Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/19204
DOI URL: http://dx.doi.org/10.21474/IJAR01/19204

RESEARCH ARTICLE

ACROMEGALY WITH NORMAL PITUITARY MRI AND NO IDENTIFIABLE ECTOPIC SECRETION: WHAT'S THE CHALLENGE?

Mariam Hamaichat, Muhammad Malad and Ahmed AnasGuerboub

Manuscript Info

Manuscript History
Received: 31 May 2024
Final Accepted: 30 June 2024
Published: July 2024

Key words:-
Acromegaly, Growth Hormone, Normal MRI, Ectopic, Somatostatin Analogues

Abstract

Somatotropic pituitary adenoma is the most common etiology of acromegaly, most often detected at the macroadenoma stage. Some cases of acromegaly with normal pituitary magnetic resonance imaging (MRI) have been described in the literature, necessitating the search for an ectopic origin, which may also be normal; this is a rare entity whose management and follow-up are not codified. Exploratory pituitary surgery or medical treatment with somatostatin analogues, dopaminergic agonists, or growth hormone (GH) antagonists may be proposed as a treatment. We report a case of acromegaly with normal pituitary MRI and no identifiable ectopic secretion, in which we opted for medical treatment with somatostatin analogues to stabilise the disease and limit its complications, with active monitoring of biological and morphological parameters.

Introduction:-

Acromegaly is a rare disorder, with an estimated prevalence of 5.9 per 100,000 and an incidence of 0.38 cases per 100,000 per year [1]. It is secondary to chronic exposure to an endogenous excess of growth hormone (GH) and elevated levels of insulin-like growth factor 1 (IGF-1). In 98% of cases, it is associated with excessive, uncontrollable GH production by a pituitary adenoma [2]. These are usually pituitary macroadenomas (larger than 10 mm) visible on magnetic resonance imaging (MRI) of the sellar region. Ectopic secretion of GH or GHRH (growth hormone-releasing hormone) accounts for less than 2% of cases [2]. Acromegaly with normal pituitary MRI and no identifiable ectopic lesion, as described in this article, is an even rarer entity, with only a dozen cases reported in the literature.

Case Repport

We report the case of a 55-year-old female patient who was referred to our endocrinology department by her primary care physician for a multiheteronodulargoiter,it was discovered during a cervical ultrasound performed for cervical discomfort and track change. Initial contact with the patient revealed a bulging forehead with protruding superciliary arches and enlarged hands. Her medical history included diabetes mellitus for 3 years on oral antidiabetic medication, well balanced, and hypertension on dual therapy, well controlled. She has been treated in rheumatology for osteoarthritis for 2 years and underwent right carpal tunnel surgery 1 year ago. The patient reports a change in her face, a positive ring sign, and a change in shoe size over the past few years. Based on this clinical picture, acromegaly was suspected. The patient's IGF-1 level was 1.9 times the normal range for her age, and the GH nadir was 0.9 µg/L (>0.2 µg/L) on the 75g oral glucose tolerance test (OGTT). These results confirmed the diagnosis of acromegaly (see Table 1). As part of the etiologic work-up, a 1.5 Tesla hypothalomo-hypophyseal MRI with Gadolinium injection was requested but was normal. It was repeated with diffusion, T1, T2, FLAIR, and

Corresponding Author:-Mariam Hamaichat

gradient echo sequences, and dynamic sequences, returned without abnormalities (see Figure 1 and Figure 2). Since no pituitary adenoma could be identified on MRI, an ectopic lesion was investigated with a thoraco-abdomino-pelvic computed tomography (CT) scan, which was without abnormalities, and a GHRH assay, which was normal. The available treatment modalities were discussed with the patient and she opted for medical treatment with somatostatin analogues. The patient was then started on lanreotide 120 mg monthly injection.

Discussion:-

Acromegaly is a chronic disease with an insidious onset. The effects of excess IGF-1 on its target organs are responsible for the clinical manifestations and for the metabolic, respiratory, rheumatologic and cardiac complications [3]. A positive diagnosis is based on IGF-1 levels: a value greater than 1.3 times normal for the patient's age confirms acromegaly. For greater certainty, a GH inhibition test using orally induced hyperglycemia with 75 g of glucose may be useful (GH nadir > 0.4 µg/L if body mass index (BMI) < 25 kg/m^2 and GH > 0.2 µg/L if BMI > 25 kg/m^2) [4].

The most common etiology of acromegaly is GH hypersecretion by a pituitary adenoma. Given the delay in diagnosis of the disease, ranging from 4 to 10 years, adenomas are usually discovered at the macroadenoma stage and are well identified on pituitary MRI [5]. Other causes of acromegaly are rare, accounting for less than 2% of cases [2]. We distinguish between ectopic GH-secreting pituitary adenomas, ectopic GH secretion by a neuroendocrine tumor, which is extremely rare, hypothalamic tumors, GHRH-secreting sellargangliocytomas, and the most common type of ectopic acromegaly, which is due to GHRH-secreting neuroendocrine tumors, in which case MRI may show pituitary hyperplasia secondary to GHRH hypersecretion [6].

Acromegaly with normal pituitary MRI is a very rare situation that requires a search for ectopic GH or GHRH secretion. In our case, pituitary MRI was performed at 1.5 Tesla using three-plane slices with diffusion, T1, T2, FLAIR, and gradient echo sequences, supplemented by dynamic MRI sequences. No pituitary adenoma was found and the search for ectopic secretion was negative. In the literature, only five publications have reported similar cases of acromegaly with normal MRI and no evidence of an ectopic lesion. Doppman [7] reported 3 cases in 1990, Daud [8] reported one case in 2009, a series of 6 cases was reported by Lonser [5] in 2010 and another case by Khandelwal [9] in 2011, all of these patients benefited from exploratory surgery of the sellar region, which in all cases objectified a pituitary microadenoma, varying in size from 5 to 9 mm. On the other hand, Ong [10] also reported the case of a 76-year-old patient diagnosed as acromegalic with normal pituitary MRI and no individualisable ectopic lesion, who was treated with medical therapy, initially with octreotide 20 mg alone, in one injection per month, then combined with cabergoline at a dose of 4 mg per week, with a good biological response and normalization of IGF-1 levels.

In typical forms of acromegaly, trans-sphenoidal surgery is the first-line treatment [11]. It is the only treatment that can achieve complete remission of the disease [12]. However, even in reference centers, success rates are highly dependent on the size of the adenoma and the degree of invasion. In the series by Cecilia et al (n=548), the success rate of the first surgery reached 91.5% in microadenomas, versus 82% in noninvasivemacroadenomas. However, the results were significantly worse in the group of patients with invasive macroadenomas [13]. Regarding medical treatment, somatostatin analogues have a track record of more than 30 years in the medical management of acromegaly [14]. First-generation long-acting analogues (octreotide and lanreotide) are recommended as first-line therapy when surgery is not the treatment of choice (contraindication, patient refusal, etc.) [15]. Biological remission with normalization of IGF-1 levels can be achieved in 55-70% of patients on octreotide [16]. With lanreotide, IGF-1 normalization rates can reach 45.5% after 12 months of treatment and up to 55.6% after 24 months of treatment, with better long-term clinical tolerability [17]. In the PRIMARYS study, the control rate was slightly higher, with a remission rate of 54% at 12 months and 68% at 48 months [18]. In addition to its anti-secretory effect, lanreotide also has a significant anti-tumor effect, which can reach 50% [12]. If somatostatin analogues alone do not achieve the desired result, treatment can be combined with dopaminergic agonists (cabergoline) or a GH receptor antagonist (pegvisomant) [11].

Cabergoline can be used as monotherapy for the medical treatment of acromegaly. Normalisation of IGF-1 levels with cabergoline has been reported in one third of patients [19]. IGF-1 levels at 1.5 times the normal range before initiation of cabergoline are a good predictor of remission [19]. For pegvisomant, a multicenter cohort "ACROSTUDY" (n=2221) showed an improvement in IGF-1 levels in 53.7% of patients during the first year of

treatment, increasing to 75.4% over 10 years of treatment, at the expense of an endocranial response with 7.1% tumor volume increase and 71.1% stabilisation [20].

In our patient's case, the treatment options were either transsphenoidal exploratory surgery or medical management, with close monitoring, to detect the appearance of a pituitary adenoma. When the patient refused surgery, we chose medical treatment. The choice between somatostatin analogues and pegvisomant was based on several parameters: antisecretory efficacy, tolerability of treatment, and accessibility of treatment in our country. In fact, given the unavailability of pegvisomant in Morocco, the need to take it daily, and the frequency of its side effects, especially hepatic [20], our choice was more oriented towards lanreotide 120 mg injected once a month. Our proposed monitoring method is IGF-1 monitoring every 3 months for the first 6 months of treatment, then biannually. There are no specific recommendations for monitoring acromegaly with negative imaging. Good control of the disease is generally defined by normalisation of IGF-1 levels, preferably in the upper half of the normal range for the age group [4]. Testing should be scheduled 3 months after treatment initiation and within one week of the next injection [4]. In addition, the expected IGF-1 target in our patient's case is 55 to 234 ng/mL. Regarding imaging, we suggest imaging at 6 months, then at 1 year, and later depending on the results.

Conclusion:-

At the time of diagnosis of acromegaly, a pituitary macroadenoma is often objectified by pituitary MRI, while the absence of visualisation of an adenoma should prompt a search for ectopic secretion of GH or GHRH. In cases where all these investigations are normal, as in our patient, this leads to the diagnosis of acromegaly with negative imaging, whose management is not codified. Medical treatment with somatostatin analogues, cabergoline or GH receptor antagonists may then be warranted. The goal of these treatments is to stabilise the disease and its complications.

Table 1:-Results of GH inhibition test with 75g glucose OGTT.

Time (min)	GH levels (µg/L)
T0	1.436
T30	1.205
T60	**0.929**
T90	1.090
T120	1.063
T150	1.438
T180	1.968

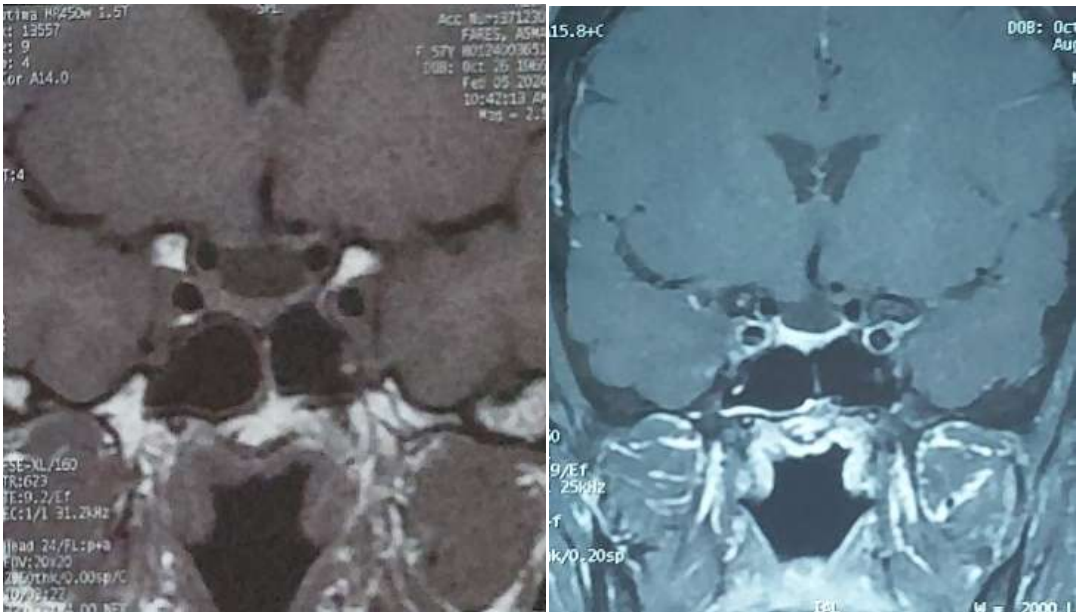

Figure 1:- T1-weighted coronal section before and after injection of Gadolinium.

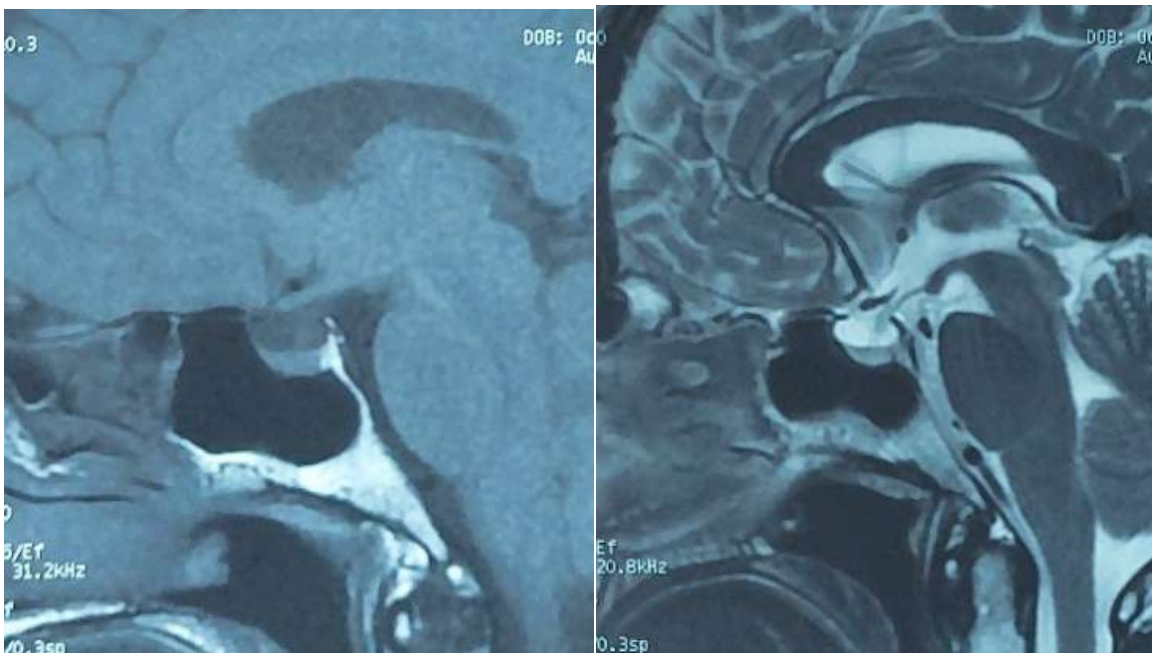

Figure 2:- T1- and T2-weighted sagittal section.

References:-

[1] Crisafulli S, Luxi N, Sultana J, Fontana A, Spagnolo F, Giuffrida G, Ferraù F, Gianfrilli D, Cozzolino A, Cristina De Martino M, Gatto F, Barone-Adesi F, Cannavò S, Trifirò G. Global epidemiology of acromegaly: a systematic review and meta-analysis. Eur J Endocrinol. 2021 Jul 1;185(2):251-263. doi: 10.1530/EJE-21-0216. PMID: 34061771.

[2] Ramírez C, Hernández-Ramirez LC, Espinosa-de-los-Monteros AL, Franco JM, Guinto G, Mercado M. Ectopic acromegaly due to a GH-secreting pituitary adenoma in the sphenoid sinus: a case report and review of the literature. BMC Res Notes. 2013 Oct 12;6:411. doi: 10.1186/1756-0500-6-411. PMID: 24119925; PMCID: PMC3874769.

[3] Colao A, Grasso LFS, Giustina A, Melmed S, Chanson P, Pereira AM, Pivonello R. Acromegaly. Nat Rev Dis Primers. 2019 Mar 21;5(1):20. doi: 10.1038/s41572-019-0071-6. Erratum in: Nat Rev Dis Primers. 2019 Oct 21;5(1):72. PMID: 30899019.

[4] Giustina A, Biermasz N, Casanueva FF, Fleseriu M, Mortini P, Strasburger C, van der Lely AJ, Wass J, Melmed S; Acromegaly Consensus Group. Consensus on criteria for acromegaly diagnosis and remission. Pituitary. 2024 Feb;27(1):7-22. doi: 10.1007/s11102-023-01360-1. Epub 2023 Nov 3. Erratum in: Pituitary. 2023 Dec 6;: PMID: 37923946; PMCID: PMC10837217.

[5] Lonser RR, Kindzelski BA, Mehta GU, Jane JA Jr, Oldfield EH. Acromegaly without imaging evidence of pituitary adenoma. J ClinEndocrinolMetab. 2010 Sep;95(9):4192-6. doi: 10.1210/jc.2010-0570. Epub 2010 Jul 7. PMID: 20610592; PMCID: PMC2936064.

[6] Fainstein-Day P, Ullmann TE, Dalurzo MCL, Sevlever GE, Smith DE. The clinical and biochemical spectrum of ectopic acromegaly. Best Pract Res ClinEndocrinolMetab. 2024 May;38(3):101877. doi: 10.1016/j.beem.2024.101877. Epub 2024 Feb 14. PMID: 38413286.

[7] Doppman JL, Miller DL, Patronas NJ, Oldfield EH, Merriam GR, Frank SJ, Flack MR, Weintraub BD, Gorden P. The diagnosis of acromegaly: value of inferior petrosal sinus sampling. AJR Am J Roentgenol. 1990 May;154(5):1075-7. doi: 10.2214/ajr.154.5.2108545. PMID: 2108545.

[8] Daud S, Hamrahian AH, Weil RJ, Hamaty M, Prayson RA, Olansky L. Acromegaly with negative pituitary MRI and no evidence of ectopic source: the role of transphenoidal pituitary exploration? Pituitary. 2011 Dec;14(4):414-7. doi: 10.1007/s11102-009-0205-z. PMID: 19904612.

[9] Khandelwal D, Khadgawat R, Mukund A, Suri A. Acromegaly with no pituitary adenoma and no evidence of ectopic source. Indian J EndocrinolMetab. 2011 Sep;15Suppl 3(Suppl3):S250-2. doi: 10.4103/2230-8210.84878. PMID: 22029034; PMCID: PMC3183531.

[10] Ong N, Sy RA. "Overgrowth: Missing a Tumor" Acromegaly without Imaging Evidence of Pituitary Adenoma and No Ectopic Source: A Case Report. J ASEAN Fed Endocr Soc. 2017;32(2):173-177. doi: 10.15605/jafes.032.02.13. Epub 2017 Sep 6. PMID: 33442103; PMCID: PMC7784194.

[11] Giustina A, Barkhoudarian G, Beckers A, Ben-Shlomo A, Biermasz N, Biller B, Boguszewski C, Bolanowski M, Bollerslev J, Bonert V, Bronstein MD, Buchfelder M, Casanueva F, Chanson P, Clemmons D, Fleseriu M, Formenti AM, Freda P, Gadelha M, Geer E, Gurnell M, Heaney AP, Ho KKY, Ioachimescu AG, Lamberts S, Laws E, Losa M, Maffei P, Mamelak A, Mercado M, Molitch M, Mortini P, Pereira AM, Petersenn S, Post K, Puig-Domingo M, Salvatori R, Samson SL, Shimon I, Strasburger C, Swearingen B, Trainer P, Vance ML, Wass J, Wierman ME, Yuen KCJ, Zatelli MC, Melmed S. Multidisciplinary management of acromegaly: A consensus. Rev EndocrMetabDisord. 2020 Dec;21(4):667-678. doi: 10.1007/s11154-020-09588-z. Epub 2020 Sep 10. PMID: 32914330; PMCID: PMC7942783.
[12] Protocol national de diagnostic et de soins PNDS, Centre de référence des maladies rares de l'Hypophyse (CRMR HYPO), HAS, 2021.
[13] FernándezMateos C, García-Uria M, Morante TL, García-Uría J. Acromegaly: surgical results in 548 patients. Pituitary. 2017 Oct;20(5):522-528. doi: 10.1007/s11102-017-0813-y. Erratum in: Pituitary. 2017 Jul 5;: PMID: 28589294.
[14] Giustina A, Karamouzis I, Patelli I, Mazziotti G. Octreotide for acromegaly treatment: a reappraisal. Expert OpinPharmacother. 2013 Dec;14(17):2433-47. doi: 10.1517/14656566.2013.847090. Epub 2013 Oct 14. PMID: 24124691.
[15] Gadelha MR, Wildemberg LE, Kasuki L. The Future of Somatostatin Receptor Ligands in Acromegaly. J ClinEndocrinolMetab. 2022 Jan 18;107(2):297-308. doi: 10.1210/clinem/dgab726. PMID: 34618894; PMCID: PMC8764337.
[16] McKeage K, Cheer S, Wagstaff AJ. Octreotide long-acting release (LAR): a review of its use in the management of acromegaly. Drugs. 2003;63(22):2473-99. doi: 10.2165/00003495-200363220-00014. PMID: 14609359.
[17] Störmann S, Schopohl J, Bullmann C, Terkamp C, Christ-Crain M, Finke R, Flitsch J, Kreitschmann-Andermahr I, Luger A, Stalla G, Houchard A, Helbig D, Petersenn S. Multicenter, Observational Study of LanreotideAutogel for the Treatment of Patients with Acromegaly in Routine Clinical Practice in Germany, Austria and Switzerland. ExpClinEndocrinol Diabetes. 2021 Mar;129(3):224-233. doi: 10.1055/a-1247-4713. Epub 2020 Dec 7. PMID: 33285601.
[18] Caron PJ, Bevan JS, Petersenn S, Flanagan D, Tabarin A, Prévost G, Maisonobe P, Clermont A; PRIMARYS Investigators. Tumor shrinkage with lanreotideAutogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. J ClinEndocrinolMetab. 2014 Apr;99(4):1282-90. doi: 10.1210/jc.2013-3318. Epub 2013 Jan 1. PMID: 24423301; PMCID: PMC4009579.
[19] Shimon I. Real-world value of cabergoline in the treatment of acromegaly. Best Pract Res ClinEndocrinolMetab. 2024 Feb 28:101887. doi: 10.1016/j.beem.2024.101887. Epub ahead of print. PMID: 38443225.
[20] Fleseriu M, Führer-Sakel D, van der Lely AJ, De Marinis L, Brue T, van der Lans-Bussemaker J, Hey-Hadavi J, Camacho-Hubner C, Wajnrajch MP, Valluri SR, Palladino AA, Gomez R, Salvatori R. More than a decade of real-world experience of pegvisomant for acromegaly: ACROSTUDY. Eur J Endocrinol. 2021 Aug 27;185(4):525-538. doi: 10.1530/EJE-21-0239. PMID: 34342594; PMCID: PMC8428076.