CRIA Syndrome: Cleavage-Resistant RIPK1-Induced Autoinflammatory Syndrome:

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CRIA syndrome (Cleavage-Resistant RIPK1-Induced Autoinflammatory Syndrome) is an extremely rare, chronic, autosomal dominantly inherited autoinflammatory disease. It was discovered in late 2019 by researchers at the National Human Genome Research Institute. It is caused by gain-of-function (GoF) mutations in the RIPK1 (Receptor-Interacting Serine/Threonine-Protein Kinase 1) gene that impairs caspase-8-mediated cleavage. The result of this leads to uncontrolled activation of the RIPK1 kinase activity ultimately causing systemic inflammation. Immunologists, rheumatologists and genetic experts are the main doctors who can diagnose/identify it.

CRIA syndrome is caused by genetics. It is diagnosed using clinical features, blood work and screening for the genetic mutation. There are common mutations associated with this disease that prevent RIPK1 from being cleaved at Asp324, leading to excessive kinase activity. Under normal conditions, caspase-8 cleaves RIPK1 to block necroptosis and reduce inflammation. In CRIA syndrome, cleavage-resistant RIPK1 builds up and becomes hyperactive, triggering many symptoms that mimic autoimmune diseases and other chronic illnesses. CRIA syndrome triggers necroptosis (programmed inflammatory cell death), increased cytokine release, especially IL-6, and TNF and systemic and organ-specific inflammation. CRIA syndrome attacks joints, the eyes, muscles, the immune and inflammatory system, the neurological system, the gastrointestinal system, the lymphatic system, the hepatosplenic system, blood, the skin system and much more.

The clinical features of CRIA syndrome usually begin in early childhood to late teenage years. Not all patients experience all the known symptoms, but they share a common presentation. Some of these symptoms occur in “flares” (a period of time where symptoms are present) while some are daily. These features include systemic symptoms like recurring fevers, malaise and fatigue. Because of this, it is probably underdiagnosed as it appears as many immunodeficiencies, autoinflammatory diseases and autoimmune diseases. This disease also causes lymphadenopathy (swollen lymph nodes) and an enlarged liver and spleen. In addition, it causes arthritis (joint pain with swelling), or arthralgia (joint pain without swelling) and myalgia (muscle pain and weakness). CRIA syndrome also causes severe abdominal pain, vomiting, nausea and diarrhea. It can cause rashes that look similar to psoriasis and can trigger already existing eczema. In even rarer cases, CRIA syndrome can affect the neurological system causing brain fog and headaches. Lastly, in the blood, it causes chronic anemia due to chronic inflammation which causes symptoms of anemia (dizziness, shortness of breath, fatigue, etc), elevated inflammatory markers (CRP, ferritin, etc) and leukocytosis. These symptoms can be so severe that they require hospitalization but the severity depends on the specific individual. Severe complications of this disease due to not taking the treatment or rapid progression include life-threatening organ failure and amyloidosis (a rare disease where abnormal proteins called amyloids build up in many organs and tissues, causing them to stiffen and malfunction).

As of now, this disease is extremely rare and under researched and its exact prevalence is unknown due to factors such as being misdiagnosed. It has fewer than 20 cases reported worldwide in the scientific literature as of 2024. It is not listed in large population databases (gnomAD) with pathogenic allele frequencies, meaning mutations causing CRIA are not found in the general population. As said before, some researchers suggest CRIA may be underdiagnosed, particularly in patients with undiagnosed autoinflammatory symptoms or undifferentiated/unclassified autoinflammatory syndromes (uAID's).

The main risk factor for this syndrome is having the genetic mutation. Since it is dominant, one mutated allele can cause disease even if the other is normal. Many cases can arise spontaneously with no family history, especially in isolated pediatric presentations. However, a positive family history of early-onset autoinflammatory or periodic fever syndromes such as TRAPS or FMF increases risk. Some carriers may be mildly symptomatic or undiagnosed, masking inheritance patterns. While CRIA syndrome is genetically driven, the severity and frequency of flares may be influenced by viral infections, physical stress or trauma, weather changes, immune activation or hormonal changes.

Since this disease causes chronic inflammatory flares, management of the syndrome focuses on suppressing inflammation, blocking downstream cytokines, and targeting RIPK1 pathways (currently experimental). There is no discovered cure as of now. For acute flare ups, corticosteroids like prednisone are prescribed because they rapidly suppress systemic inflammation. NSAIDS are often insufficient alone but can reduce fevers and mild inflammation. For long term management, targeted biologics are a key treatment. Anti–IL-6 Therapy is the most effective reported therapy that blocks the IL-6 receptors to prevent flares and symptoms. Anti–TNF Therapy has variable results but may help with gastrointestinal symptoms. JAK Inhibitors suppress multiple cytokine pathways but only have shown a partial response. In addition, colchicine, an anti-inflammatory, might be used on top of another treatment to further limit flares and symptoms. It can help very little in more severe cases, but can help significantly in very mild ones.

In notable patterns from real clinical cases, the age of onset is between 6 and 16. The fever pattern is recurring, lasting 3-7 days. The GI symptoms are very common and often can be linked to irritable bowel disease (IBD) and ulcerative colitis (UC). The systemic signs are lymphadenopathy, hepatosplenomegaly, fatigue and fever. Most mutations were de novo (occurred spontaneously), but familial cases with variable severity exist. In terms of treatment, IL-6 blockers are consistently effective, corticosteroids help during flares but not long-term and RIPK1 inhibitors are not yet available, and may be a future innovation.

Since this disease was recently discovered, its original innovations are still used today such as the biologics. However AI-assisted diagnosis tools can help catch the syndrome early and limit misdiagnosing. A rarely used innovation is a Hematopoietic Stem Cell Transplantation (HSCT). This is only considered in severe, refractory cases with early-onset life-threatening inflammation. There are very few HSCT's reported. In general, autoinflammatory gene panels now increasingly include RIPK1 thanks to the CRIA discovery which will help a lot more people

get diagnosed, especially diagnosed faster. In conclusion, CRIA syndrome is an extremely rare genetic, chronic autoinflammatory disease causing systemic hyperinflammation. It is currently under-researched and frequently misdiagnosed, but with growing awareness in the healthcare field, it will hopefully gain the recognition it deserves in the future.

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