GALICIA CLÍNICA

Revista oficial da Sociedade Galega de Medicina Interna (SOGAMI)



Fundada en 1929 por el Dr. Aurelio Gutiérrez Moyano

**Incluida en Latindex, IME-Biomedicina del CSIC, Dialnet, Dulcinea, Directory of Open Access Journals, ROAD (Directory of Open Access scholarly Resources), WorldCat, Suncat, Miar, Scilit, CiteFactor y Emerging Source Citation Index (ESCI)**

Edita: SOGAMI / ISSN: 0304-4866

www.galiciaclinica.info
www.meiga.info



Incluida en Latindex, IME-Biomedicina del CSIC, Dialnet, Dulcinea, Directory of Open Access Journals, ROAD (Directory of Open Access scholarly Resources), WorldCat, Suncat, Miar, Scilit, CiteFactor y Emerging Source Citation Index (ESCI).

Volumen 81 | Número 2
Abril 2020

# Índice

*Summary*

# Sostenibilidad del sistema sanitario: compromiso ético de los médicos

Prof. Dr. Juan Viñas Salas

*Catedrático de Cirugía y Ex- Rector de la Universidad de Lleida.*

La salud es un bien preciado por todas las personas. La sociedad del bienestar exige que el Estado se responsabilice de su salud. En nuestro país la asistencia sanitaria está garantizada por el Estado, estando transferida a las Comunidades Autónomas. Es una conquista de la sociedad que da tranquilidad a la población, pues cuando una persona cae enferma, sabe que será atendida por un médico de familia, por un especialista o por urgencias de un hospital o ingresada si lo precisa sin que le pidan dinero; y que los actos médicos y las medicinas más caras (MHDA – Medicación Hospitalaria de Dispensación Ambulatoria) no las han de pagar. Somos una población privilegiada pues solo disfruta de este derecho una pequeña parte de la humanidad del planeta.

La asistencia sanitaria cuesta mucho dinero que los ciudadanos pagamos con nuestros impuestos. Cada año es más cara por varios motivos, sobretodo porque las personas vivimos más años y porque los constantes avances científico-tecnológicos ponen a disposición de los médicos máquinas diagnósticas y terapéuticas y medicamentos cada vez más sofisticados y caros, ya que su descubrimiento y aceptación por las agencias suponen grandes inversiones que realizan las empresas privadas, cuyos accionistas desean ganar dinero. Es muy escasa la investigación pública en estos campos. También las exigencias de la máxima seguridad para el enfermo y las mejoras hoteleras de los centros sanitarios incrementan el coste de la asistencia sanitaria.

En un sistema capitalista de libre mercado como el que tenemos el mercado sanitario no puede ser libre del todo, ya que la asistencia sanitaria está socializada y el mercado es cautivo, pues los compradores están obligados a ello. Son necesarias legislaciones y acuerdos que controlen este mercado sanitario, y unos gobiernos valientes y comprometidos que no caigan en la servidumbre de los grandes capitalistas. Hace pocos años vivimos el escándalo del tratamiento de la hepatitis C, desde la aparición de los antivirales en 2012, la aprobación de la financiación pública con restricciones en 2014 debido al alto coste del tratamiento, que no se generalizó hasta 2017. Supuso para los sistemas de salud un coste adicional no previsto inicialmente que tuvieron que asumir progresivamente, ya que el Sofosbuvir estaba patentado y tenía un precio muy elevado y cada país negociaba un precio diferente[1,2].

Cada año crece el porcentaje de dinero destinado a la sanidad por encima del PBI, hecho que aumenta la deuda del país, haciendo prever que algún día dejará de ser sostenible. España destina a la sanidad dos puntos menos que la media de los países de la OCDE: 5,2% frente al 7,3%, aunque estas cifras varían según como se recojan[3]. La realidad es que existen listas de espera tanto para diversas cirugías como para pruebas diagnósticas y visitas al especialista, que suponen un deterioro de la asistencia para los pacientes: 168.540 personas estaban esperando visita al especialista en Galicia el año 2019, 9.707 más de 3 meses, habiendo otras comunidades autónomas con más listas de espera[4,5].

Para cuadrar los presupuestos sanitarios y ofrecer una asistencia sanitaria de calidad y equitativa o se disminuye el gasto o se incrementan los presupuestos, lo que se consigue aumentando la presión fiscal a la ciudadanía, y esto tiene un límite o se empobrece al país empeorando la situación, aunque una distribución justa de los impuestos es necesaria, con más impuestos directos, haciendo que los que más tienen paguen más, haya menos fraude fiscal.

¿Qué hacer para racionalizar el gasto sanitario y sacar más rendimiento al dinero invertido en la sanidad? Hay que actuar a todos los niveles.

Queda claro que urge cambiar la política sanitaria para hacer frente a este grave problema sanitario, que se acentúa cada año. Es responsabilidad de los políticos que realizan macrogestión: hacen las leyes y elaboran y aprueban los presupuestos. No estoy seguro que todos ellos sean conscientes

Correspondencia: vynies@cirurgia.udl.cat

Cómo citar este artículo: Viñas Salas J
Sostenibilidad del sistema sanitario: compromiso ético de los médicos. Galicia Clin 2020; 81 (2): 30-31

Recibido: 12-02-2020; Aceptado: 26-02-2020 // http://doi.org/10.22546/56/2286

*"El estilo de vida de los ciudadanos debe cambiar para mejorar su salud, prevenir enfermedades y así disminuir el gasto sanitario"*

que cuando aprietan el botón en el Parlamento con unas cifras determinadas están manteniendo o creando listas de espera, decidiendo que no aumentan las camas generales y de UVI, el número de médicos y de los otros profesionales de la salud, la reposición de aparataje médico, etc., con las consecuencias que ello representa para los enfermos.

También la organización de la asistencia sanitaria debe mejorar y ponerse al día, ya que estamos en el siglo XXI y en el sistema público seguimos arrastrando legislación de la época de la dictadura. Los cambios de los estatutos y reglamentos de régimen interior son necesarios para dar más protagonismo a los profesionales sanitarios, más corresponsabilidad y capacidad de decisión con su correspondiente rendición de cuentas. Especialmente a los médicos que son los líderes naturales del sistema por su formación y papel social.

Los ciudadanos hacemos autogestión con nuestro estilo de vida. El estilo de vida de los ciudadanos debe cambiar para mejorar su salud, prevenir enfermedades y así disminuir el gasto sanitario. Una dieta saludable y hacer ejercicio evita muchas enfermedades. Beber con moderación bebidas alcohólicas, no fumar, reducir el estrés, no destruir el medio ambiente y otras varias acciones evitan enfermedades y ahorran mucho dinero que se puede utilizar para otras necesidades del sistema sanitario. Se deben hacer distintas acciones transversales en varios ministerios y consejerías para obtener frutos.

Los gestores de los centros sanitarios realizan mesogestión: Ellos reciben unos presupuestos de las consejerías de sanidad y su obligación ética es que se obtenga con ellos el máximo de salud con el mínimo "coeficiente de roce". Deben distribuir el dinero con la máxima eficiencia resistiendo a las presiones que puedan tener para favorecer a unos, aunque otros menos "poderosos" tienen más necesidad e invertir en sus servicios resolvería mayores defectos. Deben cuadrar el presupuesto; no es su responsabilidad directa el recibir más o menos dinero, por lo que no se les puede exigir.

Los profesionales de la salud hacemos microgestión. Tenemos unos recursos a nuestra disposición– desde despachos, aparatos, capacidad de indicar actuaciones médicas, de recetar, etc. y debemos usarlos de la manera más eficiente posible. Tenemos una gran responsabilidad en colaborar en la sostenibilidad del sistema sanitario. De hecho, nosotros lo podemos hacer quebrar dependiendo de nuestra actuación.

Si podemos diagnosticar una enfermedad con menos gasto en pruebas diagnósticas debemos hacerlo. Se requiere una habilidad clínica fruto de formación y experiencia y aceptar que no existe el riesgo cero ni la certeza absoluta. Muchas veces mejorar un 1% la certeza supone una gran inversión. Debemos recetar aquellos medicamentos eficaces que sean más baratos, siendo eficientes.

Los médicos debemos defender siempre a los pacientes que atenemos, pero al mismo tiempo debemos tener en cuenta no malgastar para que haya recursos para los siguientes pacientes. Ser médicos bien formados actuando con calidad asistencial y realizando los mínimos errores diagnósticos y terapéuticos no sólo beneficia al enfermo concreto que atendemos, sino también a los demás al ahorrar dinero que supone el tratar las complicaciones y efectos secundarios de los errores médicos.

## BIBLIOGRAFÍA


1. Vigario A. *«España cura a todos los pacientes de hepatitis C tras gastar 1800 millones»*. El economista. 20 de noviembre de 2017
2. https://www.diariofarma.com/2016/11/25/hepatitis-c-30-precios-diferentes-problema
3. https://www.redaccionmedica.com/secciones/sanidad-hoy/espana-reduce-una-decima-su-gasto-sanitario-publico-y-esta-la-17-de-europa-4821
4. https://www.epdata.es/datos/listas-espera-sanidad-publica-datos-graficos-comunidad-autonoma/28/galicia/301
5. https://www.sergas.es/Asistencia-sanitaria/Documents/1164/web_cex_2019-12_SAACI-%C3%81REA_2019-12.pdf

# Potentially inappropriate medications and potential prescribing omissions. Identification and relevance

Soraia Azevedo[1], Rosana Maia[2], Emília Guerreiro[2]

*[1]ULSAM - Ponte de Lima. [2]ULSAM - Viana do Castelo*

## ABSTRACT

**Introduction:** Europe presents 19% of the population aged 65 or over (elderly), who are especially susceptible to inadequate prescriptions (potentially inappropriate medications (PIM) and potential prescribing omissions (PPO)), identified by the STOPP and START criteria. This study has as main objectives the identification of PIM and PPO and associated factors. Material and Methods: This is a cross sectional study, using a sample of 254 elderly individuals from the Internal Medicine Service. Results: 81.9% of patients are polymedicated, 72.4% have at least one PIM and 57.5% have at least one PPO. The most frequently identified PIM was benzodiazepine and PPO was the anti-pneumococcal vaccine. There was a direct correlation between the number of PIM and chronic medication ($r(254)=0.348$, $p<0.001$) and inverse with the Katz scale (dependence) ($r(254)=-0.324$, $p<0.001$). In the cases of the domicile it was verified association between PIM and the days of internment ($U=3653$, $p=0.025$). PIM were associated with death in less than 6 months after discharge ($U=3396$, $p=0.007$) and the presence of intercurrences at admission ($U=5766$, $p=0.005$). There is a relationship between the number of co-morbidities and having at least one PIM ($U=5378$, $p=0.041$) or at least one PPO ($U=6271$, $p=0.005$). Diabetes mellitus (DM) type 2, neurological and psychiatric disease are associated with PIM, while obesity, DM type 2, arterial hypertension, dyslipidemia and cardiac pathology with PPO. Discussion and Conclusion: In a population that is older each year, with more comorbidities and more polymedicated, PIM and PPO are increasingly relevant.

**Keywords:** START and STOPP criteria; polymedication; potentially inappropriate medications (PIM); potential prescribing omissions (PPO).

## INTRODUCTION

In 2017, Europe had about 19% of the population with 65 years old or over (elderly)[1]. With age comorbidities increase and physiological changes occur that modify the pharmacokinetics and pharmacodynamics of the drugs[2]. Therefore, this group is especially susceptible to polymedication, drug interactions and adverse effects, thus have an increased risk of inadequate prescriptions.[3] Inappropriate prescriptions include potentially inappropriate medications (PIM) or omissions (PPO)[4,5]. In order to be possible to identify PIM, STOPP (Screening Tool of Older PersonsÂ´ Prescriptions) were created, while PPO are identified by the START criteria (Screening Tool to Alert to Right Treatment). The STOPP / START criteria were primarily published in 2008 and updated in 2015, validated by a consensus of European experts[5]. Since PIM and PPO are associated with several adverse effects, it is important to determine the prevalence, identify the contributors, and review prescribing indications, so that it is possible the optimization of the therapy[6,7,8]. Another possible consequence of aging is dependence, which is associated with an increase of costs and decrease of life quality. The Katz scale allows the evaluation of the elderly´s autonomy to perform the basic and crucial activities of daily life, called Basic Activities of Daily Life (BADL) [9].

The prevalence of PIM and PPO is high, varying according to the place where the evaluation is performed. In primary care PIM values ranged from 21.4% to 42.0%, and PPO from 22.7% to 32.0%[10,11]. In secondary health care PIM approaches 34.5% and PPO 57.9%[12]. In the institutionalized elderly, the prevalence of PIM can exceed 75.0%.[13]In Portugal and others European countries studies on this subject are scarce, with small samples and focus mostly on the population of nursing homes[14]. Thereby the need for new more embracing studies.

At the level of PIM associations, there are few factors studied, these include the absence of dementia, severe comorbidities and multiple medications[13].

So it is fundamental to approach this theme in our community, increasingly aged. This study has as main objectives the identification of PIM and PPO and associated factors.

## MATERIAL AND METHODS

This is a cross sectional observational study. The research protocol was approved by the Ethics Committee of the Hospital: Unidade Local de Saúde do Alto Minho (ULSAM).

Patients with 65 or more years of age hospitalized on the Medical Service of ULSAM from January 01 to November 30, 2017, randomly selected were included. Patients in palliative care and deaths during hospitalization were excluded because it was not possible to evaluate the PPO introduced and PIM suspended. In bedridden and end-of-life, PPO was not considered, except for symptomatic treatments, as the remaining therapeutic incarceration was considered.

There is no consensus about the definition of polymedication, but the value of 5 or more drugs is the most consensual, and this was the value attributed[15].

Correspondencia: soraiaazvd@gmail.com

Cómo citar este artículo: Azevedo S, Maia R, Guerreiro E
Potentially inappropriate medications and potential prescribing omissions. Identification and relevance. Galicia Clin 2020; 81 (2): 32-38

Recibido: 19/04/2019; Aceptado: 10/06/2019 // http://doi.org/10.22546/56/1957

The degree of dependence was assessed by the Katz scale before the acute phase, on admission and on discharge[9].

To evaluate PIM and PPO, the STOPP/START criteria were used, but updated according to the latest recommendations. Particularly in regard to hypocoagulation in atrial fibrillation[16], to the prescription of proton pump inhibitors (PPIs)[17] and to anti-pneumococcal vaccination[18].

The classification of the professions was made by the Portuguese classification of professions 2010. The evaluation of the number of external consultations only took into account the consultations made by doctors.

It was considered excessive alcohol consumption, if superior to the recommended one (up to 10gr, 20gr if man from 18 to 64 years); addiction was considered as a psychiatric disease[19].

## STATISTICAL ANALYSIS

Statistical analysis was performed in the Statistical Package for the Social Sciences (SPSS) version 24. The descriptive statistical analysis was performed by the evaluation of the absolute and relative frequencies of the categorical variables and by the calculation of the mean, median and standard deviation in the continuous variables. The study of the normality of the distribution of continuous variables was made with the Kolmogorov-Smirnov Test (KS) and Shapiro-Wilk test (SW). In the comparison of means between groups, for the variables with normal distribution, the Student t Test (t) was applied. In the ones that a normal distribution was not verified and for the ordinal independent variables with more than 3 categories, The Mann-Whitney U test (U) was applied, but only if the independent variable was binary. If it had more than 2 categories, The Kruskal-wallis H Test was used. In case it was dependent variables, the Wilcoxon Test was used. For the evaluation of the relationship between two categorical variables, the Qui-Quadrado Test ($\chi 2$) was used, and when its assumptions were not assured Fisher´s Exact Test was used. To measure the degree of correlation between two quantitative variables Pearson´s Correlation Coefficient was used. The value of statistical significance for all tests was defined as 2-sided $p < 0.050$.

Results:The age of the 254 cases ranged from 65 to 99 years, with a median of 80 years (SD=7.97), not presenting a normal distribution, 55.5% of the cases are female and 44.5% are male. 78.7% (200) of the cases come from home/with families, 15.4% (39) of households, 3.15% (8) from host families and 2.75% (7) from national integrated network of integrated care (NINIC).The sample was characterized by the degree of dependence (by the Katz scale) before the acute phase, at admission, at discharge and its variation (Table 1). Patients were more dependent after hospitalization than before the acute phase ($Z=-5.57$, $p < 0.001$), but were less dependent at discharge than at admisson.

The number of comorbidities ranged from 1 to 16, with a median of 6.5. The comorbidities were characterized (Table 2).

The number of drugs prescribed ranged from 0 to 19, with a median of 8, out of a total of 1953 medications usually taken by 254 patients. 81.9% (208 cases) were polymedicated and only 3 (1.18%) of the patients had no chronic medica-

Table 1. Characterization of the sample regarding the degree of dependence.

| Katz Scale | Before acute phase of illness | Admission | Discharge |
|---|---|---|---|
| Total dependence (Katz: 0) | 63 (24.8%) | 87 (34.3%) | 77 (30.3%) |
| Severe dependence (Katz: 1) | 12 (4.72%) | 9 (3.54%) | 13 (5.12%) |
| Severe dependence (Katz: 2) | 20 (7.87%) | 19 (7.48%) | 19 (7.48%) |
| Moderate dependence (Katz: 3) | 14 (5.51%) | 14 (5.51%) | 11 (23.4%) |
| Moderate dependence (Katz: 4) | 25 (9.84%) | 43 (16.9%) | 34 (13.4%) |
| Slight dependence (Katz: 5) | 23 (9.06%) | 26 (10.2%) | 23 (9.05%) |
| Independence (Katz: 6) | 97 (38.2%) | 56 (22.0%) | 77 (30.3%) |
| **Variation of dependence** | | | |
| Katz Scale at discharge < Katz Scale before acute phase of illness | 40 (15.7%) | | |
| Katz Scale at discharge > Katz Scale before acute phase of illness | 0 (0.0%) | | |
| Katz Scale at discharge = Katz Scale before acute phase of illness | 214 (84.3%) | | |

Table 2. Characterization of the sample regarding comorbidities.

| Identification of the comorbidities | (n (%valid)) |
|---|---|
| Obesity or overweight BMI >25 kg/m$^2$ | 68 (26.8%) |
| Type 2 diabetes Mellitus | 97 (38.2%) |
| Arterial hypertension | 195 (76.8%) |
| Dyslipidemia | 143 (56.3%) |
| Hyperuricemia | 34 (13.4%) |
| Excessive consumption of alcohol | 20 (7.87%) |
| Smoking<br>Non smoker<br>Former smoker<br>Smoker | <br>199 (82.2%)<br>36 (14.9%)<br>7 (2.90%) |
| Pulmonary Pathology *<br>COPD clinical / probable diagnosis<br>COPD established<br>Others | 78 (30.7%)<br>27 (34.6%)<br>24 (30.8%)<br>27 (34.6%) |
| Heart Pathology<br>Atrial fibrillation<br>Cardiac insufficiency<br>Valvular Disease<br>Ischemic Heart Disease<br>Pacemaker<br>Prosthesis<br>Others | 146 (57.5%)<br>90 (61.6%)<br>76 (52.1%)<br>37 (25.3%)<br>28 (19.2%)<br>16 (11.0%)<br>11 (6.59%)<br>19 (15.39%) |
| Neurological Pathology<br>Dementia, including Alzheimer's disease<br>Ischemic stroke<br>Hemorrhagic stroke<br>Parkinson's disease or parkinsonism<br>Others | 119 (46.9%)<br>61 (51.3%)<br>50 (42.0%)<br>10 (8.40%)<br>14 (11.8%)<br>25 (21.00%) |
| Psychiatric Pathology<br>Depression<br>Alcohol addiction<br>Other psychiatric conditions | 71 (28.0%)<br>57 (80.3%)<br>8 (11.3%)<br>7 (9.86%) |
| Hematologic Pathology<br>Anemia<br>Other hematological diseases | 51 (20.1%)<br>37 (72.5%)<br>18 (35.32%) |
| Malignant neoplasm | 56 (22.0%) |
| Dizziness | 12 (4.72%) |
| Benign Prostatic Hyperplasia | 37 (32.7%)** |
| Chronic Kidney Disease | 50 (19.7%) |
| Chronic Hepatic Disease | 6 (2.36%) |
| Other comorbidities | 175 (68.9%) |

* Excluded pulmonary neoplasms included in neoplastic diseases
** Percentage of the number of men

PIM: Potentially Inappropriate Medications; PPO: Potential Prescribing Omissions; BMI: body mass index; COPD: chronic obstructive pulmonary disease; OSA: obstructive sleep apnea; TAVI: transcatheter aortic valve implantation.

tions. The PIM number ranged from 0 to 5, with a median of 1, in a total of 326, and 72.4% (184) of the patients have at least one PIM prescribed. The PPO number ranged from 0 to 4, with a median of 1, in a total of 203, and 57.5% (146) of the patients have at least one PPO. PIM and PPO were identified (Table 3). Excluding vaccinations of PPO, however, 28% of patients (71) had at least one PPO.

There was no correlation between age and PIM number (r(254)=0.019, p=0.760) nor PPO (r(254)=0.80, p=0.203), however excluding vaccinations of PPO was a positive correlation between age and PPO (r(254)=0.131, p=0.037). There is a correlation between greater dependence (smaller Katz scale) and more PIM (r(254)=-0.324, p<0.00) and, excluding vaccinations, PPOs were inversely associated with dependence (r (254) = -0.191, p = 0.002). There were no statistically significant differences between the previous profession and the PIM number (Fisher exact test=12.55, p=0.115), or PPO (Fisher exact test=10.23, p=0,258). Also schooling has no association with PIM (Fisher exact test=4.90, p=0.717) nor with PPO (Fisher exact test=8.75, p=0.207).

Of the hospitalized patients with over 65 years, 17.7% had prostration as the cause of admission, 76.0% were patients taking benzodiazepines, antipsychotics and or tricyclic antidepressants, even so, of which 26.3% had even 2 or more classes of drugs with sedative effect.

Of the patients, 31.7% have a diagnosis of presumably bacterial pneumonia or acute chronic obstructive pulmonary disease (COPD). Of these, 35.6% had indication to make an anti-pneumococcal vaccine.

The days of hospitalization ranged from 1 to 46 days, with a median of 8 days. The number of days of hospitalization was not correlated with the number of PIM (r(254)=0.062, p=0.323) neither PPO (r(254)=0.096, p=0.128). However, when only the patients from home were evaluated, there were differences in the days of hospitalization (U=3653, p=0.025). That is, the PIM led to longer hospitalizations.

There was re-hospitalization in 5.12% of the cases (less than 5 days after discharge), 10,6% were hospitalized between 5 and 30 days after discharge and 7.1% between 1 and 6 months after discharge. However, the number of days for new hospitalization was not correlated with the number of PIM (r(254)=-0.041, p=0.518) or PPO (r(254)=0.094, p=0.136).

There was no relationship between the number of PIM and hospitalizations in the last 12 months (U=7002, p=0.482) or PPO (U=6517, p=-0.097).

Up to 6 months after a high frequency of 43 deaths (16.9% of the 254 cases), 20.7% of the total cases had less than one PIM and 7.17% of those who had no PIM. There is a relation between PIM number and death in less than 6 months after discharge (U=3396, p=0.007), but this was not verified with PPO (U=4496, p=-0.921).

Table 3. Identification of PIM and PPO.

| **PIM and justification** | | | **(n (%valid))** |
|---|---|---|---|
| Benzodiazepines more than 4 weeks | | | 79 (31.1%) |
| PPI without gastric disease, no history of complicated ulcer, without more than 2 risk factors or for more than 8 weeks | | | 77 (30.3%) |
| Other antipsychotics than quetiapine or clozapine | | | 23 (9.06%) |
| Antiaggregation as primary prevention (without known arterial disease) (1 of the cases with associated anaemia) | | | 22 (8.66%) |
| Association between antiaggregant and hypocoagulant or double antiaggregation without clinical criteria | | | 14 (5.51%) |
| Risperidone, in addition to having extrapyramidal effects, is associated with an increased risk of stroke | | | 12 (4.72%) |
| Antidepressants in patients without depressive symptoms | | | 11 (4.33%) |
| Thiazide or thiazide-like diuretic in patients with history of gout | | | 11 (4.33%) |
| Drugs unsuitable for renal function (GFR: ml/min/1.73m2) | Dapagliflozin with GFR < 60 | 1 | 3.15% |
| | NSAIDs with GFR < 50 | 2 | |
| | Metformin with GFR < 30 | 3 | |
| | Allopurinol 300mg with advanced DRC | 2 | |
| Prevention of Cerebrovascular or Cardiovascular Disease in bedridden and life expectation less than a year | | | 7 (2.76%) |
| Sulfunyloreas of long duration of action, high risk of hypoglycemia | | | 7 (2.76%) |
| Other antidepressants other than SRIs or new mechanisms of action (safer and less pharmacological interactions) | | | 6 (2.36%) |
| Sedative drugs without clinical criteria | | | 5 (1.97%) |
| Atrial fibrillation with rhythm control without frequency control | | | 5 (1.97%) |
| Antianginal agents without known angina or ischemic heart disease | | | 5 (1.97%) |
| Systemic corticosteroid in COPD without optimization of inhaled therapy | | | 4 (1.57%) |
| Fenofibrate / ezetimibe without statin (statins are the first line in the treatment of dyslipidemia) | | | 4 (1.57%) |
| Drugs that aggravate parkinsonism and CI association with MAOI (eg: cinnarizine, mirtazapine) | | | 4 (1.57%) |
| Strong opioids without further attempts to control pain | | | 3 (1.18%) |
| Central-acting antihypertensives (others safer classes are available) | | | 3 (1.18%) |
| Others | | | 16 (6.27%) |
| **PPO and justification** | | | **(n (%valid))** |
| Anti-pneumococcal vaccine * | | | 93 (36.6%) |
| Vitamin D in institutionalized patients with a high risk of falls | | | 27 (10.6%) |
| Anti-resorptive therapy | For previous frailty fracture | 17 | 7.87% |
| | By known osteoporosis | 3 | |
| Flu's vaccine | | | 19 (7.48%) |
| Inhaled bronchodilators or corticosteroids in patients with COPD | | | 12 (5.51%) |
| Hypoagulation in patients with atrial fibrillation, without contraindications | | | 7 (2.76%) |
| Laxatives in patients receiving opioids and with constipation | | | 6 (2.36%) |
| Statin by previous ischemic stroke or known dyslipidemia | | | 4 (1.57%) |
| Others | | | 15 (7.06%) |

PIM: Potentially Inappropriate Medications; PPO: Potential Prescribing Omissions; PPI: Proton Pump Inhibitors; GFR: glomerular filtration rate; NSAIDs: non steroid anti-inflammatory drugs; COPD: chronic obstructive pulmonary disease;

Patients with the highest number of PIM had plus intercurrences during the hospitalization period (U=5766, p=0.005), the cases that had at least one PIM 38.0% had intercurrences during hospitalization, while the number of PPO did not influenced the occurrence of intercurrences (U=7024, p=0.641).

A total of 326 PIM were obtained, with 182 (55.8%) being suspended and total of 203 PPO, 156 (76.8%) were introduced. But neither the PIM suspension (U=3305, p=0.303) nor the PPO introduction (U=1693, p=0.544) significantly affected the time to re-hospitalization after discharge.

There is a significant relation between the number of comorbidities and the minimum of one PIM (U=5378, p=0.041) and the minimum of one PPO (U=6271, p=0.005). The patients with more comorbidities had a greater probability of PIM and PPO. A Diabetes Mellitus (DM) type 2, a neurological and psychiatric disorder, is associated with the number of PIM and obesity, DM type 2, arterial hypertension, dyslipidaemia and cardiac pathology with PPO numbers (Table 4).

A correlation between the number of external consultations and the number of PIM (r(254)=-0.067, p=0.290) or PPO (r(254)=-0.100, p=0.113) was not verified. There was a direct correlation between the number of drugs usually taken by patients and the number of PIM (r(254)=0.348, p<0.001), but not with PPO (r(254)=0.088, p=0.163).

## DISCUSSION

The age and gender distribution of this sample is similar of the European population over 65 years of age, in which 57.9% are women and 42.1% are men[1]. In the last years we have witnessed an increase in the average life expectancy, being in 2015, 83.9 years for women and 77.7 years for men[20]. But it is not enough to continue giving years to life without giving life to years. In our sample, nearly one-quarter of the patients were already fully dependent and 37.0% were partially dependent before admission, higher values of dependence than those reported for developed societies, such as our country, and with significant worsening after discharge[21]. In this study there was a direct relation between the degree of dependence and the number of PIM. The question is whether these are inadequate because patients no longer need them or if they have contributed in any way to the degree of dependence. Comorbidities are also common, with a median of 6,5 per patient and are related both to PIM and to PPO. That is, people with more comorbidities have more PIM and PPO. Since DM type 2, neurological and psychiatric diseases are associated with PIM. Other studies show an association with absence of dementia, severe comorbidities and multiple medications[13].

There are no published studies that show the comorbidities associated with PPO. This study demonstrates the association with obesity, DM type 2, arterial hypertension, dyslipidaemia and cardiac pathology. That is of special emphasis since this pathologies are very common among the elderly population.

Table 4. Association between comorbidities and PIM and PPO.

| | PIM Number | PPO Number |
|---|---|---|
| Obesity / Overweight | U=6254, p=0.889 | U=4850, p=0.002 |
| Arterial hypertension | U=5670, p=0.862 | U=3408, p<0.001 |
| Diabetes Mellitus type 2 | U=6427, p=0.036 | U=6237, p=0.011 |
| Dyslipidemia | U=7731, p=0.713 | U=6691, p=0.021 |
| Excessive consumption of alcohol | U=1951, p=0.278 | U=2012, p=0.365 |
| Smoking (non-smoker, ex-smoker, smoker) | H(2)=2.78, p=0.250 | H(2)=0,149, p=0.928 |
| Pulmonary disease | U=6505, p=0.615 | U=6670, p=0.851 |
| Cardiac disease | U=7535, p=0.531 | U=6455, p=0.008 |
| Hematologic disease | U=5007, p=0.708 | U=4986, p=0.662 |
| Neurological disease | U=7,88, p=0.005 | U=7339, p=0.200 |
| Psychiatric disease | U=4906, p=0.002 | U=6187, p=0.525 |
| Cancer | U=4858, p=0.141 | U=5533, p=0.981 |
| Chronic kidney disease | U=4491, p=0.174 | U=4525, p=0.183 |
| Chronic hepatic disease | U=624, p=0.484 | U=526, p=0.186 |

PIM: Potentially Inappropriate Medications; PPO: Potential Prescribing Omissions.

After being proved in several studies the association of PIM with adverse pharmacological effects, hospitalizations, morbidity and mortality, functional disability and many problems that could be prevented such as falls and confusion and, consequently, associated with more costs[7,8,9,22,23]. There is, moreover, a study that states that about 30% of hospital admissions are secondary to adverse drug effects[22]. But not only PIM have harmful consequences for health status, PPO may also have. This study uses the STOPP and START criteria so that PPO can be evaluated in addition to PIM. It reinforces the significance of PIM due to its association with the days of hospitalization (in the patients coming from the home), the death in less than 6 months after the discharge and the presence of intercurrences in the hospitalization.

The risks of polymedication and pharmacological interactions are several and known[10,24,25]. In this study 81.9% of patients are polymedicated, values much higher than those reported in other studies (20-75%)[25,26]. Existing a direct correlation between the number of drugs usually taken and PIM. 72.4% of the cases have at least one PIM and 57.5% at least one PPO. Values similar to other results of small Portuguese studies about PIM (74.0%), but not about PPO (29.0%), which may be due to the clinical guideline standard about pneumococcal vaccine[18,27]. PIM values are much higher than other international studies[12,28]. The most frequently identified PIM were benzodiazepines, PPIs and antipsychotics.

Benzodiazepines are associated with physical dependence, anterograde amnesia and risk of falls. On the other hand, they are also associated with more health spending, even when other health/disease factors are taken into account[29,30]. Antipsychotics (other than quetiapine and clozapine) are associated with a higher risk of stroke, extrapyramidal effects and mortality[29,32]. Chronic use of PPIs is associated with an increased risk of pneumonia, enteric infections especially per Clostridium difficile and spontaneous bacterial peritonitis due to acid suppression[33,34,35].

The most common PPOs were anti-pneumococcal vaccine, anti-resorptive therapy and vitamin D. According to the clinical guideline standard vaccination against Streptococcus pneumoniae infections is recommended in immunocompetent patients with chronic heart, liver, renal or respiratory disease, pre-transplantation of organ or donation of bone marrow, DM and in case of cerebrospinal fluid fistulas or cochlear implants. In immunocompromised patients it is recommended for splenic dysfunction, primary immunodeficiency, human immunodeficiency virus (HIV) infection, transplant recipients, active neoplastic disease, and iatrogenic immunosuppression[18]. Anti-reabsorption therapy is recommended in patients with bone densitometry revealing osteoporosis and patients with fragility fracture regardless of the value of the densitometry[36]. Vitamin D should be routinely given to institutionalized elderly people because they have low consumption, low sun exposure and low cutaneous synthesis[37].

Of hospitalized patients, 31.7% had a diagnosis of presumably bacterial pneumonia or acute COPD. Of these, 35.6% were indicated according to the Portuguese standard to have had the anti-pneumococcal vaccine. It should be noted that bedridden and low life expectance patients were taken into account in the percentage of pneumonia diagnosed, but were not considered to be indicated for vaccination regardless of the remaining background. Although vaccination did not have an absolute efficacy it could eventually have made some difference. The cause of admission was prostration in 17.7% of the cases, it is clinically evident that a significant portion of this prostration may be related to changes in systemic inflammatory response syndrome. Nevertheless, 76.0% of these patients were taking benzodiazepines, antipsychotics and or tricyclic antidepressants. It is important to emphasize that of these, 26.3% had even 2 or more classes of drugs with sedative effect.

Having a relation between the number of PIM and the number of medications usually taken, it is worrying the increase in the number of chronic medication in the elderly population either in outpatient, nursing and inpatient patients[28].

Of a total of 326 PIM, 182 (55.8%) were suspended and from a total of 203 PPO 156 (76.8%) were introduced. This, along with the correlation between PIM and the number of medications usually taken, once again shows the need to consider the introduction of new medication. This article comes to prove the relevance of identifying the PPO and introducing them and the PIM and suspending them. But not everything depends on the prescribers, there are PPO patients only because they refuse to do them. Let´s look at the example of the flu vaccine that is given for free to all the elderly in Portugal and 7.48% of the elderly did not do it.

## CONCLUSION

This study, along with others already published, proves the importance of PIM and PPO. In Europe, we have older people who are more dependent, with more comorbidities, more polymedicated. In Portugal we have more PIM than other countries. With aging, improved health care and basic hygiene conditions, we will increasingly have older patients with more comorbidities and therefore with a higher risk of PIM and PPO, which makes this subject even more relevant. We are probably at the point where it is no longer possible to continue to medicate without an international/national strategy for polymedication.

## BIBLIOGRAPHY


1. The share of elderly people continues to increase. Eurostat. Data extracted in May 2018
2. Benson JM. Antimicrobial Pharmacokinetics and Pharmacodynamics in Older Adults. Infect Dis Clin North Am. 2017 Dec;31(4):609-617
3. Scott I, Jayathissa S. Quality of drug prescribing in older patients: is there a problem and can we improve it? Intern Med J. 2010; 40:7–18.
4. Onder G et al. Strategies to reduce the risk of iatrogenic illness in complex older adults. Age Ageing. 2013 May; 42(3):284-91.
5. OÂ´Mahony D et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2.Age Ageing.2015 Mar; 44(2):213-8.

6. Hamilton H, Gallagher P, Ryan C, Byrne S, OÂ´Mahony D. Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. Arch Intern Med. 2011;171:1013–9
7. OÂ´Connor MN et al. Prevention of Hospital-Acquired Adverse Drug Reactions in Older People Using Screening Tool of Older PersonsÂ´ Prescriptions and Screening Tool to Alert to Right Treatment Criteria: A Cluster Randomized Controlled Trial. J Am Geriatr Soc.2016 Aug;64(8):1558-66.
8. Gallagher PF, OÂ´Connor MN, OÂ´Mahony D. Prevention of potentially inappropriate prescribing for elderly patients: a randomized controlled trial using STOPP/START criteria.Clin Pharmacol Ther. 2011;89:845–54.
9. Núcleo de Estudos de Geriatria da Sociedade Portuguesa de Medicina Interna. Avaliação Geriátrica Global "A pedra angular dos Cuidados ao Idoso". 6.
10. Ryan C Potentially inappropriate prescribing in an Irish elderly population in primary care.Br J Clin Pharmacol. 2009 Dec; 68(6): 936–947.
11. Lesende M. et al. Potentiality of STOPP/START criteria used in primary care to effectively change inappropriate prescribing in elderly patients. European Geriatric Medicine, 2013 Nov; Volume 4, Issue 5, 293–298
12. Gallagher PF, OÂ´Mahony D. Screening Tool of Older Persons potentially Inappropriate Prescriptions (STOPP): application to acutely ill elderly patients and comparison with Beer' criteria. Age Ageing.2008; 37:673-9.
13. Tamura BK,Bell CL,Inaba M,Masaki KH. Factors associated with polypharmacy in nursing home residents. Clin Geriatr Med.2012 May;28(2):199-216.
14. da Costa FA et al. Potentially inappropriate medications in a sample of Portuguese nursing home residents: Does the choice of screening tools matter? Int J Clin Pharm.2016 Oct;38(5):1103-11.
15. Hovstadius B, Petersson G. Factors leading to excessive polypharmacy. Clinics in geriatric medicine. 2012;28(2):159-72
16. Kirchhof P. et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European Heart Journal, Volume 37, Issue 38, 2016, 2893–2962
17. Lanza FL, Chan FK, Quigley EM Guidelines for prevention of NSAID-related ulcer complications. Am J Gastroenterol. 2009 Mar;104(3):728-38
18. DGS. Vacinação contra infeções por Streptococcus pneumoniae de grupos com risco acrescido para doença invasiva pneumocócica (DIP). Adultos (≥18 anos de idade). Norma nº011/2015 de 23/06/2015 atualizada a 06/11/2015
19. DGS. Deteção Precoce e Intervenção Breve no Consumo Excessivo de Álcool. Norma nº030/2012 de 28/12/2012 atualizada a 18/12/2014
20. GBD 2016 Causes of Death Collaborators, Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016 Volume 390, No. 10100, 1151–1210, 16 September 2017
21. Heikkien E.: What are the main risk factors for disability in old age and how can disability be prevented? WHO Regional Office for Europe's Health Evidence Network (HEN), 2003.
22. Berdot S, Bertrand M, Dartigues JF, et al. Inappropriate medication use and risk of falls - A prospective study in a large community-dwelling elderly cohort. BMC Geriatr. 2009;9:30.
23. Redston MR et al. Prevalence of Potentially Inappropriate Medication Use in Older Inpatients with and without Cognitive Impairment: A Systematic Review. J Alzheimers Dis. 2017 Dec 16.
24. Maher RL, Hanlon J, and Hajjar ER: Clinical consequences of polypharmacy in elderly. Expert Opin Drug Saf 2014; 13: 57-65
25. Robert L. et al. Clinical Consequences of Polypharmacy in Elderly. Expert Opin Drug Saf. 2014 Jan; 13(1):
26. Onder G et al.: Polypharmacy in nursing home in Europe: results from the SHELTER study. J Gerontol A Biol Sci Med Sci 2012; 67:698-704.
27. M.M. Moraes, A. Matias, M.A. Soares, J. Gorjão Clara. Potentially inappropriate medicines use, by STOPP/START criteria, in a group of old patients admitted to a Portuguese hospital. European Geriatric Medicine 2013 sep, Volume 4, Supplement 1, S195
28. Ruscin MJ: Drug therapy in the elderly. In Porter RS & Kaplan JL (eds): The Merck Manual, 3090-3098. Merck, Sharp & Dohme Corp., 2011.
29. Ćurković M, Dodig-Ćurković K, Erić AP, Kralik K, Pivac N. Psychotropic medications in older adults: a review. Psychiatria Danubina, 2016; 28 (1): 13-24
30. Uzun S1, Kozumplik O, Jakovljević M, Sedić B. Side effects of treatment with benzodiazepines. Psychiatr Danub. 2010 Mar; 22(1):90-3.
31. Dionne PA, Vasiliadis HM, Préville M. The economic impact attributable to the inappropriate prescription of benzodiazepines in the elderly living in the community. Value in Health, 2011-05-01; 14(3): A106-A106
32. Guthrie B, Clark SA, McCowan C. The burden of psychotropic drug prescribingin people with dementia: a populationdatabase study. Age and Ageing, 1 September 2010; 39(5): 637–642
33. Laheij RJF, Sturkenboom MCJM, Hassing RJ, et al: Risk of community-acquired pneumonia and use of gastric acid-suppression drugs. JAMA 2004; 292: 1955-1960
34. Leonard J, Marshall JK, and Moayyedi P: Systematic review of the risk of enteric infections in patients taking acid suppression. Am J Gastroenterol 2007; 102: 2047-2056
35. Deshpande A, Pant C, Pasupuleti V, et al: Association between PPI therapy and Clostridium difficile Infection: A ContePPOrary Systematic Review and Meta-Analysis. Clin Gastroenterol Hepatol 2012; 10: 225-233
36. Sociedade Portuguesa de Reumatologia (SPR) e pela Sociedade Portuguesa de Doenças Ósseas Metabólicas. Recomendações para o diagnóstico e terapêutica da Osteoporose. 2007
37. Reid I.R., Bolland M.J., and Grey A.: Effects of vitamin D supplements of bone mineral density: a systematic review and meta-analysis. Lancet 2014; 343: pp. 146-155

# Demencia rápidamente progresiva por encefalitis límbica por anticuerpos LGI-1 y encefalopatía de Hashimoto. Presentación de dos casos y revisión de la literatura

*Rapidly progressive dementia caused by limbic encephalitis due to LGI-1 antibodies and hashimoto encephalopathy. Report of two cases and literature review*

Miguel Angel Nuñez Viejo, Ana Latorre Díez

*Servicio de Medicina Interna. Complejo Hospitalario Universitario de Ourense*

## RESUMEN

Las demencias rápidamente progresivas (DRP) engloban un grupo muy heterogéneo de entidades caracterizadas por la aparición de trastornos cognitivos y conductuales relevantes que evolucionan en pocas semanas o meses. La triada clínica habitual consiste en pérdida de memoria, alteraciones psiquiátricas y crisis epilépticas. Aunque el síndrome de DRP engloba numerosos cuadros clínicos, es habitual pensar en un origen autoinmune paraneoplásico, infeccioso o asociado a enfermedades priónicas. Para su diagnóstico son necesarios estudios de imagen, el examen del líquido cefalorraquídeo y pruebas serológicas como la determinación de antígenos. Es importante establecer un diagnóstico diferencial precoz entre encefalopatías autoinmunes y demencias por trastornos neurodegenerativos, sobre todo en las de origen paraneoplásico, debido a que el tratamiento de la neoplasia es más efectivo en las fases tempranas de la enfermedad y puede evitar el daño neuronal irreversible. Presentamos dos casos de pacientes con deterioro cognitivo de pocos días de evolución debido a una encefalitis límbica no paraneoplásica y una encefalopatía de Hashimoto, causas poco habituales pero reversibles de demencia rápidamente progresiva.

**Palabras clave:** Demencia rápidamente progresiva. Encefalitis límbica. Anticuerpos antiLGI-1. Encefalopatía autoinmune. Encefalopatía de Hashimoto.

## ABSTRACT

Rapidly progressive dementias (RPD) are a very heterogeneous group of diseases characterized by acute cognitive impairment and behavioral disorders in a few weeks or months. Clinically most of times consists of memory loss, psychiatric disorders and epilepsy. Although RPD can be part of multiple clinical conditions, most common causes include autoimmune diseases, infectious or prion diseases and rarely, as a manifestation of a paraneoplastic syndrome. Image studies, cerebral spinal fluid evaluation, and serologic tests such as antigen determination are the most useful in diagnosing a neurological paraneoplastic syndrome. It's very interesting an early diagnosis because the treatment is more effective in the early stages of illnes and can prevent irreversible neuronal damage. We present two cases of patients with rapidly cognitive impairmen due to limbic encephalitis and Hashimoto encephalopathy, rare but reversible causes of dementia.

**Keywords:** rapidly progressive dementia, limbic encephalitis, LGI-1 antibodies, autoimmune encephalopathy, Hashimoto encephalopathy, antithyroid antibodies, paraneoplastic syndrome, antineuronal antibodies.

## INTRODUCCIÓN

Las demencias rápidamente progresivas (DRP) comprenden un grupo de enfermedades caracterizadas por el desarrollo de trastornos cognitivos y de conducta que evolucionan en el curso de semanas a pocos meses[1]. La presentación clínica habitual consiste en pérdida de memoria, alteraciones psiquiátricas (incluidas alucinaciones), crisis epilépticas, ataxia, alteraciones del sueño, disautonomía, mioclonías y otros trastornos del movimiento[1].

Las causas más importantes de DRP (tabla 1) incluyen las encefalopatías por priones, particularmente la enfermedad de Creutzfeldt-Jakob; encefalopatías autoinmunes como la encefalitis límbica (paraneoplásica o no paraneoplásica) y las encefalopatías que responden a corticosteroides; vasculitis; infecciones como la enfermedad de Whipple; neoplasias, particularmente el linfoma intravascular; causas toxicometabólicas y la seudodemencia asociada a depresión[1]. No obstante, en todo paciente con DRP debe descartarse el estado de mal epiléptico no convulsivo[2].

Conviene también recordar que las demencias neurodegenerativas clásicas, como la enfermedad de Alzheimer, la demencia frontotemporal, la demencia con cuerpos de Lewy, la degeneración corticobasal y la parálisis supranuclear progresiva, pueden en ocasiones tener un comportamiento rápidamente progresivo y evolucionar en el curso de uno a dos años[3-5], aunque es muy raro por lo general. Las que con mayor frecuencia pueden progresar de esta forma son la demencia con cuerpos de Lewy, la degeneración corticobasal y, en algunos casos, la demencia frontotemporal. La enfermedad de Alzheimer con angiopatía amiloide cerebral también puede evolucionar en forma subaguda[5].

El diagnóstico y estudio de pacientes con DRP debe incluir exámenes de laboratorio a fin de descartar causas metabólicas o nutricionales como el déficit de vitamina B12, un electroencefalograma (EEG), una resonancia magnética (RM) cerebral, examen del líquido cefalorraquídeo (LCR) y la búsqueda de autoanticuerpos (tabla 2).

Correspondencia: manuvi2004@hotmail.com

Cómo citar este artículo: Nuñez Viejo MA, Latorre Díez A
Demencia rápidamente progresiva por encefalitis límbica por anticuerpos LGI-1 y encefalopatía de Hashimoto. Presentación de dos casos y revisión de la literatura. Galicia Clin 2020; 81 (2): 39-45

Recibido: 29/12/2018; Aceptado: 14/01/2019 // http://doi.org/10.22546/56/1872

Tabla 1. Demencias rápidamente progresivas

| Enfermedades neurodegenerativas |
|---|
| - Enfermedades priónicas (enfermedad de Creutzfeldt-Jakob, Kuru, otras…)<br>- Demencias neurodegenerativas clásicas con curso atípico (muy poco frec.), sobre todo la demencia con cuerpos de Lewy y la degeneración corticobasal |
| **Infecciones del sistema nervioso central** |
| **Infecciones víricas**<br>- Encefalitis convencionales<br>- Demencia asociada al VIH<br>- Leucoencefalopatía multifocal progresiva<br>- Panencefalitis esclerosante subaguda<br>**Infecciones bacterianas**<br>- Sífilis<br>- Brucelosis<br>- Tuberculosis<br>- Enfermedad de Lyme<br>- Enfermedad de Whipple |
| **Otras**<br>- Infecciones fúngicas<br>- Parasitosis |
| **Encefalopatías autoinmunes, inflamatorias y granulomatosis** |
| **Encefalitis límbica (asociadas a anticuerpos antineuronales)**<br>- Paraneoplásica<br>- No paraneoplásica<br>**Encefalopatías que responden a corticoides**<br>- Asociada a anticuerpos antitiroideos (encefalitis de Hashimoto)<br>- Conectivopatías: síndrome de Sjögren, lupus eritematoso sistémico<br>- Sarcoidosis y otras granulomatosis<br>- Encefalopatías sin anticuerpos asociados<br>**Vasculopatías inflamatorias**<br>- Vasculitis aislada del sistema nervioso y vasculitis sistémicas<br>- Síndrome antifosfolipídico<br>- Síndrome de Susac<br>**Formas cognitivas de Esclerosis Múltiple** |
| **Enfermedades cerebrovasculares** |
| - Infartos cerebrales múltiples y estratégicos<br>- Trombosis de senos venosos<br>- Fístulas durales y otras malformaciones vasculares |
| **Neoplasias** |
| - Neoplasias primarias (linfoma intravascular, linfoma primario del SNC, gliomatosis *cerebri*...)<br>- Metástasis y carcinomatosis meníngea<br>- Síndromes paraneoplásicos no autoinmunes |
| **Hidrocefalias** |
| - Hidrocefalias idiopáticas (síndrome de Hacking-Adams o hidrocefalia normotensiva)<br>- Hidrocefalias secundarias |
| **Intoxicaciones** |
| - Tóxicos ambientales<br>- Drogas<br>- Fármacos |
| **Cuadros metabólicos, endocrinos y carenciales** |
| - Déficit de vitamina B1, vitamina B12, vitamina E, niacina y folato<br>- Insuficiencia renal, hepática, cardiaca y respiratoria<br>- Alteraciones hidroelectrolíticas: hipercalcemia, hiponatremia<br>- Enfermedades endocrinas (tiroides -tirotoxicosis, mixedema-, paratiroides, suprarrenales)<br>- Otras: enfermedad de Wilson, Porfiria |
| **Epilepsia** |
| **Enfermedades psiquiátricas** |

Tabla 2. Estudios complementarios de interés en el diagnóstico de las demencias rápidamente progresivas

| Laboratorio de rutina |
|---|
| - Hemograma, coagulación y VSG<br>- Bioquímica básica con pruebas de función hepática y perfil férrico y tiroideo (TSH)<br>- Calcio<br>- Ácido fólico y vitamina B12<br>- ECA |
| **Serología** |
| - Sífilis<br>- VIH |
| **Pruebas reumatológicas** |
| - ANA<br>- Anti-Ro y anti-La |
| **Autoanticuerpos** |
| - Intracelulares (o paraneoplásicos clásicos): Hu, Yo, Ri, Ma, Ma2, CV2/CRMP-5 y amfifisina<br>- Antígenos de membrana neuronal: contra los canales de potasio voltaje-dependientes (anti-LGI1), contra el receptor de glutamato o N-metil-D-aspartato (anti-RNMDA), contra el neurópilo del hipocampo<br>- Antitiroideos: contra la peroxidasa tiroidea (anti-TPO), anti-tiroglobulina (TG) y anti-receptor de TSH (TSI) |
| **Otras pruebas** |
| - EEG<br>- RM cerebral con gadolinio (con secuencia FLAIR y difusión)<br>- En algunos casos:<br>- TC tórax, abdomen y pelvis<br>- Ecografía de pelvis o testicular<br>- PET/TC con FDG<br>- Biopsia periférica (glándula lagrimal o salival) |
| **Examen de LCR** |
| - Citología, glucosa, proteínas, bandas oligoclonales, VDRL<br>- PCR para enfermedad de Whipple<br>- Proteína 14-3-3 o enolasa específica<br>- Antígeno para criptococo<br>- PCR herpesvirus y otros<br>- Cultivo: bacterias, hongos y Mycobacterium tuberculosis |
| **Angiografía** |
| **Biopsia de cerebro y leptomeninges** |

HIV, virus de la inmunodeficiencia humana; ANA, anticuerpos antinucleares; PCR, reacción en cadena de la polimerasa.

En ocasiones, la biopsia cerebral puede ser útil[6], pero no se recomienda su realización si la sospecha diagnóstica es una enfermedad por priones. Tiene una sensibilidad muy variable y su principal indicación es la sospecha de una enfermedad potencialmente tratable, en presencia de una lesión bien definida y accesible cuya localización no entrañe el riesgo de un daño neurológico mayor derivado del propio procedimiento.

Si tras haber realizado todos los estudios necesarios y excluido el origen infeccioso, no puede establecerse la causa de una DRP, está justificado el tratamiento empírico con dosis altas de corticoides en pacientes que sufran un rápido deterioro[1,7].

## CASO CLÍNICO 1

Se trata de un paciente varón de 56 años con antecedentes de bebedor, exfumador, obesidad, hipertensión arterial, diabetes mellitus tipo 2 y dislipemia, que ingresó en mayo de 2012 en el servicio de Medicina Interna por deterioro cognitivo de aproximadamente dos semanas de evolución, con episodios de desconexión del medio y desorientación temporo-espacial, alucinaciones visuales y movimientos clónicos de extremidades superiores de predominio nocturno, estos últimos ya desde unos meses antes, motivo por el que había consultado con un neurólogo privado sin encontrarse patología alguna y que habían mejorado parcialmente con la administración de lamotrigina. En ningún momento presentó generalización de las crisis, periodo postcrítico ni relajación de esfínteres, pero sí cefalea acompañante de forma ocasional. La familia refería además episodios de sudoración, insomnio, apneas e hipersomnia diurna. Negaban pérdida de peso o síndrome constitucional asociado. Como último dato, el enfermo comentaba un antecedente de herpes zoster cutáneo intercostal un mes antes del ingreso, resuelto tras completar tratamiento con brivudina.

En el examen físico no hubo hallazgos destacables, salvo hipertrofia parotídea como estigma de su enolismo crónico, y a nivel neurológico un examen cognitivo deteriorado (MMSE 28/30) a expensas de errores en la memoria inmediata y en el cálculo. Tanto a nivel motor y sensitivo, como en la coordinación y la marcha no se encontró alteración alguna.

Con la clínica sugerida se llevaron a cabo pruebas complementarias encaminadas al diagnóstico diferencial planteado: *infeccioso* (sobre todo encefalitis por herpes dado el antecedente mencionado); enfermedad por *priones; tóxico,* Wernicke; *vascular; paraneoplásico* y, por último; *autoinmune,* encefalitis límbica.

En los estudios complementarios destacó hiponatremia (Na+ 129 mmol/L), ya presente en los controles analíticos del último mes, y una VSG ligeramente elevada (30 mm/1h). En cuanto al examen del LCR, bioquímica, citología y ADA fueron normales, la proteína 14-3-3 negativa al igual que la detección de anticuerpos paraneoplásicos (Anti-Ma2, Anti-Ma, Anti-Amfifisina, Anti-CV2/CRMP5, Anti-RNMDA, Anti-Ri, Anti-Yo y Anti-Hu), pero la determinación de anticuerpos anti-canales de potasio voltaje-dependiente LGI-1 fue positiva a título alto: 92,3 pmol/L (normal < 10), al igual que en sangre [663,60 pmol/L (normal < 100)]. El EEG mostró actividad epileptiforme a nivel frontal y en área temporal izquierda. En la RM cerebral se apreció una hiperintensidad en ambos lóbulos temporales (figura 1) y el PET/TC reveló datos de hipermetabolismo al mismo nivel (figura 2). El SPECT cerebral encontró alteraciones de la perfusión cerebral de la corteza parietal bilateral, con disminución de la perfusión de la porción inferior del asta lateral del lóbulo temporal izquierdo, hallazgos sugestivos de proceso neurodegenerativo.

El resto de los estudios (hemograma, cortisol, calcio, bioquímica, tóxicos en orina, estudio inmunológico, marcadores tumorales, estudio de hipercoagulabilidad, estudio de anemia, coagulación, cultivo de orina y hemocultivo, cultivo de LCR, serologías, radiografía de tórax, ecografía pélvica y testicular, TC de tórax-abdomen-pelvis y PET/TC corporal) fueron negativos.

Finalmente, ante el cuadro clínico sugestivo (deterioro cognitivo, alteraciones del comportamiento y crisis epilépticas) y los hallazgos descritos, unido a la ausencia de neoplasia en el estudio realizado y la presencia de anticuerpos LGI-1 tanto en sangre como en LCR, se concluyó el diagnóstico de encefalitis límbica por anticuerpos contra los canales de potasio voltaje-dependientes.

Figura 1. Corte transversal de RM cerebral que muestra un aumento de señal en región temporal profunda de hemisferio izquierdo y corteza temporal medial derecha, así como moderado engrosamiento cortical de la circunvolución parahipocámpica medial, datos compatibles con encefalitis límbica.

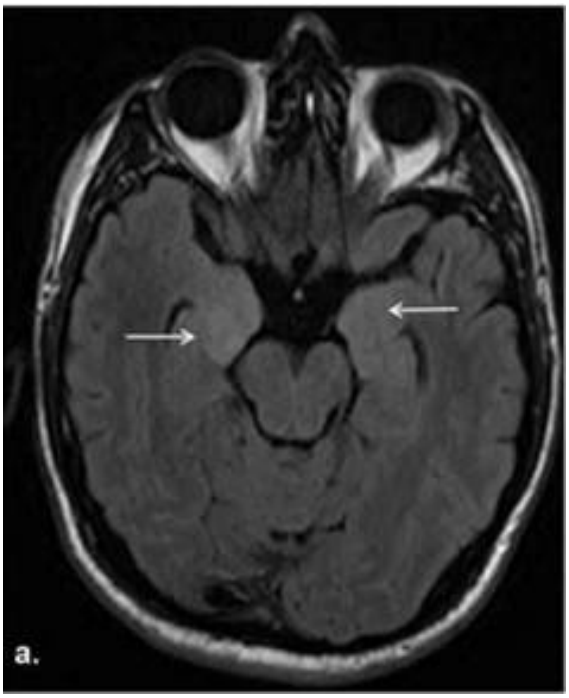
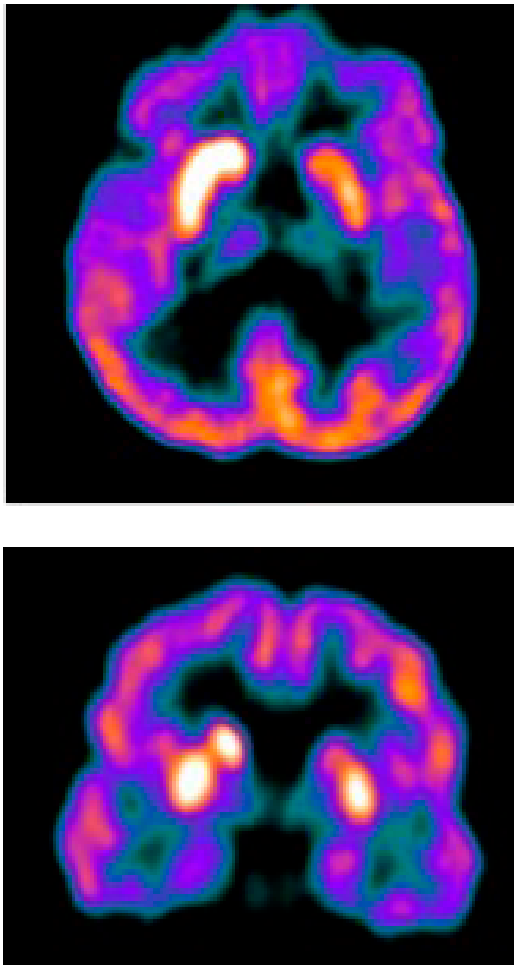



Figura 2. Imagen de estudio de PET-TC cerebral donde se objetiva un aumento focal de la captación de FDG en el lóbulo temporal izquierdo y asimetría en la captación a nivel ganglionar basal ipsilateral.



En cuanto a la evolución, desde el punto de vista neurológico a las pocas horas de su ingreso presentó cuadro de agitación psicomotriz con desorientación, comenzando 72 horas después con fiebre, alucinaciones visuales, desaturación y deterioro del nivel de conciencia que obligó a su traslado a la Unidad de Cuidados Intensivos. Ante el resultado positivo de anticuerpos anti-LGI1 obtenido en el estudio del LCR se inició tratamiento con corticoides (prednisona), micofenolato sódico y bolus de inmunoglobulinas, con buena respuesta que permitió en pocas semanas el alta hospitalaria. Durante su estancia, en todo momento mantuvo cifras bajas de sodio alcanzando valores mínimos de 117 mEq, natremia que sólo pudo corregirse con la administración de tolvaptan. En el seguimiento posterior en la consulta de Medicina Interna se ha comprobado mejoría neurológica progresiva hasta tal punto que ha recuperado la memoria, no ha tenido nuevos episodios de alucinaciones visuales ni trastornos del sueño y no existe evidencia alguna de deterioro cognitivo.

## CASO CLÍNICO 2

Mujer de 81 años con antecedentes de hipertensión arterial e hipertensión pulmonar leve, diagnosticada en 2014 de un carcinoma de mama con afectación metastásica hepática y ósea, que había progresado a diferentes líneas de quimioterapia, estando en el momento del ingreso en tratamiento con letrozol y lapatinib. Previamente, en mayo de 2017, había recibido radioterapia antiálgica sobre las lesiones óseas por un cuadro de dolor para el que estaba recibiendo opioides.

Ingresó en junio de 2017 en Medicina Interna procedente del Servicio de Urgencias por alteración conductual de aproximadamente dos semanas de evolución, junto con episodios de agitación nocturna, desorientación, agresividad y negativa a la ingesta. Previo al ingreso, la enferma vivía sola, no tenía antecedentes de deterioro cognitivo y era totalmente independiente para las actividades básicas.

En el examen físico no había datos relevantes salvo a nivel neurológico, donde destacaba desorientación temporo-espacial, deterioro cognitivo (MMSE 24/30) y bradipsiquia con alteración del curso del pensamiento y lenguaje incoherente, incontinencia de esfínteres y agitación psicomotriz con episodios de agresividad tanto física como verbal.

Con la clínica sugerida se decidió ingreso para estudio y se solicitaron pruebas complementarias encaminadas al diagnóstico diferencial planteado: *neoplásico,* afectación metastásica cerebral, carcinomatosis meníngea; *tóxico,* neurotoxicidad inducida por opioides; *metabólico,* hipercalcemia tumoral, hiponatremia, encefalopatía hepática; *infeccioso; vascular* y, por último; *autoinmune,* encefalitis límbica paraneoplásica.

En lo referente a los estudios complementarios tanto bioquímica como hemograma no mostraban alteraciones y los valores de vitamina B12 y ácido fólico, al igual que el perfil tiroideo, también eran normales. Se descartaron infecciones intercurrentes y se amplió el estudio con serologías víricas, incluyendo sífilis y VIH, todas negativas. Sin embargo, en el estudio inmunológico en plasma se encontraron los siguientes hallazgos: ANA positivos (1/80), Ac antitiroperoxidasa (TPO) 219 UI/mL (normal 0 - 35 UI/mL) y Ac antitiroglobulina (TG) 417 UI/mL (normal < 50 UI/mL), con anticuerpos anti-receptor de TSH (TSI o TR) normales. Se completó el estudio con un EEG, que mostró una moderada desorganización y lentificación global del trazado, con brotes lentos difusos intermitentes de moderada frecuencia, y un TC craneal y una RM cerebral, que no mostraron alteraciones, descartándose así la afectación metastásica cerebral y meníngea. En el análisis del LCR también se confirmó la positividad de anti-TPO y anti-TG y se objetivó un leve aumento de proteínas, siendo negativo el resto del examen bioquímico y microbiológico, incluídas proteína 14-3-3 y detección de anticuerpos paraneoplásicos.

Ante el cuadro clínico descrito (deterioro cognitivo, alteración del comportamiento), la ausencia de afectación neoplásica del SNC y la presencia de anticuerpos antitiroideos en sangre y LCR, se estableció el diagnóstico de encefalopatía de Hashimoto. Esto, unido al rápido deterioro neurológico con disminución del nivel de consciencia que experimentó la enferma, obligó al tratamiento precoz con altas dosis de corticoides, con mejoría sorprendente en las primeras 72 horas de tratamiento. La evolución fue favorable y la enferma fue dada de alta una semana después. Por parte de Oncología Médica se descartó continuar tratamiento citotóxico, de forma que fue derivada a la Unidad de Cuidados Paliativos para seguimiento ambulatorio en consulta.

## DISCUSIÓN

### *Encefalitis límbica*

Las enfermedades autoinmunes asociadas a la aparición de autoanticuerpos específicos son la causa más frecuente de DRP potencialmente tratable[2]. Entre ellas se encuentra la encefalitis límbica, entidad poco frecuente y de difícil diagnóstico que se caracteriza clínicamente por una triada consistente en deterioro cognitivo, crisis epilépticas y manifestaciones psiquiátricas[7-9], habitualmente de inicio subagudo -en días a semanas-, aunque en algunos casos pueden instaurarse de forma brusca. En personas adultas, las crisis epilépticas tienen su origen en el lóbulo temporal[10] y las manifestaciones psiquiátricas incluyen una gran variedad de alteraciones, como cambios en la personalidad y estado de ánimo, depresión, psicosis, alucinaciones y deterioro de la memoria a corto plazo. Por regla general, la atención está conservada, dato clínico que suele ser de utilidad para diferenciarla de los síndromes confusionales[8-10].

La causa de la encefalitis límbica permaneció sin explicación hasta la identificación de anticuerpos contra antígenos presentes en neuronas y células tumorales en los pacientes afectados, hallazgo que confirmó la teoría de que obedece a una causa inmune. Así, la encefalitis límbica autoinmune se debe a la presencia de autoanticuerpos y pueden detectarse hasta en el 80% de los enfermos[11,12]. Existen dos grandes grupos: aquellas que ocurren como una manifestación paraneoplásica, y las no paraneoplásicas[13].

En general, los síndromes paraneoplásicos se definen como manifestaciones en sitios remotos a neoplasias malignas o sus metástasis, no relacionadas con el crecimiento tumoral[14], infección, alteraciones metabólicas, cirugía o cualquiera otra forma de tratamiento oncológico. La frecuencia de los síndromes paraneoplásicos con sintomatología neurológica es menor a 0,5/100.000 casos por año, y las neoplasias más frecuentemente asociadas son el carcinoma pulmonar

de células pequeñas (CPCP), el cáncer de testículo y el timoma[9,13], aunque es frecuente que la neoplasia no se detecte[15,16]. Dentro de los síndromes paraneoplásicos del sistema nervioso, los más frecuentes son el síndrome miasténico (Lambert-Eaton), que afecta al 3% de los pacientes con cáncer de pulmón de células pequeñas; la miastenia grave, que se presenta en el 15% de los pacientes con timomas; y la neuropatía periférica desmielinizante, que se ha observado hasta en el 50% de los pacientes con una variante rara de plasmocitoma conocida como POEMS. Estos síndromes paraneoplásicos en el sistema nervioso central (SNC) tienen mayor incidencia en mujeres y en personas mayores de 50 años, y en su caso la sintomatología neurológica suele preceder casi siempre al diagnóstico tumoral.

Hay dos categorías de anticuerpos asociados con encefalitis límbica. Una incluye anticuerpos contra antígenos intracelulares y que sólo ocurre en el contexto de enfermedad paraneoplásica (también llamados *anticuerpos paraneoplásicos clásicos)*. Dentro de este grupo los más importantes son el anticuerpo anti-Hu y el anti-CRMP-5, asociados con el CPCP, y el anticuerpo anti-Ma2, más relacionado con neoplasias testiculares[11,12]. El otro grupo de *anticuerpos* está dirigido *contra antígenos de membrana* y pueden o no estar asociados con una neoplasia oculta[10]. Un ejemplo importante son los anticuerpos contra los canales del potasio voltaje-dependientes, que se acompañan de neoplasias en el 20% de los casos[17,18], fundamentalmente CPCP y timomas. También existen anticuerpos dirigidos contra los receptores del glutamato o NMDA (N-metil-D-aspartato), que con frecuencia se asocian al teratoma de ovario en mujeres, en cuyo caso el cuadro clínico es complejo y se caracteriza por trastornos psiquiátricos graves, catatonía, discinesias orofaciales, hipoventilación y disautonomía.

Los estudios analíticos rutinarios suelen ser normales, pero en el caso de la encefalitis límbica asociada a anticuerpos contra los canales de potasio suele observarse hiponatremia con relativa frecuencia. La RM cerebral puede mostrar imágenes de utilidad para el diagnóstico hasta en el 70% de los enfermos. Típicamente se aprecia un aumento de señal en la porción medial de los lóbulos temporales y, en fases más avanzadas, atrofia del hipocampo y de la amígdala de forma bilateral[19]. El electroencefalograma es útil en los casos de presentación en forma de cuadro confusional o con alteración del nivel de conciencia. En cerca del 50% de los enfermos puede mostrar actividad epileptiforme temporal uni o bilateral, o hallazgos más inespecíficos, como enlentecimiento difuso o focal temporal[19]. El examen del LCR es útil de cara a descartar infecciones. Puede ser normal o mostrar un ligero aumento de proteínas y pleocitosis linfocitaria (< 30 células)[20]. El electromiograma (EMG) también puede ser útil en algunos casos como en pacientes con anticuerpos contra los canales de potasio o el síndrome de Lambert-Eaton[21]. En el caso de pacientes con sintomatología neurológica típica de encefalitis límbica también se pueden apreciar alteraciones metabólicas a nivel del hipocampo en el estudio mediante FDG-PET/TC. Esta técnica es una herramienta diagnóstica de gran valor, ya que permite la detección temprana y evalúa la actividad metabólica corporal, con lo que puede descartarse además la presencia de una neoplasia maligna oculta[16].

Por tanto, el diagnóstico de una encefalitis límbica se basa fundamentalmente en el cuadro clínico, la RM cerebral, el EEG y los hallazgos en el LCR y se confirma con la determinación de autoanticuerpos en suero, LCR o ambos[11,12]. Sin embargo, la ausencia de anticuerpos no excluye el diagnóstico, así como su única presencia tampoco lo confirma, al no ser ésta la única condición necesaria.

Dado que estos síndromes pueden confundirse fácilmente con trastornos psiquiátricos, el diagnóstico y tratamiento tempranos son de suma importancia para evitar un daño neuronal irreversible. El tratamiento de la encefalitis límbica paraneoplásica requiere dos enfoques diferenciados. Por un lado, el tratamiento supresor de la respuesta inmune generada por el daño neurológico, y por otro el tratamiento de la neoplasia subyacente si existe, tratamiento que, con frecuencia, es el único efectivo. En cuanto al primero, cabe señalar que, mientras que las encefalitis relacionadas con antígenos intracelulares son principalmente mediadas por respuestas citotóxicas (linfocitos T) y responden poco al tratamiento, las encefalitis relacionadas con antígenos de membrana, como los canales de potasio voltaje-dependiente y los receptores del glutamato, parecen ser mediadas por anticuerpos y suelen mejorar con el tratamiento en un alto porcentaje (60-80%)[11,12].

Los tratamientos inmunosupresores incluyen ciclofosfamida, tacrolimus e incluso anticuerpos monoclonales, como el rituximab[22], aunque también se puede recurrir a la administración de inmunoglobulinas intravenosas o la plasmaféresis. Las dosis altas de corticoides suelen mejorar los síntomas a corto plazo, pero aumentan el riesgo de psicosis. Muchos pacientes requieren tratamiento antiepiléptico permanente[22-23].

En cuanto a la encefalitis límbica por anticuerpos anti-canales de potasio se trata de una alteración del sistema autoinmune bien conocida y definida, aunque poco descrita en la literatura. La etiología más común es la autoinmune, aunque puede verse asociada a procesos neoplásicos[24]. De los casos descritos hasta ahora se concluye que suele afectar a la región medial de los lóbulos temporales, sobre todo el hipocampo, lo que en la clínica se correlaciona con cambios en el carácter, irritabilidad, ansiedad, depresión, alteraciones del comportamiento, desorientación, inversión del ritmo sueño-vigilia y alucinaciones, amnesia anterógrada, crisis parciales complejas, trastornos del movimiento hipo-hipercinético y disminución del nivel de conciencia[24-26]. Puede acompañarse de trastornos autonómicos y endocrinos –suele asociar hiponatremia hasta en el 15-20% de los casos paraneoplásicos, sobre todo por desarrollo de SIADH-. Como hallazgo analítico es común encontrar anticuerpos contra las neuronas del hipocampo que son anticuerpos anti-canales de potasio voltaje dependien-

tes. Estos anticuerpos están dirigidos en realidad contra una proteína del complejo molecular llamada LGI-1 *(leucine-rich glioma-inactivated)*[18]. El estudio del LCR es normal o con mínimos cambios inflamatorios.

Las claves para el diagnóstico de esta entidad son clínicamente la alteración de la memoria y la aparición de crisis comiciales, y en los estudios complementarios valores de sodio repetidamente por debajo de la normalidad, engrosamiento a nivel de hipocampo izdo. en la RM y signos EEG de lesión temporal izquierda[26]. Esta entidad se puede asociar a enfermedad neoplásica en un 20% de los pacientes, por lo que se debe hacer un estudio encaminado al despistaje de tumores concomitantes[27]. Como se ha mencionado antes, el tratamiento más aceptado en la actualidad incluye corticoides en combinación con inmunoglobulinas o plasmaféresis e inmunosupresores.

### *Encefalopatía de Hashimoto*

La encefalitis de Hashimoto es una rara entidad en la que coexisten un deterioro cognitivo rápidamente progresivo (deterioro neurológico y funcional en un periodo inferior a dos años) y la presencia de anticuerpos antitiroideos -como los anti-peroxidasa tiroidea (TPO) y los anti-tiroglobulina (TG)- en títulos elevados, generalmente en ausencia de manifestaciones clínicas y de laboratorio de hipotiroidismo y sin que exista infección ni lesión estructural del sistema nervioso central (SNC)[28-32]. También se conoce como encefalopatía que responde a esteroides asociada con anticuerpos antitiroideos (del inglés *SREAT)* y, de manera más general, como meningoencefalitis autoinmune no vasculítica.

Presenta una prevalencia de 2,1 casos por cada 100.000 habitantes, y afecta sobre todo a mujeres (con una proporción 5:1) de 50-60 años. La etiología es desconocida, aunque se considera que tiene un carácter autoinmune por la presencia de anticuerpos antitiroideos y la buena respuesta al tratamiento con esteroides[32,33]. En cuanto a la fisiopatología existen dos teorías: la primera, en la que los anticuerpos anti-peroxidasa tiroidea (TPO) además de encontrarse elevados en suero, también presentan niveles altos en líquido cefalorraquídeo (LCR), lo que iniciaría la cascada inflamatoria al unirse a los astrocitos y alteraría la función del SNC[34]; y la segunda, que defiende la existencia de anticuerpos contra antígenos del endotelio vascular cerebral, lo que conllevaría un daño neuronal.

Aunque los síntomas son muy variados, se describen dos formas de presentación[34,35]: la primera y más típica, de tipo vasculítico o stroke-like, consiste en un deterioro cognitivo insidioso, fluctuante y con disminución del nivel de consciencia y en la que hasta el 80% de los pacientes presentan afasia transitoria, por lo que puede confundirse con un accidente cerebrovascular; y la segunda, que se comporta como una encefalopatía rápidamente progresiva con deterioro cognitivo, ataxia, mioclonías, crisis epilépticas, cefalea y manifestaciones psiquiátricas.

La determinación de anticuerpos antitiroideos (sobre todo anti-TPO y anti-TG) es esencial para el diagnóstico de la encefalitis de Hashimoto. No obstante, no está clara la relación entre la severidad de los síntomas neurológicos y la concentración sanguínea de anticuerpos. No se consideran un hallazgo específico de esta entidad, pues pueden estar elevados hasta en el 20% de la población general sana. También pueden estar elevados en LCR, pero no está clara la especificidad ni sensibilidad de su determinación. En el estudio de LCR lo habitual es encontrar una leve elevación de proteínas, raros los niveles mayores de 100 mg/dL, y una mínima pleocitosis con predominio de linfocitos. En algunos casos se ha descrito elevación de la proteína 14-3-3, hallazgo típicamente asociado a la enfermedad de Creutzfeldt-Jakob[36] y del que se desconoce su significado patológico en esta entidad. En cuanto a los niveles de hormonas tiroideas lo habitual es que no se encuentren alterados, pero en un 23-35% de los pacientes puede existir un hipotiroidismo subclínico y en torno al 7% tienen hipertiroidismo.

La RM cerebral es habitualmente normal, aunque en ocasiones pueden hallarse cambios en las sustancia blanca subcortical o aumento de señal a nivel meníngeo[37]. El LCR puede mostrar un patrón inflamatorio inespecífico. En sangre se describe con frecuencia una elevación de VSG y de transaminasas. El EEG suele ser anormal y muestra enlentecimiento uni o bilateral[38].

El diagnóstico es de exclusión, pues debido a la baja prevalencia no existen criterios definidos al respecto. No obstante, de forma general se acepta el mismo cuando el paciente presenta deterioro neurológico rápidamente progresivo, anticuerpos antitiroideos positivos a título elevado, no existe otra causa que justifique la clínica y se objetiva una respuesta considerable al tratamiento con corticoides[34,35,38]. El diagnóstico diferencial debe hacerse con la enfermedad de Creutzfeldt-Jakob (ECJ), la encefalitis límbica paraneoplásica, las vasculitis y las enfermedades psiquiátricas.

El tratamiento precoz mejora el pronóstico, de ahí la importancia de sospechar la enfermedad. Los corticoides a altas dosis son los fármacos de primera línea y la respuesta clínica favorable apoya el diagnóstico. La mayoría de los pacientes presentan mejoría a las pocas semanas, aunque a veces la respuesta es sorprendente ya con las primeras dosis. En aproximadamente la mitad de los casos se puede llegar a suspender el tratamiento, pero con frecuencia se describen recaídas que obligan a realizar un tratamiento a largo plazo y recurrir al uso de inmunosupresores como la azatioprina, el metotrexato o el micofenolato de mofetilo a fin de reducir los requerimientos de esteroides[39], mientras que en casos refractarios suele recurrirse a la plasmaféresis[36,40]. La suspensión definitiva del tratamiento puede considerarse en enfermos que se mantengan estables durante al menos un año, siendo necesario su seguimiento posterior por la posibilidad de que desarrollen hipotiroidismo.

## BIBLIOGRAFÍA


1. Geschwind MD, Shu H, Haman A, et al. Rapidly Progressive Dementia. Ann Neurol 2008; 64:97-108.
2. Kaplan PW. The clinical features, diagnosis, and prognosis of nonconvulsive status epilepticus. Neurologist 2005;11:348-361.
3. Roberson ED, Hesse JH, Rose KD, et al. Frontotemporal dementia progresses to death faster than Alzheimer disease. Neurology 2005;65:719-725.
4. Rascovsky K, Salmon DP, Lipton AM, et al. Rate of progression differs in frontotemporal dementia and Alzheimer disease. Neurology 2005;65:397-403.
5. Lopez O, Claassen D, Boller F. Alzheimer's disease, cerebral amyloid angiopathy, and dementia of acute onset. Aging (Milano)1991;3:171-175.
6. Josephson SA, Papanastassiou AM, Berger MS, et al. The diagnostic utility of brain biopsy procedures in patients with rapidly deteriorating neurological conditions or dementia. J Neurosurg 2007;106:72-75.
7. Vernino S, Geschwind MD, Boeve B. Autoimmune encephalopathies. Neurologist 2007;13:140-147.
8. Tuzun E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist 2007;13:261-271.
9. Gultekin SH, Rosenfeld MR, Voltz R, et al. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain 2000;123:1481-1494.
10. Dropcho EJ. Update on paraneoplastic syndromes. Curr Opin Neurol 2005;18:331-336.
11. Graus F, Saiz A. Encefalitis límbica: un síndrome probablemente infradiagnosticado. Neurologia 2005;20(1):24-30.
12. Dalmau J, Bataller L. Encefalitis límbica: los nuevos antígenos de membrana y propuesta de una clasificación clínicoinmunológica con implicaciones terapéuticas. Neurología 2007;22(8):526-537.
13. Rosenfeld MR, Dalmau J. Update on paraneoplastic neurologic disorders. Oncologist 2010;15(6):603-617.
14. Ramos Rivas M, Rojas Velasco G, Acuña Hidalgo R, et al. Encefalitis límbica paraneoplásica: una entidad de difícil diagnóstico. Rev Neurol 2009;48:311-316.
15. Ances BM, Vitaliani R, Taylor RA, et al. Treatment-responsive limbic encephalitis identified by neutrophil antibodies: MRI and PET correlates. Brain 2005;128:1764-1777.
16. Troester F, Weske G, Schlaudraff E, et al. Image of the month. FDG-PET in paraneoplastic limbic encephalitis. Eur J Nucl Med Mol Imaging. 2009;36:539.
17. Vincent A, Buckley C, Lang B, Irani S. Clinical spectrum of voltage-gated potassium channel autoimmunity. Neurology 2009;72:99.
18. Lai M, Huijbers MG, Lancaster E, et al. Investigation of LGI-1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol 2010;9(8):776-785.
19. Lawn ND, Westmoreland BF, Kiely MJ, et al. Clinical, magnetic resonance imaging, and electroencephalographic findings in paraneoplastic limbic encephalitis. Mayo Clin Proc 2003;78:1363-1368.
20. Jarius S, Hoffmann L, Clover L, et al. CSF findings in patients with voltage gated potassium channel antibody associated limbic encephalitis. J Neurol Sci 2008;268:74-77.
21. Merchut MP. Management of voltage-gated potassium channel antibody disorders. Neurol Clin 2010; 28(4):941-959.
22. Shams'ili S, de Beukelaar J, Gratama JW, et al. An uncontrolled trial of rituximab for antibody associated paraneoplastic neurological syndromes. J Neurol 2006;253:16-20.
23. Vernino S, O'Neill BP, Marks RS, et al. Immunomodulatory treatment trial for paraneoplastic neurological disorders. Neuro-oncol 2004;6:55-62.
24. Brierley JB, Corsellis JA, Hierons R, Nevin S. Subacute encephalitis of later adult life. Mainly affecting the limbic areas. Brain 1960;83:357-368.
25. Soler B, Godoy J, Mellado P. Encefalitis límbica por anticuerpos anticanales de potasio dependientes de voltaje. Caso clínico. Rev Med Chile 2009;137:675-679.
26. Schott JM. Limbic encephalitis: a clinician's guide. Practical Neurology 2006;6:143-153.
27. McKeon A. Autoimmune Encephalopathies and Dementias. Continuum: Lifelong Learning in Neurology 2016;22(2, Dementia):538–558.
28. Shaw PJ, Walls TJ, Newman PK, et al. Hashimoto's encephalopathy: a steroid-responsive disorder associated with high anti- thyroid antibody titers–report of 5 cases. Neurology 1991;41:228-233.
29. Castillo P, Woodruff B, Caselli R, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. Arch Neurol 2006;63:197-202.
30. Chong JY, Rowland LP, Utiger RD. Hashimoto encephalopathy: syndrome or myth? Arch Neurol 2003;60:164-171.
31. Chong JY, Rowland LP. What's in a NAIM? Hashimoto encephalopathy, steroid-responsive encepha- lopathy associated with autoimmune thyroiditis, or nonvasculitic autoimmune meningoencephalitis? Arch Neurol 2006;63:175-176.
32. Pinedo Torres I, Paz Ibarra J. Current knowledge on Hashimoto's encephalopathy: a literature review. Medwave 2018;18(06):e7298.
33. Sadan O, Seyman E, Ash E, et al. Adult-onset temporal lobe epilepsy, cognitive decline, multi-antiepileptic drug hypersensitivity, and Hashimoto's encephalopathy: Two case studies. Epilepsy Behav Case Rep 2013;1:132-135.
34. Zhou J, Xu B, Lopes J, et al. Hashimoto encephalopathy: literature review. Acta Neurol Scand 2016;135(3):285-290.
35. Montagna G, Imperiali M, Agazzi P, et al. Hashimoto's encephalopathy: A rare proteiform disorder. Autoimmun Rev 2016;15(5):466-76.
36. Vander T, Hallevy C, Alsaed I, et al. 14-3-3 protein in the CSF of a patient with Hashimoto's encephalopathy. J Neurol. 2004;251(10):1273.
37. Bohnen NI, Parnell KJ, Harper CM. Reversible MRI findings in a patient with Hashimoto's encephalopathy. Neurology 1997;49:246-247.
38. Kothbauer-Margreiter I, Sturzenegger M, Komor J, et al. Encephalopathy associated with Hashimoto thyroiditis: diagnosis and treatment. J Neurol 1996;243:585-593.
39. Hussain NS, Rumbaugh J, Kerr D, et al. Effects of prednisone and plasma exchange on cognitive impairment in Hashimoto encephalopathy. Neurology 2005;64:165-166.
40. Lee S, Donlon S, Caplan J. Steroid Responsive Encephalopathy Associated with Autoimmune Thyroiditis (SREAT) or Hashimoto's Encephalopathy: A Case and Review. Psychosomatics 2011;52(2):99-108.

# Ruptured cerebral mycotic aneurysm, an unusual infective endocarditis presentation

Tiago Alves[1], Rita Ivo[2], Marta Rebelo[2], Eduarda Carmo[2]

*[1]Centro Hospitalar do Médio Tejo. [2]Centro Hospitalar Lisboa Ocidental*

## ABSTRACT

Although septic embolization associated with infective endocarditis is relatively frequent, mycotic cerebral aneurysms are a rare and potentially fatal complication. The authors report the case of a woman admitted with a cerebral haemorrhage due to mycotic aneurysm rupture, which led to a subacute infective endocarditis diagnosis. The patient underwent craniotomy with aneurysm excision and mitral valvuloplasty due to severe valvular insufficiency, with a favorable clinical outcome. The authors make a brief review, highlighting the challenge of the management of these patients, especially at surgical approach, which requires an individualized therapy strategy based on patient evolution.

**Keywords:** mycotic, aneurysm, infective endocarditis. Intracranial haemorrhage.

**Palabras clave:** Aneurisma micótico. Endocarditis infecciosa. Hemorragia intracranial.

## INTRODUCTION:

Septic embolization associated with infective endocarditis (IE) is relatively frequent, however vascular wall involvement by septic emboli is a rare condition, especially at the brain. The term mycotic aneurysm (MA), coined in 1885 by Osler, defines an aneurysmal degeneration of an artery caused by vascular wall inflammation through septic embolization in patients with IE[1]. The mycotic designation results from the "fresh fungus vegetation" appearance and not from the etiological agent[1]. MA present high morbidity and mortality due to the risk of rupture. The authors describe the case of a patient with subacute IE complicated by ruptured MA.

## CASE REPORT

A 20-year-old woman, previously healthy, admitted at the Emergency Department with a high intensity (9/10) holocranial headache, associated with vomiting and drowsiness. The patient also reported episodes of fever, with no defined pattern and partial response to antipyretics, asthenia and weight loss (10% of initial weight), with 2 months of evolution. In these period, the patient was medicated with antibiotics, whose names she couldn't tell, but without symptomatic improvement.

At the emergency room, the patient was drowsy with a Glasgow Coma Scale: 14points, with isochoric pupils, but presenting a left homonymous hemianopsia at the neurological examination, without others deficits. Febrile (TT:38.5ºC), normotensive (105/62mmHg), tachycardic (105bpm) and eupneic. The skin and mucous membranes were pale, without clinical signs of poor peripheral perfusion. At the cardiac exam was recognized an holosystolic murmur, grade III/VI, predominant in the mitral focus and with irradiation to the axilla. The remaining physical exam was normal.

Laboratory results showed leukocytosis (24.500/ul) with neutrophilia (19.900/ul), erythrocyte sedimentation rate:79mm/h, C-reactive protein:11.9mg/dl and microcytic anemia (Hb:10.2g/dl, VGM:79.2fl).

Due to the symptomatology and neurological findings a head computerized tomography (CT) scan was performed, revealing an acute intraparenchymal hematoma occipital corticossubcortical and right parietal with extravasation to the ventricular system with a maximum diameter of 5.8 cm in the axial plane, causing deformation of the supratentorial ventricular system and subfalcine herniation with a midline shift of 5mm to the left. There was also a collapse of the quadrigeminal and peri-mesencephalic cisterns, along with ectasia of the ventricular system, evidencing hydrocephalus (figure 1). The angiography revealed an oval distal mycotic aneurysm in the right posterior cerebral artery (parieto-occipital branch) with a 3.5mm diameter (figure 2).

The Neurosurgery team was called and the patient underwent a craniotomy with hematoma drainage and aneurysm excision. For the postoperative care the patient was transferred to the Intensive Care Unit and an etiological investigation was performed.

The transthoracic echocardiogram showed a voluminous vegetation, with 21mm at the greater axis, adherent to the atrial face of the posterior leaflet of the mitral valve, leading to a severe mitral regurgitation in the Doppler-Corgrated and PISA analysis (EROA=0.6cm$^2$, Vreg=68mL) and mild to moderate left atrial enlargement (Volume index 47mL/m$^2$). Based on the available data, with a probable IE according to the modified Duke criteria. Blood samples were obtained for blood cultures and empirical antibiotic therapy with vancomycin, flucloxacillin and gentamicin was started. The multiples blood cultures remained negative after prolonged incubation, as well as the *Coxiella burnetii, Bartonella, Toxoplasma, Legionella, Mycoplasma* and *Chlamydia* spp serologic tests. The autoimmune study, with antinuclear antibodies, antiphospholipid antibody and rheumatoid factor, was also negative. The only positive result found was a high antistreptolysin O title (515IU/mL) at the admission, which doesn't allow to state a *Streptococcus* group bacteria aetiology, but may suggest his involvement. Due to severe mitral regurgitation, Cardiothoracic Surgery was contacted and, after a multidisciplinary decision, the surgery was postponed at this stage. The recent cerebral haemorrhage was a contraindication for the anticoagulation required for surgery, which would imply extracorporeal circulation. A CT scan was repeated within 48 hours showing sero-aero-haematic residues from craniotomy, aneurysm excision and no hydrocephalus or midline shift.

Correspondencia: tiago.pereira.alves88@gmail.com

Cómo citar este artículo: Alves T, Ivo R, Rebelo M, Carmo E
Ruptured cerebral mycotic aneurysm, an unusual infective endocarditis presentation.. Galicia Clin 2020; 81 (2): 46-47

Recibido: 18/12/2018; Aceptado: 18/01/2019 // http://doi.org/10.22546/56/1859

Figure 1. Acute intraparenchymal hematoma occipital corticossubcortical

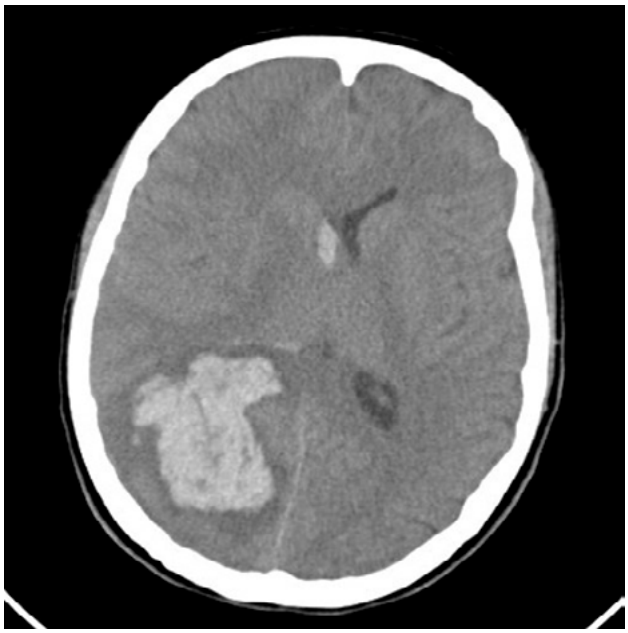
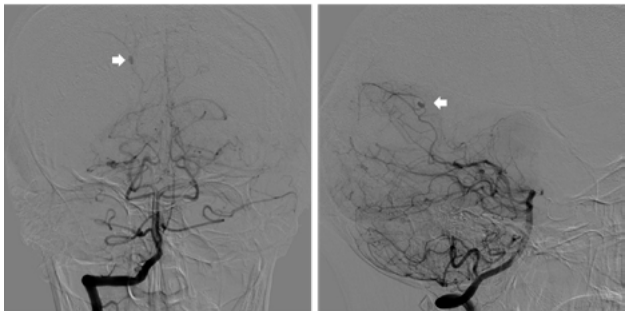


Figure 2. Angiography of the mycotic aneurysm in coronal and sagital plane



After 4 weeks under antibiotic therapy and with a good neurological evolution the patient was submitted to mitral valvuloplasty. No post-operative complication occurred. The histopathology of the excised material revealed fibrin and an extensive polymorphonuclear inflammatory infiltrate, the fungal research with periodic acid-schiff and Grocott`s silver stain was negative.

The patient fulfilled a total of 6 weeks with the same empirical antibiotic therapy initially started without further neurological aggravation and improvement of left homonymous hemianopsia.

## DISCUSSION

MA, despite the term, are in fact pseudo aneurysms since there is no involvement of all layers of the vascular wall. The most consensual theory for degeneration of the vascular wall results from septic embolization through the vasa vasorum severe inflammation of the adventitia, with intimal proliferation and destruction of internal elastic lamina[2].

As mentioned above, MA are a rare complication of IE, with an incidence of 2 to 3%[3]. The development of these aneurysmal formations is more frequently associated with bacterial subacute IE, predominating the *Streptococcus viridans* and *Staphylococcus aureus* as aetiological agents. Other agents, such as mycobacteria, viruses or fungi, may be also involved. The most frequently described symptoms are headache, fever, vomiting, ocular palsy, convulsions, hemiparesis, drowsiness or loss of consciousness[3].

In this case, the patient presented a new mitral regurgitation, positive echocardiogram for IE, fever and vascular phenomena, totalling 1 major and 2 minor criteria of modified Duke criteria, allowing the probable IE diagnosis. The histopathology after valve surgery revealed fibrin tissue and an extensive polymorphonuclear inflammatory infiltrate, without microorganism identification, however, it is important to remind the patient was under 4 weeks of empirical antibiotic therapy for IE at that time. The negative extend blood cultures may be explained by the patient's antibiotic use at the hospital admission. The serologic and autoimmune study was negative, only revealing the patient a high Antistreptolysin O title that may raise the suspicion of a *Streptococcus* group bacteria involvement.

The ruptured aneurism with intraparenchymal haemorrhage at admission is frequently related to a high morbidity and mortality. An early neurosurgical intervention is vital for the favourable outcome. In recent cases, morbidity and mortality rates have been decreasing due to neurosurgical advances[4].

The severe mitral regurgitation triggered by the IE also lacked surgical intervention, but the aneurysm rupture has, as well, implications at this approach. In the unruptured aneurysm, cardiac surgery can be performed without additional risk. The decision if cardiac or cerebral intervention should be performed first is based on the evaluation of aneurysm haemorrhagic risk versus heart failure severity. In the presence of a recent treated ruptured aneurysm, the haemorrhagic risk of valvuloplasty surgery is high, since it involves heparin-coated extracorporeal circulation, therefore, it is recommended to delay the cardiac intervention. In the literature, studies indicate a period superior to one month as ideal time delay.5 This interval may differ depending on the magnitude of heart failure, so an individualized evaluation is imperative.

In conclusion, the authors emphasize the importance of the early diagnosis in IE and, although rare, ruptured cerebral MA are a challenging complication, demanding a patient centred approach.

## REFERENCES


1. Osler W. The Gulstonian lectures on malignant endocarditis, Br Med J, 1885; vol.1:467-91.
2. Kannoth S and Thomas SV. Intracranial microbial aneurysm (infectious aneurysm): current options for diagnosis and management. Neurocritical Care,2009; vol.11(1):120-129.
3. Kuo I, Long T, Nguyen N, Chaudry B, Karp M, and Sanossian N. Ruptured Intracranial Mycotic Aneurysm in Infective Endocarditis: A Natural History. Case Reports in Medicine, 2010, ID168408.
4. Kannoth S, Iyer R, Thomas SV, Furtado SV, Rajesh BJ, Kesavadas C et al. Intracranial infectious aneurysm: Presentation, management and outcome. J. Neurol. Sci, Vol:256 (1):3-9.
5. Rossi M, Gallo A, De Silva RJ, Sayeed R. What is the optimal timing for surgery in infective endocarditis with cerebrovascular complications?. Interact Cardiovasc Thorac Surg. 2011;14(1):72-80.

# Takayasu arteritis: showed by a hypertensive crisis

Rita Rocha, Adriana Sousa, Vânia Rodrigues, Alcina Ponte
*Centro Hospitalar de Leiria. Portugal*

## INTRODUCTION

Takayasu Arteritis (TA) is a primary granulomatous large vessel vasculitis, affecting predominantly young women[1]. It mainly affects the aorta and its major branches. TA and the required immunosuppressive therapy cause considerable morbidity and mortality[2]. Early in the disease course, symptoms can be non-specific, leading to a difficult diagnosis[3]. Consequences of vascular stenosis, occlusions, and, less commonly, vascular dilation, account for the typical clinical presentation; the latter can sometimes lead to aneurysmal rupture or dissection. Though the importance of a comprehensive history and a thorough physical examination cannot be over-emphasized, clinical assessment is frequently inaccurate when evaluating disease activity, which may sometimes progress silently. Also the diagnostic modalities currently used are unsatisfactory. X-Ray angiography, the "gold standard" for TA diagnosis, can image luminal defects but does not detect changes of the vessel wall[4]. The diagnosis of TA can be confirmed with histopathological examination; however, tissue from blood vessels is obtained only in the minority of patients requiring a surgical intervention. There are currently no specific biomarkers for diagnosing TA. Identifying disease activity in TA is challenging[3].

Glucocorticosteroids are anchor drugs for this disease, like other vasculitis. Most cases in Japan respond with 0.3–0.5 mg/kg/day prednisolone, but we frequently found that some patients revealed flare-ups during tapering of glucocorticosteroids. Since TAK mainly affects young women, side-effects of glucocorticosteroids, especially moon face, severely damage their quality of life. Immunosuppressive agents, including methotrexate, cyclosporine, cyclophosphamide, mycophenolate mofetil and TACROLIMUS have been used for patients with TAK. Biological agents targeting tumor necrosis factor (TNF) have also been used for patients with TAK. Since IL-6 is highly expressed within inflamed arteries and serum levels correlate with disease activity, blocking IL-6 showed effectiveness in TA. Tocilizumab is a humanized monoclonal antibody against the IL-6 receptor, and the first report of successful use of tocilizumab in a patient with refractory TA was published in 2008. Later, nine additional cases of TA treated with tocilizumab 8 mg/kg every 4 weeks were reported. In the majority of the cases, disease activity improved and CS doses were discontinued or tapered. Abatacept is another promising biologic agent inhibiting the co-stimulation of T cells, and is currently being investigated in the first randomized, placebo-controlled trial of LVV patients including TA[7].

This article aims the description of a clinical case of a serious appearance form of an uncommon disease, Takayasu's arteritis.

**Keywords:** Takayasu Arteritis, Large vessel vasculitis, renal artery stenosis

**Palabras clave:** Arteritis de Takayasu. Vasculitis de grandes vasos. Estenosis de la arteria renal

## CLINICAL CASE

Female, 61 years old, caucasian with personal background of a Takayasu's arteritis (TA) without medication and without medical follow-up, Hypertension and Depressive syndrome, presented to the emergency department (ED) with fever, dyspnea with polypnea, productive cough with severe hypoxemia. The physical examination showed a pulmonary auscultation with loud crackles in both lung bases. Laboratory tests showed a marked increase of inflammatory parameters. Thorax X-Ray confirms evident condensations compatible with bilateral pneumonia. Patient was admitted with a diagnosis of Community Acquired Pneumonia. On the 2nd day at the ED, the patient had an acute lung edema associated with hypertensive crisis with respiratory failure and was transferred to the Intensive Care Unit. He was extubated after eight days and accomplished empirical antibiotic Clarithromycin and Ceftriaxone treatment. After eight days and after stabilization, patient was then transferred to the Internal Medicine Service.

Based on a long-term fever, a suspicion of relapsing Takayasu's arteritis was registered.

Inpatient made a CT angiography, examination towards the systemic arteries from the base of the skull to the distal portion of the lower limbs, showing the following aspects:

- Unchanged pulmonary arteries;
- In the circle of Willis there's an occlusion of the posterior communicating artery, the anterior cerebral artery and the right anterior communicating artery;
- Examination to the supra-aortic trunks shows the absence of significant changes in the permeability of the right carotid and right vertebral arteries. On the left there's an early carotid stenosis, chronic occlusion of the left subclavian artery, with this artery permeabilized with stolen blood by a vertebral artery. There's evident occlusion of the carotid artery along its entire length. The other visible portions of the left vertebral artery and carotid artery have a tapered diameter tapered in a general way;
- No changes to the diameter or the permeability of the thoracic and abdominal aorta. However, there are mural thrombi and extensive calcifications;
- In the distal branches of the abdominal aorta stands a stenosis of the right renal artery, which is uneven across its path and with a more pronounced stenotic segment with hemodynamic meaning. Consistent to that, there's a diffuse decrease in the thickness of the parenchyma, compared to the one observed on the left.
- Celiac trunk with stenosis but the irrigation is assured by the superior mesenteric artery. In the inferior mesenteric artery there's evident sub-occlusive stenosis of the proximal portion.

Correspondencia: anaritamrocha@gmail.com

Cómo citar este artículo: Rocha R, Sousa A, Rodrigues V, Ponte A
Takayasu arteritis: showed by a hypertensive crisis. Galicia Clin 2020; 81 (2): 48-50
Recibido: 19/12/2018; Aceptado: 14/01/2019 // http://doi.org/10.22546/56/1865

- At the arteries of the lower limbs can be observed a diffuse stenosis of primitives and external iliac arteries, as well as in the common and superficial femoral arteries;
- Popliteal Arteries and infra-popliteal trunks without any modifications observed.

Pharmacological stent was implanted in the renal artery, whose stenosis probably caused the hypertensive crisis and consequently the Lung edema. The patient starts GC therapy during the internment with GC bolus of 250mg before oral steroids. Inpatient started double platelet anti-aggregation therapy.

The internment took place without further complications and patient was discharged with an indication of smoking cessation and steroid prednisolone 30mg to 10mg at breakfast and dinner every day, anti-hypertensives, platelet anti-aggregation and statin therapy. Patient started to be followed-up at regular autoimmune medical consultations and in the Imaging follow-up study: "Regular caliber of the remaining arterial structures, without any evidences of significant ectasia and/or stenosis. There weren't any abnormal vascular structures identified. A stent is evident at the right renal artery, which remains permeable".

With regard to the admission, recent exams noticed some improvements in stenosis and occlusions.

## DISCUSSION

Takayasu arteritis (TA) is a large vessel vasculitis (LVV) characterized by granulomatous inflammation of the vessel wall with an unknown etiopathogenesis, often resistant to treatment and associated with high morbidity and mortality[6]. TA predominantly affects young females during the second or third decades of life and mainly involves the aortic arch and its primary branches, ascending aorta, thoracic descending aorta and abdominal aorta[4]. Although there is considerable variability in disease expression, the initial vascular lesions frequently occur in the left middle or proximal subclavian artery[4].

Is one of the 2 main causes of large vessel vasculitis, giant cell arteritis being the other[2]. The pathogenesis of Takayasu's arteritis is poorly understood.

Vascular symptoms are rare at presentation, but evidence of vascular involvement and insufficiency becomes clinically apparent as the disease progresses due to dilation, narrowing, or occlusion of the proximal or distal branches of the aorta. 1 Clinical manifestations of TA are quite variable, ranging from tissue ischemia due to vascular stenosis and occlusion, and to aneurysm formation that may occasionally rupture or dissect. Systemic symptoms (fever, malaise, weight loss, night sweats, polyarthralgia or arthritis) may predominate at the onset of TA[2].

In addition to a careful history and physical examination, diagnosis of TA should be based on laboratory studies (acute phase reactants), and imaging studies. Rarely, histology of the resected vessel is also available, and may help establishing the diagnosis and assess its severity[7].

In most cases the diagnosis is based upon suggestive clinical features and imaging of the arterial tree by MRI, CT, or angiography that demonstrates smoothly tapered luminal narrowing or occlusion that is accompanied by thickening of the wall of the vessel that is best demonstrated by CT or MRI.

Contrast arteriography may be preferred to CT or MRI for diagnosis if there is life- or limb-threatening ischemia for which immediate revascularization is anticipated since this may be accomplished by angioplasty and/or stenting of the affected vessel or vessels.

Smoking in the context of an inflammatory vascular disease is strongly discouraged. Patients should be repeatedly reminded of this, and referred for appropriate counseling if necessary. Diet is important for bone health and cardiovascular health in general, and also for maintaining a healthy body weight while on glucocorticoids, but it has not been shown to have a clear role in affecting the disease course as such[2].

Low salt intake, calcium and vitamin D supplementation and regular exercise are essential to reduce the metabolic side effects of CS agents. Monitoring and control of blood pressure may be difficult in cases with absent or reduced pulses in some extremities. Blood pressure measurements should be made in the unaffected extremities[7].

Corticosteroids have been the mainstay of therapy for active TA[8].

The response to high dose prednisolone is generally favorable, but relapses may occur while gradually tapering the dose and adverse effects of long-term treatment can cause problems. Therefore, many physicians tend to start conventional IS agents together with the initial CS treatment or while tapering the CS dose. Since MTX is an inexpensive, easily available and relatively safe agent that is widely used in rheumatology, it is the first choice of many physicians[7].

Surgical treatment, which should preferably be avoided, is also needed at times based on specific circumstances. Results of surgery are often unsatisfactory if TA is active preoperatively. When TA is felt to be in remission, the short term results of revascularization procedures may be acceptable, but relapses occur quite often when patients are followed over several years. It is imperative that better biomarkers and better imaging modalities be devised for accurate evaluation of ongoing vascular inflammation, so that the effect of therapy can be precisely quantified. A more detailed understanding of the pathogenesis of TA is likely to provide new targets for therapy[2].

Takayasu's arteritis is a rare and complex disease that can complicate and eminently end fatally. Therefore, patients with Takayasu´s arteritis must be followed up carefully, with a regular follow-up imaging, not allowing medication errors[2].

## BIBLIOGRAPHY


1. Schmidt J, Kermani TA, Bacani AK, Crowson CS, Cooper LT, Matteson EL, et al. Diagnostic features, treatment, and outcomes of Takayasu arteritis in a US cohort of 126 patients. Mayo Clin Proc 2013;88:822–30.
2. Chaterjee, S., Flamm, S. D., Tan, C. D., & Rodriguez, E. R. (2014). Clinical Diagnosis and Management of Large Vessel Vasculitis: Takayasu Arteritis. *Current Cardiology Reports.*
3. Barra, L., Kanji, T., Pagnoux, C., & Vasc, C. (2018). Imaging modalities for the diagnosis and disease activity assessment of Takayasu's arteritis: A systematic review and meta-analysis. *Autoimmunity Reviews*, 175-187.
4. Andrews A, Pennell DJ, Hossain MS, Davies KA, Haskard DO, Mason JC. Non-invasive imaging in the diagnosis and management of Takayasu's arteritis. Ann Rheum Dis 2004;63:995–1000
5. Terao, C., Yoshifuji H., Mimori, T.. (2014) Recent advances in Takayasu arteritis. *International Journal of Rheumatic Diseases,* 238-247.
6. Pacheco, R. L., Latorraca, C. d., Souza, A. W., Daniela, P. V., & Riera, R. (2017). Clinical interventions for Takayasu arteritis: A systematic review. *The international Journal of Clinical Practice.*
7. Keser, G., Direskeneli, H., & Aksu, K. (May 2015 vol 53). Management of Takayasu arteritis: a systematic review. *Oxford Journal of Reheumatology,* 793-80
8. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Limitations of therapy and a guarded prognosis in an American cohort of Takayasu arteritis patients. Arthritis Rheum. 2007;56:1000–9

# Heart failure: the importance of getting the right cause

Sara Freitas[1], Joana Marques[1], Ana Grilo[1], Pedro António[2]

[1]Servicio de Medicina Interna, Hospital Beatriz Ângelo, Loures, Portugal
[2] Servicio de Cardiología, Hospital de Santa Maria, Lisboa, Portugal

## ABSTRACT

Amyloidosis is a systemic disease, with an incidence of 5-12 people per million per year. Autopsy studies suggest a higher incidence[1]. Is characterized by deposition of amyloid fibrils in extracellular tissue of various organs and systems, and therefore with multiple possible presentations. The causative amyloid fibril deposits are of monoclonal light chain (AL) or transthyretin (TTR) in most cases. TTR amyloidosis may be acquired, associated with wild type TTR or hereditary (associated with variants in TTR gene[2] (table 1).

The AL amyloidosis condition can occur alone or associated with multiple myeloma or other B-cell dyscrasias[3]. The main affected organs in AL amyloidosis are the heart, kidney, liver, gastrointestinal tract and the peripheral and autonomic nervous systems. Patients often present with non-specific symptoms, such as asthenia, weight loss, palpitations and syncopal attacks[4]. Thus, diagnosis is usually delayed, and renal and cardiac failure can be forms of presentation.

We report a case of a 68-year-old woman, who presented with new onset heart failure as the main presentation form of multiple myeloma with associated cardiac amyloidosis. This case highlights the need of a high level of suspicion in order establish an early diagnosis and initiate specific therapy, and therefore delay the development of this condition.

**Keywords:** Amyloidosis; heart failure; multiple myeloma.

**Palabras Clave:** Amilosis, insuficiencia cardiaca, mieloma múltiple.

## CLINICAL CASE

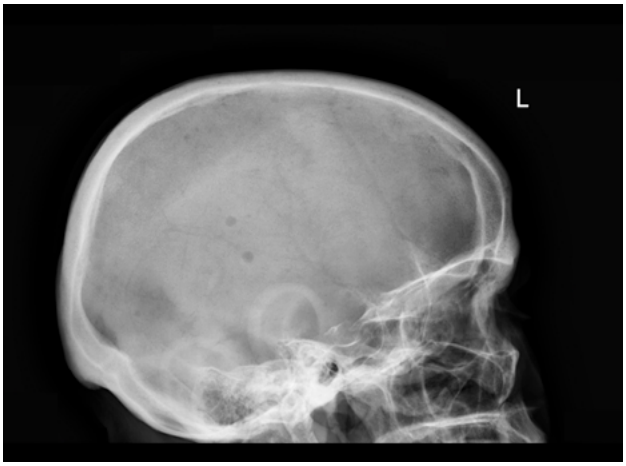
A 68-year-old woman, with no relevant medical history, was admitted in the emergency department due to asthenia and marked limitation in activity due to shortness of breath when walking short distances, progressive in the last 3 months.

On examination she had profuse sweating, blood pressure (BP) 89/52mmHg, heart rate of 55bpm, eupnoeic at FiO2 21%, rhythmic heartbeat, without murmurs, and presented mild crepitations on the right pulmonary base. There was no peripheral oedema nor other abnormalities at examination. The electrocardiogram (ECG) showed junctional rhythm, frequent ventricular ectopies, low voltage in frontal leads and pathological Q waves in inferior and anterior (V1 to V4). Plasma levels of N-terminal pro b-type natriuretic peptide (NT pro-BNP) were markedly increased (7676 pg/ml) and troponin levels were mildly increased (table 2). Echocardiogram showed concentric left ventricle hypertrophy with posterior wall thickening (14 mm), interventricular septum thickening (17mm), mild pericardial effusion and high left ventricle (LV) filling pressures (E/E': 25.08). The LV ejection fraction was preserved (59.7%).

An infiltrative cardiomyopathy was suspected in the context of possible systemic disease and the patient was admitted at the Internal Medicine department. Plasma cell dyscrasia with high free light chain lambda was detected (table 2). Myelogram showed 24% plasma cells, but bone marrow biopsy was inconclusive (without sufficient tissue).

No amyloid deposits were found in abdominal fat, stomach, duodenum or rectum biopsies. Radionuclide bone scintigraphy with $^{99m}$Tc–Hydroxymethylene diphosphonate (HMDP) showed multiple rib fractures but no evidence of myocardium involvement. Multiple lytic lesions were documented on the scull x-ray (figure 1). Thoraco-abdominal TC scan revealed mild pleural effusion plus heterogenic bone trabeculation and centimetric lytic bone lesions in pelvic bones.

Figure 1. Lateral radiography of skull showing multiple lytic lesions.



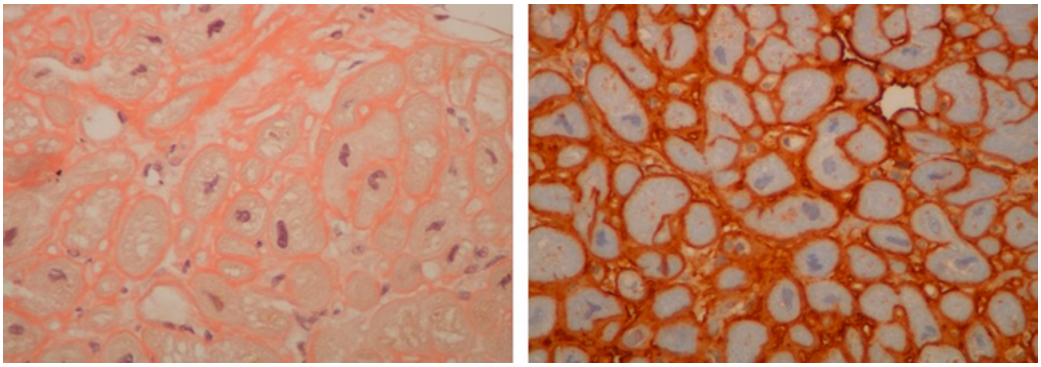

During hospitalization the patient developed symptomatic bradycardia and a pacemaker was implanted. Due to intracardiac thrombus detection, hypocoagulation treatment was initiated.

After clinical stabilization she was discharged on diuretic treatment and referred to the Haematology clinic. However, shortly after she

Correspondencia: saracmfreitas@gmail.com

Cómo citar este artículo: Freitas S, Marques J, Grilo A, António P
Heart failure: the importance of getting the right cause. Galicia Clin 2020; 81 (2): 51-53
Recibido: 19/12/2018; Aceptado: 25/12/2018 // http://doi.org/10.22546/56/1864

Figure 2. Myocardial biopsy. Congo red staining of the interstitial amyloid (left). Lambda light chain positive immunostaining in the pericellular deposit consistent with AL amyloidosis with an immunoperoxidase method (right).



deteriorates again and was readmitted with heart failure (HF), this time at the Cardiology department. Endomyocardial biopsy was performed and amyloid fibrils were detected with Congo red staining and sulphated alcian blue staining. Immunocytochemical test was positive for lambda chains (figure 2). Despite the targeted treatment, unfortunately the patient died 3 weeks later a due to refractory HF.

## DISCUSSION

Cardiac involvement is common in AL amyloidosis, (approximately in 60%[5]) but only in 5% is present isolated cardiac involvement[6]. Myocardium involvement is also common in ATTR[7].

Usually right-sided congestive HF symptoms dominate. Low BP, also present in our patient, is very common, mainly due to poor cardiac output but also due to peripheral vasomotor disfunction secondary to autonomic neuropathy[8].

NT pro-BNP has prognostic value and elevated troponin levels are common reflecting myocardial cardiac injury[7]. Low voltage in ECG is more common in AL-type amyloidosis and has a documented prevalence of 46% to 74%[5,9,10].

Typical findings in echocardiogram include thickening of ventricular walls (commonly in a concentric pattern), diastolic dysfunction, restrictive filling in advanced disease, atrial septum thickening, biatrial enlargement, thickened valves and pericardial effusion. However, although a widely accessible tool, echocardiogram is neither sensitive nor specific for cardiac amyloidosis[8].

Cardiac magnetic resonance imaging has much greater diagnostic value, with some characteristic findings as diffuse subendocardial or transmural gadolinium enhancement coupled with myocardial and blood-pool gadolinium kinetics[2].

Scintigraphy is an important tool in cardiac amyloidosis investigation. For instance, 99mTC-HMDP is an effective radiotracer in identifying TTR cardiac amyloidosis but not in AL

Table 1. Amyloidosis types with frequent cardiac involvement, clinical features, diagnostic modalities and treatment. HF – heart failure; HFpEF – heart failure with preserved ejection fraction (adapted from Bhogal et al., 20187)

| Amyloidosis type | Primary light chain amyloidosis (AL) | Familial amyloidosis (ATTR) | Senile cardiac amyloidosis (SSA) |
|---|---|---|---|
| **Protein involved** | Monoclonal light chain | Variants of transthyretin with >120 mutations | Wild type transthyretin |
| **Cardiac features** | HFpEF, atrial/ventricular arrhythmias and first/second degree or advanced heart block | HFpEF, atrial/ventricular arrhythmias and first/second degree or advanced heart block | HFpEF, atrial/ventricular arrhythmias and first/second degree or advanced heart block |
| **Extracardiac features** | Characteristic findings: periorbital edema and macroglossia<br>Other findings: hepatomegaly, nephrotic syndrome, purpura, easy bruising, carpel tunnel syndrome, peripheral neuropathy | Hepatomegaly, nephrotic syndrome, purpura, easy bruising, carpel tunnel syndrome, peripheral neuropathy | Bilateral carpel tunnel syndrome |
| **Diagnostic modalities** | Serum and urine protein electrophoresis, detection of free light chains, biopsy of affected organs | Technetium pyrophosphate, genetic testing, biopsy of affected organs | Exclusion diagnostic, biopsy of affected organs |
| **Treatment** | HF therapy, chemotherapy, heart transplant followed by autologous SCT | HF therapy, liver transplant, combined liver and heart transplant, Tafamidis | HF therapy, liver transplant |

Table 2. Relevant laboratory values. LDH: lactate dehydrogenase; NT- pro BNP: N-terminal pro b-type natriuretic peptide; CRP: C reactive protein; Ig: immunoglobulins;

| Exam | Results (normal range) |
|---|---|
| Haemoglobin | 12.3 (12-16g/dl) |
| Glucose | 81 (74-106mg/dl) |
| Urea | 70 (17-49mg/dl) |
| Creatinine | 1,07 (0,5-0,9mg/dl) |
| LDH | 355 (132-214IU/L) |
| Troponin I | 0.34 (<0.16ug/L) |
| NT pro-BNP | 7676 (<300pq/ml) |
| Albumin | 2.5 (3.5-5.2g/dl) |
| CRP | 0.37 (<0.5mg/dl) |
| Sodium | 143 (136-145mmol/L) |
| Potassium | 3.9 (3.1-5.1mmol/L) |
| Calcium corrected to hypoalbuminemia | 7.7 (8.8-10.2mg/dl) |
| Serum protein electrophoresis | Normal range |
| Urine analysis | Mild proteinuria |
| Serum immunofixation | monoclonal spike light chain lambda/free light chain lambda |
| Serum Ig A,G,M and D | Normal range |
| Serum free light chain lambda | 403 (8.3-27mg/L) |
| Serum free light chain kappa | 7 (6.7-22.4mg/L) |
| Serum free kappa/lambda ratio | 0.02 (0.31-1.56) |
| 24h-urine light chain lambda | 24.6 (<1mg/dl) |
| 24h-urine light chain kappa | 0.9 (<1mg/dl) |
| Bence Jones protein | detected |
| Beta-2 microglobulin | 2.52 (0.9-1mg/dl) |

amyloidosis[11]. This explains the absence of cardiac involvement evidence in this case report.

The diagnosis is usually obtained through biopsy of a clinically affected organ, with Congo histology demonstrating pathognomonic green birefringence appearance under polarized light. Fat pad biopsy and rectal mucosa are usually initially preferred since they are mild invasive procedures. When those are negative, endomyocardial biopsy may be necessary since it has 100% sensitivity[6].

Treatment depends on the type of amyloidosis, main organ involvement and disease extent (table 1). In AL amyloidosis the base treatment is chemotherapy with or without stem cell transplantation, according to the underlying disease and stage. However, the presence of cardiac amyloidosis increases morbimortality rates from intensive chemotherapy[12].

Cardiac amyloidosis treatment consists mainly on diuretics although this therapy should be carefully managed to prevent severe hypotension. Other drugs like beta-blockers, digoxin and certain calcium blockers should be avoided. Cardiac pacing may be necessary when there are conduction disturbances[12], as described in this case. The prognosis of AL amyloidosis with cardiac involvement is poor, with a mean survival of 10-14 months and the cause of death in 50% of cases is cardiac[6].

In conclusion, AL amyloidosis is a rare, serious disease that requires a high suspicion level in order to diagnose based on clinical, imagological and histological exams. This is essential in order to initiate appropriate treatment at an initial stage of the disease since the prognosis is poor, in particular when cardiac involvement is present.

## LEARNING POINTS

- A high level of suspicion is crucial to diagnose amyloidosis;
- A positive biopsy establishes the definite diagnosis, but other diagnostic technics are extremely important in guiding the investigation;
- Determining the underlying cause of amyloidosis is essential in order to initiate specific treatment.

## REFERENCES


1. Keller FA, Jamshidi P, Boeck B De, Glatz K, Nowackc M. Cardiac Amyloidosis Presenting With Myocardial Ischemia: Case Report and Literature Review. *J Med Cases.* 2016;7:531–5.
2. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation.* 2016;133:2404–12.
3. Triantafyllou AI, Kapelakis IE, Triantafyllou EA, Lampropoulos KM, Manolis AS. Cardiac Amyloidosis: Mini Review and a Case Report. *Int J Cardiol Lipidol Res.* 2015;2:14–9.
4. Magesh B, Kadeli D, Bohra S, Krishnaprasath V, Keshava R. Cardiac amyloidosis, an infiltrative heart disease presenting as arrhythmia - A case report. *J Clin Diagnostic Res.* 2017;11:14-5.
5. Dubrey S, Cha K, Anserson J, Chamarthi B, Reisinger J, Skinner M, et al. The clinical features and outcomes of immunoglobulin light-chain amyloidosis with heart involvement. *Q J Med.* 1998;91:141–57.
6. Fernandes A, Caetano F, Almeida I, Paiva L, Gomes P, Mota P, et al. Diagnostic approach to cardiac amyloidosis: A case report. *Rev Port Cardiol.* 2016;35:1–7.
7. Bhogal S, Ladia V, Sitwala P, Cook E, Bajaj K, Ramu V, et al. Cardiac Amyloidosis: An Updated Review With Emphasis on Diagnosis and Future Directions. *Curr Probl Cardiol.* 2018;43:10–34.
8. Fikrle M, Palecek T, Kuchynka P, Nemecek E, Bauerova L, Straub J, et al. Cardiac amyloidosis: A comprehensive review. *Cor Vasa.* 2013;55:60–75.
9. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. *Am J Cardiol* 2005;95:535–7.
10. Rahman JE, Helou EF, Gelzer-Bell R, Thompson RE, Kuo C, Rodriguez ER, et al. Noninvasive Diagnosis of Biopsy-Proven Cardiac Amyloidosis. *J Am Coll Cardiol.* 2004;43:410–5.
11. Andrikopoulou E, Bhambhvani P. Nuclear imaging of cardiac amyloidosis. *J Nucl Cardiol.* 2017;18:1–4.
12. Selvanayagam JB, Hawkins PN, Paul B, Myerson SG, Neubauer S. Evaluation and Management of the Cardiac Amyloidosis. *J Am Coll Cardiol.* 2007;50:2101–10.

# Insulinoma masquerading as neurologic disease – Case report and review of the literature

Catarina Machado. Patrícia Tavares. Sara Monteiro. M. João Oliveira

*Servicio de Endocrinología, Centro Hospitalar de Vila Nova de Gaia/Espinho*

## INTRODUCTION

Insulinomas are the most frequent etiology of hypoglycemia in a non-diabetic patient and the most common functional neuroendocrine tumors of the pancreas, with an annual incidence of about 4 cases per million[1, 2]. The majority of insulinomas are "well-differentiated endocrine tumors" or grade 1 tumors, as defined by World Health Organization[3]. Most tumors are benign, solitary and occur sporadically. However, about 10% are associated with multiple endocrine neoplasia type 1 (MEN-1)[1,2].

Despite the majority being benign tumors, hypoglycemic symptoms caused by the hyperinsulinemia are frequently debilitating[4]. Whipple triad (hypoglycemia, symptoms of hypoglycemia – either adrenergic or neuroglycopenic – and relief of these symptoms after administration of glucose) is usually present and should alert to the diagnosis[2,5].

After the diagnosis is made, locating the tumor can be challenging because most tumors are small[4]. Nonetheless, locating the tumor is crucial, once the only definite treatment is surgical excision[1,2]. The majority of patients reach normalization of glucose levels after surgery. Incomplete resection leads to persistent symptoms and although uncommon in sporadic insulinomas, recurrence can be as high as 20% in patients with MEN-1 syndrome[6,7].

**Keywords:** Insulinoma. Endocrine Tumors. Hypoglycemia.

**Palabras clave:** Insulinoma. Tumores endocrinos. Hipoglucemia.

## CASE REPORT

A healthy 36-year-old male was admitted in the emergency room with altered mental status and hypoglycemia (50 mg/dL). The patient recalled recurrent symptoms of diaphoresis, tremors, blurred vision and palpitations, sometimes with loss of consciousness and incontinence of urinary sphincter, for the past 4 months. Blood glucose levels had never been evaluated during these episodes. Because of these symptoms, he consulted with a Neurologist and was diagnosed with epilepsy and started on levetiracetam 500 mg twice daily. Cranial tomography and cranial magnetic resonance were unremarkable.

A careful anamnesis allowed to better clarify these symptoms: they occurred before meals and were relieved with eating carbon hydrates; they were associated with weight gain and there had been no improvement with the use of the anticonvulsive therapy. He had no family history of endocrine disease. Physical examination was unremarkable.

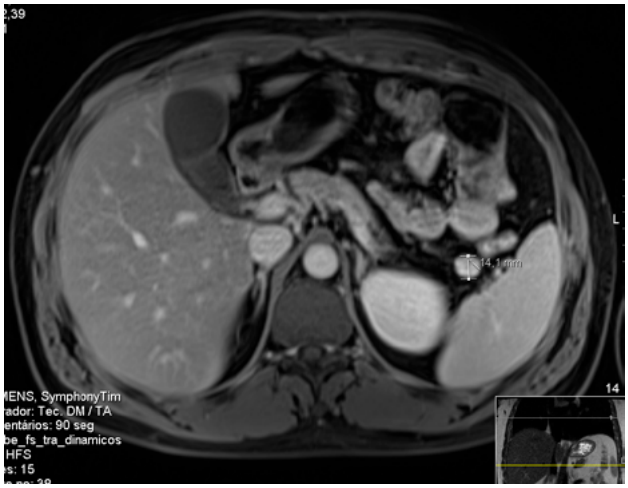
A prolonged supervised fasting test was applied and led to symptomatic hypoglycemia with hyperinsulinemia (Table 1).

Anti-insulin antibodies were negative. Other hormonal studies, including serum morning cortisol, parathormone (PTH) and adrenocorticotropine (ACTH) levels were normal, making the diagnosis of multiple endocrine neoplasia unlikely.

Abdominal magnetic resonance (MRI) demonstrated a well-defined enhanced lesion in the tail of the pancreas measuring 14mm (Image 1).

Because of its location near the spleen, questioning whether the lesion was intrapancreatic or an accessory spleen, a $^{68}$Ga-DOTA-NOC PET scan was performed. On the PET scan, there was a discrete expression of somatostatin receptors adjacent to the lateral end of the tail of the pancreas, in the same location as in the MRI (Image 2).

Image 1. Abdominal Magnetic Resonance – there is a well-defined enhanced lesion in the tail of the pancreas.



He maintained severe hypoglycemia despite glucose fluid administration and nutritional adequate plan so he was started on medical therapy with octreotide 300 mg daily and diazoxide 900 mg daily.

Table 1

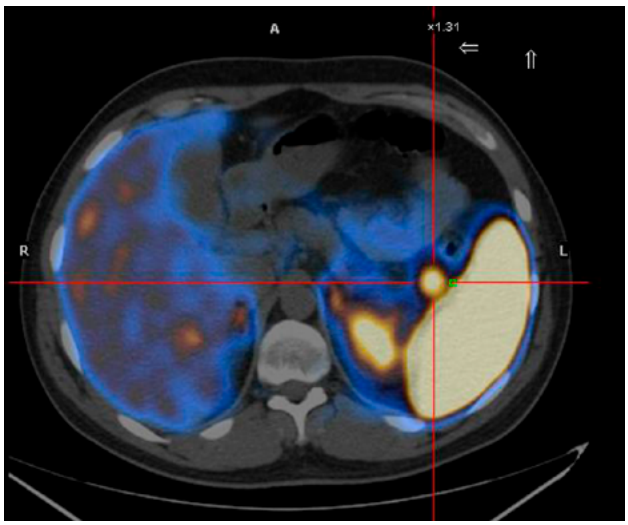
| | 6h | 7h | 8h | 10' | 20' | 30´ |
|---|---|---|---|---|---|---|
| **Glucose (mg/dL)** | 55 | 40 | 38 | 54 | 75 | 88 |
| **Insulin (uUI/mL)** | 60,1 | 52,1 | 68,7 | 24,1 | 28,8 | 194,7 |
| **C-Peptide (ng/mL)** | 6,25 | 5,96 | 7,07 | 4,4 | 4,09 | 10,8 |

Correspondencia: catarina_mmachado@hotmail.com

Cómo citar este artículo: Machado C, Tavares P, Monteiro S, Oliveira MJ
Insulinoma masquerading as neurologic disease – Case report and review of the literature. Galicia Clin 2020; 81 (2): 54-56

Recibido: 23/12/2018; Aceptado: 18/01/2019 // http://doi.org/10.22546/56/1871

Image 2. 68Ga-DOTA-NOC PET-SCAN - Discrete expression of somatostatin receptors adjacent to the lateral end of the tail of the pancreas.




Nodule enucleation was performed by laparoscopy surgery, with no immediate complications. Pathological examination revealed an encapsulated pancreatic mass measuring 17x14x15mm. Mitotic index was <2 per 10 consecutive high-power fields (HPF) and proliferation index ki-67 was estimated <2%, making the diagnosis of low grade neuroendocrine tumor of the pancreas. Tumor cells showed a positive staining for insulin, synaptophysin and cromogranine in the immunohistochemical analysis.

Shortly after surgical treatment, glucose levels increased to the normal range.

The patient was discharged without any hypoglycemic symptoms after 7 days. He remains asymptomatic 6 months after surgery.

## DISCUSSION

The symptoms of insulinoma are usually nonspecific and can vary. Hypoglycemia can present either with adrenergic symptoms, such as palpitations, tremor, anxiety, hunger or sweating, or neuroglycopenic symptoms, such as slurred speech, mental confusion, blurred vision, difficulty to concentrate or epilepsy episodes[1,2,6,8]. These symptoms may be attributed to either psychiatric or neurologic diseases, delaying the diagnosis[1]. Measuring blood glucose levels upon these symptoms is therefore crucial to adequate diagnose a hypoglycemia.

The diagnosis of an insulinoma should be thought when a previous healthy non-diabetic individual presents with hypoglycemia[9]. Hypoglycemia usually occurs after a fasting period or is triggered by exercise, but postprandial hypoglycemia may also occur and does not exclude the diagnosis[1,10].

After a symptomatic hypoglycemia with hyperinsulinemia is documented, the diagnosis of insulinoma is made. This occurs more often following a 72h prolonged fasting test, which is the gold standard for diagnosing an insulinoma[4]. The biochemical pattern of insulinoma is hypoglycemia (blood glucose levels < 55mg/dL) with inappropriate insulin and C peptide levels (> 3uU/mL and >0,2 nmol/L, respectively)[4,11]. Once insulinoma is diagnosed, genetic testing for MEN1 is recommended[2].

Following diagnosis, localization is essential once the definite curative treatment is surgery[1,2]. Insulinomas are typically small nodules; the majority is smaller than 20 mm, making its localization challenging[4,7]. As insulinomas are almost always found in the pancreas, image techniques should be directed at the upper abdomen[4]. Contrast enhanced computer tomography (CT) scan, magnetic resonance imaging (MRI) and trans abdominal ultrasonography may locate approximately 75% of insulinomas[11]. CT scan is usually the first to consider as it has a sensitivity greater than 90% in detecting insulinomas[4].

When anatomic localization is either negative or unclear, more invasive techniques such as endoscopic ultrasound (EUS) or selective intra-arterial calcium stimulation with hepatic samples may be necessary[4,11,12]. Nuclear imaging is based on the expression of certain receptors in neuroendocrine tumors. Because a large variety of endocrine tumors express somatostatin receptors[4], imaging with somatostatin analogs may help to locate the tumor and also inform about the potential use of radionuclide therapy in metastatic tumors[13]. Positron emission tomography (PET) with radiotracers such as 18F-fluorodeoxyglucose (18F-FDG) or 18 F- dihydroxyphenylalanine (18F-DOPA) can also be used in the detection of insulinomas[4]. The first is of limited use because most insulinomas have low FDG uptake[14]. When even with all these available modalities the location of the insulinoma is not apparent pre-operatively, intraoperative pancreatic ultrasonography almost invariably localizes the tumor[7,11].

Surgery is the treatment of choice is curative in the majority of the cases[1,7]. Surgical procedure depends on the size and the location of the tumor[6,15] with laparoscopic surgery being the most used currently[7]. Surgical techniques include tumor enucleation or pancreatic resection[1]. If the tumor is small and solitary, tumor enucleation is the procedure of choice[4,15]. Pancreatic resection (distal or median pancreatectomy or pancreaticoduodenectomy) is reserved for adherent lesions, tumors too close to adjacent structures or if malignancy is suspected[1,15].

Histologically, insulinomas show diffuse expression of neuroendocrine markers, such as synaptophysin and chromogranin[8,12]. Well-differentiated tumors may be distinguished from poor-differentiated ones by mitotic rate (number of mitose per 10 HPF) and proliferation index (Ki-67 proliferation index). Histologically, there are no markers of malignancy, and the diagnosis is made once metastasis occurs[12].

Medical treatment of insulinomas is aimed at preventing hypoglycemia and is generally used prior to surgery, in unresectable tumors or inoperable patients, or when patients refuse surgery[1,7,11,12]. Diet, including frequent feedings with long acting carbon hydrates, diazoxide or octreotide may

be tried even though restoring euglycaemia with the use of pharmacological drugs is difficult[1,7,8].

In poor surgical candidates, alcohol ablation, radiofrequency ablation and embolization of the tumor are other possible therapeutic options[4,7].

## CONCLUSION

Insulinomas are rare neuroendocrine tumors, the majority is benign and sporadic, but it can be part of the MEN-1 syndrome[1]. The diagnosis of insulinoma may be challenging due to its rarity and variable presentation. O other diseases, such as neurologic, may be considered first[1,7]. It is important to considerer the diagnosis since chronic and severe hypoglycemia can be fatal.

Biochemical diagnosis is usually easy, but preoperative localization may be demanding. CT scan may be used as first line, with other imaging techniques being reserved for tumors undetected on CT[4,7].

Surgery is the treatment of choice and is usually curative. Restoring euglycemia prior to the may be difficult and multiple drugs are usually needed[1,7].

## REFERENCES


1. Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, et al. Diagnosis and management of insulinoma. World journal of gastroenterology. 2013;19(6):829-37.
2. Anderson CW, Bennett JJ. Clinical Presentation and Diagnosis of Pancreatic Neuroendocrine Tumors. Surgical oncology clinics of North America. 2016;25(2):363-74.
3. Rindi G, Kloppel G. Endocrine tumors of the gut and pancreas tumor biology and classification. Neuroendocrinology. 2004;80 Suppl 1:12-5.
4. Rayamajhi SJ, Lee J, Mittal BR, Jessop AC, Chasen B, Bhosale P. Cross sectional and nuclear medicine imaging of pancreatic insulinomas. Abdominal radiology. 2017;42(2):531-43.
5. Kloppel G, Heitz PU. Pancreatic endocrine tumors. Pathology, research and practice. 1988;183(2):155-68.
6. Anakal MG, Kalra P, Dharmalingam M, Indushekhar S, Rao V, Prasanna Kumar KM. Insulinoma case series: Experience of a tertiary care center. Indian journal of endocrinology and metabolism. 2014;18(6):858-62.
7. Mehrabi A, Fischer L, Hafezi M, Dirlewanger A, Grenacher L, Diener MK, et al. A systematic review of localization, surgical treatment options, and outcome of insulinoma. Pancreas. 2014;43(5):675-86.
8. Dimitriadis GK, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Medical management of secretory syndromes related to gastroenteropancreatic neuroendocrine tumours. Endocrine-related cancer. 2016;23(9):R423-36.
9. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism. 2009;94(3):709-28.
10. Shreenivas AV, Leung V. A rare case of insulinoma presenting with postprandial hypoglycemia. The American journal of case reports. 2014;15:488-91.
11. Shlomo Melmed KSP, P. Reed Larsen, Henry M. Kronenberg. Williams Textbook of Endocrinology 13th Edition: Elsevier; 2016.
12. Tarchouli M, Ali AA, Ratbi MB, Belhamidi M, Essarghini M, Aboulfeth el M, et al. Long-standing insulinoma: two case reports and review of the literature. BMC research notes. 2015;8:444.
13. Makis W, McCann K, McEwan AJ. Metastatic Insulinoma Pancreatic Neuroendocrine Tumor Treated With 177Lu-DOTATATE Induction and Maintenance Peptide Receptor Radionuclide Therapy: A Suggested Protocol. Clinical nuclear medicine. 2016;41(1):53-4.
14. Adams S, Baum R, Rink T, Schumm-Drager PM, Usadel KH, Hor G. Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. European journal of nuclear medicine. 1998;25(1):79-83.
15. Abboud B, Boujaoude J. Occult sporadic insulinoma: localization and surgical strategy. World journal of gastroenterology. 2008;14(5):657-65.

# Lung abscess in immunocompromised

We present the case of a 44-year-old man, construction worker, hypertensive, smoker, with rheumatoid arthritis under prednisolone 10mg/day for 10 months. Gingival crevice disease. The patient was referred to the Emergency Department after 5 days of right chest pain with pleuritic features, cough, purulent sputum and dyspnea grade 3 mMRC, along with several weeks of indolent symptoms (anorexia, weight loss and night sweats). Polypneic with abdominal breathing and hypotensive. Initial blood tests showed an increase in inflammatory markers, hypoxemic respiratory failure and hyperlactacidemia. A thick walls cavitation, with an hydroaereal level was present in the chest X-ray (Fig 1). Thoracic computerized tomography (CT) shows a voluminous apparently loculated image occupying almost all of the right lung field associated with homolateral pleural effusion; a nodular image of about 28 mm with hydroaereal content located to the lower left lobe and at least two other identical smaller images in the same lobe (Fig 2). Diagnosed with lung abscess (LA), he was admitted to Intensive Care in septic shock under invasive ventilation and aminergic support, starting empirically piperacillin/tazobactam. The evaluation of pleural effusion (PE) reveals empyema fluid with an increased ADA of 158 IU/L. Tube thoracostomy with 3 chest tubes was performed. No structural changes in bronchofibroscopy (FB). PE culture identifies H. influenzae, S. parasanguinis and S. salivarius, allowing targeted therapy with clindamycin, fulfilling 35 days. Sterile blood cultures. PE cytology without malignancy. Tuberculosis excluded (PE and sputum with negative acid-fast bacilli (AFB) smear and culture; negative polymerase-chain-reaction assay for M. tuberculosis on bronchoalveolar lavage (BAL) and PE). Follow-up at 3 months with sterile BAL cultures and negative AFB BAL smear. CT improvement, with only residual changes, 6 months later.

LA consists of pulmonary parenchymal necrosis caused by microbial infection. Primary in 80% of cases. Inoculum aspiration from gingival crevice, poor dental hygiene are the main causes[1]. It as been noticed the close relationship with bacteria found in the oral cavity and gingival sulci. Steroids and smoking are important risk factors[2,3]. Cough, sputum, fever and systemic manifestations are a common presentation. Typically diagnosed with chest X-ray, anatomical definition is improved with CT. Despite difficult cultural isolation due to frequent contamination, Gram and sputum cultures are indicated as well as blood and PE cultures. FB is important in obtaining a cultural sample and exclusion of another etiology. Bacillary disease should be excluded. Anaerobes are present in 60-80% of cases, with frequently associated oral Streptococcus, 90% are polymicrobial[4]. Our patient's agents were facultative oral anaerobes. Etiological agents and associated comorbidities are essential in defining therapeutic strategy[5,6].

Figure 1. Chest X-ray

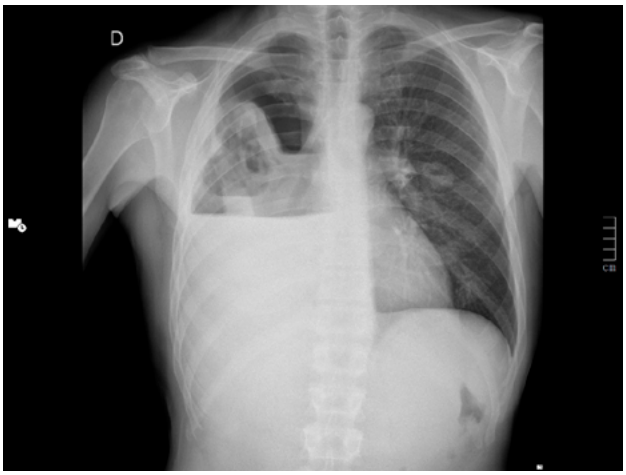
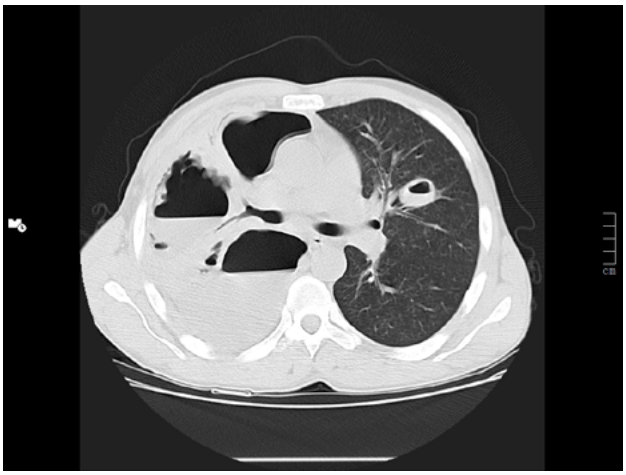



Figure 2. Thoracic computerized tomography



Antibiotics are usually maintained until radiological resolution or stable residual lesion, this may require several months and can be performed with an outpatient oral regimen. Bronchial obstruction, diameter >6cm, neoplasia, immunodepression and resistant microorganisms are predictors of poor therapeutic response[7,8], 90-95% of primary abscesses can cure[9,10]. Mortality rate in the immunocompromised may exceed 75%[11].

In summary, the authors, regarding an exuberant radiological presentation, intend to emphasize the relevance of microbiological isolation in targeting antimicrobial options, enabling faster outpatient treatment, avoiding prolonged hospitalization and complications inherent to it.

## ACKNOWLEDGEMENTS

The authors gratefully acknowledge to Dr. Ricardo Meireles (Internal Medicine Department, Centro Hospitalar do Tâmega e Sousa, Penafiel, Portugal) and the Pulmonology Department (Centro Hospitalar do Tâmega e Sousa, Penafiel, Portugal)

## BIBLIOGRAPHY

1. Puligandla PS, Laberge JM. Respiratory infections: pneumonia, lung abscess, and empyema. Semin Pediatr Surg 2008;17:42-52.
2. Gonçalves AM, Menezes Falcão L, Ravara L. Pulmonary abcess, a revision. Rev Port Pneumol 2008;14:141-9.
3. Magalhães L, Valadares D, Oliveira JR, et al. Lung abscesses: review of 60 cases. Rev Port Pneumol
4. Madhani K, McGrath E, Guglani L. A 10-year retrospective review of pediatric lung abscesses from a single center. Ann Thorac Med 2016; 11:191.
5. Goldstein EJ, Citron DM, Warren Y, et al. In vitro activity of gemifloxacin (SB 265805) against anaerobes. Antimicrob Agents Chemother 1999; 43:2231.
6. Levison ME, Mangura CT, Lorber B, et al. Clindamycin compared with penicillin for the treatment of anaerobic lung abscess. Ann Intern Med 1983; 98:466.
7. Clinical conferences at the Johns Hopkins Hospital: lung abscess. Johns Hopkins Med J 1982; 150:141.
8. Hirshberg B, Sklair-Levi M, Nir-Paz R, et al. Factors predicting mortality of patients with lung abscess. Chest 1999; 115:746.
9. Bartlett JG. Lung abscess and necrotizing pneumonia. In: Infectious Diseases, Gorbach SL, Bartlett JG, Blacklow NR (Eds), W.B. Saunders, Philadelphia 1992.
10. Bartlett JG. Treatment of anaerobic pleuropulmonary infections. Ann Intern Med 1975; 83:376.
11. Pohlson EC, McNamara JJ, Char C, Kurata L. Lung abscess: a changing pattern of the disease. Am J Surg 1985; 150:97.

## DIAGNOSIS

# Lung abscess in immunocompromised

Teresa Dias Moreira, Lígia Rodrigues dos Santos

*Internal Medicine Department, Centro Hospitalar do Tâmega e Sousa, Penafiel, Portugal.*

Correspondencia: teresa_margaridam@hotmail.com

Cómo citar este artículo: Dias Moreira T, Rodrigues dos Santos L. Lung abscess in immunocompromised. Galicia Clin 2020; 81 (2): 57-58

Recibido: 22/12/2018; Aceptado: 23/01/2019 // http://doi.org/10.22546/56/1868

# Myopathy, what is the most likely diagnosis

Dermatomyositis is an idiopathic inflammatory myopathy with characteristic cutaneous manifestations and it may also provoke multiorganic failure[1,2].

We describe the clinical case of a 56-year-old woman with no relevant pathological medical record. She was admitted due to myalgia, polyarthralgia of the great joints, muscular weakness, asthenia and macular-papular erythema in areas of sun exposure, with 1 month of evolution and progressive aggravation. The objective examination revealed: poikiloderma (V grade in the thoracic-cervical region), erythematous papules in the metacarpophalangeal joints, pronounced muscular weakness in the upper limbs at the proximal level and pain at the palpation of the muscular masses in the upper and lower limbs. Analysis of lactate dehydrogenase (333 U/l), aldolase (10.3 IU/l), sedimentation rate in the first hour (52 mm/1st hour) and C reactive protein (190 mg /L), normal creatinine kinase. Hemogram, liver profile, renal function and immunological study without alterations. Serologies: HIV; Hepatitis B and C; screening for negative Borrelia. Normal electrocardiogram. Electromyography showed signs of sarcoplasmic membrane irritability. Cutaneous biopsy: compatible with Gottron's papule, normal muscle biopsy and specific Anti-SRP and anti-MI-2 antibodies. No evidence of digestive tract, mammary, skin, thyroid neoplasia; nor masses or adenomegalias identified. The patient initiated corticoid therapy with significant improvement.

The risk of neoplasia is 5-7 times higher in dermatomyositis than in the general population[1,2]. The prognosis is related to the severity of the myopathy and the presence of associated neoplasia, esophageal and/or cardiopulmonary failure[1,2]. In the case described above, no poor prognostic factors were identified and the patient presented good clinical evolution (and during the 4 years of current follow-up, and even after the corticoid suspension, there was no recurrence of disease and no neoplasia was identified).

Figure 1. Poikiloderma.

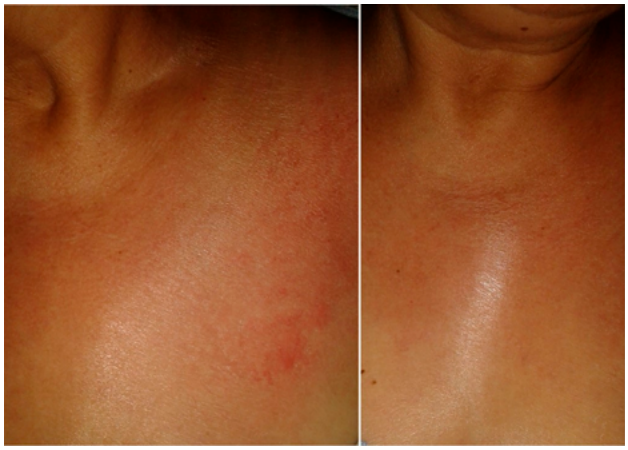
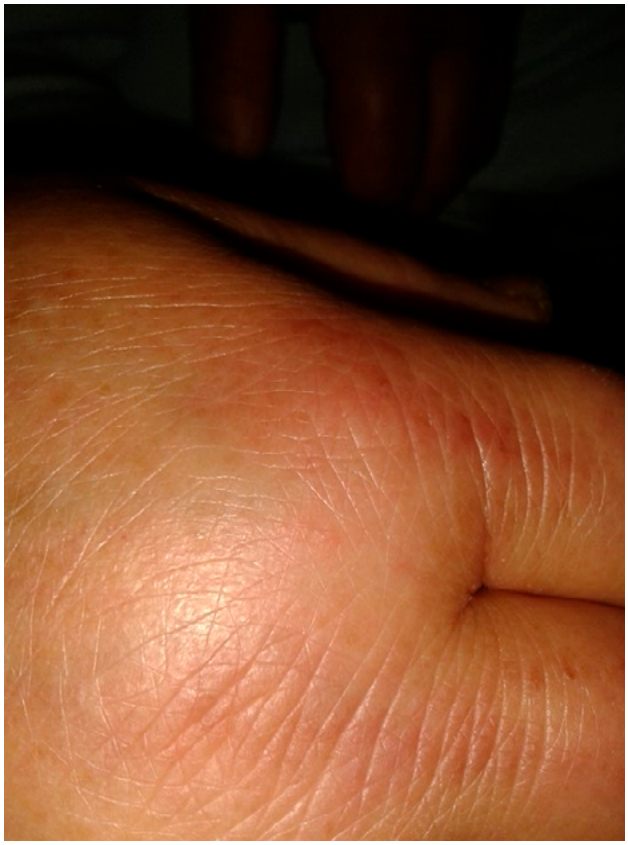


Figure 2. Gottron's papules.



## REFERENCES


1. Troyanov Y; Targoff IN; Tremblay JL; *et al.* Novel classification of idiopathic inflammatory myopathies based on overlap syndrome features and autoantibodies: analysis of 100 French Canadian patients. Medicine (Baltimore). 2005;84(4):231.
2. Castro AS; Barroso A; Parente B; Dermatomyositis as the first manifestation of a lung tumor. Rev Port Pneumol . 2013 Jul-Aug;19(4):179-83.


## DIAGNOSIS

Dermatomyositis


Albina Moreira, Miguel Silva

*Serviço de Medicina Interna, Unidade Local de Saúde Matosinhos, Hospital Pedro Hispano. Portugal*

Correspondencia: sof.hora@gmail.com



Cómo citar este artículo: Moreira A, Silva M
Myopathy, what is the most likely diagnosis. Galicia Clin 2020; 81 (2): 59

Recibido: 08/01/2019; Aceptado: 18/01/2019 // http://doi.org/10.22546/56/1874

# When adults suffer from the children´s diseases

A 32-year-old man patient was referred to the urgency department for cutaneous lesions with perioral and palmar involvement. Four days before, the patient has started with fever and odynophagia. The patient also revealed the existence of recent contact with a child diagnosed with Hand, Foot and Mouth disease.

On physical exam, he presented vesico-papular lesions with erythematous base in palms (Figure 1) and slight mucous discharge in cavum with few erythematous lesions (Figure 2). On reevaluation, two days later, the rash was found to have reached the plantar surface (Figure 3). Analytically only with slight elevation of inflammatory parameters. Conservative treatment was instituted, associated with transmission prevention measures. The patient has recovered fully within two weeks of the onset of symptoms.

Hand, Foot and Mouth disease is a self-limiting viral infection caused by Enterovirus, which Coxsackie A16 and Enterovirus 71 are the most common serotypes[1,2,3]. The disease usually occurs in children under 5 years of age and in immunocompromised adults[1,4]. It is rare in immunocompetent adults, infecting 11% of the exposed adults and only 1% of them exhibit some clinical manifestation[2].

The virus is transmitted by the oral/fecal-oral route and is more prevalent in developing countries[1]. The diagnosis is clinical, so laboratory confirmation is not usually required[4].

The major challenges include differential diagnosis (herpes simplex, herpangina, chickenpox, erythema multiforme, aphthous stomatitis) and potential complications, especially of Enterovirus 71 (myocarditis, encephalitis, aseptic meningitis and pulmonary edema)[1,3,4].

The treatment is symptomatic and the disease resolves in 7-10 days, usually without complications[1].

Figure 1. Vesico-papular lesions on palms.

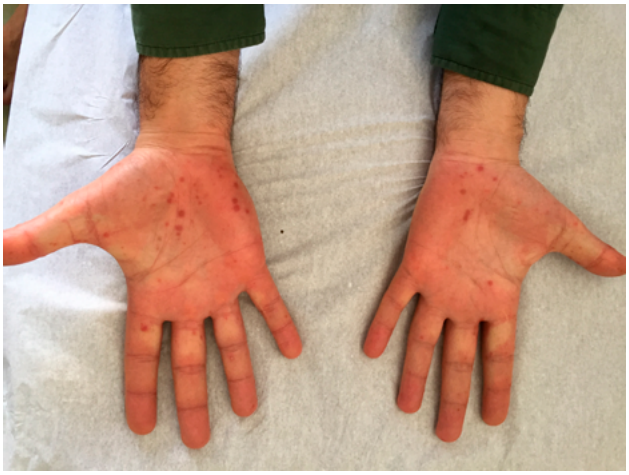


Figure 2. Oral erythematous and perioral vesicular lesions.

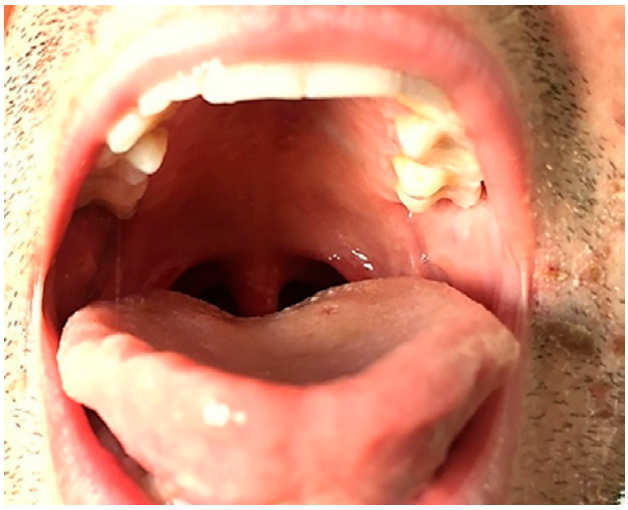
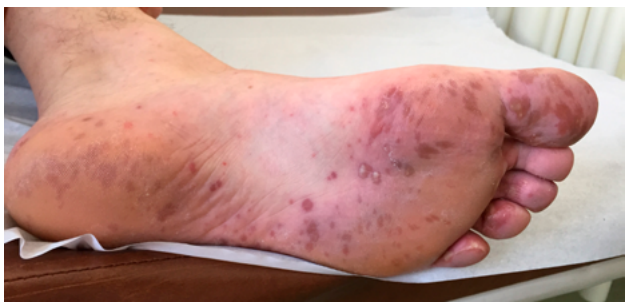


Figure 3. Vesico-papular lesions in plants.



## REFERENCES


1. Omaña-Cepeda C, Martínez-Valverde A, Sabater-Recolons M, Jané-Salas E, Marí-Roig A, López-López J. A literature review and case report of hand, foot and mouth disease in an immunocompetent adult. BMC Res Notes. 2016; 9:165.
2. Downing C, et al. Coxsackievirus A6 associated hand, foot and mouth disease in adults: Clinical presentation and review of the literature. J Clin Virol. 2014; 62:122.
3. Kaminska K, Martinetti G, Lucchini R, Kaya G, Mainetti C. Coxsakievirus A6 and Hand, Foot and Mouth Disease: Three Case Reports of Familial Child-to-Immunocompetent Adult Transmission and a Literature Review. Case Rep Dermatol. 2013; 5:203-209.
4. Murase C, Akiyama M. Hand, Foot and Mouth Disease in an Adult. N Engl J Med. 2018; 378:e20.


## DIAGNOSIS

### Hand, Foot and Mouth disease


Ângela Mota, João Tavares

*Centro Hospitalar Tondela-Viseu, E.P.E. Portugal*

Correspondencia: angelamota1987@gmail.com



Cómo citar este artículo: Mota Â, Tavares J
When adults suffer from the children´s diseases. Galicia Clin 2020; 81 (2): 60

Recibido: 20/01/2019; Aceptado: 30/01/2019 // http://doi.org/10.22546/56/1890

# Normas de publicación

Galicia Clínica es la revista oficial de la Sociedad Gallega de Medicina Interna (SOGAMI). Se publican 4 números al año, simultáneamente en papel y en www.galiciaclinica.info, incluyéndose en el segundo de ellos las comunicaciones enviadas a la correspondiente Reunión Ordinaria de la SOGAMI.

**Normas de publicación**

GALICIA CLÍNICA evaluará la publicación de trabajos médicos relacionados preferentemente con Medicina Interna y sus subespecialidades, y / o con problemas médicos prevalentes en la Comunidad Autónoma de Galicia. Las obras serán aceptadas para su consideración en español e inglés.

Para el envío de originales se ha habilitado un formulario en la pagina web www.galiciaclinica.info. El sistema confirmará la entrega y permitirá consultar el estado del manuscrito. No se aceptaran originales enviados por otros métodos.

El comité editorial, eventualmente con la ayuda de revisores externos, evaluará los trabajos enviados decidiendo si procede su publicación, si es necesario realizar correcciones o si se desestima la publicación. Una vez aceptado, se enviarán al autor las pruebas de imprenta para la corrección de posibles erratas.

Los trabajos reunirán los requisitos de uniformidad habituales en revistas biomédicas. Dichos requisitos se pueden consultar en "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, Updated April 2010", disponible en http://www.icmje.org. Se recomienda encarecidamente leer en especial la sección "Preparing a Manuscript for Submission to a Biomedical Journal" (http://www.icmje.org/recommendations/browse/manuscript-preparation/) y seguir fielmente sus indicaciones a la hora de redactar el trabajo a enviar.

Se recomienda el empleo de los programas más habituales de edición de texto (Ej., Word) tanto para el texto como para las tablas. Dado que la mayoría de las páginas se imprimen en blanco y negro, se aconseja evitar en tablas y figuras en la medida de lo posible el uso de colores o tramas que no tengan el adecuado contraste para su identificación. Las figuras o imágenes se enviaran en archivo aparte, como archivo de imagen (jpeg o similar) o como PDF con una resolución de 300 ppp. a tamaño de impresión definitivo.

Todos los trabajos deben remitirse con el título en el idioma nativo y en inglés y con al menos 3 keywords.

La bibliografía será referenciada según las normas del ICMJE https://www.nlm.nih.gov/bsd/uniform_requirements.html

**Correcciones:** Los autores, tras realizar las correcciones sugeridas por los revisores, deben enviar una carta de respuesta al revisor, es decir, deberán remitir el manuscrito corregido y acompañado de una carta respondiendo a los comentarios del revisor punto por punto.

La revista presenta las siguientes secciones:

**Editoriales:** Habitualmente encargados por la dirección de la revista. Su extensión máxima será de 8 paginas de 30 líneas y se admitirá una figura o una tabla y quince citas bibliográficas. El número máximo de firmantes será de dos.

**Revisiones**: Habitualmente encargadas por la dirección de la revista. La extensión máxima recomendada del texto es de 30 páginas de 30 líneas, a las que se podrán añadir 6 figuras y 6 tablas, y un máximo de 50 citas bibliográficas. El número máximo de firmantes será de tres.

**Originales**: Trabajos de investigación sobre cualquier aspecto medico. La estructura general de los trabajos será la tradicional: Título: en el idioma original y en inglés, Resumen, Palabras clave (que deben corresponder a las materias médicas encabezadas -MESH- del Index Medicus), Introducción, Material y métodos, Resultados, Discusión, Bibliografía. La extensión máxima recomendada del texto es de 20 páginas de 30 líneas, a las que se podrán añadir 5 figuras y 5 tablas, y un máximo de 30 citas bibliográficas. El número máximo de firmantes será de ocho. El resumen debe estar estructurado en los siguientes epígrafes: objetivos, material y métodos, resultados y conclusiones.

**Originales breves**: Trabajos de investigación que por sus características no precisan un mayor espacio. Estructura similar a la de los originales. Su extensión máxima será de 10 páginas de 30 líneas, 3 figuras, 3 tablas y 20 citas bibliográficas. El número máximo de firmantes será de seis.

**Notas clínicas**: Descripción de casos clínicos de excepcional interés. Constarán de una breve introducción, caso clínico, y discusión correspondiente. Su extensión máxima será de 6 páginas, 2 figuras y dos tablas y 15 citas bibliográficas. El número máximo de firmantes será de cuatro.

**Cartas al director**: Comentarios, opiniones u observaciones sobre los diversos trabajos publicados con anterioridad en la revista. La extensión máxima será de 4 paginas de 30 líneas y se admitirá una figura o una tabla y diez citas bibliográficas. El número máximo de firmantes será de dos.

**Preguntas clínicas**: En esta sección se tratará de responder de forma concreta y sucinta a preguntas clínicas concretas que, bien han motivado una controversia, o cuestionan actitudes arraigadas en la práctica diaria. La extensión máxima será de 6 páginas de 30 líneas, dos figuras y dos tablas y 15 citas bibliográficas. El número máximo de firmantes será de dos.

**Imágenes médicas**: Imágenes curiosas, insólitas o demostrativas. Se acompañarán con un texto breve, como máximo 1 pagina de 30 líneas, en el que se explique el caso clínico, con una breve discusión acerca de la importancia de la imagen. El número máximo de firmantes será de dos.

**Resúmenes de Tesis doctorales**: Elaborados por el autor, describirán el trabajo realizado; su extensión máxima será de 2 paginas de 30 líneas. Debe incluirse un apéndice con los datos correspondientes a Universidad, departamento, director de la tesis y fecha de presentación.

**Otros**: La dirección de la revista considerara para su publicación cualquier artículo relacionado con la medicina en cualquier aspecto, aunque no se incluya exactamente dentro de los supuestos anteriores. En este caso se recomienda antes de su envío contactar con la dirección para acordar las características del mismo.

Todas las opiniones o afirmaciones expresadas en los artículos corresponden a los autores de los mismos. Tanto el comité editorial como la SOGAMI declinan cualquier responsabilidad a este respecto.

Los trabajos publicados serán propiedad de GALICIA CLÍNICA, cediendo los autores todos los derechos a la misma. El envío de un artículo a través del sistema electrónico de la revista supone la aceptación de este punto . En el caso de que los trabajos enviados incluyan imágenes, figuras, tablas o textos sometidos a copyright, será responsabilidad de los autores la obtención de los permisos necesarios para su publicación.

**Consideraciones generales sobre la estructura de los artículos**

Los trabajos reunirán los requisitos de uniformidad habituales en revistas biomédicas. Dichos requisitos se pueden consultar en "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, Updated April 2010", disponible en http://www.icmje.org. Se recomienda encarecidamente leer en especial la sección "Preparing a Manuscript for Submission to a Biomedical Journal" (http://www.icmje.org/recommendations/browse/manuscript-preparation/) y seguir fielmente sus indicaciones a la hora de redactar el trabajo a enviar.

**Referencias**: Indique las referencias en el texto con un número en superíndice de forma correlativa según el orden de aparición. Las referencias irán numeradas de esta forma en la lista final después del manuscrito de acuerdo al formato recomendado por el ICJME. El listado completo puede encontrarse en este enlace: https://www.nlm.nih.gov/bsd/uniform_requirements.html, siendo las referencias más habituales las siguientes:

- Artículo de revista:

  Halpern SD, Ubel PA, Caplan AL. Solid-organ transplantation in HIV-infected patients. N Engl J Med. 2002;347:284-7.

  Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, et al. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935:40-6.

- Libro de autores individuales:

  Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4ª ed. St. Louis: Mosby; 2002.

En relación con los artículos de revista, se incluirán los seis primeros autores seguidos por "et al" y se utilizarán las abreviaturas de las revistas del catálogo de Pubmed/Medline (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals).

Los autores deben incluir las referencias a las fuentes primarias siempre que sea posible, evitando las fuentes secundarias o las referencias a trabajos no publicados, comunicaciones en congresos, etc. Es responsabilidad de los autores asegurar la exactitud de las referencias citadas.


SOCIEDADE GALEGA DE MEDICINA INTERNA
SOGAMI