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S100 proteins show promise as biomarkers in juvenile idiopathic arthritis

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Dr. TurnierPediatric rheumatologic diseases present inherent challenges in initial diagnosis and continued monitoring of disease activity.

At disease onset, characteristic symptoms may take time to accumulate, and diagnoses are frequently of exclusion. Patients then may go on to have subclinical inflammation or relapsing disease.

Not all juvenile idiopathic arthritis (JIA) patients respond alike to a given disease-modifying antirheumatic drug (DMARD), such as methotrexate or biologic agents. Many patients can require a trial of multiple DMARDs prior to showing significant improvement in active inflammation. In fact, recent data from a JIA cohort in the Pediatric Rheumatology Care and Outcomes Improvement Network demonstrated that only 39% of patients achieved clinically inactive disease during their most recent clinic visit (Bingham CA, et al. *Arthritis Rheumatol.* 2014;66(S3):S1-S2).

Traditional laboratory-based biomarkers such as C-reactive protein and erythrocyte sedimentation rate are nonspecific markers of inflammation and do not routinely correlate with disease activity in JIA. There is a great need for novel biomarkers to expedite diagnosis, improve monitoring of disease activity and stratify patients' risk for life-threatening disease complications.

Diagnosing inflammatory disease

S100 proteins represent a family of approximately 24 calcium-binding proteins, some of which are exclusively expressed by phagocytic cells. The S100 protein most studied in inflammatory disease is the S100A8/9 complex, also known as calprotectin.

Fecal calprotectin currently is used as a clinical test to help differentiate children with gastrointestinal symptoms who are more likely to have inflammatory bowel disease (IBD). Fecal calprotectin has proven superior in predicting a diagnosis of IBD when compared to other commonly used biomarkers, with an area under the receiver operating characteristic curve of 0.93 (Henderson P, et al. *Am J Gastroenterol.* 2012;107:941-949).

Extremely elevated levels of a related S100 protein called S100A12 have been shown to identify patients with systemic JIA (sJIA) as a cause of fever of unknown origin (Wittkowski H, et al. *Arthritis Rheum.* 2008;58:3924-3931).

Highly elevated calprotectin and S100A12 levels also have both been demonstrated to help distinguish sJIA patients with new onset disease and subclinical macrophage activation syndrome (MAS) in an abstract presented at the 2015 American College of Rheumatology Annual Meeting (Turnier JL, et al. *Arthritis Rheumatol.* 2015;67(S10):2472). MAS must be diagnosed promptly, as it is a potentially fatal complication of sJIA, manifested by persistent fever, cytopenias, hepatosplenomegaly, lymphadenopathy, elevated transaminases and coagulopathy.

Predicting response to therapy

There is a need for biomarkers that can help predict response to a given therapy for JIA patients. S100 proteins have shown promise in serving as biomarkers of disease activity and response to therapy in JIA.

Elevated calprotectin levels have been found to predict disease flares and correlate with clinical disease activity in sJIA patients (Holzinger D, et al. *Ann Rheum Dis.* 2012;71:974-980). A recent study found that high calprotectin levels might help predict whether patients will respond to therapy with methotrexate (Moncrieffe H, et al. *Rheumatology.* 2013;52:1467-1476). This has high treatment implications, as methotrexate is the initial DMARD used for many patients with JIA.

The incorporation of predictive biomarkers such as calprotectin into a clinical treatment algorithm could help direct individualized therapy for JIA patients. Higher calprotectin levels at the time of stopping DMARD therapy have been shown to predict risk of future disease flare in JIA patients, both with methotrexate and etanercept (Foell D, et al. *JAMA.* 2010;303:1266-1273; Anink J, et al. *Arthritis Res Ther.* 2015;17:200*).*

It is a great challenge for a pediatric rheumatologist to determine when or even if DMARD therapy can be withdrawn for a JIA patient, so a biomarker that could estimate likelihood of flare could guide treatment decisions and expectations for families of JIA patients.

Future of an S100 clinical assay in JIA

Further research is ongoing to determine if measurement of S100 proteins has a role in the management of JIA. Recent studies are promising, with evidence of S100A12 aiding in sJIA diagnosis and S100A8/9 or calprotectin predicting diseases flares.

The relative stability of S100 proteins also contributes to their potential as future biomarkers. S100 proteins appear to be ideal candidate biomarkers for better monitoring of disease control in JIA.

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