ISSN : 2350-0743

www.ijramr.com

International Journal of Recent Advances in Multidisciplinary Research
Vol. 05, Issue 10, pp.4191-4193, October, 2018

CASE REPORT

CYCLIC NEUTROPENIA AS A CAUSE OF CHRONIC GASTROENTERITIS: CASE REPORT

***Alejandro Baeza Comas**

Naval University, Health Postgraduate School, Mexico

ARTICLE INFO

Article History:
Received 14th July, 2018
Received in revised form
17th August, 2018
Accepted 10th September, 2018
Published online 30th October, 2018

Keywords:
Immunodeficiency,
Chronic diarrhea,
Neutropenia.

ABSTRACT

Introduction: Primary immunodeficiencies are genetic disorders of the immune system, which result in a wide variety of clinical manifestations, most often manifest at an early age; and although a large part of these have an autosomal recessive hereditary form; it is not a necessary pattern in its natural history. One way to classify immunodeficiencies is in two categories: 1) the innate system (alterations in complement and phagocytic cells) and 2) adaptive system (including mechanisms of the humoral and cellular system) (Bonilla *et al.,* 2005). However, the most recent classification is that of 2015 proposed by the "International Union of Immunology Societies"; describing nine groups of diseases (Gutierrez Saborido *et al.,* 2016). The wide variety of clinical manifestations and the low prevalence of these make them a challenge for the clinician who needs a high suspicion, where manifestations such as diarrhea is usually variable and this may be of infectious or autoinflammatory cause (Hernandez Martinez *et al.,* 2016). **Objective:** To present the case of a patient with a primary immunodeficiency, a 2-year-old male patient who started the approach from a seemingly chronic diarrhea without evidence of another manifestacón. Observe in consecutive studies the periodic variation in the levels of Absolute neutrophils which were related to diarrhea. **Conclusion:** The approach of an immunodeficiency; Whether primary or secondary, it is always a challenge for the general practitioner and for the pediatrician; in this case, from an infectious recurrence and a finding in laboratory studies, the approach is initiated, however many of these clinical pictures are asymptomatic at the beginning or are only a finding at the time of the approach as in the case reviewed, however, was the chronicity of the diarrheic picture that did not suspect the relationship with immunodeficiency.

INTRODUCTION

The approach of a patient with immunocompromise is never easy, the lack of suspicion and experience in their treatment makes these diseases difficult to diagnose. Similarly talk about the immune system is to understand the mechanism of action of each cell of the same; so that understanding that an immunodeficiency can not only be secondary to a decrease in the number of these cells, it can also be secondary to an alteration in the functioning of the same. Often these pictures are asymptomatic however in most cases the suspicion begins when the patient presents infectious episodes of recurrence or when seeing a poor response to antibiotic management. In the following case, the approach starts from a picture of acute gastroenteritis; however, findings such as neutropenia in a fortuitous way make it decided to start the diagnostic approach of a primary immunodeficiency and subsequently its treatment.

CASE REPORT

A 2-year-old male patient living in Mexico City with no relevant history, starting the condition at 4 months with a gastroenteritis episode of 12 days of evolution without fever, managed only with symptomatic treatment, taking control studies where there were 5600 leukocytes with moderate neutropenia of 900 cel./abs. , presenting a second event of gastroenteritis two months later, related to the type of feeding, one month later requesting new laboratory studies without observing cytopenias, with studies in fecal stools with the presence of reducing sugars; therefore it is suspected of lactose intolerance, being treated with a lactose-exclusive diet, requesting in the follow-up consultations immunological profile where a total IgE lower than 5mg / dL and specific IgE for wheat, soy, egg is observed , negative cocoa, without ruling out allergic process not mediated by IgE, so it is decided to continue with a hydrolyzed formula with improvement. Go back to your appointment of control with Gastroenterology service at 2 years of age with improvement in the evacuations observing in control studies a moderate neutropenia. A month later, she returned to the follow-up clinic, presenting a new gastroenteritis event of two days' evolution, characterized by liquid evacuations without mucus or blood associated with abdominal distention, colic meteorism denying the presence of fever, referring the mother presenting in the last 2 months. 3 similar events treated in a symptomatic way. On June 20 of the current year, the patient presented again with gastroenteritis and dehydration, accompanied by fever, so it was decided to enter the emergency department observing severe neutropenia again. Due to repeated clinical and biochemical findings, a relationship between gastroenteritis and documented neutropenia was found, and primary immunodeficiency was suspected. An initial approach was initiated, initially ruling out autoimmune processes or secondary immunodeficiency.

Corresponding author:* **Alejandro Baeza Comas,
Naval University, Health Postgraduate School, Mexico.

Table 1. Hematologicalbiometrics

Date	Total leukocytes	Absolute neutrophils	Lymphocytes	Platelets	Hemoglobin
24/12/16	5600	900	3900	398 00	12.1
22/01/17	5400	2600	2200	436 000	14
11/01/17	5800	800	4300	451 000	12.6
12/04/18	3600	500	2600	364 000	11.8
18/08/18	5600	1000	3700	355 000	12
23/04/18	6000	2600	2600	340 000	12.4
30/04/18	5800	2500	2500	458 000	11.9
07/05/18	5400	1200	3200	435 000	11.9
14/05/18	4800	1400	2700	466 000	11.7
21/05/18	5200	900	3500	377 000	12.2
28/05/18	4000	800	2600	336 000	12.4
04/06/18	5100	500	3900	356 000	12.8
11/06/18	4900	800	3400	381 000	13.1
16/06/18	4700	3800	600	318 000	13.6
18/06/18	3900	2400	1100	299 000	12.7
20/06/18	2400	500	1500	235 000	12.8
22/06/18	9900	5300	3600	270 000	13.3
25/06/18	4400	500	3300	379 000	13.3
02/07/18	5200	1300	3200	429 000	12.6

Given the possible diagnosis of cyclic neutropenia, which is why it is performed jointly with the Hematology service, requesting repeat biometrics weekly hematic

DISCUSSION

The concept of primary immunodeficiency (PID) encompasses a heterogeneous group of diseases that have in common alterations in the number or function of the cells of the immune system; encompassing the innate or adaptive immune system (Bonilla *et al.,* 2005; Mahlaoui *et al.,* 2007). More than 300 pathologies are estimated in this group of diseases. And it was from 1952 that Ogden Bruton was the first to publish a case of agammaglobulinemia linked to the X chromosome, later identifying alterations in the BTK gene (Gutierrez Saborido *et al.,* 2016; Coría Ramirez *et al.*) where studies on this type of diseases began to be carried out. Until today where in Europe there are more than 20,000 patients with this group of diseases (Mahlaoui *et al.,* 2017) having a prevalence in developed countries of 1 between 200,000 live births and being born each year between 150 to 200 children with an IDP . In Mexico, from 2000 to 2005, a birth rate of 22.3 per 1, 000 inhabitants was reported, however the biases of prevalence and lack of diagnostic suspicion make them underreporting in this type of diseases. The beginning of the study protocol of a patient with immunodeficiency starts from the presence of certain characteristics of infectious diseases; among those that call the most attention: the recurrence of symptoms, severity and chronicity, as well as the etiological agents involved (Arizcorreta Yarza *et al.,* 2016). As we mentioned, according to the classification of immunodeficiencies are those related to defects in phagocytosis; where a defect in the number or function of the cells involved is of importance for their diagnosis. Among these cells are neutrophils; which also called granulocytes or polymorphonuclear leukocytes, one of its functions is the elimination of bacteria and fungi through proteases, antimicrobial peptides and reactive oxygen metabolites, also participating in the inflammatory response through the production of eicosanoids and other molecules that intervene in cell signaling (Córdova Calderón *et al.,* 2010). Neutropenia is characterized by a decrease in the absolute number of neutrophils, and classified as mild when there is between 1000 and 1500 cells / mm, moderate between 500 and 1000 cells / mm and severe with <500 absolute neutrophils (Boxer, 2012; Farrugia and Dufor, 2015).

In relation to the clinical case presented, a congenital and hereditary cause of neutropenia is thought, however, it should not be forgotten that the first cause of these symptoms is secondary to active infectious processes. Neutropenia of congenital or hereditary origin commonly present during the first year of life and are often related to alterations in the oral mucosa, cellulitis and recurrent infections, being of vital importance the association between oral manifestations and congenital alterations (Dale, 2016). Among the congenital causes of neutropenia in childhood, there are several syndromes; where physical examination and laboratory findings help suspect a genetic alteration. In this case, cyclic neutropenia is suspected as a trigger for the patient's diarrhea; which was first described in 1910 by Leale, is a picture of autosomal dominant character, result of a mutation of the gene ELA 2 position 13.3 of the short arm of chromosome 19 (Padayachi and Haffejee, 2016), and this has the characteristic of having a character oscillating in the neutrophil count, usually at 21-day intervals (Oliva Olvera *et al.,* 2015). In a first phase the neutrophil count is extremely low for 3-5 days so that they subsequently increase to more than 2000 cel./mm (Dale *et al.,* 2017), when Patients are found in the nadir of neutropenia. Patients present alterations in the oral mucosa, as well as develop cellulitis and abscesses. The treatment of these patients is by granulocyte colony stimulating factor (G-CSF), under normal conditions the G-CSF is produced by the bone marrow, and this increases production against a bacterial infection resulting in an increase in the maturation and production of neutrophils in the bone marrow (Oliva Olvera *et al.,* 2015). Together, the approach includes ruling out other causes of neutropenia with conditions in myelopoiesis and extrinsic factors such as malnutrition, medication intake and other types of autoimmune neutropenia; such as chronic congenital neutropenia, chronic idiopathic neutropenia, Schawachman-Diamond syndrome (Padayachi and Haffejee, 2016). However, what led us to the guided diagnostic protocol was through the pattern of neutropenia as seen in Table 1, however always the approach of an apparent chronic diarrhea was ruling out as a first option infectious causes, the cases reported in the literature are similar to the previously presented, where the manifestations at the mucous level are the most related to this type of condition as well as the onset of symptoms in the first year of life. If we observe carefully the presented table, the variant and oscillating pattern of neutrophils; being this the only altered line, which goes with a

recovery between three to five days and presenting new neutropenia at approximately 21 days. In the cases found in the literature, patients have an adequate response to treatment with G-CSF, which is applied every 21 days; According to the pattern of neutropenia, however, we always have to take into account that neutrophil levels influence the immune response and these patients are always susceptible to infectious symptoms and etiological agents considered as aggressive.

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