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REVIEW ARTICLE

Multisystem inflammatory syndrome in children with COVID-19: a view from the pathophysiology

Síndrome inflamatorio multisistémico en niños con COVID-19: una mirada desde la fisiopatología

Amanda Avello Rodríguez [1*], https://orcid.org/0000-0002-3336-6450

Déborah Luque Laffita [1], https://orcid.org/0000-0001-8590-5674

Daniela Dueñas Bermúdez [1], https://orcid.org/0000-0002-4497-5112

Mabel Anay Rodríguez Monteagudo [1], https://orcid.org/0000-0001-8681-6083

[1] University of Medical Sciences of Cienfuegos. "Raúl Dorticós Torrado" Faculty of Medical Sciences, Cienfuegos, Cuba.

*** Corresponding author:** amandaavello01@gmail.com

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ABSTRACT

Introduction: multisystem inflammatory syndrome is an entity associated with SARS-CoV-2 infection in infants, which, although rare, is generally associated with severe manifestations.

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Objective: to describe the fundamental aspects of multisystem inflammatory syndrome in children with COVID-19 from the view of its pathophysiological and immunological bases.

Methodological design: a total of 31 bibliographic sources were selected, most of them original articles and reviews, with more than 75 % updating, from the main medical bibliographic bases on the web.

Development: multisystem inflammatory syndrome in children with COVID-19 represents an entity independent of severe acute COVID-19 infection and Kawasaki disease. It is a post-infectious hyperinflammatory phenomenon, where superantigen-type activation could be important in its pathogenesis, leading to the characteristic cytokine storm, endothelial dysfunction, ischemic and thrombotic phenomena, shock and multi-organ dysfunction. They tend to be patients without comorbidities and present fever, skin lesions, conjunctival injection, gastrointestinal symptoms and cardiovascular dysfunction.

Conclusions: the tendency towards severity in these previously healthy patients, who develop a poorly organized immune response, indicates the need to prevent the disease in all children and adolescents, and to give them correct follow-up after 4-6 weeks from the start of the infection.

Keywords: Child; COVID-19; SARS-CoV-2; Systemic Inflammatory Response Syndrome

RESUMEN

Introducción: el síndrome inflamatorio multisistémico es una entidad asociada a la infección por SARS-CoV-2 en infantes, que, aunque poco frecuente, se asocia por lo general a manifestaciones graves.

Objetivo: describir los aspectos fundamentales del síndrome inflamatorio multisistémico en niños con COVID-19 desde el punto de vista de sus bases fisiopatológicas e inmunológicas.

Diseño Metodológico: se seleccionaron un total de 31 fuentes bibliográficas, la mayoría artículos originales y de revisión, con más de un 75 % de actualización en las principales bases bibliográficas médicas en la web.

Desarrollo: el síndrome inflamatorio multisistémico en niños con COVID-19 constituye una entidad independiente de la infección aguda severa por COVID-19 y de la enfermedad de Kawasaki. Se trata de un fenómeno

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hiperinflamatorio post-infeccioso, donde una activación de tipo superantígeno pudiera ser importante en su patogenia, conllevando a la característica tormenta de citocinas, disfunción endotelial, fenómenos isquémicos y trombóticos, choque y disfunción multiorgánica. Suelen ser pacientes sin comorbilidades y presentar fiebre, lesiones en piel, inyección conjuntival, síntomas gastrointestinales y disfunción cardiovascular.

Conclusiones: la tendencia a la gravedad en estos pacientes previamente sanos, que desarrollan una respuesta inmune mal organizada, indica la necesidad de prevenir la enfermedad en todos los niños y adolescentes y darles un correcto seguimiento luego de las 4-6 semanas del inicio de la infección.

Palabras clave: COVID-19; Niño; SARS-CoV-2; Síndrome de Respuesta Inflamatoria Sistémica

INTRODUCTION

The inflammatory process that the body triggers in response to different infectious or non-infectious aggressions (such as burns, trauma, pancreatitis, among other events) and that can lead to multi-organ dysfunction is called systemic inflammatory response syndrome (SIRS). It was defined by the Consensus Conference of the American College of Chest Physicians and the Society of Critical Care Medicine, in 1992, as part of the classification of the stages of sepsis. In 2005, the first definitions of pediatric sepsis were published, which were an adaptation of the original criteria for adults. (1)

Subsequently, in 2016, the Third International Consensus for Sepsis and Septic Shock was published, in which SIRS disappeared from the definitions and was disassociated from sepsis. However, in practice, a large part of health institutions continue to use it. (2)

The systemic inflammatory response syndrome secondary to proven or suspected infection constitutes sepsis. The Greek word sepsis comes from the time of Homer, where it was used to mean "decomposition" or "putrefaction." Despite its longevity, this devastating disease has been complex to understand and characterize. After the appearance of antibiotics, it was observed that patients continued to die septic (even without circulating pathogens), which led to the clarification that the host also played a fundamental role in the etiopathogenesis. (2) In recent years the incidence of this entity has progressively decreased with the use of vaccines and other preventive measures, mainly in developed countries.

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The COVID-19 pandemic, associated with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first observed in Wuhan, China, in December 2019, [3] evolved into an accelerated pace. The first reports indicate that only 2 to 6 % of children and adolescents presented severe forms of the disease. However, starting in mid-April 2020, groups of pediatric patients infected with SARS-CoV-2, previously asymptomatic, began to be described, who manifested a systemic hyperinflammatory state with involvement of multiple organs and prominent cardiogenic shock with myocardial dysfunction, generally requiring intensive life support. This entity was recognized as multisystem inflammatory syndrome in children (SIMS-N) or pediatric multisystem inflammatory syndrome. [4-8]

Although a global incidence of SIMS-N has been estimated at only 0,016 % to 0,31 % of children infected with SARS-CoV-2. [9] The appearance of this very serious condition in minors, with a mortality of up to 4 %, [4] has relevant implications for health services and requires the preparation of general practitioners and pediatric specialists in this regard. By July 2020, only two Cuban children had presented this condition and, subsequently, the incidence continued to be low. [10]

It is of great interest to understand the complex pathophysiology of the disease to achieve advances in prevention, early identification and treatment strategies. Therefore, the objective of this article is to describe the fundamental aspects of the multisystem inflammatory syndrome in children with COVID-19 from the point of view of its pathophysiological and immunological bases.

MATERIALS AND METHODS

A bibliographic search was carried out using as descriptors: COVID-19, SARS-CoV-2, Child and Systemic Inflammatory Response Syndrome in the Scielo and PubMed databases, as well as the Google Scholar search engine, to locate the articles. Scientific literature in English and Spanish was taken into account, with more than 75 % corresponding to the last 3 years. To select the articles, a critical reading of them was carried out, analyzing the variability, reliability and validity of the results, finally selecting 31 sources, including original articles, review articles, two books and the Organization's website World Health.

DEVELOPMENT

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Systemic inflammatory response syndrome is determined in pediatric age by two or more of the following elements: rectal temperature greater than 37,9 °C or less than 36 °C, tachycardia with heart rate greater than 2 standard deviations for age or bradycardia, especially in newborns and small infants, tachypnea and leukocytosis. (11)

It constitutes an inflammatory cascade that begins when the host's defense system does not adequately recognize the triggering incident, does not eliminate it, or both. The inflammatory cascade is initiated by toxins or superantigens through binding to macrophages or activation of lymphocytes. The vascular endothelium becomes, at the same time, a target of tissue injury and a source of mediators that can cause additional injuries. Several diseases such as staphylococcal toxic shock and Kawasaki disease (KD) can cause it. (12)

At the beginning of the pandemic, SIMS-N was diagnosed as a "COVID-19-associated Kawasaki disease." Indeed, almost 40-50 % of SIMS-N cases meet the definition of Kawasaki disease or atypical Kawasaki disease. (8) However, the condition rapidly evolved into a clinically well-recognized syndrome, distinct from Kawasaki disease, which international organizations identified as multisystem inflammatory syndrome in children (SIMS-N). (4,5) In Europe, this new entity was named pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2. (4)

Definitions of this disease vary slightly between different medical organizations and faculties. Basically, it is characterized by a history of COVID-19 4-6 weeks before the appearance of symptoms, that is, fever, mucosal lesions, skin lesions such as erythema multiforme, injectable conjunctivitis, diarrhea, vomiting, abdominal pain, neurological disorders, increased content of inflammatory markers in serum, absence of infections and dysfunctions of organs, especially the cardiovascular system. (10)

The preliminary definition of the then-called multisystem inflammatory syndrome in children and adolescents temporally associated with COVID-19, provided by the WHO, was as follows: (13)

1) **Children and adolescents 0-19 years of age:** with fever of 3 or more days of evolution.

2) **At least 2 of the following clinical criteria:**

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- Rash, bilateral non-purulent conjunctivitis, signs of mucocutaneous inflammation (in the mouth, hands or feet).
- Hypotension or shock.
- Myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including echocardiographic findings or elevation of troponin or BNP).
- Evidence of coagulopathy (elevated prothrombin time or partial thromboplastin time, elevated D-dimer).
- Acute gastrointestinal symptoms (diarrhea, vomiting or abdominal pain).

3) **Elevated inflammatory markers:** (such as accelerated erythrocyte sedimentation rate, C-reactive protein or elevated procalcitonin).

4) **Evidence of SARS-CoV-2 infection:** (positive RT-PCR, positive serology or antigen test for SARS-CoV-2) or contact with individuals affected by COVID-19.

5) **No other plausible microbial cause of inflammation:** including bacterial sepsis and staphylococcal/streptococcal toxic shock syndrome.

Epidemiology and differences with other entities

Since the first reports, it was found that the majority of pediatric patients with multisystem inflammatory syndrome tested positive for the serological test for SARS-CoV-2 (87 %) and, less commonly, positive for the RT-PCR (32 %). [14] On the other hand, most reports of this syndrome among children followed the peak incidence of Covid-19 in April 2020 by about 4 to 6 weeks. All of this suggested that it constitutes a post-infectious inflammatory response, instead of being related to early infection. [15-17]

Indeed, the entity appears to have different clinical and epidemiological characteristics when compared to severe acute COVID-19 infection in children. In a large North American study, severe acute infection was found to be associated with the presence of comorbidities, respiratory symptoms, and respiratory dysfunction. In contrast, of the children diagnosed with SIMS-N, 90 % reported gastrointestinal symptoms and 66,7 % cardiovascular involvement, requiring inotropic support, while a smaller number reported lower respiratory tract symptoms and comorbidities. [18]

On the other hand, in a meta-analysis [3] a mean age of 8,6 years was found, with a range of 3 months to 20 years. This contrasts significantly with

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Kawasaki disease, in which the incidence is highest in children between 6 months and 5-6 years of age, and a much lower peak age is observed. A hypothesis to explain this difference could lie in the nature and etiology of KD, since, around the age of 9, children have already been exposed and developed immunity to a set of viruses that could enhance said disease; however, since SARS-CoV-2 is a new virus, it hits all ages equally. [19]

The male gender is slightly associated with SIMS-N. The meta-analysis by Radia et al., [16] showed a 56 % male prevalence, while the study by Kornitzer et al., [9] showed 59,67 %. A fatality rate twice as high as in females was also found, which is consistent with what was observed in adults and has been proposed that could be due to a greater expression of ACE2 in men and immunological consequences linked to the X chromosome. [17,20]

The incidence rates of SIMS-N vary by race, with 25-62 % of African-descendant patients, 30-40 % of Hispanics, 15-25 % of whites, and up to 28 % of Asians having been reported, [21] unlike the EK, which is seen more frequently among Asians and people of Asian descent.

Comorbidities have been reported in only 20-30 % of SIMS-N cases, with obesity and asthma being more common. [18,21] Even so, there is no evidence that these constitute risk factors. [22]

Etiopathogenesis

Although the pathogenesis of SIMS-N is not exactly known, different mechanisms are proposed, fundamentally extrapolated from severe forms of COVID-19 infection in adults, as well as other conditions with a similar course in children.

SARS-CoV-2 initiates its pathogenic mechanism by binding by its S protein (spike) to the surface of the angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed in significant quantities in epithelial cells of the nasal cavity, alveolar cells of the lung (mainly type II pneumocytes), cardiomyocytes and the vascular endothelium, among other sites. This provides a favorable route for the involvement of various organs. [7,15]

However, the post-infectious nature of SIMS-N suggests that a poorly organized immune response, exacerbated by IgG antibodies, plays a more important role in its pathogenesis than direct cellular damage from the viral infection. [14] The massive release of inflammatory mediators with exaggerated activation of the immune system resembles the aforementioned

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systemic inflammatory response syndrome, and the well-known "cytokine storm," which is, effectively, a delayed hyperinflammatory phenomenon.

Due to the differences in the frequency of appearance in different ethnic populations and in the course of the disease in different groups of patients, it is believed that some genetic factor could influence the etiology of SIMS-N, [19] although these risk factors They are poorly understood. Broadly speaking, the genetic associations with COVID-19 found include genes involved in antiviral functions, virus entry into the cell, regulation of immunity, leukocyte chemotaxis and lymphocyte cytolytic function. Although scarce, some research in children with SIMS-N has identified mutations in genes related to the perforin cytolytic pathway, which would cause a disruption of lymphocyte-mediated cytolytic function and could result in an increase in the release of proinflammatory cytokines by target cells. [23]

One of the hypotheses proposed for the massive release of cytokines is that it is caused by the ability of the coronavirus to block the responses of type I and III interferons in patients who had a high initial viral load or who were unable to control viral replication and this results in subsequent excessive release. [24] Furthermore, infection of dendritic cells and macrophages by SARS-CoV-2 induces the production of low levels of antiviral cytokines and increases the production of proinflammatory cytokines (tumor necrosis factor or TNF, IL-1, IL-6, and interferon-γ). [7]

It is also proposed that, although adaptive immunity is crucial to eliminate the virus, direct infection of T cells by SARS-CoV-2 could contribute to lymphopenia and worsen the antiviral response. Likewise, non-receptor binding domains of the S protein that target neutralizing antibodies could cause an antibody-mediated potentiation effect, which accelerates viral replication and results in cell destruction. [25] Virus-antibody complexes, after interaction with Fc receptors, as well as subsequent complement activation, could also mediate the dysregulation of the response and increase the release of cytokines. [17]

However, with respect to the pathogenesis of SIMS-N, the hypothesis that states that the S protein of SARS-CoV-2 acts as a superantigen has taken on more importance, causing the activation and nonspecific proliferation of T lymphocytes on a large scale, and resulting in in a massive production of proinflammatory cytokines by these and by antigen-presenting cells. The similarity of the clinical and diagnostic characteristics of this entity with toxic shock syndrome, including gastrointestinal and neurological symptoms, cardiac involvement, lymphopenia, elevated levels of C-reactive protein,

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ferritin, and D-dimer, support this hypothesis. On the other hand, its post-infectious nature and prevalence in children between 5 and 15 years old makes it demographically similar to rheumatic fever, caused by the superantigen-producing bacteria Streptococcus pyogenes. [19,26,27]

A study [26] based on computational models demonstrated that the S glycoprotein of SARS-CoV-2 exhibits a high affinity motif for binding to the TCR (T cell receptor) and that it can form a ternary complex with the HLA (human leukocyte antigen) class II. This motif is not found in SARS-CoV; instead, it is similar to that of staphylococcal enterotoxin B (SEB). Therefore, it is believed that it could act as a superantigen.

Another more recent study [27] characterized the TCR repertoire of SIMS-N patients and found a profound expansion of the TCRβ variable 11-2 gene (TRBV11-2), with up to 24 % of T cell clones being occupied by the phenotype of this variant, with identical TRBV genes but completely heterogeneous CDR3 (complementarity determining region 3), which was correlated with the severity and cytokine levels in SIMS-N. Overall, these data suggest that a CDR3-independent interaction between the S protein (via the previously reported motif) of SARS-CoV-2 and TCRβ leads to the expansion and possibly activation of hyperinflammatory T cells. , with a pattern similar to a superantigen stimulation, which supports this hypothesis.

Furthermore, these patients shared certain alleles of HLA class I, suggesting a strong association with these molecules, [27] which contrasts with the previous study and what was observed in typical bacterial superantigens, which act through interactions with HLA II. However, the authors of the study argue that the idea that HLA I can act as ligands for superantigens such as SEB has previously been reported.

A role for autoantibodies in the pathophysiology of SIMS-N has also been suggested. These could originate from cross-reactivity between SARS-CoV-2 and its own antigens, provoke the formation of immune complexes and unleash an attack against host tissues directed by immune cells. This hypothesis is supported by the effectiveness of intravenous immunoglobulins (IVIG) in the treatment of SIMS-N, since they are commonly used to activate inhibitory Fc receptors and prevent membrane attack complexes by complement factors and, therefore, mitigate autoantibody-mediated pathology. [24,28]

Studies have been carried out to locate autoreactive antibodies in the plasma or serum of patients with SIMS-N. Autoantibodies bound to proteins involved

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in signaling in immune cells and structural proteins in the heart and blood vessels were found, suggesting possible targets of autoimmune attack, as well as other characteristics of classic autoimmune diseases, suggesting that SIMS-N could have some elements of its pathophysiology in common with these. (24,28)

As a final result, proinflammatory cytokines activate coagulation via the tissue factor pathway, stimulate the complement cascade and the release of inflammatory kinins. Excessive production of IL-6, IL-10 and TNF is inversely correlated with the total number of lymphocytes; Specifically, IL-6 reduces the cytolytic function of NK (natural killer) cells. On the other hand, polymorphonuclear leukocytes secrete ferritin, which has an immunosuppressive action and inhibits the differentiation of myeloid cells and T and B lymphocytes, worsening the host's acquired immune response. (7,13)

The overproduction of all these inflammatory mediators can lead to an increased risk of hyperpermeability and vascular leak, decreased peripheral vascular resistance, high fever, myocardial depression/dysfunction/damage, exudative enteropathy, intestinal ischemia associated with procoagulant and vasculitis phenomena, levels reduced C3 and C4, hypoalbuminemia and hyponatremia, severe multiorgan damage and shock. (3,17)

As explained, there are several possible pathways for the triggering of cytokine storm, inflammation and tissue damage in SIMS-N. The general findings made so far do not allow us to lean towards a single hypothesis or determine how the coupling of several mechanisms would occur. Therefore, deeper computational and statistical analyzes are needed in this regard.

Clinical findings and their anatomopathological bases

In general, it has been found that SIMS-N commonly follows one of these three clinical patterns: (1) persistent fever with elevated inflammatory markers, but without notable organ dysfunction; (2) acute myocarditis, such as presentation with shock and myocardial dysfunction and consequent renal or respiratory failure; (3) Kawasaki-like disease with coronary aneurysms, some of which progress to shock, requiring vasopressors. However, manifestations overlap and patterns of presentation are not mutually exclusive. (4)

The study by Kornitzer et al., (9) revealed symptoms with a high predictive value for the evolution of the infection towards SIMS-N. Symptoms such as rash, myalgia, weakness and fever were strongly associated, as were

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gastrointestinal symptoms, such as abdominal pain, nausea/vomiting and diarrhea. It has been proposed that gastrointestinal symptoms can be explained by mesenteric lymphadenopathy, secondary to lymphoid hyperplasia, and by intestinal parietal ischemia secondary to vasculitis, [29] as well as inflammatory processes frequently found on ultrasound.

Reports of dermatological manifestations generally use different and non-specific terms, making it difficult to compare them. In a large study of children with SIMS-N, non-specific rash, bilateral conjunctivitis, oral mucosal changes, and peripheral extremity changes were mainly identified. [18]

Neurocognitive and respiratory symptoms and congestive heart failure also occur with variable frequencies at the beginning. As already mentioned, respiratory symptoms associated with lung damage are not common, which contrasts with the pattern followed by children with acute COVID-19 infection, with prominent respiratory disease. The most frequent radiological findings in chest examinations are cardiomegaly, pleural effusion and passive atelectasis, and ground glass opacities are more suggestive of corresponding to pulmonary edema. [22]

When patients with SIMS-N presenting with myocarditis were studied by MRI, signs of diffuse myocardial edema and hyperemia were found, without evidence of fibrotic replacement or focal necrosis, contrary to what was observed in adults with COVID-19-related myocarditis. [30] This suggests that the histopathology of this cardiac damage occurs, as in KD, as a consequence of the inflammatory infiltration of macrophages and neutrophils in the myocardial interstitium, secondary to cytokine storm and not due to degeneration or necrosis of cardiomyocytes due to viral infiltration and the immune response to this damage. [6,27] On the other hand, the majority of severe cardiovascular conditions in SIMS-N are resolved within 30 days, responding better to treatment in contrast to other childhood myocarditis. [18]

In conjunction with resolution of systemic inflammation, BNP levels are usually restored within 2 days, but troponin may remain elevated for a longer period until repair of damaged cells occurs. Additionally, elevated troponin is associated with higher mortality rates. [31] Analyzing the results of the electrocardiogram, some authors have identified a prolonged QT interval, occasional ventricular arrhythmias and diffuse elevation of the ST segment, as a result of myocardial inflammation and indicating greater severity. [7]

Echocardiography also has an important role, since many patients present with a decreased left ventricular ejection fraction, coronary artery aneurysm

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(more frequently detected when computed tomography is used), [22] coronary artery dilation, abnormally echogenic coronary arteries, pericardial effusion and mitral regurgitation. [4] Pro-inflammatory cytokines contribute, in part, to the destruction of vascular matrix proteins, as well as the structural integrity of the vessels, which can culminate in coronary dilation and aneurysm formation, [17] with induced vasculitis considered less likely by an immune complex.

Inflammatory markers in peripheral blood in SIMS-N tend to normalize around 4-5 days after admission. [4] Lymphopenia and thrombocytopenia are very common, [21] suggesting an exhaustion of lymphocytes, especially cytotoxic ones, due to their targeting of target organs and a microthrombotic process, respectively. It is noteworthy that lymphopenia is common in adults with COVID-19 (83 %), but not in children (3 %), [6] so it can be considered a distinguishing feature of SIMS-N.

The most common complications of this syndrome are shock, myocardial dysfunction, acute kidney injury, acute liver failure, and acute respiratory failure (mainly secondary to cardiogenic causes). [4] The level of dependence on respiratory support has been found higher than the values reported in COVID-19 patients with lung involvement, both children and adults. [20] The tendency towards severity in these previously healthy patients, who develop a poorly organized immune response, indicates the need to prevent the disease in all children and adolescents and give them correct follow-up after 4-6 weeks from the start of the infection.

CONCLUSIONS

It has been shown that multisystem inflammatory syndrome in children with COVID-19 constitutes an entity independent of severe acute COVID-19 infection and Kawasaki disease, because they present epidemiological and clinical differences. Everything indicates that this syndrome constitutes a post-infectious hyperinflammatory phenomenon and it has been reported that superantigen-type activation could play an important role in its pathogenesis, leading to the cytokine storm characteristic of the disease, endothelial dysfunction, ischemic and thrombotic phenomena, shock and multiple organ dysfunction.

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STATEMENT OF AUTHORSHIP

AAR: conceptualization, research, methodology, project administration, validation, original draft writing, review, editing.

DLL: methodology, writing-original draft and editing.

DDB: research, writing-review and editing.

MARM: supervision, validation and visualization of the final version of the article.

CONFLICTS OF INTEREST

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