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Melatonin: A hypothesis for Kawasaki disease treatment

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ABSTRACT

Kawasaki disease (KD) is the most common cause of acquired heart disease with unknown etiology among children in developed countries. Acute inflammation of the vasculature, genetic susceptibility and immunopathogenesis based on a transmittable and infectious origin, are the pathologic events involved in the early inflammatory etiology and progression of this disease. However, the exact causes of KD remain unknown. Current proposed recommendations include three therapy lines; firstly, an initial standard therapy with intravenous immunoglobulin (IVIG) followed by aspirin. Secondly, in cases of high risk of coronary lesions, the adjunctive therapy with corticosteroid is commonly considered. Thirdly, in KD patients refractory to the previous therapies, tumor necrosis factor (TNF-α) antagonists are being used to modulate pro-inflammatory cytokines. In view of this status quo, our starting hypothesis is that the ubiquitous and non-toxic neurohormone melatonin could be of critical importance in developing novel adjuvant therapies against KD, as it occurs with a plethora of other diseases. Considering its pleiotropic properties, particularly its antiinflammatory and immunoregulatory capacities, melatonin should be of great therapeutic interest for helping to control the main pathologic features of KD patients. In addition, this multifunctional indole has a safe pharmacological profile, enhancing the therapeutic activity of several drugs and reducing their possible side effects. Consequently, melatoniṅs actions to manage KD need to be tested in further clinical studies.

Introduction

In 1967, Dr. Tomisaku Kawasaki reported a new illness, characterized by a large number of pathological features and clinical symptoms, which he named mucocutaneous lymph node syndrome [1], currently, the scientific community knows it as Kawasaki disease (KD). It commonly affects infants and young children between 6 months and 5 years of age [2]. The clinical features include a self-limited systemic type of acute pediatric inflammation of the vasculature of multiple organs: the coronary arteries, heart, joints, liver, central nervous system [3], muscle [4], kidney and urinary tract [5,6]. Even though KD is the primary cause of acquired heart disease among children in developed countries, and that its incidence is continuously increasing, the aetiopathogenesis remains to be elucidated. In this regard, it is commonly accepted that inflammation and immune dysregulation [7], oxidative stress [8], an infectious agent [9] and/or the genetic susceptibility to the disease [10], may be involved in the initiation and progression of KD.

This complex multifactorial disease requires a three-pronged therapeutic approach; i) Intravenous immunoglobulin (IVIG) and aspirin, as initial or first therapy, ii) Corticosteroids, for children unresponsive to two IVIG doses, as second-line therapy, and finally, iii) TNF-α blockers such as infliximab and/or etanercept for patients who do not respond to the previous therapeutic cycles.

Herein, we focus on several complications of KD such as inflammatory processes, candidate susceptibility genes, or abnormal immune responses induced by infectious agents, with a special emphasis on the therapeutic aspects that could make melatonin a potential clinical resource for the management of KD patients.

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Inflammatory response and immune dysregulation in KD

Coronary artery lesions are the most common and significant complication in KD. Although the fundamental molecular basis remains unclear, inflammation seems to play an important role in KD evolving towards acute inflammatory vasculitis and the coronary or systemic damage of arteries. In KD patients, several studies have reported a significant elevation of adipokine levels with respect to healthy children [11,12], necrotizing arteritis due to neutrophilic infiltration [13], and the recruitment and activation of monocytes [14]. Proinflammatory cytokines, TNF- α, IL-1β, IL-6 and IFN-γ, are clearly elevated during the acute phase of KD. In this scenario, the severity of vasculitis in the acute phase may, perhaps, predispose to long-term structural and functional changes in the arteries of KD patients. Furthermore, inducible nitric oxide synthase (iNOS), which is present in myocardial cells, vascular smooth muscle cells, leukocytes and inflammatory cells, is up-regulated during the inflammatory response; thus, it promotes an increase of nitric oxide (NO), the vascular tension regulator, which leads to vascular wall dilatation and damage [15].

The identification of specific immune response pathways that are dysregulated in KD patients are essential traits to be addressed in further investigations. In this context, T cells and their main negative modulator, the inositol 1,4,5-triphosphate 3-kinase (ITPKC), have been implicated in the cascades of KD immunopathogenesis. In KD patients, indeed, the loss of this control induces the activation of T cells and the production of cytokines [16]. It has also been shown that the relative proportion of T helper 17 (Th17) cells and the production of certain cytokines (IL-17, IL-6 and IL-23) are significantly up-regulated in patients with acute KD [17]. Similarly, other authors have documented that key proinflammatory cytokines such as TNF- α and IL-6, are aberrantly expressed in different experimental models of vasculitis [18,19].

Role of oxidative stress in KD

Inflammation and oxidative stress are closely related to cardiovascular pathology [20]. Therefore, an excessive generation of reactive oxygen and nitrogen species seems to be associated with cardiovascular pathogenesis in KD, which suggests that oxidative stress plays an important role in the progressive inflammation of the vascular endothelium and smooth muscle [21–23]. It is well known that oxidative stress provokes vasculitis in the acute phase of KD [24]. Accordingly, have been evaluated the oxidative stress and the endothelial dysfunction in the youngest KD patients and it has been concluded that oxidative stress may have a pathogenic functional impact on the arterial wall [8].

In addition to the above, nitrosative stress may also be involved in the increased risk of KD-associated vascular complications, particularly during platelet stimulation and defective apoptosis [25].

Infectious agents involved in KD

Abnormal immune responses are important in the pathogenesis of KD. Multiple viral etiologies and bacterial superantigenic toxin triggers have been suggested to be involved, among them, adenovirus, parvovirus, herpesvirus, leptospirosis, streptococci and/or staphylococci [2]. Therefore, the presence of infectious agents, in genetically predisposed individuals (particularly, Asians), induces a widespread immunological reaction, which results in the release of proinflammatory cytokines and chemokines that signal the development of vasculitis and the progression of KD. One decade ago, it was hypothesized that perhaps an infectious agent that enters in the respiratory tract, through macrophages, could infect coronary arteries, where IgA plasma cells and CD8 + T lymphocytes may cause vascular injury [26]. However, to date, no causative infectious agents have been isolated from affected children to confirm this hypothesis [27], although there are clinical similarities between KD and several toxin-mediated diseases, such as scarlet fever and toxic shock syndrome.

Genetic susceptibility in KD

Although KD pathogenesis remains unclear, strong evidence suggests that genetic susceptibility partially determines the condition. With a highest incidence among Asians [28], the suspected genetic predisposition makes it possible to find new targets for the treatment of KD. In this regard, it is known that certain functional single nucleotide polymorphisms (SNPs) linked to inositol 1,4,5-triphosphate 3-kinase (ITPKC), caspase-3 (CASP3), B lymphocyte kinase (BLK), human leukocyte antigen (HLA) and the TGF-β (transforming growth factor β) signaling pathway, may confer susceptibility to KD. These genetic variants increase the risk of coronary artery aneurysms and have been found associated with the lack of response to the standard first-line treatment with IVIG and aspirin [10]. So, the functional SNP (itpkc3) of *ITP3K* gene (ITPKC) is a negative modulator of T-cells, via the Ca^{2+} nuclear factor of activated T-cells (NFAT) signaling pathway; this increases the immune reactivity during the acute phase of this disease through the release of IL-2 by activated T-cells [29]. Thus, it has been recently proposed that cytosolic Ca^{2+}-overload is a key factor in susceptibility to KD and disease outcome, due to SNPs in the genes encoding ITPKC and $Na^{\pm}/Ca^{2+}$ exchanger, which thereby increases the risk of coronary artery lesions [30].

CASP3 is involved in immune cell apoptosis, and multiple SNP variants have been associated with KD in the Japanese and US populations with European family background [31]. Among other KD-associated genes, two recent genome-wide association studies (GWAS) in the Asian population have found the src family tyrosine kinase BLK, expressed in the B cell lineage, is significantly up-regulated in KD patients, indicating a regulatory role of B cells in the immune homeostasis of KD [10]. TGF-β signaling pathway is pivotal in tissue remodeling and inflammation, particularly in determining the balance of proinflammatory/anti-inflammatory T cells [32]. Therefore, genetic polymorphic variations in the TGF-β pathway may induce T cell dyshomeostasis associated with KD susceptibility [33]. Finally, HLA and variants have also been reported as candidate genes for KD [34].

In summary, to date an increasing number of genes and variants of KD patients seem to confer morbidity (as enhanced susceptibility to the coronary artery lesions) and resistance to the standard first-line treatment.

Therapy for the treatment of KD

As discussed above, the unrevealed origin of KD forces clinicians to address more than one therapy. Therefore, and according to the guidelines of the American Heart Association (AHA) and the recommendations of the American Academy of Pediatrics (AAP), to reduce the inflammatory process combined aspirin plus IVIG should be used as first-line adjunctive treatment, because most acute KD cases have shown positive outcome with this treatment [35]. Thus, IVIG treatment at a single dose of 2 g/kg (within 10 days of the onset) is considered the “gold standard” in reducing both fever duration and prevalence of coronary artery aneurysms in KD patients [36]. Although, it has been postulated that IVIG may counteract microbial toxins and down-regulate immune responses, the mechanism through which it modulates inflammation remains unclear and needs further research. Nonetheless, around 10–20% of patients of KD patients are unresponsive to initial dose of IVIG, show fever status persistent beyond 36 h of treatment with IVIG, and unfortunately have a greater risk of developing cardiac complications and death [16]. According to the AHA guidelines for the management of these refractory KD cases, a second dose of 2 g/kg IVIG or steroids is recommended [35].

Corticosteroids have been widely and successfully used in other types of vasculitis of diverse etiology. However, their use remains

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