphatase, which are elevated in active disease and tend to decrease in response to antiresorptive treatment.<sup>2</sup>

## References

- Dumitrescu CE, Collins MT. McCune-Albright syndrome. *Orphanet J Rare Dis.* 2008;3:12.
- Chapurlat RD, Orcel P. Fibrous dysplasia of bone and McCune-Albright syndrome. *Best Pract Res Clin Rheumatol.* 2008;22:55–69.
- Akintoye S, Chebli C, Booher S, Feuillan P, Kushner H, Leroith D, et al. Characterization of gsp-mediated growth hormone excess in the context of McCune-Albright syndrome. *J Clin Endocrinol Metab.* 2002;87:5104–12.
- Horvath A, Stratakis CA. Clinical and molecular genetics of acromegaly: MEN1, Carney complex, McCune-Albright syndrome, familial acromegaly and genetic defects in sporadic tumors. *Rev Endocr Metab Disord.* 2008;9:1–11.
- Giustina A, Chanson P, Bronstein MD, Klibanski A, Lamberts S, Casanueva FF, et al. A consensus on criteria for cure of acromegaly. *J Clin Endocrinol Metab.* 2010;95:3141–8.
- Chung KF, Alaghband-Zadeh J, Guz A. Acromegaly and hyperprolactinemia in McCune-Albright syndrome – evidence of hypothalamic dysfunction. *Am J Dis Child.* 1983;137:134–6.
- Shires R, Whyte MP, Avioli LV. Idiopathic hypothalamic hypogonadotropic hypogonadism with polyostotic fibrous dysplasia. *Arch Intern Med.* 1979;139:1187–9.
- Razzaque MS. The FGF23-Klotho axis: endocrine regulation of phosphate homeostasis. *Nat Rev Endocrinol.* 2009;5:611–9.
- Plotkin H, Rauch F, Zeitlin L, Munns C, Travers R, Glorieux FH. Effect of pamidronate treatment in children with polyostotic fibrous dysplasia of bone. *J Clin Endocrinol Metab.* 2003;88:4569–75.
- Mansoori LS, Catel CP, Rothman MS. Bisphosphonate treatment in polyostotic fibrous dysplasia of the cranium: case report and literature review. *Endocr Pract.* 2010;16:851–4.

Marcos M. Lima-Martínez\*, Victor Gil, Maracelly Mederico, Roald Gómez-Pérez

*Unidad de Endocrinología, Instituto Autónomo Hospital Universitario de los Andes, Mérida, Venezuela*

\*Corresponding author.

E-mail address: marcoslimamedical@hotmail.com (M.M. Lima-Martínez).

## Factitious hypoglycemia<sup>☆</sup>

### Hipoglucemia facticia

Hypoglycemia is defined as plasma glucose levels less than 50 mg/dL.<sup>1</sup> However, the definition of hypoglycemia may vary depending on whether glucose is measured in venous or capillary blood. The cut-off point of the glucose level that triggers a physiological response to hypoglycemia and the resultant symptoms may also vary. The diagnosis of hyperglycemia is based on Whipple's triad: low blood glucose level, symptoms of hypoglycemia, and symptom improvement once blood glucose returns to normal. Hypoglycemia causes adrenergic symptoms such as tachycardia, palpitations, tremor, sweating, pallor and anxiety, and non-adrenergic or neuroglycopenic symptoms including hunger, headache, weakness, visual disturbances, confusion, lethargy, seizures, and even coma.<sup>1</sup> The most common cause in our environment is glucose lowering treatment

(oral hypoglycemic drugs and insulin). Other potential causes include end-stage renal failure, sepsis, hormone deficiencies, big mesenchymal tumors, insulinoma, congenital metabolic diseases, etc. Plasma glucose levels in the hypoglycemic range not associated with clinical signs are sometimes detected. Such cases may be due to the inadequate perception of hypoglycemic symptoms or to "factitious hypoglycemia". The case of a patient with an uncommon cause of hypoglycemia is reported below.

The patient was an 83-year-old male with a history of high blood pressure treated with spironolactone 25 mg daily and furosemide 20 mg daily, hypercholesterolemia treated with atorvastatin 40 mg daily, chronic renal failure secondary to nephroangiosclerosis, paroxysmal atrial fibrillation, cognitive impairment, vascular parkinsonism, and depressive syndrome. He had also been seen by different specialists due to frequent presyncopal episodes and based on laboratory tests reporting a WBC count of 22,400/ $\mu$ L, a RBC count of  $6.3 \times 10^6$ / $\mu$ L, hemoglobin 17.1 g/dL, hematocrit 53%, and a platelet count of 441,000/ $\mu$ L, he had been diagnosed with moderate pancytopenia. Tests for myeloproliferative syndrome were negative. The patient was

<sup>☆</sup> Please, cite this article as: Gutiérrez Medina S, et al. Hipoglucemia facticia. *Endocrinol Nutr.* 2013;60:147–9.