Plasma amino acid concentration in patients with IgG4-related disease

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Immunoglobulin G subclass 4-related disease (IgG4-RD) is a systemic fibroinflammatory disorder characterised by elevated serum IgG4 levels and IgG4+ plasmocytic infiltration in the inflamed organs. Although excess production of Th2 cytokines is associated with the development of the disease, the aetiology remains unclear (1). Recent studies have shown that amino acid metabolism plays an important role in the pathophysiology of autoimmune diseases by orchestrating T cell proliferation, survival, and differentiation (2). This fact suggests that amino acid metabolism may be associated with the pathophysiology of IgG4-RD through affecting T cell differentiation.

Plasma concentrations of amino acids reflect total amino acid metabolism in whole body, which is comprised of dietary intake, tissue breakdown and de-novo synthesis, and can be easily measured in clinical practice using a standardised metabolomic assay (3). Previous studies have shown that plasma amino acid concentration is altered in various diseases including cancers, heart failure and neurodegenerative disorders, and therefore can be useful for detecting the early phase or predicting the prognosis of the diseases (4). However, the association between plasma amino acid concentration and IgG4-RD has never been evaluated even though amino acid metabolism plays an important role in immune response.

Therefore, we assessed plasma amino acid concentration in patients with IgG4-RD based on the 2020 revised comprehensive diagnostic criteria (5). Subjects were recruited at the Rheumatology and Clinical Immunology clinic in Sapporo Medical University Hospital between September 2021 and June 2023. Plasma samples were collected from the patients early in the morning on the 2nd hospital day before starting glucocorticoid therapy. Plasma concentrations of 45 amino acids were measured by the standardised liquid chromatography-mass spectrometry (LSI Medience Corporation, Tokyo, Japan). Reference interval of each plasma amino acid concentration was defined according to 95th percentile of the healthy population in Japan.

A total of 27 (14 male and 13 female) patients with IgG4-RD were included in this study. The median age of the patients was 65 years old (range: 49–87 years). Organ involvements, sialadenitis and dacryoadenitis were found in 19 and 14 patients, respectively. In addition, 11 patients had pancreas-hepatobiliary diseases, 10 had kidney diseases, 6 had respiratory diseases and 6 had retroperitoneum diseases (Fig. 1A). Among the patients with IgG4-RD, citrulline (Cit) concentrations were increased in 9 patients.

Fig. 1. Plasma amino acid concentration in patients with immunoglobulin G subclass 4-related disease (IgG4-RD).
A: A heat map showing organ involvements and plasma amino acid concentration in 27 patients with IgG4-RD.
B: A schema showing catabolism in skeletal muscles and the urea cycle in liver.
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IgG4-RD compared to other autoimmune diseases. Recent studies have shown that patients with rheumatoid arthritis, a Th17-dominant autoimmune disease, have the different plasma amino acid profile, suggesting the activation of alanine-asparagine-glutamate and glycine-serine-threonine metabolisms (9, 10). We speculate that the difference in amino acid metabolism could designate autoimmune phenotypes by affecting T cell differentiation. Through the pilot work, we have found, for the first time, abnormal plasma concentrations of amino acids, especially 3-Me-His, Cit, Orn, and Arg, in patients with IgG4-RD. This result encourages future works focusing on immunometabolism to clarify the pathophysiology of IgG4-RD.

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References


