Presentaba bradipsiquia, nistagmo horizontorrotatorio inagotable en dextro- y levoversión con componente vertical en la supraversión, hemianopsia homónima izquierda por confrontación y marcha levemente inestable.

Se realizó una tomografía computarizada (TC) craneal (fig. 1A) donde se objetivaron múltiples lesiones ocupantes de espacio con captación de contraste en ambos hemisferios cerebrales, con edema perilesional asociado y desplazamiento de línea media.

Una radiografía de tórax confirmó opacidad parahiliar izquierda con probables adenopatías asociadas (fig. 1B), compatible con lesión primaria tumoral con metástasis cerebrales secundarias, iniciándose dexametasona intravenosa.

Se realizó una TC de tórax, que objetivó lesión cavitada paramediastínica en el segmento apical del lóbulo superior izquierdo (LSI) de $7 \times 4 \times 5$ cm, con lesiones nodulares en LSI y língula, sospechosas de tuberculosis. Se realizó fibrobroncoscopia en la que no se objetivaron hallazgos macroscópicos, enviándose muestras para citología y microbiología.

Una resonancia magnética (RM) cerebral (fig. 1C) mostró lesiones intraparenquimatosas en ambos hemisferios cerebrales, con una disposición yuxtacortical y en ganglios basales, de morfología anular, con anillo periférico de hiposeñal FLAIR y edema circundante, además de lesiones en el pedúnculo mesencefálico derecho y hemisferio cerebeloso izquierdo.

Los estudios microbiológicos para microorganismos atípicos, VIH e IGRA Quantiferon TB® fueron negativos, confirmándose buen control glucémico con hemoglobina glucosilada del 5,2%. Los estudios inmunológicos básicos, cuantificación de inmunoglobulinas y complemento fueron normales.

En el cultivo del lavado broncoalveolar se aisló *Nocardia farcinica* sensible a imipenem, amikacina, levofloxacino, cotrimoxazol y linezolid, por lo que se inició tratamiento con imipenem y cotrimoxazol y se suspendió el tratamiento esteroideo. En las siguientes 24 h el paciente empeoró clínicamente, con bajo nivel de consciencia, ausencia de respuesta a estímulos verbales e hipotonía e hipoparesia en el miembro inferior izquierdo. Ante la posibilidad de incremento del edema cerebral, así como probable reacción de Jarisch-Herxheimer, se reinició pauta esteroidea, con evolución favorable posterior.

El paciente completó el ciclo de imipenem y cotrimoxazol durante 3 semanas, pudiendo reducirse paulatinamente los corticoides, manteniendo posteriormente tratamiento con cotrimoxazol hasta completar 2 años, con recuperación neurológica completa y resolución radiológica pulmonar en la TC con mínimas lesiones residuales en la RM craneal.

La infección del sistema nervioso central por *Nocardia* es rara, ocurriendo principalmente en pacientes inmunodeprimidos, aunque está descrita en pacientes inmunocompetentes, no encontrándose ningún factor de riesgo aparente para el desarrollo de la misma en nuestro caso.

La nocardiosis es una infección producida por una bacteria grampositiva aeróbica del grupo *Actinomyces*[1,2]. En la mayoría de casos se contrae por la inhalación a través del tracto respiratorio[2]. La afectación del sistema nervioso central es rara, siendo la presentación más frecuente una lesión única, con mayor mortalidad respecto de otras etiologías de abscesos cerebrales (30%).

La mayoría de casos descritos en la literatura corresponden a pacientes inmunosuprimidos[2], pero también ha sido descrita en pacientes inmunocompetentes[1,3] o con enfermedad pulmonar obstructiva crónica[4].

El tratamiento de las formas con afectación cerebral se debe mantener durante un tiempo prolongado. *N. farcinica* suele presentar resistencia a cotrimoxazol, por lo que el antibiograma es esencial a la hora de ajustar la antibioterapia. Se recomienda iniciar tratamiento con dos fármacos, reduciendo posteriormente a uno, que se deberá mantener un mínimo de 6-12 meses (al menos 12 meses en pacientes inmunodeprimidos). En casos graves se puede valorar añadir un tercer fármaco, normalmente linezolid[5].

Es importante considerar la nocardiosis, en concreto por *N. farcinica,* en pacientes con neumonía con evolución desfavorable con antibioterapia convencional[6], especialmente ante formas pseudotumorales o cavitadas, así como en el diagnóstico diferencial de lesiones focales cerebrales únicas o múltiples, independientemente del estado de inmunocompetencia.

Bibliografía

1. Vinciguerra L, Murr C, Böse J. *Nocardia farcinica:* Multiple brain abscesses in an immunocompetent patient. J Neuroinfect Dis. 2015;6:182.
2. Budzik J, Hosseini M, Mackinnon A, Taxy J. Disseminated *Nocardia farcinica*: Literature review and fatal outcome in an immunocompetent patient. Surg Infect. 2012;13:163–70.
3. Boamah H, Puranam P, Sandre RM. Disseminated *Nocardia farcinica* in an immunocompetent patient. IDCases. 2016;6:9–12.
4. Del Campo Matías F, Pérez Castrillón JL, González García JL, Pérez Pascual P. *Nocardia farcinica* pneumoniae in chronic obstructive pulmonary disease patient. An Med Interna. 2004;21:554–6.
5. Wilson JW. Nocardiosis: updates and clinical overview. Mayo Clin Proc. 2012;87:403–7.
6. De La Iglesia P, Viejo G, Gómez B, de Miguel D, del Valle A, Otero L. Fatal pulmonary *Nocardia farcinica* infection. J Clin Microbiol. 2002;40:1098–9.

Lucía Ordieres-Ortega*, María Dolores Pulfer y Juan Carlos Cano-Ballesteros

Servicio de Medicina Interna, Hospital General Universitario Gregorio Marañón, Madrid, España

* Autor para correspondencia.
Correo electrónico: lucia.oomere@gmail.com (L. Ordieres-Ortega).

https://doi.org/10.1016/j.eimc.2020.05.020

Clostridiodes difficile associated disease risk and proton pump inhibitors in critically ill children

Asociación del tratamiento con inhibidores de bombas de protones con la enfermedad por Clostridioides difficile *en niños en estado critico*

Proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H2RA) are frequently used in critically ill patients for prevention gastrointestinal hemorrhage.[1] However, they can lead to bacterial overgrowth with an increased risk of *Clostridioides difficile* associated disease (CDAD). Association between PPI and the risk of *C. difficile*-associated diarrhea has been supported by several studies.[2,3] There are few data about the incidence of CDAD in critically ill children[4] and the relationship with gastric acid suppression.

We conducted a retrospective, observational, study including critically ill child with CDAD or *C. difficile* carriage (CDC) during 6 years. CDAD was defined as the presence of abdominal distension, abdominal pain and/or liquid stools associated with signs of systemic inflammatory response syndrome and/or a rise in the acute phase reactants. CDC was defined as the isolation of the bacillus in

Table 1
Comparison between patients treated with Ranitidine and Omeprazole.

	Ranitidine	Omeprazole	*p*
Number of children	1655	356	
Positive culture	0.4%	4.5%	<0.001.
Clostridiodes difficile associated disease	0.2%	2.8%	<0.001
Asymptomatic colonization	0.4%	1.7%	<0.001.
Mortality	0%	0.5%	1.000

the absence of signs of infection. Toxigenic *C. difficile* was isolated by stool culture. Cytotoxicity assay was performed in human fibroblast (MRC-5) cell culture and the isolated strains of *C. difficile* (CD) were then retested for toxin production. The strains were typed by ribotyping assay.

2526 patients were admitted to the Pediatric Intensive Care Unit (70% of them were cardiac patients). 1655 took ranitidine, 356 PPI, 178 both drugs and 337 did not receive any treatment.

Twenty-two patients (1.1%) had a positive culture for CD. The mean age was 1.5 ± 1.9 years and 54.5% were males. 13 children were diagnosed as CDAD (incidence of infection of 0.6%) and 9 as asymptomatic carriages. All of them were cardiac patients and received broad-spectrum antibiotic therapy. The incidence of a positive culture was 4.5% with PPI group and 0.4% with ranitidine ($p < 0.001$). The incidence of both CDAD and asymptomatic colonization was significantly higher in patients taking PPI (2.8% and 1.7% respectively) than with H2RAs (0.2% and 0.4% respectively), $p < 0.001$. (Table 1). Only one child had recurrent CD and was on PPI therapy for a long time. Two patients died, both of which were in the PPI group.

Colonization of the feces occurs in 16–35% of hospitalized patients, increasing proportionally in relation to the length of hospital stay and, in particular, after antibiotic therapy. Patients can be asymptomatic or present with fulminant colitis. The most common presentation is diarrhea, fever, colicky abdominal pain, and leukocytosis in a patient treated with broad-spectrum antibiotics.

Although CDAD is relatively rare in children, mainly before 12–24 months of age, its incidence among hospitalized children is increasing,[5,6] especially in those with oncological, postsurgical or critical illness.[4]

Some studies show an association between CD and PPI,[7] but few have analyzed the association between CD and acid suppressant drugs in children[8,9] and in critically ill adult patients.[10] Our study is the first that analyzed the association between these two factors in critically ill children concluding that PPI may increase the incidence of CD more than H2RAs. It is important, to distinguish between true disease and asymptomatic carriages due to the high prevalence of fecal colonization in children.

Several factors may be involved in this association. PPI induce a more potent gastric acid suppression that may alter the intestinal microbiota and stimulate the growth of CD. It also induces a delay in gastric emptying which can predispose to bacterial overgrowth. Moreover, the presence of bile salts in gastric contents may contribute to spore germination in the stomach. Second, in PPI inhibit neutrophil bactericidal activity, chemotaxis and phagocytosis and may favor CD infection.

Our study is a retrospective study and there are other factors that can predispose to CD infection which have not been analyzed, such as immunological status or the concomitant use of other drugs that are associated with this infection.

In conclusion, the use of PPI in critically ill children may increase not only the asymptomatic carriages but also the risk of CDAD which can worsen the prognosis of these patients. For this reason, the use of gastric acid suppressant therapy, especially PPI, should be bounded to patients with a high risk of gastrointestinal bleeding. On the other hand, although CD carriage rates are high in the pediatric population, critically ill children are exposed to several factors that make it necessary to provide an adequate epidemiological surveillance.

Funding

Mother-Child Health and Development Network (Red SAMID) of Carlos III Health Institute, RETICS funded by the PN I+D+I 200-2011 (Spain), ISCIII-Sub-Directorate General for Research Assessment and Promotion and the European Regional Development Fund (ERDF), network ref. RD16/0026/0007.

Acknowledgements

To the Gregorio Marañón Pharmacy Service for the help for develop this study.

Bibliografía

1. Duffett M, Chan A, Closs J, McGloin R, McKelvie G, Pong S, et al. Stress ulcer prophylaxis in critically ill children: a multicenter observational study. Pediatr Crit Care Med. 2020;21:e107–13.
2. Anjewierden S, Han Z, Foster CB, Pant C, Deshpande A. Risk factors for *Clostridium difficile* infection in pediatric inpatients: a meta-analysis and systematic review. Infect Control Hosp Epidemiol. 2019;40:420–6.
3. Chang TH, Hsu WY, Yang TY, Lu CY, Hsueh PR, Chen JM, et al. Increased age and proton pump inhibitors are associated with severe *Clostridium difficile* infections in children. J Microbiol Immunol Infect. 2018;S1684–1182, http://dx.doi.org/10.1016/j.jmii.2018.09.002, 30183-X.
4. Bustinza A, Solana MJ, Padilla B, López-Herce J, Santiago MJ, Marin M. Nosocomial outbreak of *Clostridium difficile*-associated disease in a pediatric intensive care unit in Madrid. Infect Control Hosp Epidemiol. 2009;30:199–201.
5. Nylund CM, Goudie A, Garza JM, Fairbrother G, Cohen MB. *Clostridium difficile* infection in hospitalized children in the United States. Arch Pediatr Adolesc Med. 2011;165:451–7.
6. Zilberberg MD, Tillotson GS, McDonald C. *Clostridium difficile* infections among hospitalized children United States, 1997–2006. Emerg Infect Dis. 2010;16:604–9.
7. Pohl JF. *Clostridium difficile* infection and proton pump inhibitors. Curr Opin Pediatr. 2012;24:627–31.
8. Nylund CM, Eide M, Gorman GH. Association of *Clostridium difficile* infections with acid suppresion medications in children. J Pediatr. 2014;165:979–84.
9. Jimenez J, Drees M, Loveridge-Lenza B, Eppes S, del Rosario F. Exposure to gastric acid-suppression therapy is associated with health care and community-associated *Clostridium difficile* infection in children. J Pediatr Gastroenterol Nutr. 2015;61:208–11.
10. Buendgens L, Bruensing J, Matthes M, Dückers H, Luedde T, Trautwein C, et al. Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing *Clostridium difficile*-associated diarrhea. J Crit Care. 2014;29:11–5.

María José Solana [a,b,c], Amaya Bustinza [a], Jorge López [a,b,c], Jesús López-Herce [a,b,c,d,*]

[a] *Pediatric Intensive Care Department, University General Hospital Gregorio Marañón, Madrid, Spain*
[b] *Gregorio Marañón Health Research Institute, Madrid, Spain*
[c] *Mother-Child Health and Development Network (Red SAMID) of Carlos III Health Institute, RETICS funded by the PN I+D+I 200-2011 (Spain), ISCIII-Sub-Directorate General for Research Assessment and Promotion and the European Regional Development Fund (ERDF), network ref. RD16/0026/0007, Spain*
[d] *Public Health, Pediatric and Maternal Department, Medicine School, Complutense University of Madrid, Spain*

* Corresponding author.
E-mail address: pielvi@hotmail.com (J. López-Herce).

https://doi.org/10.1016/j.eimc.2020.06.004