

In terms of follow-up, imaging tests are recommended every three-to-six months for G1/G2 NET and every two-to-three months for G3 NET.⁷ Follow-up should be lifelong, although frequency can be extended to every 1–2 years as time progresses.⁷ Imaging for somatostatin receptors (Octreoscan/PET with gallium) is recommended at 12–36 months if over-expression was demonstrated by imaging in the primary tumour.⁷ These guidelines were followed in our patient, and hypercalcaemia was detected by the blood tests, alerting to the possibility of recurrence. CgA is usually used, as well as NSE, the latter being particularly useful in G2 and G3 when CgA levels are normal.⁷ In our case, however, both values were normal. There are currently no recommendations in cases similar to ours, due to their exceptional nature, but what should be emphasised is the importance of long-term follow-up in these patients, including serum calcium levels when ordering blood tests.

In conclusion, early diagnosis of pNET associated with PTHrP-mediated hypercalcaemia is important as they tend to be more aggressive. Therefore, when hypercalcaemia is detected, once the most common causes have been ruled out, a targeted study should be conducted, as early diagnosis can improve the prognosis for these patients. After surgery, long-term follow-up should be carried out, and serum calcium monitoring can be useful for early diagnosis of recurrence.

Ethical considerations

Informed consent was obtained from all individual participants included in the study.

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References

1. Grunbaum A, Kremer R. Parathyroid hormone-related protein (PTHrP) and malignancy. *Vitam Horm*. 2022;120:133–77.

2. Giannetta E, Sesti F, Modica R, Grossrubatscher EM, Guarnotta V, Ragni A, et al. Case report: unmasking hypercalcemia in patients with neuroendocrine neoplasms. experience from six Italian referral centers. *Front Endocrinol (Lausanne)*. 2021;12:665698.
3. Kamp K, Feelders RA, van Adrichem RC, de Rijke YB, van Nederveen FH, Kwekkeboom DJ, et al. Parathyroid hormone-related peptide (PTHrP) secretion by gastroenteropancreatic neuroendocrine tumors (GEP-NETs): clinical features, diagnosis, management, and follow-up. *J Clin Endocrinol Metab*. 2014;99(9):3060–9.
4. Milanese A, Yu R, Wolin EM. Humoral hypercalcemia of malignancy caused by parathyroid hormone-related peptide-secreting neuroendocrine tumors. Report of six cases. *Case Reports Pancreatol*. 2013;13(3):324–6.
5. Pitts S, Mahipal A, Bajor D, Mohamed A. Hypercalcemia of malignancy caused by parathyroid hormone-related peptide-secreting pancreatic neuroendocrine tumors (PTHrP-PNETs): case report. *Front Oncol*. 2023;13:1197288.
6. Srirajaskanthan R, McStay M, Toumpanakis C, Meyer T, Caplin ME. Parathyroid hormone-related peptide-secreting pancreatic neuroendocrine tumours: case series and literature review. *Neuroendocrinology*. 2009;89:48–55.
7. Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2020;31(7):844–60.

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Concern about hypoglycaemia is mainly nocturnal: An infodemiology study



La preocupación por la hipoglucemia es principalmente nocturna: un estudio de infodemiología

Dear Editor,

Hypoglycaemia is associated with long-term negative consequences in people with diabetes, such as an increase in glycaemic variability and a higher risk of mortality.¹ A hypo-

glycaemic episode can involve acute symptoms, such as irritability, shakiness, tachycardia and confusion, which can progress to loss of consciousness, seizure, coma or death.¹ Considering the unpleasant symptoms that can accompany hypoglycaemia and its potential short- and long-term risks, it can often lead to anxiety and fear in people with diabetes,^{2,3} leading to a reduction in their quality of life.^{2,4} Nocturnal hypoglycaemia is common in patients with diabetes, given that almost 50% of all episodes of severe hypoglycaemia occur during sleep.⁵ Thus, nocturnal hypoglycaemia can affect sleep quality.^{2,6}

Considering that people might tend to search the Internet about a topic whenever it comes to their minds or worries them, we thought that people with diabetes worldwide would probably search more often for “hypoglycaemia” at

the time of day when they have the most episodes, or whenever those episodes are severe enough to cause concern. These data could provide indirect insight into the hourly worldwide awareness of hypoglycaemia, as studies exploring the global interest in hypoglycaemia are lacking.

Google is undoubtedly the most popular Internet search engine. Google Trends is a tool Google developed in 2006 that can provide an analysis of the popularity of Google searches across various regions over time, showing the size of a term's search volume during every time period in the Internet's history. Mainly since 2020, Google Trends has been used by the scientific community to analyse social interest in various subjects, focusing particularly on the COVID-19 pandemic.⁷ To our knowledge, there are only a few Google Trends-based studies on diabetes,^{7–9} none of which have targeted hypoglycaemia.

To analyse the time of day when the term "hypoglycaemia" was searched more frequently worldwide, we recorded day-by-day Google Trends data from five countries (United States, Brazil, Spain, United Kingdom and Australia) for 14 days (1–14 July 2023). So as to adapt this Google Trends search to the most spoken language of each country, the term was searched as "hypoglycemia" for the United States, as "hipoglicemia" for Brazil, as "hipoglucemia" for Spain, and as "hypoglycaemia" for the United Kingdom and Australia. Every search was adapted to each country's capital city time zone. Search data were obtained for each country every eight minutes for the 14 days of the study. This allowed us to calculate an hour-by-hour average Google interest in hypoglycaemia across these countries during this period (Fig. 1A). As the figure shows, the time of day when most of the Google searches for "hypoglycaemia" occurred was at night (especially from 3 a.m. to 5 a.m.), which was common to all the five countries studied. The average interest score from 0.00 a.m. to 6.00 a.m. (night-time) was higher than the average interest score from 6.01 a.m. to 11.59 p.m. (daytime) in each and every country ($p < 0.01$ for every country, Student's t -test). The mean hourly night-time interest score for all the five countries combined (17 points) was higher than the mean hourly daytime score (11 points; $p < 0.001$). The eight-minute time of day with the maximum searches in each country during each of these 14 days was also recorded, showing that the time of greatest interest in searching for hypoglycaemia was also at night (Fig. 1B). The same study was repeated two months later, with similar results (data not shown). Taken together, these results could reflect that the time of day with maximum interest in hypoglycaemia is at night, probably showing that people with diabetes tend to have more severe or worrying hypoglycaemic episodes at night, while sleeping.

The study has limitations to be acknowledged. In general, infodemiology studies are mainly conceived as hypothesis generators. We cannot guarantee that the reason a person is searching Google for hypoglycaemia is because they have diabetes or are experiencing a hypoglycaemic episode. Moreover, the entire population is not fully represented, given that some people might use other search engines and some do not have access to the Internet. Neither Asian nor African countries were included due to their non-use of the Latin alphabet or little use of Google. Finally, the peak search time can be the one generally used, and it

may be not restricted to hypoglycaemia. As a control, however, it can be observed that, when searching the words "breakfast", "lunch" and "dinner" in the United States in Google Trends, the graphs displayed show that these words are searched more often at approximately 9 a.m., 12 p.m. and 6 p.m., respectively (Supplementary Figure 1).

Understanding patients' feelings is an important aspect of managing diabetes.² Fear of hypoglycaemia at night is a particular concern.^{2,4–6} The data from the present study confirm the specific interest of the population in nocturnal hypoglycaemia. Understanding the complex interplay of emotions concerning hypoglycaemia can guide healthcare providers in improving clinical practice.²

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Conflicts of interest

None to declare.

Appendix A Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.endien.2024.02.003>.

References

1. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al., on behalf of the American Diabetes Association. 6. Glycemic targets: standards of care in diabetes-2023. *Diabetes Care*. 2023;46 Suppl 1:S97–110, <http://dx.doi.org/10.2337/dc23-s006>.
2. Brown JB, Reichert SM, Valliere Y, Webster-Bogaert S, Ratzki-Leewing A, Ryan BL, et al. Living with hypoglycemia: an exploration of patients' emotions: qualitative findings from the InHypo-DM study, Canada. *Diabetes Spectr*. 2019;32:270–6, <http://dx.doi.org/10.2337/ds18-0074>.
3. Wild D, von Maltzahn R, Brohan E, Christensen T, Clauson P, Gonder-Frederick L. A critical review of the literature on fear of hypoglycemia in diabetes: implications for diabetes management and patient education. *Patient Educ Couns*. 2007;68:10–5, <http://dx.doi.org/10.1016/j.pec.2007.05.003>.
4. Fidler C, Elmelund Christensen T, Gillard S. Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. *J Med Econ*. 2011;14:646–55, <http://dx.doi.org/10.3111/13696998.2011.610852>.
5. Allen KV, Frier BM. Nocturnal hypoglycemia: clinical manifestations and therapeutic strategies toward prevention. *Endocr Pract*. 2003;9:530–43, <http://dx.doi.org/10.4158/EP.9.6.530>.
6. Zhu B, Abu Irsheed GM, Martyn-Nemeth P, Reutrakul S. Type 1 diabetes, sleep, and hypoglycemia. *Curr Diab Rep*. 2021;21:55, <http://dx.doi.org/10.1007/s11892-021-01424-1>.
7. Tantengco OAG. Increased global online interest in diabetes during the COVID-19 pandemic: an infodemiology study. *Obes Med*. 2021;28:100374, <http://dx.doi.org/10.1016/j.obmed.2021.100374>.
8. Tkachenko N, Chotvijit S, Gupta N, Bradley E, Gilks C, Guo W, et al. Google Trends can improve surveillance of type 2 diabetes. *Sci Rep*. 2017;7:4993, <http://dx.doi.org/10.1038/s41598-017-05091-9>.

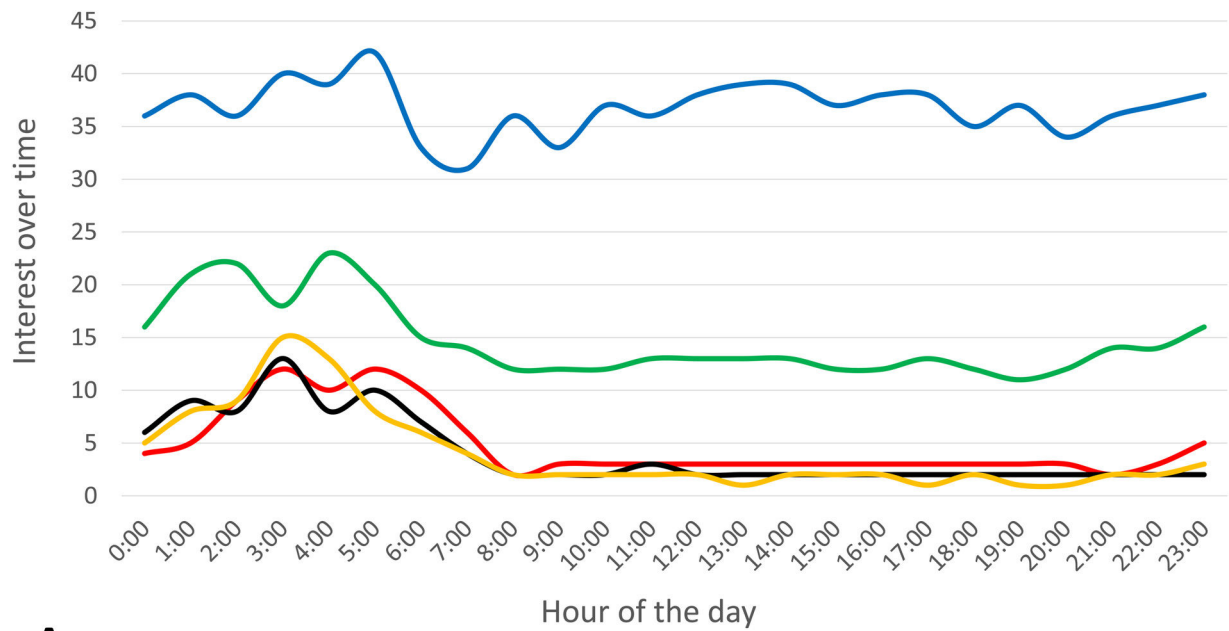
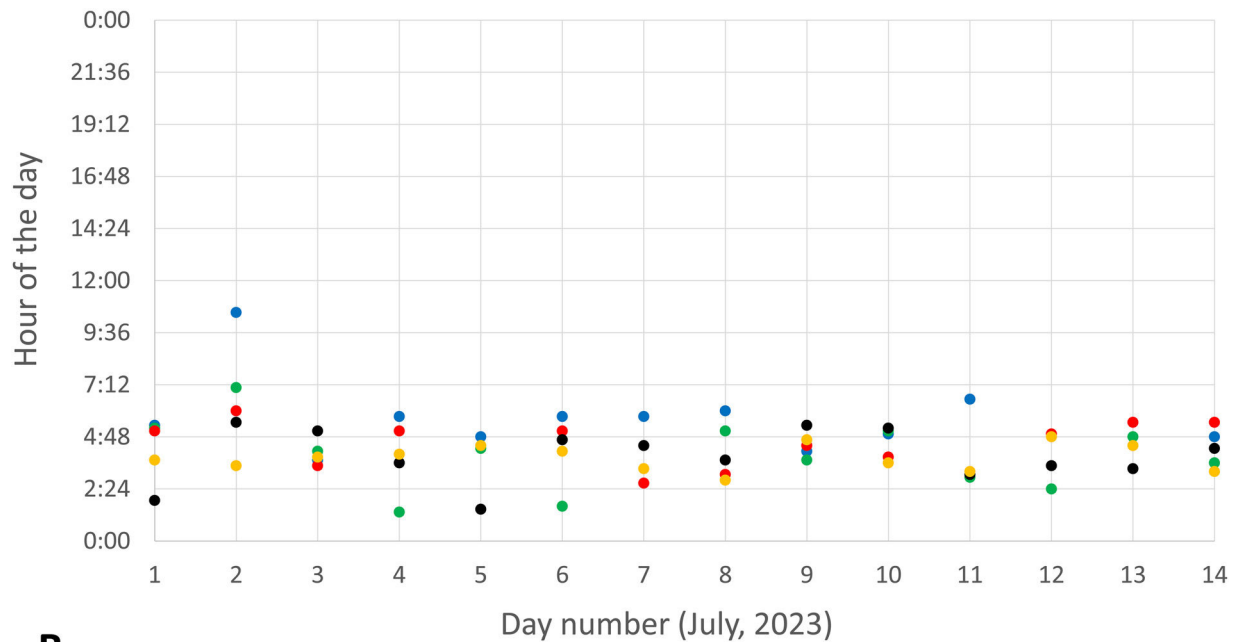
**A****B**

Figure 1 Google Trends interest in hypoglycaemia. (A) (upper panel): mean Google Trends interest in hypoglycaemia during the day for 14 consecutive days in the five countries studied. Interest score, plotted on the y-axis, does not represent an absolute volume of number of searches. For every time period, Google Trends presents data normalised on a scale from 0 to 100 points. The eight-minute period of greatest interest each day is given 100 points. The rest of the day's points are calculated by taking the time of greatest interest as a reference. For instance, if the time of greatest interest one day (100 points) got 10 Google searches, an eight-minute period at which Google received five searches would be given 50 points. Therefore, eight-minute periods with 0 searches are given 0 points. In this context, the interest score is usually directly proportional to the number of searches, which is also directly proportional to the population of each country. (B) (lower panel): dots represent the time of day with the maximum searches for every country in each of the 14 days.

9. Rasheed R, Sivaprasad S. Google trends as a surrogate marker of public awareness of diabetic retinopathy. *Eye* (Lond). 2020;34:1010–2, <http://dx.doi.org/10.1038/s41433-020-0852-x>.

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Carotid pseudoaneurysms after endoscopic transsphenoidal surgery for acromegaly



Pseudoaneurismas carotídeos tras cirugía endoscópica transesfenoidal por acromegalia

The development of pseudoaneurysms of the internal carotid artery (pICA) is a vascular complication of endoscopic endonasal transsphenoidal (EET) surgery, with an incidence of 0.55–2%.^{1,2} These are lesions composed solely of the adventitial layer of blood vessels.¹ Lack of adequate treatment can result in devastating consequences, due to the risk of rapid growth and rupture, with a mortality rate of 30–50%.^{1–4} Although therapeutic management of pICA is complex, there are multiple surgical and endovascular techniques available.^{1,2}

We present the case of a 71-year-old woman with an incidental diagnosis of acromegaly associated with a Knosp grade 1 pituitary macroadenoma (1.3 × 1.1 × 1.4 cm), with suprasellar extension and contact with the optic chiasm. The patient had no hormonal abnormalities except for increased IGF-1. She was treated by Doppler-assisted EET surgery, with reaming of the sella turcica to expose both cavernous sinuses (CS), without uncovering of the carotids or opening of the CS. Macroscopically complete excision of the soft lesion was achieved, with no special manipulation of the lateral borders or carotid arteries required. No CSF fistula was identified. Multilayer closure was performed, without requiring nasal packing.

In the immediate postoperative period (p.o.) the patient developed nasal bleeding after sneezing, requiring anterior nasal packing, which was removed 48 h later. The patient progressed well and was discharged four days after the procedure. Ten days later she had new episodes of epistaxis in the context of hypertension. An urgent surgical review was performed, cauterising slight bleeding in the rescue flap and in the right upper turbinate.

Despite that, three days later the patient had further episodes of epistaxis, which led to another surgical review and, in the absence of bleeding as a cause, to emergency CT-angiogram (Fig. 1A) and subsequent cerebral angiogra-

phy (Fig. 1B). Two images were found to be consistent with pseudoaneurysms of the right internal carotid artery. They were treated by micro-catheterisation of the right internal carotid artery distal to the aneurysmal lesions and implantation of two overlapping Derivo® flow diverter stents covering the neck of both lesions, without incident and without complications. The patient was discharged after 48 h of observation with dual antiplatelet therapy (ticagrelor 90 mg/12 h and ASA 100 mg/24 h), without further complications. Follow-up at six and 15 months confirmed stent patency and resolution of the pICA, with persistent filling of the neck of the cavernous segment, without significant hyperplasia or other complications (Figs. 1C and 1D), and the ticagrelor treatment was discontinued. The patient's IGF-1 levels are currently stable within the normal range.

As occurred with the medial pICA in the case reported here, the most commonly affected segment is the cavernous segment.⁴ Even when there is good intraoperative haemostasis and no suspicion of carotid injury, delayed lesions such as pICA or carotid-cavernous fistulae can occur.^{3,5,6} Management is complex, and a lack of adequate treatment can have devastating consequences, including death.^{1,6} Clinical series report a pICA rupture rate of up to 60%.¹

If vascular injury is suspected, an immediate angiographic study should be performed and, if negative, repeated after one week to identify possible delayed formation of pICA.^{3,4,7} Presentation with observed delayed epistaxis is described in the literature, with an incidence of 0.6–3.3 % (1–3 weeks after surgery).^{6,8}

Risk factors for vascular injury during EET surgery are anatomical bone and vascular variants, displacement of the ICA by the lesion itself or reduced intercarotid space, invasion of the CS by the lesion, previous surgical or radiotherapy treatments and expanded approaches to more complex lesions.^{1,4,7,9}

In this case, it was interesting that one of the pICA is located laterally, not directly in contact with the surgical site. Endothelial dysfunction has been described in patients with acromegaly due to structural and functional changes that make the vessels stiffer and less elastic⁹, a factor which could explain the development of acromegaly, possibly due