Short communication

Advances in the co-host immune response to multisystem inflammatory syndrome and Kawasaki disease in children with AI-guided features

Abstract/Purpose: To investigate the effect of artificial intelligence in the immune response mechanism of children with multi-system inflammatory syndrome and Kawasaki disease. Methods: Domestic and foreign literatures on immune response mechanism of the two diseases were searched, and the literatures were analyzed based on the characteristics of artificial intelligence. Results: The AI analysis showed that both pediatric syndromes were concentrated in cytokine storms centered on il-15/ IL15RA. MISC had more proinflammatory cytokine TNF-α than KD, and the tumor necrosis factor-α chimeric antibody infliximab had been used for COVID-19. Conclusion: It shows the applicability of artificial intelligence in this research direction, which can provide basis for the treatment of diseases, and points out the existing limitations of the current work and the possible development direction of artificial intelligence research in related aspects.

Keywords: Artificial Intelligence; Kawasaki Disease; Multi-System Inflammatory Syndrome (MIS-C) Immune Response

Background:As multiple systemic inflammatory syndrome (MISC) caused by severe acute respiratory syndrome coronavirus type 2(SARS-CoV-2) infection has been reported with overlapping features with Kawasaki disease, suggesting vasculitis and a possible autoimmune etiology, Severe acute respiratory syndrome Coronavirus type 2(SARS-CoV-2) is a human coronavirus. Emerged in December 2019 and quickly spread around the world, posing great medical and life challenges to us. In April 2020, children with symptoms similar to incomplete Kawasaki disease (KD) or toxic shock syndrome were reported from the United

Kingdom, followed by reports of similar children in other parts of the world. Jiao Fuyong believes that KD and corona-virus infectious diseases, including severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), 2019 coronavirus disease (COVID-19), have great similarities in epidemiological distribution pattern: obvious seasonality. Combined with a few coronaviruses that can infect humans through cross-species transmission and whose symptoms are very similar to Kawasaki disease, Kawasaki disease can be considered as a new manifestation of COVID-19 in children and should be treated accordingly [1]. The disease, later defined as coronavirus-associated pediatric multisystemic inflammatory syndrome (MIS-C), can be fatal in severe cases. Pediatric Multisystem Inflammatory syndrome (MIS-C) and Kawasaki disease are both highly inflammatory diseases associated with infectious diseases, but are they distinct syndromes or do they exist along a continuum?Artificial intelligence-guided features have provided us with new insights into the co-host immune response of children with multisystem inflammatory syndrome and Kawasaki disease. This review is aimed at reviewing the recent advances in the host immune mechanism of children with multisystem inflammatory syndrome and Kawasaki disease.

Foreign research status:

The SARS-CoV-2 pandemic has inspired many research groups to find innovative ways to understand the host immune response to the virus, the uncontrolled proportion of which has been associated with death. More than 45,000 pandemic transcriptome datasets were analyzed by searching multiple (>45,000) gene expression datasets from GEO and ArrayExpress, and 166 gene signatures were extracted using ACE2 as the "seed" gene. The basic host immune response, known as the "cytokine storm", is common to all studied viral pandemics, regardless of their severity, causative virus, case fatality rate and clinical presentation. ViP markers define the exact nature of cytokine storms and locate il-15 cytokine and its receptor, IL15RA, as invariant components. Increased IL-15 was independently associated with mortality, and cytokine levels were consistently higher in both patients who died and those who re-

covered throughout their hospitalization. A "severe" ViP trait subset of 20 genes was also found, suggesting that stress-induced aging, transcriptional inhibition, DNA damage, and apoptosis are also shared among various viral pandemics, and in patients with COVID-19, this trait is present in lung epithelial cells and NK cells. This study defined ViP and severe ViP characteristics, identified elevated il-15/IL15RA levels in the lungs of patients with fatal diseases, and identified plasma cytokine levels as predictive of disease severity and precise therapeutic targets. That is, neutralizing antibodies that eliminate SARS-CoV-2 or direct acting antiviral drugs are used [2].

Given that pediatric multisystemic inflammatory syndrome (misc) shares many clinical features with Kawasaki disease prepandemic syndrome (KD), PradiptaGhosh et al. used a computational toolkit of two gene signatures developed in the context of SARS-CoV-2 infection to compare the two syndromes. Namely, viral pandemic (ViP) and severe ViP signatures, as well as 13 transcript signatures previously shown to diagnose KD. This study confirmed the same immunophenotype among three syndromes (COVID-19, KD, and MIS-C), namely the up-regulated il-15/IL15RA pathway, and that sViP features predicted disease severity of COVID-19 (left ventricular ejection fraction may be a clinical indicator of MIS-C severity). Induction of ViP and sViP signals in acute KD also tracks disease severity, i. e. the risk of developing large CAAs. To avoid over-reliance on a single set of signatures (i. e. ViP/sViP), Ghosh et al. then used 13 Kawasaki disease-specific gene expression signatures that had previously been used to identify Kawasaki disease in children with fever, but again could not distinguish between patients with MIS-C and Kawasaki disease. After tracking indicators (i. e. ViP, sViP, IL15/IL15RA and KD-13 characteristics as well as direct measures of serum cytokines), MISC was found to have a significantly higher degree of host immune response than KD. And there are some differences: (1) The degree of thrombocytopenia in severe cases of the three diseases;(2) eosinophil penia in COVID-19 and misc, but not KD;(3) The cardiac contractility of misc was impaired, but KD was not. A comprehensive analysis of serum cytokines and transcriptomics showed that, compared with KD, the pro-inflammatory MIP1α, TNF-α and IL1 path-

ways were significantly induced in misc. These two pediatric syndromes were concentrated on cytokine storms centered on il-15/il15ra, suggesting a shared proximal pathway of immune pathogenesis. However, they differ in other laboratory parameters (platelets, eosinophils) and cardiac phenotypes (decreased cardiac function, coronary artery dilatation). These related clinical/laboratory parameters (low PLT and AEC) may be useful indicators of the severity and prognosis of misc disease and can be used to guide hospital treatment and care decisions. Currently, Infliximab, a chimeric tumor necrosis factor α antibody, has been used for COVID-19 [3].

Subsequently, Jonathan Y Lam and others developed a deep learning algorithm called KIDMATCH(Kawasaki Disease vs Pediatric Multisystem Inflammatory Syndrome), which is based ona two-stage model consisting of a feedforward neural network, using patient age, five classic clinical signs of Kawasaki disease, and 17 laboratory measurements for disease identification. It is also the first algorithm used for diagnosis that can distinguish misc, Kawasaki disease, and other similar febrile diseases. However, due to the lack of a gold standard for diagnosis of Kawasaki disease or misc, and the limited data on febrile illness and Kawasaki disease for external validation, the limitations of this work are that the current algorithm is only optimized for laboratory test values collected at initial assessment. It is not yet clear how end users should handle patients marked as uncertain and how it will handle data collected at a later point in time. Ordering more specialized tests such as ferritin, troponin, B-type natriuretic peptide or N-terminal pre-B-type natriuretic peptide and D-dimer, as well as IgG antibodies against SARS-CoV-2 may be a better solution [4]

Studies on the immune mechanism of children with multi-system inflammatory syndrome (misc) and Kawasaki disease (KD) focus on multiple directions. At present, the researches on host immunity of misc and Kawasaki disease by artificial intelligence have not been done for a long time, and relevant literatures are lacking. The number of previous researches on the pathogenesis of the two diseases is relatively large. Now give a brief description of it:

Marques et al. investigated the transcriptome of 1,596 individuals, including patients with COVID-19, compared with healthy controls, other acute inflammatory states

(HLH, pediatric multisystem inflammatory syndrome, Kawasaki disease), and different respiratory infections (seasonal coronavirus, influenza, bacterial pneumonia). In this study, a group of neutrophil-related genes was found to reflect a generalized hyperinflammatory state, and these genes were abnormally regulated at the protein level, leading to the overactivation of neutrophils in patients. Studies have shown that severe COVID-19 illness shares neutrophil activation characteristics with other distinct acute inflammatory diseases, such as HLH, KD, and bacterial pneumonia. Multilayer transcriptome and cross-tissue analyses suggest a systemic community between severe COVID-19 and other acute inflammatory states that ultimately lead to overactivation of neutrophils under the influence of associated cytokines/chemokines. Blocking cytokine signaling pathways via Leronlima, or Tocilizumab, Adalimumab, or Anakinra, has been shown to improve severe symptoms of COVID-19 in some cases. In addition, Ruxolitinib is a JAK1/JAK2 inhibitor that acts downstream of JAKk-dependent chemokines/cytokines such as IFN-γ, IL-1β, IL-6, TNF, G-CSF, CXCL9, and CXCL10. This inhibitor has shown promising efficacy in the treatment of COVID-19. Neutrophil elastase inhibitors have also been suggested to relieve SARS-CoV-2 symptoms. The limitation of this study is that it did not consider the influence of age, sex, and comorbiditions on common transcriptome characteristics of COVID-19 and other high-inflammatory diseases [5]. "Peripheral Immunophenotypes in children with SARS-CoV-2 infection-associated multisystem inflammatory syndrome" by Michael J. Carter suggested that cytokine levels were elevated during the acute infection phase of misc,Including interleukin-1β (IL-1β), IL-6, IL-8, tumor necrosis factor-α, IL-10, IL-17, interferon-γ (IFN-γ), and IL-2 receptor agonists, CRP and ferritin were elevated, as in the acute phase of Kawasaki disease. However, elevated fibrinogen, elevated D-dimer, and decreased platelet levels in the acute phase of Misc suggest a procoagulant state that is not a common feature of Kawasaki disease. mis-c acute phase helper ($CD4^+$), cytotoxic ($CD8^+$), and gamma-δ T cell lymphocytopenia were observed in the study cohort. γδT significantly reduced the proportion of $CD4^+CCR7^+$T cells in the acute phase. CD4 and CD8 counts are higher in Kawasaki disease than those observed in the misc cohort, and the proportion of hla-dr positive

$CD4^+$T cells is lower in Kawasaki disease. Activation of $CD4^+CCR7^+$T cells and gamma-δ T cell subsets has not been reported. This study showed similarities and differences in immunity between Kawasaki disease and misc, limited by the use of HLA-DR only as a marker of T cell activation, and a lack of assessment of potential genetic susceptibility [6] . CamilaRosatConsiglio et al. found that some genetic variants with medium effect size, such as ITPKC, CD40, FCGR2A and BLK, are related to KD. The inflammatory response of misc shares several features with Kawasaki disease, but differs from Kawasaki disease in terms of T cell subsets, interleukin (IL)-17A, and biomarkers associated with arterial damage. Lymphocytopenia was more pronounced in children with misc than in children with Kawasaki disease, and patients with misc also had significantly higher C-reactive protein (CRP) and ferritin levels and lower platelet counts. The phenotype of peripheral blood mononuclear cells (PBMCS) was evaluated by flow cytometry. Compared with Kawasaki disease, MISC patients had lower naive $CD4^+$T cells and TFH, increased central and efficent memory subgroups, and higher CD57 markers in mis-c. This suggests that there are some specific differences in immune cell response between patients with misc and those with Kawasaki disease. IL-17A is important in Kawasaki disease, but it is significantly reduced in patients with misc, suggesting a difference in the underlying immunopathology. Human proteome chips were used to detect antibodies in plasma samples, and many MIS-C antibodies were found to be different from those in Kawasaki disease. The overexpression of EDIL3 autoantibodies was the most obvious in Kawasaki disease, and CSNK and MAP2K2 family proteins were significantly increased in MIS-C [7]. AliceCastaldo published a study on peripheral blood cell immunotyping to distinguish misc from Kawasaki disease. The study studied the leukocyte populations of 46 patients with misc and 28 patients with KD by flow cytometry and compared them with 70 age-matched healthy children. The results showed significant lymphocytopenia in patients with misc, involving B and T, and significant neutrophilia and thrombocytosis in patients with KD, which overlaps with previous findings. Granulocyte/lymphocyte ratios contribute to the diagnosis of misc and KD with high diagnostic sensitivity, while multivariate analysis of granulocyte and T

lymphocyte counts helps to distinguish between the two diseases. Analysis of a group of circulating cells helps in early diagnosis and differentiation of the two diseases [8]. Domestic research status: At present, there is no comparison of immunity of two diseases guided by AI characteristics in China. Li Shihua, Li Huimin et al. found that HLA-drb1 and HLA-micaA4 were associated with KD, and LA-B was considered to be a risk allele for severe infection of COVID-19. Autoimmune vasculitis of KD, KDSS, or MISC is mediated by genetic variations in HLA, FcγR, and/or ADE, resulting in excessive inflammation of Th17/Treg imbalance [9]. Genetic susceptibility was identified in relation to KD and/or COVID-19.

Conclusion: Given the difficulties caused by the COVID-19 pandemic, it is particularly important to use AI to help medical researchers target key molecules and pathways from complex data, study disease mechanisms, and develop drug therapies. Limitations of the current studies include the relatively small sample size and the limited number of publicly available misc data sets for independent verification. Rigorous data studies are still needed in the future. In the future, we hope to find more extensive and precise genetic signatures from existing studies (on cytokines, cellular immunophenotypes, antibodies, genetic susceptibility, etc.), use AI algorithms to define and stratify diseases in terms of clinical or laboratory parameters, identify phenotypes and complications of disease spectrum, including cardiogenic shock (e.g. , MIS-C shock and Kawasaki disease shock syndrome),MAS(cytokine storm related cell loss and cocoagulation dysfunction caused by infection), Kawasaki disease (typical and complete Kawasaki disease phenotype caused by SARS-CoV-2 or other infectious agents), and provide evidence for the development of treatment strategies [10]. Clinical data should be further expanded in the future, using artificial intelligence as a special approach. Diagnosis, differential diagnosis and treatment of the above diseases, and clinical services.

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